Effects of Chronic Baroreceptor Stimulation on the Autonomic Cardiovascular Regulation in Patients With Drug-Resistant Arterial Hypertension

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Abstract—In patients with drug-resistant hypertension, chronic electric stimulation of the carotid baroreflex is an investigational therapy for blood pressure reduction. We hypothesized that changes in cardiac autonomic regulation can be demonstrated in response to chronic baroreceptor stimulation, and we analyzed the correlation with blood pressure changes. Twenty-one patients with drug-resistant hypertension were prospectively included in a substudy of the Device Based Therapy in Hypertension Trial. Heart rate variability and heart rate turbulence were analyzed using 24-hour ECG. Recordings were obtained 1 month after device implantation with the stimulator off and after 3 months of chronic electric stimulation (stimulator on). Chronic baroreceptor stimulation decreased office blood pressure from $185\pm31/109\pm24$ mm Hg to $154\pm23/95\pm16$ mm Hg ($P<0.0001/P=0.002$). Mean heart rate decreased from 81 ± 11 to 76 ± 10 beats per minute^{-1} ($P=0.001$). Heart rate variability frequency-domain parameters assessed using fast Fourier transformation (FFT; ratio of low frequency:high frequency: 2.78 versus 2.24 for off versus on; $P<0.001$) were significantly changed during stimulation of the carotid baroreceptor, and heart rate turbulence onset was significantly decreased (turbulence onset: -0.002 versus -0.015 for off versus on; $P=0.004$). In conclusion, chronic baroreceptor stimulation causes sustained changes in heart rate variability and heart rate turbulence that are consistent with inhibition of sympathetic activity and increase of parasympathetic activity in patients with drug-resistant systemic hypertension; these changes correlate with blood pressure reduction. Whether the autonomic modulation has favorable cardiovascular effects beyond blood pressure control should be investigated in further studies. (*Hypertension*. 2009;54:530-536.)

Key Words: baroreflex ■ arterial hypertension ■ electric baroreflex stimulation ■ heart rate variability ■ heart rate turbulence ■ drug-resistant arterial hypertension ■ cardiac autonomic system

Systemic arterial hypertension is one of the leading cardiovascular diseases in the world and a major cardiovascular risk for coronary artery disease, cerebrovascular disease, and heart and renal failure. Despite carefully assessing causes and stratifying therapeutic approaches using all of the existing antihypertensive pharmacological agents, not all hypertensive patients sufficiently respond to pharmacological treatment. Stimulation of the carotid baroreceptor (SCB) was considered several decades ago as a potential treatment for blood pressure (BP) lowering in humans.[1–3] The roles of carotid baroreceptors in acute regulation of BP and the acute effect of SCB are well documented.[3,4] However, whether arterial baroreceptors play a role in long-term regulation of arterial pressure is still debated,[5] and the benefit of chronic SCB as treatment of hypertension in humans is currently under investigation. Lohmeier et al[6,7] demonstrated that electric activation of the baroreflex lasting 7 days produces sustained hypotension in dogs using an implantable stimula-

tion device (Rheos, CVRx Inc). The same authors showed that electric baroreflex activation reduced mean arterial pressure, as well as plasma norepinephrine and renin concentrations, not only in the acute phase but also throughout 7 days. Implantation of permanent bilateral perivascular carotid sinus electrodes and a pulse generator for chronic SCB was shown to be feasible in humans.[8–11] The DEBuT-HT (Device Based Therapy in Hypertension) Trial was conducted to test the safety and efficacy of chronic electric baroreceptor stimulation with the Rheos device for BP control in patients with drug-resistant essential arterial hypertension.[12]

We hypothesized in the present study a long-term modulation of the sympathetic and parasympathetic activities during chronic SCB with a corresponding decrease in BP, and we investigated a subgroup of the DEBuT-HT study population. The modulation of the autonomic nervous system was assessed by analysis of heart rate variability (HRV) and heart rate turbulence (HRT) before and during SCB.[13–15] Both

methods are clinically established to analyze the sympatho-vagal modulation of sinus node activity.

Methods

Study Design

This study is a substudy of the prospective, multicenter, nonrandomized phase II DEBuT-HT Trial, which was conducted to assess the safety and efficacy of the electric carotid sinus baroreceptor stimulation Rheos device for chronic BP reduction in patients with drug-resistant arterial hypertension. The 21 patients included in this substudy were from Bern and Maastricht.

Patients

Patients with essential arterial hypertension and uncontrolled BP (>160/90 mm Hg) despite medical treatment with ≥3 antihypertensive agents (including a diuretic) for >2 months and aged ≥21 years were eligible to be included in the prospective, nonrandomized, multicenter DEBuT-HT Trial. Exclusion criteria included secondary hypertension, known cerebrovascular disease, carotid artery stenosis (defined as >50% luminal stenosis), previous carotid artery surgery, previous radiotherapy of the carotid sinus region, persistent atrial fibrillation, significant orthostatic hypotension, clinically significant cardiac valvular disease, heart transplantation, dialysis, and pregnancy. In addition, patients with an implanted pacemaker, defibrillator, or neurological stimulator were excluded.[8]

The DEBuT-HT Trial study protocol was approved by the ethics committees in Bern and Maastricht, and written informed consent was obtained from all of the patients before entering into the study. Although 24-hour ECG recordings were performed in all of the DEBut-HT Trial study centers for the purpose of safety according to study protocol, only patients from Bern and Maastricht were included in the present substudy. Patients were enrolled from March 2004 to July 2007.

Study Protocol

The surgical procedure and intraoperative testing of the baroreceptor stimulation device have been described previously.[8–10] After surgical implantation, the device was left turned off during the healing process. One month after implantation, a baseline 24-hour ECG was registered with the stimulation device turned off ("off" mode). Afterward, the Rheos system was turned on, and a dose-response test was performed in the manner described here. Bilateral carotid baroreceptor stimulation was started at a pulse amplitude of 1 volt. After 1 minute of stimulation, BP was measured and recorded. This step was repeated with outputs of 2, 3, 4, 5, and 6 volts. On the basis of the patient's BP response, the electric parameters of the device were then programmed to achieve ≈10% reduction in the current patient's BP. The goal was not to achieve maximal BP reduction. At follow-up visits, a 24-hour ECG was also recorded. The 24-hour ECG obtained after optimization of electric therapy at the 3-month visit ("on" mode) was compared with the recording obtained with the device in the off mode (1 month after implantation). Pharmacological antihypertensive therapy (see Table 1) was continued without any change throughout the study period.

Twenty-Four–Hour ECG Recordings

The 24-hour ECGs were recorded with 2 bipolar electrodes in the V2 and V5 positions using the CardioDay system (Getemed) in Bern and the Marquette system (GE Marquette Medical Systems) in Maastricht. Sample rates for both Holter ECG recordings were 128 Hz. Raw data were labeled for normal QRS complexes, supraventricular and ventricular premature depolarizations (both with prematurity ≤80%), arrhythmias, electric noise, and other aberrant electrocardiographic signals by a well-trained technician using a custom-written program developed in the IDL environment (IDL version 6.2, ITT Visual Information Solutions). The program was permitted to identify the R waves (times of occurrence defined by the local maxima) and to edit the detected events manually. The entire Holter recordings were carefully inspected to ensure that all of the R waves

Table 1. Patient Characteristics and Pharmacological Antihypertensive Treatment at Inclusion

Characteristics	Data (N=21)
Men, %	11 (52)
Age, mean±SD, y	53±10
Office BP at inclusion, mm Hg	
Systolic	190±34
Diastolic	108±14
Heart rate, bpm	79±13
Antihypertensive treatment, n (%)	
No. of patients with 3 different agents	2 (10)
No. of patients with 4 to 5 different agents	15 (71)
No. of patients with ≥6 different agents	4 (19)
Class of drug used, n (%)	
β-Blockers	17 (81)
Angiotensin-converting enzyme inhibitors	9 (43)
Angiotensin receptor antagonists	12 (57)
Loop diuretics	4 (19)
Thiazide diuretics	17 (81)
Aldosterone antagonists	5 (24)
Potassium-sparing diuretics	2 (10)
Calcium channel blockers	15 (71)
Peripheral α-blockers	9 (43)
Central α-agonists	5 (24)
Direct vasodilators	5 (24)
Nitrates	1 (5)

were detected correctly, and, thus, that correct R-R interval series were generated.

Heart Rate Variability

Series of R-R intervals were derived from the 24-hour ECG data for the analysis of HRV according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[13] The following time-domain and frequency-domain HRV analyses were conducted on 24-hour R-R interval sequences devoid of ectopic beats and artifacts using the HRV analysis software developed by Niskanen et al[16] (kindly provided by Drs J. Niskanen and P. A. Karjalainen). HRV analysis was conducted on nondetrended 24-hour R-R interval series.

Time-Domain Analysis

SD of all of the normal R-R intervals (NN) during a 24-hour period (SDNN; milliseconds), reflecting both long- and short-term NN interval variations, and SDNN index (mean of the SDs of all of the NN intervals for all 5-minute segments in 24 hours; milliseconds), reflecting short-term variations, were determined. In addition, the percentage of intervals of >50 ms than the preceding interval (pNN50, %) and the root mean square successive difference of all NN intervals (RMSSD, milliseconds) were computed.[13]

Frequency-Domain Analysis

The HRV power (in milliseconds squared) in the high-frequency (HF; 0.15 to 0.50 Hz) and low-frequency (LF; 0.04 to 0.15 Hz) bands was computed on the basis of the Welch's periodogram (based on the FFT) using windows of 1500 seconds (25 minutes), with an overlap of 750 seconds. The LF:HF ratio was computed as well.[13]

Heart Rate Turbulence

Turbulence onset (TO) reflects the initial acceleration of sinus rhythm after a single premature atrial or ventricular beat, whereas turbulence slope (TS) describes the rate of heart rate deceleration after the sinus acceleration. Available physiological investigations confirm that the initial heart rate acceleration is triggered by transient vagal inhibition in response to the missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction. A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment.[17] Both parameters were derived from 24-hour Holter data for supraventricular premature depolarization and ventricular premature depolarization according to the method of Schmidt et al[15] using HRT View (version 1.11, Klinikum rechts der Isar).

A prerequisite for the determination of HRT parameters is the presence of sinus rhythm free of ectopic beats and artifacts immediately ≥2 beats before and >16 beats after the considered single premature beats. Because TO and TS must be averaged for several ectopic beats, their predictive power is low in the presence of only 1 ectopic beat. Therefore, we analyzed HRT only in the presence of ≥2 either atrial or ventricular premature beats, fulfilling the analysis criteria above. HRT analysis was conducted on nondetrended R-R interval series as well.

Statistical Analysis

Normally distributed data are presented as mean±SD, whereas medians are used for data with nonnormal distribution. Baseline and follow-up clinical data, HRV and HRT measurements were compared using the Wilcoxon signed-rank test. Univariate correlations were performed with Spearman rank correlation. Statistical significance was assumed for $P<0.05$. Statistical analyses were performed using StatView (version 4.57, Abacus Concepts) and SPSS for Windows (version 15.0.1, SPSS Inc).

Results

Baseline Characteristics

The characteristics of the 21 patients are shown in Table 1. At inclusion, systolic and diastolic office BPs were significantly above the recommended target of 140/90 mm Hg despite a pharmacological treatment with 3 to 8 different antihypertensive agents (Table 1), and, on average, they were consistent with hypertension stage III for systolic and stage II for diastolic BP values.

Effect of Chronic Electric Baroreceptor Stimulation on HRV

HRV Time-Domain Results

HRV time domains are measures from series of instantaneous heart rates or cycle intervals. Results from the HRV time-domain analysis are reported in Table 2. Mean heart rate over 24 hours significantly decreased during stimulation therapy ($P=0.001$). All of the time-domain HRV parameters significantly changed during SCB when compared with baseline values. RMSSD, pNN50, SDNN, and SDNN index significantly increased during stimulation therapy, consistent with decreased sympathetic activity and increased parasympathetic activity.

HRV Frequency-Domain Results

HRV frequency-domain measures power spectral density/variation as a function of frequency. In the FFT analysis, the spectral power of the HF and components was significantly changed during SCB (Table 2). The HF component significi-

Table 2. Twenty-Four–Hour HRV Time-Domain and Frequency-Domain Measures and Office BP Values in 21 Patients Before and With Chronic Electrical Baroreflex Stimulation

Variable	Stimulator Off	Stimulator On	P
Time-domain measures			
Heart rate, 1/min	81±11	76±10	0.001
R-R intervals, ms	743±182	818±107	0.002
SDNN, ms	89±20	95±23	0.2
SDNN index, ms	37±10	44±13	<0.001
pNN50, %	1.3 (2.2)	2.6 (4.8)	<0.001
RMSSD, ms	18.6±6.7	24.3±9.5	<0.001
Frequency-domain measures (FFT)			
HF power, ms^2	42 (59)	67 (105)	<0.001
LF power, ms^2	150 (196)	117 (135)	<0.001
Ratio LF:HF	2.78 (2.75)	2.24 (2.09)	<0.001
Office BP			
Systolic BP, mm Hg	184±31	154±23	<0.001
Diastolic BP, mm Hg	109±23	95±15	0.002

SDNN index indicates the mean of the SDNN intervals for all 5-minute segments in 4 hours. Data are mean±SD or median (mean).

cantly increased in power during SCB compared with the data without stimulation, whereas the LF component was diminished in power. Consequently, there was a decrease of the LF:HF ratio (Table 2 and Figure 1), which can be attributed to a sustained decline of the adrenergic level and increased vagal activity during chronic baroreceptor stimulation.

Day and Night HRV

Tables 3 and 4 display the same analysis for night and day measurements. All of the changes found in the 24-hour analysis were also observed during day and night. Although the heart rate was significantly lower during the night, the changes in HRV measurements during chronic baroreceptor stimulation appeared similar during the day and night.

Effect of Chronic Electric Baroreceptor Stimulation on HRT

TO reflects the initial acceleration of sinus rhythm after a single premature atrial or ventricular beat, whereas TS describes the heart rate deceleration after the previous sinus rhythm acceleration. Analysis of HRT after supraventricular premature beats was available in 17 patients and after ventricular premature beats in 13 patients before and during chronic SCB (Table 5). TO and TS were significantly altered during stimulation therapy consistent with an enhanced parasympathetic activity and decreased sympathetic activity by chronic baroreflex activation (Table 4).

BP Results and Correlation to HRV and HRT Results

Chronic SCB, applied on top of the continued antihypertensive pharmacotherapy, significantly lowered systolic and diastolic office BP (Table 1 and Figure 1). Overall, changes in systolic and diastolic BPs correlated significantly in the 21
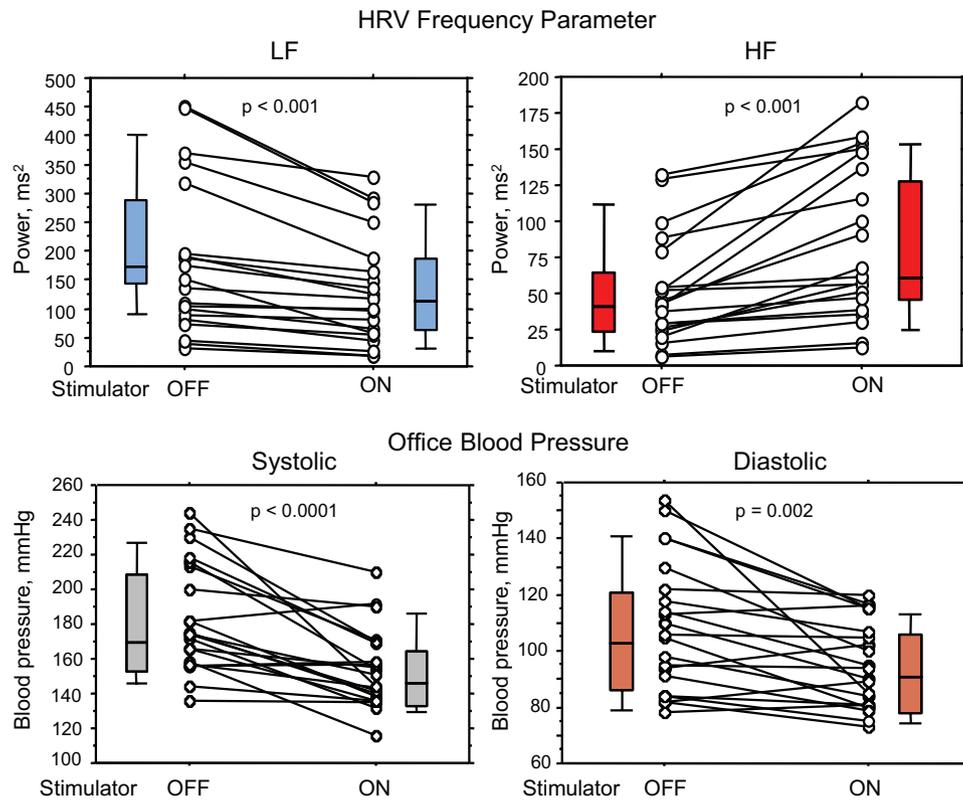
HRV Frequency Parameter

Figure 1. Top, Effect of chronic electric baroreceptor stimulation on LF and HF power, reflecting significant changes in the sympatho-vagal activity consistent with an enhanced vagal outflow and a decreased sympathetic activity during chronic carotid receptor stimulation (ON) vs the control without stimulation (OFF). Bottom, Effect of chronic electric baroreceptor stimulation on office systolic (left) and diastolic (right) BPs.

patients (correlation coefficient: 0.81; $P<0.0001$). Diastolic BP decreased in all but 1 patient with a systolic BP decrement of ≥10 mm Hg. In 4 patients there was only a modest or no response of systolic (<10 mm Hg) and diastolic BPs. Only 1 patient without systolic BP change showed a decrease in diastolic BP. The magnitude of BP reduction was related to baseline systolic ($P=0.001$; correlation coefficient: 0.66) and

baseline diastolic BP levels ($P=0.001$; correlation coefficient: 0.69). The changes in heart rate did not correlate significantly with the changes in BP ($P=0.39$ for systolic BP and $P=0.23$ for diastolic BP).

As illustrated in Figure 2, we found a significant positive correlation between the decrease in systolic BP and the LF:HF ratio for the nonparametric analysis ($P=0.02$).

Table 3.   HRV Measures Analyzed in 21 Patients During Day Before (Off) and During Chronic Electrical Baroreflex Stimulation (On)

Variable	Stimulator Off	Stimulator On	*P*
Time-domain measures			
Heart rate, 1/min	86±13	81±13	0.01
R-R intervals, ms	718±110	764±121	0.009
SDNN, ms	56±16	66±20	0.01
SDNN index, ms	31±9	38±12	0.006
pNN50, %	0.3 (0.6)	1.6 (2.6)	<0.001
RMSSD, ms	14.1±4.0	19.7±6.7	0.001
Frequency-domain measures (FFT)			
HF power, ms^2	27 (24)	36 (55)	<0.001
LF power, ms^2	103 (120)	74 (92)	0.033
Ratio LF:HF	3.63 (3.7)	2.44 (2.46)	<0.001

SDNN index indicates the mean of the SDNN intervals for all 5-minute segments in 4 hours. Data are mean±SD or median (mean).

Table 4.   HRV Measures Analyzed in 21 Patients During the Night Before (Off) and During Chronic Electrical Baroreflex Stimulation (On)

Variable	Stimulator Off	Stimulator On	*P*
Time-domain measures			
Heart rate, 1/min	69±9	65±8	0.006
R-R intervals, ms	885±124	938±111	0.006
SDNN, ms	60±18	71±22	0.003
SDNN index, ms	41±14	51±19	<0.001
pNN50, %	1.9 (4.6)	5.2 (10.7)	<0.001
RMSSD, ms	22.4±9.9	32.2±16.8	<0.001
Frequency-domain measures (FFT)			
HF power, ms^2	67 (97)	116 (196)	<0.001
LF power, ms^2	199 (245)	126 (215)	0.007
Ratio LF:HF	2.10 (2.63)	1.63 (1.81)	<0.001

SDNN index indicates the mean of the SDNN intervals for all 5-minute segments in 4 hours. Data are mean±SD or median (mean).

Table 5. HRT Measures (Median) for TO and TS in Patients Before and With Chronic Electrical Baroreceptor Stimulation After Supraventricular Premature Depolarizations and Ventricular Premature Depolarizations

Turbulence Measures	Stimulator Off	Stimulator On	*P*
TO SVPD, % (n=17)	0.018	0.007	0.076
TS SVPD, ms per beat (n=17)	1.94	4.2	0.01
TO VPD, % (n=13)	−0.002	−0.015	0.004
TS VPD, ms per beat (n=13)	3.75	5.6	0.02

SVPD indicates supraventricular premature depolarization; VPD, ventricular premature depolarization.

Changes in diastolic pressure did not correlate with variations in HRV or HRT parameters.

Discussion

The study demonstrates that chronic bilateral electric SCB is associated with a sustained modulation of HRV and HRT in drug-resistant, severely hypertensive patients. Changes in HRV parameters and changes in HRT are consistent with a decrease of sympathetic activity and an increase of vagal tone. These changes are correlated with a significant decrease in systolic BP. Thus, chronic SCB likely contributes to a better BP control through sympathovagal modulation in severely hypertensive patients.

Previous studies showed the acute effect of SCB on BP measurements.[1,2,10] In addition, short-term (usually 5- to 7-day) experimental observations provided evidence that the efferent response to BP stimuli persists over 5 to 7 days in diverse experimental settings.[18–24] Lohmeier et al[6] demonstrated that electric activation of the baroreflex for 7 days using the same stimulation device as that in our study produces sustained hypotension in dogs. Our study provides for the first time evidence in humans that chronic SCB has a sustained effect on HRV parameters, HRT, and BP values in drug-resistant, severely hypertensive patients without adaptation blunting the effect of stimulation.

In humans, alterations of the cardiac autonomic balance and BP changes over several days have been reported after vascular interventions close to the carotid bifurcation. Carotid arterial stenting was associated with a short-term parasympathetic predominance that was associated with decreased BP.[25–27] This may be attributed to stimulation of the baroreceptors through stretching of the carotid sinus by angioplasty and stent deployment. In contrast, HRV measurements in patients after carotid endarterectomy showed an increased sympathetic and a decreased vagal activity during the first 4 days postprocedure compared with baseline.[27] Carotid endarterectomy and complete bilateral surgical removal of carotid body tumors led to a significant postoperative hypertension.[26,28,29] The mechanism responsible for the baroreflex dysfunction, increased sympathetic activity, and arterial hypertension postsurgery is suspected to be related to the damaging of carotid baroreceptors and the afferent nerves situated on the adventitial site. In the present study, the first Holter recording with the device off was performed 1 month after surgery. An alteration of carotid baroreceptor function at the time of the baseline measurements cannot be fully ruled
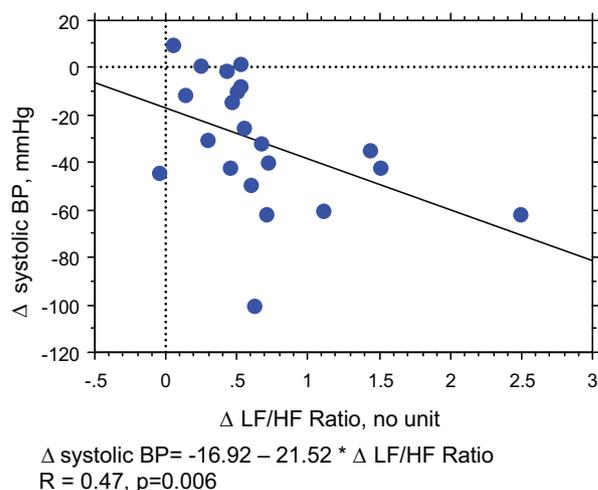

Δ systolic BP= -16.92 − 21.52 * Δ LF/HF Ratio
R = 0.47, p=0.006

Figure 2. Correlation between the systolic BP difference (Δ systolic BP) and the LF:HF ratio from the FFT model.

out. However, all of the patients had clinically fully recovered from surgery. In addition, the integrity of the carotid baroreflex was verified intraoperatively. Therefore, it is very likely that the HRV and HRT changes observed are really showing the effect of SCB.

Although significant, the correlation between BP reduction and HRV parameters was not very strong. Thus, it may be difficult to predict the BP response to chronic SCB with HRV and HRT parameters. There were important interindividual differences in BP reduction, for example, there were 6 patients without a BP decrease in response to chronic SCB therapy. The interindividual variability in the response to treatment may be related to factors affecting the autonomous nervous system, such as diabetic polyneuropathy; to factors responsible for salt retention, such as renal failure; or to conditions associated with an increased sympathetic activity, such as neurovascular compression at the rostral ventrolateral medulla.[30] None of these conditions were exclusion criteria. In addition, some drug interference with the effect of SCB is possible, that is, 5 patients received central α-agonists and 9 were treated with peripheral α-blockers. All of these factors may have influenced the response to SCB and the relationship between HRV parameters and BP changes.

Previous studies in patients with congestive heart failure or postmyocardial infarction have demonstrated that decreases in HRV and HRT are predictors for cardiovascular mortality and morbidity.[14,15,31–33] Increased vagal tone exerts pronounced antiarrhythmic effects counteracting the proarrhythmic effects of the sympathetic nervous activity. SCB prolonged survival in dogs with heart failure provoked by rapid pacing,[34] which was possibly mediated by modulation of the cardiac autonomic system. Indeed, modulation of the autonomic system by SCB may have beneficial effects beyond BP control in humans, and future studies in larger populations are needed.

HRV is sensitive to changes in respiration, and it cannot be excluded in this study that SCB could have affected breathing patterns, given the proximity of chemoreceptors. Extrinsic stimulation of the corresponding afferent axons may possibly

induce a regulatory increase of ventilation and possibly exert a feedback on HRV. Blood gas analyses would represent the method of choice to exclude a possible respiratory alkalosis as an adverse effect. However, these analyses were not implemented in the DEBuT-HT Trial study protocol. Nevertheless, no obvious hyperventilation was observed clinically by the investigators during the follow-up visits for the tuning of the stimulation device.

The current study is subject to certain limitations. There was no control group, and the BP measurements were not performed in a blinded fashion. Although HRV measurements and HRT are established noninvasive parameters reflecting sympathetic and parasympathetic activities, they are no direct measurements of nerve trafficking; HRV and HRT can be influenced by many factors, including cardiac adrenergic receptor sensitivity and pharmacological treatment.[35] However, all of these variables remained stable during the follow-up, and it is likely that observed HRV changes truly reflect the effect of SCB on the cardiovascular autonomic system. A longer follow-up period might have given additional information. However, in these severely hypertensive patients, changes in medication may be needed and cardiovascular events may occur, and such confounding factors would considerably limit the interpretation of the data.

Perspectives

SCB is associated with HRV and HRT changes that are consistent with a decrease of sympathetic activity and an increase of vagal tone. These changes are correlated with a significant decrease in BP. Thus, the data suggest that the modulation of the autonomic nervous system contributes to a better BP control through SCB in severely hypertensive patients. Whether the modulation of the autonomic system has favorable cardiovascular effects beyond BP control should be investigated in further studies.

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Disclosures

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