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An Implantable Carotid Sinus Baroreflex Activating System: Surgical Technique and Short-Term Outcome from a Multi-Center Feasibility Trial for the Treatment of Resistant Hypertension

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Objectives. *To assess perioperative outcomes and blood pressure (BP) responses to an implantable carotid sinus baroreflex activating system being investigated for the treatment of resistant hypertension.*
Methods. *We report on the first seventeen patients enrolled in a multicenter study . Bilateral perivascular carotid sinus electrodes (CSL) and a pulse generator (IPG) are permanently implanted. Optimal placement of the CSL is determined by intraoperative BP responses to test activations. Acute BP responses were tested postoperatively and during the first four months of follow-up.*
Results. *Prior to implant, BP was 189.6 ± 27.5/110.7 ± 15.3 mmHg despite stable therapy (5.2 ± 1.8 antihypertensive drugs). The mean procedure time was 202 ± 43 minutes. No perioperative strokes or deaths occurred. System tests performed 1 or up to 3 days postoperatively resulted in significant (all* $p \leq 0.0001$*) mean maximum reduction, with standard deviations and 95% confidence limits for systolic BP, diastolic BP and heart rate of 28 ± 22 (17, 39) mmHg, 16 ± 11 (10, 22) mmHg and 8 ± 4 (6, 11) BPM, respectively. Repeated testing during 3 months of therapeutic electrical activation demonstrated a durable response.*
Conclusions. *These preliminary data suggest an acceptable safety of the procedure with a low rate of adverse events and support further clinical development of baroreflex activation as a new concept to treat resistant hypertension.*

Keywords: Hypertension; Surgery; Baroreflex; Carotid sinus; Medical device; Autonomic nervous system.

Introduction

The role of vascular surgeons in the treatment of arterial hypertension is usually restricted to the correction of secondary causes of hypertension, such as repair of renal artery stenosis, or resection of pheochromocytoma and aldosterone-producing adenomas. Many other vascular procedures treat the sequelae of atherosclerosis in patients with longstanding uncontrolled arterial hypertension. Even with advances in medical therapy, a significant proportion of hypertensive patients fail to reach their goal blood pressure due to refractoriness to multi-drug treatment or poor compliance.[1–8] In such patients, new treatment options are needed to reduce hypertension induced cardiovascular morbidity.[9,10]

A key mechanism of blood pressure control, recently re-evaluated as a potential therapeutic, approach is the electrical activation of the carotid baroreflex. In the 1960s and 1970s the carotid baroreflex was modulated as part of the treatment of resistant hypertension and refractory angina pectoris. The carotid sinus nerves were chronically stimulated using implanted nerve electrodes and an implantable radiofrequency controlled receiver.[11–17] This technique never became established as a viable therapy for

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hypertension. This was partially due to the simultaneous development of new agents used in the treatment of hypertension (e.g. Minoxidil and ACE-Inhibitors) and technical limitations of implantable medical devices of that era, e.g. stimulation of tissues adjacent to the carotid sinus nerves causing pain in patients equipped with the device and poor energy transmission properties since the device was not fully implantable. These earlier and more recent observations from data in chronically instrumented animals, demonstrate that the carotid baroreflex can influence the long-term regulation of arterial blood pressure.[18–23]

A new implantable active medical device, (Rheos®, CVRx. Inc., Maple Grove, MN, USA) activates the carotid baroreflex through electrical stimulation of the carotid sinus wall: Electrodes implanted on the exterior surface of the carotid sinus wall are connected to a battery powered impulse generator (IPG). This concept was initially validated in animal studies,[21–23] and subsequently in patients undergoing elective carotid surgery in which acute unilateral electrical stimulation of the carotid sinus wall reduced blood pressure and heart rate. These hemodynamic effects increased gradually as the amplitude (voltage) of stimulation was increased in a stepwise manner.[24]

For an early assessment of perioperative outcomes and blood pressure (BP) responses we now report the perioperative data from the first 17 patients with drug resistant hypertension enrolled in a European multicenter feasibility study.[25] The study protocol hypothesizes that chronic electrical stimulation of the carotid sinus wall added to stable maximal drug therapy will result in sustained reductions of systolic blood pressure of at least 10 mmHg with an acceptable risk benefit ratio.

This preliminary analysis focuses on our early experience and perioperative outcomes and details of the surgical procedure. As such it does not allow full statistical analysis of the prospectively defined primary and secondary outcome variables as planned for the complete trial.

Methods

Study and study criteria

The study is currently conducted in 6 clinical centers in Europe. It was approved by the institutional review board at each participating center, and all patients provided written informed consent before the start of the study. The main eligibility criteria are given in Table 1. Patients who fulfill these criteria are enrolled into a prospective, non-randomized, self-controlled registry of safety and efficacy of blood pressure reduction. To facilitate this assessment the patient's antihypertensive regimen is held constant during the first four months of the study unless doing so would compromise patient safety. Per protocol, the first three patients are to be excluded from efficacy and safety analyses and will only be individually summarized in the final study report. The formal primary endpoints of the study are to be analysed at 4 month follow-up, i.e. after 3 months of continued electrical baroreflex activation therapy. For safety, all adverse events are evaluated and the device and procedure related adverse events rate is estimated. For efficacy, the trial hypothesis calls for a reduction in systolic (office-cuff) blood pressure of at least 10 mmHg at that timepoint. A total of 50 patients are to be enrolled in order to yield at least 45 evaluable patients for the primary endpoints.

Table 1. Main Inclusion/Exclusion Criteria

Age: ≥20 yrs
Bilateral carotid bifurcations located at or below C3–C4 No Carotid Stenosis > 50% No prior surgery or radiation in the carotid sinus region
Drug resistant Hypertension (not secondary to a treatable cause) And SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg despite adhering to two months of stable full therapy with at least three antihypertensive medications, of which at least one must be a diuretic.

Device and surgical technique

The active implantable device

The implantable Baroreflex Hypertension Therapy (BHT) system consists of bilateral Carotid Sinus Leads (CSL) and a battery powered, programmable active IPG. Biocompatible materials are used on all surfaces The CSL conducts the activation energy from the IPG to stimulate the baroreceptor fibers in the vessel walls of both carotid sinuses. These impulses are transmitted to the brainstem, where the increased nerve traffic originating from baroreceptor afferents is interpreted as an elevated blood pressure and results in central nervous system modulation of sympathetic and vagal outflows which reduce blood pressure and heart rate.

This device is fully programmable by an external system, linked telemetrically to the IPG and allows the physician to non-invasively adjust the stimulation parameters delivered to the CSL. The patient can temporarily disable or turn off the IPG, respectively by using a magnet or a Patient Wand. Stimulation impulses can be delivered to one or both CSLs. The range of the main programmable electrical parameters is given in Table 2.

Table 2. IPG Stimulation Parameters

Sequence of Stimuli	Frequency (Hz)	Amplitude (V)	Impulse Duration (μs)
Continuous stimuli or bursts of variable duration	10–100	1–7.5 (in steps of 0.5 V)	120–760

Tests of hemodynamic responses to acute device activation

Electrical parameters can be separately adjusted for each of the two CSLs (left and right) in order to adapt to potential differences in stimulation thresholds and hemodynamic responses.

The standard settings for testing the blood pressure response at least once postoperatively at predischarge and at every follow-up visit are the following: Continuous bilateral stimulation with a frequency of 100 Hz and an impulse width of 480 μs. Stimulus amplitude (V = Voltage) is increased in steps of 1 V from 1–6 V, each for 5 minutes. Acute changes in office cuff blood pressure and pulse rate are measured with an automated device.

During these tests the patient is allowed to rest quietly. The postoperative and 1-Month follow-up tests were performed prior to the initiation of chronic therapy. For subsequent tests during BHT, the device was turned off for 5 to 30 minutes before any acute testing. Additional acute tests are regularly done with other frequencies and impulse widths at the follow-up visits to further explore how each patient responds to BHT. Therapy is programmed individually for each patient taking into account results of their office blood pressure, 24-hour ambulatory blood pressure, when available, and responses to acute tests.

Preparation for surgery

On the day of surgery morning doses of antihypertensive medications were held, except for beta-adrenergic blockers and aspirin was given unless otherwise contraindicated. An infusion of sodium nitroprusside, or nitroglycerine, was used to control blood pressure preoperatively and all other antihypertensive medications were administered in the immediate postoperative period. All procedures were performed under general anesthesia. It is critical to the conduct of the procedure that agents which blunt the baroreflex be avoided, as has been briefly communicated previously,[26] and thus will not be expanded upon at this time. The level of the carotid bifurcation was marked on each side using ultrasound guidance. A catheter was placed in the nondominant radial artery for continuous monitoring of the patients blood pressure.

Access to the carotid sinus

The patient was positioned and the surgical field prepared which allowed access for three incisions, one over each carotid bifurcation and a third inferior to the clavicle for the IPG. A transverse or vertical was made at the level of the bifurcation, at the discretion of the attending surgeon. The incision was deepened and the common carotid artery was exposed according to the standard practice of the surgeon. The vagus nerve was identified and protected. The carotid dissection was extended cephalad exposing the bifurcation. In this process the Ansa cervicalis may be divided, however, all other nerves including the hypoglossal which was mobilized if needed, were preserved. The carotid artery bifurcation was then mobilized circumferentially, however, dissection within the bifurcation was avoided so as to minimize the risk of injury to the neurovascular bundle. If the geometry of the carotid bifurcation was such that the angle between the internal and external carotid arteries was great and the arteries separate rapidly, the internal carotid artery was dissected circumferentially two centimeters above the flow divider to facilitate fixation of the electrode around the sinus without directly dissecting near the flow divider of the carotid bifurcation where the carotid sinus nerve was most likely to be located.

Carotid sinus lead application and testing

At this time patients receiving inhalational agents, as part of their anesthetic regimen, had the agents reduced, or temporarily discontinued, and supplemental narcotics, barbiturates and/or benzodiazepines administered intravenously to maintain adequate anesthesia.

The electrode was positioned on the bifurcation in the area of the carotid sinus. If the carotid sinus was clearly seen the electrode is applied with the active area centered on the sinus. If the sinus was not a discrete structure the lead is positioned around the carotid bifurcation so that the active area was centered on the internal carotid artery at a point opposite the neurovascular bundle within the bifurcation. The electrode was positioned on the distal five millimeters of the common carotid artery extending cephalad onto the bifurcation. The electrode was then tested to assess the hemodynamic response. The electrode was then repositioned in the cephalad-caudal orientation as well as being rotated around the long axis of the carotid artery until the location providing the optimal hemodynamic response was identified. Several locations were tested to assure that the position producing the optimal response was identified. During testing the electrode and lead were connected to the IPG and briefly

activated with impulses of 3 V, 100 Hz and a pulse width of 480 μs once blood pressure and heart rhythm were stable and not influenced by mechanical manipulation. Within 1 minute, stimulation using these parameters at a correct location should reduce systolic blood pressure by at least 10–20 mmHg and heart rate by 5–10 beats/minute. Once the optimal location was confirmed the electrode was sutured in place (6-O polyprophylene; Prolene®). The design of the electrode allowed all suturing to be performed on the superficial aspect of the artery and for sutures to be placed on the common and external carotid arteries avoiding direct suturing to the carotid sinus thus reducing the risk of injury to these structures. The procedure was then repeated on the contralateral side.

Lead tunneling procedure and IPG implantation

After confirming lead position and appropriate electrode function the level of anesthesia was deepened to allow tunneling of the lead bodies. This was accomplished by administering inhalational agents or intravenous narcotics or benzodiazepines. Next a subcutaneous pocket was made inferior to the clavicle for the IPG (IPG pocket). A tunnel was created from the cervical incision ipsilateral to the IPG pocket to the space between the sternal and clavicular heads of the sternocleidomastoid muscle (SCM). This was between the vessels and the SCM and was large enough to allow the index finger to be is inserted from above down to the fascial layer between the heads of the SCM. A tunnel was fashioned from the IPG pocket up to the space between the heads of the SCM which was then opened from below by spreading a clamp on the tip of the index finger thus protecting the underlying neurovascular structures. The lead from the ipsilateral electrode was advanced through the tunnel to the IPG pocket leaving excess lead body in the cervical incision to avoid traction on the electrode arterial interface. Next a tunnel was created between the two cervical incisions just deep to the SCM crossing the neck at the lowest point possible while avoiding injury to the thyroid and any superficial vessels. The lead body from the contralateral electrode system was advanced through the tunnel to the cervical incision ipsilateral to the IPG pocket and then through the tunnel to the IPG pocket. The lead bodies were repositioned within the tunnels with loops in each incision providing strain relief thus avoiding traction on the electrode-arterial interface. The leads were then connected to the IPG. In Fig. 1, the bilateral positioning of the CSL and location of the IPG is given schematically together with an X-Ray where the typical location of both CSLs can be seen. The unit was again interrogated to confirm the adequacy of the electrical connections. The hemodynamic

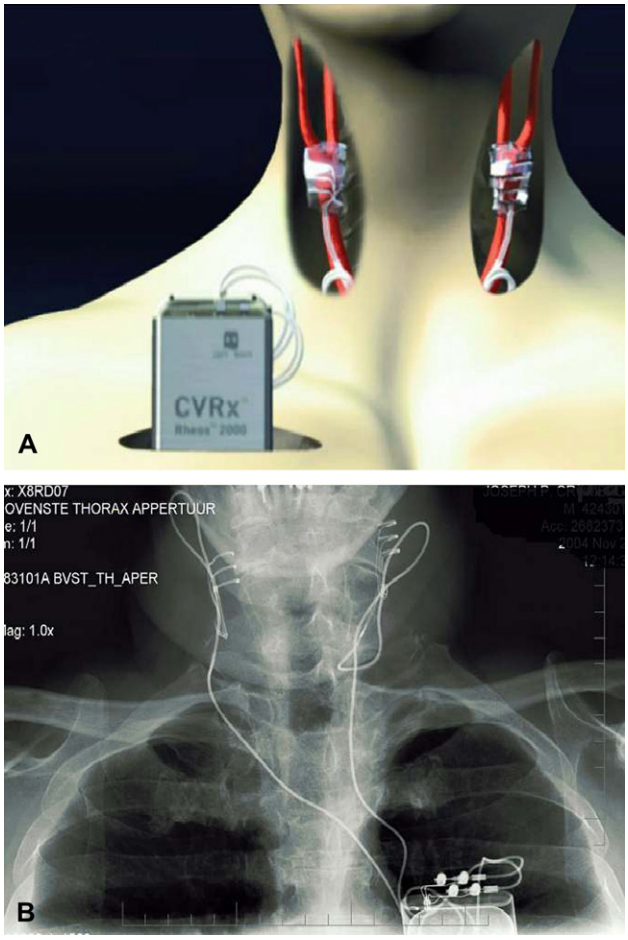

Fig. 1. Postition of Carotid Sinus Leads and Impulse Generator. A: Schematic presentation of positions of bilateral perivascular carotid sinus stimulation electrodes and the impulse generator. B: Postoperative radiograph of a patient after implantation of the BHT device.

response to a bilateral acute stimulation test was used to confirm appropriate function if the anesthetic agents used during the final phase of the procedure do not blunt the baroreflex. The IPG was then turned off. The IPG was sutured in place with permanent suture (3-O Prolene®) and the IPG pocket and cervical incisions closed in layers with absorbable sutures.

Safety analysis

The safety analysis describes and analyses perioperative procedure- and device-related adverse events as reported by the investigators. All adverse events are also reviewed by an independent adverse events committee. The perioperative period includes the time during which the implant procedure is being conducted and the 30 day period following the procedure.

Statistical analysis

Summary statistics (mean, standard deviation, minimum and maximum for continuous variables and frequency for categorical) were computed for baseline and follow-up variables of interest. The maximal response during dose response testing is calculated as the largest difference between the baseline measure at 0 volts and the measures obtained at 1−6 volts. The mean maximal change in blood pressure and heart rate during dose response testing is given along with the standard deviation and confidence limits. *P*-values for tests of significant maximal reductions in blood pressure and heart rate during dose response testing are by the t-Test for the mean change differing from zero. Ninty-five percent confidence intervals are provided to assist in determining the clinical significance of the differences. A repeated measure ANOVA was used to model the changes in blood pressure and heart rate for increasing doses and across visits. Unless otherwise specified, data are expressed as mean ± standard deviation.

Results

Seventeen patients were enrolled between June 2004 and December 2005, all with severe hypertension despite a multi-drug therapy with a mean of >5 concomitant antihypertensive drugs (see Table 3 for their characteristics at entry). Implant procedures were successfully completed in all patients within an average of 202 ± 43 minutes including 121 ± 87 minutes used for determining and testing the optimal location for CSL placement. The first acute tests, performed in the awake state were conducted on postoperative day 1−3, prior to discharge from the hospital. At this time, these tests gave significant (all: $p \leq 0.0001$) maximal reductions of systolic and diastolic blood pressure and heart rate from 177 ± 29 mmHg, 99 ± 16 mmHg and 80 ± 15 BPM at baseline, to 141 ± 34 mmHg, 78 ± 21 mmHg and 68 ± 14 BPM, respectively, which were observed at a mean amplitude of 4.6 ± 1.7 V. Mean maximal changes, with standard deviations and 95% confidence limits for systolic pressure, diastolic pressure and heart rate are 28 ± 22 (17, 39), 16 ± 11 (10, 22) and 8 ± 4 (6, 11).

These tests, repeated monthly, showed consistent acute dose-dependent reductions in SBP, DBP and HR in that the degree of hemodynamic change was directly related to the amplitude(voltage) of stimulation. In Fig. 2 the results for the 1-month follow-up (the formal baseline of the study) and 4 months follow up in the cohort completing 3 months of baroreflex activation therapy ($N = 16$) are presented. Data for Blood Pressure and Heart Rate during the testing at both time points are given in Table 4. At both time points the relationship between amplitude of stimulation and hemodynamic response remained highly linear while the control measurements (0 V) before testing were lower at 4 months when compared to the 1 month assessments. These lower control values after 3 months of therapy with the device turned off briefly (10−30 minutes) are related to the therapeutic effect of BHT which has been previously reported for a subset of these patients.[25] A repeated measures ANOVA analysis of blood pressure and heart rate readings during testing across voltage steps tested (0 volts to 6 volts) and visit (1 and 4 months) demonstrated significant differences across doses ($p < 0.0001$ for each) and by visit ($p = 0.003$ for SBP, $p = 0.0001$ for DBP and $p < 0.0001$ for HR).

Table 3. Patient Characteristics at Entry

Characteristic	Mean ± SD
Gender (m/f)	8 m, 9 f
Age (years)	52.3 ± 8.6 (33−67)
Height (cm)	170.9 ± 10.4
Weight (kg)	91.9 ± 25.0
BMI (kg/m^2)	31.0 ± 6.2
Office Cuff Blood Pressure and Pulse Rate	
Systolic Blood Pressure (mmHg)	189.6 ± 27.5
Diastolic Blood Pressure (mmHg)	110.7 ± 15.3
Pulse Rate (BPM)	75.2 ± 12.6
Number of Antihypertensive Drugs in Combination	5.2 ± 1.8

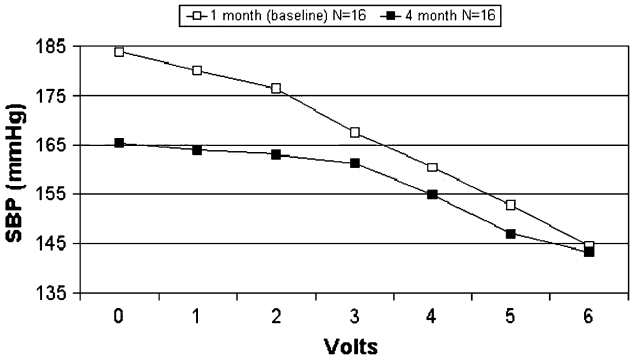

Fig. 2. Systolic Blood Pressure during Electrical Baroreflex Activation System Tests. With bilateral activation, the amplitude of the IPG (V = Voltage) is increased in steps of 1 V from 0 V (Baseline) to 6 V, each for 5 minutes. Mean systolic blood pressure at each step is given for the test results in 16 patients. The 1-Month follow-up tests (open symbols) were performed prior to the initiation of chronic therapy. At the 4-Month follow-up test (closed symbols), the device was turned off for 5 to 30 minutes before any acute testing was started.

Table 4. Blood Pressure and Heart Rate during 1 and 4 Month System Tests

Parameter and Time Point	Baroreflex Activation IPG Stimulation Amplitude (V)						
	0	1	2	3	4	5	6
SBP (mmHg)							
1-Month	184 ± 28	180 ± 29	176 ± 30	167 ± 32	160 ± 36	153 ± 31	144 ± 36
4-Month	165 ± 21	164 ± 21	163 ± 27	160 ± 23	155 ± 27	147 ± 30	143 ± 30
DBP (mmHg)							
1-Month	105 ± 17	104 ± 18	105 ± 17	98 ± 21	94 ± 22	92 ± 21	84 ± 24
4-Month	95 ± 17	94 ± 16	93 ± 17	92 ± 15	89 ± 17	84 ± 17	81 ± 17
HR (BPM)							
1-Month	80 ± 14	78 ± 14	77 ± 15	74 ± 14	72 ± 14	71 ± 15	68 ± 14
4-Month	68 ± 11	67 ± 10	68 ± 11	65 ± 11	65 ± 11	64 ± 12	62 ± 12

The implantation procedure was generally well tolerated. No unexpected serious procedure- or device related adverse events or perioperative deaths were reported. In the perioperative period, there were 38 procedure related adverse events reported in 17 patients, 2 system related events in 2 patients and one event determined to be related to both the procedure and system. Table 5 summarizes the assessment of perioperative adverse events, which were related to the procedure and/or the device. Of these events, 3 were classified as serious adverse events: 1. Infection, which led to the complete surgical removal of the device in one patient. The IPG pocket was infected with an spreading infection along the leads to the neck incision at both side. High fever and serious pain with redness, necessitated surgical reintervention and explantation of the system. 2. Procedure-related hypoglossal nerve injury with symptoms of hoarsiness and eating disturbances which improved during follow up. In this patient the electrodes had to be placed high on the carotid bifurcation which resulted in an accidentally injury to the nerve, that was sutured immediatedly with fine sutures (polypropylene 7x0), and 3. one case of intraoperative bradycardia (to 20 beats/min), which recovered spontanuously without any sustained effect. System and procedure- related bradycardia has occurred during system testing when brief periods of stimulation are applied to determine and/or confirm the effects of electrode positioning. Such episodes are expected and related to the mechanism of baroreflex activation and end within seconds by turning off the device.

Table 5. Perioperative Device and/or Procedure Related Adverse Events

Adverse Event	Device Related	Procedure Related	*N* Events	*N* Patients with event
Infection*	0	1	1	1
Hypoglossal Nerve Injury	0	1	1	1
Intraoperative Bradycardia	2	1	2	2
Pain	1	6	7	5
Wound Complication	0	3	3	3
Extravascular Tissue Stimulation	0	1	1	1
Anaesthesia Complications	0	2	2	2
Injury to local tissue		1	1	1
Other		22	23	16
Total	3	38	41	17

*During follow up, the complete device was surgically removed.

Discussion

The results of acute dose response testing observed during postoperative activation of this implanted device confirm that the regulation of blood pressure and heart rate, by the central nervous system, is strongly influenced by input from the carotid baroreceptor pathways in patients with hypertension that is refractory to multi-drug therapy. Furthermore these reductions in blood pressure were consistently achieved throughout the first three months of active therapy. Finally these results suggest that the Rheos system can be implanted safely in this group of patients with significant cardiovascular risk factors.

Patients were only included in this study when that fulfilled to strict inclusion criteria like the height of the bloodpressure, number of antihypertensive medications and local factors at the carotid bifurcation site, as determined by duplex scanning. This means that any carotid artery stenosis $> 50\%$ was an exclusion criteria. In this respect one may wonder, whether the risk on future significant (symptomatic) carotid artery stenosis may play a role in the decision to treat hypertensive patients with the Rheos system. To date this question remains unanswered and long-term follow up probably will give insight into this issue, with emphasis on the risk of carotid endarteriectomy in these patients.

The data demonstrated that during acute testing the reduction in BP occurs in a dose dependent manner, although in these tests only the amplitude of stimulation was adjusted. These observations are consistent with the findings of Schmidli *et al*. in a group of patients undergoing carotid artery surgery who underwent short term unilateral electrical stimulation of the carotid sinus wall.[24]

At four months as compared to the one month data there are some differences, which require discussion and further study. The baseline blood pressure is significantly lower, even though the device was turned off for 5–30 minutes, at the 4-month time point: 165 ± 21 mmHg vs. 184 ± 28 mmHg at the 1-month time point. This chronic blood pressure lowering effect of baroreflex activation therapy has been previously reported in a smaller cohort of these patients by de Leeuw and colleagues.[25] and is demonstrated again in our data. Thus, effects of chronic baroreflex activation therapy appear to be maintained in part during this brief time that the therapy was inactive. The lack of a rebound to baseline or greater blood pressures is encouraging from a safety perspective for BHT, but does confound our ability to easily interpret the test findings. The second observation is that of an apparent threshold effect at the 4-month time point. This may reflect the development and organization of scar tissue within the surgical field. This observation will require data from longer follow-up and ongoing animal studies before a comprehensive explanation can be provided.

Since we observed a qualitatively reproducible linear relationship between the hemodynamic response to BHT and the voltage of stimulation used for BHT, these acute tests may be considered ''dose response'' tests of BHT. The electrical parameters chosen for the acute dose response tests used a stepwise increase voltage with a constant frequency of 100 Hz and impulse width of 0.48 ms. Voltage increases are thought to increase the recruitment of afferent baroreceptor fibers which elicits a spatial summation at the brainstem neuronal network involved in the processing of the carotid baroreflex.[27,28] A high stimulation frequency is expected to minimize additional confounding influences of potential differences in transmission properties of the afferent neuronal fibers.[29,30]

The observations in this study, while new, are not unexpected given previous work using carotid sinus nerve stimulation. These studies conducted in the 1960s and 1970s evaluated the role of therapeutic modulation of the carotid baroreflex in the treatment of refractory hypertension and angina.[11–17] The current system is novel in that it uses perivascular electrodes to activate the baroreflex. The current system addresses many of the challenges of the earlier devices. Extraneous nerve and muscle stimulation and pain resulting from current spread have been largely solved with modern electrode technologies. The technique of placement of the electrode on the carotid sinus reduces the possibility of damage to the carotid sinus nerves and allows the use of established techniques employed in the treatment of atherosclerosis of the carotid bifurcation. Finally, advances in implantable medical devices allow the system to reliably deliver stable and controlled therapy that can be customized for each patient.

The long term SBP reduction of more than 20 mmHg observed even with the device turned off briefly before the 3-month dose response testing is impressive and exceeds the blood pressure lowering effects demonstrated in a recent trial of a new antihypertensive agent in patients with refractory hypertension.[31]

A second similar study is underway in the USA.[32] At the time of this report, 39 patients have been enrolled worldwide in both studies. The available worldwide safety data from 39 implant procedures corroborate our findings. With regard to procedure and device related adverse events, the perioperative infection which occurred in one of our patients was treated with complete removal of the system and is unfortunately an expected event seen with the implantation of ICDs[33] and other similar implantable medical devices. Taking the worldwide experience with the RHEOS device for BHT into account, 2 such infections have occurred (one in addition to our observation in the US trial) which is within the expected rate of device-related infections and infection-related explants.[33–36]

In conclusion, the preliminary data from our cohort of 17 patients suggest that the Rheos® implant procedure can be performed with reasonably safety. However, we did saw serious complications in a minority of patients. This combined with the sustained hemodynamic response demonstrated for up to 4 months postoperatively, still support further clinical development of baroreflex activation as a new concept to treat resistant hypertension. Such a concept is in line with the treatment goal of sympathetic deactivation as reviewed recently by Grassi.[37] Long-term therapeutic results of this ongoing safety and efficacy trial are needed as the basis for a multi-center, controlled trial of the device for this indication.

Conflicts of Interest: The authors from CVRx, RK and RC, declare potential conflicts of interest as employees and shareholders of the sponsor CVRx Inc and the authors EI and TP are consultants for the sponsor. There are no other conflicts of interests in this study.

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