Baroreceptor Stimulation for Resistant Hypertension

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Hypertension (HTN) is a worldwide epidemic. When untreated, HTN places patients at an elevated risk for several health conditions, including cardiovascular disease and end-organ damage. This effect is particularly pronounced in a subset of patients who experience treatment-resistant HTN despite the utilization of conventional medication and lifestyle interventions. For these challenging patients, ongoing research efforts continue to explore and develop novel nonpharmacologic therapies for resistant HTN. One such avenue is the regulation of the sympathetic nervous system, a large component of circulatory physiology. Innovative therapies have evolved to harness the ability to deliver electrical stimulation to baroreceptors in an effort to modulate the sympathetic system involvement in HTN. This review discusses baroreflex activation therapy and its role in the management of resistant HTN.

Keywords: baroreflex activation therapy; Barostim neo; blood pressure; carotid baroreceptor stimulation; hypertension; resistant hypertension; Rheos; sympathetic nervous system.

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Hypertension (HTN) is the most prevalent chronic disease worldwide, a known risk factor for various maladies including coronary artery disease, cerebrovascular accident, heart failure, peripheral vascular disease, vision loss, chronic kidney disease, and death.1 Approximately, 1 out of every 3 US adults has high blood pressure, with the projected prevalence increasing as the population continues to age.2 As lifestyle modifications and pharmacologic therapy are the mainstays of treatment, challenges arise when encountering treatment-resistant HTN. A substantial number of patients fail to achieve goal blood pressures despite the vast array of drug classes available and continued advances in medical therapies. Resistant HTN is defined as failure to achieve goal blood pressure (<140/90 mm Hg for most patients, <130/80 mm Hg for patients with diabetes or chronic kidney disease) when adhering to maximally tolerated doses of 3 appropriate antihypertensive drugs including a diuretic. Resistant HTN is often associated with multiple other cardiovascular risk factors including chronic kidney disease, diabetes, obesity, and sleep apnea.3 This population carries a 3-fold risk of experiencing adverse cardiovascular outcomes compared to those with treatment-responsive HTN.4 The exact prevalence of resistant HTN is unknown, though estimated to be as high as 20–30% of hypertensive patients.3 These patients remain at increased risk of cardiovascular disease and end-organ damage and are subjected to the ever-increasing difficulties of polypharmacy, medication side effects, and economic and psychosocial barriers to complicated medication regimens.

In this continuously evolving healthcare arena, technological advances have led to the development of novel nonpharmacologic therapies for resistant HTN, including baroreflex activation therapy (BAT). Manipulation of the sympathetic system has been demonstrated to be an effective therapy almost a century ago, with surgical sympathectomy first pioneered in the 1930s whereby the sympathetic ganglia are surgically severed in hopes of reducing the vasoconstrictive effects of the sympathetic nervous system. Though initially aimed to improve circulation in patients with peripheral vascular disease, this technique was subsequently tailored towards patients with malignant HTN with some success. However, the high degree of morbidity associated with the procedure—including, but not limited to impotence, severe orthostatic hypotension, and incontinence—was quick to overshadow its benefits, causing a decline in its use for the treatment of HTN.5–7 Moreover, the irreversible nature of surgical sympathectomy places the patient at elevated risk for profound hypotension in several clinical scenarios, such as in the setting of sepsis with associated vasodilation.8 More recently, innovative therapies have evolved to harness the ability to deliver electrical stimulation to baroreceptors (pressure sensors) in the carotid arteries, acting on the sympathetic nervous system, and leading to a reduction in blood pressure by decreasing sympathetic outflow and an increase in vagal tone (Figure 1).

Iatrogenic carotid baroreceptor activation was initially achieved through local pulsatile electrical stimulation of the baroreceptors in a dog model,9 illustrating the potential of substantial blood pressure reduction through prolonged baroreflex activation. These findings led to the development of an implantable device for human use through which pulsatile baroreceptor stimulation aimed to achieve long-term blood pressure management. Studies conclude that even small reductions in blood pressure can lower the risk of cardiovascular disease and stroke.10 Thus continued efforts on improving the management of HTN, particularly resistant HTN, are of utmost importance.

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**TRIAL DATA ON BAT**

**Device-based therapy in HTN trial**

The first trial to assess the feasibility of BAT in humans with a long-term implantable device was the Device-Based Therapy in Hypertension Trial (DEBuT-HT), which used the Rheos Baroreflex Hypertension Therapy Device (CVRx, Minneapolis, MN). This device consisted of a pulse generator (similar to a pacemaker), along with 2 leads with electrical stimulators tunneled from the generator and wrapped around bilateral carotid bulbs via finger-like projections (Figure 2). Though similar to the placement of a pacemaker, with the generator displacing a volume of about 43.4 cc in the pectoralis region, implantation of this original CVRx Rheos device required a more extensive surgical procedure involving exposure of the bilateral carotid bulbs. The DEBuT-HT trial enrolled 45 patients with resistant HTN who were initially followed for 3 months and then annually for 2 years. This particular trial was not placebo controlled and was largely designed to assess the safety of BAT, though efficacy of the therapy was assessed at 3 months, 1 year, and 2 years. At each of the 3 points of blood pressure measurement, the mean systolic blood pressure (SBP) and diastolic blood pressure were significantly lower when compared to

![Figure 1](https://example.com/f1.png)

**Figure 1.** The physiological effects of the autonomic nervous system, as related to carotid baroreceptor stimulation, with end-organ modulation on the heart, vasculature, and kidneys.

![Figure 2](https://example.com/f2.png)

**Figure 2.** This figure compares, side by side, the original CVRx Rheos device used in the Rheos Pivotal Trial (left) and the second-generation device, Barostim neo (right) from the Barostim Neo Trial. Please note the smaller pulse generator and simplified single lead apparatus designed for unilateral implantation.
baseline. The mean SBP was reduced by 21±4 at 3 months, 30±6 at 1 year, and 33±8 mm Hg at 2 years; the mean diastolic blood pressure was reduced by 12±2 at 3 months, 20±4 at 1 year, and 22±6 mm Hg at 2 years. Interestingly, during each follow-up visit the device would be temporarily turned off in clinic, resulting in the immediate elevation of blood pressure to the patient’s prestudy baseline. The antihypertensive effect was quickly reestablished with reinitiation of therapy.11 This demonstrated potential reversibility, a major benefit in various clinical scenarios involving vasmotor collapse, as compared to sympathetic denervation.

**Rheos Pivotal Trial**

The Rheos Pivotal Trial, which was the first large-scale, double-blind, randomized, placebo-controlled trial to evaluate BAT, followed the promising findings of the DEBuT-HT trial. The inclusion criteria varied minimally between the 2 trials, where the blood pressure cutoff for resistant HTN was >160/80 rather than >160/90, and patients were required to have an ambulatory SBP >135 averaged over a 24-hour period. This criterion was evaluated at a core laboratory and excluded patients who had orthostatic hypotension.

The Rheos Pivotal Trial randomized 265 patients with resistant HTN to 1 of 2 groups in a 2:1 (181:84) ratio 1 month following CVRx Rheos device implantation.12 The patients were randomized to either group A, who had their devices immediately switched on at the 1-month visit, or group B, who were assigned to have their devices turned on after a 6-month deferment period. Both groups were followed for 12 months from randomization.

The Rheos Pivotal Trial evaluated 5 primary endpoints: acute efficacy, sustained efficacy, procedural safety, BAT safety, and device safety. Of these prespecified endpoints, 3 were successfully met; the trial did not meet the primary acute efficacy and procedural safety endpoints. Acute efficacy was less than the predefined 20% superiority margin; 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 group. In regards to procedural safety, where the endpoint was predefined as >82% procedure-related adverse event-free rate within 30 days of implantation (based on rates seen with implantable cardioverter defibrillators and pacemakers), the study’s rate was 74.8%.

The experimental design required certain assumptions that could not be verified from prior studies given the novelty of the device and the unique patient population studied. One example is the procedure safety endpoint, where the prespecified event-free objective performance criterion was based on historic implant safety of implantable cardioverter defibrillators. In retrospect, given the surgical exposure of the carotid bulbs during Rheos device implantation, the risk profile is more similar to an open carotid endarterectomy than a defibrillator implant. In actuality, the adverse event profile of the Rheos device implantation compares favorably with trials involving carotid endarterectomy.11 Establishing such a poor comparison in event-free rates highlights the shortcomings of trial design, ultimately leading to the inability to reach statistical significance on 2 of the 5 prespecified primary endpoints.

Failure to meet the acute efficacy endpoint may be secondary to the inability to take into account multiple confounders associated with excess variability, Hawthorne effect, and placebo effect. The unanticipated blood pressure differences from preimplant to randomization (1 month after implantation) were likely due to the variability in timing of the blood pressure measurements, limits in the number of blood pressure measurements during the screening period and following device implantation, and the lack of restriction on medication adjustments from enrollment to trial initiation. The identification of such shortcomings provided the basis for improvement for future studies.

Overall, the trial was most encouraging in that the patients who did demonstrate initial reduction in blood pressure were able to maintain it throughout the 12-month follow-up period. The sustained efficacy endpoint was therefore met by maintaining at least half the initial 6-month reduction in SBP out to 12 months (88% of responders, \( P < 0.001 \)). The BAT safety endpoint was also met with a 91.7% therapy-related event-free rate in group A and 89.3% in group B (\( P < 0.001 \)). The device safety endpoint was also reached with an 87.2% event-free rate (lower confidence interval of 83.8%) measured against a predefined objective performance criterion of 72% (\( P < 0.001 \)).

The Rheos Pivotal Trial reach a SBP ≤140 mm Hg, which was not significantly different from the control group. However, at 1-year follow-up, both groups A and B showed a mean reduction of 25 mm Hg in SBP. While the acute response endpoint was not reached, having over 50% of patients in the Rheos Pivotal Trial reach a SBP ≤140 mm Hg was highly encouraging, particularly when those patients who did demonstrate lower blood pressure initially were able to maintain the benefit at 12 months.

Lastly, 7 deaths were reported within the Rheos Pivotal Trial follow-up: 3 intracerebral hemorrhages; 2 cardiopulmonary arrests; 1 ruptured abdominal aortic aneurysm; and 1 drug overdose.12 None of these deaths were related to either the device or the procedure itself, but rather related to complications of long-term HTN.

**Long-term follow-up in the Rheos Pivotal Trial**

Given these promising results, the Food and Drug Administration allowed investigators to continue following the study population of the Rheos Pivotal Trial, and those deemed to be clinically significant responders were permitted to obtain device battery replacements through an Investigational Device Exemption. Of the original 322 patients who underwent CVRx Rheos device implantation, 271 patients comprised the long-term Rheos Pivotal Trial follow-up study. These patients qualified as clinically significant responders to BAT after 12 months by achieving sustained goal SBP (≤140 mm Hg or ≤130 mm Hg in patients with diabetes or renal disease) or a sustained drop of ≥20 mm Hg from baseline measurements. Alternatively, a patient qualified as a clinically significant responder if, through deactivation of their device due to an unexpectedly low measured blood pressure, there was a resulting ≥20 mm Hg in SBP on 2 of 3 subsequent visits or an
episode of hypertensive urgency requiring at least overnight hospitalization with a SBP ≥220 mm Hg. During the average follow-up of 28 months, with a maximum follow-up of 53 months, the reduction that was demonstrated at 12 months was maintained throughout. The average SBP achieved and maintained was over 30 points lower than baseline across the entire cohort of 271 patients. Moreover, these patients also demonstrated a reduction in the number of antihypertensive medications utilized, from an average of 5.3 ± 1.9 to 4.7 ± 2.1 medications. It would have been interesting to explore whether or not the dosing of the remaining antihypertensive medications were reduced as well, keeping in mind that these patients had to adhere to maximally tolerated doses of 3 appropriate antihypertensive drugs, including a diuretic, just to qualify for the Rheos Pivotal Trial. Of note, where as the original trial had preset device programing, investigators of the follow-up trial were permitted to implement programming changes to further tailor device therapies to individual patients.

**Rheos Pivotal Trial at 5-year follow-up**

With continued follow-up, a subsequent study was published aiming to confirm sustained improvement in blood pressure and to provide better understanding of long-term safety. At the time of the most recent follow up, 216 patients remained active with BAT, with 207 receiving therapy for at least 3 years of follow-up and 40 patients receiving at least 5 years. Blood pressure was significantly reduced over at least 5 years of follow up, with a mean SBP reduction of >30 mm Hg and average diastolic blood pressure reduction of >16 mm Hg as compared to baseline measurements, with the degree of blood pressure reduction sustained throughout the study period. Following 1 year of therapy, the study noted an overall device and/or procedure-related complication rate of 0.037 per patient-year; rate of stroke and myocardial infarction was 0.014 and 0.0050 per patient-year, respectively. Such a favorable risk/benefit profile holds promise for improved healthcare, particularly with the continued enhancement of therapy delivery.

**Barostim neo trial**

The Barostim neo (CVRx,) is a second-generation device designed to improve upon the original Rheos device by utilizing a smaller pulse generator and simplified lead/electrode apparatus designed for unilateral implantation (Figure 2). Unilateral implantation with the single-button electrode sutured to the carotid sinus reduced the necessary neck dissection and minimized exposure of the external carotid artery (Figure 3). Such a minimally invasive system resulted in a simpler and safer procedure, and provided a safety profile more comparable to a pacemaker. The movement to unilateral from bilateral stimulation was based on promising data from the original Rheos Pivotal Trial, where approximately 75% of the participants received unilateral carotid stimulation. There is a well-defined benefit of unilateral, particularly right-sided BAT, as compared to bilateral BAT when applied in patients with resistant HTN.

The Barostim neo trial evaluated BAT delivered through a more minimally invasive Barostim neo system in a single-arm, open-label study of 30 patients with resistant HTN. Improving on the study design limitations of the original Rheos Pivotal trial, stable medical therapy was required for ≥4 weeks before establishing pretreatment baseline blood pressure for comparison. Following device implantation, there was a 2-week deferment before initiating BAT. Of note, BAT was individually programmed and tailored for optimal response rather than administered in a uniform approach. Outcomes were assessed and compared to a baseline SBP measured before implantation and treatment. Background medical therapy for HTN was unchanged during follow-up, again improving on prior study design flaws of the Rheos Pivotal Trial. Arterial pressures progressively improved, with an average SBP reduction of 26.1 ± 3.3 mm Hg (P < 0.001) achieved at the 3-month visit, which was maintained through the 6-month follow-up, with an average reduction of 26.0 ± 4.4 mm Hg (P < 0.001). Overall, 43% of patients reached goal SBP of <140 at 6 months of treatment.

Interestingly, 6 of the 30 patients with resistant HTN enrolled for this study had undergone previous renal denervation, an endovascular catheter-based procedure aimed at treating resistant HTN through renal nerve ablation. These particular patients, despite having higher baseline blood pressure than patients without previous renal denervation, demonstrated a reduction in SBP of 22.3 ± 9.8 mm Hg and
diastolic blood pressure of 11.3 ± 8.1 mm Hg (Figure 4).\textsuperscript{15} Such remarkable findings encourage continued follow-up and evaluation of second-generation devices.

The Barostim \textit{neo} Hypertension Pivotal Trial is a prospective, randomized, controlled trial currently taking place in up to 60 clinical sites in the United States. Approximately 310 resistant HTN patients will be randomized to medical therapy vs. BAT utilizing the Barostim \textit{neo} system in a safety and efficacy trial with a study follow-up period of 3 years.\textsuperscript{17}

**Future trends**

This continued progress is a testament to the notion that, with continued research advancement and ever evolving technology, the potential of this therapeutic modality is tremendous. BAT has shown a great deal of promise through its mechanism of modulating the sympathetic system involvement in HTN, reducing sympathetic stimuli which lead to increased salt and water retention, vasoconstriction, and myocardial contractility, all of which contribute to the pathology of resistant HTN.

Heart failure, the leading cause of hospitalization among adults >65 years of age in the United States,\textsuperscript{19} is intertwined with the very same physiological system BAT targets. In heart failure there is increased sympathetic activity and decreased parasympathetic activity, which results in vasoconstriction, sodium and water retention in the kidney, and heart remodeling. Recent research has already produced robust data in support of the use of Barostim \textit{neo} devices in the management of heart failure.\textsuperscript{19,20}

We continue to identify other populations of patients who would likely benefit from BAT; examples include high-risk patients with hypertensive crises that may warrant the emergent application of BAT devices, patients with eclampsia, or even hypertensive patients simply intolerant of available lifestyle and pharmacological therapies.\textsuperscript{21} A recent case report by Weipert \textit{et al.}\textsuperscript{22} described the emergent placement of BAT for treatment of a hypertensive crisis in the setting of a Stanford B aortic dissection. The patient described was refractory to multiple medications utilized, remaining at elevated risk for significant morbidity and mortality. The emergent application of BAT resulted in successful control of blood pressure, eventually leading to a discharge home with a manageable medication regimen. As studies have already shown, through BAT we would expect the likely decrease in the amount of medication required for control of HTN, leading to an overall improved side-effect profile as well compliance with therapy.

Future directions to optimize safety include percutaneous placement of leads \textit{via} venous access placement, taking advantage of internal jugular-carotid bulb juxtaposition, and leadless baroreceptor stimulation. Ideally, placement of the system would be as minimally invasive as pacemaker implantation. Finally, potential utilization of vagotonic devices in the management of not only HTN, but also heart failure, remains to be further developed.

In conclusion, BAT has demonstrated very promising results, achieving sustained reduction in blood pressure in patients with resistant HTN. Overall safety profile has also been improved, with safety concerns raised with the original device in the Rheos Pivotal Trial addressed by the smaller and more simplified Barostim \textit{neo} device. These trials have clearly demonstrated the vast potential for BAT in the treatment of resistant HTN. The therapy can be adjusted to meet each patient’s individual therapy needs and is fully reversible, allowing for more versatility when tailoring a patient’s treatment regimen. Unlike its pharmacologic counterpart, patients are 100% compliant with BAT therapy.

Management of resistant HTN remains challenging despite continued advances in medical therapy, public health, and pharmacology. Patients with resistant HTN remain at high risk for disastrous consequences and require advanced therapy that goes beyond standard pharmaceutical and lifestyle management. Economic, political, and demographic pressures underscore the importance of effective management of these patients. Ultimately, it will take a combination of new therapies, such as BAT, as well as traditional medication and lifestyle interventions to successfully combat this cardiovascular epidemic.

**Figure 4.** Upper panel: Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Column height and bars represent average and standard deviation *$P < 0.05$. Lower panel: Changes in SBP, DBP, and HR relative to screening averages at month 3 for patients ($n = 6$) having a history of renal nerve ablation versus patients ($n = 24$) without a history of renal nerve ablation. Column height and bars represent average and standard error. (From Hoppe \textit{et al.})\textsuperscript{15}
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DISCLOSURE

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