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Renal Sympathetic Nerve Ablation: The New Frontier in the Treatment of Hypertension

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Abstract The sympathetic nervous system plays an important role in circulatory and metabolic control and has clearly been established as a major contributor to the development of hypertension, as elevated sympathetic nerve activity initiates and sustains the elevation of blood pressure. Increased sympathetic outflow to the heart, resulting in increased cardiac output and neurally mediated vasoconstriction of peripheral blood vessels, is an obvious example of a neural pathophysiologic pathway leading to elevated blood pressure. The consequences of increased sympathetic outflow to the kidneys, perhaps most important in this context, are sodium and water retention, increased renin release, and alterations of renal blood flow—effects that contribute substantially to both acute and long-term blood pressure elevations. Accordingly, renal sympathetic nerve ablation appears to be a logical therapeutic approach for the treatment of hypertension. Recent reports on a novel catheter-based renal nerve ablation procedure reviewed in this article are promising.

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Introduction

Nonoptimal blood pressure is the leading cause of death globally, responsible for 7 million deaths annually [1]. The burden of blood pressure–related disease is a neglected priority: on the basis of a single blood pressure measurement greater than 140 mm Hg systolic or 90 mm Hg diastolic, about one in four adults worldwide would be classified as hypertensive [2]. Currently, this equates to approximately 1 billion individuals, and this number is expected to grow to 1.5 billion (about 30% of the global population) by 2025, solely as a consequence of increases in both total population size and the proportions within populations reaching older ages. In regions with higher income, the number of hypertensive individuals is predicted to grow by 70 million people from 2000 to 2025. Current therapeutic strategies for hypertension are based mainly on lifestyle interventions and pharmacologic approaches, but the rates of control of blood pressure and the therapeutic efforts to prevent progression of hypertensive target organ damage remain unsatisfactory; additional options are required.

Clearly, the pathogenesis of primary hypertension is multifactorial. However, the contribution of renal sympathetic nerve activity to the development and progression of hypertension and its clinical consequences has been convincingly demonstrated in both preclinical and human experiments. Consequently, renal denervation has been used successfully as a therapeutic strategy to prevent hypertension in a variety of experimental models [3–6]. In humans, surgical approaches using splanchnicectomy and radical sympathectomy were applied as early as the 1920 s

and 1930 s to reduce blood pressure in severely hypertensive patients [7, 8]. Although these approaches were associated with high periprocedural complication rates and morbidity from extensive denervation (which did not specifically target the renal nerves), improvements in blood pressure control and survival were demonstrated in treated patients. 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 glomerular filtration rate or renal blood flow. The experience from kidney transplantation in humans, in the process of which sympathetic nerves of the kidneys are severed, is perhaps the most persuasive evidence to demonstrate that the denervated kidney is capable of maintaining electrolyte and volume homeostasis, suggesting that selective ablation of renal nerves is unlikely to result in adverse consequences. Based on these findings and in view of the demand for alternative treatment options, specific targeting of renal sympathetic nerves as a major player in the pathophysiology of hypertension and perhaps other conditions characterized by elevated renal sympathetic nerve activity (eg, kidney disease, heart failure) appears to be an attractive therapeutic approach.

Sympathetic Nervous System Activation in Essential Hypertension and Its Sequelae

Essential hypertension is commonly neurogenic, both initiated and sustained by increased sympathetic nervous system activation. Studies employing radiotracer dilution methods to measure overflow of norepinephrine from the kidneys to plasma revealed increased rates of renal norepinephrine spillover in patients with essential hypertension [9, 10]. In addition, norepinephrine spillover from the heart is often elevated, particularly in young hypertensive subjects, resulting in a typical hemodynamic profile that is characterized by increased heart rate, cardiac output, and renovascular resistance [11]. Interestingly, activation of cardiorenal sympathetic nerve activity is even more pronounced in heart failure, a common clinical consequence of long-term and sustained blood pressure elevation. An exaggerated increase of norepinephrine overflow from the heart and the kidneys to plasma has been demonstrated in heart failure patients [12]; this overflow can be attenuated significantly by intravenous infusion of the centrally acting α2-adrenoceptor agonist clonidine [13]. Complementary to the beneficial effects of antiadrenergic therapy in the heart, inhibition of sympathetic outflow to the kidneys counteracts salt and water retention, a hallmark of heart failure. Accordingly, a recent study demonstrated renal sympathetic activation to be a strong negative predictor of all-cause mortality and heart transplantation in patients with congestive heart failure [14], indicating that therapeutic efforts to reduce sympathetic outflow to the kidneys may have the potential to improve survival in patients with heart failure.

The Renal Nerves: A Closer Look

Efferent Sympathetic Renal Nerves

Postganglionic sympathetic nerve fibers innervate all essential renal structures, including the renal vasculature, the tubules, and the juxtaglomerular apparatus [15]. Renal sympathetic activation leads to volume retention via sodium reabsorption [16], a reduction of renal blood flow [17, 18], and activation of the renin-angiotensin-aldosterone system via stimulation of renin release from the juxtaglomerular apparatus [19]. Conversely, angiotensin II can stimulate sympathetic nerve activity via central mechanisms and facilitation of adrenergic neurotransmission at the sympathetic nerve terminal. These components of the neural regulation of renal function are considerably stimulated in hypertension and clearly contribute to the rise in blood pressure. Therapeutic efforts applying pharmacologic principles to counteract consequences of renal efferent sympathetic stimulation include the use of centrally acting sympatholytic drugs such as clonidine and moxonidine, as well as the use of beta blockers, which inhibit renin release. Targeting the downstream consequences of elevated efferent sympathetic outflow to the kidneys (ie, initiation of the renin-angiotensin-aldosterone cascade) has also proven very successful, as angiotensin converting enzyme inhibitors and angiotensin receptor blockers substantially improve blood pressure control and cardiovascular outcomes. Nevertheless, current pharmacologic strategies are plagued by several limitations, including limited efficacy, compliance issues, and adverse effects. In addition, about 15% of hypertensive patients are estimated to have resistant hypertension, defined as uncontrolled blood pressure despite the use of at least three antihypertensive drugs at appropriate doses, commonly including a diuretic. There is a compelling need for additional or alternative therapies for these patients, who have an exaggerated risk of cardiovascular morbidity and mortality. Given the relative importance of renal sympathetic nerves in blood pressure control, renal sympathetic nerve ablation potentially offers a direct, organ-specific strategy that targets various mechanisms crucially involved in initiating and maintaining blood pressure elevations in these patients.

Afferent Sensory Renal Nerves

It is important to understand that renal nerves comprise both efferent and afferent fibers. The kidneys have a dense

afferent sensory and efferent sympathetic innervation and are thereby strategically positioned to be the origin as well as the target of sympathetic activation [20]. Communication with integral structures in the central nervous system occurs via afferent sensory renal nerves. Recent studies suggest that conditions such as renal ischemia, hypoxia, and oxidative stress result in increased renal afferent activity [21–23]. 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 [24, 25]. Interestingly, abrogation of renal sensory afferent nerves has been demonstrated to reduce both blood pressure and organ-specific damage caused by chronic sympathetic overactivity in various experimental models [26, 27]. Hence, functional denervation of the human kidney by targeting both efferent sympathetic nerves and afferent sensory nerves appears to be a valuable treatment strategy for hypertension and perhaps other clinical conditions characterized by increased overall nerve activity and particularly renal sympathetic nerve activity.

Experimental Evidence for Therapeutic Benefits of Renal Denervation

Renal denervation has frequently been applied in animal models of disease, mainly as a research tool to unravel the contribution of renal sympathetic efferent and sensory afferent nerves to renal and systemic organ function under normal and pathologic conditions. Although most of the experiments were not explicitly designed to identify the potential clinical utility of renal denervation, they do provide significant information on this issue. Surgical ligation and reanastomosis of the renal artery or surgical stripping of the renal nerve adventitia with local application of phenol (without manipulating the ureter) has commonly been used to achieve renal denervation. Another early approach involved selective renal infusion of 6-hydroxydopamine to poison the nerve terminals [28]. Preclinical experiments using renal denervation as a therapeutic strategy have included multiple animal species (rodents, swine, dogs, sheep) and numerous pathologic conditions, including not only various models of hypertension but also heart failure and kidney disease. These studies consistently demonstrated the importance of renal sympathetic efferent and sensory afferent nerves and their contribution to the pathophysiology of hypertension, heart failure, and chronic kidney disease. Simultaneously, these experiments revealed the potential therapeutic value of renal denervation, particularly in regards to hypertension.

In many diverse animal models of experimental hypertension (including genetic, salt-sensitive, obesity-related, and renal artery stenosis mimics, as well as reduced uterine perfusion–juvenile hypertension), bilateral renal denervation prevented the development of hypertension or attenuated its magnitude [4], although this effect did not occur in all models studied. The one-kidney, one-clip model of hypertension particularly does not appear to be dependent on intact renal nerves [29]. Nevertheless, these findings suggest that the renal sympathetic nerves probably serve as the critical link between the sympathetic nervous system and the kidney in hypertension [26].

In view of the current worldwide epidemic of obesity and its common association with elevated blood pressure, experimental models of obesity-related hypertension are of specific interest. The potential of renal denervation to treat obesity-related hypertension, associated with sodium retention and increased sympathetic nervous system activation, was recently explored in a model of chronically instrumented dogs fed a high-fat diet [6]. In this model, which resulted in a 50% increase in body mass in both control and denervated dogs, two important findings were noted: Blood pressure significantly increased in the controls but did not change in the denervated dogs, and sodium retention in the denervated dogs was half that in the controls. This study demonstrated chronic durability of benefit and identified no abnormalities of renal function following surgical denervation [6].

The potential of therapeutic renal denervation to attenuate hypertension and the progression of renal disease has also been explored in experimental studies. In the 5/6 nephrectomy rat model of chronic renal failure and hypertension, dorsal rhizotomy prevented the rise of blood pressure [20]. This model suggests that afferent impulses from the kidney to central integrative structures in the brain may be responsible for elevating blood pressure in chronic renal failure, which is commonly associated with hypertension. Renal injury caused by unilateral phenol injection in rats reliably causes hypertension associated with both increases in norepinephrine secretion from the posterior hypothalamus and increased renal sympathetic efferent and afferent nerve activity of both kidneys [22]. Immediately following direct renal injection of phenol, renal sympathetic efferent activity and afferent activity were elevated, associated with falling urinary sodium excretion and increased renal norepinephrine. Surgical renal denervation of the phenol-treated kidney prevented the increase in blood pressure [22]. Several other models of renal disease and interventions targeting the sympathetic nervous system have been studied and reviewed in detail by Joles and Koomans [30], further supporting the protective effects of sympatholytic interventions.

Therapeutic Renal Denervation in Human Hypertension

The preclinical science surrounding renal denervation has supported human surgical efforts to modify renal innervation, particularly for the treatment of hypertension [7, 8]. These efforts, including posterior thoracolumbar sympathectomy and surgical nephrectomy, have all been plagued by the complexity and morbidity associated with the surgical procedure and have been 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 following 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) may 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.

The Role of Renal Sympathetic Nerves in Other Conditions Commonly Associated with Hypertension: Chronic and End-Stage Renal Disease

The number of patients with chronic and end-stage renal failure is increasing dramatically worldwide [31, 32]. Hypertension is present in the vast majority of these patients [33] and plays a key role in the progressive deterioration of renal function and in the exceedingly high rate of cardiovascular events, the primary cause of morbidity and mortality [34, 35]. Although such a role of hypertension is widely accepted, control of blood pressure in this population group is often poor [36, 37]. The elevated blood pressure commonly present in patients with chronic and end-stage renal disease is of multifactorial etiology. Hypervolemia and activation of the renin-angiotensin-aldosterone system (RAS) are important factors contributing to the increase in blood pressure [38], and previous research into therapeutic strategies therefore focussed primarily on interventions targeting volume control and the RAS. Indeed, RAS inhibition has been demonstrated to slow the progression of renal disease and proteinuria [39].

Involvement of the sympathetic nervous system in the development of hypertension, progression of renal failure, and cardiovascular prognosis in patients with renal disease unfortunately has been somewhat neglected in the past despite convincing evidence of increased sympathetic activity in various forms of hypertension, including essential hypertension [10], obesity-related hypertension [40], hypertension associated with obstructive sleep apnea [41], and preeclampsia [42]. However, recent investigations have clearly established that activation of the sympathetic nervous system is commonly associated with chronic renal failure, most likely contributing to the poor prognosis in this patient group. Indeed, elevated plasma norepinephrine levels have been demonstrated to be predictive of both death and increased cardiovascular events in patients with end-stage renal disease [43]. Accordingly, progression of renal failure can be delayed by the centrally acting sympatholytic agent moxonidine in patients with chronic kidney disease [44]. Moxonidine has also been demonstrated to reduce microalbuminuria in normotensive patients with type 1 diabetes, in the absence of any significant blood pressure changes [45]. Furthermore, nephrectomy in patients with end-stage renal disease is associated with consistent reductions in blood pressure and total systemic vascular resistance [46], perhaps indicating the potential therapeutic utility of denervation of the native kidney for blood pressure lowering and target-organ protection in these patients. Indeed, a recent case report demonstrated a substantial 54-gram decrease in left ventricular mass within 4 months following bilateral nephrectomy [47], supporting the concept that heightened sympathetic outflow, particularly to the heart, is a main contributor to hypertensive left ventricular hypertrophy [48].

Catheter-Based Renal Nerve Ablation as a Treatment for Resistant Hypertension

As indicated above, the concept of therapeutic renal denervation for the treatment of severely elevated blood pressure is not new. Surgical methods of sympathectomy have been used successfully since the 1920 s to achieve better blood pressure control and cardiovascular outcomes in patients with severe hypertension. However, these techniques were commonly associated with high perioperative morbidity and mortality, as well as long-term complications including bowel, bladder, and erectile dysfunction and profound postural hypotension [7, 8]. With the availability of effective antihypertensive drugs, surgical approaches have been largely abandoned as a common mode of antihypertensive treatment. Of note, the techniques used in the past did not specifically target the renal nerves, but more recent evidence suggests that these nerves are the crucial link between sympathetic nervous system activation and hypertension. Targeting the renal sympathetic nerves more specifically remains a very attractive therapeutic approach. In view of the latest evidence and the substantial proportion of hypertensive patients who cannot tolerate pharmacologic treatment or are unresponsive to it, additional and alternative treatment options are clearly needed.

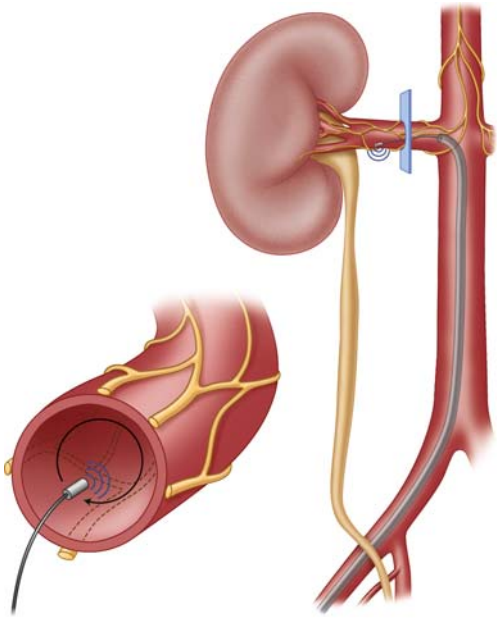

Fig. 1 Schematic illustration of the percutaneous catheter-based approach to functionally denervate the human kidney. As in a routine angiogram, access to the renal artery is obtained via a sheath in the femoral artery. Renal artery angiography is performed to assess anatomic eligibility for the procedure and to confirm the absence of significant renal artery stenosis. The treatment catheter is then introduced into the renal artery and positioned in the distal aspect of the artery; it is then manipulated to ensure sufficient contact between the tip of the catheter and the vessel wall. The proximal end of the catheter is connected to a radiofrequency (RF) generator to apply a discrete RF ablation lasting 2 min. Up to six ablations are performed in each artery; the ablations are separated both longitudinally and rotationally to achieve circumferential coverage of the renal artery. Catheter tip temperature and impedance are constantly monitored during ablation, and RF energy delivery is regulated according to a predetermined algorithm

In this context, a novel treatment option based on the above-mentioned principles has recently been tested successfully in patients with resistant hypertension.

In this approach, renal sympathetic nerve ablation is achieved percutaneously via the lumen of the renal artery using a catheter connected to a radiofrequency (RF) generator (Fig. 1). Access to the renal artery is typically obtained via the right femoral artery, and anatomic eligibility for the procedure is confirmed by renal angiography. The treatment catheter (Symplicity; Ardian, Inc., Palo Alto, CA) is introduced into each renal artery and discrete RF ablations lasting up to 2 min each are applied to achieve up to six 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.

The renal sympathetic nerves are derived from numerous spinal ganglia, and paraspinal ganglionectomy has been associated with severe and systemic adverse effects. Similarly, pharmacologic 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. Consequently, a catheter-based approach appears to be a safe and attractive approach to selectively target the renal nerves. Preclinical studies in juvenile swine demonstrated that such a catheter-based approach could be used safely and markedly reduced the content of norepinephrine in the treated kidney by more than 85%, an effect very similar to the effect of direct surgical renal denervation via artery transection and re-anastomosis. Importantly, no significant vascular or renal injury was evident 6 months after the procedure in these animal studies, justifying the initiation of a first-in-man evaluation of the safety and blood pressure-lowering efficacy of selective renal nerve ablation using this percutaneous, catheter-based treatment approach in patients with treatment-resistant hypertension [49••].

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±20/15 mm Hg. Of note, participating patients were using an average of 4.7±1.5 hypertensive drugs, including all drug classes currently recommended by national and international guidelines. The median duration of the procedure to bilaterally ablate the renal nerves was 38 min. Vascular safety analysis consisting of renal angiography at 14 to 30 days after the procedure and MR angiography at 6 months post-procedure revealed no long-term adverse clinical sequelae associated with the procedure, particularly no instances of renal artery aneurysm or stenosis. Participating patients had repeated exposure to contrast media during serial angiographies, but calculated estimated glomerular filtration rate (eGFR) data indicated no significant deterioration of renal function, indicative of a favorable vascular and renal safety profile. The ablation procedure was accompanied by diffuse, nonradiating visceral abdominal pain that did not persist beyond the RF energy application and could be managed by intravenous narcotics and sedatives.

In addition to demonstrating the safety of the procedure, it is mandatory to provide evidence for its effectiveness in reducing renal sympathetic nerve activity. As a measure of renal sympathetic nerve activity, radiotracer dilution methods were applied in 10 patients to assess overflow of norepinephrine from the kidneys into the circulation. These analyses revealed a mean reduction in norepinephrine spillover of 47% (95% CI, 28%–65%) in response to the RF procedure as assessed 1 month after bilateral denervation, convincingly demonstrating the efficacy of the procedure in achieving efferent renal sympathetic denervation.

Importantly, catheter-based renal nerve ablation was associated with a significant reduction in both systolic and diastolic blood pressure, which was first observed at 1 month, was further reduced at 3 months, and persisted through subsequent evaluations out to 12 months. Mean (± 95% CI) decreases in office blood pressure were -14/-10±4/3 mm Hg at 1 month, -21/-10±7/4 at 3 months, -22/-11±10/5 at 6 months, -24/-11±9/5 at 9 months, and -27/-17±16/11 mm Hg at 12 months. Several patients are now approaching the 2-year follow-up, and the blood pressure reductions observed appear to be sustained over this period, suggesting the absence of nerve fiber recovery, nerve fiber regrowth, or development of counter-regulatory blood pressure–elevating mechanisms. Alternatively, if any of these mechanisms have occurred, they do not appear to affect the blood pressure reductions achieved. Renal and heart transplant models indicate that renal sympathetic efferent nerves may regrow after injury, raising the possibility of finite time limits for the physiologic effects of the procedure. This issue will have to be thoroughly addressed in the ongoing long-term follow-up of these patients, although the physiologic importance of anatomic regrowth of efferent nerve fibers in sustaining blood pressure remains unproven.

Given that renal nerves comprise both efferent sympathetic and afferent sensory fibers, it is likely that this catheter-based approach also results in reduced signaling from renal afferent sensory nerves; this idea is supported by the occurrence of pain during the procedure. Although afferent signaling cannot be measured directly in humans, the recent demonstration of a substantial and progressive reduction in central sympathetic outflow at baseline and at 1 and 12 months follow-up accompanying the progressive blood pressure reduction [50••] as a result of the procedure may indicate that alterations in afferent fiber signaling may indeed play an important role in the blood pressure effects associated with this procedure. Interestingly, in contrast to efferent sympathetic fibers, renal sensory afferent fibers are unlikely to regrow.

In addition to the direct consequences of the procedure, it may also be important to consider that renal denervation decreases renin secretion by about 50% [50••]; this decrease in turn may affect central sympathetic outflow by altering circulating angiotensin II levels. Furthermore, cardiac baroreflex sensitivity was also 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 compared with baseline, from 184 to 169 grams (78.8 to 73.1 g/m^2) at the 12-month follow-up [50••].

Conclusions

In summary, findings from initial safety and proof-of-concept studies indicate that renal nerve ablation achieved via a catheter-based approach using RF energy is safe and has the potential to improve blood pressure control and alleviate the sequelae of elevated blood pressure in patients with treatment-resistant hypertension. These beneficial effects appear to be mediated via interference with both efferent sympathetic and afferent sensory nerves.

Could this novel approach also be useful in less severe forms of hypertension or in other conditions characterized by heightened renal sympathetic nerve activity, such as chronic and end-stage renal disease? In regards to milder forms of hypertension, no such data have yet been obtained. However, given the favorable safety profile of the procedure, with the occurrence of renal artery dissection in only 1 of more than 100 patients treated so far, application of this procedure, which may be potentially curative, in patients with less severe forms of hypertension does not appear to be unreasonable.

Patients with either chronic or end-stage renal disease intuitively appear to be very suitable candidates for such an approach, given the evidence from both experimental and human studies to indicate that efferent sympathetic and afferent sensory signaling is crucially involved in both the sympathetic activation and the hypertension almost invariably present in these patients. Indeed, such a trial (NCT00551304) is currently under way in patients with end-stage renal failure complicated by hypertension, and preliminary findings indicate similar beneficial effects in this patient cohort.

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