Research Article

Baroreflex Activation Therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial

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Abstract

The objective of this study was to assess long-term blood pressure control in resistant hypertension patients receiving Baroreflex Activation Therapy (BAT). Following completion of the randomized Rheos Pivotal Trial, patients participated in open-label, nonrandomized follow-up to assess safety and efficacy of BAT. Blood pressure reductions were measured relative to a pre-implant baseline as well as the results achieved at the completion of 1 year of follow-up in the randomized phase. Clinically significant responder status was assessed according to FDA-mandated criteria. Of the 322 patients implanted, 76\% (n = 245) qualified as clinically significant responders, an additional 10\% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Medication use was reduced by the end of the randomized phase and remained lower through the follow-up period. Among responders, 55\% achieved goal blood pressures (<140 mm Hg or <130 mm Hg in diabetes or kidney disease). Blood pressures of all active patients remained stable from completion of the randomized phase through long-term follow-up of 22 to 53 months. J Am Soc Hypertens 2012;6(2):152–158. © 2012 American Society of Hypertension. All rights reserved.

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Introduction

Despite the availability of a wide variety of pharmacotherapies, resistant hypertension (HTN) persists as a significant public health challenge, comprising approximately 20\% to 30\% of all hypertensive patients.\textsuperscript{1-3} The cost of HTN to the US health care system in 2010 alone has been estimated at $76.6 billion.\textsuperscript{4} Prevalence of resistant HTN in the industrialized world is expected to continue to rise as the population ages. The burden of HTN on the health care system, as well as increased cardiovascular mortality related to resistant HTN, requires intervention beyond standard pharmacological therapy.\textsuperscript{5}

Baroreflex Activation Therapy (BAT) is a unique approach to HTN therapy wherein electrical stimulation of carotid sinus baroreceptors evokes coordinated reductions
in sympathetic traffic to the heart, vasculature, and kidneys, as well as augmented parasympathetic activity. The net effect of BAT is to preserve homeostasis at a lower-energy state by restoring sympatho-vagal balance while promoting natriuresis and redistribution of blood volume away from the central compartment.\(^6\) BAT is applied by implanting a stimulator similar to a pacemaker, along with one or more leads attached to the carotid sinus.

To test if BAT is effective at lowering blood pressure (BP) in resistant patients, the Rheos Pivotal Trial (NCT00442286) was conducted. The study was a randomized, double-blind, controlled trial that evaluated the effects of BAT over 12 months in 322 patients (Figure 1).\(^7\) Of the 322 patients implanted with the first-generation Rheos System, 265 were randomized 1 month after implantation in a 2:1 ratio to receive BAT immediately (active therapy, Group A) or after a 6-month deferral (control, Group B), respectively. The remaining patients received therapy immediately in an open-label fashion (roll-in). The trial had 5 coprimary end points. Three of the end points were met (all \(P < .001\)): sustained pressure reduction through 12 months, noninferiority of safety for comparing control to active therapy through 6 months, and device safety through 12 months. At 6 months, change in systolic BP (SBP) and percentage of patients achieving SBP lower than 140 mm Hg demonstrated statistically and clinically significant treatment benefits in the active therapy group relative to control.

As previously described,\(^7\) the trial data monitoring committee notified the sponsor during follow-up that they believed one of the trial end points would not be met. In response, the US Food and Drug Administration (FDA) determined that the study should continue following all patients until at least 12 months of therapy, and that all consenting patients continue to receive active therapy after 12 months until battery depletion.

Until a permanent mechanism could be established, the FDA instituted a process for approval of routine battery replacement through individual compassionate use applications. This approach rapidly became untenable, as the agency was inundated with petitions detailing physician opinion that BAT provided clinical benefit. To resolve the situation, FDA established rigorous criteria to identify clinically significant responders to BAT so that they could continue to receive therapy long term. The purpose of the present publication is to describe the results of the responder qualification process and the long-term follow-up that it has enabled.

**Methods**

**Study Design and Patient Population**

The long-term follow-up (post-month 12) portion of the Rheos Pivotal Trial is a single-arm, open-label continuation of the randomized protocol previously described. The trial was approved by FDA as part of an investigational device exemption. Institutional review boards of participating US institutions and ethics committees of participating European institutions approved the protocol. Participating patients provided their written, informed consent. All patients actively participating in the Rheos Pivotal Trial were eligible to participate in long-term follow-up unless the treating physician determined that a patient should not continue with the therapy.

**Procedures**

At each of the biannually scheduled visits, patient medications, vital signs, and BP were collected. BP during office visits continued to be assessed using an automated system (BpTRU, VSM Medtech Ltd., Vancouver, Canada). The

**Figure 1.** Overview of active patients throughout trial. Patients consenting to the Rheos Pivotal Trial totaled 590, 322 of whom were implanted and 271 presently remain active. Arterial blood pressure dropped significantly with the application of BAT and the reduced pressures persist.
BpTRU protocol was carried out at a consistent time of day and within 4 to 6 hours of the most recent dose of antihypertensive medication. The automated system acquired 6 brachial cuff measurements at 1-minute intervals. The final 5 measurements were averaged to obtain the official BP reading.

At each follow-up visit, BAT parameters could be changed by a clinician or a field clinical engineer from the sponsor, working at the direction of a clinician. With knowledge about device programming and increased comfort with the therapy accumulated during the randomized portion of the study, all programmed parameters and device modes were available for programming during long-term follow-up. This included chronic use of duty-cycled therapies. Final programmed parameters were recorded at the end of each scheduled visit. As during the first 12 months of the trial, the ability to adjust concomitant pharmacotherapy remained unrestricted: physicians could make changes to drugs and dosages as deemed medically necessary at any time.

For patients who required device replacement before the establishment of standardized criteria, compassionate use applications were individually adjudicated by the FDA to qualify responders eligible for continued BAT. With the institution of objective protocol criteria, patients became eligible to qualify as responders following at least 6 months of BAT when they required a device placement. The FDA-mandated responder assessment allowed patients to qualify as clinically significant responders by several mechanisms.

A patient qualified as a clinically significant responder if, in a sustained manner, goal SBP had been achieved (≤140 mm Hg or ≤130 mm Hg in diabetes or renal disease) or if SBP had dropped by 20 mm Hg or more from device activation, as measured by a BpTRU automated device, using the averaging method described previously. Device activations occurred 1 month after implantation for patients in Group A and in the roll-in group and at 7 months after implantation for patients randomized into Group B. A sustained manner was defined as meeting the criteria in 2 of the last 3 assessments within predefined visit windows or at visits no fewer than 30 days apart, as well as at the mean of these 3 assessments.

Alternatively, a patient could qualify as a responder through deactivation of the device. This technique was used to assess responsiveness of therapy in patients who may have exhibited an unrepresentatively low SBP at 1 or 7 months postimplantation. In this scenario, a pre-deactivation baseline was acquired before the device was turned off. The patient was blinded to the date and time of deactivation to avoid bias from anxiety or other subjective factors. The patient was monitored for 30 days following deactivation. If an increase in SBP by 20 mm Hg or more was observed at 2 of 3 assessments at 24 hours or more apart 1 week or more after deactivating the device, as well as at the mean of the 3 assessments, the patient was classified a clinically significant responder. If the patient had been free of hypertensive crises for the 3 months before deactivation but experienced a hypertensive crisis requiring hospitalization at least overnight with SBP of 220 mm Hg or higher by clinic measurement (not necessarily BpTRU) during the observation period, the patient also qualified as a clinically significant responder.

For the purposes of capturing an accurate representation of the long-term population, patients were classified into the following 3 groups for analysis. (1) Clinically significant responders: Patients whose devices have been replaced by satisfying protocol criteria, patients who have received device replacements by successfully completing the compassionate use application process in which clinical benefit was adjudicated by the FDA, and those patients who presently fulfill protocol criteria but have not yet required device replacement. (2) Indeterminate: Patients who have not yet required device replacement and do not presently fulfill responder criteria. These patients may ultimately qualify as clinically significant responders through protocol criteria or the compassionate use process. (3) Withdrawn: Patients who are no longer participating in the trial.

Statistics

Statistical analysis was performed using SAS version 9.2 software (SAS Institute, Cary, NC). Comparisons within patients were made with paired-sample t tests for continuous variables. An alpha level of 0.05 was used to denote statistical significance. Data are presented as mean ± SD of the mean unless otherwise noted.

Results

Patient Cohort

The status of the 322 patients implanted in the original Rheos Pivotal Trial is shown in Figure 2. Twenty-one patients were withdrawn before approval of the long-term protocol. Of the 301 patients active when the protocol was approved, 25 patients did not consent (2 deaths, 5 explants, and 18 withdrawals), and 276 either consented or remained eligible to consent to the long-term phase of the protocol. The vast majority of these patients (244, 88%) are clinically significant responders. The average follow-up to date is 28 ± 9 months (maximum, 53 months), with a total of 9200 patient-months of follow-up. Although not counted as clinically significant responders, 10 of the 46 withdrawn patients demonstrated clinically significant therapeutic effects of BAT (SBP drop of 20 mm Hg or SBP at goal) before exiting the protocol for other reasons.

Efficacy

Clinical characteristics for the responder, indeterminate, and withdrawn groups are shown in Table 1. Demographic
characteristics of the groups did not differ from each other or the entire cohort, as previously reported. Among active patients, significant reductions are observed in systolic and diastolic pressure, averaging 35/16 mm Hg in the responder group, 19/10 mm Hg in the indeterminate group, and 33/14 mm Hg in the withdrawn group. All pressure reductions were significant ($P < .001$). Fifty-five percent of the patients classified as responders achieved goal pressures.

Figure 3 illustrates the timeline of SBP and SBP reductions for all patients from screening through 12 months and long-term follow-up. During the randomized phase, a clear separation is noted between the active therapy and control groups at month 6. By month 12, SBP has dropped more than 30 mm Hg relative to preimplantation to the low 140s, as all patients were then receiving therapy. From month 12 to the latest follow-up (overall duration 22 to 53 months) SBP reductions remained more than 30 mm Hg ($>20$ mm Hg versus preactivation), maintaining an average of 143 mm Hg.

For responders, the number of prescribed medications fell significantly between preimplantation and month 12 from $5.3 \pm 1.9$ to $4.7 \pm 2.1$ and remained lower than preimplantation at the most recent follow-up ($P \leq .001$). No significant changes in the overall number of medications were detected in the indeterminate and withdrawn groups. All classes of antihypertensive medications were reduced among responders at 12 months versus preimplantation (all $P < .05$). The largest reductions occurred in use of beta-blockers and sympatholytics. At the most recent follow-up, only the use of calcium channel blockers had increased significantly relative to month 12 ($P = .03$).

During long-term follow-up, the full range of programmed parameters and device modes was permitted to maintain and improve BP responses. At the most recent visit, 40% of responders were programmed to device settings that were not allowed during the first 12 months, and 28% were programmed to a duty-cycled mode. There were 73 patients who would not have qualified at their month 12 visit but have since qualified as responders. About half (49%) of these patients benefited from device settings not allowed during the first 12 months with an additional SBP drop of $20 \pm 26$ mm Hg from month 12.

More than a third (34%) were programmed to a duty-cycled mode and had an additional SBP drop of $23 \pm 28$ mm Hg. Prolonging battery life was another factor for the selection of a duty-cycle mode in some patients.

**Safety**

There have been a total of 13 deaths throughout the course of the Rheos Pivotal Trial. Nine occurred before approval of the long-term follow-up study. Two occurred in patients who had not yet enrolled in the long-term study (1 unclassified death during sleep and 1 ischemic encephalopathy), and 2 occurred in patients after qualifying as clinically significant responders (2 cardiopulmonary arrests). None of the deaths were adjudicated to be related to either the procedure or the device.

**Discussion**

With more than 9000 patient-months of aggregate follow-up covering up to 4.4 years, continuing observations of
efficacy strongly support BAT as a therapy with great potential in resistant HTN. Of the 322 patients implanted in the Rheos Pivotal Trial, three-fourths experienced therapeutic benefit, thereby qualifying as therapy responders per FDA criteria. The response rate may increase, as the status of 32 patients (10% of the original cohort) is as yet undetermined. Of the remaining 46 patients originally enrolled in the trial, 10 (3%) demonstrated clinically significant pressure reductions before being withdrawn for other reasons. Among responders to BAT, SBP has dropped an average of 35/31 mm Hg versus preimplantation, with more than half of the responder group achieving goal pressures amidst chronically reduced medication usage throughout follow-up. Long-term assessment of pressure stability among all active patients indicates that pressure reductions achieved by month 12 are maintained through an average of 28 (maximum 53) months of follow-up. These durable reductions in arterial pressure have occurred in a population believed to have had medically uncontrollable pressures before entering the trial.

The use of preimplantation rather than postimplantation BpTRU readings as the point of comparison for BP is worthy of some discussion. Although the original Rheos Pivotal Trial used a baseline 1-month postimplantation (“month 0”) as a baseline, several factors indicate that preimplantation values should be preferred. Safeguards were established in the Rheos Pivotal Trial so that a preimplantation BP reading could be obtained only if 3 clinic pressure measurements showed SBP of 160 mm Hg or higher within the 3 months before enrollment, in addition to a 24-hour average ambulatory SBP of 135 mm Hg or higher after at least 1 month of maximally tolerated medical therapy. Thus, any regression to the mean should have been at least partially accounted for in the preimplantation reading. Indeed, in the 322 patients who received the implant, the average of the 3 historical BPs recorded during screening was 183/16 mm Hg (181/18 in the full cohort of 462 patient screened, Figure 1), whereas the preimplantation BpTRU average had dropped to 178/23 mm Hg ($P < .0001$). A bias toward reduction of the postimplantation reading versus preimplantation along with increased variability suggests a combination of placebo and/or Hawthorne effects, which may have been exacerbated by inconsistent degrees of recovery of patients from surgery. Some of these effects

<p>| Table 1 | Baseline and follow-up characteristics for all implanted patients |</p>
<table>
<thead>
<tr>
<th>Responder</th>
<th>Indeterminate</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Implant</strong></td>
<td><strong>Month 12</strong></td>
<td><strong>Last Visit</strong></td>
</tr>
<tr>
<td>(n = 244)</td>
<td>(n = 233)</td>
<td>(n = 239)</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>177 (22)</td>
<td>139 (27)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>102 (15)</td>
<td>85 (16)</td>
</tr>
<tr>
<td><strong>Heart rate (mm Hg)</strong></td>
<td>73 (15)</td>
<td>71 (14)</td>
</tr>
<tr>
<td><strong>No. of BP meds</strong></td>
<td>5.3 (1.9)</td>
<td>4.7 (2.1)*</td>
</tr>
<tr>
<td><strong>BP meds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>35 (14)</td>
<td>61 (26)</td>
</tr>
<tr>
<td>4</td>
<td>54 (22)</td>
<td>57 (24)</td>
</tr>
<tr>
<td>≥5</td>
<td>155 (64)</td>
<td>115 (49)</td>
</tr>
<tr>
<td><strong>ACE inhibitor</strong></td>
<td>130 (53)</td>
<td>115 (49)*</td>
</tr>
<tr>
<td><strong>Alpha blocker</strong></td>
<td>34 (14)</td>
<td>23 (10)*</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blocker</strong></td>
<td>120 (49)</td>
<td>100 (43)*</td>
</tr>
<tr>
<td><strong>Beta-blocker</strong></td>
<td>207 (85)</td>
<td>170 (73)*</td>
</tr>
<tr>
<td><strong>Calcium channel blocker</strong></td>
<td>157 (64)</td>
<td>138 (59)*</td>
</tr>
<tr>
<td><strong>Diuretic</strong></td>
<td>229 (94)</td>
<td>205 (88)*</td>
</tr>
<tr>
<td><strong>Minoxidil</strong></td>
<td>37 (15)</td>
<td>25 (11)*</td>
</tr>
<tr>
<td><strong>Other sympatholytic</strong></td>
<td>116 (48)</td>
<td>74 (32)*</td>
</tr>
</tbody>
</table>

Values are absolute n (%) or mean ± SD.
BP, blood pressure.
* Denotes significant change in medication at month 12 relative to pre-implant ($P < .05$).
† Denotes significant change in medication at most-recent follow-up relative to month 12 ($P < .05$).
would presumably be transient, as supported by the significant differences in reduction of SBP and achievement of goal pressure observed at month 6. The context of real-world clinical decision-making also supports the use of preimplantation for baseline, as only the historical and current state of the patient can be considered when deciding on a course of action.

The method by which the BpTRU was used to confirm sustained reductions in arterial pressure attributable to BAT also has important ramifications. The BpTRU process requires the presence of a clinician during the first reading, but the patient has to be left isolated during the 5 subsequent automated readings. The automated algorithm has been shown to correlate with average daytime ambulatory blood pressure. In addition, the average SBP from the system has a low bias (≈2 mm Hg) versus ambulatory daytime average. In contrast, conventional office cuff readings, manual or automated, tend to overestimate pressure, do not correlate well with ambulatory pressures, and exhibit digit preferences. Thus, the results of BpTRU pressures reported in the Rhoes Pivotal Trial can be regarded as unbiased estimates of pressure reduction that are indicative of the patient’s ambulatory state. Therefore, it is reasonable to expect that the sustained reduction of SBP of 35 mm Hg observed among responders should ultimately reduce the rate of cardiovascular events, such as myocardial infarction, stroke, and incident heart failure, in this population.

Pharmacological investigations of treatments for resistant HTN have demonstrated efficacy with a high side-effect profile. Most recently, a study of darusentan demonstrated reductions in office cuff pressures of up to 18/10 mm Hg over 14 weeks, but 27% of patients experienced pulmonary edema. The manufacturer has abandoned efforts to further develop the drug.

Partial renal denervation by transmural renal artery ablation has also been studied and promoted as an alternative and/or complementary approach to BAT. Early results of safety and efficacy have been promising, with reductions in office cuff systolic pressure of 20 to 30 mm Hg maintained during follow-up of up to 24 months in 18 patients. To date, studies of renal artery ablation have used a parallel medical management group for comparison rather than a sham control. Blood pressure measurement in the trials was conducted with single-sample methods prone to the white-coat effect and regression to the mean on subsequent readings. With regard to safety, questions persist regarding long-term impact of renal artery ablation on renal artery stenosis and kidney function. A single-blind, randomized, controlled trial that may clarify these issues has recently been approved by the FDA, and recruitment has begun.
The foremost limitation of the Rheos Pivotal Trial is the dilution of statistical power by the high observed variability in BP measurements, mostly at the month 0 time point (1 month postimplantation) that was prespecified as the trial baseline. Statistical power to detect effects of BAT throughout the trial has also been hampered by baseline levels of and adjustments to aggressive medical therapy. BAT directly affects sympathetic outflow and, as a consequence, indirectly influences the renin-angiotensin-aldosterone system. Both of these axes are affected by the wide array of medical therapies used in resistant HTN that may diminish the measurable impact of BAT. Future studies with stable background therapies and/or fewer confounding therapies seem reasonable to consider. With regard to long-term follow-up, the strength of conclusions is limited by exclusion of those patients deemed nonresponders, as well as a lack of formal hypothesis testing.

Taken together, the weight of evidence suggests that BAT is safe, efficacious, and worthy of continued study in resistant HTN. Clinical evaluation of a second-generation, minimally invasive BAT system, the Barostim neo, began in February of 2011. An intercontinental validation study of neo in HTN has completed enrollment (n = 40) and Conformité Européenne marking was recently issued. Enrollment of a new intercontinental randomized HTN trial will begin shortly. A heart failure protocol similar in design to the HTN validation study is also actively enrolling. Lessons learned from the Rheos Pivotal Trial and ongoing studies of Barostim neo are expected to continue to improve the design and quality of results from future trials of BAT.

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References