Baroreflex Activation Therapy

Effects of Baroreflex Activation Therapy on Ambulatory Blood Pressure in Patients With Resistant Hypertension

Manuel Wallbach, Luca-Yves Lehnig, Charlotte Schroer, Stephan Lüders, Enrico Böhning, Gerhard A. Müller, Rolf Wachter, Michael J. Koziolek

Abstract—Baroreflex activation therapy (BAT) has been demonstrated to decrease office blood pressure (BP) in the randomized, double-blind Rheos trial. There are limited data on 24-hour BP changes measured by ambulatory BP measurements (ABPMs) using the first generation rheos BAT system suggesting a significant reduction but there are no information about the effect of the currently used, unilateral BAT neo device on ABPM. Patients treated with the BAT neo device for uncontrolled resistant hypertension were prospectively included into this study. ABPM was performed before BAT implantation and 6 months after initiation of BAT. A total of 51 patients were included into this study, 7 dropped out from analysis because of missing or insufficient follow-up. After 6 months, 24-hour ambulatory systolic (from 148±17 mmHg to 140±23 mmHg, \(P<0.01\)), diastolic (from 82±13 mmHg to 77±15 mmHg, \(P<0.01\)), day- and night-time systolic and diastolic BP (all \(P\leq0.01\)) significantly decreased while the number of prescribed antihypertensive classes could be reduced from 6.5±1.5 to 6.0±1.8 (\(P=0.03\)). Heart rate and pulse pressure remained unchanged. BAT was equally effective in reducing ambulatory BP in all subgroups of patients. This is the first study demonstrating a significant BP reduction in ABPM in patients undergoing chronically stimulation of the carotid sinus using the BAT neo device. About that BAT-reduced office BP and improved relevant aspects of ABPM, BAT might be considered as a new therapeutic option to reduce cardiovascular risk in patients with resistant hypertension. Randomized controlled trials are needed to evaluate BAT effects on ABPM in patients with resistant hypertension accurately. (Hypertension. 2016;67:701-709. DOI: 10.1161/HYPERTENSIONAHA.115.06717.) • Online Data Supplement

Key Words: ambulatory blood pressure monitoring • baroreflex activation • blood pressure • carotid sinus • resistant hypertension

Baroreflex activation therapy (BAT) represents a novel option in the treatment of resistant hypertension (HTN)\(^1,2\) and congestive heart failure with reduced ejection fraction\(^3,4\) by modulating the autonomic nervous system. In BAT, an implantable programmable pulse generator (IPG) is placed underneath the pectoralis major muscle.\(^5,6\) The device mimics the body’s blood pressure (BP) regulator by electrically activating the baroreceptors that sense an aberrant increase in the BP level.\(^7\) Bypassing mechanotransduction by electric activation of the carotid sinus provides afferent baroreceptor input into the brain. Consequently, central sympathetic outflow is reduced in a sustained manner.\(^8\)

The first BAT device (rheos) was connected with 2 electrodes applied around both carotid sinus. Thereby, the leads conduct the activation energy from the IPG to the baroreceptor fibers in the vessel walls of one or both carotid sinus.\(^9\) With this device system, 2 milestone studies have been performed, that is, the prospective, nonrandomized European multicenter feasibility and safety study Device Based Therapy in Hypertension (DEBuT-HT) Trial\(^2\) as well as the large-scale, randomized, double-blinded, placebo-controlled Rheos Pivotal Trial.\(^1\) Within the Rheos Pivotal Trial office, BP was averaged from 5 measurements and within the DEBuT-HT Trial office BP measurements were taken at every scheduled visit with a validated electronic device reaching a significant office BP drop in both studies.\(^1,2\) Ambulatory BP measurements (ABPM) data were available only in the minority of patients of the DEBuT-HT Trial with a significant BP decrease after 1 (n=15) and 2 years (n=8).

The BAT neo system has a much smaller IPG and further refinements in hardware and software including only 1 lead with an unilateral electrode placed on 1 carotid sinus because of side-dominance toward the right carotid sinus in hypertensive disease\(^10\) commonly right sided.\(^11\) Thus, the effectiveness of this device must be challenged. The BAT neo system demonstrated safety and significantly lowered office BP in a nonrandomized, open-label trial consistent with studies of the first-generation system.\(^12\) However, no data about the impact
of BAT neo on 24-hour ambulatory blood pressure (ABP) is available to date. Here, we report prospectively evaluated ABPM data in patients with therapy–refractory HTN treated with the BAT neo device.

Methods

Patients, BAT, and Study Protocol

Patients fulfilling diagnosis of resistant HTN with BP above national and international targets,13 getting optimal therapy for secondary reasons were treated with BAT and prospectively evaluated in this study. In particular, patients who had the combination of the following criteria were consecutively enrolled from January 2012 to January 2015: (1) office systolic BP (SBP) ≥140 mm Hg in general or ≥130 mm Hg for patients with chronic kidney disease and proteinuria, confirmed by multiple measurements, despite maximal tolerated and optimized therapy with at least 3 antihypertensive medications, including a diuretic; and (2) age ≥18 years. Inclusion criteria were in accordance with European Conformity (CE) marking approval for medical devices in Europe. Exclusion criteria were pregnancy, untreated secondary cause for HTN, acute myocardial infarction, unstable angina, stroke, or transient ischemic attack within the previous 6 months. Anatomic exclusion criterion was stenosis of the carotid artery >70% (routinely assessed in all patients by ultrasound and duplex sonography using North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria).14 All patients involved in this study were already treated for HTN for at least 1 year. Baseline medication was unchanged for at least 3 months before implantation of the device. Optimization of antihypertensive therapy was considered in all patients before BAT. For BAT, the Barostim neo (CVRx, Minneapolis, MN) was used as described previously.16–17 The BAT device consists of a lead, which is sutured directly on 1-side carotid sinus and a pulse generator implanted in an infraclavicular position in a minimal invasive procedure, including intraoperative testing for optimal placement of the lead for BP response. Thereafter, BAT was initiated 4 weeks after implantation and the stimulation was individually increased by adaption of programmed parameters (pulse amplitude [1–20 mA], pulse width [15–500 ms] and frequency 10-100 pulses/s) during monthly follow-up according to patients’ office BP and tolerance. Follow-up data were acquired as described before15–17 6 months after starting BAT.

Antihypertensive medication was reduced if ≥1 of the following parameters were fulfilled: (1) BP was below individual target, (2) patients with BP above target who developed severe symptoms were associated with BP reduction (eg, dizziness), and (3) typical antihypertensive medication associated side effects (eg, hyperkalemia using aldosterone antagonist). All patients underwent a complete history and physical examination, assessment of vital signs, and review of medications. Relevant concomitant diseases were evaluated by anamnesis, chart reviews as well as routine clinical and laboratory investigations. Patients were interviewed whether they had taken their complete medication at defined dose. The primary end point was the change in systolic 24-hour BP levels. The experimental design required assumptions that could not be verified a priori because of the novelty of the device and the patient population being studied. Given the distinct office BP reduction at 6 months observed in the Rheos trial (≥26 mm Hg), this study was initially planned for 30 patients.18 Because the SD of ABPM data were subject to some uncertainty at study initiation, an interim sample size review was conducted after enrollment of 30 patients. Sample size reviews are used when the variance is unknown at the start of the study.18 An SD of 17 mm Hg was observed for systolic 24-hour ABP after enrollment of 30 patients and, based on this, a 10 mm Hg difference could be detected with 46 patients at 90% power and 5% significance. Assuming a dropout rate of 10% during follow-up, as observed within the Rheos trial, the study aimed to include at least 51 patients.18 After inclusion of 30 patients, we requested the extension of the study which was given by the local ethics committee and this study group is reported here. As secondary end points, mean BP reductions in office, day-, and night-time BP were evaluated.

Patients with SBP reduction of ≥10 mm Hg in office or ≥5 mm Hg in ABPM, or both, were subsequently defined as responders to BAT.16 In addition, we analyzed the proportion of responders using the office-based definition (BP reduction of ≥10 mm Hg in office SBP) and the ABPM-based definition (SBP reduction of ≥5 mm Hg in ABPM) separately. All patients provided informed consent before the initiation of protocol-mandated procedures. The study was approved by the local Ethical Committee of Göttingen (September 19, 2011). The investigation conforms to the principles outlined in the Declaration of Helsinki.

Office BP Measurement

At baseline, BP was measured at each arm, and the arm with the higher BP was used for all subsequent readings. In the 2 patients undergoing hemodialysis, the arm without the arteriovenous fistula was used for BP measurement. Brachial BP of the arm was recorded after 10 minutes of supine rest using a semiautomatic oscillometric device (Bosch+Soehn GmbH [Jüningen, Germany]) 2x within a 3-minute interval according to the Joint National Committee Guidelines.20 The mean values of these 2 measurements were averaged. BP was measured on the same side throughout the study.

Twenty-Four–Hour ABPM

ABPM was performed using an oscillometric Spacelabs Model 90207 Recorder (Spacelabs Healthcare, Nürnberg, Germany) with readings taken every 15 minutes in daytime and every 30 minutes at nighttime. ABP readings were averaged for 24 hours, day (7 AM to 10 PM), and night (10 PM to 7 AM). Within the 2 patients undergoing hemodialysis, ABPM was performed on nondialysis days. Patients were assessed while adhering to their usual diurnal activity and nocturnal sleep routine. According to the European Society of Cardiology/European Society of Hypertension guidelines, only recordings with >70% valid measurements, at least 20 valid awake (≥2 valid daytime/h) and 7 valid asleep (≥1 valid nighttime/h) BP measurements were included in the analysis.21 Patients were graded according to their dipping pattern into 4 groups: extreme dippers/ hyperdippers (night-time BP fall ≥20%), dippers (night-time BP fall ≥10% and ≤20%), nondippers (night-time BP fall <10% and ≥20%), and inverse dippers (night-time BP>day-time BP).

Statistical Analysis

The data were evaluated using the statistical Software Statistica 12 and Microsoft Excel 2010. To analyze differences between baseline and 6 months in the investigated variables, a paired 2-sided t test was used. The Pearson correlation coefficient was used to describe the relationship between 2 metric variables. Univariate linear regression analyses were performed to examine predictors of changes in ambulatory SBP. Results are expressed as mean±SD and as number with percentage for categorical variables. Various patient characteristics between responders and nonresponders were compared by an independent t test or the fisher exact test, where appropriate. Changes in BP were expressed as mean change (with 95% confidence intervals). A linear mixed model was used to estimate the change in SBP using medication status as a time-varying covariate effect. Two-way ANOVA was performed to analyze the effect of BAT in subgroups. The threshold for statistical significance was chosen to be P<0.05.

Results

Patients

A total of 51 patients with therapy-resistant HTN were analyzed. Seven patients were excluded from analyzes because of missing or insufficient follow-up ABPM data (1 patient died because of a pneumonic sepsis and 6 patients refused ABPM). Baseline data of the analyzed 44 patients are shown in Table 1. This cohort included 16 patients (36%) with chronic kidney disease stage ≥3 including 2 patients (5%) with chronic...
kidney disease stage 5D and 1 renal transplant recipient (2%) stage 4T. Fourteen patients (32%) had a history of renal denervation (RDN). Diabetes mellitus was diagnosed in 16 patients (36%). Seven patients (16%) were current smokers and 21 (48%) stopped smoking previously. Thirty patients (68%) had a body mass index ≥30 kg/m².

**Programmed Parameters, Tolerability, and Safety**

Patients tolerated BAT well, as device programming was titrated so that patients did not experience side effects (eg, tingling or hypotension). On average, pulse amplitude on activation was 5.7±1.1 mA and steadily increased to 6.8±2.3 mA (P<0.01) at 6 months. Simultaneously, pulse width and frequency were increased from 78±57 ms to 129±94 ms (P<0.01), 44±9 pulses/s to 48±13 pulses/s (P=0.02), respectively. According to previous reports, BAT showed a device- and procedure-related major adverse neurological and cardiovascular events free rate of 98% in this study.1223 One procedure-related major adverse neurological and cardiovascular events occurred, consisting of 1 contralateral stroke (2%). Of the 44 patients who completed follow-up, 10 (23%) experienced a minor procedure-related complication. In 5 patients (11%), disturbance of wound healing, and in 4 patients (9%) a postoperative hematoma occurred. In 1 patient (2%), a hematoma of the vocal cord seemed transiently after device implantation. In 2 patients (5%), there were device-related complications. The first was because of movement of the IPG, resulting in disturbance of wound healing, and in 4 patients (9%) a postoperative hematoma occurred. In 1 patient (2%), a hematoma of the vocal cord seemed transiently after device implantation.

**Office BP and Antihypertensive Treatment**

All patients included in this study showed uncontrolled BP levels in office measurements, despite the intake of 6.5±1.5 antihypertensive drug in average. Office BP was 171±24 mmHg over 91±18 mmHg at baseline. After 6 months of BAT office, BP decreased to 151±26 over 82±17 mmHg (both P<0.01), whereas antihypertensives could be reduced significantly to 6.0±1.8 (P=0.03). Office BP and antihypertensive medication at baseline and month 6 are summarized in Table 2.

**ABPM Data and Correlation Analyses**

Twenty-four–hour SBP decreased from 148±17 mmHg to 140±23 mmHg (P<0.01) and diastolic BP (DBP) from 82±13 mmHg to 77±15 mmHg (P<0.01). Individual office and ambulatory BP measurements before and during treatment as well as individual BP changes in systolic and diastolic office and ambulatory BP are shown in Figure 1. Correlation analyses between BP changes in office measurements and ABPM revealed significant correlation for systolic (r=0.413; P<0.01) and diastolic (r=0.321; P=0.03) values.

Day- and night-time SBP and DBP significantly decreased as depicted in Table 3. To analyze if reduction in the average number of antihypertensive medications leads to underestimation of treatment effect of BAT on lowering BP, further analysis was performed. A linear mixed model to estimate the change in SBP using medication status as a time-varying covariate did not significantly alter the results and revealed a change of ambulatory 24-hour SBP and office SBP of −7(−13 to [−1]) mmHg and −22(−30 to [−13]) mmHg, respectively.

At baseline, 0 patients (0%) could be classified as extreme dippers, 16 (36%) as dippers, 20 (45%) as nondippers, and 8 (18%) as inverse dippers. After 6 months of BAT, classification rates were 2 (5%), 15 (34%), 20 (45%), and 7 (16%), respectively. A subgroup of patients (n=14; 36%) investigated in this study had previously undergone RDN. The effect of BAT on lowering office BP and 24-hour ABP was lower in patients with prior RDN, but this did not reach statistical significance using 2-way ANOVA with group (prior RDN and no prior RDN) and time (baseline and 6 months) as the variable analyzing office (systolic P=0.29; diastolic P=0.47) and 24-hour ABP (systolic P=0.19; diastolic P=0.86). Data on BP in patients with prior RDN are presented in Tables S1 and S2 in the online-only Data Supplement.

**Response to BAT**

In 34 of 44 patients (77%), SBP dropped ≥10 mmHg in office or ≥5 mmHg in ABPM, or both. These patients were classified as therapy responders. Except for the occurrence of diabetes mellitus, there were no differences between responders and nonresponders at baseline with respect to sex, age, medical history, comorbidities, office, and ABPM data or antihypertensive treatment. Comparison of responders and nonresponders is shown in Table 4. About the literature, there is no standard definition classifying responder to antihypertensive treatment. Because it is supposed that ABP is superior to office BP for prediction of cardiovascular mortality, we analyzed responder in ABPM and office measurement separately.24 In applying the criterion of drop in systolic ABP ≥5 mmHg, 24 patients (55%) were defined as responders in ABPM. Precisely, 19 patients (79%) who met the responder criterion in ABPM
Table 2. Office Blood Pressure and Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6-Mo BAT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>171±24</td>
<td>151±26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>91±18</td>
<td>82±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>72±12</td>
<td>69±11</td>
<td>0.10</td>
</tr>
<tr>
<td>No. of antihypertensives</td>
<td>6.5±1.5</td>
<td>6.0±1.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are means±SD or n (%). n=44. ACE indicates angiotensin-converting enzyme; AT1, angiotensin II type 1; and BAT, baroreflex activation therapy.

Discussion

BAT offers a novel and safe therapy to systemically diminish sympathetic and augment parasympathetic activity.1,12 By this way, BAT rhes system effectively reduces SBP and DBP in patients with resistant HTN,1,2,12 whereas there are no data from controlled clinical trials proving the safety and efficacy of the neo device. Patients included into this study showed slightly higher BP office SBP at baseline (171±24 mm Hg) compared with participants in the Rheos trial (169±26 mm Hg), whereas the number of prescribed antihypertensives were even higher (6.5±1.5 versus 5.2±1.6 in Rheos trial).1 In fact, it must be stated, that though reaching sustained BP reduction at month 12 and more patients in the treatment group did reach SBP ≤140 mm Hg at 6 months, the Rheos trial could not meet the predefined acute efficacy end point at month 6, because response rates (≥10 mm Hg drop in office SBP) were 54% in BAT-treated patients and 46% in the sham group. In the present trial, responder rate in office-based measurements was 66% and, therefore, slightly higher compared with the Rheos trial.1 Because the BAT neo consists of a much smaller lead, which is just fixed unilateral on the carotid sinus, the effectiveness of this device must be challenged. Therefore, it is of interest, that the BAT neo device has demonstrated to equally reduce office BP.12 Data of the effect of this new system on ABP, however, were to date lacking. Our study is the first demonstrating a significant 24-hour, day-, and night-time BP reduction in ABPM in patients treated with the BAT neo device. These results are of special interest, because the mean BP of all measurements made >24 hour is considered to be the one that provides better information compared with office BP measurements.23 It is less affected by sporadic situations that may arise during the day or night or by sporadic errors.25 Because it is a valuable predictor for cardiovascular events, the use of ABPM is considered to be crucial for BP control in hypertensive patients.26 As the intensity of antihypertensive drug treatment in our patients was de-escalated during follow-up and, therefore, the treatment effect of this device may have been underestimated, these results strongly suggest that the BP changes were related to the device rather than to medical therapy.

There are experimental data demonstrating that prior RDN does not abolish BP-lowering effect of BAT.27 Subgroup analyses suggest that BP response to BAT might be attenuated in patients with prior RDN, but because of the rather modest sample size, these data do not allow a reliable conclusion on the impact of RDN on BAT effectivity. Indeed, the effects of BAT in patients with prior RDN in a larger cohort would be highly interesting to understand their response to a second device-based attempt to reduce sympathetic outflow.

Previous studies have shown that BP reduction in clinical trials is more pronounced in the clinic than at home and higher at home than in the ABPM.28–30 This is in concordance with results from this study and might be caused, at least in part, by regression to the mean.31 The fact that ABPM was not used to qualify patients for entry into the study means that some patients with ABPM levels in the nonhypertensive range were included (n=7; 15.9%). This will likely contribute to the lower ABPM response in this study. As a large body of evidence exists demonstrating a close epidemiological relationship between the indicators obtained using ABPM, organ damage, and cardiovascular prognosis,24 physicians should be aware that office BP may be an invalid tool to monitor BAT effects or even to use it as the basis of IPG reprogramming. Whether

could also be classified as responder in office-based measurements. Figure 2 shows proportion of responders in systolic ABP and systolic office BP, respectively.

Withdrawal of at least 1 antihypertensive drug was realizable in 16 patients (36%) because of confirmed BP levels on or below target. Antihypertensive treatment was increased in 10 patients (23%) who remained above target BP and excluding these patients from analysis did not significantly alter the results. Only 15.9% of our patients (n=7) had 24-hour ABP within target and, therefore, fulfill the criterion of pseudoresistance. Hence, the patients in this subgroups.

Univariate linear regression analyzes for change in ambulatory SBP at 6 months according to age, dipping pattern at baseline, sex, diabetes mellitus, history of smoking, body mass index, number of antihypertensives, office SBP, and ambulatory SBP are shown in Table S3, indicating that BAT was equally effective in ABP reduction in all the analyzed subgroups.

Discussion

BAT offers a novel and safe therapy to systemically diminish sympathetic and augment parasympathetic activity.1,12 By this way, BAT rhes system effectively reduces SBP and DBP
telemedical home BP measurements, which have been shown to correlate closer to ABPM, might provide a benefit for BAT programming, remains to be shown.32

In the DEBuT-HT study using the BAT rheos system, BP reduction rates in ABPM were $-13/_{-8}$ mm Hg after 1 year (n=15) and $-24/-13$ mm Hg after 2 years (n=8).2 To date, there exist only 2 prospective, sham-controlled trials, which aimed to reduce sympathetic outflow, that is, the SIMPLICITY HTN-3 (using RDN) and the Rheos pivotal trial (using BAT rheos, no ABPM). In SIMPLICITY HTN-3, the change in systolic ABPM was $-7_{\pm15}$ mm Hg in the denervation group and $-5_{\pm17}$ mm Hg in the sham-procedure group,33 whereas in the Rheos pivotal trial office, SBP decreased by $-16_{\pm29}$ mm Hg in BAT group and $-9_{\pm29}$ mm Hg in sham-procedure group after 6 months.1

These data revealed an office BP reduction of $-20(-28$ to $-12)/{-9(-13$ to $-4)}$ mm Hg, which is comparable with the effects observed within the Rheos trial. Herein, BAT neo device treatment reduced ABP by $-8(-2$ to $-14)/{-5(-1$ to $-9)}$ mm Hg after 6 months (both $p<0.01$) similar to results achieved in RDN but below the rates of the DEBuT-HT study subgroup. The latter data, however, were collected after 1 and 2 years.2 This offers 1 limitation of this study, because the 6-month observation period does not allow estimation of the entire BAT effects. Recently, de Leeuw et al34 presented 6-year data of BAT-treated patients showing a further decline in office BP compared with prior 6 months data.1 Thereby, it must be considered that even modest BP reduction results in significant attenuation of cardiovascular mortality.35

Of all the indicators obtained during ABPM, night-time BP is the one that is best correlated with sympathetic nervous activity and prognosis.25,36 For example, the ABPM substudy of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) showed that night-time SBP is superior compared with office SBP in predicting stroke37 or the Dublin outcome study showed that nocturnal BP is as an independent predictor of composite cardiovascular end points.38 Herein, BAT significantly reduced night-time SBP and DBP by $-9(-3$ to $-15)/{-5(-1$ to $-9)}$ mm Hg after 6 months. The decrease in BP caused by rest and sleep, usually at night, has a favorable impact on reducing the pressure burden related to the organ damage. A nondipper or inverse-dipper pattern are both associated with a worse prognosis and related with target organ damage.25 In this study, however, no improvement in the dipping status could be achieved by BAT. This might be
caused by the fact that IPG reprogramming during monthly follow-up was driven by office and home BP measurements and not by ABP data. Moreover, the nonimprovement of dipping status might be caused (1) by the poor reproducibility of dipper classification in patients over time and (2) by the fact that ABPM was performed as usually done in clinical practice with fixed time intervals for day- and night-time periods, which might affect the dipping calculation.\textsuperscript{39,40} Given the rather modest sample size of this study, especially in light of the poor reproducibility of dipper status, there may have been inadequate statistical power to detect a real change in dipper status as well.

In this study, 77\% of the patients fulfilled the criteria, that is, BP reduction of ≥10 mm Hg in office SBP or reduction of ≥5 mm Hg in ambulatory BP, or both, to be classified as responders. According to drop in ambulatory SBP ≥5 mm Hg, 55\% of patients were classified as responders. The fact, that IPG reprogramming during follow-up targeted office BP and not ABP may have contributed to the lower ABPM responder rate. BAT was similarly effective in different subgroups, so that preliminary predictors of BAT response could not be identified. In RDN studies, responder rate varied from \textapprox60\%\textsuperscript{41,42} to 70\%\textsuperscript{33} but with discrepancies in the underlying responder definition.

Major limitations of the study are the small sample size and a heterogeneous cohort, which is the consequence of the current availability of this intervention. For several interventional HTN trials, it was shown that the use of a sham group, which is lacking in this study, is crucial in defining real outcomes.\textsuperscript{43} However, it must be considered that ABPM is relatively immune to regression to the mean. Thereby, postinclusion ABPM change during this study is not because of regression to the mean though that does not mean that it is all device-related as it could represent the device plus changes in diet and other lifestyle factors as well as greater compliance with prescribed antihypertensive medications (even if the total number of drugs prescribed decreased). As a reasonable compromise to estimate the extent of potential bias on BP reduction because of the open-label design, meta-analysis of 5 randomized controlled trials (2 blinded

Table 3. Changes of ABPM Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6-Mo BAT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h blood pressure</td>
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<tr>
<td>Systolic, mm Hg</td>
<td>148±17</td>
<td>140±23</td>
<td>&lt;0.01</td>
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<tr>
<td>Maximum systolic, mm Hg</td>
<td>190±23</td>
<td>182±32</td>
<td>0.07</td>
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<tr>
<td>Diastolic, mm Hg</td>
<td>82±13</td>
<td>77±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximum diastolic, mm Hg</td>
<td>117±22</td>
<td>108±27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>65±13</td>
<td>63±15</td>
<td>0.76</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>71±10</td>
<td>69±12</td>
<td>0.22</td>
</tr>
<tr>
<td>Daytime</td>
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<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>151±17</td>
<td>143±24</td>
<td>&lt;0.01</td>
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<td>Diastolic, mm Hg</td>
<td>85±13</td>
<td>79±16</td>
<td>&lt;0.01</td>
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<tr>
<td>Nighttime</td>
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<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>142±19</td>
<td>133±22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>77±13</td>
<td>72±15</td>
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</tr>
</tbody>
</table>

Values are mean±SD. n=44. ABPM indicates ambulatory blood pressure monitoring; and BAT, baroreflex activation therapy.

# Table 4. Comparison of Baseline Characteristics of Responders and Nonresponders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>16 (47%)</td>
<td>4 (40%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±12</td>
<td>55±14</td>
<td>0.49</td>
</tr>
<tr>
<td>Risk factors and target organ damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior renal denervation</td>
<td>9 (26%)</td>
<td>5 (50%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Adipositas stage ≥1 (BMI≥30 kg/m²)</td>
<td>22 (65%)</td>
<td>8 (80%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (27%)</td>
<td>7 (56%)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of smoking</td>
<td>22 (65%)</td>
<td>6 (70%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Microalbuminuria/macroalbuminuria*</td>
<td>17 (50%)</td>
<td>7 (70%)</td>
<td>0.23</td>
</tr>
<tr>
<td>CKD ≥CKD stage 3</td>
<td>12 (35%)</td>
<td>4 (40%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Office blood pressure at baseline</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>173±24</td>
<td>167±27</td>
<td>0.56</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>93±17</td>
<td>85±22</td>
<td>0.24</td>
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<td>ABPM at baseline</td>
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<tr>
<td>Systolic, mm Hg</td>
<td>146±15</td>
<td>155±20</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>82±12</td>
<td>82±16</td>
<td>0.89</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>71±10</td>
<td>70±8</td>
<td>0.89</td>
</tr>
<tr>
<td>No. of antihypertensives at baseline</td>
<td>6.4±1.5</td>
<td>6.8±1.2</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). Patients with systolic blood pressure reduction of ≥10 mm Hg in office or ≥5 mm Hg in ABPM, or both, were subsequently defined as responders to baroreflex activation therapy. ABPM indicates ambulatory blood pressure monitoring; BMI, body mass index; and CKD, chronic kidney disease.

*For analysis of albuminuria, 1 patient with CKD stage 5D dropped out because of a lack of residual diuresis (n=33 for responders).
In this prospective observational trial, BAT neo reduces office, 24-hour, day- and night-time BP in patients with treatment-resistant arterial HTN on top of background antihypertensive medication. However, sustainable evaluation of BAT effects on ABPM in patients with resistant HTN will need randomized controlled trials in a double-blind design using sham procedure.

**Acknowledgments**

Parts of the present work had been published in abstract form at the national congress of hypertension 2015. We thank Mrs C. Biegler for assistance, Dr Zenker, Department of Thoracic-Cardiac-Vascular Surgery, for BAT implantation, and the employees of CVRx for technical support.

**Sources of Funding**

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**Disclosures**

M. Wallbach, M.J. Koziolek, and R. Wachter have received speaking honoraria and research grant from CVRx. R. Wachter declares having received lecture fees and enumeration for including subjects in clinical trials from CVRx. R. Wachter has received consultant fees from CVRx. M.J. Koziolek is a member of the CVRx Barostim Hypertension Registry Steering Committee. The other authors report no conflicts.

**References**


null


**Novelty and Significance**

**What Is New?**
- Baroreflex activation therapy (BAT) offers a new approach to reduce sympathetic activity and blood pressure in resistant arterial hypertension. BAT already demonstrated a successful office blood pressure reduction in patients with drug-resistant hypertension. The influence of the unilateral BAT neo device on 24-hour blood pressure has not been studied to date.

**What Is Relevant?**
- BAT neo reduces 24-hour, day- and night-time systolic blood pressure in patients with treatment-resistant arterial hypertension in addition to medical antihypertensive medication after 6 months in this observational trial. Dipping status remained unchanged.

**Summary**
In this prospective observational study, the effect of BAT by the BAT neo system on ambulatory blood pressure was investigated. In patients with resistant hypertension, the unilateral BAT neo significantly reduced 24-hour blood pressure within 6 months. Further sham-controlled studies are needed to confirm the benefit of BAT on 24-hour blood pressure.
Effects of Baroreflex Activation Therapy on Ambulatory Blood Pressure in Patients With Resistant Hypertension

Manuel Wallbach, Luca-Yves Lehnig, Charlotte Schroer, Stephan Lüders, Enrico Böhning, Gerhard A. Müller, Rolf Wachter and Michael J. Koziolok

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Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/02/22/HYPERTENSIONAHA.115.06717.DC1
EFFECTS OF BAROREFLEX ACTIVATION THERAPY ON AMBULATORY BLOOD PRESSURE IN PATIENTS WITH RESISTANT HYPERTENSION

Manuel WALLBACH, Luca-Yves LEHNIG, Charlotte SCHROER, Stephan LÜDERS, Enrico BÖHNING, Gerhard A. MÜLLER, Rolf WACHTER, Michael J. KOZIOLEK

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Running title: Effects of BAT on 24-hour ABP

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SUPPLEMENTAL REFERENCES


### Table S1. Ambulatory blood pressure in patients who prior underwent renal denervation (RDN).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6 months BAT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Office blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>177±31</td>
<td>166±31</td>
<td>0.14</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>91±20</td>
<td>87±24</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±13</td>
<td>73±12</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>ABPM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>152±20</td>
<td>153±26</td>
<td>0.99</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>83±14</td>
<td>84±18</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Number of Antihypertensives</strong></td>
<td>6.3±1.7</td>
<td>6.3±1.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are mean±SD. Ambulatory blood pressure measurement (ABPM); beats per minute (bpm).
Table S2. Comparison of patients with and without prior renal denervation (RDN).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior RDN</th>
<th>No Prior RDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>Office blood pressure at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>177±31</td>
<td>169±21</td>
<td>0.36</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>91±20</td>
<td>90±17</td>
<td>0.92</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±13</td>
<td>72±13</td>
<td>0.91</td>
</tr>
<tr>
<td>Systolic office blood pressure change</td>
<td>-11±26</td>
<td>-24±26</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic office blood pressure change</td>
<td>-4±12</td>
<td>-11±15</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>24-hour ABP at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>152±20</td>
<td>146±15</td>
<td>0.26</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>83±14</td>
<td>82±12</td>
<td>0.75</td>
</tr>
<tr>
<td>Systolic ABP change</td>
<td>0±16</td>
<td>-12±18</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic ABP change</td>
<td>1±10</td>
<td>-8±13</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are mean±SD or n(%). Ambulatory blood pressure (ABP); Ambulatory blood pressure measurement (ABPM); change in blood pressure from baseline to month 6; beats per minute (bpm).
Table S3. Univariate Analyses of change in ambulatory systolic BP

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B Coefficient (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.173 (0.152)</td>
<td>0.26</td>
</tr>
<tr>
<td>Dipper at baseline, n</td>
<td>0.058 (0.154)</td>
<td>0.71</td>
</tr>
<tr>
<td>Sex, male&gt;female</td>
<td>0.003 (0.154)</td>
<td>0.98</td>
</tr>
<tr>
<td>Diabetes, yes&gt;no</td>
<td>0.091 (0.154)</td>
<td>0.56</td>
</tr>
<tr>
<td>History of smoking, yes&gt;no</td>
<td>-0.017 (0.154)</td>
<td>0.91</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>-0.088 (0.154)</td>
<td>0.57</td>
</tr>
<tr>
<td>Number of antihypertensives</td>
<td>0.057 (0.154)</td>
<td>0.71</td>
</tr>
<tr>
<td>Office SBP at baseline (mmHg)</td>
<td>-0.013 (0.154)</td>
<td>0.93</td>
</tr>
<tr>
<td>Ambulatory SBP at baseline (mmHg)</td>
<td>-0.167 (0.152)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Dependent variable: change in ambulatory systolic BP (mmHg); BMI (body mass index); SBP (systolic blood pressure). Patients were considered as dippers if nighttime systolic blood pressure drop was ≥10 %. Standard error (SE)
<table>
<thead>
<tr>
<th>Trial/References</th>
<th>Device</th>
<th>N</th>
<th>Office SBP Change at month 6 (mmHg)</th>
<th>ABPM Change at month 6 (mmHg)</th>
<th>Control Group</th>
<th>N</th>
<th>Office SBP Change at month 6 (mmHg)</th>
<th>ABPM Change at month 6 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity HTN-2</td>
<td>RDN</td>
<td>52</td>
<td>-32±23</td>
<td>-</td>
<td>Randomized</td>
<td>54</td>
<td>+1±21</td>
<td>-</td>
</tr>
<tr>
<td>Pokushalov et al.</td>
<td>RDN</td>
<td>13</td>
<td>-28±7</td>
<td>-</td>
<td>Randomized</td>
<td>14</td>
<td>-5±5</td>
<td>-</td>
</tr>
<tr>
<td>Simplicity HTN-3</td>
<td>RDN</td>
<td>364</td>
<td>-14±24</td>
<td>-7±15</td>
<td>Randomized,</td>
<td>171</td>
<td>-12±26</td>
<td>-5±17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheos Trial</td>
<td>BAT</td>
<td>181</td>
<td>-16±29</td>
<td>-</td>
<td>Randomized,</td>
<td>84</td>
<td>-9±29</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROX CONTROL</td>
<td>AV-coupler</td>
<td>44</td>
<td>-27±23</td>
<td>-14±20</td>
<td>Randomized</td>
<td>39</td>
<td>-4±22</td>
<td>-1±17</td>
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<tr>
<td>HTN study</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-8.2 CI[-10.9-(-5.6)]</td>
<td>-4.3 CI[-6.5-(-1.9)]</td>
</tr>
</tbody>
</table>

Table S4. Results of studies of devices versus control in resistant hypertension

Analysis of control groups in resistant HTN trials investigating devices for blood pressure reduction. Mean difference in systolic office and ambulatory 24-hour blood pressure for randomized, controlled trials using devices to treat resistant hypertension; Baroreflex activation therapy (BAT); renal denervation (RDN); arteriovenous coupler (AV-coupler); confidence interval (CI); * standard deviation was derived graphically from publication. The fixed effect model was used to generate an average estimate. Trials were identified through a search of the MEDLINE databases.
FIGURES

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Device</th>
<th>Mean [mmHg]</th>
<th>SD [mmHg]</th>
<th>Total</th>
<th>Control</th>
<th>Mean [mmHg]</th>
<th>SD [mmHg]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity HTN-3</td>
<td>-14</td>
<td>24</td>
<td>364</td>
<td></td>
<td>-12</td>
<td>26</td>
<td>171</td>
<td></td>
<td>34.5%</td>
<td>-2.00</td>
<td>[-5.81, 1.81]</td>
</tr>
<tr>
<td>Polukhalov et al.</td>
<td>-20</td>
<td>7</td>
<td>13</td>
<td></td>
<td>-5</td>
<td>5</td>
<td>14</td>
<td></td>
<td>34.3%</td>
<td>-23.00</td>
<td>[-27.62, -18.38]</td>
</tr>
<tr>
<td>Rhox Trial</td>
<td>-18</td>
<td>29</td>
<td>181</td>
<td></td>
<td>-9</td>
<td>29</td>
<td>84</td>
<td></td>
<td>13.6%</td>
<td>-7.00</td>
<td>[-14.50, 0.50]</td>
</tr>
<tr>
<td>Symplicity HTN-2</td>
<td>-32</td>
<td>23</td>
<td>52</td>
<td></td>
<td>1</td>
<td>21</td>
<td>54</td>
<td></td>
<td>10.4%</td>
<td>-33.00</td>
<td>[-41.39, -24.61]</td>
</tr>
<tr>
<td>ROX CONTROL-HTN study</td>
<td>-27</td>
<td>23</td>
<td>44</td>
<td></td>
<td>-4</td>
<td>22</td>
<td>39</td>
<td></td>
<td>7.8%</td>
<td>-23.00</td>
<td>[-32.66, -13.31]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>654</td>
<td>362</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-14.72</td>
<td>[-17.43, -12.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 66.65, df = 4 (P < 0.00001), I² = 94%
Test for overall effect: Z = 10.65 (P < 0.00001)

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Device</th>
<th>Mean [mmHg]</th>
<th>SD [mmHg]</th>
<th>Total</th>
<th>Control</th>
<th>Mean [mmHg]</th>
<th>SD [mmHg]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROX CONTROL-HTN study</td>
<td>-14</td>
<td>20</td>
<td>44</td>
<td></td>
<td>-1</td>
<td>17</td>
<td>39</td>
<td></td>
<td>12.3%</td>
<td>-13.00</td>
<td>[-20.06, 5.04]</td>
</tr>
<tr>
<td>Symplicity HTN-3</td>
<td>-7</td>
<td>15</td>
<td>364</td>
<td></td>
<td>-5</td>
<td>17</td>
<td>171</td>
<td></td>
<td>87.7%</td>
<td>-2.00</td>
<td>[-4.98, 0.98]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>408</td>
<td>210</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.35</td>
<td>[-6.14, -0.56]</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 8.43, df = 1 (P = 0.01), I² = 84%
Test for overall effect: Z = 2.35 (P = 0.02)

Figure S1. Forest plot A) Office SBP Change in randomized device trials. Mean differences in SBP for randomized controlled trials using devices to treat resistant hypertension at 6 months follow-up. B) Ambulatory SBP Change in randomized device trials. Mean differences in systolic 24-hour ABP in two randomized controlled trials using devices to treat resistant hypertension at 6 months follow-up. Analysis was performed using RevMan V.5.3 (Nordic Cochrane Centre, Copenhagen, the Cochrane collaboration 2014) using the inverse variance method for mean difference if there was not more than a moderate degree of heterogeneity. The fixed effect model was used to generate an average estimate.