

Renal Denervation as a Therapeutic Approach for Hypertension

Novel Implications for an Old Concept

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Hypertension, heart failure, and chronic kidney disease represent a significant and growing global health issue. Current therapeutic strategies for these conditions are mainly based on lifestyle interventions and pharmacological approaches, but the rates of control of blood pressure and the therapeutic efforts to prevent progression of heart failure, chronic kidney disease, and their sequelae remain unsatisfactory, and additional options are required.

The contribution of renal sympathetic nerve activity to the development and progression of these disease states has been convincingly demonstrated in both preclinical and human experiments. Preclinical experiments in models of hypertension, myocardial infarction, heart failure, chronic kidney disease, and diabetic nephropathy have successfully used renal denervation as both an experimental tool and a therapeutic strategy.¹⁻⁶ In the absence of appropriate drugs to pharmacologically reduce blood pressure in severely hypertensive patients, therapeutic splanchnicectomy and even radical surgical sympathectomy were used since the 1930s. In patients with end stage renal disease (ESRD) and uncontrollable hypertension, an even more radical approach, such as bilateral nephrectomy, is sometimes considered. Surgical renal denervation has been shown to be an effective means of reducing sympathetic outflow to the kidneys, increasing urine output (natriuresis and diuresis), and reducing renin release, without adversely affecting other functions of the kidney, such as glomerular filtration rate and renal blood flow. The human transplant experience has clearly demonstrated that the denervated kidney reliably supports electrolyte and volume homeostasis in free-living humans. On the basis of these findings and in view of the demand for alternative treatment options, targeting the renal sympathetic nerves as a major player in the pathophysiology of hypertension, kidney disease, and heart failure is a very attractive therapeutic approach.

Role of Renal Sympathetic Nerves in Cardiovascular and Kidney Disease

The renal sympathetic nervous system has been identified as a major contributor to the complex pathophysiology of hypertension, states of volume overload (such as heart failure), and progressive renal disease, both experimentally and in humans.¹⁻⁶ Studies using radiotracer dilution methodology to measure overflow of norepinephrine (NE) from the kidneys to plasma revealed increased renal NE spillover rates in patients with essential hypertension,^{7,8} particularly so in young hypertensive subjects, which, in concert with increased NE spillover from the heart, is consistent with the hemodynamic profile typically seen in early hypertension, characterized by increased heart rate, cardiac output, and renovascular resistance.⁹ It is now widely accepted that essential hypertension is commonly neurogenic, both initiated and sustained by sympathetic nervous system overactivity.

Activation of cardiorenal sympathetic nerve activity is even more pronounced in heart failure, as demonstrated by an exaggerated increase of NE overflow from the heart and the kidneys to plasma in this patient group.¹⁰ Not surprisingly, IV infusion of the centrally acting α_2 -adrenoceptor agonist clonidine, at modest doses, significantly attenuates cardiac and renal sympathetic tone in heart failure patients.¹¹ In addition to the beneficial effects of antiadrenergic therapy in the heart, the renal sympatholytic effects may counteract the salt and water retention that is a hallmark of the condition. In line with this notion is the recent demonstration of a strong negative predictive value of renal sympathetic activation on all-cause mortality and heart transplantation in patients with congestive heart failure, which is independent of overall sympathetic activity, glomerular filtration rate, and left ventricular ejection fraction.¹² These findings clearly suggest that treatment regimens that further reduce renal sympathetic stimulation have the potential to improve survival in patients with heart failure.

Received July 1, 2009; first decision July 15, 2009; revision accepted September 15, 2009.

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This trial has been registered at www.clinicaltrials.gov (identifiers NCT00483808 and NCT00551304).

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(*Hypertension*. 2009;54:1195-1201.)

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.109.138610

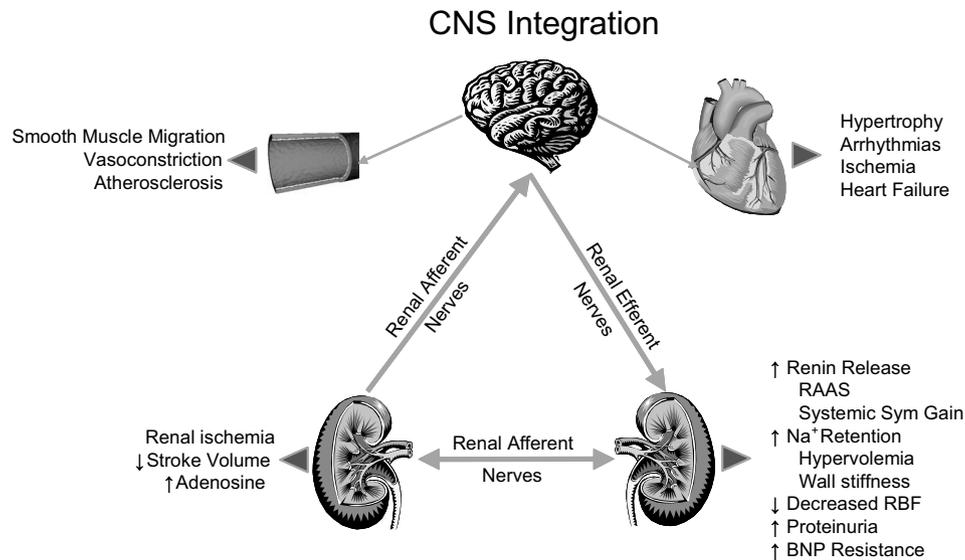


Figure. Several forms of renal injury can induce activation of sensory afferent signals. These afferent signals are centrally integrated and result in increased sympathetic outflow, which is not only directed toward the kidneys, thereby inducing increased renin secretion, sodium retention, and vasoconstriction, but also toward other organs that have a dense sympathetic innervation, such as the heart and the peripheral vasculature, resulting in the described adverse effects of sympathetic activation, several aspects of which also contribute to the rise in blood pressure. RAAS indicates renin-angiotensin-aldosterone system; Na, sodium; RBF, renal blood flow; BNP, brain natriuretic peptide; sym, sympathetic.

Both chronic and ESRD are characterized by heightened sympathetic nervous activation.^{13,14} In patients with chronic kidney disease, progression of renal failure can be delayed by the centrally acting sympatholytic agent moxonidine.¹⁵ Moxonidine has also been demonstrated to reduce microalbuminuria in normotensive patients with type 1 diabetes mellitus, in the absence of any significant blood pressure changes.¹⁶ In patients with ESRD, plasma levels of NE above the median have been demonstrated to be predictive for both all-cause death and death from cardiovascular disease.¹⁷ There is now compelling evidence to suggest that sensory afferent signals originating from the diseased kidneys are major contributors to initiate and sustain renal sympathetic efferent activation in this patient group, which facilitates the occurrence of the well-known adverse consequences of chronic sympathetic overactivity, such as hypertension,⁸ left ventricular hypertrophy,^{18,19} ventricular arrhythmias, and sudden cardiac death. Although altered activities of both renal sympathetic efferent and sensory afferent nerves have been associated with these conditions in experimental models (Figure), their respective roles in the human situation remain elusive.

Renal Sympathetic Efferent Activity

Sympathetic nerves to the kidneys terminate in the blood vessels, the juxtaglomerular apparatus, and the renal tubules.²⁰ Stimulation of the renal sympathetic nerves causes increased renin release,²¹ increased sodium reabsorption,²² and a reduction of renal blood flow.^{23,24} These components of the neural regulation of renal function are considerably stimulated in disease states characterized by heightened sympathetic tone and clearly contribute to the rise in blood pressure in hypertensive patients. The reduction of renal blood flow and glomerular filtration rate as a result of renal sympathetic efferent stimulation is likely a cornerstone of the

loss of renal function in cardiorenal syndrome, a complication of chronic heart failure, and consistent with its fluctuating clinical course.²⁵ Pharmacological strategies to thwart the consequences of renal efferent sympathetic stimulation include centrally acting sympatholytic drugs, β -blockers (intended to reduce renin release), angiotensin-converting enzyme inhibitors, and receptor blockers (intended to block the action of angiotensin II and aldosterone activation consequent to renin release) and diuretics (intended to counter the renal sympathetic-mediated sodium and water retention). However, the current pharmacological strategies have significant limitations, including limited efficacy, compliance issues, adverse effects, and others. Thus, a compelling need for additional or alternative therapies exists. Renal denervation potentially offers a more direct, organ-specific strategy by targeting a mechanism crucially involved in initiating this vicious cycle.

Renal Sensory Afferent Nerve Activity

The kidneys communicate with integral structures in the central nervous system via the renal sensory afferent nerves. Intrarenal pathology, such as ischemia, hypoxia, or other injury, results in an increase in renal afferent activity.^{26–28} Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control, such as the heart and peripheral blood vessels, by modulating posterior hypothalamic activity.^{29,30} Abrogation of renal sensory afferent nerves has been demonstrated in various models to have salutary effects not only on blood pressure but also on organ-specific damage caused by chronic sympathetic overactivity.^{31,32} Thus, renal denervation is likely to be valuable in the treatment of several clinical conditions characterized by increased overall and particularly renal sympathetic activity, such as hypertension, left ventricular hypertrophy, chronic

and ESRD, inappropriate fluid retention in heart failure, cardiorenal syndrome, and sudden death.

Preclinical Studies of Therapeutic Renal Denervation

Therapeutic renal denervation has been explored in animal models of disease. The vast majority of these experiments have used renal denervation as a tool to reveal the contribution of renal sympathetic efferent and sensory afferent nerves to renal and systemic organ function under normal and pathological conditions. Although most of the experiments were not explicitly designed to identify the potential clinical use of renal denervation, they actually provide significant information. Renal denervation has most often been performed by surgical ligation and reanastomosis of the renal artery or surgical stripping of the renal nerve adventitia with a local application of phenol (without manipulating the ureter). Another early approach involved selective renal infusion of 6-hydroxydopamine to poison the nerve terminals.^{33–36} Preclinical experiments using renal denervation as a therapeutic strategy have included multiple animal species (rodents, swine, canine, and ovine) and numerous disease states: hypertension (genetic, salt sensitive, obesity related, renal artery stenosis mimics, and reduced uterine perfusion–juvenile hypertension), postmyocardial infarction (coronary ligation), heart failure (coronary ligation, rapid atrial pacing, or high output failure associated with fistula), and kidney disease (surgical or chemical partial nephrectomy). Consistently, these studies have exploited renal denervation to reveal that renal sympathetic efferent and sensory afferent nerves contribute to the pathology in hypertension, heart failure, and chronic kidney disease. Simultaneously, these experiments revealed the potential therapeutic value of renal denervation.

Hypertension

DiBona concluded in his 2002 review of the interaction of the sympathetic nervous system and the kidney³¹:

the renal sympathetic nerves probably serve as the critical link between the sympathetic nervous system and the kidney in hypertension. In support of this view are studies in both experimental models of hypertension in animals and hypertensive human subjects that demonstrate increased RSNA preceding the onset or early in the course of hypertension, prevention or attenuation of hypertension by renal denervation (combined afferent and efferent renal denervation), and prevention or reversal of hypertension by afferent renal denervation in chronic renal disease.

DiBona³¹ based these conclusions on data derived from a large number of diverse animal models of experimental hypertension, where bilateral renal denervation prevented the development or attenuated the magnitude of hypertension.² Indeed, pronounced effects of renal denervation on blood pressure were demonstrated in multiple diverse models of hypertension, including salt-sensitive swine⁴; genetically hypertensive rats³⁷; 2-kidney, 1-clip Goldblatt hypertension³⁸;

and 1-kidney renal hypertension.³⁹ Although the vast majority of studies in various hypertension models did demonstrate favorable effects of renal denervation on blood pressure control, there are also reports, particularly from the 1-kidney, 1-clip model, suggesting that intact renal nerves are not necessary for the development or maintenance of hypertension⁴⁰ and that, regardless of the severity and duration of hypertension, renal denervation may not achieve attenuation of either the development or the maintenance of 1-kidney, 1-clip Goldblatt in this rat model of hypertension.⁴¹

The potential of renal denervation to treat obesity-related hypertension, associated with sodium retention and increased sympathetic nervous system activity, was explored in a model of high-fat–fed, chronically instrumented dogs.⁶ In this model, which resulted in a 50% increase in body mass in both control and denervated dogs, 2 important findings were noted: first, although blood pressure significantly increased in the control, there was no change in the denervated dogs, and, second, sodium retention in the denervated dogs was half that of the controls. This study demonstrated chronic durability of benefit and identified no abnormalities of renal function after surgical denervation.⁶

Postmyocardial Infarction and Congestive Heart Failure

Early exploration of the relation between renal sympathetic activity and heart failure identified that increased renal sympathetic activity is associated with resistance to the natriuretic action of atrial natriuretic peptide.⁴² Subsequent work by DiBona and Sawin⁴³ documented the salutary effects of bilateral renal nerve ligation in rats with cirrhosis attributed to common bile duct ligation or rats with heart failure after left anterior descending artery ligation. The investigation revealed that sodium retention was attributable in part to renal sympathetic efferent nerve activity, which was abolished by renal nerve ligation. On the basis of measurements of postprandial sodium excretion, similar conclusions were reached from work on renal denervated dogs with an arteriovenous fistula and the syndrome of compensated high-output heart failure⁴⁴; however, long-term ventricular pressure was not monitored in these models. The ligation of renal nerves protected against expression of postprandial natriuretic resistance and the development of congestion or rises in ventricular filling pressures. Recently, the therapeutic value of renal denervation in heart failure was evaluated in a similar experimental model of coronary ligation–induced myocardial infarction in rats.⁴⁵ This study, in which renal denervation was performed before onset of myocardial infarction, demonstrated reduced ventricular filling pressure and improved ventricular function compared with nondenervated controls. As in hypertension, deliberate renal denervation has been exploited to gain physiological insights into pathological conditions. At the same time, however, these studies revealed a possible and attractive therapeutic target, namely, the renal sympathetic nerves.

Chronic Kidney Disease

Sympathetic overactivity is a hallmark of patients with chronic renal disease and renal failure. The use of clinical microneu-

rography has unambiguously demonstrated high levels of muscle sympathetic nerve activity in patients with ESRD.^{13,14,46} It is most likely, although not proven in humans, that afferent signaling from the diseased kidneys plays a crucial role in the central sympathetic activation evident in this patient group,^{47,48} possibly further enhanced by impaired autofeedback regulation of hypothalamic NE release.⁴⁹

The potential of therapeutic renal denervation to attenuate the progression of renal disease has been explored in preclinical studies. Using a model of 5/6 nephrectomized rats to study the sympathetic nervous system and hypertension, dorsal rhizotomy prevented the rise of blood pressure and NE secretion from the posterior hypothalamus.⁵⁰ This model suggests that afferent impulses from the kidney to central integrative structures in the brain may be responsible for the rise in blood pressure in chronic renal failure. Renal injury caused by unilateral phenol injection reliably causes hypertension in rats associated with both increases in NE secretion from the posterior hypothalamus and downregulation of neuronal NO synthase in association with increased renal sympathetic efferent and afferent nerve activity of both kidneys.²⁷ Immediately after direct renal injection of phenol, renal sympathetic efferent and afferent activities were elevated, associated with falling urinary sodium excretion and increased renal NE. Surgical renal denervation of the phenol-treated kidney prevented the increase in blood pressure and plasma NE, a rise of interleukin 1b, and a decrease in neuronal NO synthase in the posterior hypothalamus.²⁷ Several other models of renal disease and interventions targeting the sympathetic nervous system have been studied and reviewed in detail by Joles and Koomans,⁵¹ further supporting the protective effects of sympatholytic interventions.

Application of renal denervation to prevent the development of structural renal changes attributed to early diabetic nephropathy has also been explored.⁵² This preclinical model used bilateral surgical renal denervation before the induction of diabetes mellitus with streptozotocin in rats. Functional and anatomic studies were performed 2 weeks after the onset of diabetes mellitus. In these experiments, therapeutic renal denervation resulted in the prevention of physiological and anatomic findings associated with early diabetic nephropathy, allowing the authors to speculate about the therapeutic value of renal denervation performed to prevent renal disease.⁵² Just as in the cases of hypertension, heart failure, and myocardial infarction, renal denervation has been used as a physiological tool to elucidate the role of these nerves in pathological states, revealing a potential therapeutic strategy: therapeutic renal denervation. By analogy, hypertensive patients with renal disease frequently remain hypertensive despite reaching true dry weight and taking maximal doses of angiotensin II blockade, highlighting the potentially powerful role of both efferent renal sympathetic nerves and probably afferent renal sensory nerves in hypertension associated with chronic kidney disease. Renal denervation targeting both types of renal nerves thus appears as a logical and attractive therapeutic target for these patients.⁵³

Therapeutic Renal Denervation in Humans

The preclinical science surrounding renal denervation has supported human surgical efforts to modify renal innervation,

particularly for the treatment of hypertension.^{54,55} These efforts, including posterior thoracolumbar sympathectomy and surgical nephrectomy, have all been plagued by the complexity and morbidity associated with the surgical procedure and further encumbered by their unpredictable efficacy in causing functional renal denervation. For example, in no case did the investigators demonstrate denervation of the human kidney after the procedure, nor, in these legacy clinical trials, did they specifically target isolated renal denervation as opposed to generic thoracolumbar sympathetic denervation. The irregular success of the procedure (notably in the reduction of blood pressure) might appropriately be attributed to the occasional renal denervation that was effected by the surgical procedure. The occasional dramatic success of the unproven surgical strategy fuels enthusiasm for the development of a safe, effective, and targeted procedure to functionally denervate the human kidneys.

Blood Pressure Regulation in ESRD: Nephrectomy of Native Nonfunctioning Kidney as a Model for Therapeutic Renal Denervation

The role of the kidney in the development and maintenance of hypertension is well described. Reports of nephrectomy in patients with ESRD, maintained on dialysis or posttransplantation, confirm the potential value of renal denervation of the native kidney, which was associated with consistent reduction in blood pressure and total systemic vascular resistance.⁵⁶ The potential therapeutic use of denervation of the native kidney in ESRD patients with hypertension and left ventricular hypertrophy has been highlighted recently in a case report demonstrating a decrease of left ventricular mass of 54 g within 4 months after bilateral nephrectomy,⁵⁷ supporting the concept of heightened sympathetic outflow, particularly to the heart, being a main contributor to hypertensive left ventricular hypertrophy.¹⁹

Novel Developments: Catheter-Based Renal Denervation

The renal sympathetic nervous system has been identified as a major contributor to the complex pathophysiology of hypertension, states of volume overload (such as heart failure), and progressive renal disease, both experimentally and in humans. Surgical methods of sympathectomy were associated with high perioperative morbidity and mortality, as well as long-term complications, including bowel, bladder, and erectile dysfunction, in addition to profound postural hypotension.^{54,55} Nevertheless, targeting the renal sympathetic nerves more specifically remained as a very attractive therapeutic approach despite anatomic and physiological obstacles to the design of either pharmacological or device-based solutions. The renal sympathetic nerves are derived from numerous spinal ganglia, and paraspinal gangliectomy has been associated with severe and systemic adverse effects. Similarly, pharmacological assault on sympathetic nerve function is associated with systemic complications. The sympathetic renal nerves arborize throughout the adventitia of the renal artery, eliminating convenient anatomic access.

The retroperitoneal location of the kidney increases the technical difficulty of access to the nerves.

In spite of these many obstacles, recent developments appear to have the potential to overcome these anatomic and technical difficulties and to provide new hope for the treatment of resistant hypertension and perhaps other clinical conditions commonly associated with increased renal sympathetic nerve activity. In a recently published safety and proof-of-concept trial, a novel, percutaneous, catheter-based approach was applied to selectively ablate the renal sympathetic nerves without affecting other abdominal, pelvic, or lower extremity innervation.⁵⁸ In this approach, renal sympathetic nerve ablation is achieved percutaneously via the lumen of the main renal artery using a catheter connected to a radiofrequency (RF) generator. After gaining access via the femoral artery and confirmation of anatomic eligibility with renal angiography, the treatment catheter (Symplicity, Ardian, Inc) is introduced into each renal artery, and discrete RF ablations lasting ≤ 2 minutes each are applied to achieve ≤ 6 ablations separated both longitudinally and rotationally within each renal artery. Catheter tip temperature and impedance are constantly monitored during ablation, and RF energy delivery is regulated according to a predetermined algorithm. Preclinical studies were performed in juvenile swine and demonstrated that the procedure markedly reduced the content of NE in the treated kidney by $>85\%$, which is very similar to the effects of direct surgical renal denervation via artery transection and reanastomosis. Importantly, no significant vascular or renal injury was evident at 6 months postprocedure in these animal studies. These promising preclinical results justified the initiation of a first-in-human evaluation of the safety and blood pressure-lowering efficacy of selective renal denervation using this percutaneous, catheter-based treatment approach in patients with difficult-to-control and resistant hypertension.⁵⁸ Treatment was performed in a total of 45 patients with a mean age of 58 ± 9 years and an average blood pressure of $177/101 \pm 20/15$ mm Hg, despite being on an average of 4.7 ± 1.5 hypertensive medications. The median duration of the procedure was 38 minutes, and safety analysis revealed no long-term adverse clinical sequelae associated with the procedure; particularly no instances of renal artery aneurysm or stenosis were detected, as assessed by renal angiography at 14 to 30 days after the procedure and by magnetic resonance angiographies at 6 months postprocedure. Calculated estimated glomerular filtration rate data indicated no significant deterioration of renal function, indicative of a favorable vascular and renal safety profile. The ablation procedure was accompanied by diffuse visceral nonradiating abdominal pain, which did not persist beyond the RF energy application and could be managed by IV narcotics and sedatives.

A highly significant reduction in both systolic and diastolic blood pressures that was first observed at 1 month was further reduced at 3 months and persisted through subsequent evaluations out to 12 months in 9 patients who had reached the 12-month follow-up at the time of publication. Mean ($\pm 95\%$ CI) decreases in office blood pressure were $-14/-10 \pm 4/3$, $-21/-10 \pm 7/4$, $-22/-11 \pm 10/5$, $-24/-11 \pm 9/5$, and $-27/-17 \pm 16/11$ mm Hg at 1, 3, 6, 9, and 12 months, respectively.

Most importantly, radiotracer dilution methodologies were applied in 10 patients to assess overflow of NE from the kidneys into the circulation and revealed a substantial reduction in NE spillover of 47% (95% CI: 28% to 65%) in response to the RF procedure as assessed after 1 month postdenervation, indicating the efficacy of the procedure in achieving efferent renal sympathetic denervation. These same 10 patients had a mean 6-month office blood pressure reduction of 22/12 mm Hg.

In summary, catheter-based therapeutic renal denervation appeared to be a quick and safe procedure that resulted in a large and persistent decrease in blood pressure in patients resistant to multiple existing antihypertensive drug classes. Importantly, no attenuation of blood pressure reduction was detected in the follow-up period (≤ 12 months), suggesting the absence of nerve fiber recovery and nerve fiber regrowth or the development of counterregulatory blood pressure-elevating mechanisms. Renal and heart transplant models have indicated that renal sympathetic efferent nerves may regrow after injury, raising the possibility of finite time limits in the physiological effects of the procedure, an issue that will have to be addressed in longer term follow-up studies. However, the physiological importance of anatomic regrowth of efferent nerve fibers in sustaining blood pressure remains unproven. Furthermore, in contrast to efferent sympathetic fibers, renal sensory afferent fibers are not known to have the potential to regrow, and these afferent fibers are likely to be affected by the procedure, as evidenced by the occurrence of pain during the procedure. Although afferent signaling cannot be measured directly in humans, alterations in afferent fiber signaling are likely to play an important role in the blood pressure effects associated with this procedure, as indicated by the recent demonstration of a substantial and progressive reduction in central sympathetic outflow at 1 and 12 months of follow-up that was accompanied by a progressive reduction in blood pressure.⁵⁹ In this regard, it is also important to consider that renal denervation decreases renin secretion, which may affect central sympathetic outflow via alterations of circulating angiotensin II levels. Furthermore, cardiac baroreflex sensitivity was improved after renal denervation (from 7.8 to 11.7 ms/mm Hg), and cardiovascular imaging using MRI revealed a substantial reduction of left ventricular mass from 184 to 169 g (78.8 to 73.1 g/m²) at 12 months of follow-up compared with baseline.⁵⁹ Renal NE spillover was, however, measured only 1 month postdenervation and at that time confirmed successful reduction of renal sympathetic efferent activity while simultaneously noting the reduction of total body NE spillover. Although these are short-term findings, it is certainly notable that the reduction of total body NE spillover is greater than the reduction of renal NE spillover, confirming a reduction of central sympathetic drive. These findings indicate that renal denervation achieved via this novel catheter-based approach has the potential to improve blood pressure control and alleviate the sequelae of elevated blood pressure, most likely via interference with both efferent sympathetic and afferent sensory nerves and potentially further central mechanisms.

Another proof-of-concept trial is currently underway in patients with end stage renal failure (clinicaltrials.gov iden-

tifier NCT00551304) complicated by hypertension, and preliminary findings indicate similar beneficial effects in this patient cohort.

Taken together, the safety and efficacy findings of these initial studies confirm the importance of renal sympathetic nerves in resistant hypertension and suggest that renal sympathetic denervation has the potential of therapeutic benefit in this patient population. Clearly, randomized, controlled trials will be necessary to confirm these initial findings and to ultimately prove that catheter-based renal sympathetic denervation could represent a significant advance in the management of resistant hypertension and may even provide a cure for less severe forms of hypertension.

Sources of Funding

This work was supported by Ardian, Inc.

Disclosures

P.A.S. is an employee of Ardian, Inc. M.P.S., H.K., R.W., A.W., and M.D.E. are principal investigators in clinical trials NCT00483808 and NCT00551304, sponsored by Ardian Inc.

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Hypertension. 2009;54:1195-1201; originally published online October 12, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.138610

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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