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REVIEW

Renal Sympathetic Denervation in the Treatment of Resistant Hypertension

Catalina Sánchez-Álvarez, MD[a]; Miguel González-Vélez, MD[a]; Erik Stilp, MD[b]; Charisse Ward, MD, MPH[b]; Carlos Mena-Hurtado, MD, FACC, FSCAI[b]*

[a]*CES University, Medellín, Colombia;* [b]*Yale University, Department of Medicine, Section of Cardiology, New Haven, Connecticut*

Arterial hypertension (HTN†) is a major health problem worldwide. Treatment-resistant hypertension (trHTN) is defined as the failure to achieve target blood pressure despite the concomitant use of maximally tolerated doses of three different antihypertensive medications, including a diuretic. trHTN is associated with considerable morbidity and mortality. Renal sympathetic denervation (RDn) is available and implemented abroad as a strategy for the treatment of trHTN and is currently under clinical investigation in the United States. Selective renal sympathectomy via an endovascular approach effectively decreases renal sympathetic nerve hyperactivity leading to a decrease in blood pressure. The Symplicity catheter, currently under investigation in the United States, is a 6-French compatible system advanced under fluoroscopic guidance via percutaneous access of the common femoral artery to the distal lumen of each of the main renal arteries. Radiofrequency (RF) energy is then applied to the endoluminal surface of the renal arteries via an electrode located at the tip of the catheter. Two clinical trials (Symplicity HTN 1 and Symplicity HTN 2) have shown the efficacy of RDn with a post-procedure decline of 27/17mmHg at 12 months and 32/12 mmHg at 6 months, respectively, with few minor adverse events. Symplicity HTN-3 study is a, multicenter, prospective, single-blind, randomized, controlled study currently under way and will provide further insights about the safety and efficacy of renal denervation in patients with trHTN.

*To whom all correspondence should be addressed: Carlos Mena-Hurtado, Yale School of Medicine, Department of Medicine, Section of Cardiology, 333 Cedar St, New Haven, CT 06510; Tele: 203-785-4129; Fax: 203-483-8314; Email: carlos.mena-hurtado@yale.edu.

†Abbreviations: HTN, hypertension; trHTN, treatment-resistant hypertension; BP, blood pressure; RDn, renal denervation; GFR, glomerular filtration rate; RF, radiofrequency; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; CAD, coronary artery disease; HLD, hyperlipidemia; LVH, left ventricular hypertrophy; CKD, chronic kidney disease; LV, left ventricle; LVEF, left ventricular ejection fraction; ADA, American Diabetes Association.

Keywords: uncontrolled hypertension, treatment resistant hypertension, renal denervation, hypertension, vascular diseases, cardiovascular diseases

INTRODUCTION

Arterial hypertension (HTN) is a major public health problem and a leading cause of morbidity and mortality in the United States and worldwide. A patient's risk of cardiovascular death doubles with each 20/10 mmHg increase in arterial blood pressure (BP) [1]. In 2010, 32.2 percent of the adult population in the United States had HTN, and only 50 percent of them had a BP within established goals, despite implementation of lifestyle modification strategies and pharmaceutical therapy [2,3].

Treatment-resistant hypertension (trHTN) is defined by the American Heart Association (AHA) as the failure to achieve target BP despite the concomitant use of maximally tolerated doses of at least three different antihypertensive agents, including a diuretic [1,4]. Based on data from clinical trials, patients with trHTN have markedly increased cardiovascular morbidity and mortality, having an approximately 1.5-3 fold increase in the risk of myocardial infarction (MI), stroke, and death compared to patients whose hypertension is adequately controlled [5,6].

Although there is limited data on the prevalence of trHTN [7], a study conducted between 2003 and 2008 found a prevalence of 8.9 percent among non-institutionalized, non-pregnant adults with hypertension, a percentage that represented 12.8 percent of the drug-treated hypertensive adults [8]. Another study demonstrated that among patients with incident hypertension, approximately 2 percent developed trHTN within a median of 1.5 years from the onset of therapy [9]. Minimally invasive radiofrequency renal denervation (RDn) is currently emerging as a safe and effective therapy for trHTN, and it will be reviewed here.

RENAL SYMPATHETIC SYSTEM AND RENAL SYMPATHETIC NERVE ABLATION

That renal sympathetic nervous system plays a critical influence in the pathophysiology of HTN has been known for decades [10,11]. The adventitia of the renal arteries has efferent and afferent sympathetic nerves. Renal sympathetic activation via the efferent nerves initiates an elegant cascade resulting in elevated blood pressure. Efferent sympathetic outflow leads to vasoconstriction with a subsequent reduction in glomerular blood flow, a lowering of the glomerular filtration rate (GFR), release of renin by the juxtaglomerular cells, and the subsequent activation of the renin-angiotensin-aldosterone axis leading to increased tubular reabsorption of sodium and water [10,12-14]. Decreased GFR also prompts additional systemic sympathetic release of catecholamines [10,15]. As a consequence, BP increases by a rise in total blood volume and increased peripheral vascular resistance [11].

Patients with trHTN are known to have higher catecholamine levels and higher rates of efferent sympathetic renal activity compared to normotensive individuals [16,17]. Dr. Reginald Smithwick proposed radical thoracolumbar surgical sympathectomy, also called the "Smithwick intervention," for the treatment of intractable hypertension in the 1940s [18]. Sympathectomy was highly effective in lowering BP and in improving survival in this group of patients, decreasing 5-year mortality by more than 50 percent when compared to medical therapies of the period [18]. However, this procedure ablates the whole thoracolumbar sympathetic chain, making it non-renal specific and causing higher rates of complications, such as severe orthostatic hypotension, bladder, bowel and erectile dysfunction, and forcing the discontinuation of this approach [19,20]. The new, more specific technique only ablates the renal sympathetic chain reducing the above mentioned complications.

The recent expansion of minimally invasive endovascular procedures had led to the development of a radiofrequency catheter-based approach to renal denervation that eliminates the surgical morbidity and non-selectivity of the previously used Smithwick's sympathectomy. Renal denervation achieves a similar efficacy in decreasing renal sympathetic activity as surgical sympathectomy [20]. Renal denervation is available and implemented abroad

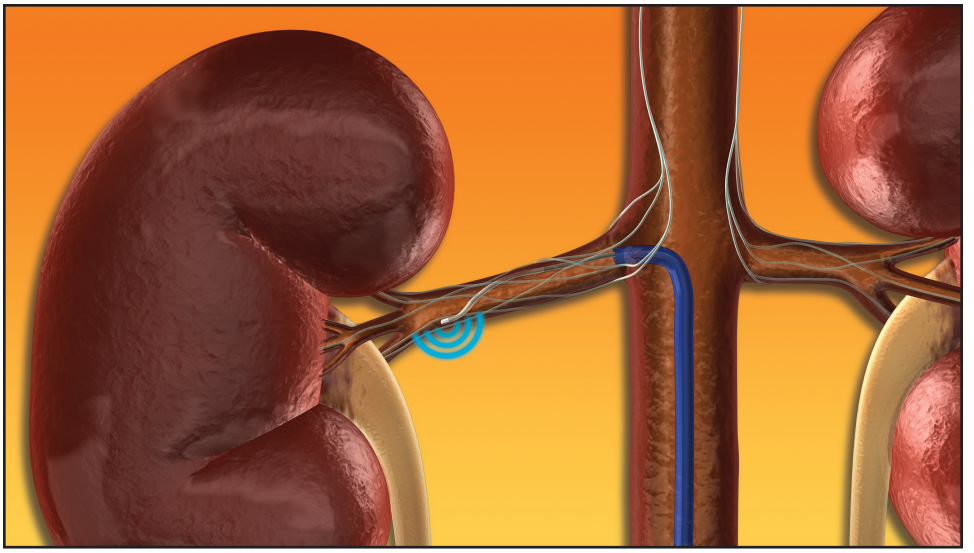

Figure 1. Percutaneous sympathetic renal denervation with the Symplicity catheter system. Note that the catheter is curved to achieve close contact with the endoluminal surface of the renal artery. The grey lines, surrounding the renal artery, represent the sympathetic nerves where the radiofrequency will be delivered to create the desired effect. (Courtesy of Medtronic).

as a strategy for the treatment of trHTN and is currently under clinical investigation in the United States.

DESCRIPTION OF THE PROCEDURE

RDn is a procedure that achieves selective renal sympathectomy via an endovascular approach. The Symplicity catheter (Symplicity®, Ardian, Inc., Palo Alto, CA, USA), currently under investigation in the United States, is 6-French compatible system advanced under fluoroscopic guidance via percutaneous access of the common femoral artery to the distal lumen of each of the main renal arteries.

Radiofrequency (RF) treatments are then applied to the endoluminal surface of the renal arteries via an electrode located at the tip of the catheter [20-22]. The flexible tip of the Symplicity catheter is designed to deflect and straighten to achieve close contact with the endoluminal surface of the renal arteries, facilitating direct RF ablation [21] (Figure 1). Ablative treatment is performed in a helical pattern and is applied from distal to proximal in each of the renal arteries. Four to six catheter passes are required in each vessel, with approximately 5mm of longitudinal and rotational space between each ablated surface (Figure 2). After the two renal arteries are ablated, the tip of the catheter is straightened and removed and a renal artery angiogram is performed to confirm the absence of renal artery dissection or thrombosis [21].

Patient Selection on the Symplicity HTN Trials

RDn trial patients all have trHTN, defined as an average systolic blood pressure (SBP) of 160mmHg, on three office measurements while taking maximally tolerated doses of at least three antihypertensives, one of which must be a diuretic. Prior to enrollment in the trials, patients were evaluated by a hypertension expert in a specialized center in order to ensure the veracity of the trHTN. Lifestyle modifications were assured, and treatment regimens were adequately modified to optimal doses.

Secondary hypertension and pseudo-resistant hypertension (measured by ambulatory blood pressure monitoring) had to be excluded as well as an assessment of adequate renal function (GFR $\geq$45mL/min/1.73m^2). Finally,

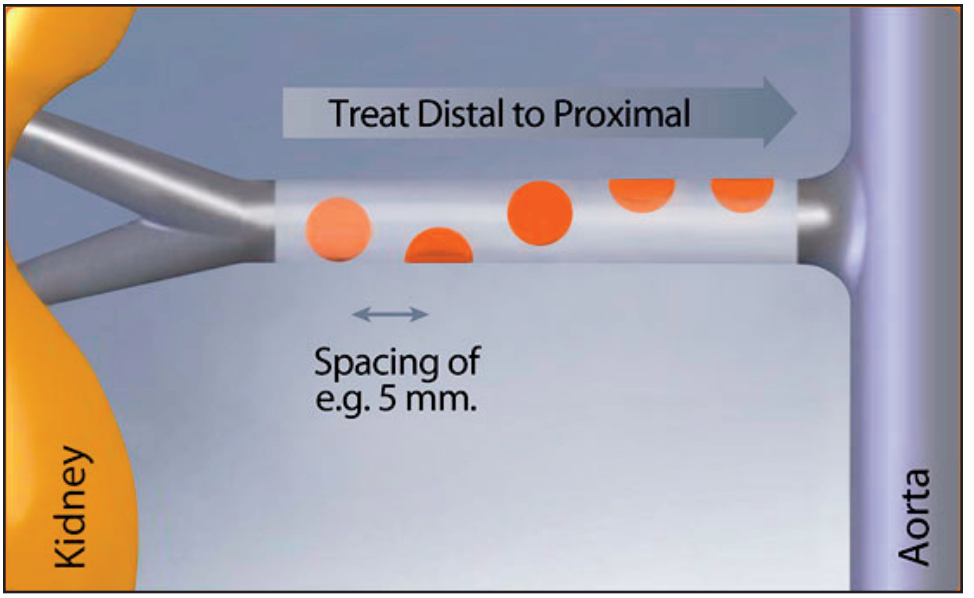

Figure 2. Sympathetic renal denervation scheme. The radiofrequency is delivered from distal to proximal and in a helical pattern within the renal artery. (Courtesy of Medtronic).

patients with deficient or previously instrumented renal arteries were excluded [23].

RENAL DENERVATION, STUDIES, AND RESULTS

Symplicity HTN-1 Trial

Symplicity-1 was a first-in-man multicenter trial completed in 2008 designed to show the safety and efficacy of RDn for trHTN via the Symplicity catheter [20]. Fifty patients of at least 18 years of age were enrolled; of these, five patients were excluded due to anatomical contraindications to the procedure [20]. All patients had a systolic blood pressure (SBP) ≥160mmHg, despite treatment with three or more antihypertensive medications (including a diuretic), and an estimated GFR ≥45mL/min/1.73m^2. The exclusion criteria included patients with a previously confirmed diagnosis of type 1 diabetes mellitus (T1DM), according to the diagnostic criteria of the American Diabetes Association (ADA); renovascular anatomic abnormalities, such as previous renal stenting, angioplasty or severe renal stenosis, a known secondary cause of hypertension; presence of an implantable cardioverter, defibrillator, or pacemaker; and active treatment with coumadin, clonidine, moxonidine, or rilmenidine (these drugs were excluded because they are centrally acting agents and reduce the sympathetic drive as their mechanism of action; therefore, it was thought that the RDn intervention could work less effectively in patients taking these medications) [20].

This trial met primary safety and efficacy goals, the latter assessed by measuring renal noradrenaline spillover before and after the intervention in 10 patients, showing a 42 percent reduction [1]. A significant and persistent reduction in the systolic and diastolic pressure in the patients treated with the RDN approach was also reported. The decline in BP began approximately 1 month after the procedure and had a consistent decrease in the following months with drops of -21/-10 at 3 months, -22/-11 at 6 months, -24/-11 at 9 months, and a maximum drop of -27/-17mmHg at 12 months of follow-up [20] (Table 1).

For a cohort of patients, follow-up was later extended to 24 months and broadened to include a larger group of similar subjects who were treated with RDN in a non-randomized distribution. The 24-month follow-up showed persistence in the BP reduction after 2 years of treatment without significant adverse events [24] (Table 1).

Table 1. Comparison of clinical characteristics, demographics, results, and complications of the Symplicity HTN-1 trial and the 24 months follow-up and the Symplicity HTN-2 trial.

	Symplicity HTN-1		24 Months Follow-up from the Symplicity HTN-1 Investigators	Symplicity HTN-2	
	Treated group	**Not treated**	**Treated**	**RDN group**	**Control group**
Design of trial	Multicenter; Prospective; Non-randomized	Multicenter; Prospective; Non-randomized	Multicenter; Prospective; Non-randomized	Multicenter; Prospective; Randomized	Multicenter; Prospective; Randomized
Number of patients	n = 45	n = 5	n = 153	n = 52	n = 54
Mean age	58 (SD: 9)	51 (SD: 8)	57 (SD: 11)	58 (SD:12)	58 (SD:12)
Comorbidities	T2DM: 14 (31%) CAD: 10 (22%) HLD: 29 (64%)	T2DM: 2 (40%) CAD: 1 (20%) HLD: 5 (100%)	T2DM: 31% CAD: 22% HLD: 68%	BMI: 31 Kg/m^2 T2DM: 21 (40%) CAD: 10 (19%) HLD: 27 (52%)	BMI: 31 Kg/m^2 T2DM: 15 (28%) CAD: 4 (7%) HLD: 28 (52%)
# Medications	4.7 (SD: 1.4)	4.6 (SD: 0.5)	5.1 (SD: 1.4)	5.2 (SD: 1.5)	5.3 (SD: 1.8)
Baseline BP (mmHg)	177/101 (SD: 20/15)		176/98 (SD: 17/15)	178/97 (SD: 18/16)	178/98 (SD: 16/17)
BP 1m	-14/-10	+3/-2	-20/-10	-20/-7	0/0
BP 3m	-21/-10	+2/+3	-24/-11	-24/-8	-4/-2
BP 6m	-22/-11	+14/+9	-25/-11	-32/-12	1/0
BP 9m	-24/-11	+26/+17	-	-	-
BP 12m	-27/-17	-	-23/-11	-	-
BP 18m	-	-	-26/-14	-	-
BP 24m	-	-	-32/-14	-	-
eGFR (mL/min/1.73 m²)	81 (54–169)	-	83 (SD: 20)	77 (SD: 19)	86 (SD: 20)
Complications	• Diffuse visceral non-radiating abdominal pain (#1). • Renal artery dissection progressionafter the RF (#1). • Pseudo-aneurysm at the femoral access site (#10).		• Renal artery dissection before the RF (#1). • Pseudoaneurism/hematome in the femoral access site (#3). • Transient intra-procedural bradycardia (#15).	• Pseudo-aneurysm at the femoral access site (#1). • Post-procedural drop in the BP (#1). • Urinary tract infection (#1). • Paraesthesias (#1). • Back pain (#1). • Transient intra-procedural bradycardia (#7).	

Data are mean (SD, standard deviation) or number (%). CAD: coronary artery disease; HLD: hyperlipidemia; T2DM: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate. (#) means absolute number of patients presenting the complication.

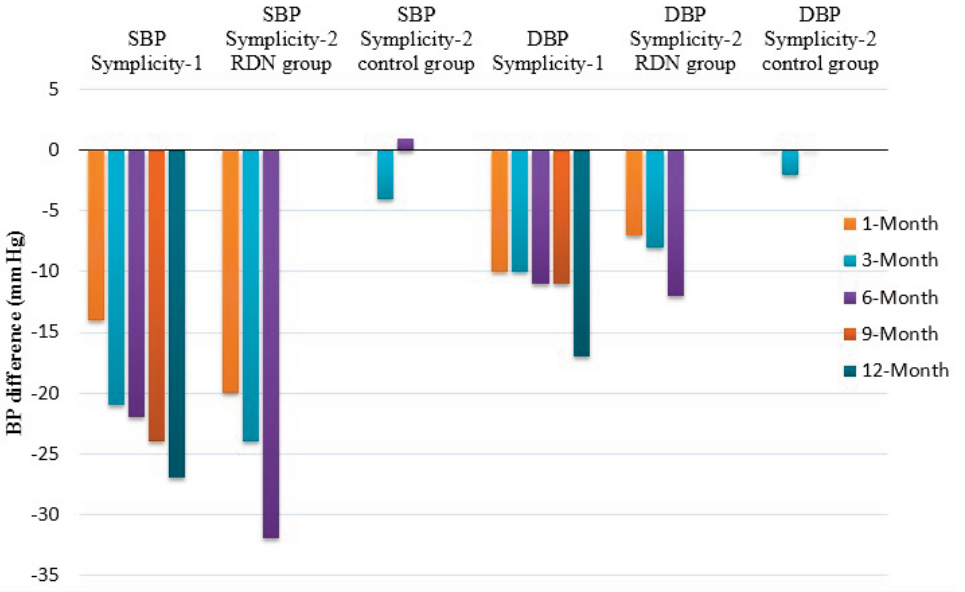

Figure 3. Comparison of the decrease in the blood pressure in the patients of the Symplicity HTN-1 trial and the Symplicity HTN-2 trial.

Although simple, the procedure has its own inherent risks and complications, the most severe being renal artery dissections after the radiofrequency and less severe but more frequent pseudo-aneurysms at the femoral access site and transient intraprocedural bradycardia.

After follow-up, the number of antihypertensive medications was unchanged compared to baseline (5.0 versus 5.1; P = 0.11), with 27 patients who underwent the procedure having decreased medications and 18 having increased medication.

Symplicity Trial HTN-2

Symplicity-2 was a multicenter, prospective un-blinded, randomized trial completed in January 2010 [24]. One hundred six patients were enrolled and randomly allocated to a control group (n = 54 patients) and RDN group (n = 52 patients) (Table 1). The study included patients between 18 and 85 years with a baseline SBP of ≥160mmHg (or ≥150mmHg in patients with type 2 DM) despite compliance with three or more antihypertensive medications at maximally tolerated doses. Patients with an eGFR < 45ml/min/1.73m^2, T1DM, substantial stenotic valvular heart disease, contraindications to magnetic resonance imaging, pregnancy or planned pregnancy, or a history of myocardial infarction, unstable angina, or cerebrovascular accident in the 6 months prior to study initiation were excluded.

Patients in the two treatment arms had similar BP, comorbidities, age, race, and number of antihypertensive medications used; however, the eGFR was lower in the treatment group (77 ml/min per 1.73m^2 vs 86 ml/min per 1.73m^2; p=0.013) [25]. Patients in the two groups had ambulatory BP monitoring before and after the procedure at 1, 3, and 6 months (Table 1). During the 6-month follow-up, a reduction of 33/11mmHg in the office-based BP was found in the RDn group compared to the control group (p < 0.0001), with a difference of 22/12mmHg (p < 0.0001) identified in home BP readings. Eighty-four percent of the patients who underwent RDN had a reduction of ≥ 10mmHg in the SBP versus 35 percent of the control group (p < 0.0001) [25] (Figure 3).

Regarding modifications of antihypertensive drugs, during the follow-up after the procedure, 10 (20 percent) of 49 patients who underwent the procedure had drug reductions and four (8 percent) had drug increases, compared with three (6 percent) of the 51 controls who had drug decreases (p = 0.04) and six (12 percent) of the controls who had drug increases (p = 0.74). Overall,

the Simplicity trials HTN-1 and HTN-2 have not shown a significant decrease in medications after the procedure.

Symplicity Trial HTN-3

Symplicity-3 is the first single-blind multi-center, prospective, randomized control trial that started in September 2011, given the favorable results of Symplicity-1 and 2. The trial seeks to enroll approximately 500 patients, again evaluating the efficacy and safety of catheter-based bilateral RDn for patients with trHTN, with an ultimate goal of the U.S. Food and Drug Administration approval for the Symplicity catheter [25]. Inclusion criteria include ≥18 and ≤80 years of age at the time of the randomization, SBP ≥160 mmHg despite a stable treatment regimen with three or more antihypertensive medications, at least one of which is a diuretic [26].

The primary outcome measure is the change in office-based SBP from baseline to 6 months after the randomization [25,26]. The primary safety end point is the incidence of a major adverse event (renal artery dissection, severe bradycardia, death, among others) the first month after the randomization, except for renal artery stenosis that will be measured 6 months after the procedure. A secondary endpoint is the change in 24-hour SBP average by ambulatory blood pressure monitoring from baseline to 6 months [26,27].

RENAL DENERVATION IN OTHER DISEASE PROCESSES

Excess sympathetic activity has also been found to be a key component in the pathophysiology of multiple diseases other than trHTN, including left ventricular hypertrophy (LVH), glucose intolerance, chronic kidney disease (CKD), and sleep apnea [15,28-32]. The fact that these conditions have increased sympathetic activation as a common denominator has led researchers to theorize that RDN can also affect the maladaptive pathophysiology in these disease states.

A paper published in the *Journal of the American College of Cardiology* evaluated the effect of RDN on left ventricular (LV) mass in patients with trHTN, the results of which showed a significant reduction in the systolic and diastolic BP of 27.8/8.8 mmHg ($p = 0.001$) and in the LV mass index from 53.9 ± 5.6 g/m$^{2.7}$ to 44.7 ± 14.9 g/m$^{2.7}$, 6 months after the procedure [28]. The thickness of the interventricular septum and the size of the left atrium also declined compared to the baseline. Parameters of left ventricular diastolic function and left ventricular ejection fraction (LVEF) improved after the RDn [28].

Improvement in glucose metabolism has also been reported as a consequence of RDn. In a trial published in 2011, a statistically significant reduction in fasting glucose was observed 3 months following RDn (118 ±3.4 to 108 ±3.8 mg/dL $p = 0.039$) [29]. Serum insulin levels (20.8 ±3.0 to 9.3 ±2.5 μIU/mL $p = 0.006$), C-peptide levels (5.3 ±0.6 to 3.0 ±0.9 ng/mL $p = 0.002$), insulin resistance (HOMA-IR) (6.0 ±0.9 to 2.4 ±0.8 $p = 0.001$), and mean 2-hour glucose levels during an oral glucose tolerance test (by 27 mg/dL, $p = 0.012$) also improved [30]. Finally, a small and non-randomized study performed in 10 patients with trHTN and sleep apnea showed a decrease in the apnea-hypopnea index 6 months after RDn was performed (median of 16.3 Vs 4.5 events per hour p 0.059), in addition to similar reduction in BP as seen in the Symplicity trials [31].

CONCLUSIONS

HTN is a multifactorial disease process that is a well-established and well-studied cardiovascular risk factor. Despite the advent of highly effective and sophisticated pharmaceutical options for the treatment of HTN, some patients have trHTN and this has led to ongoing efforts to develop new strategies to effectively impact trHTN and decrease the burden of cardiovascular morbidity and mortality in this high-risk population. The deleterious impact of increased sympathetic activation and subsequent cascade that leads to the development and perpetuation of HTN, along with the effectiveness of the rad-

ical surgical sympathectomy in the 1940s, opened the door for minimally invasive RDn. Early studies of RDn have shown a favorable safety profile and have achieved statistically significant reductions in BP not yet seen in patients with trHTN, while uncovering other potentially useful clinical effects in areas that share a common pathophysiology related to sympathetic activity such as sleep apnea, CKD, and LVH.

The long-term safety and efficacy of RDn is still under investigation. Patients from the Symplicity trials have been followed to 24 months, and sustained blood pressure reduction has been demonstrated without the addition of new antihypertensive medications and without the development of new adverse outcomes [24]. Studies with longer follow-up, of alternative catheters capable of performing RDn, and investigating the effect of RDn on other disease states are still needed.

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