Improved Cardiac Structure and Diastolic Flow Velocities in Early-Stage Heart Failure with Chronic Treatment using an Implantable Device: Results from European and United States Trials of the Rheos® System

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Introduction

Cardiac structure and function are abnormal in heart failure (HF). Early stage HF is often linked to abnormalities in left ventricular (LV) diastolic function and arterial stiffness both of which compromise diastolic filling in the LV. Echocardiographic measurements of these abnormalities are correlated with patient outcome. Medical and device therapies have been shown to improve cardiac structure and/or function in a variety of HF populations. However, the effect of chronic device-based activation of the baroreflex on cardiac structure and diastolic filling is unknown.

Rheos® Therapy uses Baroreflex Activation Therapy™ (BAT™) technology to chronically activate the baroreflex. Preliminary results show that BAT significantly reduces systolic and diastolic blood pressure in subjects with drug-resistant hypertension.

The purpose of this investigation is to assess the impact of Rheos Therapy on echocardiographic measures of cardiac structure, function, and diastolic filling in patients with drug-resistant hypertension. All of these patients were also classified as early-stage HF (Stage A-B) via the ACC/AHA classification scheme.

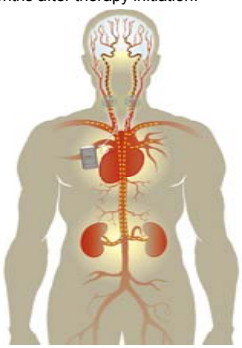
Methods

As a prospectively-designed sub-study of the DEBuT-HT and US Feasibility clinical trials, serial echocardiograms were acquired on a subset of participating patients. Patients had multi-drug resistant hypertension with systolic blood pressure (SBP) ≥ 160 mmHg and were on a stable medication regimen of ≥ 3 drugs which included a diuretic.

All patients were implanted with the Rheos System. The system remained off for 1 month and then was activated. Follow-up occurred 3 and 12 months after therapy initiation.

Mechanisms of Rheos Therapy

The Rheos System is designed to electrically activate the carotid baroreceptors, the body's natural cardiovascular regulation sensors. When the baroreceptors are activated, signals are sent through neural pathways to the brain and interpreted as a rise in blood pressure. The brain works to counteract this perceived rise in blood pressure by sending signals to other parts of the body (heart, blood vessels and kidneys) that relax the blood vessels and inhibit the production of stress-related hormones. These changes enable the heart to increase output, while maintaining or reducing workload, thereby alleviating symptoms of heart failure and reducing blood pressure.



Echocardiogram analysis was performed at a blinded core laboratory. Cardiac structure and function were quantified with standard 2-dimensional parasternal long-axis and apical echocardiogram views. Left Ventricular Mass Index (LVMI) and LV geometry were classified according to standards of the American Society of Echocardiography.

Changes in experimental observations were measured relative to baseline values in each patient. Differences were tested for significance from zero using two-sided t-tests.

Results

Baseline Demographics (N=33)

Sex (%male)		55%		Age		52.4 ± 10.4	
Race (% Caucasian)		82%		BMI (kg/m²)		32.8 ± 7.3	
NYHA 0	18%	I	27%	II	42%	III	3%

Values: Mean ± SD

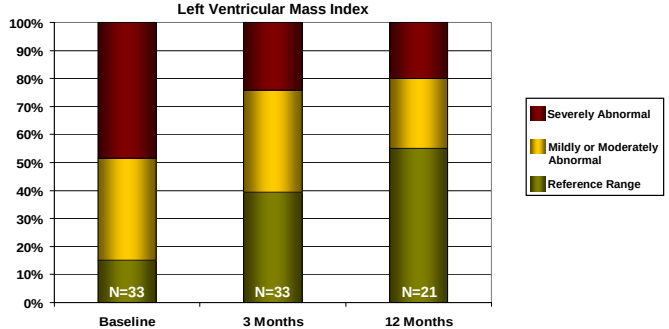
Office Cuff BP and Medication	Baseline N=33	Δ 3 Months N=33	Δ 12 Months N=21
Office Cuff Systolic BP (mmHg)	178.9 ± 25.1	–22.0 ± 30.3‡	–25.7 ± 26.0 ‡
Office Cuff Diastolic BP (mmHg)	104.4 ± 17.4	–11.0 ± 19.6†	–12.9 ± 19.8 *
Anti-hypertensive/HF Medications (#)	5.2 ± 1.7	–0.2 ± 1.5	–0.6 ± 0.8†

Cardiac Structure	Baseline N=33	Δ 3 Months N=33	Δ 12 Months N=21
Left Atrial Dimension (mm)	44.9 ± 6.5	–1.0 ± 2.7°	–2.4 ± 3.5*
Left Ventricular Outflow Tract (mm)	19.6 ± 1.9	+0.6 ± 1.1*	+1.0 ± 1.4†
Septal Wall Thickness (mm)	14.5 ± 3.0	–1.2 ± 1.3‡	–1.6 ± 1.9‡
LV Posterior Wall Thickness (mm)	14.0 ± 2.3	–0.9 ± 0.8‡	–1.4 ± 1.1‡
LV Mass (g)	302.7 ± 93.2	–39.4 ± 38.4‡	–52.8 ± 42.8‡
LV Mass Index (g/m²)	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‡
LV End-Diastolic Diameter (mm)	49.8 ± 5.1	–0.8 ± 3.1	–1.6 ± 2.5 *
LV End-Systolic Diameter (mm)	30.8 ± 4.6	–1.1 ± 3.1°	–2.4 ± 4.7 °

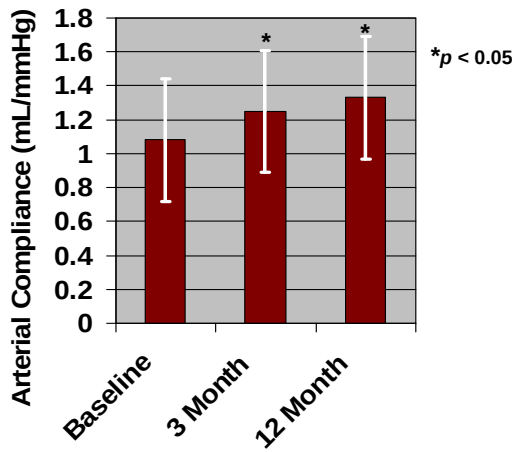
Cardiac Function	Baseline N=33	Δ 3 Months N=33	Δ 12 Months N=21
Heart Rate (bpm)	72.1 ± 10.6	–4.5 ± 9.1*	–2.7 ± 8.1
Mitral E Wave Velocity (cm/s)	78 ± 20	–1 ± 13	–6 ± 14
Mitral A Wave Velocity (cm/s)	83 ± 19	–2 ± 12	–11 ± 14†
Midwall Fractional Shortening (%)	13.8 ± 2.8	+0.9 ± 2.2°	+1.7 ± 2.7*
LV Ejection Fraction (%)	66.1 ± 5.4	+1.2 ± 2.9°	+1.9 ± 6.8

Significance of paired t-test vs. baseline: °$p \le 0.05$ *$p \le 0.01$ †$p \le 0.005$ ‡$p \le 0.001$

Left Ventricular Mass Index



Chronic Sustained Improvements in Arterial Compliance



- No significant change in BMI was observed in the cohort over 12 months of follow-up.
- Patients with a NYHA ≥ I had a significant improvement (488 ± 143 m to 560 ± 135, p =0.02, N = 8) in 6-minute Walk Distance after 12 months of active therapy.
- Given the positive correlation of arterial compliance and LV diastolic pressures (Borlaug et al 2007), the improvements observed in arterial compliance likely contributed to increases in diastolic function.
- Reduced arterial pressure is accompanied by substantial cardiac remodeling with diminished LV mass index and left atrial dimension as well as a trend from concentric hypertrophy to normal LV geometry.

Conclusions

- In addition to sustained BP reduction, chronic Rheos Therapy in early-stage HF patients remodels left atrial and ventricular chambers.
- Modest improvements in cardiac systolic function accompanies the structural changes. Diastolic function may also be improved.
- Reduced mitral A wave velocity coupled with decreased left atrial dimension and LV mass index suggests that the therapy reduces LV diastolic filling pressure.
- A feasibility study is now underway to assess potential benefit of Rheos Therapy in patients with more advanced HF as compared to this cohort.