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Novel Baroreflex Activation Therapy in Resistant Hypertension

Results of a European Multi-Center Feasibility Study

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Objectives This study assessed the safety and efficacy of a novel implantable device therapy in resistant hypertension patients.

Background Despite the availability of potent antihypertensive drugs, a substantial proportion of patients remain hypertensive. A new implantable device (Rheos system, CVRx, Inc., Minneapolis, Minnesota) that activates the carotid baroreflex may help these patients.

Methods Forty-five subjects with systolic blood pressure ≥160 mm Hg or diastolic ≥90 mm Hg despite at least 3 antihypertensive drugs were enrolled in a prospective, nonrandomized feasibility study to assess whether Rheos therapy could safely lower blood pressure. Subjects were followed up for as long as 2 years. An external programmer was used to optimize and individualize efficacy.

Results Baseline mean blood pressure was 179/105 mm Hg and heart rate was 80 beats/min, with a median of 5 antihypertensive drugs. After 3 months of device therapy, mean blood pressure was reduced by 21/12 mm Hg. This result was sustained in 17 subjects who completed 2 years of follow-up, with a mean reduction of 33/22 mm Hg. The device exhibited a favorable safety profile.

Conclusions The Rheos device sustainably reduces blood pressure in resistant hypertensive subjects with multiple comorbidities receiving numerous medications. This unique therapy offers a safe individualized treatment option for these high-risk subjects. This novel approach holds promise for patients with resistant hypertension and is currently under evaluation in a prospective, placebo-controlled clinical trial. (J Am Coll Cardiol 2010;56:1254–8)

Despite the availability of potent antihypertensive medications, a sizeable proportion of the hypertensive population remains treatment resistant (1). Early attempts to treat such patients with electrical carotid sinus nerve stimulation (2–4) have been summarized previously (5,6), but these efforts were not successful because of technical problems. Recent advances in device technology and an increasing number of patients whose hypertension cannot be controlled with medications have led to renewed interest in this approach.

Recently, a novel implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota) has been developed that works by electrical stimulation of the carotid sinus (7).

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The device enhances afferent nerve traffic from the baroreceptors to the cardiovascular control centers in the brain, which subsequently reduce sympathetic outflow and blood pressure (BP). Canine studies have demonstrated sustained falls in arterial pressure in normotensive and hypertensive dogs (6,8–10). Observations in patients undergoing elective carotid surgery have confirmed that short-term activation of the baroreflex acutely lowers BP in humans (11).

Methods

The DEBuT-HT (Device Based Therapy in Hypertension Trial) was a multicenter, prospective, nonrandomized feasibility study. Its purpose was to assess the safety and efficacy of the Rheos system over 3 months in resistant hypertensive subjects. The medical ethics committees of all participating centers approved the study protocol, and written informed consent was obtained from subjects. After the 3 months, subjects consented to an extended follow-up phase.

Subjects were >21 years of age, and BP was ≥160/90 mm Hg despite receiving at least 3 antihypertensive agents, including a diuretic. Subjects were certified compliant and medications were kept constant for 2 months before entry and during the first 3 months of therapy, except when medically necessary. Carotid bifurcations were assessed by ultrasonographic examination to be at or below the C3 to C4 level to ensure operative suitability.

Abbreviations and Acronyms

BP = blood pressure

SAE = serious adverse event

Exclusions included baroreflex failure, significant orthostatic hypotension, cardiac arrhythmias, chronic atrial fibrillation, clinically significant cardiac valvular disease or hypertension secondary to a treatable cause, carotid artery atherosclerosis with >50% stenosis as determined by ultrasonography, prior implant or radiation in the carotid sinus region, currently implanted electrical medical devices, dialysis, and pregnancy or contemplating pregnancy.

The Rheos system consists of a pulse generator, 2 leads, and a programmer. The implant procedure has been described previously (12,13). The device was activated 1 month after implant, which is the study baseline time point. At each follow-up visit, therapy was individualized with the programmer to produce an optimal BP reduction.

Subjects were followed up monthly for the first 3 months and thereafter at least annually. All information on antihypertensive agents including dosage was recorded. Office BP measurements were taken at every scheduled visit with a validated electronic device, and readings were repeated when 2 consecutive measurements varied by >5 mm Hg. The recorded BP was the mean of the last 2 readings. In addition, ambulatory BP measurements were performed with at least 40 measurements during 24 h using a validated device.

Table 1 Baseline Characteristics

	Total Enrolled (n = 45)	Completed 3-Month Follow-Up (n = 37)	Completed 1-Year Follow-Up (n = 26)	Completed 2-Year Follow-Up (n = 17)
Demographics				
Sex, male	26 (58)	21 (57)	14 (54)	8 (47)
Race, Caucasian	45 (100)	37 (100)	26 (100)	17 (100)
Age, yrs	54 ± 9	55 ± 9	53 ± 9	51 ± 9
Body mass index, kg/m^2	32 ± 6	32 ± 7	33 ± 7	31 ± 6
Office measurements				
SBP, mm Hg	179 ± 29	179 ± 28	180 ± 31	188 ± 32
DBP, mm Hg	105 ± 22	105 ± 22	108 ± 24	114 ± 23
HR, beats/min	80 ± 13	80 ± 13	80 ± 15	81 ± 11
Antihypertensive treatment				
Number	5 (3–9)	5 (3–9)	5 (3–9)	5 (3–8)
Antihypertensive therapy index	38 (10–82)	38 (10–82)	40 (10-82)	34 (10–56)
Antihypertensive treatment per class				
ACE inhibitor/A2 blocker	41 (91)	34 (92)	24 (92)	16 (94)
Beta-blocker	37 (82)	29 (78)	21 (81)	14 (82)
Alpha-blocker	21 (47)	16 (43)	11 (42)	6 (35)
Calcium-channel blocker	34 (76)	29 (78)	21 (81)	12 (71)
Diuretic	45 (100)	37 (100)	26 (100)	17 (100)
Sympatholitic	17 (38)	14 (38)	10 (39)	6 (35)
Direct vasodilator	5 (11)	3 (8)	3 (12)	1 (6)
Medical history				
Cardiovascular disease	34 (76)	28 (76)	21 (81)	13 (76)
Diabetes mellitus	14 (31)	11 (30)	9 (35)	3 (18)

Values are n (%), mean ± SD, or median (range). Data presented for all enrolled participants (n = 45) and for the cohorts that completed 3 months (n = 37), 1 year (n = 26), and 2 years (n = 17) of device therapy.

ACE = angiotensin-converting enzyme; A2 = angiotensin 2; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

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An independent committee adjudicated adverse events to determine the severity and relationship to the procedure or device. Death, life-threatening situation, inpatient hospitalization, prolongation of existing hospitalization, or persistent or significant disability were classified as serious adverse events (SAEs).

Functional safety measures were recorded at baseline, after 3 months, and at 1 year of device therapy, including patient's ability to exercise during a 6-min hall walk test, and orthostatic blood pressure changes at 1, 3, and 5 min of upright standing after 5 min in supine position. Orthostatic hypotension was defined as a fall in BP by at least 20/10 mm Hg, within 3 to 5 min of quiet standing. Renal function was assessed using serum creatinine as measured by a central laboratory. Carotid artery ultrasonography was performed to assess carotid artery stenosis.

A cohort of 10 eligible patients who for various reasons declined participation in this trial were followed up by regular care. Their physicians recorded office BP, antihypertensive treatment, and SAEs.

Statistical analyses. Data are presented as mean ± SD or mean change ± SE unless indicated otherwise. Statistical analysis was performed parametrically and 2-sided using SAS version 9.1 statistical software (SAS Institute, Cary, North Carolina). A p value <0.05 was considered statistically significant. The time to first procedure or device-related SAE was calculated according to the Kaplan-Meier method. The BP responses were calculated as the difference between a follow-up visit and the baseline visit by a paired *t* test for the cohort of subjects who had reached that visit by the time of analysis. No adjustments to p values were made due to comparisons at multiple visits.

Results

Forty-five subjects at 9 clinical centers were implanted between March 2004 and November 2007. Subject characteristics are presented in Table 1. The first 3 subjects enrolled were excluded from the safety and efficacy analyses per protocol. Of the remaining 42 subjects, there were 4 dropouts and 1 missed visit, resulting in 37 subjects evaluable. The 4 dropouts did not differ from the 37 evaluable subjects in any systematic way. As of this report, 26 and 17 subjects completed 1 and 2 years of device therapy, respectively.

All subjects received full doses of antihypertensive medications per standard medical practice. The median number at baseline was 5 (range 3 to 9). No significant changes occurred during the study period.

Safety results. Figure 1A shows the percentage of subjects who remained free from a procedure- or device-related SAE. Of 42 subjects, 7 experienced a procedure-related SAE and 1 subject experienced a device-related SAE. One fatal procedure-related event occurred 6 days after implant due to angioneurotic edema before device activation. The cause could not be determined definitively, but a drug reaction is suspected. Three subjects had the device explanted before activation because of infection. However, in 1 subject, the leads were not removed, and a device was reimplanted 12 months later. Three additional procedure-related SAEs occurred within 30 days of the original implant: perioperative stroke with minimal residual effects, tongue paresis (no abnormalities on brain magnetic resonance imaging) most likely due to intraoperative injury to the hypoglossal nerve, and moderate pulmonary edema that resolved within 6 days. The only device-related SAE was due to movement of the implantable pulse generator, resulting in the need for further surgery to reposition the implantable pulse generator, which resolved the problem.

Most procedure-related events were directly related to the incision or the anesthetic procedure, and most device-related events were related to nonoptimal device placement. The unrelated SAEs were likely related to subjects' individual risks. The percentage of unrelated SAEs in this treated

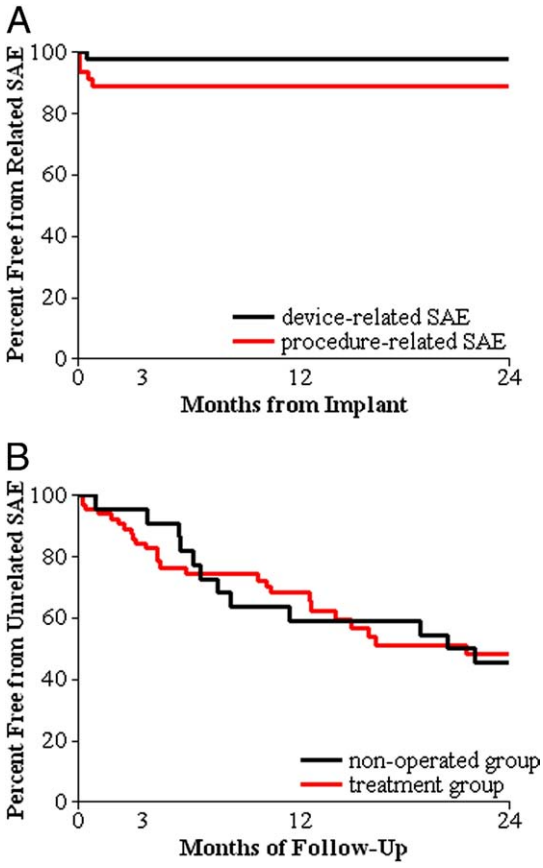

Figure 1 **Kaplan-Meier Analysis, Percentage of Participants Free From SAE**

(A) Percentage of patients who remained free from a procedure-related serious adverse event (SAE) **(red line)** and a device-related SAE **(black line)**. **(B)** Percentages of patients who remained free from a device-unrelated SAE in the surgery group **(red line)** and the nonsurgery group **(black line)**. The latter group consists of patients who were eligible but refused device implant.

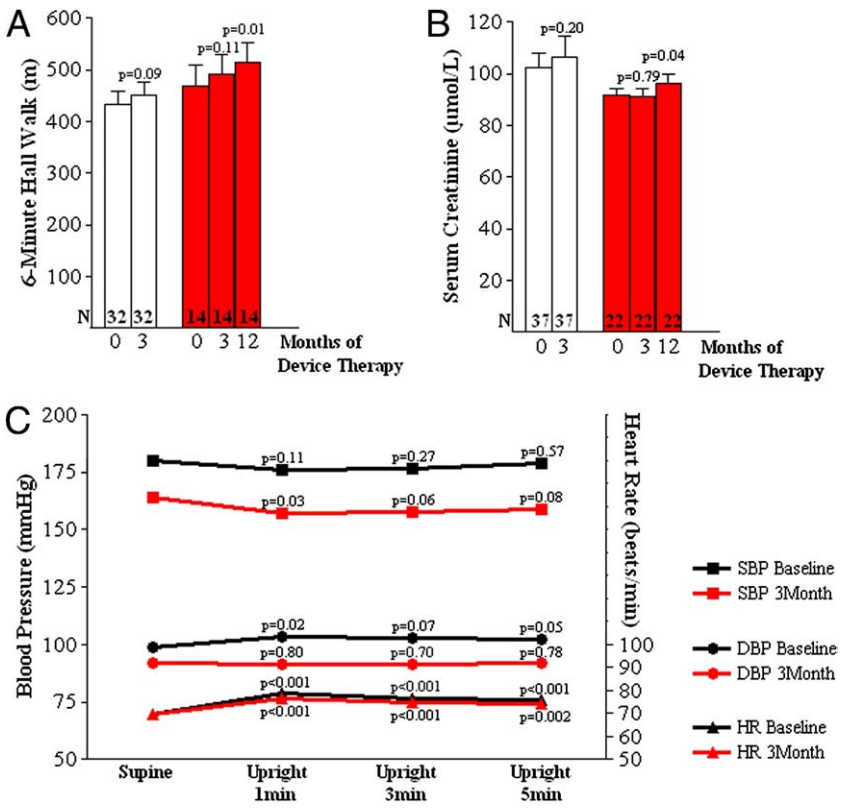

Figure 2 **Functional Safety Results After 3 Months and 1 Year of Device Therapy**

(A) Distance walked during the 6-min hall walk test, and **(B)** serum creatinine. Number of participants are shown in the **bars**. Means ± SE; p values refer to the changes at each time point compared with baseline. **(C)** Orthostatic blood pressure readings at baseline and after 3 months of device therapy for 28 participants. **Black squares** = systolic blood pressure (SBP) baseline; **red squares** = SBP 3 months; **black circles** = diastolic blood pressure (DBP) baseline; **red circles** = DBP 3 months; **black triangles** = heart rate (HR) baseline; **red triangles** = HR 3 months.

group was comparable to the percentage of SAEs in the cohort of declined participants (Fig. 1B).

Figure 2 presents functional safety measures. Walk distance at 6-min hall walk at 1 year significantly rose by 48 m ($p = 0.01$) among 14 participants for whom this was measured. Serum creatinine had significantly increased after 1 year of therapy in 22 participants. None of the patients had carotid artery stenosis at the 1-year visit. No evidence for orthostatic hypotension was found, and no events of collapse or syncope were reported in the 32 participants with readings at baseline and after 3 months of device therapy.

Efficacy results. Data on mean change in BP are presented in Table 2. Office BP measurement shows a significant decrease at every visit, with all decrements being highly significant as compared with baseline. Because of several test failures, mean 24-h ambulatory BP monitoring recordings are

Table 2 **Blood Pressure Results, Mean Change (Δ) Presented for Office and Ambulatory Readings**

	Δ 3 Months	Δ 1 Year	Δ 2 Years
Office blood pressure	n = 37	n = 26	n = 17
SBP, mm Hg	−21 ± 4 ($p < 0.001$)	−30 ± 6 ($p < 0.001$)	−33 ± 8 ($p = 0.001$)
DBP, mm Hg	−12 ± 2 ($p < 0.001$)	−20 ± 4 ($p < 0.001$)	−22 ± 6 ($p = 0.002$)
HR, beats/min	−8 ± 2 ($p < 0.001$)	−8 ± 2 ($p = 0.001$)	−11 ± 4 ($p = 0.008$)
Ambulatory blood pressure	n = 26	n = 15	n = 8
SBP, mm Hg	−6 ± 3 ($p = 0.102$)	−13 ± 3 ($p < 0.001$)	−24 ± 8 ($p = 0.017$)
DBP, mm Hg	−4 ± 2 ($p = 0.041$)	−8 ± 2 ($p = 0.001$)	−13 ± 5 ($p = 0.049$)
HR, beats/min	−5 ± 2 ($p = 0.001$)	−6 ± 2 ($p = 0.012$)	−11 ± 34 ($p = 0.005$)

Values are mean change ± SE.
Abbreviations as in Table 1.

not available in all participants but, nevertheless, the data show modest reductions during the first 3 months of device therapy and even significant reductions after 1 and 2 years.

The cohort of declined participants failed to show a significant change in office BP, whereas the mean number of antihypertensive agents was slightly increased.

At each visit, the device was temporarily turned off to assess the BP level without carotid artery stimulation. Remarkably, BP immediately increased to its baseline levels, only to fall again when the device was reactivated.

Discussion

The DEBuT-HT study evaluated the safety and efficacy of the Rheos system for the treatment of resistant hypertension in a high-risk patient population. In this first-in-human study, the SAE rate compares favorably with that in the published carotid surgical literature (14,15). It is expected to decline as experience with the procedure matures. Most participants tolerated the device well and were not encumbered by its presence. The SAEs were likely related to the subject's individual risks and comorbidities.

The BP data showed statistically significant mean decreases of 21/12 mm Hg after 3 months of Rheos therapy and improved further over 2 years of follow-up, with a mean BP reduction of 33/22 mm Hg. The intensity of antihypertensive drug treatment was unchanged, suggesting that the BP changes were related to the device rather than to medical therapy. Rheos provided a clinically meaningful reduction in BP beyond what was achievable with drug treatment for these difficult-to-manage patients.

Conclusions

A first-in-human evaluation of baroreflex activation therapy for resistant hypertension has been completed. The Rheos system provided clinically meaningful and sustained reductions in BP in high-risk patients. The procedure and therapy demonstrated favorable safety, and each was well tolerated. The programmability of the system allowed therapy to be individualized for each subject. This novel approach holds promise for patients with resistant hypertension and is currently under evaluation in a prospective, placebo-controlled clinical trial.

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