Renal Nerve Ablation for Resistant Hypertension
How Did We Get Here, Present Status, and Future Directions

Vasilios Papademetriou, MD; Amir Adel Rashidi, MD; Costas Tsioufis, MD; Michael Doumas, MD

Sympathetic renal denervation, or renal nerve ablation (RNA), has become the new buzz word in hypertension and interventional cardiology. Recent advances in catheter-based approaches have allowed sympathetic fiber interruption through transvascular techniques that are minimally invasive and can be delivered expeditiously and safely. Radiofrequency (RF) energy sources are currently the preferred modalities, but other sources of energy, such as cryoablation, microwave, high-intensity focus ultrasound, and local neurotoxic agent infusion, are under intense investigation. Results thus far have been encouraging and offer promise for the future. The role of the sympathetic nervous system (SNS) in the development of resistant hypertension and cardiovascular disease has long been known, and a great deal of work has been done through the years trying to explore potential interventions to interrupt the sympathetic influence on systemic vasculature and target organs. In this article we attempt an overview of time-dependent interventions on the SNS and examine approaches used in humans and in the many experimental models that offer a better understanding of the role of sympathetic activity in cardiovascular disease. Naturally we focus on methods and techniques addressing sympathetic renal denervation in patients with drug-resistant hypertension, examine the current state of the art, and attempt to look into the future.

Historic Perspective

In 1889, after meticulous experiments on dogs, Bradford reported that stimulation of dorsal and splanchnic nerves causes changes in blood pressure (BP) and kidney size measured by plethysmography. Whether BP increased or decreased depended on the anatomic area stimulated, as well as the electric impulse frequency, but outcomes were consistent and reproducible. Neurosurgical treatment of hypertension was independently suggested by researchers in 1923. Adson, however, was the first to performed surgical sympathectomy for the treatment of malignant hypertension in 1925. During the following years and in the 1930s, Peet in Ann Arbor, Page and Heuer in New York, and Adson, Craig, and Brown from the Mayo Clinic operated and reported on series of patients all experiencing malignant hypertension. At the same time, renal decapsulation, which was considered a form of sympathectomy by disrupting the fibers between the capsule and the renal cortex, was being performed to treat unexplained hematuria and perinephritis. Sen reported a significant but not permanent decrease in BP in 85 subjects who underwent decapsulation between 1925 and 1935.

Surgical denervation of the kidneys alone was first performed in humans by Papin and Ambard in 1924 in an attempt to relieve intractable pain originating from the kidney. The first case of bilateral sympathetic denervation of the kidney to treat severe essential hypertension was presented in 1934 by Page and Heuer. The patient was a 25-year-old woman who reported easy fatigability and had severe headaches and BP in the range of 208/140 mm Hg. The patient underwent surgical staged, bilateral renal sympathectomy with no clinically meaningful effect on BP after follow-up for 5 months. However, the case established that the procedure was safe and had no negative effect on renal function. In 1935, Page and Heuer reported bilateral renal denervation in 5 patients with chronic and progressive nephritis, which resulted in no change in renal clearance or concentrating ability of the kidney but caused diminished proteinuria and a decrease in BP that lasted for months in the majority of those patients. Because of these early unsatisfactory results, surgical renal denervation gave way to the more radical sympathectomy procedure, the surgical removal of splanchnic nerves (splanchnicectomy), which showed dramatic results in the majority of patients with malignant hypertension. Peet published series and case reports of patients with malignant hypertension responding in a dramatic way to supradiaphragmatic splanchnicectomy. Figure 1 shows the BP response of a 22-year-old patient with known severe hypertension for >3 years. She had been in bedrest for 8 months because of the severity of symptoms, yet her BP remained at 280/190 mm Hg. Fundoscopic examination revealed stage IV retinopathy with evidence of early papilledema, flame-shaped hemorrhages, and cotton wool exudates. On June 24, 1934 she underwent bilateral supradiaphragmatic splanchnicectomy, and postoperatively her BP was reduced to 110/90 mm Hg. Fundoscopic examination 2 months later demonstrated complete resolution of papilledema, with hemorrhages and exudates resolved. The patient became asymptomatic, and 13 years later was free of any hypertensive complications with BP remaining within the normal range (Figure 1).

Since then and for the subsequent 2 decades, surgical sympathectomy (thoracolumbar splanchnicectomy) became...
the procedure of choice for patients with severe/malignant hypertension not responding to diet or to then-limited pharmacologic therapy. Between 1938 and 1947, Smithwick and Thompson\(^\text{10}\) published results from 3500 patients with severe/malignant hypertension. Of those, 2400 patients underwent thoracolumbar splanchnicectomy, and the rest were followed on a medical regimen. Of those, 1266 patients who had splanchnicectomy, and 467 patients on medical therapy had follow-up of 5 to 14 years and were included in the final analysis. At 5 years of follow-up, all-cause mortality was 19% in the surgical series and 54% in the medically treated patients. Of the surgically treated patients, only 45% demonstrated substantial BP reduction, but mortality benefits were realized across the board. Peet et al\(^\text{11}\) reported 51.4% significant BP reduction and 3.4% operative mortality in 350 patients with severe/malignant hypertension. However, an important limiting complication was postural hypotension, which was encountered in many patients postoperatively.

In the mid-1950s the first oral antihypertensive medication became available for the treatment of hypertension, and for the first time a well-tolerated regimen could be given long term.\(^\text{12}\) Pharmacologic therapy helped treat many patients with severe hypertension, and the number of patients progressing to accelerated/malignant stage gradually diminished,\(^\text{13}\) thus settling the issue for the next 5 decades. Very few patients not responding to pharmacologic therapy have been referred for splanchnicectomy in recent years. However, during this time a great deal of research has been pursued to uncover and better understand the role of the SNS and, in particular, of the renal sympathetic nerves in the development and maintenance of hypertension.\(^\text{14}\)

A wealth of experimental data in animals and humans point toward an important role of SNS overactivity for the development and persistence of hypertension.\(^\text{15}\) Excessive SNS activity is involved in the metabolic syndrome, obesity, structural and functional myocardial alterations,\(^\text{16}\) and several other disease states, including congestive heart failure (HF), chronic kidney disease, polycystic ovary syndrome, obstructive sleep apnea, and cirrhosis.\(^\text{17–21}\) SNS regulation is multifactorial, and several mechanisms modulate sympathetic activity.\(^\text{15}\)

### Renal Nerves: Efferent and Afferent Sympathetic Fibers

Kidneys act both as generators and recipients of sympathetic signals (Figure 2).\(^\text{22}\) Sympathetic afferent fibers originate from the kidneys and travel to the central nervous system, where,
after processing, coordinated by the nucleus tractus solitaries of the midbrain, they regulate sympathetic outflow and promote SNS overactivity in response to renal injury. On the other hand, renal efferent sympathetic nerves originate from the brain, travel through the spinal cord, reach the kidney from the second sympathetic ganglia, course through the adventitia of the renal arteries, and innervate the peripheral segments in the renal cortex, ending in glomerular arterioles, where they can affect renal function. Overactivity of the efferent sympathetic fibers results in enhanced renin release, increased sodium and water absorption, reduced renal blood flow, and glomerular filtration rate. It seems that both the afferent and efferent fibers contribute to the development and persistence of hypertension.

By the 1980s it was well established that kidneys are important sensory organs with abundant baroreceptors and chemo-receptors and significant afferent innervation. In 1987, Webb and Brody published results from a thesis in which they addressed signal trafficking via the afferent sympathetic fibers in a rat model. Through extensive instrumentation and careful monitoring, they demonstrated that electric stimulation of the afferent sympathetic fibers can reduce BP in a dose-dependent manner. They also demonstrated that BP responses could be abolished by spinal transection and interruption of the efferent sympathetic fibers coursing through the spine. Subsequently, in a controlled study, Campese and Kogosov showed that resection of the afferent renal nerves through ventral rhizotomy can prevent activation of the noradrenergic neurons in the hypothalamus and can prevent the development of hypertension in rats with chronic renal insufficiency.

In other studies, Converse et al showed that patients on hemodialysis who have undergone bilateral nephrectomy have significantly lower peripheral vascular resistance and BP. Similar findings were reported by Hausberg et al in renal transplant recipients before and after surgical removal of native kidneys. Bilateral nephrectomy results in the interruption of both the afferent and efferent sympathetic fibers. Renal nerve stimulation results in vasoconstriction of the renal vasculature. Others have demonstrated that sympathetic nerve endings directly release norepinephrine on renal epithelial cells and can cause a 30% to 40% increase in sodium and water reabsorption via α-1 adrenergic receptors even before any hemodynamic changes could be detected. In 1981, Osborn et al demonstrated that low-frequency stimulation of the renal nerve in dogs can directly mediate renin secretion via β-1 adrenergic receptors. In other experiments, surgical renal denervation has been shown to affect hypertension. In deoxycorticosterone acetate--treated
miniature swine with established hypertension, O'Hagan et al. demonstrated that renal denervation results in immense natriuresis and BP reduction. Similarly, Huang et al. in a hyperinsulinemia-induced hypertension model demonstrated that renal denervation can prevent hypertension development if done early or can normalize BP after hypertension is established (Figure 3).

RNA for Drug-Resistant Hypertension
Renal sympathetic denervation has been performed, through the years, both in experimental models and in humans by surgical exposure of renal nerves. The renal nerves were interrupted or resected using mostly a surgical scalpel, although later electrocautery, cryoaolation, and thermal (RF) ablation have also been used. With progress in technology and the advent of transcatheter techniques, it was natural to progress to transvascular methods to interrupt nerve integrity. Catheter-based RF ablation techniques have been used in electrophysiology for more than 2 decades to ablate accessory pathways and abnormal cardiac structures in patients with Wolff-Parkinson-White syndrome or supraventricular and ventricular arrhythmia. In 1999, a series of experiments completed at the University of Oklahoma using a basket catheter demonstrated that it was possible to stimulate and ablate autonomic nerves on the outside of blood vessels. Notably, Schauerte et al. used an innovative approach to stimulate and ablate the vagal nerve to treat patients with vagally mediated atrial fibrillation (AF). RF energy was applied transvascularly to ablate the vagal nerve. The currently used technique for catheter-based RNA uses a very similar concept.

Patients with drug-resistant hypertension have increased sympathetic outflow. Resistant hypertension is defined as failure to achieve BP goals despite the use of at least 3 antihypertensive drugs, 1 of which is a diuretic. The exact prevalence of resistant hypertension is not known, but by current estimates, ≈12% of patients with hypertension are resistant to treatment. This would translate into ≈120 million patients worldwide.

Given resistance to drug therapy, activation of SNS, the role of renal nerves in the development of hypertension, and the ease of approach of the sympathetic fibers by catheter based techniques, resistant hypertension was the perfect candidate for interventional approaches. Sympathetic fibers course in the adventitia of the renal arteries, are mostly situated within 2 to 3 mm from the inner layer of the renal artery, and can be easily reached and interrupted transvascularly using thermal energy. To date, RF thermal energy has been delivered using either a single-tip electrode catheter or multielectrode systems. The objective of RF ablation is to place discrete lesions in a circumferential pattern but not at the same cross-section of the vessel, so as to minimize the risk of renal artery stenosis.

As of today, 6 devices received the CE marking to be used for RNA. The first device used in humans (Symplicity/Ardian, Metronic) was a 6-French, steerable RF ablation catheter inserted percutaneously through a femoral sheath and a guide catheter engaging each renal artery sequentially. This catheter is easy to use but it creates lesions with a less predictable geometric pattern. The St Jude’s multielectrode ablation system (EnligHTN) has 4 electrodes mounted on a basket that can easily achieve circumferential distribution.

Figure 3. Renal denervation in 2 animal models. A, Immense natriuresis and blood pressure reduction in a deoxycorticosterone acetate (DOCA)-treated miniature swine model. B, Prevention of hypertension with early renal nerve ablation (RNA) and blood pressure (BP) reduction to normal when RNA was performed 4 weeks after insulin infusion. Reprinted from Huang et al. with permission from Hypertension and from O'Hagan et al. with permission from American Journal of Hypertension.
of lesions. The basket is collapsed, can be expanded by an external mechanism, can achieve good wall apposition, and can deliver thermal injury and fiber interruption in a desirable and predictable way. The other 2 systems, the Vessix V2 system (Vessix Vascular-Boston Scientific), and the OneShot system (Covidien), have the electrodes mounted on a balloon. The Iberis system (Terumo) has a 4-French shaft that enables radial access. The Paradise system using ultrasound technology has also been approved in Europe (ReCor Medical).

Below we briefly review the studies performed to date and attempt a well-intended critique of existing data.

The first in-human proof-of-concept study (Symplicity I) evaluated 50 patients with treatment-resistant hypertension. Of those, 45 were eligible for RNA and composed the treatment group. BP reduction with RNA was significant, smaller in the first month after RNA (–14/–10 mm Hg), and more pronounced at 6-month and 1-year follow-up (–27/–17 mm Hg; Figure 4). Ambulatory BP monitoring (ABPM) was done in a small number of patients and demonstrated much less BP reduction (–11 mm Hg for systolic BP [SBP]).

The second study was randomized but not blinded and performed soon after in a larger sample of 106 patients with resistant hypertension and similar characteristics to the proof-of-concept study. RNA was performed in 52 patients, whereas standard antihypertensive medications were continued in the remaining 54 patients. BP dropped significantly in the first month in the active RNA group, but BP reduction was much greater at 6 months (–32/–12 mm Hg). BP change was minimal in the control group (1/0 mm Hg). BP reduction was significantly less in a smaller group of 20 patients who underwent ambulatory BP measurement (–11/–7 mm Hg).

The Symplicity trials created a great deal of enthusiasm and captured the imagination of the hypertension and interventional community alike. Nevertheless, these early studies...
were accompanied by a number of questions and inconsistencies, described below.

Initial office BP reduction was modest and improved with time. The number of patients reported at each time point was different (smaller at later time points), which raises the possibility that nonresponders were excluded. Other possibilities include regression to the mean, improvement in patient compliance, medication manipulation, or lifestyle changes. Remodeling of resistance vessels has also been suggested by the authors. The lack of placebo effect noted in Symplicity II is also highly unusual for hypertension studies. The bigger problem, however, with the Symplicity and other trials is the discrepancy between office BP measurements and ABPM. A small disparity in office and average 24-hour ambulatory BP reduction is expected and has been reported previously; large disparities, however, are unusual and raise questions.43

There was a considerable discrepancy between average office BP and average 24-hour BP at baseline, as well as a big difference in the magnitude of BP reduction during follow up in the Symplicity trials (Figure 4). Ambulatory BP was performed only in a small subset of patients (12 of 45 patients in Symplicity I and 20 of 49 patients in the active group of Symplicity II), and BP reduction was only 41% and 34% of office BP reduction in the 2 studies. A meta-analysis of antihypertensive drug therapy revealed that ambulatory BP reduction should be ≥65% of the reduction seen in office BP.44 Similar disparities have been noted in most recently published denervation trials.

We recently reported the 6-month data from the first-in-human trial, EnligHTN I.45 This study included 46 patients with resistant hypertension and baseline characteristics similar to the Symplicity population. All of the patients underwent RNA using a standardized technique aiming to achieve complete renal denervation. In this first in-human study, office BP was reduced significantly and substantially in the first month (–28/–10 mm Hg) and remained at the same levels for ≤6 months. Results from all of the patients were reported at all of the time points. Ambulatory BP measurement was performed in all of the patients and demonstrated a ≤10/≤5-mm Hg reduction in average 24-hour BP, which also remained the same until the 6-month follow-up. However,
the discrepancy between office and ambulatory BP reduction remained. Baseline office SBP and heart rate correlated significantly with BP response at 6 months.46

Although several other studies reported significant BP reduction after RNA, only a few performed ABPM to evaluate the magnitude of BP reduction (Figure 4). A small study was performed by Witkowski et al32 in 10 patients with sleep apnea and drug-resistant hypertension. The authors found a significant reduction in office BP at 3 and 6 months after RDN (−34/−13 mm Hg) but only a small change in SBP measured by ABPM (−6 mm Hg). Another small study, by Hering et al,48 in 15 patients with moderate and severe chronic kidney disease and resistant hypertension showed impressive office BP reduction at 3 and 6 months post-RNA (−27/−14 and −29/−14 mm Hg, respectively), but ABPM reductions were small and did not reach statistical significance (−6/−7 and −5/−6 mm Hg, respectively). A pilot study using the OneShot system in 8 patients with resistant hypertension showed similar results.49 After RNA, office BP was reduced by −34/−12 mm Hg at 6 months, but ABPM reductions were once again disappointingly small (−3/−4 mm Hg).

Recently, a larger study presented a series of patients who underwent RNA for resistant hypertension and specifically examined the BP response as measured by ABPM.50 In this study, 346 patients with uncontrolled hypertension were evaluated. Of those, 303 patients were found by daytime ABPM to have true resistant hypertension, and 43 had pseudoresistant hypertension (office SBP, 161±20 mm Hg; 24-hour SBP, 121±20 mm Hg). At 3, 6, and 12 months of follow-up, office SBP was reduced by 21/24/27 mm Hg and office diastolic BP by 9/9/12 mm Hg. In patients with true treatment-resistant hypertension, there was a significant reduction in 24-hour SBP (10/10/12 mm Hg; P<0.001) and diastolic BP (5/5/7 mm Hg; P<0.001) at 3, 6, and 12 months, respectively. There was no effect on ABPM in pseudoresistant patients, whereas office BP was reduced to a similar extent. The findings of this larger study were in line with the findings of the 2 Symplicity trials and the EnligHTN I study, confirming the antihypertensive effect of RNA but once again demonstrating a much smaller BP reduction when assessed by ABPM. This article was accompanied by an editorial that criticized the results.51 Figure 4 presents baseline office and 24-hour ambulatory BPs and BP changes after RNA in 5 studies that included both measures. Consistently the ABPM measurements are substantially lower than the office measurements.

The mechanisms underlying the disparity between office and ambulatory BP reduction remain poorly understood. We proposed recently that the white coat effect might be implicated, at least in part,43 whereas regression to the mean and other unclarified mechanisms might also apply. Of great interest, the reduction in office and ambulatory BP was almost identical in a recent study of 54 patients with moderate true resistant hypertension (office BP between 140/90 and 160/100 mm Hg).52 The findings of the latter study offer another potential contributing factor, that is, the level of BP values before applying RNA. It is known that the magnitude of BP reduction greatly depends on pretreatment levels, both with drug therapy53 and RNA.54,55 It is therefore expected for BP reduction to be larger when pretreatment BP is higher (usually the office BP) than when it is lower (usually the ambulatory BP). Indeed, it was found that the reduction in ambulatory BP tends to approach the office BP fall as the pretreatment BP levels become lower.56 However, further basic and clinical research is needed to clarify the mechanisms underlying the disparity and identify ways to overcome this problem.

Other published studies presented negative results. In 1 study, 12 patients with difficult-to-control hypertension underwent RNA,57 and results were recorded before and 5 months after denervation. Results indicated that RNA did not change resting muscle sympathetic nerve activity, heart rate, or heart rate variability, and there was no change in office BP. One explanation for the results of this study is patient selection. Patients had lower baseline BP (157/85 mm Hg), and more importantly many of them (5 of 12; 42%) had normal BP (SBP <140 mm Hg), questioning the choice of RNA for patient management.58 Furthermore, there was no evidence of sympathetic activation (heart rate of 60 beats per minute and normal muscle sympathetic nerve activity discharge) at baseline,59 despite this, heart rate was reduced in 60% of these patients.

Future Directions: Other Potential Applications of RNA

RNA might be beneficial in other disease states characterized by enhanced sympathetic activity, including chronic kidney disease, congestive HF, sympathetically driven arrhythmias, obstructive sleep apnea, and polycystic ovary syndrome. RNA may eventually find a role as a supplemental procedure to improve outcomes in high-risk patients, such as patients with coronary heart disease and or chronic kidney disease. The Table presents a number of disease states accompanied

<table>
<thead>
<tr>
<th>Cardiometabolic Targets</th>
<th>Other Disease States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome*</td>
<td>Chronic kidney disease 1-3a‡</td>
</tr>
<tr>
<td>Obesity*</td>
<td>Chronic kidney disease 3b-4†</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>Chronic kidney disease ESRD†</td>
</tr>
<tr>
<td>Hypertension mild*</td>
<td>Chronic kidney disease peritoneal</td>
</tr>
<tr>
<td>Hypertension difficult to control†</td>
<td>hemodialysis*</td>
</tr>
<tr>
<td>Hypertension resistant‡</td>
<td>Polycystic kidney disease†</td>
</tr>
<tr>
<td>Atherosclerosis*</td>
<td>Loin hematuria*</td>
</tr>
<tr>
<td>Coronary artery disease*</td>
<td>Obstructive sleep apnea†</td>
</tr>
<tr>
<td>Left ventricular hypertrophy†</td>
<td>Polycystic ovary syndrome†</td>
</tr>
<tr>
<td>Diastolic LV dysfunction†</td>
<td>Cirrhosis*</td>
</tr>
<tr>
<td>Heart failure with preserved EF*</td>
<td></td>
</tr>
<tr>
<td>Systolic heart failure†</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia†</td>
<td></td>
</tr>
<tr>
<td>Sudden death*</td>
<td></td>
</tr>
</tbody>
</table>

LV indicates left ventricular; EF, ejection fraction; ESRD, end-stage renal disease.
*No data available.
†Limited data available.
‡Robust data available.
by sympathetic overactivity that potentially can benefit from RNA. Case reports or small pilot studies have been reported in many of these populations and they are briefly mentioned below.

**Hypertension**

Drug-resistant hypertension will remain the primary target for RNA, because this is a population with unmet medical need and data so far look encouraging. When the randomized, blinded control trials in the United States are completed (assuming positive results), RNA may become the procedure of choice for these patients. Before getting there, however, attention should be focused on key issues, such as preprocedural diagnostic workup, eligibility criteria for RNA, predictors of response, and markers of success.

The diagnostic workup should aim to exclude secondary causes of resistance (renal artery stenosis, primary hyperaldosteronism, pheochromocytoma, hyperthyroidism, etc), anatomic abnormalities that would preclude RNA (multiple, small caliper renal arteries or very tortuous or heavily calcified renal arteries), and most importantly white coat hypertension. Large observational studies have shown that white coat hypertension can be detected in approximately one third of patients with resistant hypertension. The importance of pseudoresistance has been highlighted in the study by Mahfoud et al, which demonstrated no response to RNA measured by ABPM in this population. We, therefore, strongly believe that ABPM should be mandatory in all patients considered for RNA to exclude population. We, therefore, strongly believe that ABPM should be mandatory in all patients considered for RNA to exclude pseudoresistance. Adherence to drug therapy and lifestyle modification should also be thoroughly assessed, because they frequently account for drug resistance. Furthermore, optimization of the drug regimen to include an aldosterone antagonist (spironolactone or eplerenone) should be implemented in most patients before considering RNA. Exceptions, however, can be considered for patients with drug-resistant hypertension because of habitual noncompliance or inability or unwillingness to take prescribed medication.

The criteria for RNA eligibility currently include patients with resistant hypertension and SBP levels >160 mm Hg (150 mm Hg for patients with diabetes mellitus and established cardiovascular disease), largely on the basis of the 2 Symplicity trials and the EnligHTN I study. However, pilot studies already explore the efficacy and safety of RNA in milder forms of resistant hypertension, that is, SBP between 140 and 160 mm Hg. In 2 studies of 20 and 54 such patients, BP was reduced by 13/5 and 13/7 mm Hg, respectively, at 6 months post-RNA. The European Society of Hypertension and the European Society of Cardiology have recently published position articles regarding RNA in an effort to clarify eligibility criteria and avoid the wide application of RNA in patients with questionable efficacy.

Efforts to identify predictors of response and markers of procedural success currently remain elusive. As of today, only baseline BP and, to a lesser extent, baseline heart rate have been shown to correlate with BP response after RNA, whereas indices of sympathetic overactivity, such as muscle sympathetic nerve activity or plasma noradrenaline levels, do not correlate with BP response. Renal blood flow and electric stimulation of renal arterial nerves have been recently proposed as markers of procedural success; but both markers need validation in larger studies. Of note, heart rate was significantly reduced after RNA in some studies, suggesting that heart rate reduction might serve as a sensitive surrogate of RNA success.

Finally, the relative contribution of afferent and efferent denervation in BP reduction in humans needs further exploration. Partial attenuation of systemic sympathetic activity, indicating afferent denervation, has been shown in some but not all studies, whereas functional signals of efferent denervation have been reported in some studies as well. However, available data do not allow conclusions on whether denervation of afferent or efferent fibers is the main contributor to BP reduction.

**Milder Forms of Hypertension**

RNA may have a role in the vastly larger population with mild-to-moderate hypertension, but it is still too early to tell. It seems very attractive to use RNA in this population to achieve better BP control, to decrease the amount of antihypertensive medication needed, or even to avoid lifelong drug therapy altogether. Milder forms of hypertension, however, are less likely to be associated with SNS activation, and patients with lower baseline BP are less likely to respond to RNA. Yet, there may be subgroups of these patients who can benefit from the procedure. These include patients who can be controlled on a medical regimen but are intolerant to medication, those who report frequent adverse effects, or those who simply they do not like taking medicines. However, long-term (>5 years) efficacy and safety data are needed before RNA can be recommended for this population. Another attractive population for RNA includes the newly diagnosed young patients with known SNS overactivity. If RNA proves to be effective and safe in this patient population, it may be possible to avoid, attenuate, or delay lifelong drug therapy and even prevent target organ damage.

**Heart Failure**

A vast amount of evidence indicates that SNS is overactivated in HF and greatly contributes to the poor outcome of this patient population. Furthermore, HF is characterized by neurohormonal activation, increased vascular resistance, and sodium and fluid retention, all of which can be favorably influenced by renal denervation. Therefore, RNA seems an attractive adjunct procedure to existing drug therapies in patients with either systolic or diastolic HF. The inhibitory effects of RNA on the renin-angiotensin system may confer an additional benefit in these patients. In a small nonrandomized study of 7 HF patients with reduced ejection fraction (Renal Artery Denervation in Chronic Heart Failure-Pilot study), RNA showed an increase in exercise capacity, and a larger study to assess cardiovascular outcomes (Renal Sympathetic Denervation for Patients With Chronic Heart Failure [RSD4CHF]) is currently underway. Likewise, significant improvements in myocardial structural and functional characteristics have been observed in patients with resistant hypertension and left ventricular hypertrophy. Some of these patients (approximately one fourth) presented...
with HF and preserved ejection fraction.69 A large outcome study (Denervation of the renAI sympathetic nerves in heart Failure With nOrmal Lv Ejection Fraction [DIASTOLE]) in HF patients with preserved ejection fraction is now underway.

**Chronic Kidney Disease**

Overactivity of SNS has long been shown in animal models with CKD and has recently been verified in patients with end-stage renal disease (ESRD) undergoing hemodialysis27 and in renal transplant28 patients. The diseased kidneys have been shown to be the source of SNS overactivity, which was attenuated by bilateral surgical removal of the native kidneys.27,28 Therefore, RNA seems an attractive option for the inhibition of SNS overactivity in these patients. Indeed, RNA was successful and effective in 2 case reports of patients with ESRD,71,72 in a larger group of 15 patients with moderate and severe CKD,48 and in a study of 9 patients with ESRD.73 Large multicenter studies are currently underway to further evaluate the effects of RNA in CKD. It is worth noting that, in this population, available data indicate that renal function does not deteriorate after RNA, and safety and efficacy for BP response are similar as that found in patients without CKD.49 Renal function was meticulously assessed using biomarkers for functional and structural kidney damage and found to remain unaltered both in patients with and without CKD,74 thus addressing previously raised concerns.75 Furthermore, renal function may improve with time in patients with mild-to-moderate CKD, because RNA may result in improvement in renal blood flow. This group of patients is known to have high cardiovascular risk,70 which may be partially mediated by sympathetic activation and merits further study. Patients with mild-to-moderate CKD should specifically be studied for improvement in cardiovascular outcomes after RNA, or studies of RNA should be specifically designed for this patient population. Finally, RNA is under investigation for the alleviation of pain in patients with polycystic kidney disease and loin pain hematuria.

**Cardiac Arrhythmias**

The SNS plays a crucial role in the pathogenesis and maintenance of atrial and ventricular arrhythmias.76 Data presented recently at the annual American College of Cardiology meeting from our group from 14 patients with resistant hypertension indicate that RNA can result in impressive reduction of both supraventricular and ventricular ectopic activity.79

The effect of RNA on AF has been addressed in other studies. Data in pigs80 and dogs81 indicate that RNA reduces the inducibility of AF and attenuates the ventricular rate. In humans, 27 patients with a history of symptomatic paroxysmal or persistent refractory AF and resistant hypertension were randomly assigned to pulmonary vein isolation (PVI) only or PVI with RNA.82 RNA with PVI was more effective than PVI alone in preventing the recurrence of atrial fibrillation and reducing BP (–27/–12 mmHg) at 6 months and 1 year. A large, multicenter randomized study (Adjunctive Renal Sympathetic Denervation to Modify Hypertension as Upstream Therapy in the Treatment of Atrial Fibrillation [H-FIBI]) is currently underway, and results are eagerly awaited. RNA was recently performed in 2 patients with congestive HF and ventricular tachy-arrhythmias (monomorphic ventricular tachycardia, recurrent polymorphic ventricular tachycardia, and ventricular fibrillation) resistant to therapy.83 RNA resulted in successful termination of ventricular arrhythmias and patient discharge.

**Obstructive Sleep Apnea**

Sympathetic activity is enhanced and is thought to play a pivotal role in obstructive sleep apnea.16,20 In animal models of obstructive sleep apnea, RNA attenuated postapneic BP elevations in pigs and increased water excretion in rats.80,84 RNA was evaluated recently in 10 patients with obstructive sleep apnea and resistant hypertension in a small, uncontrolled study.47 BP results have been discussed above. In addition, a significant improvement in sleep apnea severity was observed. The median apnea-hypopnea index was reduced from 16.3 episodes per hour at baseline to 4.5 events per hour post-RNA, suggesting that sympathetic overactivity is a major contributor in sleep apnea severity and that RNA-induced attenuation of sympathetic drive significantly alleviates disease expression. The study, however, is small, and larger numbers are needed to evaluate the role of RNA as an adjunct therapy to continuous positive airway pressure in patients with sleep apnea.

**Polycystic Ovary Syndrome**

Polycystic ovary syndrome is a common disorder in women of reproductive age, characterized by endocrine abnormalities coupled with metabolic disturbances. Sympathetic activity is enhanced in women with this syndrome.19 RNA performed in 2 young women with polycystic ovary syndrome resulted in moderate office BP reduction, substantial improvement in insulin sensitivity, and reappearance of menses in 1 patient who remained amenorrheic for 3 years. These data suggest that RNA may result not only in BP reduction but also in improvement in disease state. It is too early, however, to draw any definite conclusions.

There are many more disease states that can potentially become therapeutic targets for RNA that are beyond the scope of this contemporary review (Table). These include patients with metabolic syndrome/diabetes mellitus because RNA has been shown to improve insulin resistance,86 patients presenting with ST elevation myocardial infarction to prevent reverse left ventricular remodeling (RNA can potentially be done after primary percutaneous coronary intervention), and high-risk patients to improve cardiovascular outcomes. The latter will require long-term studies that include a large number of high-risk patients, preferably with evidence of SNS activation, including patients with CKD. One such study is underway (in the design phase) and currently is planned to include >5000 patients (EnlightMENT).

**Commentary**

Any new procedure or therapeutic approach to be accepted by the medical community needs to be safe and effective. The safety of RNA has been pretty well established. So far, only rare cases of renal artery stenosis have been reported, and no other signals of serious adverse events have been identified. Long-term safety data, however, need to be accumulated. So
far, vascular complications have been reported rarely and were inconsequential. Small hematomas, pseudo-aneurisms, minor bleeds, some vasospasm of the renal artery post-RNA, and 1 dissection requiring stenting, but no serious or life-threatening adverse events, have been reported. The concern of renal artery stenosis development is legitimate and has been observed previously with RF ablation for AF in pulmonary veins and coronary arteries adjacent to accessory pathways in patients with Wolff-Parkinson-White syndrome. Fortunately, so far only 2 cases of several thousand procedures have been reported as procedure related. The effect on renal function has been closely watched, and so far only minor deterioration of estimated glomerular filtration rate and increase in serum creatinine has been noted. No major renal function events have been reported.

There is little doubt that RNA is effective in most patients with renal-mediated sympathetic hyperactivity and resistant hypertension. The overall magnitude of BP response, however, still needs to be determined. BP is a dynamic measure and has considerable variability, particularly among patients with resistant hypertension. Until well-done, blinded, placebo-controlled, sham-masked studies are completed, we will not be certain about the true effect of RNA in this population. Sham-controlled studies are underway in the United States (Symplicity III and EnligHTN IV).* These studies will include a large number of patients with strict evaluation at baseline, a sham-controlled arm, and separate teams performing the interventional procedure and medical follow-up. Patients in these studies will be evaluated by means of office BP and ABPM. Without doubt, these studies will provide credible information and allow the field to move forward. When these studies are completed, we may find out that the BP reduction overall is smaller than currently reported, but in these high-risk patients with uncontrolled hypertension, any BP reduction is welcome. It is also a fact that current data suggest that not all patients respond to RNA. There are undoubtedly some patients who demonstrate dramatic BP reductions and others who do not respond at all. Presumably the good responders are those with renomediated sympathetic activation, whereas the nonresponders have hypertension mediated by other mechanisms. It is urgent and important, therefore, to seek and develop markers of good response so as to appropriately direct RNA to the right patient population. The effect of RNA in the many other disease states accompanied by sympathetic hyperactivity (Table) deserves careful study and consideration.

Acknowledgments

We acknowledge the contribution of Drs Doumas and Rashidi in the creation of some of the figures included in this article. This was above and beyond their contribution to the writing of the article.

Disclosures

Drs Papademetriou and Tsitouris are investigators and coauthors of the EnligHTN I article and consultants to St Jude Medical. The other authors report no conflicts.

References


*About three months after this paper was accepted for publication it became known that EnligHTN IV was suspended (due to slow enrollment). Continuation of the study will be re-evaluated after the results of Symplicity HTN III are fully analyzed. In the meantime, the sponsors of Symplicity HTN III announced that the study failed to meet its primary end point, although the study met its primary safety objective. While details from Symplicity III are anxiously awaited, we feel that these developments in no way affect statements and opinions expressed throughout this manuscript.


Key Words: cardiology ■ hypertension ■ kidney
Renal Nerve Ablation for Resistant Hypertension: How Did We Get Here, Present Status, and Future Directions
Vasilios Papademetriou, Amir Adel Rashidi, Costas Tsioufis and Michael Doumas

Circulation. 2014;129:1440-1451
doi: 10.1161/CIRCULATIONAHA.113.005405

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/13/1440

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/