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The Role of Nonpharmacologic Device Interventions in the Management of Drug-Resistant Hypertension

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Abstract Resistant systemic hypertension in patients is defined as the inability to control blood pressure despite taking at least three antihypertensive drugs, one of which is a diuretic. Two nonpharmacologic approaches are being evaluated in resistant hypertensive patients. First, the Rheos® Baroreflex Hypertension Therapy system is an implantable device that activates the carotid baroreflex through electrical stimulation of the carotid sinus wall. Sustained and clinically lower blood pressure has been observed in patient clinical trials. The second approach is a catheter-based strategy which denervates the renal afferent and efferent autonomic nervous system. This strategy has also been shown to be effective in drug-resistant patients, and has also been shown to decrease renin production, preserve renal function, improve glucose tolerance, and reduce left ventricular hypertrophy. Both carotid sinus stimulation and renal denervation are now being evaluated in clinical trials for the long-term control of hypertension.

Keywords Carotid sinus · Baroreceptors · Afferent sympathetic nerves · Efferent sympathetic nerves · Renal denervation · Baroreflex inhibition · Autonomic denervation · Resistant hypertension · Rheos® · Symplicity™ catheter · Sympathectomy · Renal sympathectomy · Autonomic dysfunction · Renal hypertension

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Introduction

Hypertension, defined as blood pressure (BP) greater than or equal to 140/90 mmHg, is estimated to affect a third of the adult population of the USA and accounts for 6 % of all deaths worldwide [1•]. It is a major risk factor for chronic renal failure, congestive heart failure, coronary artery disease, and stroke [1•]. In the USA, the total cost of treating hypertension in 2010 was estimated to be $76.6 billion [2], yet only 50 % of patients have their BP well controlled [3]. The American Heart Association guidelines defined resistant hypertension as BP that remains above the goal despite the use of maximally tolerated doses of at least three antihypertensives drugs, including a diuretic [4]. When evaluating a patient for resistant hypertension, one should rule out common secondary forms of hypertension, such as obstructive sleep apnea, primary aldosteronism, and renal artery stenosis [4]. As patients with resistant hypertension have a higher risk of cardiovascular disease [5••], they have become the focus of newer device-based approaches for reducing high BP. There are recent encouraging results with the carotid sinus stimulator [6, 7, 8••, 9••, 10, 11] and renal artery sympathetic denervation [9••, 12–16], The main objective of this article is to review and evaluate the results of preclinical and clinical studies of the implantable carotid sinus stimulator (Rheos®) and catheter-based renal sympathetic denervation (RSD).

Electrical Stimulation of the Carotid Sinus

The Role of the Baroreflex in Blood Pressure Regulation

The arterial baroreflex adjusts the BP to ensure that excessive rises and falls do not occur [17, 18]. With sustained increases in arterial pressure, the baroreflex will adapt to the new "normal" and reset itself to respond to elevated pressures with

reduced sensitivity [17]. Increased intravascular volume activates the stretch-sensitive nerve fibers of the baroreceptors located in the carotid sinuses, the aortic arch, and the great vessels of the thorax. Increased arterial pressure leads to increased afferent signaling via the glossopharyngeal and vagus nerves to the nucleus tractus solitarii in the dorsal medulla [17]. The central nervous system apparently perceives this increased signaling as a rise in BP and attempts to counteract the elevation in BP by the transmission of signals to various end organs. The effector branch of this response from both the rostral ventrolateral medullary area and the nucleus ambiguus in the medulla leads to decreased sympathetic outflow (an inhibitory effect) and increased parasympathetic outflow (an excitatory effect) [19]. The end result is a decrease in heart rate (HR), contractility, vascular tone, and a reduction in arterial pressure [17, 19].

Experimental research for carotid sinus stimulation as an approach to treat hypertension has been conducted in animal models [20–22].

Rheos® Baroreflex Hypertension Therapy System Device Profile

The Rheos® Baroreflex Hypertension Therapy system has three major components: the Rheos® implantable pulse generator (IPG), the Rheos® programmer system, and the bilateral Rheos® carotid sinus leads [23, 24]. The IPG consists of a battery and circuit system delivering between 1 and 7.5 V of activation energy in a temporally variable pattern. Similar to the system used for programming cardiac pacemakers, the programmer system is a computer-based programming system that communicates with the IPG via radiofrequency coupling. The IPG is 90 mm high, 48 mm wide, and 12 mm thick, and weighs 95 g. It is directly connected to the carotid sinus leads, which are 50 cm long. The carotid sinus leads are available in two different sizes: the smaller model is capable of covering the free wall of the carotid sinus; the larger model is recommended for bigger arteries or larger anatomic variants of the carotid sinus.

Illig et al. [25] described the surgical implantation of this device following open carotid exposure under narcotic anesthesia so as to preserve the reflex. The electrode was centered on the carotid sinus once bifurcation had been identified, and the lead was connected to the IPG. The carotid sinus was stimulated at a low voltage, and the BP-lowering effect was observed, generally within 30 s. The electrode was sutured in those areas yielding an optimal BP-lowering response. The IPG was implanted in a pocket below the right clavicle, to avoid confusion with cardiac pacemakers which are implanted on the left. Subcutaneous tunnels were fashioned to connect the electrodes to the IPG.

The Device-Based Therapy in Hypertension Trial (DEBuT-HT) reported that the device and procedure are safe, with no cases of carotid stenosis or orthostatic hypotension demonstrated [26]. However, the preliminary safety results from the Rheos® Pivotal Trial reported the following procedural complications that occurred in at least 2 % of patients: nerve damage (9 %), surgical complications (5 %), respiratory complications (2 %), and wound complications (2 %). However, a 43 % reduction in hypertensive crises was seen, and long-term follow-up demonstrated very few serious adverse events related to the device [27]. Chronic baroreceptor stimulation had no adverse effects on renal function [28•].

Human Studies with the Rheos® Device for Management of Hypertension

Of the 45 patients enrolled in the Rheos® DEBuT-HT [29], only 18 successfully completed a mean duration of 58± 6 months of chronic therapy with the Rheos® device. BP and HR were compared at the baseline, 3 months, 1 year, 2 years, 3 years and 4 years. The baseline values were 193± 36 mmHg for systolic BP (SBP), 111±20 mmHg for diastolic BP (DBP), and 74±13 bpm for HR. At 4 years, 72 % of patients were able to achieve a sustained drop in SBP of at least 30 mmHg ($p<0.001$), with 67 % of patients having SBP <140 mmHg at that time. The mean reduction in DBP was 30 ±6 mmHg ($p<0.001$) and the reduction in HR was 5±2 bpm ($p=0.02$). The average number of antihypertensive medications was reduced from 5.0 at the baseline to 3.4. Chronic baroreceptor stimulation caused sustained changes in HR variability and heart turbulence, consistent with inhibition of sympathetic activity and an increase in parasympathetic activity [30–32]. The Rheos® system demonstrated that an implantable device can complement medical therapy as a chronic treatment option in patients with resistant hypertension.

The Rheos® Pivotal Trial, currently in progress, is an FDA-approved randomized, double-blind, parallel-design phase 3 trial with 267 patients from the USA and Europe who meet the criteria for stage 2 drug-resistant hypertension (office cuff SBP≥160 mmHg and DBP≥80 mmHg despite maximally tolerated doses of at least three antihypertensive medications, one of which is a diuretic) [31]. Patients with significant carotid atherosclerosis and an estimated glomerular filtration rate (eGFR) of less than 30 mL/min are excluded from the study [31]. The current goal of the trial is to demonstrate the device's efficacy and safety in reducing SBP (10 mmHg) as measured by an office cuff after 6 months and 1 year of device activation, as well as the short-term and long-term safety of the device during implantation and activation periods. Other measurements include the antihypertensive therapeutic index at 6 months, 24-h ambulatory mean SBP at 6 months, quality-of-life measurements (SF-12, Hypertension Symptoms Checklist, Pittsburgh Sleep Quality

Index, Hospital Anxiety and Depression Scale), and various biochemical markers (brain natriuretic peptide, plasma aldosterone, plasma renin activity, hemoglobin A_{1C}, and plasma vasopressin) [31]. The results at 6 months after implantation have shown SBP and DBP to decrease by 33.7 mmHg and 15.3 mmHg, respectively, compared with preimplantation values ($p<0.001$). Fifty-three patients achieved a goal BP of less than 140 mmHg and 69 % experienced a reduction of at least 20 mmHg [27].

Carotid sinus stimulation may provide additional cardiovascular benefit. In a prospective substudy of the DEBuT-HT and the original US feasibility trials using the Rheos® device, therapy in early-stage heart failure patients with drug-resistant hypertension lowered BP and effectively reversed cardiac remodeling [33]. The amount of "severely abnormal" tissue in the left ventricular mass was decreased by approximately 30 %, so most patients were then in the "reference range." Left ventricular mass index (LVMI) and left atrial dimension also decreased after 12 months of therapy ($p\leq0.01$). Also, there was an approximately 25 % increase of measured "normal geometry" and a decrease in left ventricular concentric hypertrophy.

In another analysis of the same data, 3 months of Rheos® therapy reduced LVMI similarly to a 12-month course of angiotensin receptor blocker therapy. Furthermore, 12 months of Rheos® therapy provided almost twice the effect of reducing LVMI as 12 months of angiotensin receptor blocker therapy [34].

Renal Sympathetic Denervation

The Role of Renal Sympathetic Nerves in High Blood Pressure

The autonomic nervous system controls the kidneys via an intricate network of postganglionic sympathetic neuronal innervations (Fig. 1) [35, 36]. Sympathetic innervation, along with other factors [37], plays an important role in the pathogenesis of hypertension [8••], as shown by the results of the radical sympathectomy procedure (splanchnicectomy), which often reduced elevated BP in patients with hypertension [35, 36, 38–40].

The kidneys' contribution to the pathogenesis and maintenance of high BP is linked to their afferent and efferent sympathetic nerve output [41]. Sympathetic innervation of the kidneys and the increase in norepinephrine production or spillover are strongly correlated [42–44], especially in obese patients. Renal sympathetic tone is doubled in hypertensive patients compared with normotensive individuals [43], and the increase in norepinephrine level leads to increased stimulation of the cardiac sympathetic nerves. The risk of a patient developing left ventricular hypertrophy and ventricular arrhythmias with subsequent sudden cardiac death is increased [43].

Increased sympathetic innervation leads to enhanced renin secretion. Norepinephrine is released directly to the granular juxtaglomerular cells, which are then stimulated to secrete renin [45, 46]. This renin release occurs with less sympathetic stimulation than that needed to reduce sodium excretion and renal blood flow [47]. Renin level may be increased indirectly by renal sympathetic innervations when a reduced influx of sodium chloride into the macula densa and lower perfusion pressures in the renal artery lead to a change in renal hemodynamics, in turn causing an increase in renin secretion [45, 46]. Subjects with RSD have failed to release renin in clinical situations where release is normally increased, such as a head-up tilt and volume depletion [47].

Stimulation of the renal sympathetic nerves leads to enhanced sodium and water reabsorption and renal arteriolar vasoconstriction by way of activation of α_1-adrenoceptors on the renal epithelial cells [48, 49], and decreased renal blood flow [45, 46], and has been shown to decrease sodium and water excretion by as much as 40 % in animal models [50–55]. Conversely, the ability to reabsorb sodium and water is greatly reduced in cases of RSD [50, 51, 56–59]; thus, some of the BP-lowering effect of RSD may be related to natriuresis.

The growth and hypertrophy of vascular smooth muscle in the renal vasculature are also affected by renal sympathetic innervation [60]. Norepinephrine secreted by sympathetic nerves stimulates α_1-adrenoceptors, which in turn activate growth-promoting mitogen-activated protein kinases which promote hypertrophy of the smooth muscle cells in the renal vasculature [60]. In a hypertensive rat model, the wall-to-lumen ratio was greater than in normotensive controls [61]. These same rats underwent RSD, which substantially decreased the wall-to-lumen ratio [61], suggesting that increased renal sympathetic tone in hypertension can cause hypertrophy of the vascular smooth muscle.

The kidneys influence the sympathetic nervous system by way of afferent renal nerves (Fig. 1) [8••, 45], most of which originate in the pelvic wall of the kidneys and respond to stretch, hypoxia, and renal ischemia [8••, 45, 62–65]. Nerve signals go from the ipsilateral dorsal root ganglia to the central nervous system, especially the paraventricular nucleus of the hypothalamus [66–69], where they have an important influence in the autonomic control of the cardiovascular system [69–71]. Stimulated renal afferent nerves activate the sympathetic control centers in the brain, causing an increase in systemic vascular resistance, and thereby an increase in BP [48, 72–75]. Surgical ablation of renal afferent nerves blocks this increase in sympathetic tone [8••, 76–78].

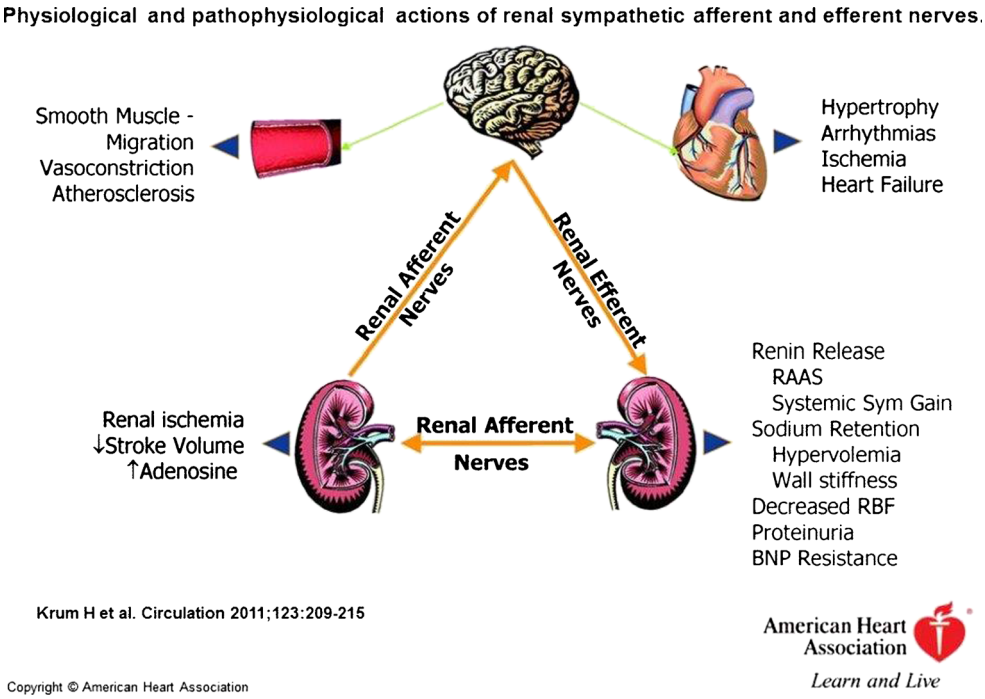

Fig. 1 Physiologic and pathophysiological actions of renal sympathetic afferent and efferent nerves. *BNP* brain natriuretic peptide, *RAAS* renin–angiotensin–aldosterone system, *RBF* renal blood flow. (From [8••] with permission)

Clinical Trials

A minimally invasive endovascular catheter-based approach was developed to directly target the sympathetic nerves adjacent to the renal artery [8••]. The Symplicity catheter (Ardian, Mountain View, CA, USA) with a radiofrequency ablation device applied via an electrode on the tip of the catheter is inserted via the femoral artery and advanced into the distal renal artery using a 6-F or 8-F guide [15•]. The procedure is performed via multiple radiofrequency treatments, each lasting approximately 2 min. The first ablations are performed distally in the renal artery; the catheter is retracted 5 mm, rotated circumferentially, and then radiofrequency ablation is repeated. This procedure is performed four to six times until the entire circumference of the artery has received an ablation treatment (average duration of 45-60 min) [79]. Loin pain has been managed with conscious intravenous sedation, and renal artery dissection has been a rare complication [8••]. More serious complications, such as renal artery thrombosis and embolization, were not seen [8••].

Symplicity-1 [14], the first clinical trial, recruited 50 patients with SBPs ranging between 160 and 180 mmHg despite the use of three antihypertensive drugs. Prior to the procedure, patients underwent renal imaging studies to exclude significant atherosclerotic renal artery disease and congenital renal artery anatomic abnormalities. Five patients were excluded from the trial for anatomical reasons (mainly dual renal artery systems). Significant reductions in both SBP and DBP were documented with both office-based and ambulatory BP monitoring measurements in the postprocedure period (1–36 months). RSD did not affect the HR. One intraprocedural renal artery dissection occurred before RSD.

The Symplicity HTN-2 trial [12], a randomized controlled study in drug-refractory hypertensive patients, reported on patients with SBP≥160 mmHg (SBP≥150 mmHg in patients with diabetes) who were randomized into RSD and control groups. Patients with type 1 diabetes or glomerular filtration rates of less than 45 mL/min per 1.73 m^2 were excluded. At 6 months, the primary end points were assessed in 49 of the 52 patients who underwent RSD and 51 of 54 controls. A significant difference in BP between the treatment and control groups was seen [2, 80]. The baseline BPs were 178±18/97±16 mmHg and 178±16/98±17 mmHg in the intervention and control groups, respectively. At 1 month, the RSD group demonstrated a decrease in office-based BP of 20/7 mmHg compared with no change in office-based BP in the control group (0/0 mmHg). At 3 months, the decreases were 24/8 mmHg in the RSD group and 4/2 mmHg in the control group. The final results at 6 months were decreases of 32±23/12±11 mmHg in the RSD group and 1±21/0±10 mmHg in the control group. Home BP measurements and average BP derived from 24-h ambulatory BP monitoring were similar.

The number of antihypertensive medications required was decreased by 20 % (ten of 49 patients) in the RSD group compared with 6 % (three of 51 patients) in the control group. However, 8 % (four of 49) of the RSD group and 12 % (six of 51) of the controls required an increase in their drug regimen. Of the patients who had no change in their drug regimen, the RSD patients had a decrease in BP of 31±22/12±11 mm Hg compared with a decrease of 0±20/-1±10 mm Hg in the

control group [80]. During the 6 months' follow-up, renal function as assessed by serum creatinine concentrations, eGFR, and cystatin C concentrations, and albumin-to-creatinine ratios were similar in both groups.

No significant adverse effects occurred during the 6-month study. No subjects died during the study. Transient bradycardia requiring atropine without any resulting sequelae occurred in seven of 52 patients (13 %) during the procedure. Minor events occurring after the procedure included a femoral artery pseudoaneurysm treated with manual compression, a postprocedural decrease in BP treated with a reduction in antihypertensive medications, a case of back pain treated with analgesics that resolved within 1 month, an extended hospital stay for paresthesia, and a urinary tract infection. Vascular imaging studies showed possible progression of a preexisting atherosclerotic lesion in one patient in the treated group, but the lesion was not at the site of radiofrequency administration and thus probably not related to the procedure. Cardiovascular events that occurred during the trial in the intervention group included a case of nausea and edema, possibly related to hypertension, a hypertensive crisis, a hypotensive episode, a case of stent placement secondary to angina, and a transient ischemic attack. Cardiovascular events that occurred in the control group included a case of stent placement secondary to angina and two transient ischemic attacks.

In a substudy of Symplicity HTN-2, BP at maximal exercise was reduced in the treatment group compared with controls, without decreases in cardiac function, peak oxygen consumption, or the work performed [81].

Additional cardiovascular benefits may follow RSD. One study showed that RSD reduced left ventricular mass and improved diastolic function [82]. A small randomized study suggested that patients with atrial fibrillation who underwent ablation pathway treatment had less recurrent atrial fibrillation if they had cardiac ablation in combination with RSD [83]. A pilot study showed that following RSD, patients had a 9 % reduction in their fasting blood glucose levels and a 12 % drop in fasting insulin levels [84].

RSD may be safe and effective in patients with moderately severe chronic renal failure with mean eGFR of 31 mL/min per 1.73 m^2, a group that was excluded from the Symplicity trials. Recently, 15 such patients were treated with RSD, which was effective in lowering BP, and renal function remained stable at 6 months' follow-up [85].

Symplicity HTN-3 is a randomized placebo-controlled study performed in the USA which enrolled 530 patients with drug-resistant hypertension and SBP>160 mmHg [86]. Enrollment was completed in May 2013. Patients who were randomized to receive placebo (one third of the study population) underwent a sham procedure. The primary end point of the study was the change in office SBP at 6 months, and the 6-month change in the average 24-h SBP assessed by ambulatory BP monitoring was a secondary end point. The primary safety end point was the incidence of major adverse effects that occurred from 1 month until 6 months after treatment.

The favorable feature of Symplicity HTN-3 was its single-blind design (both Symplicity to diminish the placebo effect and BP assessors who were blinded to treatment and predesignated at follow-up to minimize bias) [87].

Compared with the results of Symplicity HTN-1 and Symplicity HTN-2, RSD in the Symplicity HTN-3 failed to achieve its primary efficacy end point [88–91]. Safety issues arose during the trial. The results of Symplicity HTN-3 raise significant doubts about the long-term benefit of RSD. Symplicity-4 was designed for patients with SBP> 140 mmHg. It is planned to suspend enrollment in this trial.

Other Ablation Systems

New ablation systems for RSD are currently being evaluated [87, 92•, 93•, 94•, 95]. These systems include (1) use of a guiding sheet versus balloon-steered catheter, (2) radiofrequency versus ultrasound energy application, (3) single versus multiple radiofrequency electrodes (4), single-delivery versus repeated energy delivery, and (5) temperature control by cooling.

A study with a multielectrode RSD system developed by St. Jude Medical (St. Paul, MN, USA) was terminated recently because of slow enrollment [88]. EnligHTN-IV, a large phase 3 sham-controlled trial, was designed to evaluate this system in 590 patients with resistant hypertension [88, 92•].

Whether or not these newer RSD systems will continue to be of use following the results of the Symplicity HTN-3 trial will need to be determined in future trials.

Conclusion

An opportunity exists to provide a novel and alternative approach to lowering BP in patients with drug-resistant hypertension [96]. The Rheos® device capitalizes on a normal physiological response (the baroreflex) and exogenously activates the reflex to obtain neurohumorally mediated decreases in BP. It has been shown to reduce sympathetic outflow and increase parasympathetic outflow [97]. The results of long-term clinical trials with this device are eagerly awaited.

The negative findings of the Symplicity HTN-3 trial, a rigorous sham-controlled study, raise significant questions regarding the efficacy of RSD in the long-term management of resistant hypertension.

There are other RSD systems still under investigation, including the St. Jude Medical catheter, which uses an expandable basket of electrodes to facilitate fixation in the renal artery; the OneShot (Covidien), which provides radiofrequency energy and a helical ablation pattern for a more complete

denervation; the Vessix (Boston Scientific) balloon catheter with radiofrequency electrodes mounted on the balloon surface; and the Paradise catheter (ReCor Medical), which emits ultrasound circumferentially.

Compliance with Ethical Guidelines

Conflict of Interest William H Frishman and Daniel Glicklich declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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