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Chronic Baroreflex Activation by the Rheos® System: An Overview of Results from European and North American Feasibility Studies

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Abstract—**The baroreflex, whose role is well-known in short-term blood pressure regulation, has until recently been unexploited as a practical therapy for hypertension. Recent advancements in approach and technology embodied in the Rheos® System have enabled chronic electrical activation of the baroreflex. Chronic results from feasibility studies indicate that Rheos Therapy has an acceptable safety profile and may lead to long-term control of pressure in drug-resistant hypertension patients. Other effects include significant reductions in left ventricular mass and left atrial size. The spectrum of therapeutic impact suggests that Rheos Therapy may improve long-term outcomes in drug-resistant hypertension and possibly benefit related populations. Larger-scale study in randomized, controlled trials are ongoing to verify chronic benefits.**

I. Introduction

MORE than 73 million Americans, approximately one-third of the population, are afflicted with hypertension. Each year, hypertension is listed as primary cause of death in >50,000 patients and contributes to death in an additional >250,000 patients. The total estimated cost of hypertension to the US healthcare system in 2009 exceeds $73 billion. Of all hypertensive patients, fewer than 50% are classified as having the condition controlled. While advancements in awareness, treatment, and control of hypertension continue, prevalence is expected to increase as the population ages [1].

Control of hypertension is important in preventing further progression of cardiovascular disease, including heart failure, myocardial infarction, and stroke. Such adverse outcomes appear to be often preceded by cardiovascular remodeling, including increased left ventricular mass, left atrial dilatation, and increased major artery intimal-medial thickness. These structural changes are associated with cardiovascular pathophysiology which includes diastolic dysfunction, atrial fibrillation, and arterial stiffness. Evidence suggests that therapies which ameliorate hypertension-induced pathophysiology will delay and/or lessen the severity the major adverse outcomes that result from long-term hypertension [2-5].

Current standard-of-care therapy for hypertension includes the use of diuretics, angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers, and dihydropyridine calcium channel blockers [6]. These therapies have been shown to be safe and effective in multiple randomized, controlled clinical trials. While standard-of-care treatment provides acceptable control of hypertension in many patients, a substantial proportion of patients remain above goal blood pressures. In such patients, physicians must currently resort to second-line therapies that in some cases lack a strong evidence basis for improving outcomes. Second-line therapies include beta blockers, alpha blockers, direct vasodilators, and central sympatholytics. Despite the addition of second-line therapy, many patients remain well above goal pressures [7]. Novel medical therapies, such as renin inhibitors, may hold promise for some patients [8]. However, it is likely that a significant number of patients will remain uncontrolled. Moreover, many drugs have undesirable side effects and/or are not tolerated well by patients, resulting in poor compliance with prescribed medications. Additional options for control of hypertension are thus required.

The baroreflex is a well-known contributor to the regulation of blood pressure. Baroreceptors located in the carotid sinuses, aortic arch, and other locations are intrinsically activated by increases in arterial pressure. Activation of the receptors results in afferent nerve activity conducted via the glossopharyngeal nerve to the nucleus of the solitary tract (NTS) in the medulla. In the NTS, the afferent traffic inhibits sympathetic tone and increases in parasympathetic tone. These changes in autonomic tone result in decreases of heart rate, systemic vascular resistance, and arterial pressure [9].

Baroreflex effects have been therapeutically exploited for centuries. In contemporary practice, carotid sinus massage is used as a treatment for supraventricular tachycardia. Building on physiologic effects of the baroreflex and its known therapeutic value, attempts were made starting in the 1960's to electrically modulate the baroreflex as a therapy. These early attempts elicited the baroreflex through electrical stimulation of the carotid sinus nerve, which contains sensory afferent fibers including those from the carotid sinus baroreceptors. Carotid sinus nerve stimulation therapy acutely reduced pressure and alleviated angina in several reported cases [10,11]. However, shortcomings in the approach and in the devices of that era prevented widespread adoption of carotid sinus nerve stimulation as a

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therapy. Primary shortcomings of the carotid sinus nerve stimulators included difficulty of implant surgery and short device longevity. A new approach to activating the baroreflex and advancement in device technology have been required to transform electrical activation of the baroreflex into a practical therapy.

The Rheos System has overcome shortcomings of carotid sinus nerve stimulation by targeting baroreceptors directly rather than the associated afferent nerve. The targeted approach is accomplished by positioning electrodes around the carotid sinus so that a sufficient number of baroreceptors is within the stimulation field. The surgery required for this positioning is similar to the carotid endarterectomy procedure commonly performed by vascular surgeons. Similarly, the Rheos pulse generator has overcome limitations of carotid sinus nerve stimulators by incorporating technologies such as large-scale circuit integration and metal-oxide semiconductors to substantially increase longevity.

Pre-clinical studies of Rheos Therapy have demonstrated that long-term baroreflex activation chronically reduces blood pressure under a variety of challenging circumstances [12-15]. The purpose of the investigations reported here was to chronically apply Rheos Therapy in drug-resistant hypertensive patients to demonstrate safety and explore potential therapeutic benefits.

II. Methods

Patients enrolled in the DEBuT-HT and Rheos US Feasibility chronic feasibility trials in the European Union and United States, respectively. These trials were approved by the appropriate regulatory/competent authorities, ethics committees, and institutional review boards. The trials were single-arm, open-label studies primarily designed to confirm safety of Rheos Therapy. Patients were required to have drug-resistant hypertension, defined as an office cuff systolic blood pressure greater than or equal to 160 mmHg despite stable therapy with 3 or more antihypertensive drugs, at least one of which was a diuretic. The DEBuT-HT trial was originally designed for a duration of 3 months and was later extended to 12 months as DEBuT-HET. The US Feasibility study was a 12-month trial. Endpoint data were acquired at 3 and 12 months in both trials. Follow-up has continued for patients beyond 12 months in both trials.

After providing informed consent, patients were implanted with the Rheos System. The system (Figure 1) consists of a subcutaneous pacemaker-like pulse generator in the pectoral region and bilateral leads encompassing the carotid sinuses. Chronic Rheos Therapy was initiated after a month of healing and continued throughout the trials. The Rheos System provides versatile dosing options that are used to tailor therapy to the patient's needs throughout treatment.

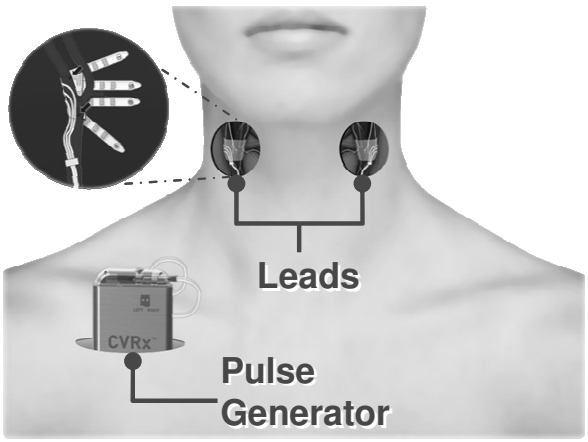

Fig. 1. The Rheos System consists of a pulse generator similar to a pacemaker implanted in the pectoral region and leads which encircle the carotid sinuses. The system is controlled by a dedicated programmer PC (not shown).

Baseline ambulatory and office cuff pressures were obtained one day prior to initiating Rheos Therapy. Baseline echocardiograms were recorded prior to implant. Echocardiograms were analyzed and categorized according to standards of the American Society of Echocardiography [16]. Changes in continuous variables were statistically assessed with paired t-tests.

III. Results

Sixty-one drug-resistant hypertensive patients enrolled in the studies. Baseline demographics and characteristics are presented in Table I and Table II, respectively. The cohort was generally non-diabetic, Caucasian, somewhat limited in physical capacity, obese, and approximately balanced in male to female ratio. Average office cuff systolic pressure at

TABLE I
Baseline Demographics (N=61)

Category		N (%)
Male		36 (59)
Caucasian		54 (89)
Diabetic		19 (31)
Renal Disease		9 (15)
NYHA Class	I	21 (34)
	II	20 (33)
	III	3 (5)

Baseline demographics for all enrollees in the DEBuT-HT and US Feasibility studies of the Rheos Device. NYHA Class denotes New York Heart Association functional class.

TABLE II
Baseline Patient Characteristics (N=61)

Characteristic	Mean ± SD
Age (years)	53.4 ± 9.8
Body Mass Index (kg/m^2)	32.8 ± 6.4
Office Cuff Systolic Pressure (mmHg)	183.6 ± 28.1
Office Cuff Diastolic Pressure (mmHg)	105.1 ± 18.4

Baseline characteristics of all enrollees in the DEBuT-HT and US Feasibility trials of the Rheos Device.

baseline was 183.6 ± 28.1 mmHg for all enrolled patients. This persistent hypertension was observed against a background of intensive medical therapy: at baseline, patients averaged 5.6 ± 1.8 antihypertensive medications (detailed in Table III).

TABLE III
BASELINE MEDICATIONS (N=61)

Medication		N (%)
Diuretic –	Thiazide	51 (82)
	Loop	18 (29)
	Other	26 (42)
ACE-Inhibitor / Angiotensin II Blocker		55 (89)
Ca Channel Blocker –	Dihydropyridine	42 (68)
	Other	10 (16)
Alpha Blocker		24 (39)
Beta Blocker		50 (81)
Other Sympatholytic		25 (40)
Minoxidil		14 (23)

Baseline medications for all patients enrolled in the DEBuT-HT and US feasibility studies of the Rheos Device.

Sixteen patients have completed follow-up through 24 months of Rheos Therapy [17]. Baseline systolic pressure, diastolic pressure, and heart rate were, respectively, 191 ± 32 mmHg, 116 ± 22 mmHg, and 81 ± 11 bpm (Mean ± SD). Changes in pressure and heart rate, illustrated in Figure 2, include a drop in office cuff systolic pressure of 38 ± 7 mmHg (Mean ± SE) at 12 months and 35 ± 8 mmHg at 24 months (both $p < 0.001$). Diastolic pressure was reduced by 27 ± 5 mmHg and 24 ± 6 mmHg at 12 and 24 Months, respectively (both $p < 0.001$). Similarly, heart rate was chronically reduced by approximately 10 bpm ($p < 0.001$ at 12 months, $p < 0.005$ at 24 months). Medication remained stable: the average number of medications over 24 months ranged from 4.6 to 4.8. Rheos Therapy also significantly reduced 24-hour mean systolic pressure by 14 mmHg ($p < 0.05$) at 12 months (N=16) [18]. No unexpected adverse events occurred during the course of follow-up.

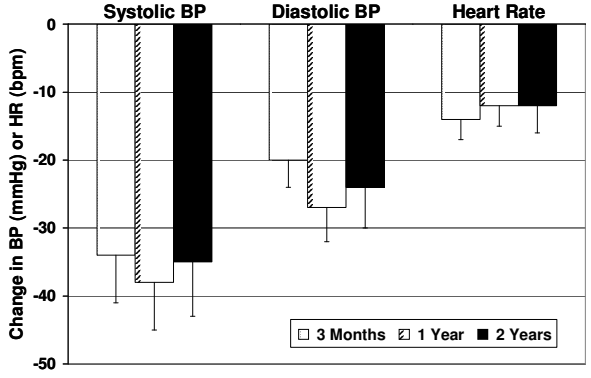

Fig. 2. Change in blood pressure and heart rate for a subset (N=16) of patients having completed 2 years of follow-up. Reductions (presented as mean ± SE) in systolic BP, diastolic BP, and HR of approximately 35 mmHg, 25 mmHg, and 10 bpm persist throughout follow-up ($p < 0.005$).

Echocardiography performed in a subset of patients revealed significant changes in cardiac structure and function during chronic Rheos Therapy [19,20] (Table IV). Most notably, the septal and posterior wall thickness of the left ventricle decreased significantly, thereby reducing left ventricular mass index (LVMI). LVMI decreased from a baseline of 138.8 ± 35.4 g/m^2 by 17.8 ± 16.0 g/m^2 (N=33) and 24.6 ± 17.9 g/m^2 (N=21) at 3 and 12 months, respectively ($p < 0.001$). In addition, increases in arterial compliance, defined as stroke volume/pulse pressure, as well as reductions in left atrial dimension and mitral A wave velocity were noted. In categorical terms, there was a substantial shift of LVMI toward the reference range (Figure 3) and left ventricular structure towards normal geometry (Figure 4). Left ventricular mass was severely abnormal in 49% of patients at baseline and 19% at 12 months, while left ventricular geometry was hypertrophic in 85% of patients at baseline and 43% at 12 months.

TABLE IV
CHANGES IN ECHOCARDIOGRAPHIC PARAMETERS

	Baseline N=33	Δ3 Months N=33	Δ12 Months N=21
Left Atrial Dimension (mm)	44.9 ± 6.5	–1.0 ± 2.7°	–2.4 ± 3.5*
LV Mass (g)	302.7 ± 93.2	–39.4 ± 38.4‡	–52.8 ± 42.8‡
LV Mass Index (g/m^2)	138.8 ± 35.4	–17.8 ± 16.0‡	–24.6 ± 17.9‡
Relative Wall Thickness	0.57 ± 0.11	–0.03 ± 0.05*	–0.04 ± 0.05‡
Mitral E Wave Velocity (cm/s)	78 ± 20	–1 ± 13	–6 ± 14
Mitral A Wave Velocity (cm/s)	83 ± 19	–2 ± 12	–11 ± 14†
Midwall Fractional Shortening (%)	13.8 ± 2.8	+0.9 ± 2.2°	+1.7 ± 2.7*
Arterial Compliance (mL/mmHg)	1.08 ± 0.36	+0.17 ± 0.37*	+0.21 ± 0.37°

Data presented as Mean ± SD. °$p \leq 0.05$, *$p \leq 0.01$, †$p \leq 0.005$, ‡$p \leq 0.001$

Changes in indices of cardiovascular structure and function derived from echocardiograms for all patients with paired data through 3 and 12 months, respectively, in the DEBuT-HT and US Feasibility trials.

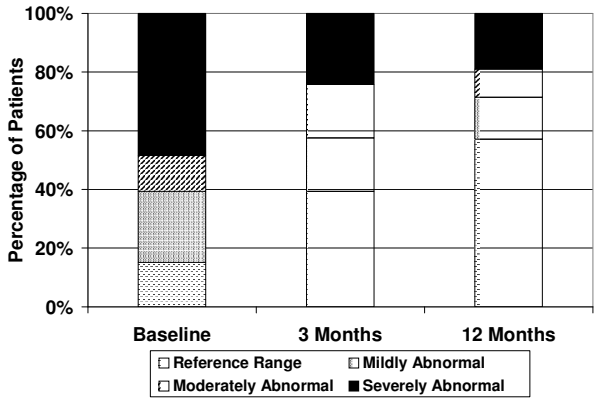

Fig. 3. Left ventricular mass index categorized according to American Society of Echocardiography standards. At baseline, 49% of patients have severely abnormal mass. At 12 months, 71% of patients have normal or mildly abnormal mass.

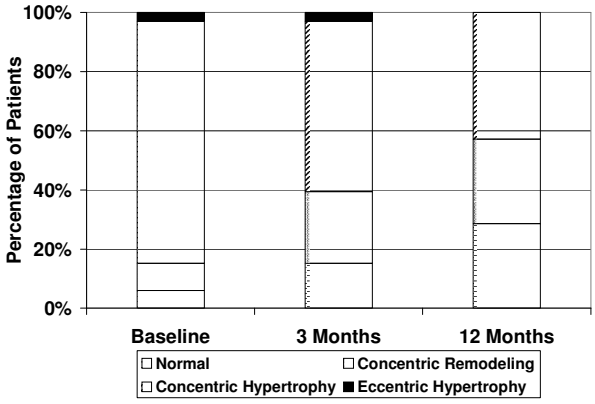

Fig. 4. Left ventricular structure throughout follow-up classified according to American Society of Echocardiography guidelines. Note substantial increases in normal geometry and concentric remodeling from a baseline of >80% concentric hypertrophy.

IV. Discussion

Results of the DEBuT-HT and Rheos US Feasibility studies indicate that Rheos Therapy has a safety profile consistent with other first-generation medical devices and therapeutic effects which strongly suggest that chronic use may positively impact patient outcome. Rheos Therapy substantially lowered arterial pressure in drug-resistant hypertensive patients against a background of intensive medical therapy.

Recent studies of beta-blocker therapy [21,22] have demonstrated that pressure reduction in and of itself is not sufficient to ensure improved patient outcome. Rather, it is possible to achieve a reduction in peripheral arterial pressure that has no discernible benefit to the patient. Observational results from the Rheos feasibility studies strongly suggest that the pressure reduction from Rheos Therapy will likely improve patient outcome. The profound reduction in left ventricular mass index achieved in these studies is perhaps the strongest indicator in this regard.

LVMI has been studied extensively as a marker of cardiac pathology related to hypertension. A series of elegant sub-studies of the LIFE trial have linked reductions of LVMI in hypertension to reduced rates of heart failure incidence, myocardial infarction, atrial fibrillation, and stroke [2-5]. Trial participants experienced a reduction in LVMI of 18% with pressure reduction of 14% at 12 months. These figures compare well with calcium-channel blockers, ACE-inhibitors, and angiotensin receptor blockers, which approximately reduce LVMI by 10% and systolic pressure by 12% from baseline systolic pressures ~160 mmHg [23].

A major outcome meta-analysis [24] has estimated that a 20 mmHg reduction in systolic pressure can approximately reduce stroke risk by 45%, myocardial infarction risk by 20%, and cardiovascular mortality risk by 45%. The reduction of systolic pressure by ≥ 20 mmHg in 75% of the patients with 2 years of follow up [17], along with reductions in LVMI exceeding that of drugs known to improve patient outcome, suggest that if Rheos Therapy were to improve outcome, the magnitude of improvement would be at least as large as the benefit conferred by current drugs of choice. This is particularly impressive when it is noted that the majority of drug trials test monotherapy, whereas Rheos Therapy was tested against a background of aggressive medical therapy.

Other echocardiographic changes reinforce the possibility that Rheos Therapy may improve outcome. Decreased left atrial dimension and mitral A wave velocity suggest that left ventricular filling pressures are being reduced as well. Such changes are consistent with an improvement in diastolic filling which would presumably ameliorate the diastolic dysfunction commonly observed in hypertensive patients. Increased fractional shortening implies that cardiac systolic performance may be improved, while reduced arterial stiffness suggests that the effect may be potentiated by reduced arterial characteristic impedance.

Motivated by these positive results, a pivotal trial of Rheos Therapy for drug-resistant hypertension is currently ongoing. The broad spectrum of clinical effects from Rheos Therapy also suggests other applications. In particular, regression of left ventricular hypertrophy and improved diastolic function along with reduction in arterial pressure suggest that patients with related pathologies in the context of heart failure may benefit from Rheos Therapy. Therefore, a feasibility study has been initiated to assess the impact of Rheos Therapy on patients with diastolic heart failure. The study is presently enrolling at several centers in Europe.

V. Conclusion

Results of clinical feasibility studies indicate that Rheos Therapy can reduce arterial pressure in drug-resistant hypertensive patients. This reduction is achieved with a safety profile commensurate with other first-generation medical devices. Reduction in left ventricular mass concomitant with arterial pressure reduction builds confidence that long-term patient outcomes may also improve. Other effects of Rheos Therapy, such as apparent reduction in left ventricular filling pressure, reduced arterial stiffness, and decreased left atrial size suggest that Rheos Therapy may be beneficial for patients with conditions with greater morbidity and mortality than hypertension, such as heart failure. Further clinical evaluation is necessary to confirm these benefits.

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REFERENCES

[1] Lloyd-Jones D. et al., "Heart disease and stroke statistics 2009 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation*, vol. 119, pp. e21-e181, Jan. 2009.

[2] Okin P.M., Devereux R.B., Jern S., Kjeldsen SE., Julius S., Nieminen M.S., Snapinn S., Harris K.E., Aurup P., Edelman J.M., Wedel H., Lindholm L.H., and Dahlöf B., "Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events," *JAMA*, vol. 292, pp. 2396-2398, Nov. 2004.

[3] Wachtell K., Okin P.M., Olsen M.H., Dahlöf B., Devereux R.B., Ibsen H., Kjeldsen S.E., Lindholm L.H., Nieminen M.S., and Thygesen K., "Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study," *Circulation*, vol. 116, pp. 700-705, Aug. 2007.

[4] Okin P.M., Devereux R.B., Harris K.E., Jern S., Kjeldsen S.E., Julius S., Edelman J.M., and Dahlöf B., "Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients," *Ann Intern Med*, vol. 147, pp. 311-319, Sep. 2007.

[5] Wachtell K., Devereux R.B., Lyle P.A., Okin P.M., and Gerdts E., "The left atrium, atrial fibrillation, and the risk of stroke in hypertensive patients with left ventricular hypertrophy," *Ther Adv Cardiovasc Dis*, vol. 2, pp. 507-513, Dec. 2008.

[6] Mancia G. et al., "2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)," *J Hypertens*, vol. 25, pp. 1105-1187, Jun. 2007.

[7] Cushman W.C., Ford C.E., Cutler J.A., Margolis K.L., Davis B.R., Grimm R.H., Black H.R., Hamilton B.P., Holland J., Nwachuku C., Papademetriou V., Probstfield J., Wright J.T., Alderman M.H., Weiss R.J., Piller L., Bettencourt J., and Walsh S.M., "Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial (ALLHAT)," *J Clin Hypertens*, vol. 4, pp. 393–404, Nov. 2002.

[8] Gradman A.H. and Kad R., "Renin inhibition in hypertension," *J Am Coll Cardiol*, vol. 51, pp. 519-528, Feb. 2008.

[9] Eckberg D.L. and Sleight P., *Human baroreflexes in health and disease*. Oxford, UK: Clarendon Press, 1992.

[10] Bilgutay A.M. and Lillehei C.W, "Treatment of hypertension with an implantable electronic device," *JAMA*, vol. 191, pp. 113-117, Feb. 1965.

[11] Braunwald E., Epstein S.E., Glick G., Wechsler A.S., and Braunwald N.S., " Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves," *NEJM*, vol. 277, pp. 1278-1283, Dec. 1967.

[12] Lohmeier T.E., Dwyer T.M., Hildebrand D.A., Irwin E.D., Rossing M.A., Serdar D.J., and Kieval R.S., "Influence of prolonged baroreflex activation on arterial pressure in angiotensin hypertension," *Hypertension*, vol. 46, pp. 1194-2000, Nov. 2005.

[13] Lohmeier T.E., Hildebrandt D.A., Dwyer T.M., Barrett A.M., Irwin E.D., Rossing M.A., and Kieval R.S., "Renal denervation does not abolish sustained baroreflex-mediated reductions in arterial pressure," *Hypertension*, vol. 49, pp. 373-379, Feb. 2007.

[14] Lohmeier T.E., Dwyer T.M., Irwin E.D., Rossing M.A., and Kieval R.S., "Prolonged activation of the baroreflex abolishes obesity-induced hypertension," *Hypertension*, vol. 49, pp. 1307-1314, Jun. 2007.

[15] Lohmeier T.E., Hildebrant D.A., Dwyer T.M., Irwin E.D., Rossing M.A., and Kieval R.S., "Prolonged activation of the baroreflex abolishes reduced kidney mass, salt-induced hypertension," *Hypertension*, vol. 50, pg. e85, Oct. 2007.

[16] Lang R.M. et al., "Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology," *J Am Soc Echocardiogr*, vol. 18, pp. 1440-1463, Dec. 2005.

[17] Scheffers I., Schmidli J., Kroon A.A., Tordoir J., Mohaupt M., Allemann Y., Jordan J., Engeli S., Liebeskind U., Luft F.C., Eckert S., Hansky B., Baal T., and de Leeuw P.W., "Sustained blood pressure reduction by baroreflex hypertension therapy with a chronically implanted system: 2-year data from the Rheos DEBuT study in patients with resistant hypertension," *J Hypertens*, vol. 26, pg. S19, Jun. 2008.

[18] Bisognano J., de Leeuw P., Irwin E., and Rossing, M., "Long term baroreflex hypertension therapy significantly lowers ambulatory blood pressures in patients with resistant hypertension," *J Clin Hypertens*, vol. 10, pg. 271, May 2008.

[19] Bisognano J.D., de Leeuw P., Bach D.S., and Lovett E.G.," Improved cardiac structure and function in early-stage heart failure and chronic treatment using an implantable device: results from European and United States trials of the Rheos System.," *J Card Fail*, vol. 14, pg. S48, Sep. 2008.

[20] de Leeuw P.W., Bisognano J.D., Bach D.S., and Lovett E.G., "Device-based reduction in blood pressure is associated with increased diameter of the left ventricular outflow tract: results from European and United States Trials of the Rheos® Hypertension System," *Circulation*, vol. 118, pg. S-887, Nov. 2008.

[21] Bangalore S., Sawhney S., and Messerli F.H., "Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension," *J Am Coll Cardiol*, vol. 52, pp. 1482-1489, Oct. 2008.

[22] Williams B., Lacy P.S., Thom S.M., Cruickshank K., Stanton A., Collier D., Hughes A.D., Thurston H., and O'Rourke M., "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study," *Circulation*, vol. 113, pp. 1213-1225, Mar. 2006.

[23] Klingbeil A.U., Schneider M., Martus P., Messerli F.H., and Schmieder R.E., "A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension," *Am J Med*, vol. 115, pp. 41-46, Jul. 2003.

[24] Staessen J.A., Wang J.G., and Thijs L., "Cardiovascular protection and blood pressure reduction: a meta-analysis," *Lancet*, vol. 358, pp. 1305-1315, Oct. 2001.