Carotid Sinus Stimulation in Resistant Hypertension

Acute Response to Unilateral Unipolar Electrical Carotid Sinus Stimulation in Patients With Resistant Arterial Hypertension

Karsten Heusser,* Jens Tank,* Julia Brinkmann, Jan Menne, Jessica Kaufeld, Silvia Linnenweber-Held, Joachim Beige, Mathias Wilhelm, André Diedrich, Hermann Haller, Jens Jordan

Abstract—Bilateral bipolar electric carotid sinus stimulation acutely reduced muscle sympathetic nerve activity (MSNA) and blood pressure (BP) in patients with resistant arterial hypertension but is no longer available. The second-generation device uses a smaller unilateral unipolar disk electrode to reduce invasiveness while saving battery life. We hypothesized that the second-generation device acutely lowers BP and MSNA in treatment-resistant hypertensive patients. Eighteen treatment-resistant hypertensive patients (9 women/9 men; 53±11 years; 33±5 kg/m²) on stable medications have been included in the study. We monitored finger and brachial BP, heart rate, and MSNA. Without stimulation, BP was 165±31/91±18 mm Hg, heart rate was 75±17 bpm, and MSNA was 48±14 bursts per minute. Acute stimulation with intensities producing side effects that were tolerable in the short term elicited interindividually variable changes in systolic BP (−16.9±15.0 mm Hg; range, 0.0 to −40.8 mm Hg; P=0.002), heart rate (−3.6±3.6 bpm; P=0.004), and MSNA (−2.0±5.8 bursts per minute; P=0.375). Stimulation intensities had to be lowered in 12 patients to avoid side effects at the expense of efficacy (systolic BP, −6.3±7.0 mm Hg; range, 2.8 to −14.5 mm Hg; P=0.028 and heart rate, −1.5±2.3 bpm; P=0.078; comparison against responses with side effects). Reductions in diastolic BP and MSNA (total activity) were correlated (r²=0.329; P=0.025). In our patient cohort, unilateral unipolar electric baroreflex stimulation acutely lowered BP. However, side effects may limit efficacy. The approach should be tested in a controlled comparative study. (Hypertension. 2016;67:585-591. DOI: 10.1161/HYPERTENSIONAHA.115.06486.) ☞ Online Data Supplement

Key Words: autonomic nervous system ■ baroreflex ■ carotid sinus ■ electrodes ■ heart rate ■ hypertension ■ pressoreceptors

Devices reducing blood pressure (BP) through stimulation of afferent baroreflex nerves have been developed decades ago but failed mainly for technical reasons. More recently, implantable devices electrically stimulating the carotid sinus have been developed and clinically tested in patients with severe treatment-resistant hypertension. The first-generation device (Rhoes) applied bilateral localized field stimulation through bipolar electrodes in tripolar configuration placed around the carotid sinuses. In carefully conducted animal experiments and an uncontrolled clinical trial on resistant hypertension, the treatment lowered BP. A mechanistic substudy showed that BP reduction was mediated through sympathetic inhibition and that normal baroreflex regulation remained intact with carotid sinus stimulation. In the controlled phase of a subsequent clinical trial, electric carotid sinus stimulation lowered BP; however, the predefined end point acute efficacy defined as proportion of ≥10 mm Hg systolic BP (SBP) responders was not significantly different between groups. The second-generation device (neo), which is approved and clinically applied in Europe, uses a small unilateral unipolar disk electrode to decrease invasiveness and to improve battery life. Patients with resistant arterial hypertension implanted with the new device showed BP reductions in an uncontrolled clinical trial. A controlled clinical trial is currently ongoing in the United States (NCT01679132). Electric fields produced by disk-shaped unipolar electrodes differ markedly from electric fields produced by bipolar circumferential electrodes, which together with modified stimulation settings could affect the efficacy in engaging carotid baroreceptors. The side-effect profile attributable to electric stimulation of surrounding anatomic structures could also differ between unipolar and bipolar electrode designs. Therefore, we tested the hypothesis that unilateral unipolar carotid sinus stimulation...
elicits acute reductions in sympathetic vasoconstrictor tone and BP in patients with treatment-resistant hypertension.

Methods

Patients
We included patients with treatment-resistant hypertension who had been implanted with the CVRx Barostim neo System for baroreflex activation therapy. All patients included in our study had previously been evaluated and treated at specialized hypertension clinics in Germany. Patients with mental inability, drug or alcohol addiction, and secondary forms of hypertension and pregnant or breast-feeding women have been excluded. The ethics committee of Hannover Medical School approved our study, and all patients gave written informed consent.

Electric Baroreflex Stimulation
The second-generation carotid sinus stimulator (neo; CVRx, Inc, Minneapolis, MN) consists of a programmable pulse generator that is implanted subcutaneously near the collar bone, a unipolar disk electrode that is sutured unilaterally to the carotid sinus wall (Figure 1), and a lead connecting generator and electrode. The device delivers constant current as rectangular pulses. Impulse width, intensity, and frequency can be programmed transcutaneously.

We subjected patients to alternating on/off protocols with different stimulation intensities that have been individually determined by stepwise adjustments of stimulation intensity. The timing of the protocol was guided by automated BP measurements whose interval was set at 2 minutes. Immediately after each second measurement, we switched the stimulation to the opposite state. Thus, each on or off period, respectively, lasted for 4 minutes. We did not inform the patients about the switching times.

Cardiovascular and Sympathetic Measurements
We conducted the experiments after an overnight fast in the morning hours while patients remained in the supine position. ECG, finger BP (Finometer MIDI; Finapres Medical Systems, Amsterdam, the Netherlands), and thoracic impedance to monitor breathing movements (Niccomo; medis GmbH, Ilmenau, Germany) were continuously recorded. Brachial oscillometric BP measurements (Dinamap Pro 100; GE Healthcare, Waukesha, Wisconsin) were performed twice during the alternating on/off protocol. Muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve (Nerve Traffic Analyzer 662C-3; Biomedical Engineering Department, University of Iowa, Iowa City, IA) as described previously. 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: burst frequency, that is, the number of MSNA bursts per minute, burst incidence, that is, the number of bursts per 100 heart beats, and total MSNA, that is, the area under the bursts per minute as arbitrary units per minute. We assessed 3 parameters of spontaneous cardiac baroreflex sensitivity (BRS) for 5-minute resting periods using cross-spectral analysis between SBP and RR-interval variances in the low-frequency band (BRS_lf) and the sequence technique (BRS_us and BRS_ds). After instrumentation, subjects rested for at least 20 minutes to achieve a stable baseline with the stimulator on or off. This implies that patients may have been studied after prolonged baroreflex activation. Then, we identified stimulation intensities eliciting side effects that were tolerable for the time of the experiment and intensities that could be applied chronically. Afterward, we started the alternating on/off protocol. In 9 patients, we were able to obtain on/off-protocol data with both of these stimulation intensities.

Statistical Analysis
Individual data originating from the alternating on/off protocol are medians. Group data are expressed as mean±SD. Responses to electric carotid sinus stimulation were grouped on the basis of side effects (present/absent). We tested group responses to the stimulation using 1-sample tests and response differences between the groups (t and Wilcoxon signed-rank test considering data distribution). In addition, for patients with response data during both conditions, that is, with and without stimulation side effects, we compared their responses using the paired t test. The relationship between measurements was assessed by correlation analysis. A P value of <0.05 was considered significant.

Results
We studied 18 treatment-resistant hypertensive patients (9 women/9 men). Baseline characteristics are given in Table 1 and Table S1 in the online-only Data Supplement. In 3 patients, we could not find a stable microneurographic recording position in the peroneal nerve. Sympathetic outflow was elevated in our patients when compared with normotensive controls taking age, sex, and body mass index into account.

Without electric carotid sinus stimulation, BP was 165±31/91±18 mm Hg, heart rate (HR) was 75±17 bpm, and MSNA was 48±14 bursts per minute while patients were on antihypertensive medications (Table S1). Figure 2 shows original finger BP, HR, and MSNA tracings during decremental stimulation intensities in a patient responding to carotid sinus...
For comparison, we also included data on acute BP responses $P = 0.098$, HR: $P = 0.078$/ $P = 0.090$, and MSNA burst $P = 0.285$/ $P = 0.042$, PP: $P = 0.028$.

Avoiding intolerable stimulation-related side effects reduced (on/off) protocols were given in Table 2: stimulation with intensities producing side effects that were tolerable in the short term changed SBP, $-16.9\pm 15.0$ mm Hg ($P = 0.002$). However, the response showed large interindividual variability ranging between 0.0 and $-40.8$ mm Hg (Figure 4, middle). Pulse pressure (PP) changed $-10.6\pm 11.0$ mm Hg ($P = 0.007$), HR changed $-3.6\pm 3.6$ bpm ($P = 0.004$), and MSNA changed $2.0\pm 5.8$ bursts per minute ($P = 0.375$).

Twelve patients reported jaw or neck pain, globus or swallowing sensation, coughing, or voice problems. We had to decrease stimulation intensities in these patients to avoid side effects with chronic treatment. The alternating on/off protocol with reduced stimulation intensity (Figure 4, right) changed SBP, $-6.4\pm 7.0$ mm Hg (range, 2.8 to $-14.5$ mm Hg; $P = 0.003$), PP, $-4.2\pm 8.4$ mm Hg ($P = 0.073$), HR, $-1.5\pm 2.3$ bpm ($P = 0.023$), and MSNA, $0.6\pm 3.5$ bursts per minute ($P = 0.701$). Avoiding intolerable stimulation-related side effects reduced efficacy in terms of BP response (SBP: $P = 0.028$/ $P = 0.042$, PP: $P = 0.285$/ $P = 0.098$, HR: $P = 0.078$/ $P = 0.090$, and MSNA burst frequency: $P = 0.286$/ $P = 0.243$; paired/unpaired comparison).

For comparison, we also included data on acute BP responses from a previous study in patients implanted with the bilateral carotid sinus stimulator Rheos (Figure 4, left). Reductions in diastolic BP (DBP) and total MSNA during the on/off protocol were correlated ($r^2 = 0.329$; $P = 0.025$; Figure 5).

To visualize intradividual variabilities in the BP response to repeated acute electric carotid sinus stimulation, we grouped patients according to their median acute BP response. In each response group, we plotted all acute responses during on/off testing (Figure 6). We did not observe breath holding or similar maneuvers that may have influenced the results. Furthermore, acute responses to electric carotid sinus stimulation were similar in patients who had been chronically stimulated ($\Delta$SBP: $-17.8$ mm Hg with side effects and $-5.3$ mm Hg without side effects) and in patients in whom the stimulator had been off before testing ($\Delta$SBP: $-15.6$ mm Hg with side effects and $-8.9$ mm Hg without side effects). Furthermore, responses to electric carotid sinus stimulation in terms of SBP or MSNA reduction were not correlated with prevailing SBP, MSNA, or HR with the stimulator off (correlations: $\Delta$SBP×total MSNA: $r^2 = 0.024$, $P = 0.579$; $\Delta$SBP×SBP: $r^2 = 0.072$, $P = 0.282$; $\Delta$SBP×HR: $r^2 = 0.077$, $P = 0.265$; total MSNA×total MSNA: $r^2 = 0.001$, $P = 0.923$; total MSNA×SBP: $r^2 = 0.001$, $P = 0.936$; total MSNA×HR: $r^2 = 0.027$, $P = 0.558$). Likewise, response magnitude cannot be predicted on the basis of spontaneous cardiac BRS parameters (correlations: $\Delta$SBP×BRS_Lf: $r^2 = 0.001$, $P = 0.923$; $\Delta$SBP×BRS_us: $r^2 = 0.001$, $P = 0.892$; $\Delta$SBP×BRS_ds: $r^2 = 0.021$, $P = 0.570$).

With chronic electric carotid sinus stimulation with intensities producing minimal or no side effects, office BP decreased ($\Delta$SBP: $-15.5\pm 14.6$ mm Hg, $P = 0.009$; $\Delta$DBP: $-9.1\pm 12.8$ mm Hg, $P = 0.137$; $\Delta$PP: $-6.4\pm 10.7$ mm Hg, $P = 0.090$; $\Delta$HR: $-5.6\pm 12.9$ mm Hg, $P = 0.201$; n=10).

**Discussion**

The main finding of our study is that electric carotid sinus stimulation using a unilateral unipolar electrode produces individually variable acute reductions in BP, HR, and MSNA in patients with resistant arterial hypertension. Reductions in BP and MSNA were related to each other. The finding supports the idea that sympathetic inhibition contributes to BP lowering through electric carotid sinus stimulation. HR reductions

**Table 1. Patient Baseline Characteristics (n=18)**

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<th>Parameter</th>
<th>Mean±SD</th>
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<tr>
<td>Age, y</td>
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<td>BMI, kg/m²</td>
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<td>HR, bpm</td>
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<td>MSNA, bursts/min</td>
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<td>Medications</td>
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a.u. indicates arbitrary units; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; medications, no. of antihypertensive medication classes; and SBP, systolic blood pressure.

**Figure 2.** Original recording. Finger blood pressure (FBP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) in a patient responding to electric carotid sinus stimulation. Shaded areas indicate stimulation intervals. The darkness level indicates stimulation intensity. Top, Stimulator settings. Each time the stimulator was on, BP, HR, and MSNA decreased in a stimulation intensity–related fashion. Please note that the baseline of the MSNA recording increased with stimulation intensity likely indicating stray currents. Bottom, Trace represents the enlarged view of the framed portion of the MSNA recording. Electric baroreflex stimulation was switched on at 0 s. Note the marked reduction in MSNA burst frequency and the effect of stray currents.
with electric carotid sinus stimulation were limited even in some patients with a BP and MSNA response. Possible explanations include different baroreceptor stimulation thresholds for vasomotor and cardiac responses\textsuperscript{19} or selective stimulation of baroreflex afferents controlling different effectors.\textsuperscript{20–22} Two thirds of our patients (12 of 18) experienced stimulation-related side effects such that stimulation intensity had to be reduced. In these patients, lowering of stimulation intensity to chronically tolerable levels was associated with marked reduction in the acute efficacy. Nevertheless, office BP improved with chronic treatment. Whether chronic reduction in office BP resulted from electric carotid sinus stimulation cannot be ascertained in the absence of a control group. In fact, we previously showed that acute responses to electric carotid sinus stimulation predict chronic ambulatory BP responses.\textsuperscript{7} Our findings are important for the clinical use of electric carotid sinus stimulators, which are approved in the European Union, and for the design of future devices.

The pathophysiology of essential hypertension is heterogeneous. The same state-of-affairs is likely true for severely affected patients not sufficiently responding to standard antihypertensive combination therapy. In these patients with treatment-resistant hypertension, sympathetic activation has been implicated in maintaining hypertensive BP levels.\textsuperscript{23} We previously observed that the contribution of sympathetic activity to BP assessed through near complete pharmacological ganglionic blockade markedly differs between patients with arterial hypertension.\textsuperscript{24} Surgical sympathectomy also elicited variable BP reductions in hypertensive patients, and some did not respond at all.\textsuperscript{25} Therefore, among patients with resistant

### Table 2. Responses to Electric Baroreflex Stimulation Taking Into Account SE Occurrence (+, Yes/−, No)

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<tr>
<th>Pat. ID</th>
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<th>ΔMSNA, Bursts per 100 Heart Beats</th>
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a.u. indicates arbitrary units; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; SBP, systolic blood pressure; and SE, side effect.
hypertension, a certain proportion of true nonresponders to a treatment reducing sympathetic activity can be expected. However, in our patients, the overall acute response to stimulation that was tolerable in the long term was surprisingly small, and more than a third of patients did not respond at all. Although we observed nonresponders in our previous study applying bilateral bipolar electric carotid sinus stimulation, reductions in BP and MSNA were more robust.

It is likely that a substantial part of the modest response in our patients is explained by insufficient carotid baroreceptor engagement. Both electrode placement and electrode design could be causative. We studied patients who had been implanted by vascular surgeons with extensive experience in implanting such devices. Moreover, we adhered to all recommendations for implantation provided by the device manufacturer. Finally, we did not observe obvious differences between patients implanted in different centers. In any case, if successful implantation were more operator dependent than with the bipolar electrode, this would pose a limitation for more widespread clinical use. We suggest that the unipolar design of the electrode may not be ideal. The electric current travels between the electrode and the pacemaker located in the upper chest such that baroreceptor stimulation may be limited by stray currents eliciting side effects through off-target electric stimulation. We noticed a peculiarity as exemplified in Figure 2 that supports the idea: The lower lane shows integrated MSNA. Although there is evident suppression of sympathetic bursts with strong stimulation (leftmost, darkest gray area), the MSNA trace is offset to a higher level (dashed line for comparison). The offset is smaller with less intense stimulation (middle and right gray area). The observation suggests the presence of stray currents reaching down to the popliteal space where they are picked up by the microneurographic electrode pair.

The anatomy of the carotid sinus and baroreceptor distribution is variable and may not always be covered by the electric field produced by a small disc–shaped electrode. Indeed, electrode design substantially affects the properties of the stimulating electric field. The unipolar design allows for greater penetration of the electric current into the media of the carotid artery where the baroreceptors are located. On the other hand, current spread to adjacent structures may precipitate side effects. Smaller electrode spacing may increase the threshold for unwanted side effects without compromising the desired response. Development of multichannel electrodes may further improve stimulation selectivity. Finally, engagement of carotid chemoreceptors, which are known to regulate sympathetic activity and BP, could differ between electrode
designs. In fact, carotid body chemoreceptors directly suppress baroreflex responses.32,33

Electric carotid sinus stimulation can lower sympathetic activity and BP in patients with resistant arterial hypertension. However, turning this interesting approach into a treatment that can be introduced into routine clinical care is challenging. Implantation of the first-generation device was more invasive because the electrode was placed on both sides, and more extensive dissection of the carotid artery was required. Furthermore, battery life was rather short. Despite these limitations, the treatment was shown to reduce BP in a controlled clinical trial.34–36 Implantation of the second-generation device is less invasive, and battery life has been improved.

Our findings in patients with treatment-resistant arterial hypertension cannot be simply extrapolated to other potential indications. Recent clinical trials using unilateral unipolar electric carotid sinus stimulation in patients with heart failure yielded promising results.34–36 However, reconfirmed efficacy of electric carotid sinus stimulation in patients with hypertension cannot be simply extrapolated to other potential indications. Recent clinical trials using unilateral unipolar electric carotid sinus stimulation in patients with heart failure yielded promising results.34–36 However, reconfirmed efficacy of electric carotid sinus stimulation, we should find ways to identify patients most likely to benefit.

In our patient cohort, unilateral unipolar electric baroreflex stimulation elicited interindividually variable reductions in sympathetic activity and BP in patients with resistant hypertension. However, side effects may limit efficacy. Pending results from controlled clinical trials, the approach should not be applied in routine clinical care. Our study suggests that careful physiological profiling can aid in assessing antihypertensive treatments and could be incorporated at an earlier stage in clinical development. The fact that compared with medications, device-based treatments require much less rigorous clinical testing in many countries should be scrutinized. The same is true for technological modifications, which—as shown in our study—may alter efficacy and side effects.

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Disclosures
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References


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**Novelty and Significance**

**What Is New?**
- Electric carotid sinus stimulation using a unipolar unilateral device elicits interindividually variable reductions in vasoconstrictor sympathetic activity and arterial pressure in patients with refractory hypertension.
- A considerable proportion of patients experiences side effects necessitating reduction of stimulation intensity.

**What Is Relevant?**
- Titrating carotid sinus stimulation intensity to chronically tolerable levels may be associated with marked reduction in efficacy.
- The efficacy of new or substantially modified antihypertensive devices has to be confirmed in properly controlled clinical trials.

**Summary**
Electric carotid sinus stimulation has been developed as a non-pharmacological option for the management of treatment-resistant arterial hypertension. Shortcomings of first-generation devices led to the development of a new approach using unilateral unipolar stimulation with a much smaller electrode. Using high-fidelity cardiovascular phenotyping, we confirmed the blood pressure-lowering potential and the contribution of baroreflex-mediated sympathoinhibition. However, introduction of this less invasive approach may have sacrificed efficacy, partly because stimulation intensity has to be reduced to diminish side effects. The device is approved in Europe and routinely implanted but has not been tested in controlled clinical trials. Our study challenges this practice.
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ONLINE SUPPLEMENT - Acute Response to Unilateral Unipolar Electrical Carotid Sinus Stimulation in Patients with Resistant Arterial Hypertension

Short title: Unipolar carotid sinus stimulation

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Germany

Phone: +49-511-532 2821
Fax: +49-511-532 2750
### Table S1: Individual patient characteristics

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BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease