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REVIEW

# Renal sympathetic denervation in resistant hypertension

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## Abstract

Resistant hypertension remains a major clinical problem despite the available multidrug therapy. Over the next decades, its incidence will likely increase given that it is strongly associated with older age and obesity. Resistant hypertension patients have an increased cardiovascular risk, thus effective antihypertensive treatment will provide substantial health benefits. The crosstalk between sympathetic nervous system and kidneys plays a crucial role in hypertension. It influences several pathophysiological mechanisms such as the central sympathetic tone, the sodium balance and the systemic neurohumoral activation. In fact, studies using several animal models demonstrated that the renal denervation prevented and attenuated hypertension in multiple species. Large reductions in blood pressure were also observed in malignant hypertension patients submitted to sympathectomy surgeries. However, these approaches had an unacceptably high rates of periprocedural complications and disabling adverse events. Recently, an innovative non-pharmacological therapy that modulates sympathetic activation has been successfully developed. Renal sympathetic percutaneous denervation is an endovascular procedure that uses radiofrequency energy to destroy the autonomic renal nerves running inside the adventitia of renal arteries. This method represents a promising new approach to the strategy of inhibiting the sympathetic nervous system. The aim of this review is to examine the background knowledge that resulted in the development of this hypertension treatment and to critically appraise the available clinical evidence.



**Key words:** Arterial hypertension; Sympathetic activity; Renal denervation; Percutaneous ablation; Resistant hypertension

**Core tip:** Renal percutaneous denervation allows modulating the central sympathetic tone and is a promising new approach to our old strategy of inhibiting sympathetic system. In this review we describe the pathophysiological knowledge that encouraged the development of this procedure. We critically examine the available clinical evidence of the impact of renal denervation on resistant hypertension. After describing the procedure and how to select the adequate patients, we discuss the future potential therapeutic roles in other disease conditions beyond resistant hypertension.

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## INTRODUCTION

Essential hypertension remains an important clinical challenge for both the individual as well as the public perspective[1]. Despite the several available antihypertensive drugs and their unquestionable beneficial effects, hypertension control is still unsatisfactory[2,3]. This problem can be explained by several factors, such as inappropriate blood pressure measurement, physician inertia, poor ad-

herence to therapy, excessive salt intake or the existence of secondary causes of hypertension[4]. Nevertheless, even after addressing these factors, uncontrolled hypertension persists in a significant proportion of patients. Resistant hypertension is defined as blood pressure that remains above the goal pressure despite the use of at least 3 antihypertensive drugs of different classes (one being a diuretic)[5]. The prevalence of resistant hypertension varies between 8.9% in the National Health and Nutritional Examination Survey and 50% in the ALLHAT Study[6]. Recently, in a large Spanish cohort of treated hypertensive patients, 12.2% exhibited resistant hypertension[7]. Over the next few decades, this incidence will likely increase given that it is strongly associated with older age and obesity[8]. The treatment of resistant hypertensive patients has not been directly studied[9]. However, their increased cardiovascular risk suggests that effective antihypertensive treatment will provide substantial health benefits.

Accumulated evidence indicates that human sympathetic nervous system deregulation contributes to the development of arterial hypertension[10]. Sympathetic overactivity has been demonstrated in both essential and secondary forms of hypertension patients, such as obstructive sleep apnea and obesity-related hypertension[11]. Over the last few decades, the focus of hypertension research has been the renin-angiotensin system[12]. Despite the indisputable efficacy and safety of drugs that inhibit the renin-angiotensin axis, reducing sympathetic chronic activation could be important in a significant proportion of uncontrolled hypertensive patients[13]. The aim of this review is to critically examine the relevance of renal sympathetic denervation in hypertension treatment.

## RENAL SYMPATHETIC DENERVATION: FROM THE BENCH TO THE BEDSIDE

### *Rationale for renal sympathetic denervation*

On the one hand, renal sympathetic nerve fibers critically influence renal function[14]. Adrenergic fibers innervate the most relevant renal structures such as the renal vasculature, the tubular epithelial cells throughout the nephron and the juxtaglomerular apparatus[15]. Increased renal sympathetic nerve activity results in a decrease in renal blood flow mediated by vasoconstriction ($\alpha$1a adrenoceptors)[16], increased renal tubular sodium and water reabsorption ($\alpha$1b adrenoceptors)[17,18], and an increased renin secretion rate ($\beta$1 adrenoceptors)[19,20]. These effects are dependent on the degree of sympathetic activation and are considered to play an important role in the development and maintenance of hypertension[21].

On the other hand, the kidneys can also influence the sympathetic system activity. Renal structures are richly innervated with baroreceptors and chemoreceptors[22]. These afferent nerves respond to various stimuli such as renal ischemia, hypoxia and oxidative stress[23,24]. The afferent signaling from the kidneys is transmitted to the central nervous system and enhances sympathetic outflow[25], not only to the kidneys but also to other structures such as the heart and peripheral arterioles[26].

It has been feasible to study the sympathetic activation in hypertensive patients by using different methods that measure sympathetic activity, such as microneurography[27,28], noradrenaline spillover[29,30] and heart rate variability[31]. A higher sympathetic nervous activation was documented in essential hypertension, obesity-related hypertension, end-stage renal disease hypertension and in obstructive sleep apnea[29,32-34]. Interestingly, multiple studies have shown that 50% of hypertensive patients had an increased sympathetic activity in the kidneys and skeletal muscle vessels[11,28].

In conclusion, this crosstalk between the kidneys and sympathetic nerves, and its role in hypertension pathophysiology disclosed renal nerves as an interesting potential therapeutic target.

## RENAL SYMPATHETIC DENERVATION

### *Preclinical studies*

The importance of renal sympathetic nerves in hypertension was suggested when its increased activity was described in genetically spontaneously hypertensive rats compared with normotensive controls[35]. Several animal models had been used to study the influence of renal sympathetic fibers on hypertension[36]. In an experimental model of hypertension associated with obesity, high-fat diet-fed dogs that underwent renal denervation did not exhibited a significant increase in blood pressure compared with the sham group and had a 50% reduction of sodium retention[37]. Additionally, in a chronic renal failure rat model, where the animals underwent a 5/6 nephrectomy, bilateral dorsal rhizotomy prevented blood pressure increases. The procedure also resulted in lower neuroadrenergic activity in integrative central nervous structures[38]. It was also effective in a salt-sensitive hypertension model, where renal denervation prevented blood pressure increase and normalized the sodium balance[39]. Ye *et al*[40] elegantly demonstrated the importance of the renal sympathetic nervous system in hypertension. In this study, kidney damage was induced by intrarenal injection of phenol in rats, which caused a persistent elevation of the blood pressure and an increase in norepinephrine secretion in the hypothalamus, even in the absence of renal failure. In this model, performing renal denervation prevented the blood pressure increase.

The efficacy of renal denervation in several models and in multiple species established the key role of renal nerves in hypertension pathophysiology.

### *Clinical studies*

**Surgical sympathectomy:** Before antihypertensive drugs became available, the therapeutic option for severe or malignant hypertension was almost limited to surgical sympathectomy. Several surgical approaches with different degrees of aggressiveness were undertaken, which determined the therapeutically effectiveness and the extent of the side effects[41]. Total sympathectomy (or splanchnicectomy) surgeries were very aggressive and

were later replaced by a more conservative approaches consisting of the removal of the sympathetic ganglia from the 8th to the 12th vertebra[42]. Several studies in patients with malignant hypertension documented that sympathectomy surgeries were associated with substantial reductions in blood pressure and an increased survival rate[43]. Favorable changes in target organ damage were also confirmed[44]. However, these approaches were associated with high periprocedural complication rates and common adverse events such as orthostatic hypotension and tachycardia, intestinal disturbances, anhidrosis, and sexual dysfunction[45]. After the development of pharmacological treatment options, these surgeries were reserved only for severe hypertension patients refractory to pharmacological treatment. Surgical and renal percutaneous sympathectomies are quite different procedures concerning the extent of denervation in particular. Nevertheless, the surgical sympathectomy studies were important because they first demonstrated that the disruption of human splanchnic autonomic fibers was associated with significant reductions in blood pressure.

**Percutaneous sympathectomy:** The first clinical study that assessed the effect of percutaneous sympathetic renal denervation in hypertension patients was published in 2009. Symplicity HTN-1[46] was a safety and proof-of-principle cohort study that enrolled 45 patients (mean age 58 ± 9 years) with resistant hypertension (defined as systolic blood pressure > 160 mmHg despite the use of at least 3 antihypertensive drugs, including a diuretic). These patients underwent a bilateral application of radiofrequency to the renal arteries. The office blood pressures after the procedure were reduced by 14/10 mmHg at 1 mo and 27/17 mmHg at 12 mo. No favorable change in blood pressure occurred in 13% of patients. This antihypertensive effect is sustained at least up to 24 mo after the procedure[47]. Additionally, a significant reduction (42%) in renal and total body norepinephrine spillover was observed in a small subgroup of the patients who underwent sympathetic activity measurements[46].

This cohort study was followed by a multicentre, prospective, randomized trial named Symplicity HTN-2 trial[48] published in 2010. One hundred and six patients with resistant hypertension were randomly allocated to renal denervation plus conventional antihypertensive drugs versus antihypertensive drugs only. The primary end-point was an office systolic blood pressure at the 6-mo follow-up visit. The office blood pressure in the catheter-based sympathectomy group indicated a reduction of 32/12 mmHg at the end of this period. The home and ambulatory blood pressure confirmed the observed office blood pressure changes falling by 20/12 and 11/7 mmHg, respectively, at 6 mo. No blood pressure changes occurred in the control group. At 12-mo follow-up, the magnitude of clinical response was sustained[49]. Although these trials have shown a significant blood pressure overall reduction, 13% ($n$ = 6) and 10% ($n$ = 5) of patients that underwent renal denervation had no decrease in systolic blood pressure in Symplicty HTN-1 and Simplicity HTN-2, respectively. No predictor of nonresponse was found in univariate analysis of these patients' clinical and procedural characteristics. We can speculate that the procedure might have failed to obtain an adequate renal denervation. Another hypothetical explanation is the heterogeneous contribution of sympathetic activity to hypertension pathophysiology. The identification of the appropriate candidates to renal denervation is a challenge that should be answered by forthcoming studies. Recently, the published interventional and observational studies on renal denervation have been systematically reviewed[50]. All studies reported significant reductions in blood pressure of resistant hypertension patients.

Brandt *et al*[51] demonstrated that renal denervation in resistant hypertension patients was associated with a regression of left ventricle hypertrophy and an improvement of the diastolic function at 6-mo follow-up visit, compared with the control group. Interestingly, a significant decrease in the left ventricular mass was also observed in patients who did not have a significant decrease in blood pressure.

## CRITICAL APPRAISAL OF TREATMENT STUDIES RESULTS

The results of the Symplicity trials are promising. Nevertheless, several limitations must be considered. Symplicity HTN-2 was an open-label trial, which means that the physician who performed the blood pressure measurement was not blinded to the type of treatment. Therefore, we cannot rule-out an ascertainment bias. In addition, there was no sham procedure in the control group, thus we cannot measure the extent of the placebo effect. The effect of treatment in the office blood pressure was concordant but more pronounced than the ambulatory blood pressure. Although this observation could represent a higher sympathetic activation with the office blood pressure measurement than during ambulatory monitoring, this discrepancy needs further elucidation. The small number of patients, the short period of follow-up and the absence of studies with hard clinical end-points precludes the establishment of the true antihypertensive effect and its prognostic importance. Some of these limitations will be addressed by the Symplicity HTN-3 trial[52]. This prospective, masked procedure, single-blind trial will randomize 530 patients and will include as a major secondary end-point, the change in the average 24-h systolic blood pressure by ambulatory blood pressure monitoring.

## SAFETY DATA

In the larger cohort of patients that underwent percutaneous renal denervation ($n$ = 153)[47], 97% experienced no complications. The four procedural complications included three pseudoaneurysm-hematomas in the arterial access site and one renal artery dissection that occurred before radiofrequency energy delivery in that artery. They were all managed without any long-term sequelae. The

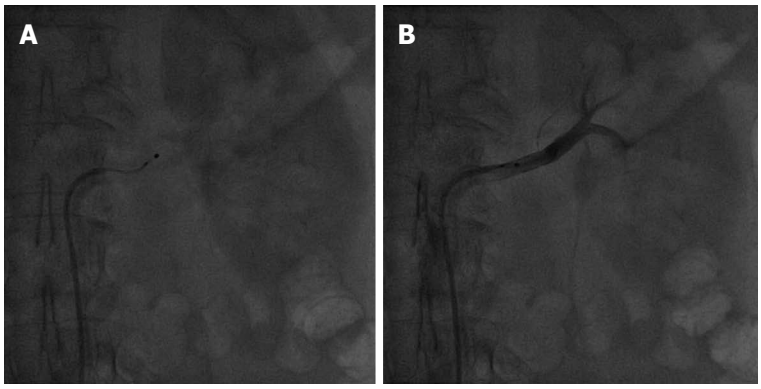


**Figure 1 Left renal artery angiogram showing the catheter inside the artery.**

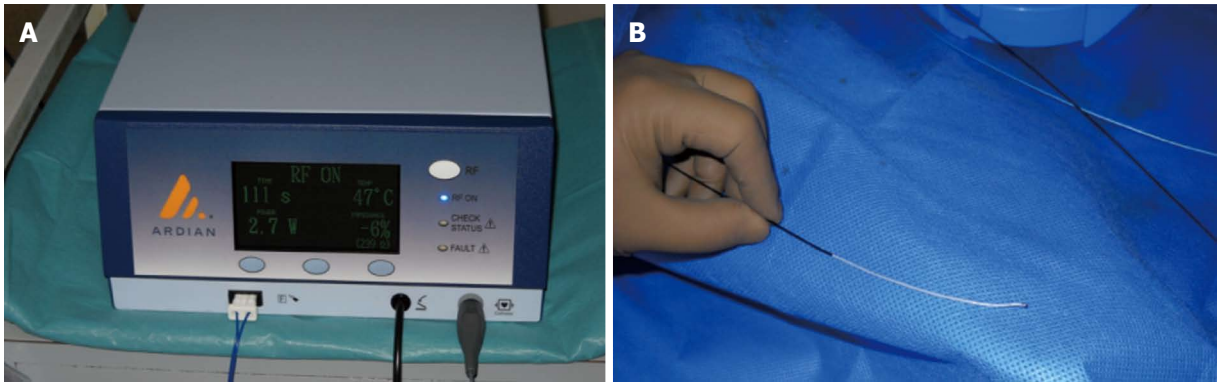


**Figure 2 The Symplicity catheter and the radiofrequency console.**

small number of procedures does not allow a strong conclusion to be made about the periprocedural safety of renal percutaneous denervation. Nevertheless, considering that the technique and the diameter of catheters are the same of coronary angiography, local femoral artery complications will likely have an incidence similar to coronary interventional procedures. In Symplicty HTN-2[48], there was one pseudoaneurysm-hematoma and no other major complication. Although the intensity of the radiofrequency energy is lower than the one used for pulmonary vein isolation in atrial fibrillation ablation, renal artery stenosis is a concern. In Symplicity HTN-2, 43 of 49 patients in the intervention group underwent renal artery imaging at the 6-mo follow-up, and no significant stenosis was diagnosed. Regarding renal function, the estimated glomerular filtration rate was stable up to 24 mo of follow-up[47,53].

The available evidence from clinical studies reveals that catheter-based renal denervation has an excellent short-term safety profile. Although unlikely, a risk of renal artery stenosis during long-term follow-up cannot be excluded.

## RENAL SYMPATHETIC DENERVATION: FROM TRIALS TO REAL LIFE

### *Description of the procedure*

The purpose of catheter-based renal sympathetic nerve ablation is to destroy the renal nerves that form a mesh-like organization inside the adventitia. This destruction is accomplished by inserting a catheter capable of delivering radiofrequency energy into the renal artery lumen. First, a guide catheter is engaged in the renal artery osteum by femoral percutaneous access. Then, a catheter specifically designed for renal denervation[54] (Symplicity, Ardian, Palo Alto, CA, United States) is introduced into the renal artery. The tip of the catheter has an electrode that is positioned, under fluoroscopic guidance (Figure 1), in contact with the artery wall to deliver low-power (less than 8 watts) radiofrequency energy for short time intervals (up to 2 min). During ablation, the catheter system continually monitors the temperature and impedance to adjust the energy that is being delivered (Figure 2). The procedure elicits abdominal visceral pain that can be managed with analgesic and sedative drugs. The denervation requires up to six separate ablations, longitudinally and circumferentially in each renal artery. The duration of this minimally invasive procedure is approximately 45 min.

### *Starting a program of percutaneous renal denervation: our experience*

We deal with an increasing number of resistant hypertension patients during our daily clinical activity. When general measures and drug therapy optimization fail to control hypertension, we then consider another treatment option for our patients. The implementation of our percutaneous renal denervation program was governed by two main concerns: minimizing the risk of the procedure

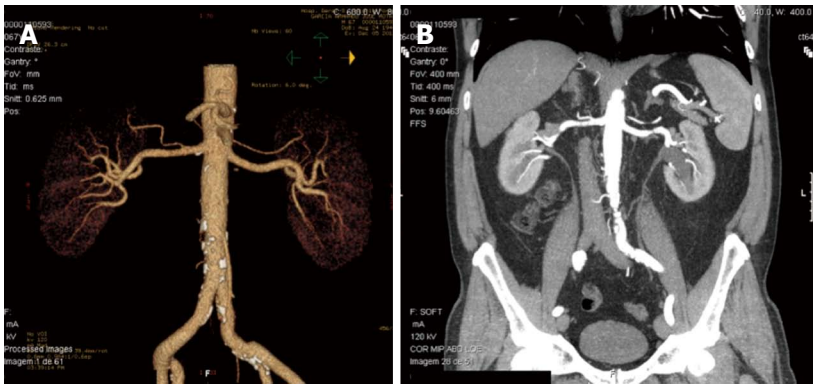


**Figure 3 Computed tomography angiography revealing normal renal arteries of a resistant hypertension patient.**

and selecting the adequate patients.

### *How to minimize the risk of the procedure?*

Despite the simplicity of this minimally invasive technique, an experienced interventional cardiologist performs the procedure. In addition to the skills needed to deal with arterial access, the certified training in this specific technique is important to assure a safe and efficient procedure. We also collaborate with an anesthesiologist, which is extremely helpful in managing the visceral pain commonly induced during the radiofrequency ablation. Our patients remain in the hospital for 24 h after the procedure for clinical monitoring. After discharge, we schedule clinical appointments at one, three, six and twelve months after the intervention.

### *How to select the patients?*

Based on the available clinical studies, adult hypertensive patients are eligible for renal denervation if they have a systolic blood pressure of 160 mmHg or more (> 150 mmHg in patients with type 2 diabetes) despite treatment with three or more antihypertensive drugs, including one diuretic. Patients are not candidates for renal denervation if they have a renal artery anatomy that precludes treatment such as a diameter less than 4 mm, length less than 20 mm or the presence of more than one main renal arteries (Figure 3). Another exclusion criterion is an estimated glomerular filtration rate of less than 45 mL/min per 1.73 $m^2$.

Before assessing whether patients meet the inclusion or exclusion criteria for the clinical studies, we evaluate the patients according to a clinical protocol[9,55]. First, we exclude those with pseudoresistance hypertension by repeating office blood pressure measurements, and we rule-out the common white-coat effect with an ambulatory blood pressure monitoring. Then, we screen for secondary causes of hypertension and, subsequently, confirm an adequate treatment regimen (up titrate to maximum tolerated doses) and patient adherence. If the blood pressure is still not controlled, we prescribe other agents as needed and tolerated such as beta-blockers, chlorthalidone or furosemide, spironolactone, and/or centrally acting sympathetic suppressants. At the end of this work-up, if the blood pressure is higher than the target goals, we assess the patient eligibility criteria for renal denervation.

## FUTURE PERSPECTIVES

This new treatment explores a revolutionary principle that allows the modulation of the sympathetic central tone and can have a beneficial role in cardiovascular diseases beyond resistant hypertension[56,57]. Renal denervation has the potential of being beneficial in milder forms of hypertension[58] or secondary forms such as end-stage renal disease-related hypertension[59,60] where sympathetic overactivity has been demonstrated. Insulin sensitivity was improved in essential hypertensive[61] and obstructive sleep apnea-related hypertension patients[62], revealing a potential role in metabolic syndrome management[63]. The maladaptive role of the chronic activation of the sympathetic nervous system is a well-known hallmark of heart failure pathophysiology[64]. Clinical studies with renal sympathetic denervation in heart failure patients are currently being performed[65,66]. We are tempted to speculate on the potential therapeutic role of renal denervation in other diseases such as hepatorenal syndrome and polycystic ovary syndrome[67]. Selective renal sympathetic denervation is a novel and promising technique that opened a new window of opportunities that deserve to be explored.

## CONCLUSION

Over the last few decades, growing knowledge about the role of the sympathetic chronic activation in the pathophysiology of hypertension has resulted in the development of the catheter-based renal sympathetic nerve ablation. This minimally invasive procedure pursues the efficacy of surgical sympathectomy and the safety of drug therapy. So far, clinical studies have demonstrated impressive and consistent blood-pressure reductions in resistant hypertensive patients. We acknowledge that there is still a lack of evidence from large placebo-controlled randomized clinical trials that are currently being conducted. Nevertheless, considering the available efficacy and safety data, renal percutaneous denervation should be considered for carefully selected patients with resistant hypertension.

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