Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy Results of the 6-Year Open Follow-Up

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Results of the 6-Year Open Follow-Up

Peter W. de Leeuw, John D. Bisognano, George L. Bakris, Mitra K. Nadim, Hermann Haller, Abraham A. Kroon; on behalf of the DEBuT-HT and Rheos Trial Investigators

See Editorial Commentary, pp 782–784

Abstract—Baroreflex activation therapy is a novel technique for treating patients with resistant hypertension. Although short-term studies have demonstrated that it lowers blood pressure, long-term results have not yet been reported. The aim of the present study is to assess the long-term efficacy and safety of baroreflex activation therapy. Long-term follow-up data were analyzed from all patients who had been included in 1 of the 3 trials that focused on treatment-resistant hypertensive patients. Altogether, 383 patients were available for analysis: 143 of these had completed 5 years of follow-up and 48 patients had completed 6 years of follow-up. In the entire cohort, office systolic blood pressure fell from 179±24 mm Hg to 144±28 mm Hg (P<0.0001), whereas office diastolic pressure dropped from 103±16 mm Hg to 85±18 mm Hg (P<0.0001). Heart rate fell from 74±15 beats per minute to 71±13 beats per minute (P<0.02). The effect of baroreflex activation therapy is greater than average in patients with signs of heart failure and less than average in patients with isolated systolic hypertension. In ≈25% of patients, it was possible to reduce the number of medications from a median of 6 to a median of 3. Temporary side effects, related to either the surgical procedure or the cardiovascular instability, do occur, but they do not require specific measures and resolve over time. After a follow-up of 6 years, baroreflex activation therapy maintains its efficacy for persistent reduction of office blood pressure in patients with resistant hypertension without major safety issues. **(*Hypertension*. 2017;69:836-843. DOI: 10.1161/HYPERTENSIONAHA.117.09086.)**

● **Online Data Supplement**

Key Words: baroreflex ■ blood pressure ■ heart failure ■ hypertension ■ pressoreceptors

Baroreflex activation therapy (BAT) is a novel way of treating hypertensive patients who respond inadequately to medical therapy. After short-term human studies had shown that electric stimulation of the carotid sinus can lower blood pressure,[1,2] the DEBuT-HT study (Device-Based Therapy of Hypertension) demonstrated a substantial and sustained reduction in blood pressure over a period of 3 months in treatment-resistant hypertensive patients.[3] Subsequently, the Rheos Pivotal Trial evaluated the effect of BAT in a double-blind, randomized, prospective, sham-controlled trial in which patients were randomized to receive BAT either immediately or 6 months after implantation of the Rheos device.[4] This study also showed that BAT can safely reduce blood pressure in patients with resistant hypertension in the long run. At this point, however, the technique has not yet been introduced into clinical practice. One of the drawbacks is that it is an invasive method, and there is still some concern as to whether efficacy is sustained over longer periods of time. In this regard, the 3 trials that have evaluated this device-based therapy (the US Rheos Feasibility Trial, the DEBuT-HT Trial, and the Rheos Pivotal Trial) offered a unique opportunity to address this problem. Indeed, after the formal completion of both trials, patients were followed up at regular intervals to assess the long-term effect of BAT on blood pressure and heart rate. The purpose of the present report, therefore, is to describe the follow-up results of BAT during a 6-year period.

Methods

The present analyses are based on the group of patients who were included in the US Rheos Feasibility Trial,[2] the DEBuT-HT Trial,[3] and

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From the Department of Medicine, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), The Netherlands (P.W.d.L., A.A.K.); Department of Medicine, Zuyderland Medisch Centrum, Sittard, The Netherlands (P.W.d.L.); Department of Medicine, University of Rochester, NY (J.D.B.); Department of Medicine, University of Chicago Medicine, IL (G.L.B.); Department of Medicine, University of Southern California, Los Angeles (M.K.N.); and Department of Nephrology, Medizinische Hochschule Hannover, Germany (H.H.).

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Correspondence to Peter W. de Leeuw, Department of Medicine, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail p.deleeuw@maastrichtuniversity.nl

the Rheos Pivotal Trial.[4] To be eligible for those trials, patients had to fulfill the criteria for treatment-resistant hypertension.[5] Detailed information about inclusion and exclusion criteria can be found in the articles relating to these studies. Also, the BAT procedure is covered in detail elsewhere.[3] Of note, none of the patients had previously undergone another device-based treatment, such as renal denervation. Although it was not feasible to assess adherence to drug treatment in all patients, we were able to monitor adherence in a small subset of patients by means of the Medication Events Monitoring System trackpads. These patients could enter the trial only when their adherence was at least 80%.

Both the US Rheos Feasibility Trial and the DEBuT-HT Trial were prospective, nonrandomized, feasibility, and safety studies, whereas the Rheos Pivotal Trial was a double-blind, sham-controlled, multicenter trial in which treatment-resistant hypertensive patients were randomized in a 2:1 ratio to either immediate BAT or deferred BAT. In the immediate group, BAT was activated 1 month after implantation; in the deferred group, BAT was activated 7 months after implantation.

In all 3 trials, the first-generation Rheos system (CVRx, Minneapolis, MN) was used. This consisted of an implantable pulse generator and leads that were tunneled subcutaneously and attached to each carotid sinus.[6] Patients were seen at regular intervals, and stimulation parameters (amplitude, frequency, and pulse width) were individually adjusted to optimize treatment. Patients were either stimulated at one side (left or right) or bilaterally, depending on which produced the greatest response. The energy needed to stimulate the baroreceptor area was expressed as power, which is calculated from pulse width, pulse amplitude, and frequency for a given impedance. Final programmed parameters were recorded at the end of each scheduled visit. After the formal completion of the trials, that is, after patients had been followed for 3 months on active treatment in the US Rheos Feasibility Trial and the DEBuT-HT Trial or 6 months in the case of the Pivotal Trial, they were seen at 6-month intervals (open follow-up). Usually, battery life came to an end approximately one-and-a-half to 2 years postimplant with the first-generation device, which necessitated the implantable pulse generator to be replaced. While waiting for the scheduled procedure, the power of the stimulation sometimes had to be reduced to save battery life. As per the requirements of the Food and Drug Administration, replacement of the implantable pulse generator was allowed only in patients who had participated in the Pivotal Trial and had shown a clinically meaningful response.

At every visit, office blood pressure and heart rate were measured using a standardized, automated device (BpTRU; VSM MedTech Ltd, Vancouver, Canada) that was programmed to take 6 measurements at 1-minute intervals and to report the average of the last 5 of these measurements. When deemed medically necessary, physicians could adapt antihypertensive medications at these visits.

Data Analysis

The data presented here are based on the blood pressure and heart rate responses obtained during 6 years of open follow-up. For analysis of these 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 means and the χ^2 test for proportions. We used multivariable analysis of variance for repeated measurements to assess time-dependent changes. Data are expressed as means±standard deviation, unless indicated otherwise. $P<0.05$ was considered to denote statistical significance.

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

Results

A total of 383 patients were implanted with the first-generation Rheos system (16 in the US Rheos Feasibility Trial, 45 in the DEBuT-HT Trial, and the remainder in the Pivotal Trial). Table 1 shows the baseline characteristics of these patients. There were no significant differences between the 3 trial populations at entry into the study. Most patients used a diuretic as was required for the diagnosis of treatment-resistant hypertension. In those who did not, the diuretic had been discontinued because of side-effects. One-third of the patients were taking an aldosterone antagonist (Table S1 in the online-only Data Supplement).

Table 1. Baseline Characteristics of the Implanted Patients

Characteristic	Total Group (n=383)	US Rheos (n=16)	DEBuT-HT (n=45)	Pivotal (n=322)
Age, y	53±10	52±12	54±19	53±10
BMI, kg/m^2	33±6	35±6	32±6	33±6
Sex, N (%)				
Male	230 (60)	10	26	194
Female	153 (40)	6	19	128
Race, N (%)				
White	301 (79)	9	45	247
African American	65 (17)	6	0	59
Other	17 (4)	1	0	16
Smoking status, N (%)				
Never smoked	190 (50)	14	24	152
Stopped smoking	129 (33)	2	13	114
Current smoker	64 (17)	0	8	56
Diabetes mellitus, N (%)	119 (31)	3	14	102
Previous stroke, N (%)	49 (13)	2	8	39
Previous CAD, N (%)	75 (20)	4	6	65
Heart failure, N (%)	30 (8)	0	1	29
CKD, N (%)	48 (13)	0	0	48
Number of antihypertensives	5 (3–12)	6 (3–10)	5 (3–10)	5 (3–12)

Values are absolute N (%) or mean±SD. BMI indicates body mass index; CAD, coronary artery disease; and CKD, chronic kidney disease.

Patients terminated during the follow-up phase (N=142) for a variety of reasons (Table 2). Thirty-four (25%) of these terminations occurred during the first year after implant, of which 23 occurred during the first 6 months. The most frequent causes of termination were the completion of the study protocol or death of the patient. In 14 cases, the patient did not qualify for Food and Drug Administration–approved implantable pulse generator replacement because of an insufficient response to BAT. Overall, batteries had an average lifetime of 1.5 years so that every patient who has been followed for over 2 years had at least 1 battery replacement.

When comparing patients who terminated therapy during the first year with those who continued for a longer time, the terminated group had a significantly higher blood pressure at baseline (190±24 mm Hg versus 178±23 mm Hg systolic and 110±13 mm Hg versus 103±16 mm Hg for diastolic; both $P<0.01$) but otherwise, these groups did not differ. Currently, 143 patients have completed the 5-year follow-up and 48 have been followed for 6 years. Median follow-up was 5 years. Compliance with the protocol was deemed to be excellent.

Table 2. Reasons for Termination of the Study

Reason for Termination	Entire Study	During the First Year
	N (%)	N (%)
Patient completed study per protocol	22 (15)	
Death	28 (20)	9 (6)
System explanted	15 (11)	4 (3)
Loss to follow-up	12 (8)	3 (2)
Patient refuses further follow-up testing	17 (12)	6 (4)
Patient not eligible for replacement device	14 (10)	
Other	34 (24)	12 (8)
Total	142 (100)	34 (23)

Long-Term Efficacy

In the entire cohort, systolic blood pressure fell over the 6-year period from 179±24 mm Hg to 144±28 mm Hg (P<0.0001), whereas diastolic pressure dropped from 103±16 mm Hg to 85±18 mm Hg (P<0.0001). Figure 1 shows the time course of these blood pressure changes. The greatest part of the ultimate fall in pressure occurred already during the first year of treatment. Although changes in heart rate were relatively small, this variable was reduced as well: from 74±15 beats per minute to 71±13 beats per minute (P<0.02). Pulse pressure fell from 76±19 to 59±17 mm Hg (P<0.0001).

Because of the variability in the duration of follow-up, the relationship of efficacy and duration of follow-up was assessed. The changes in systolic blood pressure per cohort of follow-up are depicted in Figure 2. Despite a few minor differences in response patterns between groups, shorter follow-up times do not seem to be associated with a lack of efficacy and there were no significant differences in clinical characteristics between these cohorts. Again, the greatest effect on blood pressure was already evident in the early phase after implantation of the device. Similar results were obtained when the effects on diastolic or pulse pressure were assessed. Because the occurrence of mortal events can have an impact on the analysis of morbid events, we also analyzed the data after exclusion of the patients who died. This did not alter any of the results. In the survivors, blood pressure fell from 178±23/102±16 mm Hg at baseline to 144±28/85±13 mm Hg at the end of follow-up.

In the entire population, the falls in systolic and diastolic blood pressure did not correlate with age, body mass index, or the number of medications taken before BAT. There was a weak correlation between the changes in systolic pressure and those in heart rate but, even though statistically significant, the correlation could not explain >5% of the variations.

Of note, the changes in blood pressure and heart rate did not differ between patients in the 3 trials that composed the follow up group.

Subgroup Analyses

Because the number of patients was large enough to allow subanalyses, we evaluated whether certain patient characteristics other than the baseline blood pressure itself could modify the responses to baroreflex activation. Although most subgroups differed slightly from each other in terms of baseline blood pressure and heart rate (Table S2), the responses to BAT were comparable in these groups (Figure 3) and the blood pressure reduction achieved did not differ significantly between most of the subgroups. That said, diastolic pressure was reduced to a lesser extent in patients >60 years of age, but these patients already had a lower diastolic pressure at the start of the study. Race, smoking status, the presence or absence of diabetes mellitus, coronary artery disease, or a previous stroke had no effect on the response to BAT. The use of a mineralocorticoid receptor antagonist or any other type of antihypertensive drug did not modify responses either.

The greatest falls in both systolic and diastolic blood pressure were observed in patients with signs of congestive heart failure. In these patients, who were clinically symptomatic but had preserved ejection fraction, the pressure drop amounted to 46/24 mm Hg, far more than the observed overall mean of 32/16 mm Hg (P<0.05). It should be noted that congestive heart failure patients also had significantly higher pretreatment pressures than the others.

Finally, we assessed the responses in patients with isolated systolic hypertension (ISH). Altogether, there were 69 patients with ISH, defined as a systolic pressure of 140 mm Hg or above and a diastolic pressure <90 mm Hg.[7] Patients with ISH were significantly older than those without (61±7 versus 52±10 years; P<0.001) and, except for their lower diastolic pressure, also had a significantly lower systolic blood pressure (167±17 versus 183±23 mm Hg; P<0.001). In patients with ISH, the reductions in systolic pressure (−23±7 mm Hg), diastolic pressure (−8±2 mm Hg), and heart rate (0±1 beats per minute) were less pronounced than in those without ISH, although the response was still clinically meaningful. Multivariable analysis on this effect of ISH on the efficacy of BAT appeared to persist (P<0.02) after correction for age and baseline blood pressure.

Response Patterns

Falls in blood pressure were greater as pretreatment pressures were higher but because it is statistically unsound to correlate changes in blood pressure to pretreatment blood pressure, we took the average of pre- and post-treatment blood pressure as the independent variable instead.[8] In this analysis, neither the changes in systolic nor those in diastolic pressure showed any relationship with the respective averages of pre- and post-treatment values.

In the whole group of patients, 161 (42%) had normalized their pressure, that is, had a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg, at the end of the first year of follow-up. If we define target pressure as a systolic pressure of 140 mm Hg or below, regardless of diastolic pressure, then 175 of the 383 patients (46%) had reached that goal. The proportion of patients on target varied between the entire follow-up period between 49% and 54% during the remaining time period. The only characteristics that differed between the patients who normalized and those who did not were blood pressure and heart rate at baseline. On average, blood pressure was 6/2 mm Hg higher (P<0.001) and heart rate 2 beats per minute lower (P<0.01) in the latter. The same was true when we compared nonresponders (fall in systolic pressure <10 mm Hg; n=26) with responders.

In the entire group of patients, there were 18 who initially (ie, during the first year) exhibited a fall in blood pressure

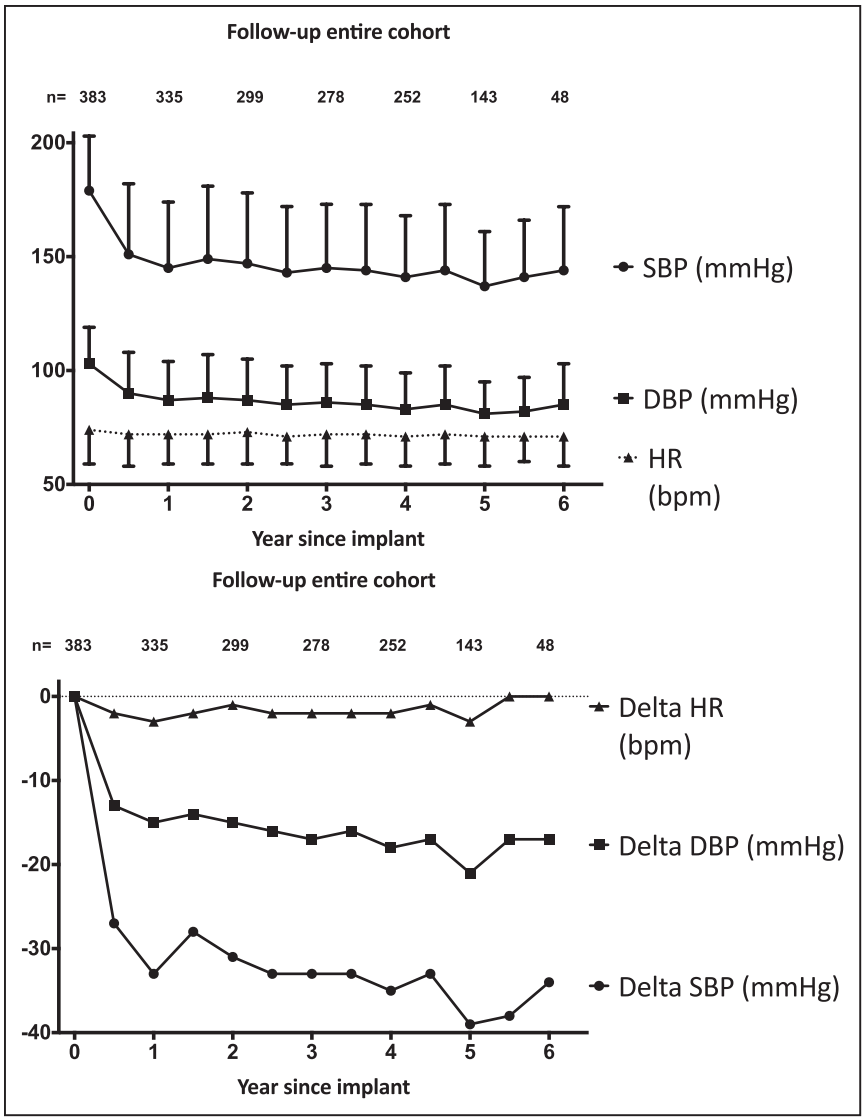

Figure 1. Time course of blood pressure and heart rate after implantation. **Upper**, Absolute blood pressure values (means and standard deviations). **Lower**, Changes in blood pressure (BP) and heart rate (HR). DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

but over time became uncontrolled again. Although most of these patients were female (12 of 18), there were no specific features that distinguished these individuals from the other patients who had a sustained response.

Medication Use

The median medication use before implant was 5 different antihypertensives, and in the whole group, this remained stable during the entire follow-up period. However, a closer look at the data revealed a rather heterogeneous pattern. In 129 patients (27%), the number of medications fell from a median of 6 to a median of 3, in 129 patients (34%) medication use remained stable at a median of 5, and in 149 patients (39%) it increased from a median of 5 to a median of 7. These 3 groups did not differ from each other regarding age, sex, initial blood pressure or heart rate, and comorbidities, but Afro-Americans were slightly less likely to have their medication tapered (18% versus 29%; $P<0.01$). When we related the power of the

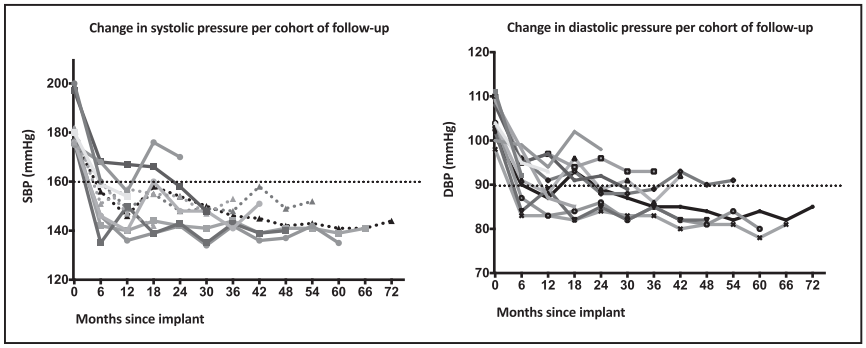

Figure 2. Changes in systolic blood pressure (SBP; **left**) and diastolic blood pressure (DBP; **right**) over time in cohorts with variable duration of follow-up. Dotted lines represent the 160 mm Hg and 90 mm Hg levels, respectively.

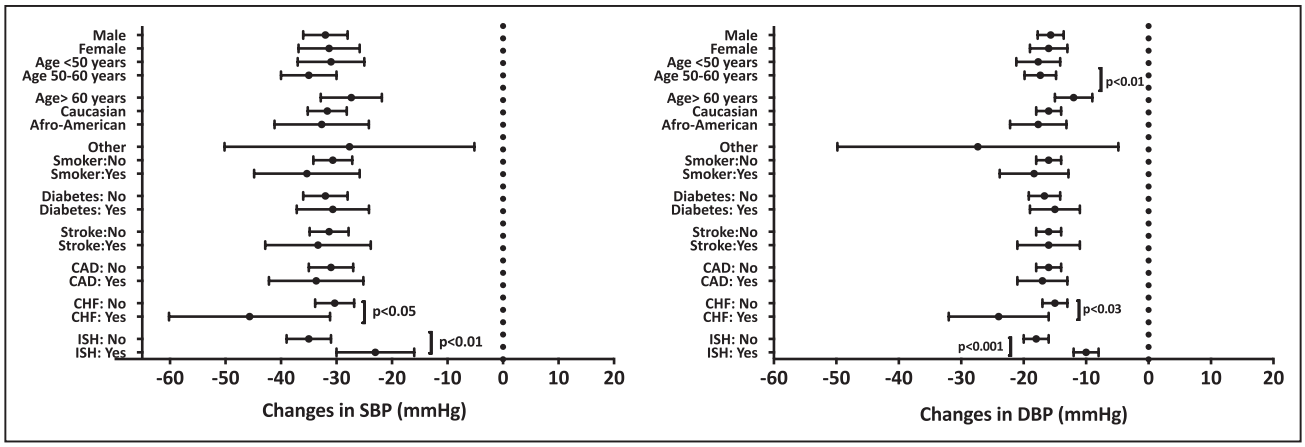

Figure 3. Final changes in systolic blood pressure (SBP; **left**) and diastolic blood pressure (DBP; **right**) in various subgroups. CAD indicates coronary artery disease; CHF, congestive heart failure; and ISH, isolated systolic hypertension. Means and 95% confidence intervals.

electric stimulation to medication use, we observed a striking concordance between the 2. In the group who needed less medication, the power of stimulation could also be reduced over time, whereas the opposite pattern was observed in the group who progressively needed more medication. Ultimately, the group that ended up with less medication and less stimulation power had a significantly lower blood pressure than the others (139/82 versus 149/88 mm Hg; $P<0.01$). Heart rate was also lower in the former group, but the difference with the other was not statistically significant. Clinically, these different groups could not be discerned from each other.

Adverse Events

In 136 of the patients who remained on active treatment, a total of 514 adverse events had been reported 12 months or longer after implantation. Of these, 335 were serious adverse events, occurring in 111 patients. However, only a minority of the serious adverse events were related to the procedure or to the system (n=26). Table 3 summarizes the nature of these serious events and the time when they occurred. Except for stroke (n=1), all complications resolved without residual effects.

Discussion

The present analyses show that BAT has a sustained effect on blood pressure after 6 years of follow-up. The largest part of the final drop in blood pressure occurs already within the first year of treatment, notably in the first 6 months, and stabilizes thereafter. Although nonresponsiveness did occur, there were only 26 patients (7% of total) in this cohort in whom systolic pressure fell by <10 mm Hg. Overall, about half of the patients reached the target pressure of 140 mm Hg systolic or below and remained relatively stable during the remainder of follow-up. The effects of BAT were similar across several subgroups and were not modified by sex, smoking status or the presence of diabetes mellitus, coronary artery disease, and stroke. Interestingly, in Afro-Americans, blood pressure fell to the same degree as it did in whites. In contrast, SYMPLICITY HTN-3, involving renal denervation that also lowers sympathetic activity, had a lesser effect in this population.[9] This is probably because of the lack of total renal denervation in that trial.[10] That same trial also showed that renal denervation lowers systolic blood pressure less effectively in patients >65 years of age. BAT, however, showed no effect of age on its potential to lower systolic

Table 3. Serious Adverse Events

Event	Days Since Implantation	Number of Events	Number of Patients (%)
IPG-related			
IPG migration	626–697	3	2 (0.6)
Surgical complication after IPG replacement	426–841	2	2 (0.6)
Total		5	4 (1.2)
CSL-related			
Lead insulation damage	385	1	1 (0.3)
Lead migration	624	1	1 (0.3)
Lead tension	545	1	1 (0.3)
Hematoma	1926	1	1 (0.3)
Total		4	4 (1.2)
Cardiovascular			
Hypertensive crisis/ urgency	489–1082	6	6 (1.9)
Hypotension without AKI	408–1746	3	2 (0.6)
Hypotension with AKI	382–1712	2	2 (0.6)
Bradycardia	833	1	1 (0.3)
Stroke	1285	1	1 (0.3)
Total		13	12 (3.4)
Other			
Neck spasms	1684	1	1 (0.3)
Seizure	679	1	1 (0.3)
UTI	1298	1	1 (0.3)
Total		3	3 (1.2)

AKI indicates acute kidney injury; CSL, carotid sinus lead; IPG, implantable pulse generator; and UTI, urinary tract infection.

blood pressure. However, diastolic pressure did not fall as much in those older than 60 years compared with younger patients. Thus, there may be some apparent differences in the efficacy of renal denervation compared with BAT, even though both techniques are indicated to reduce sympathetic traffic.[4,11,12] It is conceivable that these differences explain, at least in part, why BAT can still reduce blood pressure in patients who had previous renal denervation.[13] In a small group of predominantly female patients, the initial fall in blood pressure was followed by unresponsiveness to stimulation. Why this occurred is not entirely clear. It is conceivable that prolonged stimulation of the baroreceptors in these patients led to some fatigue of the baroreceptor system and, hence, a lower sensitivity. However, if this would be the case, it is difficult to see why such a phenomenon did not occur more frequently. However, it is possible that factors, such as reduced device performance, lesser adherence to drug treatment ,or changes in diet, played a role.

It should be stressed that the present data relate to office blood pressure measurements only. In drug trials, the effects of medication on blood pressure usually are less impressive when based on ambulatory blood pressure measurements than when based on office pressures. The same may be true for the effect of BAT. Nevertheless, a recent study from Germany showed that BAT significantly reduced ambulatory pressures as well.[14]

Isolated Systolic Hypertension

In the entire group of patients, BAT significantly reduced pulse pressure, and one would expect, therefore, that this treatment would be particularly beneficial in patients with ISH. This, however, appeared not to be the case, as the pressure drop was attenuated in patients with ISH. One could argue that this was because of the fact that they already had a lower diastolic pressure to begin with. However, this cannot be the sole explanation, as we found no convincing evidence of a relationship between the height of blood pressure and the change in pressure. A possible explanation could be that ISH occurs mainly in older patients, and sympathetic activity is less pronounced in this group.[15] Increased arterial stiffness and reduced baroreceptor sensitivity which are more prevalent at higher age may also contribute to a lesser response in patients with ISH. Interestingly, renal denervation is also less effective in these patients.[16]

Heart Failure

A striking finding is the potentiated response in patients with signs of heart failure, a condition that is associated with a markedly enhanced sympathetic drive.[17–19] In this regard, the results support those of other, recent studies of BAT in patients with heart failure and reduced ejection fraction.[20,21] Although we did not routinely assess ejection fraction in our patients, their higher systolic pressure at baseline at least suggests that their ejection fraction was not severely impaired.

Medication Need

A heterogeneous pattern occurred in the number of medications taken over time. In roughly one-third of the patients, medication use remained stable at a median of 5 medications per day. This means that hypertension became more treatable with BAT. Whether this is related to an independent effect of BAT on blood pressure, in addition to the pharmacological treatment, cannot be determined from these data. It is possible that BAT makes the cardiovascular system more sensitive to the action of antihypertensive drugs. In 39% of the patients, however, we found that not only were more medications taken but also a greater amount of electric stimulation was programmed. In 27% of the patients, the opposite was true, that is, less medications, as well as less stimulation power. Although these divergent responses cannot be readily explained, the data are at least compatible with the theory that ≈60% of patients (those with less or stable medication) exhibit some degree of true baroreceptor resetting after BAT so that hypertension becomes less severe or more receptive to pharmacological treatment. In the remainder, resetting is either absent or less pronounced. Nevertheless, even in the group with more drugs and more electric stimulation, blood pressure was reduced to almost normal levels.

Adverse Events

As is common with first-generation devices, the Rheos system was not free from adverse events. The events, which typically occurred in the initial phases after implantation, have already been described with respect to the first-generation technology in earlier publications[2–4] and which greatly improved with the introduction of the second-generation Barostim *neo* technology.[13] During prolonged follow-up, other complications were reported, but not to the extent that Rheos became unsafe, and they resolved with time.

Limitations

There are several limitations of the present study. The most important one is the fact that 2 of the 3 studies were nonrandomized, and all lacked a control group during prolonged follow-up. Only in the pivotal trial, there was a randomized comparison of true BAT versus sham BAT but only for a period of 6 months. The ideal control group for long-term evaluation would consist of patients in whom the device had been implanted but not activated. However, to follow patients with an implanted and deactivated device for so many years would be unethical. The second best would be to compare this group with another group of patients with optimal medical treatment. Logistically, this would not be easy to do and one would not expect such large differences in blood pressure as we observed in the present analysis. Still, the results of the present study should be interpreted with caution.

Second limitation is the variable follow-up period. Theoretically, this could have biased the results, as patients who do not do as well with the device are likely to drop out at an earlier stage so that the better patients remain in follow-up. We have tried to overcome this objection by presenting the data for the various cohorts with different periods of follow-up. In so doing, we found no evidence that shorter follow-up periods were related to less efficacy of the device. Third, efficacy data are based on office pressures only, and it is possible that the data are less impressive on 24-hour ambulatory monitoring.

Finally, adherence to drug treatment should be considered. Indeed, lack of adherence could have led to a false diagnosis of treatment resistance and, hence, the inclusion of the wrong type of patients. Indeed, a recent study of patients who had been referred for renal denervation showed that a significant proportion was, in fact, not adherent rather than treatment-resistant.[22] This is a problem with all hypertension trials and cannot be solved until reliable, easy-to-use, and cheap methods are available to measure adherence. Recently, it was proposed to measure antihypertensive drug levels in the patient by means of liquid chromatography–tandem mass spectrometry.[23] However, this method is expensive and can detect only those individuals who have not taken medication for a prolonged period of time, not the ones who take their drugs off and on. To get at least some insight in patients' behavior, we used, before inclusion, Medication Events Monitoring System track caps[24] in a small subset of patients, allowing us to include only those with adequate adherence. However, we still cannot rule out the possibility that these patients became temporarily more adherent because they knew they were being monitored, the so-called Hawthorne effect. Although the existence of this effect has been challenged,[25] one could argue that it also played a role during the follow-up phase, in that patients may have taken their antihypertensive drugs more punctually. Although we cannot entirely exclude such an effect, the results of the pivotal trial speak against this option. In that trial, the effect of the device was larger in the group in which BAT was started immediately than in the group with deferred BAT. In the latter group, blood pressure began to drop more substantially when the device had been switched on. Because patients did not know to which group they belonged, it seems unlikely that these differences in response were because of a Hawthorne effect.

Perspectives

We have shown that chronic BAT durably lowers blood pressure in treatment-resistant hypertensive patients. It is markedly effective when hypertension is complicated by heart failure with preserved ejection fraction. Altogether, these results justify further development and implementation of device-based therapy for resistant hypertension and heart failure, including those with reduced ejection fraction. Moreover, there is a need to assess whether unilateral stimulation with new and smaller devices will be as effective as the Rheos system. With the further development of renal denervation, it becomes important also to know whether baroreceptor activation therapy is efficacious in patients with previous renal denervation and vice versa. Because BAT requires an invasive (surgical) procedure, it is worthwhile to explore whether alternative methods such as those related to nanotechnology can eventually make the method better suitable. Finally, our results prompt for further research into how baroreceptors precisely work in hypertension, in particular on the long run, and how we can select a priori those individuals who are going to benefit most from baroreceptor activation.

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Novelty and Significance

What Is New?

- In patients with resistant hypertension, baroreceptor activation therapy produces a long-lasting and profound decline in blood pressure.
- The responses are least in patients with isolated systolic hypertension and greatest in those with heart failure with preserved ejection fraction.

What Is Relevant?

- The results have relevance for clinicians dealing with patients with treatment-resistant hypertension.
- New trials are needed to explore whether new, smaller devices produce similar results as the original device. In addition, studies are necessary to explore whether unilateral simulation may be enough to obtain a significant fall in blood pressure.

Summary

Chronic baroreceptor activation therapy durably lowers blood pressure in treatment-resistant hypertensive patients. Overall, the effects are fairly consistent among different groups. Altogether, these results justify further development and implementation of device-based therapy for resistant hypertension and heart failure.