Carotid Baroreceptor Stimulation, Sympathetic Activity, Baroreflex Function, and Blood Pressure in Hypertensive Patients

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Abstract—In animals, electric field stimulation of carotid baroreceptors elicits a depressor response through sympathetic inhibition. We tested the hypothesis that the stimulation acutely reduces sympathetic vasomotor tone and blood pressure in patients with drug treatment–resistant arterial hypertension. Furthermore, we tested whether the stimulation impairs the physiological baroreflex regulation. We studied 7 men and 5 women (ages 43 to 69 years) with treatment-resistant arterial hypertension. A bilateral electric carotid baroreflex stimulator at the level of the carotid sinus (Rheos) was implanted ≥1 month before the study. We measured intra-arterial blood pressure, heart rate, muscle sympathetic nerve activity (microneurography), cardiac baroreflex sensitivity (cross-spectral analysis and sequence method), sympathetic baroreflex sensitivity (threshold technique), plasma renin, and norepinephrine concentrations. Measurements were performed under resting conditions, with and without electric baroreflex stimulation, for ≥6 minutes during the same experiment. Intra-arterial blood pressure was 193±9/94±5 mm Hg on medications. Acute electric baroreflex stimulation decreased systolic blood pressure by 32±10 mm Hg (range: +7 to −108 mm Hg; *P* = 0.01). The depressor response was correlated with a muscle sympathetic nerve activity reduction (*r*² = 0.42; *P* < 0.05). In responders, muscle sympathetic nerve activity decreased sharply when electric stimulation started. Then, muscle sympathetic nerve activity increased but remained below the baseline level throughout the stimulation period. Heart rate decreased 4.5±1.5 bpm with stimulation (*P* < 0.05). Plasma renin concentration decreased 20±8% (*P* < 0.05). Electric field stimulation of carotid sinus baroreflex afferents acutely decreased arterial blood pressure in hypertensive patients, without negative effects on physiological baroreflex regulation. The depressor response was mediated through sympathetic inhibition. *(Hypertension. 2010;55:619-626.)*

Key Words: autonomic reflex and neurohumoral control of circulation • electrophysiology • pacemaker • clinical studies • sympathetic tone

Blood pressure increases activate stretch-sensitive baroreceptors in the carotid artery and aortic wall. Counterregulatory adjustments in sympathetic and parasympathetic activity lead to stabilization in blood pressure. The mechanism could be exploited.¹ Electric stimulation of baroreflex afferent nerves could be sensed by the brain as blood pressure increases such that sympathetic activity and blood pressure are reduced.²⁻⁴ Electric stimulators directly activating afferent baroreflex nerves were developed years earlier but failed for technical reasons.⁵⁻⁹ Recently, a novel implantable device was developed that may overcome some of these problems.¹⁰,¹¹ The device produces an electric field stimulation of the carotid sinus wall. In dogs, electric carotid baroreflex stimulation with the device produced a sustained reduction in sympathetic nervous system activity and blood pressure.¹² Moreover, in normotensive patients undergoing elective carotid surgery, short-term electric carotid baroreceptor stimulation lowered blood pressure.¹³ Finally, the particularly severe hypertension of an imperiled patient improved substantially after implantation of the device.¹ The mechanisms by which electric carotid sinus field stimulation affects blood pressure in human subjects are unknown. Also unknown is whether the device interferes with baroreflex regulation. We tested the hypothesis that electric carotid baroreceptor stimulation acutely reduces blood pressure through sympathetic inhibition in patients with drug treatment–resistant arterial hypertension. In contrast to pulse-synchronous physiological baroreceptor discharge, electric carotid sinus stimulators fire throughout the cardiac cycle. Therefore, we also asked the question whether continuous electric
carotid field stimulation adversely affects physiological baroreflex regulation.

Methods

Patients
We studied 7 men and 5 women with treatment-resistant arterial hypertension (ages 42 to 70 years) who were willing to undergo additional testing in the Franz-Volhard Clinical Research Center in Berlin, Germany. All of the patients included in our study had been evaluated previously and treated at specialized hypertension clinics in Berlin, Hannover, or Bad Oeyenhausen, Germany. Device-Based Therapy in Hypertension Trial (DEBuT-HT) was a multicenter, nonrandomized feasibility trial evaluating the safety and efficacy of electric carotid baroreflex stimulation in patients with drug treatment–resistant hypertension over a period of 3 months (DEBuT-HT, registered at www.clinicaltrials.gov [identifier NCT0071029]). To be eligible for DEBuT-HT, patients had to have 50% stenosis, previous surgery or radiation in the carotid sinus region, is thought to lead to the excitation of neural fibers located in the adventitia and media of the artery directly under the cathode. The device delivers rectangular pulses with intensities between 0.0 and 7.5 V. Moreover, the temporal pattern of electric impulses may be adjusted in terms of duration, frequency, and grouping.

Therapy in Hypertension Trial (DEBuT-HT) was a multicenter, nonrandomized feasibility trial evaluating the safety and efficacy of electric carotid baroreflex stimulation in patients with drug treatment–resistant hypertension over a period of 3 months (DEBuT-HT, registered at www.clinicaltrials.gov [identifier NCT0071029]). To be eligible for DEBuT-HT, patients had to have >160 mm Hg systolic and/or >90 mm Hg diastolic blood pressure despite treatment with ≥3 antihypertensive medications at full doses, including a diuretic. All of the patients were judged to be compliant. Participants were excluded if they had baroreflex failure, significant orthostatic hypotension, atrial fibrillation, valvular heart disease, or secondary hypertension. Patients with evidence for obstructive sleep apnea were excluded. However, formal sleep studies were not mandatory. Other exclusion criteria were carotid atherosclerosis with >50% stenosis, previous surgery or radiation in the carotid sinus region, currently implanted electric medical devices, dialysis, or pregnancy. The Charité Institutional Review Board approved our study, and all of the patients gave written informed consent.

Implantation of the Baroreflex Stimulator
The Rhoes Baroreflex Hypertension Therapy System (CVRx, Inc) consists of an internal programmable pulse generator, 2 electrode leads, and 2 field electrodes. Stimulation of the vessel wall in the carotid sinus region is thought to lead to the excitation of neural fibers located in the adventitia and media of the artery directly under the cathode. The device delivers rectangular pulses with intensities between 0.0 and 7.5 V. Moreover, the temporal pattern of electric impulses may be adjusted in terms of duration, frequency, and grouping.

The surgical procedure has been described in detail elsewhere. Briefly, the neck was incised on both sides to expose the carotid bifurcation. Intraoperatively, several electrode positions at the level of the carotid bifurcation were tested to identify a suitable electrode position. Once the location eliciting optimal hemodynamic response had been identified, the electrode was sutured in place. The internal pulse generator was placed in a subcutaneous pocket and the leads were tunneled subcutaneously. Similar to a cardiac pacemaker, pulse generator settings could be programmed transcutaneously. Because animal studies suggested that electric stimulation might interfere with wound healing, the stimulator remained switched off for the first month after implantation. Then, patients presented to the respective study site for dose-response testing and determination of individual stimulator settings eliciting the best blood pressure reduction without causing pharyngeal discomfort or coughing. The impulse width was 480 μs with a stimulation frequency between 20 and 100 Hz. The stimulation amplitude ranged between 4.0 and 7.0 V.

Cardiovascular and Sympathetic Measurements
We conducted our measurements ≥1 month after device implantation after an overnight fast in the morning hours. During the test, patients remained in the supine position. An ECG was continuously recorded (Niccomo, Medis GmbH). Beat-by-beat arterial blood pressure was measured through an indwelling catheter in the radial or brachial artery. Noninvasive finger blood pressure recording was used in 2 patients (Finapres, TNO) and adjusted against brachial artery. Noninvasive finger blood pressure recording was used in 2 patients (Finapres, TNO) and adjusted against brachial artery. Noninvasive finger blood pressure recording was used in 2 patients (Finapres, TNO) and adjusted against brachial artery.
position within the nerve. Data were analog-to-digital converted and analyzed using a program written by one of the authors (A.D.). We determined the following MSNA parameters from the integrated nerve signal: the burst frequency, that is, the number of MSNA bursts per minute; the burst incidence, that is, the number of bursts per 100 heart beats; and the total activity, that is, the area under the bursts per minute as arbitrary units per minute. For estimation of the average burst strength as a measure for the number of action potentials within 1 single burst, we calculated the mean burst area as a quotient between total activity and burst frequency.

After instrumentation, subjects rested for ≥20 minutes to achieve a stable baseline. Then, the stimulator was switched on for a period of ≥14 minutes. At the end of the first 2 periods with stimulation turned on or off, respectively, we obtained venous blood samples in 9 patients for plasma renin and norepinephrine concentration measurements. In 6 patients (patients 1 and 8 through 12), we tested the repeatability of the response to electric baroreflex stimulation by switching the stimulator on and off intermittently in 6- or 9-minute intervals.

To assess chronic blood pressure responses to baroreceptor stimulation, we obtained 24-hour recordings by oscillometric measurements at the upper arm (SpaceLabs Healthcare) before and at the end of a continuous stimulation period of ≥4 months. We did not obtain microneurography data at these points in time. To allow for comparison between acute and chronic responses, individual antihypertensive medication and stimulation parameters were kept constant throughout the study.

Heart Rate Variability
Power spectral density of heart rate variability (HRV) was estimated from 5-minute recordings of RR intervals during spontaneous breathing with the fast Fourier transformation-based Welch algorithm. Total power, power in the low-frequency range (LF: 0.04 to <0.15 Hz), high-frequency range (HF: 0.15 to <0.40 Hz), and the LF to HF ratio (LF/HF) were calculated according to the task force recommendations.15 Two patients were excluded from the analysis because of premature beats and 1 because of artifacts in the ECG signal.

Baroreflex Heart Rate Regulation
Spontaneous baroreflex sensitivity was calculated as the slope of the linear regression line between systolic blood pressures and subsequent RR intervals (within the same or the next heart beat) using the sequence technique.16,17 Sequences with ≥3 intervals, 0.5-mm Hg

Table 2. Individual Hemodynamic Variables

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<tr>
<th>Identification No.</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>HR, bpm</th>
<th>MSNA, Burst per min</th>
<th>MSNA, Burst per 100 Heartbeats</th>
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<td>60</td>
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<td>59.8</td>
<td>2.63</td>
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SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; au, arbitrary unit; …, no data.

Figure 1. A, Original recordings showing arterial blood pressure (ABP) and MSNA recordings in patient 9. When the stimulator was switched on (upper panel), ABP and MSNA acutely decreased and remained decreased during 9 minutes of continuous stimulation. After this period, the stimulator was switched off (lower panel). ABP and MSNA returned to the baseline level. B, Mean responses showing average arterial blood pressure (ABP), heart rate (HR), and MSNA responses in patient 9 over 6 cycles of alternating stimulation. During each cycle, the stimulator remained off for 9 minutes and was then switched on for 9 minutes.
blood pressure changes, and 5-ms RR interval changes were analyzed only if the correlation coefficients were >0.85. Moreover, we determined the total number of sequences and the number of significant sequences. In addition, we determined baroreflex sensitivity using cross-spectral analysis between RR intervals and systolic blood pressure variability in the low-frequency band if the coherence in the frequency band was >0.5. Both methods were applied to 5-minute recordings during spontaneous breathing. Two patients were excluded from the analysis because of premature beats.

**Sympathetic Baroreflex Sensitivity**

We assessed sympathetic baroreflex sensitivity using the threshold technique as described by Kienbaum et al. The method quantifies the percentage of cardiac cycles associated with a sympathetic burst and diastolic blood pressure.

**Statistical Analysis**

All of the data are expressed as mean±SEM. Intraindividual differences were compared by the paired t test. The relationship between measurements was assessed by correlation analysis. A value for \( P<0.05 \) was considered significant.

**Table 3. Individual Changes in Hemodynamic Variables**

<table>
<thead>
<tr>
<th>Identification No.</th>
<th>( \Delta \text{SBP, mm Hg} )</th>
<th>( \Delta \text{DBP, mm Hg} )</th>
<th>( \Delta \text{HR, bpm} )</th>
<th>Bursts per min</th>
<th>Bursts per 100 Heartbeats</th>
<th>( \Delta \text{MSNA} )</th>
<th>( 10^{-3} \text{ au per Burst}^* )</th>
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\( \Delta \text{SBP} \) indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; au, arbitrary unit; \..., no data.

**Results**

Baseline characteristics of our patients are given (Tables 1 and 2). Serum creatinine was 103±7 \( \mu \text{mol/L} \) in men and 81±5 \( \mu \text{mol/L} \) in women. The left ventricular ejection fraction was 61±3%, and the heart failure class according to the New York Heart Association was II or less. All of the patients were in sinus rhythm. Intra-arterial blood pressure on medications with the stimulator switched off was 193±9/94±5 mm Hg. Original recordings of a patient who responded to carotid baroreflex stimulation are shown (Figure 1A). In this patient, MSNA in terms of burst frequency, burst incidence, total MSNA, and burst area (mean area of a single burst) decreased sharply when electric baroreflex stimulation was begun. Then, MSNA increased but remained below the baseline level throughout the stimulation period (Figure 1B). The reduction in sympathetic activity was followed by decreased blood pressure after a few seconds. When the stimulator was switched off, MSNA increased immediately above the baseline level and then returned to the baseline level. Again, the change in sympathetic activity was followed.
within a few seconds by a concomitant blood pressure increase. The response was repeatable. MSNA and blood pressure reduction occurred each time when the stimulator was turned on as shown (Figure 2) for another subject.

Individual changes in blood pressure, heart rate, and MSNA to acute electric baroreflex stimulation are displayed (Table 3). On average, systolic blood pressure decreased 32±10 mm Hg (range: 7 to −108 mm Hg; P=0.01), and heart rate was lowered 4.5±1.5 bpm with electric baroreflex stimulation (P<0.05). The reduction in systolic blood pressure was correlated with the reduction in burst frequency (r²=0.45; P<0.05), total activity (r²=0.42; P<0.05), and burst area (r²=0.44; P<0.05) but not with burst incidence (r²=0.17; P=0.21). We observed similar correlations between reductions in diastolic blood pressure and MSNA (burst frequency: r²=0.42, P<0.05; total activity: r²=0.34, P=0.06; burst incidence: r²=0.14, P value not significant; burst area: r²=0.23, P value not significant). Blood pressure changes were also correlated or tended to correlate with reduction in norepinephrine plasma levels (r²=0.38, P=0.07 for systolic and r²=0.45, P<0.05 for diastolic blood pressure; Figure 3), whereas the numeric norepinephrine decrease with stimulation did not reach statistical significance (341±41 versus 290±48 ng/L; P=0.12). Plasma renin concentration was lowered by 20±8% with electric baroreflex stimulation (9.6±2.1 versus 6.9±1.8 ng/L; P<0.05).

Chronic 24-hour blood pressure decreased significantly (systolic pressure: −10±12 mm Hg; P<0.05) or tended to do so (diastolic pressure: −6±10 mm Hg; P=0.08). Changes in chronic 24-hour blood pressure correlated with the acute blood pressure response in the laboratory (r²=0.33 for systolic and r²=0.35 for diastolic blood pressure; P<0.05 for both).

Electrical baroreflex stimulation tended to increase HRV in terms of total and LF power. HF power and the LF/HF ratio did not change (Table 4). Baroreflex heart rate regulation determined by cross-spectral analysis and sequence technique did not worsen with baroreflex stimulation (Table 5 and Figure 4A and 4B). Even with several repeated stimulations, baroreflex heart rate regulation did not deteriorate (Figure 5). The number of total sequences (off: 6±1 sequences per minute; on: 6±1 sequences per minute), as well as the number of significant sequences (off: 6±1 sequences per minute; on: 5±1 sequences per minute), was not significantly altered by the stimulation. The sympathetic baroreflex sensitivity was −2.00±0.38%/mm Hg with the stimulator turned off and −1.92±0.43%/mm Hg with the stimulator turned on (P value not significant).

Discussion

The main finding of our study is that electric field stimulation of carotid baroreceptors acutely reduced sympathetic nerve activity in a subgroup of patients with refractory arterial hypertension. The reduction in sympathetic activity was associated with decreases in plasma renin concentration and blood pressure. Moreover, electric field stimulation of carotid baroreceptors throughout the cardiac cycle did not impair physiological baroreflex control, and our patients did not report symptoms suggestive of baroreflex dysfunction. Baroreflex regulation of heart rate and MSNA were maintained at lower blood pressure levels, implying a leftward shift of the baroreflex curves and their operating points. The findings provide a mechanism mediating the blood pressure

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<td>3.97±0.81</td>
<td>5.19±1.22</td>
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</table>

Values are mean±SEM. BRS indicates baroreflex sensitivity; US, up sequences (sequence analysis); DS, down sequences (sequence analysis).
response to electric field stimulation of the carotid baroreceptors and provide unique insight into human baroreflex physiology.

We used microneurography to monitor changes in centrally generated sympathetic activity. The method determines sympathetic vasomotor tone in human subjects. Electric baroreflex stimulation rapidly decreased MSNA and blood pressure. A similar response was observed previously in 4 patients in whom baroreflex afferent nerves were directly stimulated. It is possible that electric field stimulation of the wall of the proximal internal carotid artery is superior to direct stimulation of the carotid sinus nerve because it may coactivate efferent sympathetic fibers that increase baroreceptor sensitivity. Given the anatomic position of the field electrode, chemoreflex afferents may be spared.

The stimulation resulted in concomitant reductions in sympathetic nerve activity and blood pressure strongly suggesting a centrally mediated response. Similarly, sympatholytic medications acting in the brain, such as clonidine, reduce sympathetic nervous system activity and blood pressure. The hypothesis that blood pressure reduction is mediated through the central nervous system is further supported by the time course of the response. Normally, blood pressure reduction elicits a baroreflex-mediated increase in heart rate and in circulating renin concentrations. The latter response is mediated mainly through renal sympathetic activation. Instead, we observed reductions in heart rate and suppression of renin release with electric carotid baroreflex stimulation. Together, our observations suggest that electric field stimulation of carotid baroreceptors acutely attenuates sympathetic activation of vasculature, heart, and kidney. Blood pressure responses to acute baroreceptor stimulation were variable among patients, and they were related to the change in sympathetic activity. The finding is compatible with data from patients treated with direct carotid sinus nerve stimulation. The authors suggested that poor blood pressure responses may be explained by reduced sympathoinhibition. In our study, both MSNA burst number and burst strength responded to electric carotid sinus stimulation. However, these measures did not always change in parallel. Theoretically, the reduction in burst strength could result from a reduction in the number of recruited sympathetic nerve fibers. Another explanation could involve decreased discharge frequency of an unchanged sympathetic nerve fiber number.

Compared with the reduction in sympathetic nerve activity, heart rate responses were rather small. Resting heart rate and its variability are primarily under parasympathetic control. Because parasympathetic heart rate regulation deteriorates...
with age and more so in patients with arterial hypertension, the heart rate reduction that can be achieved with baroreflex stimulation may be limited. Indeed, patients in our study exhibited low resting heart rate variability. However, in some patients, heart rate reduction may have contributed to the depressor response (Figure 3).

Continuous nonphysiological electric stimulation might disturb the function of peripheral or central components of the arterial baroreflex and cause a condition resembling baroreflex failure.3,5,12 This clinical state was an exclusion criterion for DEBuT-HT, and carotid sinus stimulation did not cause baroreflex deficits, as judged by different methods. If anything, in a few patients the baroreflex sensitivity increased, which could be because of true improvement in baroreflex function with an increase in the maximal slope of the sigmoidal baroreflex curve or by a shift of the operating point to the steeper portion of the curve.

Whether arterial baroreflexes affect long-term control of sympathetic activity and arterial blood pressure is controversial.2,12,30,34,35 Authorities believed that the baroreflex is not involved in long-term arterial blood pressure control.30,36 Indeed, the baroreflex was thought to reset almost completely to the prevailing arterial blood pressure level, which would exclude a chronic effect on sympathetic activity and blood pressure. However, more recent studies in animals suggest that baroreflex mechanisms can drive a sustained increase in blood pressure.31 Furthermore, electric carotid baroreceptor stimulation chronically reduced blood pressure in dogs.12 Our data indicate that a patient’s response to acute carotid sinus stimulation may predict chronic changes in ambulatory blood pressure to a certain degree. The hypothesis that carotid baroreceptor stimulation improves human blood pressure in the long term is currently being tested in a randomized and double-blind clinical trial (www.clinicaltrials.gov identifier NCT00442286). The decrease in plasma renin concentration that we observed with baroreceptor stimulation is promising given the important contribution of the renin-angiotensin system in sodium balance and long-term blood pressure control.28,34,37

Heterogeneity in the contribution of baroreflex and sympathetic nervous system mechanisms to blood pressure may have contributed to variability in the response to carotid sinus stimulation in our subjects. Anatomic and functional properties of the carotid sinus, as well as the implantation procedure, may also play a role. These mechanisms should be investigated in more detail before the technology is widely adopted in clinical practice.

Remarkably, the nonphysiological stimulation mode was not associated with sympathetic or cardiac baroreflex dysfunction. The finding suggests that the plasticity of the nervous system allows for a relatively crude electric stimulus to be processed in the complex baroreflex circuit. Similarly, the abnormal and in many ways impoverished input provided by cochlear implants nonetheless restores hearing in deaf people.38 Nevertheless, on the basis of experimental data,39 we and others23 suggest that a more physiological discharge pattern of a carotid sinus stimulator with coupling to the cardiac cycle could be beneficial. For example, electric discharges could be linked to the systolic blood pressure upstroke using electrocardiography or thoracic impedance as a feedback. These measures could save battery life and, perhaps, improve efficacy.

Our investigation has limitations. The study relied on DEBuT-HT, which was designed as a nonrandomized feasibility trial without a control group. Therefore, our findings on long-term blood pressure control should be interpreted with caution. Furthermore, the number of patients enrolled in our study was relatively low. Baroreflex measurements relied on spontaneous blood pressure changes, which may have limitations in patients with high MSNA. In these patients, the baroreflex may operate near its threshold in a nonlinear portion of the baroreflex curve. Finally, antihypertensive medication, which, for clinical reasons, had to be continued, could have affected our results.

**Perspectives**

Electric field stimulation of carotid sinus baroreflex afferents acutely decreases arterial blood pressure in a subgroup of patients with treatment-resistant arterial hypertension on ≥8 antihypertensive drugs while leaving baroreflex function undisturbed. The depressor response is mediated through sympathetic inhibition. Although electric carotid sinus stimulation is not linked with the cardiac cycle, baroreflex regulation of heart rate and sympathetic vasomotor tone appears to be maintained. Moreover, our study might also suggest that acute responses to electric carotid sinus stimulation predict long-term efficacy. The role of the sympathetic nervous system with chronic treatment should be examined in future studies. The approach may have use in the treatment of hypertensive patients not responding to or not tolerating antihypertensive medications.

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**Disclosures**

During parts of study, T.P. was employed by CVRx, Inc, S.En., J.M., S.Ec., T.P., H.H., F.C.L., and J.J. participated as investigators in the Device-Based Therapy in Hypertension Trial. F.C.L. served as scientific advisor for CVRx, Inc.

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