Renal Denervation for the Treatment of Cardiovascular High Risk-Hypertension or Beyond?

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Abstract: Hypertension imposes a major burden of morbidity and mortality and is associated with sympathetic nervous system overactivity. Renal sympathetic denervation has been shown to reduce office blood pressure, ambulatory blood pressure, and sympathetic activity in patients with resistant hypertension. Therefore, the procedure has attracted a lot of attention. Beyond blood pressure, renal denervation has been shown to improve glucose tolerance, microalbuminuria, and arrhythmias in several experimental models and, in admittedly, often uncontrolled clinical studies. It has been demonstrated to reduce myocardial hypertrophy in a blood pressure-independent and blood pressure-dependent way. The first studies on heart failure with preserved and reduced ejection fraction are ongoing. Renal sympathetic denervation holds promise for future indications in hypertension and related comorbidities and consequences, such as metabolic disease, renal failure, and heart failure. Published data in a placebo-control blinded study, however, are needed. The aim of this review is to provide a critical and comprehensive overview of heretofore generated data on renal denervation in experimental models, in human hypertension, and on early developments in new indications, which should indicate the way to powered and performed, controlled clinical studies appropriately. (Circ Res. 2014;115:400-409.)

Key Words: hypertension resistant to conventional therapy ■ sympathetic nervous system

Activation of the sympathetic nervous system has early been regarded as 1 mechanism of initiation and progression of arterial hypertension. The first demonstration of renal sympathetic nervous innervation was provided by Karl Ludwig in his Latin thesis with sympathetic afferent and efferent nerves being located in the adventitia of the renal arteries. Sympathetic efferent outflow to target organs is regulated by the central nervous system, specifically the hypothalamus, the nucleus tractus solitarius, and the rostral ventrolateral medulla. In the kidneys, these efferent nerves target the renal cortex and medulla, terminating at the glomerular arterioles, the juxtaglomerular apparatus, and all levels of the renal tubules. Stimulation of splanchnic sympathetic nerves in dogs led to an increase in blood pressure (BP). Mechanistically, activation of efferent sympathetic nerves increases renin secretion in juxtaglomerular cells. In addition, $\alpha_1A$ adrenergic receptors mediate vasoconstriction and reduce renal blood flow, whereas $\alpha_1B$ adrenergic receptor stimulation leads to sodium and water retention in the proximal tubules. As a consequence, the pressure-natriuresis curve is shifted to the right, indicating that higher renal perfusion pressures are necessary to increase sodium excretion, this representing 1 pivotal mechanism for the development of hypertension.9-11 Sympathetic outflow from the central nervous system is feedback-regulated by renal afferent signaling arising from both the renal pelvis and the renal interstitium. Adenosine, released during hypoxia or injury, stimulates pelvic adenosine receptors and activates afferent signals directed to the central...
nervous system. In patients with renal failure and assumed hyperperfusion or hypoxia, application of 100% oxygen reduces sympathetic nerve activity. Direct proof for the relevant interaction between renal afferents and the activity of the central sympathetic nervous system was provided in patients with renal failure. Systemic and renal sympathetic activity is enhanced in patients with renal failure. Interestingly, in patients after renal transplantation with normal global renal function, nephrectomy of the nonfunctioning, diseased kidneys, reduced total body sympathetic activity providing evidence that it is indeed the diseased kidney and not effects of uremia that increase sympathetic activity. These observations provide the pathophysiological basis for renal denervation to reduce global sympathetic activation in various disease states. Figure 1 provides a scheme of the pathophysiological regulation.

Experience With Surgical Renal Denervation

First surgical interventions for renal denervation were performed for pain relief in patients with hydronephrosis. Decapsulation of the kidneys was regarded as one form of sympathetic activation. RAAS indicates renin–angiotensin–aldosterone-system. Thus, a vicious cycle in the interaction between brain and kidney further enhances sympathetic activity. RAAS indicates renin–angiotensin–aldosterone-system.

Interventional Renal Denervation

The first attempt to ablate autonomic nerves outside the heart with a transvascular route was provided by electrophysiologists using radiofrequency energy to interrupt cardiac parasympathetic nerves to control heart rate in vagally induced atrial fibrillation better. The first to develop a radiofrequency-based approach to denervate the kidneys was the US start-up company (ARDIAN), who tested radiofrequency ablation catheters in humans. Radiofrequency thermal energy was delivered to renal arteries at the inner surface of the vascular wall through a single tip electrode catheter. Because of the high intravascular blood flow, the endothelium of the renal artery and inner vascular layers was heated less, whereas the heat was transmitted better to the adventitial tissue, leading to functional denervation of visceral afferent and sympathetic efferent nerves, which are largely located within 0.5 to 8 mm from the endothelial layer of the renal arteries. The depth of denervation lesions typically varies between 2 and 4 mm, but is highly variable, being dependent on the influence vessel wall structures, vasa vasorum, and the denervation device. Importantly, a recent report indicated that sympathetic fibers are closer to the renal artery lumen distally, closer to the kidneys. Therefore, with current procedural practices, investigators most likely denervate incompletely, which is reflected in the much weaker (≈47%) renal denervation, measured with renal norepinephrine spillover, in patients compared with surgical.
Renal Denervation for Resistant Hypertension included patients with an entry systolic BP $\geq 160$ mm Hg (mean, 177$\pm$100 mm Hg), despite being on 4.7$\pm$1.5 antihypertensive drugs. BP was significantly reduced by 27$\pm$16/17$\pm$11 mm Hg at 12 months. This effect was recently shown to be sustained $\geq$36 months. Symplicity-HTN-2 was a parallel design controlled study with similar exclusion and inclusion criteria as Symplicity-HTN-1. Patients were randomized to either receive immediate renal denervation or delayed intervention after 6 months. After 6 months, BP in the immediate intervention group decreased by 32/12 mm Hg from a baseline value of 174/97 mm Hg. In the control group, no significant BP reduction occurred. These effects have been reported to be sustained $\geq$36 months. Similar results to those in the Symplicity trial populations were reported from the EnligHTN I study, which included 46 patients with resistant hypertension. This trial is the first published experience with a multielectrode basket device, this device being developed to achieve good vascular wall contact, and further, to achieve a 1-step procedure. Both office and 24-hour BP lowering in the EnligHTN-1 trial were comparable with the Symplicity trials. In all published trials, the procedure of renal denervation was proven to be safe. There were some complications of vasovagal reactions during the procedure, including bradycardia, local access site complications, and 1 renal artery dissection, which required renal artery stenting in Symplicity HTN-1. Renal function, even in the extended observation groups, remained stable with no effect of renal function on the BP reducing the efficacy of the procedure. Effects of renal denervation in mild to moderate hypertensives or in nonresistant hypertensives with submaximal doses of antihypertensive medication were not investigated in these studies.

Open Questions

Lack of Blinded Randomized Data

Most of the evidence on which the present use of renal denervation is derived from small or nonrandomized trials and registries without a placebo group. Other studies are just exploratory without implementation of a control group. Therefore, it is open to speculation whether the BP reduction observed in the trials is largely related to a placebo effect or the regression to the mean phenomenon. Interestingly, hospitalization per se reduces BP in patients with hypertension on placebo therapy. Finally, the Hawthorne effect describes changes in healthcare behavior after any intervention. Therefore, it is possible that the intervention of renal denervation could have positively affected adherence of a patient to antihypertensive drugs accompanied by BP reduction after the procedure. In addition, in the renal denervation groups, patients could be under either more or less intense drug therapy and subject to lifestyle and behavioral interventions, such as exercise, which could lower BP. In contrast, patients might think that their BP problem is fixed and they discontinue medication. The effect of these potential confounders remains unknown. Poor adherence to medication is a huge problem in hypertension, and in particular, in resistant hypertension. In a small pilot study, in 6 patients with treatment resistant hypertension confirmed...
by witnessed intake of medications, renal denervation did not lower BP significantly overall. However, 5 of 6 patients did exhibit a detectable BP response and, therefore, the low number of patients of this underpowered investigation limits the validity of its interpretation that renal denervation is ineffective for truly resistant hypertension.

To address some of these issues, the Symplicity HTN-3 trial was designed. This trial involved a placebo (sham procedure) group, undergoing an interventional procedure without renal denervation, and has incorporated a screening for adherence for antihypertensive medications in these patients (patients diaries). The study included 535 patients randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure with a screening failure of 63% in 88 sites throughout the United States. The procedure was done by 111 interventional cardiologists. The procedure seemed to be safe with adverse effects of 1.4% with an upper boundary of the 1-sided 95% confidence interval of 2.9% in the treatment group and 0.6% in the sham group with a difference of 0.8% (P = 0.67). The primary efficacy endpoint was not met with a BP reduction of 11.7 ± 26 mm Hg in the control, sham-operated arm, and 14.1 ± 24 mm Hg in the renal denervation arm (P = 0.255). The prespecified superiority margin was set at 5 mm Hg. There was also no difference in the 6-month differences of 24-hour ambulatory systolic BP (P = 0.979). The Symplicity HTN-3 trial incorporated a sham-operated arm to overcome potential placebo or regression to the mean effects, which could have contributed to the large BP reduction in previous uncontrolled trials. Interestingly, there were also differences in the BP reduction on 24-hour ambulatory systolic BP in the sham procedure group (4.9 ± 17.25 mm Hg). Previous trials have shown that unlike office BP, the 24-hour ambulatory BP is less or no subject to the white-coat effect. Therefore, the placebo or white-coat effect seem not to contribute to the wide scatter in Symplicity HTN-3, which was not different to the previous uncontrolled trials. For patients in Symplicity HTN-3, changes in medication were permissible until 2 weeks before the procedure. Twenty-two percent of patients increased the medication 2 to 6 weeks before randomization. Therefore, a carry-over effect cannot be excluded for the large reduction in both arms, including the sham-operated patients. Furthermore, it is an open question as to whether the procedural performance of operators was responsible for a lack of difference in Symplicity HTN-3. The response rate defined as patients declining >10 mm Hg was greater in the renal denervation group when compared with that in the sham group (53). Furthermore, it is interesting that the investigators performed fewer procedures when compared with the studies performed in Europe or Australia, where the technique is approved and intensive procedural proctoring was done when renal denervation was introduced. In Symplicity HTN-3, 31% of investigators did only 1 procedure and only 26% of operators did >5 procedures. Within these numbers, it seems impossible to generate a gradient of experience. The occurrence of denervation notches (small excavations in the renal arteries after energy exposition) was claimed to be a measure of effectiveness. This is obviously not the case because it just represents energy delivery to the arterial wall, and endothelial edema, not nerve ablation. Noteworthy, in 68% of patients 0 or 1 notch was observed (54), suggesting that energy delivery was substandard. The magnitude and time course of BP reduction after renal denervation can be variable with nonresponse rates in resistant hypertension ranging from 20% to 35%. It could well be that maladaptive vascular changes, such as arteriolar hypertrophy and reduced arterial distensibility, are responsible for limiting the efficacy of the procedure. This suggestion is speculative because data on this are lacking. The key

Ambulatory Versus Office BP

Symplicity-HTN-1 and Symplicity-HTN-2 recruited patients on the basis of office BP. In Symplicity-HTN-2, some ambulatory BP monitoring (ABPM) data were available, showing a much smaller reduction of ambulatory than of office BP. To overcome this deficiency, a multicenter study was devised to provide ABPM data in 346 patients with uncontrolled hypertension. Recruitment was done on the basis of office BP. Of 346 patients, 43 patients with pseudoresistant hypertension, exhibiting normal ABPM BP values but elevated office BP values, were identified. As expected, in these patients, renal denervation reduced office BP, but not ABP, nighttime or daytime values, which are also importantly related to cardiovascular morbidity and mortality. In the truly resistant hypertensives, ABP values and office BP were reduced, the effects on ABPM being smaller than those on office BP. However, the relative reduction of office BP and ABP in true resistant hypertension is in good agreement with drug studies as provided by a meta-analysis of randomized controlled trials. A new analysis pointed toward a smaller difference between ABPM and office BP. However, renal denervation and sham operation led to a smaller drop in SBP in Symplicity HTN-3. These data provide the interesting perspective to investigate whether pseudoresistant hypertension is also a target for renal denervation because office BP in the presence of normal or near-normal ABP is associated with increased cardiovascular risk and not completely innocent.
deficiency is that there are no intraprocedural measures for the success of renal denervation procedure, making it impossible to discriminate between procedural failure and pathophysiological failure as causes of absent pressure lowering. In the highly heterogeneous group of resistant hypertensives, no doubt, not all patients have hypertension because of hyperadrenergic activity; other mechanisms may be operative. This is presently unexplored and should be an area of future research, which urgently has to be developed. Even more interesting is the fact that the response rate increases over time with a progression of BP fall 3 to 24 months after the procedure. Nevertheless, these long-term follow-up studies are confounded by limited control of factors, such as changes in medication or their doses, improvement of medical adherence, improvement of lifestyle or exclusion of nonresponders. Renal denervation can improve vascular peripheral stiffness with a reduction of pulse wave velocity. Therefore, reversal of peripheral vascular remodeling as observed also after effective BP reduction with drugs could be involved in the late improvement in BP. Also other underestimated factors, such as vitamin D deficiency and other unrecognized confounders, may also limit the BP response to renal denervation. This is an interesting area of future research consisting of speculations and hypothesis, which have to be scrutinized in experimental and clinical studies.

In this context, several studies with poor response rates need to be acknowledged. Brinkmann et al compared the BP decline and response of central sympathetic activity after renal denervation in 12 patients. They reported no relationship to sympathetic activity and BP drops. Furthermore, the response of either parameter was low. It is interesting to note that 4 of 11 patients included in this study had BP values of 121/65, 139/71, 137/81, and 139/71 mm Hg, which can hardly be classified as difficult to control hypertension. A second study with 109 patients from 10 European centers, the BP response was apparently less than in the Symplicity trials. Approximately 30% of the patients included had baseline pressures of <160 mm Hg systolic, so that lower BP falls have to be expected. Taking those patients with BP values >180 mm Hg, the responses and also the response rates were similar to those in the Symplicity trials. At BP of 160/79 mm Hg, the response rates were 24.2% normalization, 63.6% improvement, and 21.2% no decrease. In a third study, in 6 patients eligible for renal denervation after witnessed intake of medication, the overall office and ambulatory BP did not significantly change. However, again, the baseline BP of patients was heterogeneous with only 3 patients ≥160 mm Hg office BP. However, 5 patients of 6 had a reduction in office BP and 4 of 6 patients had a reduction in ABPM. Although being underpowered, this study attempted to show that witnessed intake of drugs can be able to provide sufficient BP reduction. All studies, those with larger and smaller responses, were unblinded and highly influenced by the baseline characteristics of the patients chosen. Nevertheless, these studies and the conclusion drawn therein are valuable to limit the enthusiasm for uncritically performing procedures primarily marketed to interventionalists and transferred too early into clinical practice. Therefore, only truly resistant hypertensive individuals should be referred to experienced centers involved in clinical trials and registries to these patients as ultima ratio or to scrutinize hypotheses generated by the available, often uncontrolled clinical trials.

**Problem to Determining Response Rates**

According to the published data, the only predictor of BP response in resistant hypertension is BP at baseline. Because sympathetic activation increases not only BP but also heart rate, and in particular, heart rate during physical exercise, it is pertinent to study renal denervation effects on heart rate also. During cardiopulmonary exercise testing, renal denervation reduced not only BP at rest but also during all steps of exercise. In contrast, the heart rate response to exercise was not influenced by renal denervation, leading to an improvement in exercise capacity. Heart decline during recovery was also accelerated after renal denervation, this being another predictor of cardiovascular outcome, including sudden cardiac death. Interestingly, in patients with nonresponse to office BP, there was a significant reduction of exercise BP. After renal denervation, there was a decline in heart rate, dependent on the heart rate at baseline, which was not correlated with the BP fall. In parallel, reduction of BP was not related to the decline in heart rate (Figure 2). Summing response rates in either heart rate or BP result in a composite response rate of ≥90% after 6 months. The response to a reduction of sympathetic activity by renal denervation can result not only in BP reduction but also in other beneficial non-BP effects, which could also be surrogates of cardiovascular outcomes.

**Effects on Disease States Beyond Hypertension**

**Sleep Apnea Syndrome**

Sleep apnea is associated with sympathetic activation and obesity and is one of the most common causes of hypertension associated with treatment resistance. The frequent nocturnal arousals not only cause sympathetic activation and hypertension in sleep apnea but are also involved in the sympathetically enhanced salt and water retention with volume expansion and volume shifting to the interstitium causing glottis edema and obstructive sleep apnea, which could be part of a unifying concept. Consistent with this, Witkowski et al have shown a reduction of apnea hypopnea indices (AHI [apnea-hypoxia index] and sleep apnea severity) after renal denervation in a pilot study in patients with resistant hypertension and confirmed sleep apnea syndrome at baseline.

**Metabolic Disease**

Metabolic syndrome and resistant hypertension are closely associated and further augment hypertensive myocardial hypertrophy. In rats, insulin-induced hypertension was attenuated after renal denervation. In patients with resistant hypertension and metabolic syndrome, renal denervation reduced fasting glucose, fasting insulin, fasting C-peptide concentrations and improved insulin sensitivity and glucose tolerance tests. It will be most interesting to see whether patients with metabolic syndrome in the absence of hypertension might benefit metabolically from renal denervation.
Myocardial Hypertrophy and Heart Failure
Unloading of the left ventricle by BP reduction after renal denervation has led to a significant reversal of myocardial hypertrophy91 accompanied by an improvement of diastolic function.91,92 Perhaps surprisingly, hypertrophy reduction tended to occur already early after the procedure (ie, at 1 month)92 and showed no significant association with the degree of BP reduction. 92,93 These studies, however, were limited by the lack of blinding of the investigators91,92 but have recently been confirmed in an MRI, where MRI evaluations were blinded to the procedures and patient’s characteristics. This study showed myocardial hypertrophy reduction, which was partly BP independent.93 Because sympathetic activation in the kidneys, based on renal norepinephrine spillover measurements, is superior in the prediction of cardiovascular death in patients with heart failure when compared with plasma norepinephrine concentrations,94,95 the first trials in heart failure with preserved or reduced ejection fraction are being conducted. A pilot study showing an improvement of exercise tolerance without significant reductions of BPs has been reported in normotensive patients with impaired left ventricular function.96 Exploratory studies in heart failure with preserved ejection fraction are also ongoing.97 The rationale here is supported by the well-proven effect of neuroendocrine antagonists, such as angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists to improve outcome in heart failure with reduced ejection fraction.98 However, it has to be kept in mind that moxonodine, an antihypertensive agent, reducing central sympathetic nerve activity99 and circulating norepinephrine concentrations,100 was associated with increased morbidity and mortality.101,102 In the future, adequately powered outcome trials are urgently needed to provide data on efficacy but even more importantly on safety in patients with heart failure and preserved and impaired ventricular function.

Arrhythmias
Sympathetic activation, particularly in association with parasympathetic withdrawal, produces arrhythmias, such as atrial fibrillation.103 In a pig model for obstructive sleep apnea, renal denervation reduced induction of atrial fibrillation by programmed atrial electric stimuli104,105 and improved heart rate control in spontaneous episodes of atrial fibrillation.105 Interestingly, neuroendocrine activation, such as elevation of aldosterone and activation of plasma renin activity after repetitive obstructive respiratory event, was attenuated in this model.106 Renal denervation reduced ischemia-related ventricular fibrillation with no effects on reperfusion arrhythmias in pigs with ventricular-ischemia-reperfusion.107 In case series of patients with cardiomyopathy and electrical storm, renal denervation abolished ventricular arrhythmias and discharges from the implanted cardioverters.108 All these data were generated in normotensive animal models101–107 or patients with heart failure and normal or low BP.108 Prospective trials are pending, to substantiate the effect in atrial and ventricular arrhythmias.
Renal Effects
Impaired renal function can be the cause and consequence of hypertension.\textsuperscript{109} In a recent study, it was shown that renal denervation reduces microalbuminuria,\textsuperscript{110} predictive of cardiovascular outcomes later in renal disease progression.\textsuperscript{111,112} Renal denervation has been shown to reduce BP in a similar way in mild to moderate renal failure\textsuperscript{113} and in patients with end-stage renal disease on dialysis.\textsuperscript{114} Furthermore, BP reduction occurred in polycystic kidney disease\textsuperscript{115} and polycystic ovary syndrome.\textsuperscript{116} Prospective studies on outcomes in patients with renal disease with and without hypertension would be most interesting to provide evidence for risk reduction in those patients.

Psychological Disease
Hypertension is associated with anxiety involving the sympathetic nervous system.\textsuperscript{117,118} Depression is associated with a dysregulation of noradrenergic regulation in the central nervous system.\textsuperscript{119} Thus, concerns exist, that renal sympathetic denervation could affect psychological well-being. However, renal denervation was associated with an improvement of health-related quality of life\textsuperscript{120} and improved scales of depression and anxiety, accompanied by an improved stress-response in these patients.\textsuperscript{121} Whether these observations apply also to patients with preexisting psychological disease or individuals without hypertension require further controlled investigations because the lack of a blinded control group can cause substantial bias.

Orthostatic Dysregulation
Concerns on orthostatic dysregulation comparable with the experiences with studies on surgical splanchnicectomy ultimately limiting the use of renal denervation have been expressed. Tilting causes an acute volume shift of 1.5-L blood,\textsuperscript{122} which is followed by an activation of the sympathetic nervous system to prevent orthostatic collapse. Just before collapse and syncope occurs, there is a drop in sympathetic activity and baroreceptor function.\textsuperscript{123,124} Thus, concerns were raised whether renal denervation might cause orthostatic hypotension and presyncopes. However, in a prospectively designed study, there was no evidence that renal denervation accentuates and increases syncopes or symptomatic hypotension in responders and nonresponders to renal denervation during table tilt testing.\textsuperscript{125} This finding corresponds well with the good tolerance of the procedure in the above-mentioned trials.\textsuperscript{40-43,51}

Summary
Renal sympathetic denervation has been introduced as a novel approach to treat resistant hypertension. First, studies show that other consequences independent of BP might be targets, which have also well-characterized pathophysiological basis.\textsuperscript{126} Studies providing evidence for significant BP reductions are unblinded and based on low patient numbers. The sham-controlled Symplicity-HTN-3 trial met the primary safety end point but failed to show a significant difference in BP between sham treatment and renal denervation arms. Thus, for now, more data are needed from well-designed studies. In real-world setting, inclusion of patients and also technical performance in the centers can be different when compared with investigators performing the procedure in randomized, controlled trials. To investigate the effect in real life, registries such as the ongoing Global Symplicity Registry (GSR) with ≥5000 patients planned to be included,\textsuperscript{127} as well as smaller single-center registries\textsuperscript{128} are important to provide data on safety and efficacy in clinical practice conditions. For indications beyond hypertension, where significant BP reduction or other signs, symptoms or markers are not regarded as appropriate surrogates for outcomes, clinical end point studies adequately powered for safety and efficacy are urgently needed. Altogether renal denervation is an exciting new attempt to improve treatment of conditions associated with an elevated sympathetic activity; however, it has to be further investigated in well-designed investigations.

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