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NOVEL THERAPY

Carotid Baroreceptor Stimulation for Resistant Hypertension

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ABSTRACT

Pharmacologic therapy for hypertension is effective for the majority of patients with hypertension, but there remains a subset of the population with treatment resistant hypertension who cannot achieve their blood pressure (BP) goal despite multiple medications. For these patients at increased risk of cardiovascular disease and end-organ damage, additional therapies need to be considered. This review will cover a non-pharmacologic approach to hypertension through stimulation of the Baroreflex (Baroreflex activation therapy). While Baroreflex therapy remains investigational at this time, for patients with treatment resistant hypertension, this therapy may offer a novel option to achieve BP goals and hopefully reduce the risk of heart attack and stroke.

Keywords: Baroreflex activation therapy, Carotid baroreceptor, Treatment resistant hypertension.

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INTRODUCTION

Hypertension (HTN) affects upward 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. There are many common, generally well-tolerated pharmacotherapies that are utilized in the treatment of HTN by primary care clinicians and specialists alike. In a subset of the hypertensive population, blood pressure (BP) continues to be uncontrolled despite use of optimal pharmacologic therapy. Treatment resistant hypertension (TRH) is defined in these patients as BP being above goal despite concurrent use of three different medications of different classes, at maximally tolerated doses, one of which being a diuretic.[2] The TRH is important to define because it identifies patients at three folds increased risk of adverse cardiovascular outcomes as compared to those with treatment responsive hypertension.[3] These patients with TRH might benefit from additional evaluation and possibly nonpharmacologic therapeutic measures.

The prevalence of TRH is unclear, but has been estimated at 20 to 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 HTN (rather than essential HTN) contribute to the high prevalence of TRH, and that by treating these factors, the number of patients with true TRH will decrease.[4] The myriad of reasons for uncontrolled hypertension highlights the need to treat each patient with a personalized and thoughtful approach. This review will focus on the subset of patients with uncontrolled hypertension who have true TRH despite appropriate medical and lifestyle therapies, and will focus on the evolving field of interventional techniques for TRH.

HYPERTENSION PATHOPHYSIOLOGY

The mean arterial BP is defined as the product of cardiac output and systemic vascular resistance. These two entities are set by numerous factors and organ systems. Cardiac output is the product of heart rate (HR) and stroke volume, which in turn depends on preload and contractility. Heart rate and contractility are primarily affected by the neuroendocrine system with adrenal release of epinephrine and norepinephrine. Preload is affected by both the kidneys through the renin-angiotensin-aldosterone system (RAAS) via upregulation of aldosterone, leading to sodium retention as well as through increased central nervous system (CNS) release of antidiuretic hormone/vasopressin. Systemic vascular resistance is also affected by the kidneys through direct actions of angiotensin II on arterial vasoconstriction as well by CNS actions with increased adrenal release of norepinephrine and epinephrine, which act as direct agonists of arterial alpha receptors.

APPROACH TO TREATMENT RESISTANT HYPERTENSION

There are many pharmacologic agents targeting the aforementioned factors in the genesis of hypertension.

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Beta blockers and alpha blockers directly target the CNS causes of HTN through decrease in HR, contractility, and peripheral vasoconstriction; and lead to downstream down regulation of the RAAS system. Angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), renin antagonists and aldosterone receptor blockers primarily target the RAAS system's contribution to hypertension. Diuretics exert their effects of decreasing overall blood volume through their actions on the kidneys. Peripheral vasodilators, such as calcium channel blockers, nitrates, hydralazine and minoxidil act peripherally to decrease systemic vascular resistance.

Despite great advances in pharmacologic management, unfortunately still there are 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 where 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 HTN 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 HTN.[5-10] More recently, minimally invasive approaches to modulate the sympathetic nervous system have shown promise for reduction in HTN without such severe and intolerable side-effects. This review will focus on one such minimally invasive approach: baroreflex activation therapy (BAT).

Trial Data on Baroreflex Activation Therapy

Carotid baroreceptors decrease sympathetic outflow and also increase vagal tone, thus resulting in reduction of BP (Fig. 1). Iatrogenic carotid baroreceptor activation has been demonstrated 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] In DEBuT-HT, the CVRx Rheos device was used to assess feasibility of BAT in human patients (Fig. 2). This device was similar in size to a pacemaker, with a pulse generator displacing 43.4 cc blood, implanted in the pectoralis region. The device has two leads, which are tunneled from the generator to the bilateral 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. In order 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 up to 2 years. The 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

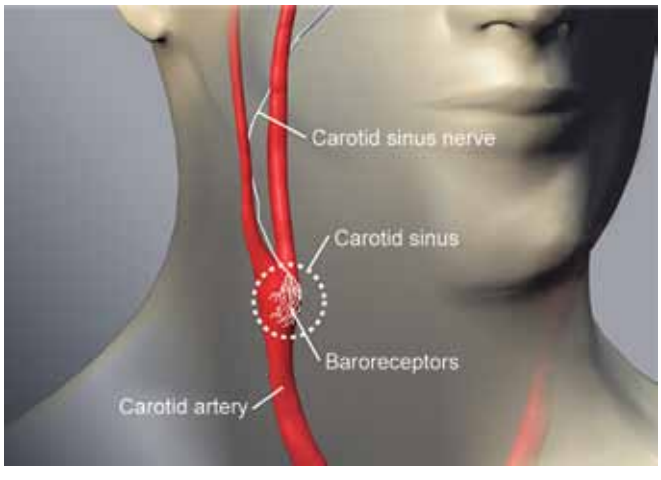

Fig. 1: Anatomy of carotid baroreceptor (*Courtesy*: CVRx)

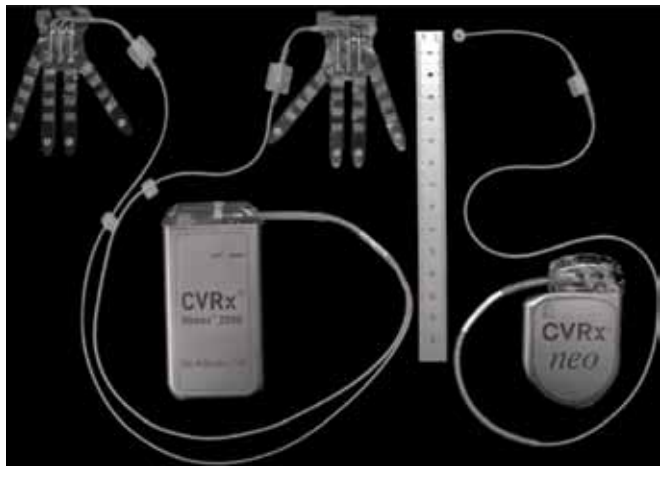

Fig. 2: Original Barostim Rheos device compared with the smaller Barostim neo device (*Courtesy*: CVRx)

temporarily turned-off the device in clinic, and reported that BP values increased to baseline almost immediately. Reinitiation of therapy subsequently 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 device trial using the same CVRx Rheos device in 265 patients with TRH.[13] The trial had similar inclusion criteria, though the BP cut-off for resistant HTN was >160/80 rather than >160/90 mm Hg, and patients were also required to have an ambulatory systolic blood pressure (SBP) >135 mm Hg, averaged over 24 hours. This additional ambulatory BP criterion was evaluated at a core laboratory and excluded patients that had orthostatic hypotension. All the patients in the Rheos pivotal trial received the Rheos device, and were randomized 1 month after implantation to either activating the pulse generator at the time of randomization or keeping it inactive for the first 6 months, and then activating it. The trial evaluated five prespecified primary end points. Two of these were efficacy endpoints (acute and sustained efficacy). The other three primary endpoints were safety endpoints (procedural, BAT and device safety). The trial did not meet the primary acute efficacy and procedural safety endpoints, but did meet the other safety and efficacy endpoints and showed improvements in prespecified secondary endpoints of reducing mean change in office based SBP as well as comparison of immediate *vs* 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 allow for 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 5th month of active therapy.

Nonsignificant primary results of the Rheos pivotal trial included: (1) the acute efficacy endpoint and (2) the procedural safety. For acute efficacy, the fraction of patients showing more than a 10-point drop in SBP at 6 months was 54% in the active therapy group as compared to 46% in the control arm. This was less than the predefined 20% superiority margin. For procedural safety, the endpoint was defined as serious procedure related event-free rate within 30 days of implantation of greater than 82%, based on literature demonstrated rate seen in similar device implantations. The actual procedural event-free rate was 74.8%, which was closer to the procedure free event rate of open carotid endarterectomy. Given the surgical exposure of the carotid bulb during the BAT implantation, carotid endarterectomy might be a more similar risk procedure like pacemaker implantation.

Significant primary results included a sustained reduction in BP. Of the patients who achieved at least a 10 mm Hg reduction in blood pressure at 6 months, 88% continued to have at least 50% of that reduction at 12 months follow-up. The other safety endpoints including BAT and device specific safety were both met. Secondary endpoint 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 had only active BAT treatment for 6 months, and had already achieved greater mean reduction in SBP than the immediate treatment therapy group at 6 months. A possible reason for this could have been an initial drop in BP across groups between study enrollment and randomization. Also to be considered is the general improvement in compliance and monitoring seen with patients enrolled in a research study as compared to regular practice.

Long-term Rheos Pivotal Follow-up

Overall, 88% of the patients from the Rheos pivotal trial were determined to be responders to the therapy after 12 months, as demonstrated by either a reduction in SBP to <140 mm Hg (<130 if diabetes or renal disease), or a clinically significant increase in SBP after deactivating the device (increase in SBP of >20 mm Hg or a hypertensive crisis with SBP >220 mm Hg requiring overnight hospitalization).[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 average number of antihypertensive drugs used from 5.3 ± 1.9 to 4.7 ± 2.1 drugs. Importantly, in contrast to the prespecified modulation of the device performed in the original trial, in the follow-up trial investigators were allowed to utilize additional programming settings to further tailor therapies to individual patients.

Five-year Rheos Follow-up

After the long-term Rheos pivotal follow-up, patients who were confirmed responders continued to be followed. As of the most recent follow-up,[15] there were 216 patients who

continued to receive active BAT, with 40 patients receiving at least 5 years and 207 receiving at least 3 years of follow-up. In this group of initial responders, SBP continued to be significantly reduced as compared to baseline by a mean of >30 mm Hg, and diastolic BP by mean of >16 mm Hg. Overall, system and procedural related complications following a year of therapy were reported as 0.037 per patient year.

Barostim Neo Trial

The Barostim neo is a second generation device which improved on the original Rheos device by decreasing the size of the pulse generator (<40 cc displacement as compared to 43.4 cc), and by reducing the number of required electrodes from two leads with four projections per lead to just one lead with a single-button electrode. For implantation, in contrast to the original device that required wrapping the bilateral carotid bulbs with electrodes, the neo device has one-sided implantation with the single-button electrode sutured to the carotid sinus. The advantage with this change 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 done based on data from the original Rheos trial, such that about 75% of the devices were programmed to unilateral stimulation without a decrease in efficacy as compared to bilateral stimulation.

The Barostim neo trial[16] was a single arm open label study utilizing the new smaller Barostim neo device in patients with TRH. 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 subsequently individually titrated for optimal response, rather than in a uniform fashion. Outcomes were assessed after 6 months of treatment and were compared to a baseline BP measured preimplantation. This baseline was different than that in the Rheos pivotal trial which was measured after the device was implanted but before the therapy was begun. Interestingly, the post-implantation, 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 as well. The fraction of patients reaching goal SBP of <140 mm Hg was 43% at 6 months of treatment.

Carotid Nitinol Stent (Mobius HD)

Given the blood pressure response seen in the BAT trials, another device was created (Mobius HD) to target the baroreflex through a different approach (Fig. 3). Rather than electrical stimulation, the Mobius HD 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 through activation of the baroreflex. The device is currently enrolling patients in a phase I trial to assess safety in humans [controlling and lowering BP with the Mobius HD.[17]

DISCUSSION

Baroreflex activation therapy has the potential to change the way that treatment resistant hypertension is managed and offers possible tremendous clinical benefit. As with all therapies, there are advantages and hurdles in BAT implementation.

For example, the BAT procedure with the barostim device can be instantly demonstrated to be effective when it is turned on. It does carry downsides in that there is a permanent implant, which requires office based monitoring, adjustment, and repeat procedures for battery changes,

Fig. 3: Mobius HD pictured alone (left panel), on a deployment catheter tip (center panel), and positioned at the site of the carotid baroreceptor (right panel) (*Courtesy*: Vascular dynamics)

which will be impacted by compliance in the real world. The highest risk aspect of the barostim implantation, the neck dissection, might become less risky with the advent of the smaller single lead barostim neo device. It will be interesting to see if an entirely intravascular stimulator lead is developed in the future, as this could decrease the risk associated with the neck dissection, while possibly increasing the risk of intravascular complications. In contrast, the Mobius HD stent could provide assured compliance in a low risk procedure. It does carry with it irreversibility, and is still in the early investigational stage.

CONCLUSION

Despite significant advances in medical therapy, TRH continues to be a challenging entity to treat, and unfortunately carries with it an increased risk of significant cardiovascular disease. For those patients in whom medical therapy is inadequate, interventional therapy offers a possible supporting role. Baroreflex activation therapy offers an exciting possibility of future treatment options, though at this time continues to be investigational and not yet ready for prime time. The true test will be demonstration of significant improvement in long-term BP control and downstream reduction in overall cardiovascular mortality, without significant morbidity or mortality related to the invasive procedure or device.

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