Neuromodulation Device Therapy for Treatment of Hypertensive Heart Disease

Thomas M. Todoran, MD; Michael R. Zile, MD

Hypertensive heart disease (HHD) is the leading cause of mortality and morbidity in the United States. Despite the availability of medical therapy it remains a challenge to treat. Autonomic nervous system imbalance resulting in overactivity of the sympathetic nervous system and underactivity of the parasympathetic nervous system is integral in the development of hypertension and ultimately the development of HHD. Emerging data suggest that neuromodulation device therapy for treatment of HHD is promising. (Circ J 2013; 77: 1351 – 1363)

Key Words: Baroreflex activation therapy; Hypertension; Spinal cord stimulation; Sympathetic renal denervation; Vagal nerve stimulation

Systemic arterial hypertension (HTN) is defined as a systolic blood pressure (SBP) >140 mmHg and/or a diastolic blood pressure (DBP) >90 mmHg in non-diabetic patients. In the presence of the important comorbid factor of diabetes mellitus, this partition value is lowered; diabetics are considered hypertensive if their blood pressure (BP) is >130/80 mmHg. HTN is a major global health burden in both developed and developing countries. It is projected that by 2025, 30% of the adult population will have HTN.1 In 2010, an estimated 78 million or 33% of adults ≥20 years old in the USA had HTN. Among adults with documented HTN, 50% are inadequately controlled while taking antihypertensive medication.2 The reason for inadequate BP control in the cross-sectional studies is multifactorial and could be related to poor compliance, suboptimal treatment regimens or treatment resistance. Chronic HTN leads to structural cardiovascular remodeling and abnormal left ventricular (LV) function. Persistently increased BP causes an increase in LV systolic wall stress (afterload), that is, induction of hypertrophy at both the LV chamber level and the level of the individual cardiomyocytes. The development of hypertrophy (LVH) is a critical stage in the clinical course of patients with hypertensive heart disease (HHD). Structural remodeling, with associated abnormalities in diastolic function, and the development of chronic heart failure (CHF) portend an increased risk of both mortal and morbid events.3–6 Treatment that results in regression of LVH is associated with a reduction in these events.7–10 However, success in reversing LVH using existing pharmaceutical regimens has neither been uniform nor complete, particularly in patients with drug-resistant, refractory HTN. Abnormalities in the autonomic nervous system (ANS) appear to contribute to both resistance to treatment and resistance to the induction of structural remodeling.11,12 The role of autonomic imbalance in patients with HHD underscores the importance of developing novel management strategies that target autonomic modulation (Table 1). These include renal sympathetic denervation (RSD), carotid baroreceptor activation therapy (BAT), vagal nerve stimulation (VNS) and spinal cord stimulation (SCS). Our principle focus is to review the developments in device management of HHD disease using neuromodulation.

Role of the ANS in HTN

The ANS is central to maintaining cardiovascular homeostasis. Autonomic imbalance resulting in sympathetic overactivity and parasympathetic underactivity has been implicated in the development of HTN, as well as other diseases frequently associated with HTN, such as insulin resistance (IR), sleep disorders, HF and kidney disease. These abnormalities are both central (CNS) and peripheral (renal). Individuals with HTN have been found to have higher plasma catecholamine levels and increased activity of sympathetic skeletal muscle vasculature than normal subjects.13

Anatomy and Physiology of the Renal Sympathetic Nervous System (SNS)

Autonomic control of the kidneys is primarily sympathetic. The SNS innervates the kidneys through a network of efferent and afferent fibers located in the adventitia along the entire length of the renal artery. These fibers originate from sympathetic ganglia along the aorta. Activation of renal efferent sympathetic nerves results in increased renin release, activation of the renin-angiotensin-aldosterone system, renal vasoconstriction, increased sodium reabsorption and increased water retention. Renal afferent sympathetic nerves are activated in re-

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of antihypertensive medications, surgical sympathectomy was used to treat severe HTN. The rationale was based on surgical RSD reducing the efferent sympathetic outflow to the kidneys, resulting in reduced release of renin, reduced tubular sodium reabsorption, and increased renal blood flow, ultimately increasing urinary output. Most studies demonstrated improved BP control, and reductions in stroke and mortality compared with medically treated patients. However, these benefits were outweighed by the significant morbidity associated with the procedure and it was eventually abandoned after the development of antihypertensive medications.

The afferent and efferent sympathetic nerves are located in the adventitia of the renal artery and this proximity of the nerve bundles to the inside of the renal artery makes it possible to deliver ablative energy using a percutaneous approach. The goal is to achieve sympathetic nerve fiber interruption by applying energy through the renal wall to a depth of 3–5 mm.

The 2 forms of energy currently being used for RSD are radiofrequency (RF) and ultrasound (US). Each of these technologies will be described.

Common to all is access to the renal artery, which is accomplished using standard techniques and equipment. Dependent response to decreased renal perfusion, renal parenchymal injury and ischemia. This activation results in stimulation of sympathetic centers in the brain and increased central efferent outflow to the heart, vasculature and the kidneys, resulting in increased BP.

The parasympathetic nervous system innervates the heart via the vagal nerve. Reduction in vagal activity results in increased heart rate (Figure 1). Sustained activation of renal efferent and afferent sympathetic nerves is a component of essential HTN. Prolonged and exaggerated activation can lead to resistant HTN (RH), progression to HHD and CHF.

RH

RH is defined as BP that remains above the goal despite concurrent use of ≥3 antihypertensive agents of different classes prescribed at maximum tolerated doses, including a diuretic. RH also includes individuals whose goal BP is achieved using ≥4 antihypertensive agents. The prevalence of RH is largely unknown.

Surgical Sympathectomy

The strongest evidence of the role of overactivity of the SNS in HTN begins with the advent of surgical sympathectomy and continues with the results of current studies examining novel device therapies. As early as the 1930s, before the availability of antihypertensive medications, surgical sympathectomy was used to treat severe HTN. The rationale was based on surgical RSD reducing the efferent sympathetic outflow to the kidneys, resulting in reduced release of renin, reduced tubular sodium reabsorption, and increased renal blood flow, ultimately increasing urinary output. Most studies demonstrated improved BP control, and reductions in stroke and mortality compared with medically treated patients. However, these benefits were outweighed by the significant morbidity associated with the procedure and it was eventually abandoned after the development of antihypertensive medications.

Table 1. Autonomic Modulation Device Trials

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Trial name</th>
<th>Clinicaltrials.gov #</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
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<td>Symplicity HTN-1</td>
<td>NCT00664638</td>
<td>HTN</td>
</tr>
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<td></td>
<td></td>
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<tr>
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</table>

BAT, baroreflex activation therapy; HF, heart failure; HTN, systemic arterial hypertension.
Device Therapy for Treatment of HT

**RF Ablation Technology**

**Symplicity®** This RSD system (Medtronic Inc, Minneapolis, MN, USA) consists of a single platinum electrode ablation catheter, RF generator and a ground pad. The catheter has a flexible tip and deflectable shaft that is positioned using controls on the handle (Figure 2A). Treatment is performed distal (5 mm from the bifurcation) to proximal at ≥5 mm intervals for a total of 4–6 sites. Using a proprietary algorithm, the RF generator continuously monitors and adjusts the power (5–8 W), delivering energy while monitoring both temperature and impedance, and automatically shutting off after 2 min or when impedance or temperature exceed program limits. Two prospective studies have been completed using Symplicity in RH patients and a third is being conducted. In addition, studies looking at other patient populations (eg, CHF) and other indications (obstructive sleep apnea [OSA] control) are also underway. Based on data from the 2 initial HTN trials, the Symplicity catheter has received CE Mark approval in Europe.

**Table 2. Differences in Device Characteristics**

<table>
<thead>
<tr>
<th>Device™</th>
<th>Symplicity™</th>
<th>EnligHTN™</th>
<th>Vessix™</th>
<th>OneShot™</th>
</tr>
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<tbody>
<tr>
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<td>Multi-array</td>
<td>Multi-array</td>
<td>Multi-array</td>
</tr>
<tr>
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<td>Single tip</td>
<td>Basket</td>
<td>Balloon</td>
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<tr>
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<td>Monopolar RF</td>
<td>Bipolar RF</td>
<td>Monopolar RF</td>
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<td>6</td>
<td>&lt;1</td>
<td>25–35</td>
</tr>
<tr>
<td>Treatment time (s)</td>
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<td>54×10²</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>No. electrodes</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>Spiral</td>
</tr>
<tr>
<td>Application</td>
<td>Multiple</td>
<td>Single</td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>Size</td>
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<td>3–7 mm</td>
<td>5, 6, 7×20 mm</td>
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<td>Cooling</td>
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<td>No</td>
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<tr>
<td>Guide</td>
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<td>8Fr.</td>
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<td>Delivery</td>
<td>Deflectable tip</td>
<td>Deflectable tip</td>
<td>Over-the-wire</td>
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</table>

**RF, radiofrequency.**
The Symplicity HTN-1 Trial was a multicenter (19 sites in Europe, Australia and USA), nonrandomized, open-label proof-of-concept study. In this first-in-human application and first series of pilot studies, patients with treatment RH (SBP ≥160mmHg on ≥3 antihypertensive medications, including a diuretic) underwent catheter-based RSD using the Symplicity system. Patients were excluded if they had hemodynamically significant renal artery stenosis, prior renal artery intervention or renal artery anatomy that precluded treatment (defined as <4 mm diameter, <20 mm length or more dual renal arteries). Primary outcomes were office BP and safety data before and at 1, 3, 6, and 12 months after the procedure. In the patients who underwent RSD, a significant reduction in both SBP and DBP was seen at 1 month after the procedure and BP was further reduced at 3 months. These reductions in BP persisted at 12 months (Figure 3A). Periprocedural complications occurred in 2 patients (out of 45): 1 renal artery dissection and a femoral artery pseudo-aneurysm. Long-term follow-up of the initial 45 patients, and an additional 108 patients who underwent RSD in a nonrandomized fashion, showed that the BP reduction was sustained through ≥2 years (Figure 3B). These changes in office BP held true even after censoring for increases in BP (Figure 3C). The procedure is safe, with only 3% (4 of 153) of patients experiencing a complication. Periprocedural complications occurred in 3% (4/153) of patients: 1 renal artery dissection and 3 access site complications. There were 81 patients in the cohort that underwent renal artery imaging at 6 months. None had significant de novo renal artery stenosis and only 1 showed progression of preexisting stenosis.17

The Symplicity HTN-2 was a multicenter (24 sites in Europe, Australia and New Zealand), prospective, randomized controlled study. Patients with treatment RH (SBP ≥160mmHg despite taking ≥3 antihypertensive medications) were randomized 1-to-1 to undergo RSD plus optimal medical therapy or to optimal medical therapy alone. The primary outcome was a change in office BP from baseline to 6 months. Secondary endpoints included acute and chronic procedural safety, com-
Device Therapy for Treatment of HT-N

A total of 530 patients with treatment-resistant HTN (SBP $\geq 160$ mmHg on $\geq 3$ antihypertensive medications, including a diuretic) will be randomized to either RSD plus optimal maximally tolerated antihypertensive medications or control (sham procedure plus optimal maximally tolerated antihypertensive medications). The sham procedure consists of a renal angiogram only. Primary outcomes are change in office BP from baseline to 6 months post-randomization, incidence of major adverse events through 1-month post-randomization and renal artery stenosis at 6 months post-randomization. A major secondary outcome is the change in average 24-h ambulatory BP from baseline to 6 months post-randomization.

Since the development of the Symplicity catheter, a plethora of catheter designs and energy applications have been developed. These additional approaches were developed to address some of the limitations of the early-generation devices. Second-generation devices have resulted in shorter ablation times and more complete ablation while using the lowest possible energy to minimize injury to the vessel. The development of multi-array electrode systems has enabled simultaneous delivery of energy, thus shortening the procedure time and making the technique easier to perform. The 2 platforms of

Figure 3. Change in office blood pressure (BP) in the Symplicity HTN-1 and HTN-2 Trials. (A) Symplicity HTN-1 unadjusted mean change in office BP at 1, 3, 6, 12, 18 and 24 months. (B) Symplicity HTN-1 mean change in office BP adjusted for medication increases post-procedure. (C) Symplicity HTN-2 mean change in office BP. (D) Symplicity HTN-2 mean change in office BP in the initial group and the cross-over group at 6 months after randomization.

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multi-array systems are catheter- and balloon-based. The development of bipolar electrode systems has resulted in lower energy requirements than the unipolar systems. The potential benefit is less injury to the endothelial surface. Alternative low energy sources such as US have the potential to minimize injury to the vessel.

EnligHTN™ This RSD system from St. Jude Medical Inc (St. Paul, MN, USA) consists of a multi-electrode RF ablation catheter and generator. The deflectable atrumatic tip of the catheter comprises a basket holding 4 evenly spaced electrodes at 90°, which allows circumferential ablation (Figure 1B). The RF generator has default settings (power output 6 W, impedance 400 ohms and electrode temperature 75°C) and uses a proprietary temperature-controlled algorithm to deliver the RF energy that produces transmural lesions. Once positioned in the renal artery, the basket is expanded to ensure all 4 electrodes make contact with the arterial wall. The generator is turned on and each electrode is activated for 90 s. Individual electrodes can be turned off. The basket is collapsed, for removal or repositioning for additional ablations. Each electrode creates a transmural lesion that disrupts the nerves, reducing or attenuating SNS activity between the kidney and the brain. There are significant advantages to using a multi-electrode over a single electrode catheter, including a reduction in the number of catheter manipulations and shorter treatment times (90 s vs. 120 s). The shorter treatment time reduces procedural pain and overall procedural time.

The EnligHTN™ RSD system currently has CE Mark approval based on the preliminary results of the ongoing prospective, open-label feasibility study, ARSENAL (Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients). Inclusion and exclusion criteria are similar to those for the Symplicity HTN 3 Trial. Primary outcome measures are all adverse events and office BP at 6 months. Among the 41 patients who have undergone EnligHTN RSD, the 1-, 3- and 6-month mean change in office BP from baseline was –28/–10, –27/–10, –26/–10 mmHg, respectively. In total, 76% of the patients had a ≥10 mmHg reduction in SBP and 33% reached their goal SBP (<140 mmHg). There were no serious complications reported. Minor procedural complications included 4 hematomas, 3 vasovagal responses during manual compression after sheath removal, and 2 transient post-procedural bradycardias.

Vessix™ This RSD system from Boston Scientific Inc (Natick, MA, USA) consists of an over-the-wire low-pressure noncompliant (3 atm) balloon catheter with 8 gold RF electrodes mounted in a helical array on the surface of the balloon and a bipolar generator (Figure 2C). The balloons are sized to accommodate 3–7 mm arteries, enabling treatment of both main and accessory renal arteries. Using a proprietary algorithm, the generator maintains the temperature at 68°C, delivering RF energy simultaneously to all or individual electrodes for a treatment time of 30 s. This fast treatment time mitigates pain for the patients.

The first-in-human pilot study of 13 adult subjects with RH (SBP ≥140 mmHg on ≥3 antihypertensive medications at maximally tolerated doses, including a diuretic) who underwent renal artery denervation (RAD) using the Vessix™ RSD system led to CE mark and Therapeutic Goods Administration approval. No periprocedural complications were reported in the pilot study cohort. REDUCE-HTN (Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter) is an ongoing prospective, open-label, post-market approval, 120-subject study at 24 sites in Europe and Australia. There are no anatomic exclusions. Primary outcome is acute procedural safety and change in office and 24-h ambulatory BP at 6 months from baseline. Secondary outcome is absence of flow-limiting renal artery stenosis at 6 months. Follow-up time is 24 months. Preliminary results from the first-in-human study and the post-market approval study found 1-, 3- and 6-month mean office BP changes from baseline of –24/–13 (n=34), –27/–10 (n=18), and –37/–15 (n=6) mmHg, respectively.

OneShot™ This RSD system from Covidien (Dublin, Ireland [formerly Maya Medical]) is an over-the-wire (0.014-inch), low-pressure (1 atm), noncompliant saline-irrigated RF balloon catheter with a helical silver monopolar electrode mounted on the surface of the balloon, and a RF generator (Figure 2D). There are 3 balloon sizes (5, 6, and 7 mm), which enables treatment of a range of renal arteries, including accessory renal arteries. The spiral RF electrode allows for single RF application of 25–30 W lasting 2 min while the saline irrigation cools and protects nontarget tissue.

To date, the OneShot™ system has been evaluated in 2 small studies: the RHAS Trial (Feasibility study to evaluate the Maya Renal Hypertension Ablation System for chronic HTN) and the RAPID Trial (RAPid Renal SymPathetic De- nervation of Resistant Hypertension Using OneShot™ Abla- tion System). RHAS was a single-center pilot study of 9 subjects with SBP ≥160 mmHg on ≥2 antihypertensive medications or inability to tolerate medical therapy and renal arteries that were 4–7 mm in diameter and with 20-mm treatable length. The primary endpoint was the ability to insert the OneShot™ RSD system into each renal artery and deliver the RF energy. Secondary endpoints were safety and efficacy. Mean BP at baseline, 30 days, and at 3 and 6 months was 185.7/91.3, 176.8/80.2, 184.1/75.5, and 174.9/73.8 mmHg. There were no no adverse events. The RAPID Trial is an ongoing, 50-subject, multicenter single-arm study. Primary endpoints are acute procedural safety and 6-month office SBP reduction compared with baseline. Secondary outcomes are long-term procedural safety and response rate (SBP reduction >10 mmHg) at 6 months compared with baseline.

Electrophysiology Ablation Catheters

There are 2 catheters that are currently being used off-label to perform renal artery ablations: the ThermoCool™ RSD system (Biosense Webster Inc, Diamond Bar, CA, USA) and Chillii II™ (Boston Scientific Inc, San Jose, CA, USA). There are several limitations to their use in RAD because they are large, bulky and designed for the 3-dimensional left atrium rather than the renal artery. Furthermore, they are designed to deliver the higher levels of energy (>10 W) that are required for ablation of the endocardium. Efficacy of ablation at lower energy levels is largely unknown.

ThermoCool™ This RSD system consists of a saline-irrigated tip catheter with 4 electrodes, CoolFlow™ pump and RF generator (Figure 2E). The irrigated tip system provides active cooling of the electrodes, reducing coagulum and char formation.

Saline-irrigated RF catheters specifically designed for RAD do not exist. The first-in-human experience has been described in 10 patients with uncontrolled HTN (SBP ≥140 mmHg on ≥3 antihypertensive medications, including a diuretic) who underwent RAD with an off-the-shelf saline-irrigated electrophysiology ablation catheter. The change in 24-h ambulatory BP at 1, 3, and 6 months was –6/-4, –22/-13 and –21/-11 mmHg, respectively. RELIEF (Renal Sympathetic De-
nervation for Management of Chronic Hypertension) is an ongoing prospective, randomized, single-blinded, controlled study of treatment of patients with uncontrolled HTN (defined as SBP ≥140 mmHg during 24-h ambulatory BP monitoring and on ≥3 antihypertensive medication that includes at least 1 diuretic) using the Celsius ThermoCool® system. The treatment group will undergo catheter-based sympathetic RSD and the control group will undergo renal angiography only. The primary outcome is a change in 24-h ambulatory BP at 6 months from baseline. Secondary outcomes are changes in both office BP and 24-h ambulatory BP up to 12 months from baseline, renal artery dimensions at baseline and 6 months, and creatinine levels at baseline and 6 months.

**Chilli IT™** This system comprises a bipolar, cooled RF ablation catheter with 4 electrodes (Figure 2F). The closed-loop cooling system continuously recirculates fluid through an internal chamber, eliminating the need for the fluid infusion of conventional saline-irrigated RF catheters.

SAVE (Impact of Renal Sympathetic Denervation on Chronic Hypertension) is a prospective, open-label study of treatment of refractory HTN (defined as ≥140/90 mmHg despite treatment with at least 3 antihypertensive medications, including at least one diuretic, or treatment with ≥4 antihypertensive medications) with either the Celsius ThermoCool® or Chilli IT™ ablation catheter. Primary outcome is change in 24-h ambulatory BP at 6 months from baseline. Secondary outcomes are office BP, renal artery dimensions, creatinine level, and antihypertensive medications up to 48 months.

**US Ablation Technology**

Currently, 3 US systems are under development: the PARADISE™ (ReCor Medical Inc, Ronkonkoma, NY, USA), TIVUS™ (CardioSonic Ltd, Tel Aviv, Israel) and Kona Surround Sound™ (Kona Medical Inc, Bellevue, WA, USA). Each system delivers US energy to the wall of the renal artery. With the PARADISE™ and TIVUS™ catheters, this is done percutaneously, whereas the Kona Surround Sound™ system delivers to the adventitia without contacting the vessel wall. Bullfrog® is approved by the Food and Drug Administration for injecting medications into tissues surrounding the blood vessel wall. The catheter consists of a micro-needle (0.9 mm in length and 130 μm in diameter) and a protective balloon that is delivered over an 0.014-inch guide wire through a 6Fr. sheath. As the balloon inflates to approximately 2 atm, the micro-needle is unsheathed and penetrates the vessel wall (Figure 2I). Once fully deployed, the neurotoxin is delivered into the perivascular space through the micro-needle. The catheter is able to deliver 5 ml per injection. The injected agent then diffuses circumferentially around and longitudinally along the vessel.

**Kona Surround Sound™** This system delivers low-intensity, focused US energy from an external transducer (Figure 2H). Safety Evaluation of Renal Denervation Using Focused Therapeutic Ultrasound on Patients With Refractory Hypertension (WAVE I) is an ongoing prospective, single-center, first-in-human feasibility study of the Kona Surround Sound™ in 20 subjects with RH. Primary outcome measure is procedural safety and the secondary outcome measure is BP reduction. Follow-up time is 6 months. For WAVE I, a transducer is positioned posteriorly and the catheter is placed in the renal artery to assist in targeting and tracking. US energy is delivered to the renal nerves.

**Pharmacologic Ablation Technology**

RSD can be accomplished by local delivery of neurotoxic agents such as vincristine, an antineoplastic drug that is also a potent neurotoxic agent and has been studied in swine where local delivery using the Bullfrog® micro-infusion catheter system (Mercator MedSystems Inc, San Leandro, CA, USA) resulted in successful chemical denervation of the renal artery.29 Bullfrog® This micro-infusion catheter is designed to inject therapeutic agents directly through blood vessel walls into the perivascular space. Bullfrog® is approved by the Food and Drug Administration for injecting medications into tissues surrounding the blood vessel wall. The catheter consists of a needle that is unsheathed and penetrates the vessel wall (Figure 2H). Once fully deployed, the neurotoxin is delivered into the perivascular space through the micro-needle. The catheter is able to deliver 5 μl per injection. The injected agent then diffuses circumferentially around and longitudinally along the vessel.

Alternate approaches to neuromodulation have been developed, including BAT, VNS and SCS. These approaches may directly compete for similar populations as RSD, but also may be useful in patients who are either not candidates for RSD or who fail RSD. Alternatively, these therapies might be used in tandem with RSD. Common reasons making patients ineligible include renal artery stenosis, prior renal artery intervention and renal artery anatomy that precludes treatment. The percent of nonresponders (defined as BP reduction <10 mmHg) after RSD has been reported to be 13% in Symplicity HTN-117 and 16% in Symplicity HTN-2.18 Predictors of nonresponders to RSD have not yet been identified. It is possible these patients fail to reach the therapeutic threshold of sympathetic denervation. Alternatively, sympathetic hyperactivity is not the cause of their HTN. At 2 years, 8% of patients from Symplicity HTN-1 were nonresponders;17 10% of patients (5 of 50 patients enrolled) in Symplicity HTN-1 and 16% (30 of 190 screened) in Symplicity HTN-2 were excluded for anatomic reasons.

**Baroreflex Activation Therapy**

Arterial baroreceptors in the carotid sinus and aortic arch provide afferent signals to the cardio regulatory and vasomotor centers in the medulla oblongata that control the sympathetic drive to the heart and peripheral vasculature. Increased BP stretches the carotid arteries and aorta, causing the baroreceptors to increase their basal rate of output to the brain stem. As a result, there is decreased sympathetic stimulation to the heart and blood vessels, lowering the heart rate, decreasing stroke volume and increasing vasodilation and thus, lowering BP. In
mal 6 volts is reached.

The Phase II Rheos™ Feasibility Trial was done at 5 centers in the USA. The device was successfully implanted in 10 subjects with RH and demonstrated an acute decrease in BP without significant morbidity. The DEBuT-HT (Device Based Therapy in Hypertension Trial) was a multicenter, prospective, nonrandomized feasibility study at 9 centers in Europe to test the safety and efficacy of the Rheos™ system in 45 subjects with RH (SBP ≥160 mmHg or diastolic ≥90 mmHg despite at least 3 antihypertensive medications). Subjects were followed up to 2 years. After 3 months of therapy, there was a statistically significant mean reduction in office BP from baseline, which improved at 1 year and was sustained at 2 years (Figure 4A). A similar reduction in ambulatory BP was observed (Figure 4B).

A substudy of the DEBU-HT study demonstrated chronic baroreceptor stimulation causes a sustained change in heart rate variability and heart rate turbulence, consistent with inhibition of sympathetic and activation of parasympathetic activity. These changes correlate with changes in BP. Additionally, muscle SNS activity has been shown to correlate with BP changes in subjects undergoing baroreceptor stimulation. Muscle sympathetic nerve activity decreased and increased in tandem with systolic, diastolic and mean arterial BP when the baroreceptor stimulation was turned on and off. The Rheos™

**Rheos™**

This baroreflex hypertension therapy system (CVRx, Minneapolis, MN, USA) is a first-generation device consisting of bilateral perivascular carotid sinus leads, implantable battery-powered pulse generator and an external programmer system (Figure 2J). Through a surgical incision, the carotid bifurcation is mobilized circumferentially. The electrode is placed on the carotid sinus and repositioned to attain maximal hemodynamic response when the electrode is tested. Once optimal location is determined, the electrode is sutured in place. The procedure is then repeated on the contralateral side. Following electrode placement, the pulse generator is placed in an infraclavicular subcutaneous pocket and the leads are tunneled and connected similarly to pacemaker placement. The device is then programmed to deliver 1–6 volts. The voltage is increased incrementally until the desired SBP is achieved or the maximum 6 volts is reached.

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**Figure 4.** Baroreceptor activation therapy trial. (A) Rheos™ Feasibility Trial office blood pressure (BP) at 1 year. (B) Rheos™ Feasibility Trial office BP at 24 months. (C) Long-term follow-up patients in the Rheos™ Feasibility Trial. (D) Mean change in office BP and heart rate in the Barostim™ neo Trial.
Pivotal Trial was a randomized, double-blinded, parallel-design study to assess the efficacy and safety of the Rheos™ system in 265 subjects with RH (SBP ≥160 mmHg with diastolic ≥80 mmHg or an average 24-h ambulatory SBP ≥135 mmHg despite ≥3 antihypertensive medications). All subjects underwent device implantation 1 month prior to randomization. They were then randomized in a 2:1 fashion to have the device “ON” (Group A) or “OFF” (Group B). At 6 months those in the device “OFF” group had their device turned “ON”. All subjects were followed for 12 months. Primary endpoints included acute efficacy (responder rate at 6 months), sustained efficacy (responder rate at 12 months), procedural safety, BAT safety, and device safety. The trial did not meet 2 of the 5 prespecified primary endpoints for acute responders or procedural safety. At 6 months, there was no difference between the groups for responders. However, compared with the pre-implant baseline, mean reductions in SBP up to 33 mmHg were observed at 12 months in both groups, with over half achieving SBP ≤140 mmHg. There were 68 (25%) procedural-related events: surgical complications (n=13), nerve injury with residual deficit (n=13), transient nerve injury (n=13), respiratory complication (n=7) and wound complication (n=7).6,36

Following completion of the randomized Rheos™ Pivotal Trial, the subjects participated in an open-label, nonrandomized follow-up to assess safety of BAT. Clinically significant responders were defined as goal SBP ≤140 mmHg or ≤130 mmHg with diabetes or renal disease or SBP decrease by ≥20 mmHg after device activation. Of the 322 patients who were implanted with the device, 76% (n=245) were responders with a mean BP reduction of −35/16 mmHg, and 55% achieved their goal BP. Although this trial did not meet all the prespecified endpoints, long-term follow-up showed a mean reduction in BP from baseline at 6 months in group A (BAT “ON”) and in both groups (A [BAT “ON”], B [BAT “OFF”]) at 12 months. Additionally, patients in the Roll-In group (BAT “ON”) had a significant reduction in BP (Figure 4C).37

Barostim neo™

Barostim neo™ (CVRx, Minneapolis, MN, USA) is a second-generation device developed for BAT and consists of a single lead implanted on the right carotid artery, an implantable pulse generator and a programmable system that is surgically implanted similar to the Rheos™ device. The lead and generator have a smaller profile than the first-generation system (Figures 2J, K). The modified implant procedure requires unilateral carotid sinus exposure only via a small incision (2.5–5 cm) and exposure of the carotid sinus though dissection of the internal carotid artery only. The lead is sutured directly to the carotid sinus, compared with the Rheos™ which requires exposure of the carotid bifurcation circumferentially and the lead completely encompasses the carotid artery.31

The Barostim neo™ Study was a single-arm, open-label study of 30 patients with RH (SBP ≥140 mmHg despite treatment with ≥3 antihypertensive medications, including 1 diuretic) who underwent baroreflex activation using this second-generation device at 7 centers in Europe and Canada. Similar efficacy to earlier studies was seen, with a mean reduction in BP from baseline at 6 months of −26.0/12.5 mmHg. The safety profile is similar to that of pacemaker implantation. Three minor procedural-related complications occurred within 30 days of implant: 1 device pocket hematoma, 1 self-inflicted wound complication and discomfort at the generator implant site.38 Based on these findings, CVRx received a CE Mark Approval for treatment of HTN. The European HTN Registry has been established to evaluate long-term outcomes.

The Barostim neo™ Hypertension Pivotal Trial is an ongoing multicenter (USA), prospective, randomized controlled trial to test the safety and efficacy of BAT using the Barostim neo™ system. An estimated 310 patients with RH (SBP ≥160 mmHg despite ≥4 maximally tolerated antihypertensive medications, including 1 diuretic for at least 4 weeks prior to screening) will be randomized in a 1:1 ratio to receive BAT plus medical therapy or medical therapy alone. Subjects who previously underwent RAD are eligible. Primary outcomes are procedural-related complications through 30 days and a change in office BP from baseline at 3 months. Secondary outcomes are change in office and 24-h ambulatory BPs from baseline at 6 months.

In addition to the effects of device-based neuromodulation on BP, there are substantial effects on cardiovascular structure and function, metabolism (including OSA and glucose control) and clinical outcomes in patients with CHF.

Neuromodulatory Therapies for Treatment of HF

In HF, there is an imbalance in the ANS, resulting in an increase in sympathetic activity and a decrease in parasympathetic activity. The current clinical therapy targeting the ANS in patients with HF includes β- and α-adrenergic agents. To date, there are 2 therapies that have been developed for treatment of HF (VNS and SCS). Comprehensive discussion of neuromodulation device therapy is beyond the scope of this review, but a brief overview of the devices and ongoing clinical trials will be described.

Vagus Nerve Stimulation

CardioFit™

The first-in-human experience of VNS for treatment of HF using the CardioFit™ System (BioControl Medical, Yehud, Israel) showed the feasibility of VNS in HF patients.39 This system consists of a stimulator, an intracardiac sensing electrode and a vagal electrode (Figure 2L). The CardioFit Trial is a small, phase II, nonrandomized study that enrolled 32 patients with HF who showed improvement in LV ejection fraction (EF) and NYHA symptoms at 6 months. Results were maintained out to 1 year.40 Increase Of Vagal Tone in CHF (INOVATE-HF) is an ongoing multicenter randomized controlled trial studying the safety and efficacy of CardioFit™ VNS for the treatment of patients with HF.41 Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF) is an ongoing phase II randomized controlled double-blind multicenter trial studying the safety and efficacy of VNS for treatment of HF using the Boston Scientific VNS System, which consists of a pulse generator and a vagal electrode.

SCS

The SCS systems consist of an implantable pulse generator and multiple leads. Each lead has electrodes on the distal tip. The pulse generator is placed in the abdomen or paraspinous region and the leads are placed in the thoracic epidural space. Electrical impulses activate specific nerve fibers.

There are 2 ongoing Phase II clinical trials of SCS in patients with advanced HF. Determining the Feasibility of spinal Cord Neuromodulation for Treatment of Chronic HF (Defeat-HF) is a randomized controlled, multicenter trial in Europe and the USA to determine the safety and efficacy of SCS for the treatment of advanced HF using the PrimeAdvanced™ Neurostimulator (Medtronic, Inc, Minneapolis, MN, USA). Spinal Cord Stimulation For HF (SCS HEART) is a smaller, nonrandomized open-label feasibility study in Australia and...
Hong Kong to determine the safety and efficacy of SCS using the St. Jude Medical SCS system (St. Paul, MN, USA).

BAT

Initial human trials looking at BAT for the treatment of both diastolic and systolic HF are underway. The Rheos™ Diastolic HF Trial is a prospective, randomized, double-blind trial assessing the safety and efficacy of treatment of diastolic HF in 60 subjects using the Rheos™ BAT System. Enrollment is complete but the results are not yet published. The Barostim HOPE4HF Trial is an ongoing prospective, randomized controlled trial in the USA for the safety and efficacy of treating patients with systolic HF using the second-generation Barostim neo™BAT system. The Barostim neo System in the Treatment of HF is the ongoing trial in Canada and Europe.

Effects of RSD and BAT on Cardiac Structure and Function

LVH is associated with significant cardiovascular morbidity and mortality. Furthermore, LVH regression has been correlated with improved outcome. The effect of RAD on LVH and diastolic function was studied in 46 patients with RH undergoing RSD as part of or an extension of the Symplicity HTN-2 trial. RAD was associated with a decrease in LV mass by 13% after just 1 month of treatment, and 17% after 6 months of treatment. These changes in LV mass caused the incidence of LVH to fall from 63% at baseline to 33% at 6 months after RAD; however, the average LV mass for the patients treated with RAD did not reach normal and some patients did not show regression of LVH. By contrast, LV mass tended to increase in the control group (Figures 5A, B). Of note, patients without LVH at baseline had no significant decrease in LV mass (ie, atrophy did not occur). A similar reduction in LV mass (of 18%) has been described in a subgroup analysis of 34 subjects from the DEBuT-HT study undergoing BAT. Because a number of pharmaceutical-based clinical trials have shown that regression of LVH has lead to an improved prognosis, it is anticipated that LVH regression induced by either RAD or BAT will also be associated with a reduction in mortal and morbid events; however, to date this remains an unproven hypothesis.

Additionally, an improvement in diastolic function was observed in those subjects who underwent RSD, in contrast to a trend towards worsening diastolic function in control subjects. RAD was associated with an improvement in LV diastolic function.
function as measured by Doppler indices of LV filling and lengthening (increased mitral annular S’ and E’) and by a reduction in the left atrial dimensions (Figures 5C,D). By contrast, these measures of diastolic function became more abnormal in the control group. Taken together, these changes suggest that there was a decrease in both left atrial and LV diastolic pressures. This effect is further substantiated by a 39% reduction in NT-proBNP, compared with only an 8% reduction in the control group.32

Metabolic Effects of RSD

In addition to HTN, increased sympathetic drive is integral to the pathophysiology of other clinical conditions such as IR and OSA. Furthermore, HTN is frequently associated with these conditions, often manifested as metabolic syndrome (MetS). The benefit of RSD may not be limited to lowering BP. It is conceivable that patients with RH and comorbid disease such as MetS and OSA could have additional benefits from RSD.

Glucose Metabolism

HTN is frequently associated with metabolic disorders such as obesity and impaired glucose metabolism or IR. Sympathetic overdrive has been identified as an important contributor to both IR and MetS.44 In addition to lowering BP, RAD has been shown to improve glucose metabolism and insulin sensitivity. In a pilot study (n=50), Mahfoud et al observed reductions in fasting glucose, insulin and c-peptide levels, as well as 2-h glucose levels, during an oral glucose tolerance test at 3 months compared with baseline in 37 patients who underwent RAD for RH. These reductions in metabolic markers did not correlate with reductions in BP. No changes were observed in the 13 control subjects.45 These results show promise that RSD may provide additional benefits of improved glucose metabolism in patients with RH, but further studies are needed before this can be used as an alternative therapy for glucose metabolism or IR.

OSA

OSA is highly prevalent in RH and is associated with increased SNS activity.46 In patients with RH and OSA, RAD has been shown to both lower BP and improve the severity of OSA. In a proof-of-concept study by Witokowski et al, a reduction in the apnea-hypopnea index (reduction in apneic events and decrease in oxygen desaturation index) and in Epworth Sleepiness Scale scores was observed in 8 of 10 patients who underwent RSD for RH.47 That study’s results suggest that RSD may provide a potential benefit for patients with RH and OSA, but larger studies are needed before generalized application of this therapy.

Mechanisms of Action

It seems likely that both a decrease in LV myocardial load and a decrease in activation of the SNS contribute to these outcomes for the following reasons. First, the decrease in LV mass at 1 month after RAD was faster and larger than in any previous study in which a pressure-overload state (HTN or aortic stenosis) was removed. Second, even in the 6 patients treated with RAD who did not have a decrease in BP, there was a significant decrease in LV mass. Third, the extent to which RAD caused LV mass regression after 6 months was greater than might have been predicted based on previous pharmacologic studies. For example, on average, drug treatment results in a 10% decrease in LV mass, whereas RAD caused a 17% decrease despite comparable decreases in BP (14% and 15%, respectively).7-10 It also seems likely that RAD caused the dramatic improvement in LV diastolic function through interdependent mechanisms that include regression of LVH, lowering of systolic arterial load, and alterations in sympathetic activation.

Patient Selection

Current data suggest that patients across the spectrum of HHD may represent reasonable target populations. Patients include those with refractory HTN, those with hypertensive LVH and those with HTN-induced HF. Even patients with HTN that is not refractory to drug treatment may be future candidates. In each of these patient groups, autonomic modulation could reduce the cost of treatment and improve patient compliance. All HHD patients with HF, regardless of their EF, may benefit. Caution should probably be applied to patients with HF and a reduced EF, restricting therapy to those with SBP >115 mmHg. One particularly appropriate application is HHD patients with HF and a preserved EF; for this group of HF patients, there is no current guideline based therapy to reduce morbidity and mortality. Neuromodulation will cause regression of LVH and improvement in diastolic function; the mechanisms responsible for these effects include both reduced LV load and the change in autonomic modulation itself. Autonomic modulation strategies hold enormous promise for the treatment of patients with HHD.

Conclusions

HTN represents a major health concern because of its contribution to cardiovascular morbidity and mortality. Treatment of RH remains a challenge, despite advances in antihypertensive medical therapy. The integral role of SNS in the pathophysiology of HTN has allowed for development of novel device-based therapies.

RAD and BAT are promising therapies. The first-generation RF ablation catheter, Symplicity, has been shown to be safe and effective with sustained results. Preliminary data using second-generation RF catheters and US ablation catheters show these devices to be promising. Most of the studies to date are small and nonrandomized. Although the results are promising, larger randomized clinical trials are needed to confirm procedural safety and durability.

BAT appears to be a viable option for treatment of patients with RH. The Rhoes™ Pivotal Trial was a negative trial and failed to meet 2 of the 5 prespecified endpoints for procedural safety and acute efficacy. Preliminary data for improved second-generation device are promising. Procedural safety and efficacy are being further examined in an ongoing large randomized clinical trial in the USA and European registry.

The sequelae of uncontrolled HTN include LVH and diastolic dysfunction, which are associated with significant morbidity and mortality. Regression of LVH with improved diastolic function has been observed in patients who have undergone RAD and BAT. Whether this will translate to improved cardiovascular outcomes is unknown and further studies are needed.

Pathologic sympathetic activation has been implicated in conditions such as glucose intolerance or IR, obesity and OSA. Moreover, these are frequent comorbid conditions with RH. Preliminary data suggest potential benefits of improved glucose metabolism and insulin sensitivity and improved sleep apnea severity in addition to the BP lowering effect of RAD.
Disclosures
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