Bilateral or Unilateral Stimulation for Baroreflex Activation Therapy

Peter W. de Leeuw, Teba Alnima, Eric Lovett, Domenic Sica, John Bisognano, Hermann Haller, Abraham A. Kroon

Abstract—Previous trials have shown that in patients with resistant hypertension device-based baroreflex activation therapy (BAT) can substantially reduce blood pressure. However, the fact that electrodes had to be implanted bilaterally may be a drawback for further development of the technique. In this study, we explored whether unilateral stimulation would produce comparable results as bilateral stimulation. In the Pivotal trial, treatment-resistant hypertensive patients were randomized to receive either immediate BAT or deferred BAT, that is, 6 months after implantation. We adjusted stimulation parameters individually so as to provide optimal baroreflex activation. Unilateral stimulation was applied unless bilateral stimulation resulted in a greater blood pressure reduction. When we pooled the 6-month data for the group with immediate BAT and the 12-month data for the group with deferred BAT, a total of 215 patients had been stimulated on one side only (127 at the right side and 88 at the left side), whereas 80 patients had been stimulated bilaterally. Although blood pressure and heart rate did not differ between the 2 groups at baseline, all these variables were significantly lower in the unilateral than in the bilateral group after the 6-month period. When we compared the effect of right-sided stimulation with those of either left-sided or bilateral stimulation, we found right-sided stimulation to be the most effective. We conclude that unilateral and in particular right-sided BAT has a more profound effect on blood pressure than bilateral or left-sided BAT.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00442286.

Key Words: hemodynamics ■ hypertension ■ pressoreceptors ■ sympathetic nervous system

Device-based baroreflex activation therapy (BAT) is a promising new approach to the treatment of drug-resistant hypertension.1,2 It is thought that stimulation of the carotid baroreceptor area lowers sympathetic outflow and increases vagal tone. Indeed, a close correlation has been observed between stimulation and muscle sympathetic nerve activity.3 Indirect measures of autonomic function also suggest that the balance between its 2 arms is shifted toward less sympathetic and more parasympathetic tone.4

The Rheos Pivotal trial (NCT00442286), which to date is the only randomized clinical trial, which evaluated the long-term effects of BAT, has used the Rheos device. This device consists of an implantable pulse generator and 2 electric leads, which are fixed around both carotid arteries at the location where the greatest response on stimulation is observed. Thus, this device requires bilateral surgery, which may be a drawback for further introduction into clinical practice. If it would be possible to stimulate on one side only with similar effects as during bilateral stimulation this would substantially enhance the clinical acceptability of this invasive procedure. Technical developments have made it possible already to implant a device with 1 stimulation lead and preliminary data suggest that it is, indeed, feasible to apply one-sided stimulation.5 Currently, trials are in progress, which evaluate the efficacy of this Barostim neo device in patients with heart failure. However, we still need to answer the question whether unilateral stimulation is as effective as bilateral stimulation. Moreover, we need to know whether in case of unilateral stimulation the left or the right side is to be preferred. Fortunately, the database of the Rheos Pivotal trial offers an opportunity to answer these questions. In this trial all patients received bilateral stimulation electrodes but during the course of the trial a number of patients were stimulated unilaterally. This report summarizes the main findings in these patients.

Patients and Methods

Patient Selection
To be eligible for inclusion in the Rheos Pivotal trial, patients had to have resistant hypertension. This was defined as an office systolic blood pressure ≥160 mm Hg with a diastolic blood pressure ≥80 mm Hg despite treatment for ≥1 month of maximally tolerated therapy with ≥3 appropriate antihypertensive medications, including...
a diuretic. In addition, the 24-hour average systolic blood pressure as obtained with ambulatory monitoring had to be ≥135 mm Hg. Exclusion criteria were secondary hypertension, clinically significant orthostatic falls in blood pressure, baroreflex failure, autonomic neuropathy, significant carotid artery stenosis, and cardiovascular complications within 3 months before implant.

The institutional review boards of all participating centers have approved the protocol of the Pivotal study and patients gave written informed consent.

Study Protocol

The design of the Pivotal trial and its main results has been published previously. In brief, the study was a randomized, double-blind, controlled, multicenter trial that evaluated the effects of BAT during a period of 12 months. One month after implantation of the Rheos system (CVRx, Minneapolis, MN) patients were randomized in a 2:1 ratio to receive either immediate BAT or deferred BAT, that is, after 6 months, respectively. During the trial patients were seen at regular intervals. At each visit, stimulation parameters were individually adjusted according to a protocol-defined algorithm to provide a gradual increase in baroreflex activation. This allowed for optimization of therapy, including the option of bilateral or unilateral stimulation. To optimize battery longevity, unilateral stimulation was applied unless bilateral stimulation resulted in a greater blood pressure reduction. In patients in whom we applied unilateral stimulation, we always chose the side where we found the greatest response on stimulation. Final programmed parameters were recorded at the end of each scheduled visit. When deemed medically necessary, physicians could change antihypertensive medications during the course of the trial.

Blood Pressure Measurements

Outpatient office blood pressure was assessed using a standardized, automated device (BpTRU, VSM Medtech Ltd, Vancouver, Canada) that was programmed to take 6 measurements at 1-minute intervals and report the average of the last 5 of these measurements. Twenty-four–hour ambulatory blood pressure monitoring was performed at the participating centers using validated devices.

Data Analysis

The efficacy data that are presented here are based on the blood pressure responses after 6 months of stimulation. Thus, the 6-month data from the group with immediate BAT and the 12-month data from the group in which BAT was started later were pooled for the analysis. For analysis of the data we used Stata statistical software, version 12.0 (Stata Corporation, College Station, TX). Differences between or within groups were assessed using t tests for mean values and the χ² test for proportions. When comparing 3 groups, we used ANOVA. Regression analysis was applied to evaluate the relationship between changes in blood pressure and those in heart rate. Data are expressed as means±SD, unless indicated otherwise.

The investigators had full access to the entire data set, and the analyses were performed independently from the sponsor of the study.

Results

As described previously, the Rheos Pivotal trial showed that at 6 months, the fall in office systolic blood pressure and the proportion of patients who reached the target systolic pressure of ≤140 mm Hg were significantly greater in those with immediate BAT as compared with the other group. Thereafter, the blood pressure reduction was sustained in the group with immediate BAT, whereas a further significant fall in pressure occurred in the group with deferred BAT. Importantly, no changes in medication occurred in either group.

In all patients, a stable stimulation program had been reached after 5 months of active stimulation. When the 6-month data for the group with immediate BAT and the 12-month data for the group with deferred BAT were pooled, there were 295 patients who had been stimulated for a period of 6 months. Of these, three-quarter (n=215) were stimulated on one side only coming into the 6-month visit, in 127 patients at the right side and in 88 at the left side. A total of 80 patients had been stimulated bilaterally. Baseline characteristics of these 3 groups are presented in the Table. No differences were apparent between the 3 groups with respect to sex, race, and number of antihypertensive drugs and whether they had been assigned to the group with immediate or deferred BAT. Office and 24-hour blood pressure and heart rate were also comparable. Age was slightly higher in the left-sided group than in the other 2 groups (P=0.05).

Between-Group Comparisons

During BAT, office systolic blood pressure fell significantly from 178±23 to 146±30 mm Hg in the group with unilateral stimulation and from 178±23 to 155±31 mm Hg in those with bilateral stimulation (P<0.001 for both). Diastolic pressure also fell significantly from 101±14 to 87±17 mm Hg in the unilateral group and from 105±16 to 95±17 mm Hg in the bilateral group (P<0.001 for both). Heart rate, however, fell from 73±15 to 71±14 bpm (P<0.02) with unilateral stimulation but did not change with bilateral stimulation (76±14 versus 75±13 bpm; NS). Although blood pressure and heart rate did not differ between the 2 groups at baseline, these variables were significantly lower in the unilateral than in the bilateral group after the 6-month period (P<0.03 for all). As shown in Figure 1, the absolute reductions in office systolic and diastolic pressure were also significantly greater with unilateral than with bilateral stimulation. The same was true for the percentage changes in these variables.

In both the unilateral and the bilateral groups, systolic and diastolic pressures dropped significantly, whereas heart rate fell in the unilateral group (P<0.01) but not in the bilateral group (P=0.36). When the outcome of treatment was defined as the percentage of patients reaching an office goal blood pressure of ≤140 mm Hg systolic, a greater proportion of

<table>
<thead>
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<th>Characteristic</th>
<th>Right (n=127)</th>
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<th>Bilateral (n=80)</th>
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*Values are mean±SD.
patients reached this goal with unilateral than with bilateral stimulation (46% versus 41%; \( P=0.003 \)). With unilateral treatment there were also more patients who besides reaching the systolic pressure goal had an office diastolic pressure of ≤90 mm Hg.

To explore whether it would matter to stimulate on the left or the right side, we also compared the 2 groups with unilateral stimulation with each other and with the bilateral group. These analyses showed that the responses of blood pressure and heart rate were greater in the group with right-sided stimulation as compared with both the group with left-sided stimulation and the group with bilateral stimulation but this was significant only for systolic pressure. No differences in responses were apparent when the left-sided and the bilateral group were compared. In terms of normalization of blood pressure, there was again a significant difference between the left-stimulated and the right-stimulated group in favor of the latter (35% versus 54%; \( P=0.008 \)). The normalization rate in the group with bilateral stimulation was 41%, which was also higher than in the group with left-sided stimulation (\( P=0.022 \)).

Finally, we plotted the changes in resting heart rate, that is, the difference in resting heart rates at 6 months and at baseline, against the corresponding changes in systolic blood pressure. Both in patients who were stimulated on the right side only and in those who were stimulated bilaterally, a similar significant correlation was found. Such a correlation was absent in the group with left-sided stimulation (Figure 2).

**Within-Group Comparisons**

Altogether, there were 30 patients who were programmed to both left and right unilateral stimulation at some time before 6 months of BAT. In those patients we calculated left–right differences in the responses of blood pressure and heart rate. In those patients in whom it was decided to continue with left-sided stimulation because of greater responsiveness (n=17) there was a smaller left–right difference than when the opposite was true. For instance, systolic blood pressure responses were 13 mm Hg greater with left-sided than with right-sided stimulation in those who ended the trial with left-sided stimulation. In those who continued with stimulation of the right carotid area the systolic blood pressure response was 25 mm Hg greater compared with stimulation on the left site. In other words, with a dominant right system the difference with the contralateral site is far greater than in the case of a left dominant system.

**Discussion**

The main finding of this study is that baroreflex activation therapy, when applied in patients with treatment-resistant hypertension, produces a greater effect with unilateral than with bilateral stimulation. In addition, our data suggest that left-sided stimulation is somewhat less effective than right-sided stimulation. Bilateral stimulation takes an intermediate position but is more similar to left-sided stimulation. Although at first sight these results seem counterintuitive, the data tally nicely with what is known from previous studies on a possible asymmetry in baroreceptor function. For instance, Tafil-Klawe et al\(^7\) studied the cardiac response to activation and deactivation of the left and right carotid baroreceptors in 30 young, healthy subjects. By applying continuous negative or positive pressure in a neck chamber for 10 seconds each, while simultaneously measuring heart rate and cardiac contractility, they were able to show that the hemodynamic responses were significantly greater when the right carotid system was activated or inactivated. They suggested that the functional asymmetry could be related to differences in central ipsilateral projection of the carotid baroreceptor afferents to the nuclei tractus solitarii. Later on, Diedrich et al\(^8\) described that under conditions of controlled respiratory rate, right-sided and bilateral baroreflex loading by 0.1-Hz sinusoidal neck suction were more effective in modulating heart rate and systolic blood pressure variability than left-sided loading. There was, however, no asymmetry in muscle sympathetic nerve discharge responses. Further observations indicated that during spontaneous breathing there is a right-sided predominance in strength of muscle sympathetic activity at rest but that this right–left difference disappears during carotid baroreflex stimulation, regardless of whether unilateral or bilateral stimulation is applied.\(^8\) In other words, it seems that sympathetic activity at rest is stronger in the right part of the body. Because sinusoidal baroreflex activation is...
able to abolish the difference, the data also suggest that this is a functional rather than an anatomically related phenomenon.\textsuperscript{8} In a study on 12 volunteers, Furlan et al\textsuperscript{9} also found greater effects of neck suction on the right side than on the left one. All these studies, however, focused on changes in heart rate and blood pressure variability and not on blood pressure alterations per se.

Although the pathophysiological pathway that is activated is likely to be different for neck suction and for BAT, both methods of modulating the baroreflex point toward functional asymmetry between the left and the right carotid baroreceptor system. Our results demonstrate that this has clinical relevance, as it is possible to produce a greater blood pressure fall when BAT occurs at the right than at the left side. Interestingly, the effect of bilateral stimulation takes a somewhat intermediate position but resembles more that of right-sided than of left-sided stimulation. This suggests some antagonism between the left and right carotid area. When, for instance, the right system is stimulated it will produce a relatively large fall in pressure, which in turn will unload the left carotid system. If the latter system is less able to activate sympathetic activity the net result will be that pressure remains low. However, when the left system is subjected to BAT, there will be a lesser reduction in pressure that to some extent will be compensated for by a active right carotid system. When this hypothesis is correct, it predicts that with bilateral stimulation the net effect may come closer to that of either left- or right-sided stimulation but will certainly not be greater. Our data are in line with that possibility. Alternatively, it may be that stimulation on only one side has a greater capacity to enhance the activity of the parasympathetic system. The larger fall in heart rate, which we observed with unilateral stimulation points toward that possibility. Given the relationship between changes in resting systolic pressure and in resting heart rate that we observed with bilateral stimulation and with stimulation of the right carotid area, we may hypothesize that the right carotid system is more tightly linked to the parasympathetic system than the left one. This may be related to the fact that the sinoatrial node is predominantly innervated by the right vagal nerve. The absence of a relationship between changes in pressure and in heart rate when someone is stimulated on the left side only suggests that either the sympathetic and the parasympathetic

\begin{figure}
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\caption{Scatter plots showing the relationship between changes in resting heart rate (HR) in beats per minute (bpm) and resting systolic blood pressure (SBP) in patients with baroreceptor activation therapy on the left side (A) or on the right side (B). C shows that the relationships are similar for right-sided and bilateral stimulation. Although, for the sake of clarity, a regression line has been depicted also for left-sided stimulation, this relationship was in fact not statistically significant.}
\end{figure}
systems are uncoupled at the level of the left carotid baroreceptors or the sensitivity of the left baroreceptor system is intrinsically different from that on the opposite side. This is clearly an area for further research.

Irrespective of the mechanism, our data indicate that the clinical efficacy of unilateral BAT may be at least comparable with that of bilateral BAT and is possibly superior to that. This justifies the further development and assessment of devices that make it possible to apply unilateral BAT and that may substantially save procedural time and costs. Notwithstanding these considerations, we also have to acknowledge that it may be difficult to predict which carotid area is the dominant one in a certain patient. In the small group of 30 patients in whom we were able to compare within each individual the responses to left- and right-sided stimulation separately, we found that in approximately half of these patients the left system was dominant and in the other half the right system. It is imperative, therefore, that we develop noninvasive tests to allow us to better predict at which site BAT will yield the best results. Until such tests are available, it is justifiable to do the implantation of a unilateral electrode at the right carotid artery.

The present data have to be interpreted with caution in view of the limitations of the study. First of all, the comparisons were not based on a randomized trial but on a post hoc analysis of the pooled data from both treatment arms in the Rheos Pivotal trial. However, the 2 groups that we compared were still similar with regard to a variety of biological characteristics. Second, one may argue that it would have been better to stimulate one side without prior knowledge of the responsiveness of that side. Every patient would then have had an equal chance to get stimulated on his or her best side. In the present study, however, we have always applied unilateral stimulation on that side that produced the greatest response. Actually, this even strengthens our conclusions because each patient did receive optimal treatment settings, which would tend to minimize any side preference, should such a phenomenon exist. Thus, it may be that the differences that we have described here are even larger in the real world. Along the same line, one could argue that choosing the side with the greatest responsiveness could have biased the results in favor of the unilateral group if patients who needed bilateral stimulation had more severe hypertension. However, baseline blood pressure data did not differ between the unilateral and the bilateral group, which argues against that potential bias. Third, all patients were on extensive antihypertensive medication and we cannot exclude the possibility that some drugs may have interfered with baroreceptor function. Even if this would be the case, it is unlikely that this would have affected both carotid areas differently. Fourth, we cannot entirely exclude the possibility that our results were because of differences in the implantation procedure. However, one would then expect more random variation without a preference for one side. Finally, it is possible that at least in some patients the extravascular stimulation has limited the response on a specific side. Again, it is difficult to see how this would lead to greater responsiveness on the right side.

In conclusion, the present study shows that unilateral and in particular right-sided BAT has a more profound effect on blood pressure than bilateral or left-sided BAT. These data warrant further studies to explore whether unilateral BAT, preferably on the right side, can replace the bilateral device that has been used to date.

Perspectives

The present data suggest that the left and right carotid system behave differently and this may have implications for our understanding of the baroreceptor system. Future scientific research in this area should try to assess whether both sides act in concert or independently from one another. It will also be relevant to explore how carotid vascular abnormalities could modify baroreceptor function on either side and whether hypertension or heart failure will alter the left–right balance. When baropacing is becoming more universally available it will become necessary with the modern, unilateral technology to measure beforehand which side in a particular patient is to be preferred for the implantation. This requires the development of simple, noninvasive tests to assess differences in baroreceptor function on both sides. Finally, we have to explore what are the determinants of left or right preponderance in baroreceptor function.

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Disclosures

All authors have received research grants and travel fees from CVRx. Dr de Leeuw is also an consultant for CVRx. Dr Sica is also a consultant for Novartis, Takeda, Merck, Boehringer-Ingelheim, and CVRx. The other authors report no conflicts.

References


### What Is New?
- Baroreceptor activation therapy has different effects on blood pressure and heart rate, depending on whether stimulation occurs unilaterally or bilaterally. It also differs between left- and right-sided stimulation.
- In general, right-sided stimulation produces a greater effect on blood pressure than either left-sided or bilateral stimulation.

### What Is Relevant?
- The notion that there is a side difference in the response to baroreceptor activation therapy makes it mandatory to develop tests that will allow the physician to choose which side is needed for implantation of the device.

### Novelty and Significance

#### Summary
This study shows that unilateral, and in particular, right-sided baroreceptor activation therapy in patients with resistant hypertension has a more profound effect on blood pressure than bilateral or left-sided activation.
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