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CAROTID BARORECEPTOR STIMULATION AND ARTERIOVENOUS SHUNTS FOR RESISTANT HYPERTENSION

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Abstract

Pharmacologic therapy for hypertension is effective for the majority of patients with hypertension, but there is a subset of the population with treatment-resistant hypertension who cannot achieve their blood pressure goal despite taking multiple medications. Since these patients are at increased risk of cardiovascular disease and end-organ damage, additional therapies must be considered. This review discusses several novel interventional therapies— including baroreflex activation therapy, baroreceptor stenting, and creation of an arteriovenous shunt—that may provide alternative options for blood pressure control in those with treatment-resistant hypertension. All of these therapies remain investigational, and each has its own strengths and weaknesses that will be critical to assess as they come to market.

Introduction

Hypertension (HTN) affects upwards of 25% of the adult population, and its incidence continues to increase.[1] This prevalent disease leads to a myriad of devastating conditions including myocardial infarction, cardiomyopathy, renal failure, and stroke. While there are many common and generally well-tolerated pharmacotherapies that are used to treat HTN, a subset of the hypertensive population is resistant to treatment. In these patients, treatment-resistant hypertension (TRH) is defined as blood pressure (BP) above goal despite the concurrent use of three medications of different classes, one of which is a diuretic, at maximally tolerated doses.[2] The characterization of TRH is important because it identifies a population at three-times the risk of experiencing adverse cardiovascular outcomes compared to those with treatment-responsive hypertension.[3] These patients might benefit from additional evaluation and possibly nonpharmacologic therapeutic measures.

The prevalence of TRH has been estimated to be between 20% and 30% of hypertensive patients.[2] Some authors have proposed that factors such as medication noncompliance, untreated obstructive sleep apnea, white-coat hypertension, and undiagnosed secondary causes of hypertension (rather than essential hypertension) contribute to the high prevalence of TRH, and that treating these factors would decrease the number of patients with true TRH.[4] The myriad explanations for uncontrolled hypertension highlights the need to treat each patient with a personalized and thoughtful approach.

Despite great advances in pharmacologic management, there unfortunately are still patients with true TRH. Some of these patients may have a relative hyperactivity of the sympathetic branch of the autonomic nervous system. In addition to the above pharmacologic agents, there have been experimental invasive approaches targeting the overactive sympathetic system in this population. Surgical sympathectomy was initially pioneered in the 1930s and is a procedure in which the sympathetic ganglia are surgically severed. The original goal of the operation was to reduce vasoconstrictive effects of the sympathetic nervous system and thus improve circulation in patients with peripheral vascular disease. The technique was subsequently used on patients with malignant hypertension with some success, but it carried significant morbidity including impotence, severe orthostatic hypotension, and incontinence. Due to this high degree of morbidity, the technique was largely abandoned for treatment of hypertension.[5-10] More recently, percutaneous approaches to modulating the sympathetic nervous system have shown potential for reducing hypertension without such severe and intolerable side effects. This review will discuss baroreflex activation therapy (BAT) via an implantable carotid sinus stimulator, BAT via carotid stenting, and creation of a percutaneous arteriovenous (AV) shunt. The topic of renal nerve denervation is addressed by Denker and Cohen in this issue (page 240).

Trial Data on Baroreflex Activation Therapy

Carotid baroreceptors decrease sympathetic outflow and increase vagal tone, thus resulting in a reduction of BP (Figure 1). Iatrogenic carotid baroreceptor activation has shown to be achievable through local pulsatile electrical stimulation of the baroreceptors in a dog model.[11] Results from this animal model demonstrated a promising reduction in BP with baroreflex activation, and an implantable device was subsequently developed for human use with the goal to achieve long-term BP control in humans through ongoing pulsatile baroreceptor stimulation.

DEBuT-HT

The first trial evaluating BAT in humans with a long-term implantable device was the DEBuT-HT trial (Device-Based Therapy in Hypertension Trial),[12] which used the Rheos® Baroreflex Hypertension Therapy device (CVRx, Inc., Minneapolis, MN) (Figure 2, left) to assess feasibility of BAT for human use. This device was similar in size to a pacemaker, with a pulse generator displacing 43.4 cc implanted in the pectoralis region. The device has two leads that are tunneled from the generator to the bilateral

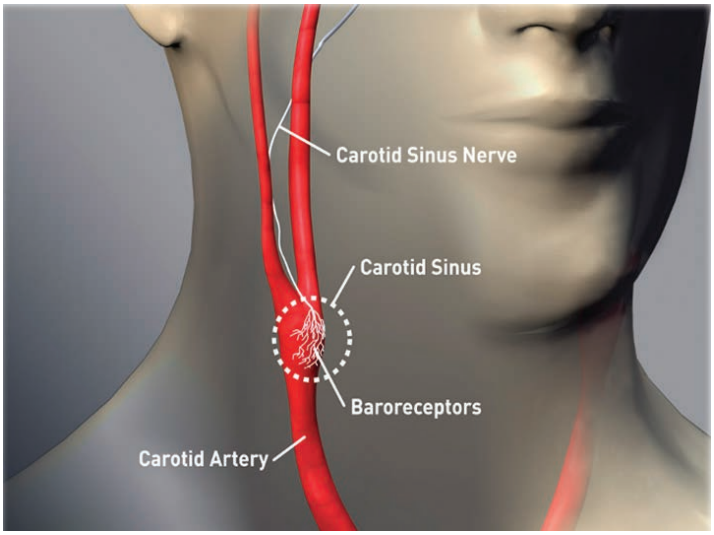

Figure 1. Graphic of how carotid baroreceptors reduce blood pressure by decreasing sympathetic outflow and increasing vagal tone.

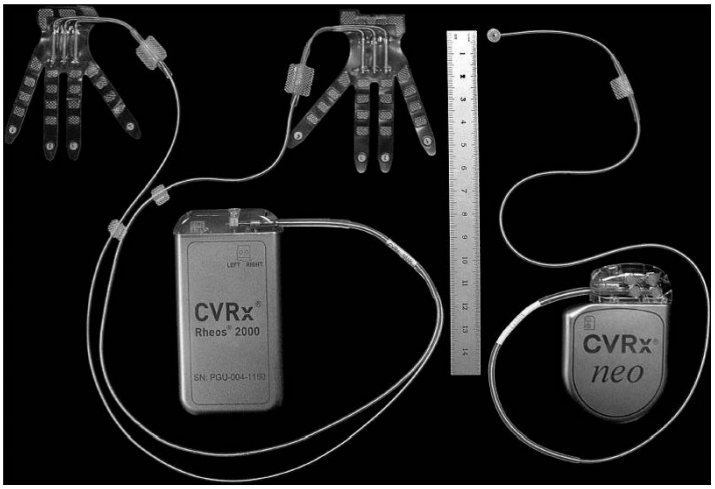

Figure 2. Left: The Rheos® Baroreflex Hypertension Therapy device (CVRx, Inc., Minneapolis, MN) used in the DEBuT-HT trial to assess feasibility of BAT for human use. Right: The CVRx Barostim *neo*™ second-generation device that improved on the Rheos device by decreasing the pulse generator size.

carotid bulbs. On the end of the leads are electrical stimulators each with four finger-like projections designed to wrap around the bilateral carotid bulbs. To achieve correct placement, surgical exposure of the carotid bulbs was necessary. DEBuT-HT enrolled 45 patients with TRH. Patients were followed for 3 months and then annually for 2 years. DEBuT-HT was not placebo controlled and was primarily designed to test safety of the system, though efficacy was assessed as well. There was a large reported reduction in BP, with mean BP reduced by 21/12 mm Hg at 3 months, 30/20 mm Hg at 1 year, and 33/22 mm Hg at 2 years. As part of the follow-up visits, the investigators temporarily turned off the device in clinic and reported that BP values increased to baseline almost immediately. Reinitiation of therapy rapidly reestablished the antihypertensive effect.

Rheos Pivotal Trial

The promising results of DEBuT-HT led to the Rheos Pivotal Trial, a large-scale, double-blind, randomized, placebo-controlled trial that used the same CVRx Rheos® device in 265 patients with TRH.[13] The trial had similar inclusion criteria, although the BP cut off for resistant HTN was > 160/80 rather than > 160/90, and patients were also required to have an ambulatory SBP > 135 averaged over 24 hours. This additional ambulatory BP criterion was evaluated at a core laboratory and excluded patients who had orthostatic hypotension. All of the patients in the Rheos Pivotal Trial received the Rheos device (CVRx®, Inc., Minneapolis, MN) and were randomized to receive either BAT for the first 6 months or delayed BAT initiation after the 6-month visit. The trial evaluated five prespecified primary end points; two of these were efficacy end points (acute efficacy and sustained efficacy), and the other three were safety end points (procedural, BAT, and device safety). While the trial did not meet the primary acute efficacy and procedural safety end points, it did meet the other safety and efficacy end points and also showed improvements in prespecified secondary end points of reducing mean change in office-based SBP as well as comparison of immediate versus delayed BAT. These results led to significant advancements in BAT that were implemented in subsequent trials.

The Rheos Pivotal trial design included two "roll-in" implantations at each study site to account for the learning curve associated with the technical procedure before enrolling their first study patient. The primary reasons for study exclusion were inappropriately low BP readings, carotid artery disease, or inappropriate surgical candidacy. Once the pulse generator was turned on, the BAT was increased in a consistent protocol-driven fashion, with optimal therapy targeted for the fifth month of active therapy.

Nonsignificant primary results of the Rheos Pivotal trial included the acute efficacy end point and the procedural safety end point. For acute efficacy, 54% of patients in the active therapy group showed more than a 10-point drop in SBP at 6 months compared to 46% in the control arm. This was less than the predefined 20% superiority margin. For procedural safety, the end point was defined as > 82% procedure-related adverse event-free rate within 30 days of implantation based on the rate seen in similar device implantations. The actual procedural event-free rate was 74.8%, which was closer to the procedural event-free rate of open carotid endarterectomy. Given the surgical exposure of the carotid bulb during BAT implantation, carotid endarterectomy might be a more similar risk procedure than pacemaker implantation.

Significant primary results included a sustained reduction in BP. Of the patients who achieved at least a 10 mm Hg reduction in BP at 6 months, 88% continued to have at least 50% of that reduction at 12-month follow-up. The other safety end points including BAT and device-specific safety were both met. Secondary end point analysis showed an interesting pattern in mean change in SBP. At 6 months, the active BAT group had a mean decrease in SBP of 16 +/- 29 mm Hg that was not significantly different from the control group, who had a mean decrease of 9 +/- 29 mm Hg. At 1 year, both the immediate and delayed groups showed a mean reduction in BP of 25 mm Hg. This was surprising given that the delayed group only had active BAT treatment for 6 months and had already achieved greater mean reduction in SBP than the immediate treatment group. Possible explanations for this include an initial drop in BP across groups between study enrollment and randomization, and general improvement in compliance and monitoring seen with patients enrolled in a research study compared to regular practice.

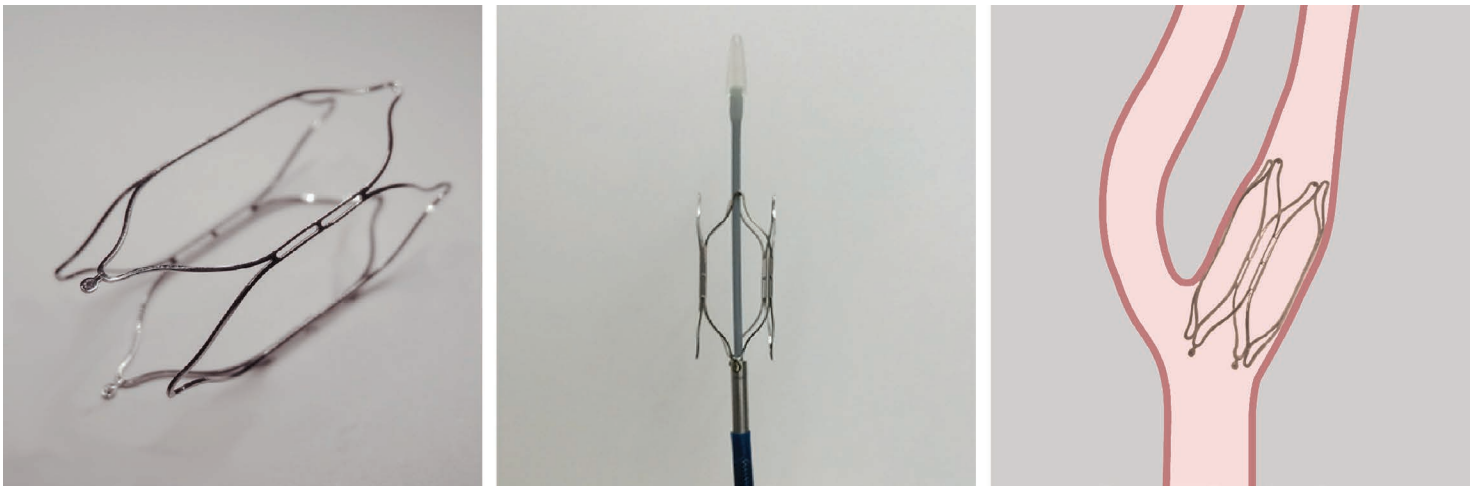

Figure 3. The MobiusHD™ implant (Vascular Dynamics, Inc., Mountain View, CA) is designed to reshape the carotid sinus in the diastolic phase and prevent migration in the systolic phase.

Long-Term Rheos Pivotal Follow-Up

Overall, 88% of the patients from the Rheos Pivotal Trial were determined to be responders to BAT after 12 months as demonstrated by either a reduction in SBP to < 140 mm Hg (< 130 with diabetes or renal disease) or a clinically significant increase in SBP after deactivating the device (increase in SBP of > 20 or a hypertensive crisis requiring overnight hospitalization with SBP > 220.[14] These patients were followed for an additional 22 to 53 months and showed continued reduction in SBP of > 30 mm Hg throughout the follow-up period. They also had a reduction in the average number of antihypertensive drugs used—from 5.3 +/- 1.9 to 4.7 +/- 2.1 drugs. It is important to note that investigators in the original trial had prespecified device modulation, whereas investigators in the follow-up trial were allowed to use additional programming settings to further tailor therapies to individual patients.

Rheos Pivotal Trial at Five-Year Follow-Up

After the long-term Rheos Pivotal Trial follow-up, patients who were confirmed responders continued to be followed. As of the most recent follow-up,[15] there were 216 total patients who continued to receive active BAT, with 40 patients receiving at least 5 years of follow-up and 207 receiving at least 3 years. In this group of initial responders, SBP continued to be significantly reduced compared to baseline by a mean of > 30 mm Hg and diastolic BP was reduced by a mean of > 16 mm Hg. Overall system- and procedural-related complications after a year of therapy were reported as 0.037 per patient year.

Barostim Neo *Trial*

The Barostim *neo*™ (CVRx®, Inc., Minneapolis, MN) is a second-generation device that improved on the original Rheos device by decreasing the size of the pulse generator (< 40 cc displacement vs 43.4 cc) (Figure 2, right) and reducing the number of required electrodes from two leads with 4 projections/lead to just one lead with a single-button electrode. As an additional improvement, the neo device has one-sided implantation with the single-button electrode sutured to the carotid sinus, whereas the original device required wrapping the bilateral carotid bulbs with electrodes. The advantage is that the neck dissection is less extensive and does not require exposure of the external carotid artery. The reduction from bilateral to unilateral stimulation was based on data from the original Rheos trial showing that about 75% of the devices were programmed to unilateral stimulation without a decrease in efficacy compared to bilateral stimulation.

The Barostim *neo* trial was a single-arm open-label study utilizing the new, smaller Barostim *neo* device in patients with TRH.[16] Notably, the investigators required stable medical therapy for at least 4 weeks with baseline BP determined by averaging two BP readings at least 24 hours apart. After device implantation, there was a 2-week delay before initiating BAT. The BAT was then individually titrated for optimal response rather than administered in a uniform fashion. Outcomes were assessed after 6 months of treatment and were compared to a baseline BP measured before implantation and treatment, which was the same baseline used in the Rheos Pivotal Trial. Interestingly, the postimplantation pretreatment SBP had already dropped by about 11 points. According to the study analysis, average BP reduction at 3 months was 26 mm Hg, which remained stable at 6 months. The percentage of patients reaching goal SBP of < 140 was 43% at 6 months of treatment.

Carotid Nitinol Stent (MobiusHD™)

Given the BP response seen in the BAT trials, the MobiusHD™ device (Vascular Dynamics, Inc, Mountain View, CA) was created to target the baroreflex through a different approach (Figure 3). Rather than electrical stimulation, the MobiusHD activates the baroreceptor by causing stretch of the carotid sinus. In contrast to traditional carotid stents used for carotid artery stenosis, this stent has fewer struts and a square shape, which leads to more pulsatile stretch on the carotid bulb and hopefully more long-term reduction in BP. The device is currently enrolling patients in a phase I trial to assess safety in humans.[17]

Arteriovenous Shunt (ROX Coupler)

Another device undergoing investigation is an arteriovenous (AV) coupler (ROX Anastomotic Coupler device, ROX Medical, San Clemente, CA) (Figure 4). In contrast to RDN and BAT, which target the overactive sympathetic nervous system, this device directly decreases resistance by creating a central iliac AV shunt. The concept that an AV shunt leads to lower BP is not new and has long been seen with both traumatic and surgical AV shunts such as those used for hemodialysis access. With shunt creation, there is an immediate reduction in systemic resistance, increase in venous

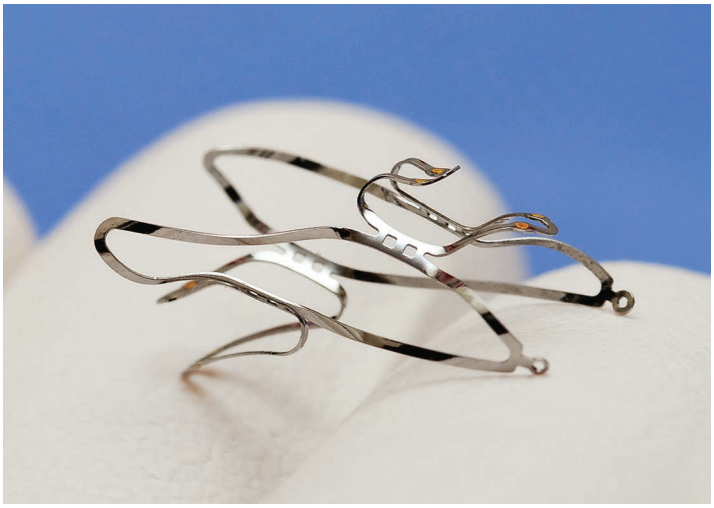

Figure 4. Currently under investigation, the ROX Anastomotic Coupler device (ROX Medical, San Clemente, CA) directly decreases resistance by creating a central iliac arteriovenous shunt.

return, and subsequent increase in cardiac output. Early studies on shunt creation for dialysis access documented that high-output cardiac failure can develop with excessive shunt flow, which necessitates either banding or ligation of the shunt.[18,19]

With the ROX Coupler system, the device is first introduced percutaneously. Once a shunt is created to connect the iliac artery and vein, the device is then implanted to keep the shunt patent. At 4 mm in size, the shunt ideally should be large enough not to close spontaneously but small enough to avoid potential high flow rates that could lead to high-output cardiac failure.[20] The initial safety and efficacy study on the device was done in 15 patients with chronic obstructive pulmonary disease (COPD), with the therapeutic target actually being improvement in functional capacity rather than change in BP. The study found no improvement in functional capacity and a significant number of adverse events, such as lower extremity edema, venous stasis, right heart failure, and deep venous thrombosis. Due to these adverse events, the fistula needed to be closed in 8 of the 15 patients at an average of 398 days after creation.[21] A subsequent study with AV fistula formation was undertaken in 24 patients with COPD and systolic BP greater than 130, with change in BP as the primary outcome. This study did find a reduction in BP of 13/19 mm Hg at 1 year after shunt creation.[20]

The ROX CONTROL HTN study was a prospective randomized controlled trial of patients with TRH.[22] Of the 77 total patients, 42 were randomized to undergo AV shunt formation with the ROX Coupler device while 35 were randomized to control. Notably, the control group did not undergo a sham procedure but did continue medical therapy alone. Patients were followed out to 6 months postprocedure, at which time the mean reduction in office BP for the device group was 23.2/17.7 mm Hg and mean reduction in ambulatory BP was 13/13.4 mm Hg. The device appeared to be better tolerated in patients with COPD than in the prior two studies, but 28 procedure- or device-related complications were reported. The authors noted that the most frequent event was venous stasis (28.6% of patients) but that all complications resolved or were treated without long-term sequelae.

Discussion

Each of the aforementioned devices has the potential to change the way treatment resistant hypertension is managed and offers the possibility of tremendous clinical benefit. However, there are still hurdles to overcome for each technique. While the BAT procedure with the Barostim *neo* device has demonstrated instant efficacy when it is activated, there is a downside in that it requires office-based monitoring, adjustment, and repeat procedures for battery changes, all of which is impacted by compliance in the real world. The neck dissection, which is the greatest risk of the Barostim implantation, may become less risky with the advent of the smaller single-lead Barostim *neo* device.

In contrast, the MobiusHD stent could provide assured compliance in a low-risk procedure. It does carry the irreversible nature seen with RDN and is still in the early investigational stage. Finally, creation of an AV shunt is an interesting approach in the field of device-based treatment of hypertension. It takes the individual variation in sympathetic nervous system out of the equation, and it assures compliance since it is a permanent implant. The results, however, are not yet proven over the long-term. It will also be important to see the rate of late vascular complications after AV fistula formation especially given the early trial experience in patients with COPD.

Conclusions

Despite significant advances in medical therapy, TRH continues to be a challenging entity to treat and unfortunately carries an increased risk of significant cardiovascular disease. For those patients in whom medical therapy is inadequate, interventional therapy offers a possible supporting role. All of the aforementioned therapies offer exciting possibilities of future options, though at this time they continue to be investigational. The true test will be whether they can demonstrate significant improvement in long-term BP control and downstream reduction in overall cardiovascular mortality without significant morbidity or mortality related to the procedure or device.

Conflict of Interest Disclosure: Dr. Gassler is a consultant for Vertex Pharmaceuticals, and Dr. Bisognano is a consultant for CVRx, which also provides grant support.

Keywords: treatment-resistant hypertension, baroreflex activation therapy, Rheos Pivotal Trial, carotid nitinol stent, arteriovenous shunt

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