Journal of the American Heart Association

ORIGINAL RESEARCH

Pacemaker-Based Cardiac Neuromodulation Therapy in Patients With Hypertension: A Pilot Study

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BACKGROUND: In prior unblinded studies, cardiac neuromodulation therapy (CNT) employing a sequence of variably timed short and longer atrioventricular intervals yielded sustained reductions of systolic blood pressure (SBP) in patients with hypertension. The effects of CNT on SBP were investigated in this double-blind randomized pilot study.

METHODS AND RESULTS: Eligible patients had daytime ambulatory SBP (aSBP) ≥130 mm Hg and office SBP ≥140 mm Hg despite taking ≥1 antihypertensive medication, and an indication for a dual-chamber pacemaker. Patients underwent Moderato device implantation, which was programmed as a standard pacemaker during a 1-month run-in phase. Patients whose daytime aSBP was ≥125 mm Hg at the end of this period were randomized (1:1, double blind) to treatment (CNT) or control (CNT inactive). The primary efficacy end point was the between-group difference of the change in 24-hour aSBP at 6 months. Of 68 patients initially enrolled and who underwent implantation with the Moderato system, 47 met criteria for study continuation and were randomized (26 treatment, 21 control). The mean age was 74.0±8.7 years, 64% were men, left ventricular ejection fraction was 59.2%±5.7%, and aSBP averaged 141.0±10.8 mm Hg despite the use of 3.3±1.5 antihypertensive medications; 81% had isolated systolic hypertension. Six months after randomization, aSBP was 11.1±10.5 mm Hg (95% CI, –15.2 to –8.1 mm Hg) lower than prerandomization in the treatment group compared with 3.1±9.5 mm Hg (–7.4 to 1.2 mm Hg) lower in controls, yielding a net treatment effect of 8.1±10.1 mm Hg (–14.2 to –1.9 mm Hg) (*P*=0.012). There were no Moderato device– or CNT-related adverse events.

CONCLUSIONS: CNT significantly reduced 24-hour aSBP in patients with hypertension with a clinical indication for a pacemaker. The majority of patients had isolated systolic hypertension, a particularly difficult group of patients to treat.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02837445.

Key Words: atrioventricular interval ■ hypertension ■ left ventricular function ■ pacemaker

See Editorial by Lauder and Mahfoud

More than a million patients undergo implantation or replacement of a pacemaker every year, of which >70% have hypertension. The high prevalence of hypertension is primarily attributable to the fact that the pacemaker population is elderly—average age of 70 years—and has a high prevalence of cardiovascular comorbidities.[1] The majority of these people have isolated systolic hypertension (ISH), and therefore their hypertension may be more difficult to treat.[2] Indeed, there is a high rate of uncontrolled

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020492

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- BackBeat Cardiac Neuromodulation Therapy is a programmable and adjustable bioelectronic therapy delivered via an active implantable cardiac pulse generator that mimics the effects of multidrug hypertension treatment by targeting preload, afterload, and sympathetic tone to immediately, substantially, and persistently lower blood pressure while simultaneously modulating the autonomic nervous system.
- The MODERATO II (Double-Blind Randomized Trial Of Cardiac Neuromodulation Therapy In Patients With Hypertension) pilot study showed that cardiac neuromodulation therapy significantly reduces 24-hour ambulatory and office systolic blood pressures in patients with hypertension despite medical therapy and an indication for a pacemaker, with the majority of patients having isolated systolic hypertension, which is a particularly difficult group to treat.

What Are the Clinical Implications?

- Patients with hypertension who require a pacemaker may benefit from cardiac neuromodulation therapy to reduce blood pressure without incurring the risk to patients of additional medications, procedures, or device implants.

Nonstandard Abbreviations and Acronyms

aBP	ambulatory blood pressure
aSBP	ambulatory systolic blood pressure
CNT	cardiac neuromodulation therapy
DBP	diastolic blood pressure
ISH	isolated systolic hypertension
MODERATO II	Double-Blind Randomized Trial Of Cardiac Neuromodulation Therapy In Patients With Hypertension
oBP	office blood pressure
oSBP	office systolic blood pressure
SBP	systolic blood pressure

hypertension despite pharmacological therapy in the pacemaker population.[3] Accordingly, hypertension therapy in the form of an algorithm embedded in a standard pacemaker is appealing for this population, since the risk-benefit profile of hypertension therapy excludes the risks associated with the clinically indicated pacemaker device and implant procedure.

In prior unblinded studies, a pacemaker-based cardiac neuromodulation therapy (CNT) delivered by the Moderato implantable pulse generator (BackBeat Medical, an Orchestra BioMed company) employing a sequence of variably timed short and longer atrioventricular intervals reduced SBP within minutes (see Figure S1).[4] Relative to baseline, sustained reductions in 24-hour ambulatory SBP (aSBP) by >10 mm Hg were demonstrated at 3-month follow-up and office SBP (oSBP) was reduced by >15 mm Hg through 2 years of follow-up.[5] The mechanism of SBP reduction involves a combination of decreased ventricular preload and modulation of the autonomic nervous system to prevent baroceptor-based sympathetic activation that might ordinarily restore SBP.[4]

Experience with other device-based treatments for hypertension have underscored the importance of accounting for the potential impact of placebo and Hawthorne effects in the assessment of their safety and effectiveness.[6] Accordingly, we conducted a prospective, double-blind, randomized pilot study of the safety and efficacy of CNT to reduce blood pressure (BP) in patients with persistent hypertension despite medical treatment and an indication for pacemaker implantation or replacement.

METHODS

The authors indicate that they will not make their data, analytic methods, and study materials available to other researchers.

Trial Design and Patient Population

The MODERATO II study was a prospective, multicenter, double-blind pilot study investigating the efficacy of BackBeat CNT in patients with persistent hypertension (defined below) and an indication for implantation or replacement of a dual-chamber pacemaker. The results of this study were intended to inform the design of a future, fully powered pivotal study to evaluate safety and efficacy. Details concerning the organization and conduct of the trial, a protocol synopsis, and a list of participating centers are provided in Data S1. The trial was sponsored by BackBeat Medical, an Orchestra BioMed company. The study was approved by the ethics committee at each participating center, and all patients provided written informed consent. This study was registered at clinicaltrials.gov (NCT02837445 Version 1.1 or 3.0).

Enrollment, Randomization, and Follow-Up

The overall study design is summarized in Figure S2; a full schedule of events is provided in Table S1. Patients indicated for implantation or replacement of

a dual-chamber pacemaker with a history of hypertension were screened at 13 centers in Europe. Individuals included in the study were required to be ≥18 years of age and be on stable (for prior 6 weeks) treatment for hypertension, with average daytime (7 AM to 10 PM) aSBP ≥130 mm Hg and oSBP ≥140 mm Hg. The main study exclusion criteria were known secondary cause of hypertension, average aSBP or oSBP >195 mm Hg, permanent atrial fibrillation or history of significant paroxysmal atrial fibrillation/flutter burden (defined as >25% of beats), left ventricular (LV) ejection fraction <50%, symptoms of heart failure (New York Heart Association class ≥II), estimated glomerular filtration rate (<30 mL/min per 1.73 m^2), or history of neurological events (stroke or transient ischemic attack within the past year). Inclusion and exclusion criteria are detailed further in the protocol synopsis of Data S1.

Patients who met the initial entry criteria underwent Moderato device implantation. The system's standard pacemaker parameters were programmed per the clinical needs of the patient and were followed for a 1-month run-in phase; CNT signals were not turned on in any patient during this phase. This allowed for assessment of Hawthorne effects on aSBP so that patients whose BPs were readily controlled by medical therapy could be excluded and only those who had hypertension despite medical therapy were included (detailed further in Data S1). To achieve this, ambulatory BP (aBP) was reassessed at a 3-week visit. Patients whose average daytime aSBP was <125 mm Hg were withdrawn from the study. Otherwise, patients were eligible for study inclusion in the randomized phase of the study and underwent CNT activation and parameter optimization as previously detailed.[5] We based criteria for continued study eligibility on aBP (which is more objective than office BP [oBP]) with a 125-mm Hg cutoff value, knowing that oBP (upon which guidelines for diagnosing and treating hypertension) would be at least 10 mm Hg higher; this was indeed confirmed as detailed in the Results section. A prerandomization echocardiogram was also performed.

Patients were randomized to either have CNT remain deactivated (control group) or for CNT to be activated (treatment group); both groups continued with prerandomization medical therapies, which were to remain constant throughout the study unless required based on clinical need. Randomization was provided by a centralized electronic system and was in blocks of 4 at each site and was stratified based on whether patients were 100% pacemaker dependent.

aBP was measured using an oscillometric Spacelabs 90207-1 monitor (Spacelabs Healthcare). Data were transferred electronically to a centralized core laboratory for blinded analysis. According to guideline recommendations, oBPs were measured with patients seated using the automatic Omron BP monitor (model number 705, Omron Healthcare, Inc). An average of at least 3 measurements were used to quantify oSBP at each visit; additional details concerning the methods used to measure aBPs and oBPs are provided in Data S1. Patients, core laboratories, and all study personnel were blinded to group assignment, except for one dedicated "unblinded" physician at each site; no known unblinding occurred. Following randomization, a 24-hour aBP monitor was applied to assess the short-term BP effects of CNT. Patients were subsequently seen at months 1, 3, and 6 following randomization for assessment of interim medical history (including any medication changes and measurement of oBP). Twenty-four-hour aBP measurements, echocardiograms, and blood tests were performed at 1 and 6 months. All of these tests were assessed in blinded core laboratories. Echocardiographic images were obtained at each time point with CNT off and on (in both groups) so that the sonographer and the reader remained blinded to treatment group.

Device and CNT Therapy Description

The Moderato system is a dual-chamber, rate-responsive pacemaker implantable pulse generator capable of delivering CNT that paces the heart with a series of specified, variably timed, alternating short (eg, 20–80 ms) and longer (eg, 100–180 ms) atrioventricular intervals; the principle has been previously described[5] and is detailed along with a typical acute BP response to initiation of CNT therapy in Figure S1.

End Points

The primary efficacy end point of this study was the between-group comparison of the change in average 24-hour aSBP from prerandomization at the end of the run-in phase to 6 months postrandomization. The primary safety end point was an evaluation of the composite rate of major cardiac adverse events, including heart failure, clinically significant arrhythmias (eg, persistent or increased atrial fibrillation burden, serious ventricular arrhythmias), myocardial infarction, stroke, heart failure, renal failure, and/or other related safety events that result in death, in the treatment versus the control groups. A series of additional exploratory end points are summarized in Data S1.

Statistical Analysis

This double-blind pilot study focused on assessing the impact of CNT on BP. Based on the prior unblinded study, it was estimated that with an anticipated SD of 10 mm Hg in the 24-hour aSBP in each group, 50 evaluable patients would provide 80% power to detect an ≥8 mm Hg between-group difference in changes in 24-hour aSBP. The study was not powered for a safety evaluation. The goal was to gather information related

to expected safety event rates in the specified patient population.

The between-group difference of changes in aSBP (primary end point) was evaluated in an intention-to-treat analysis with the primary analysis based on a *t* test. ANCOVA analysis was also performed that accounted for baseline values of aSBP. Assessments of other end points consisted of comparisons of parameter values between the last evaluated values before randomization (prerandomization and 6-month follow-up tests). In the case of aBP, the test was performed at week 3 of the run-in period. For other values, exploratory end points (detailed in Data S1) at week 4 of the run-in period immediately before randomization were used. No corrections were made for multiple comparisons of other end points. Outside of determining a *P* value for the primary end point, all other statistics (including *P* values) are considered descriptive. Continuous variables are described by means and SDs; they were compared using Student *t* test. All between-group treatment effects are summarized as means along with SDs and 95% CIs. Categorical variables are described by absolute and relative frequencies; they were compared using chi-square test or Fisher exact test. A *P* value of 0.05 was considered significant for all tests. Statistical analyses were performed with Matlab statistical toolbox (version R2019b; The MathWorks, Inc) and Excel (Microsoft).

RESULTS

Patients

Patient flow through the study is summarized in Figure 1. A total of 196 patients signed informed consent for screening, and 128 did not meet initial entry criteria: 50 (39%) because of an aSBP value <130 mm Hg; 34 (27%) with oSBP <140 mm Hg; 15 (12%) withdrew consent; 5 (4%) with LV ejection fraction <50%; and 24 (18%) for other reasons. The 68 patients who met entry criteria had a Moderato implant; their demographics are summarized in Table 1. Patients averaged 74 years of age, 57% were men, and there was a high prevalence of comorbidities, including diabetes mellitus, coronary artery disease, and history of atrial fibrillation. The Moderato system was a first-time pacemaker implant for 68% of the patients and was a replacement device in 32%. The main indications for pacing were sick sinus syndrome and second-degree atrioventricular conduction block. Ten percent of patients were 100% pacemaker dependent. Patients were taking an average of 3 to 4 antihypertensive medications; the breakdown of medications by drug class is summarized in Table 1.

Upon initial enrollment, oBP averaged 162.6±14.5/82.0±10.4 mm Hg and daytime aBP averaged 142.0±10.3/76.0±8.1 mm Hg (Table 2). Based on both ambulatory and office readings, 84% of patients had ISH with diastolic BP (DBP) <90 mm Hg.

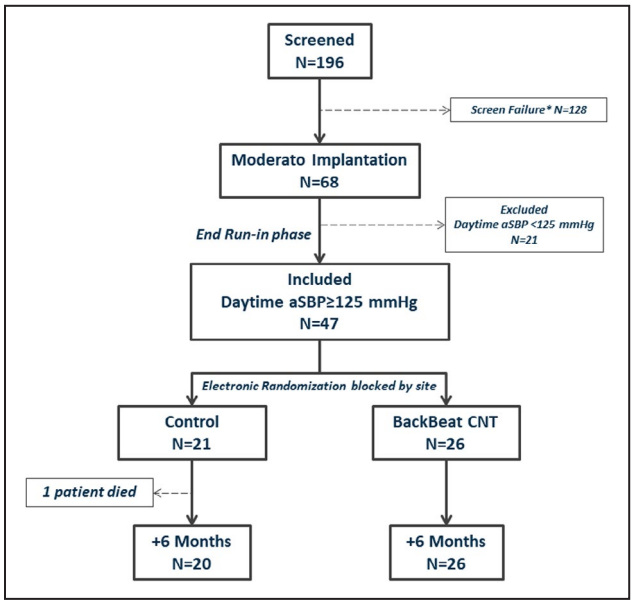

Figure 1. Flow diagram of study patients: Consolidated Standards of Reporting Trials (CONSORT) diagram showing flow of patients through the study.
*Screen failures included 50 (39%) patients with ambulatory systolic blood pressure (aSBP) <130 mm Hg; 34 (27%) with office blood pressure <140 mm Hg; 15 (12%) who withdrew consent; 5 (4%) with left ventricular ejection fraction <50%; and 18% for other reasons. CNT indicates cardiac neuromodulation therapy.

BP During the Study Run-in Phase

oBPs and aBPs decreased during the run-in phase, which can be attributed to the well-known Hawthorne effect (Table 2) discussed further in Data S1. From among the 68 patients with implantation of the Moderato system, daytime aSBP dropped below the cutoff for continued study participation in 21 patients, in whom average daytime aSBP dropped by 18 mm Hg, average 24-hour aSBP dropped by 15 mm Hg, and average oSBP dropped by 19 mm Hg. In contrast, while BP also decreased in the 47 patients who met criteria for study continuation, the magnitude of the change in BP was significantly smaller, with 24-hour aSBP decreasing by 5±10.5 mm Hg and oSBP decreasing by 9±19.3 mm Hg. There were no other significant demographic differences between those who did and those who did not qualify for study continuation (detailed in Table 2).

CNT Parameters Optimization and Randomization

All 47 patients who met study continuation criteria underwent CNT activation and parameter optimization.

Table 1. Patient Demographics

	All Patients With Implantation (n=68)	Withdrawn at the End of Run-in Because of BP Criterion (n=21)	All Randomized Following Run-in (n=47)	*P* (Withdrawn vs Randomized)	Control (n=21)	Treatment (n=26)	*P* (Control vs Treatment)
Age, y	74.2±8.3	74.7±7.5	74.0±8.7	0.755	74.9±8.5	73.2±9.0	0.518
Men	39 (57.4)	9 (42.9)	30 (63.8)	0.121	15 (71.4)	15 (57.7)	0.375
Height, cm	167.9±8.6	165.7±8.2	168.8±8.7	0.17	168.0±7.1	169.5±10.0	0.587
Weight, kg	85.8±15.1	82.6±10.6	87.1±16.7	0.258	88.5±16.0	86.1±17.5	0.630
LV ejection fraction, %	59.6±5.8	60.4±6.0	59.2±5.7	0.46	58.4±4.9	59.8±6.3	0.414
Medical history							
Diabetes mellitus	29 (42.6)	8 (38.1)	21 (44.7)	0.791	9 (42.9)	12 (46.2)	0.999
Prior atrial fibrillation	17 (25.0)	6 (28.6)	11 (23.4)	0.764	6 (28.6)	5 (19.2)	0.505
Coronary artery disease	23 (33.8)	4 (19)	19 (40.4)	0.103	9 (42.9)	10 (38.5)	0.775
Stroke	2 (2.9)	1 (4.8)	1 (2.1)	0.526	0 (0)	1 (3.8)	0.999
Pacemaker							
New implant	46 (67.6)	16 (76.2)	30 (63.8)	0.405	15 (71.4)	15 (57.7)	0.375
Replacement	22 (32.4)	5 (23.8)	17 (36.2)		6 (28.6)	11 (42.3)	
Indication							
Sick sinus syndrome	23 (33.8)	7 (33.3)	16 (34.0)	0.999	9 (42.9)	7 (26.9)	0.355
Bradycardia	13 (19.1)	4 (19.0)	9 (19.1)	0.999	5 (23.8)	4 (15.4)	0.486
Atrioventricular block I	10 (14.7)	2 (9.5)	8 (17.0)	0.712	4 (19.0)	4 (15.4)	0.999
Atrioventricular block II	20 (29.4)	4 (19.0)	16 (34.0)	0.259	5 (23.8)	11 (42.3)	0.227
Atrioventricular block III	7 (10.3)	3 (14.3)	4 (8.5)	0.668	1 (4.8)	3 (11.5)	0.617
Other	2 (2.9)	0 (0)	2 (4.3)	0.999	1 (4.8)	1 (3.8)	0.999
Medications, n	3.4±1.7	3.5±2.1	3.3±1.5	0.691	3.3±1.4	3.3±1.6	0.886
Medication use							
Loop diuretic	49 (72.1)	19 (90.5)	30 (63.8)	0.039	14 (66.7)	16 (61.5)	0.768
Potassium-sparing diuretic	5 (7.4)	1 (4.8)	4 (8.5)	0.955	2 (9.5)	2 (7.7)	0.999
ß-Blocker	24 (35.3)	5 (23.8)	19 (40.4)	0.273	6 (28.6)	13 (50)	0.232
ACEI	37 (54.4)	8 (38.1)	29 (61.7)	0.113	15 (71.4)	14 (53.8)	0.245
ARB	29 (42.6)	12 (57.1)	17 (36.2)	0.121	6 (28.6)	11 (42.3)	0.375
CCB	46 (67.6)	15 (71.4)	31 (66.0)	0.782	14 (66.7)	17 (65.4)	0.999
α-Agonist	14 (20.6)	6 (28.6)	8 (17.0)	0.336	5 (23.8)	3 (11.5)	0.437
Centrally acting agent	6 (8.8)	1 (4.8)	5 (10.6)	0.658	3 (14.3)	2 (7.7)	0.644

Values are mean±SD or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; BP, blood pressure; CCB, calcium channel blocker; and LV, left ventricular.

Table 2. BP During Screening and Prerandomization

	All Patients With Implantion(n=68)	Withdrawn at the End of Run-in Because of BP Criterion (n=21)	All Randomized Following Run-in (n=47)	*P* (Withdrawn vs Randomized)	Control (n=21)	Treatment (n=26)	*P* (Control vs Treatment)
Screening							
ISH	57 (83.8)	19 (90.5)	38 (80.9)	0.482	15 (71.4)	23 (88.5)	0.263
oSBP, mm Hg	162.6±14.5	161.3±14.4	163.1±14.6	0.654	165.2±15.3	161.4±14.1	0.381
oDBP, mm Hg	82.0±10.4	80.7±10.1	82.5±10.6	0.522	82.4±13.0	82.6±8.5	0.955
oHeart rate, beats per min	64.7±13.4	66.1±15.5	65.9±10.9	0.586	63.7±16.6	64.4±8.3	0.860
aSBP, mm Hg (d)	142.0±10.3	140.3±8.3	142.8±11.1	0.36	145.2±12.5	140.7±9.5	0.168
aDBP, mm Hg (d)	76.0±8.1	75.8±8.8	76.1±7.9	0.889	76.8±5.7	75.6±5.7	0.605
aHeart rate, beats per min (d)	67.3±10.6	69.9±9.7	66.1±10.9	0.17	66.3±12.8	65.9±9.3	0.886
aSBP, mm Hg (night)	132.1±17.1	122.3±13.0	136.6±16.9	0.001	138.2±17.3	135.2±16.9	0.558
aDBP, mm Hg (night)	68.8±9.4	65.3±9.5	70.4±9.0	0.037	71.5±11.2	69.4±6.6	0.438
aHeart rate, beats per min (night)	60.7±9.4	61.1±9.0	60.5±9.7	0.809	61.3±13.1	59.8±5.9	0.624
aSBP, mm Hg (24 h)	139.1±10.3	135.0±8.0	141.0±10.8	0.025	143.1±11.2	139.2±10.3	0.231
aDBP, mm Hg (24 h)	74.0±7.7	72.8±8.3	74.5±7.5	0.409	75.3±9.7	73.8±5.0	0.497
aHeart rate, beats per min (24 h)	65.4±9.9	67.4±9.2	64.5±10.2	0.275	65.0±12.6	64.1±8.0	0.775
Three-wk run-in phase							
aSBP, mm Hg (d)	133.1±13.4	122.0±11.3	137.9±11.3	<0.001	137.9±12.4	137.9±10.6	0.988
aDBP, mm Hg (d)	73.3±7.8	69.6±8.4	74.9±7.1	0.011	74.2±6.9	75.4±7.3	0.565
aHeart rate, beats per min (d)	70.2±9.2	69.7±6.5	70.5±10.2	0.756	69.6±9.4	71.2±10.9	0.614
aSBP, mm Hg (night)	126.9±14.2	114.5±10.5	132.2±12.2	<0.001	132.0±14.5	132.4±10.1	0.919
aDBP, mm Hg (night)	67.5±8.2	63.4±7.9	69.3±7.7	0.006	68.1±7.6	70.2±7.8	0.367
aHeart rate, beats per min (night)	65.1±6.4	64.9±5.8	65.2±6.7	0.828	64.9±6.3	65.5±7.2	0.761
aSBP, mm Hg (24 h)	131.5±13.0	120.1±10.7	136.3±10.7	<0.001	136.3±12.5	136.3±9.2	0.995
aDBP, mm Hg (24 h)	71.8±7.5	68.0±7.9	73.3±6.8	0.007	72.6±6.7	74.0±6.9	0.478
aHeart rate, beats per min (24 h)	68.9±8.2	68.5±6.2	69.1±9.0	0.786	68.4±8.5	69.6±9.5	0.670

(*Continued*)

oSBP dropped acutely by a mean of 15.1±9.7 mm Hg. Patients were then randomized (1:1) to either have CNT deactivated (control group, n=21) or to continue with active CNT (treatment group, n=26). Groups were balanced with regard to baseline characteristics (Table 1), baseline BPs, and initial immediate response to CNT (Table 2). It is important to note that patients did not experience any symptoms or sensations associated with the short atrioventricular delay beats, so this did not emerge as an issue related to tolerability of the therapy or unblinding.

BP During the Randomized Study Period

Results of 24-hour aSBP monitoring for all randomized patients are summarized in Figure 2; absolute values are summarized in Figure 2A and changes in aSBP from prerandomization values are summarized in Figure 2B.

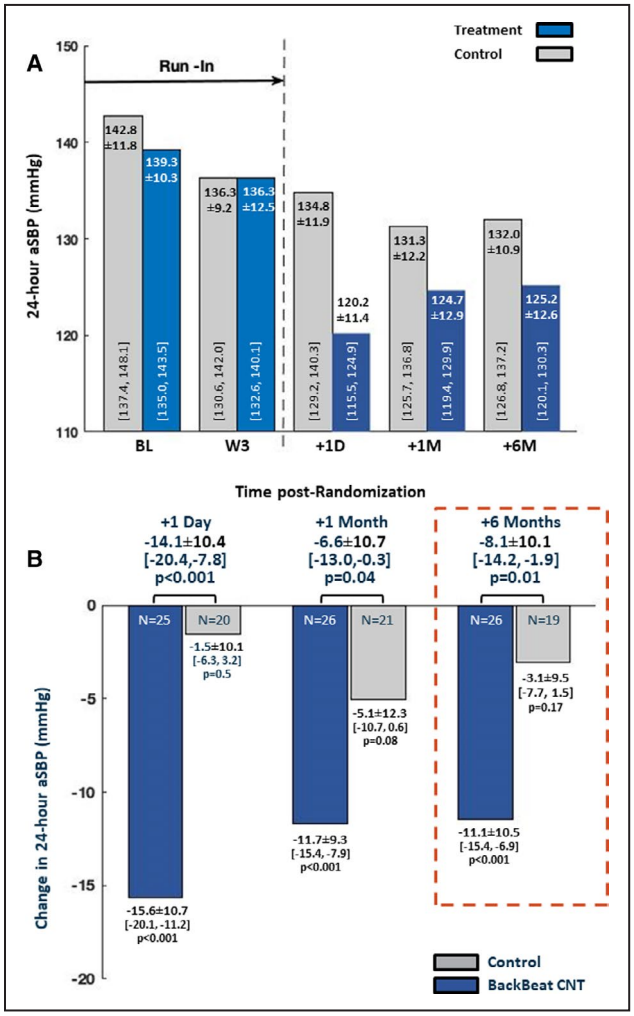

Figure 2. Ambulatory blood pressure results.
A, Comparison of 24-hour ambulatory systolic blood pressure (aSBP) between groups over the entire course of the study. **B**, Between-group comparisons of change in 24-hour aSBP relative to the 3-week prerandomization values. The +6-month data (red dashed box) show the study primary end point. CNT indicates cardiac neuromodulation therapy.

Table 2. (Continued)

	All Patients With Implantion(n=68)	Withdrawn at the End of Run-in Because of BP Criterion (n=21)	All Randomized Following Run-in (n=47)	*P* (Withdrawn vs Randomized)	Control (n=21)	Treatment (n=26)	*P* (Control vs Treatment)
Four-wk run-in phase							
oSBP, mm Hg	150.2±16.5	141.0±15.5	153.7±15.6	0.005	154.4±15.5	153.1±15.9	0.773
oDBP, mm Hg	80.9±11.4	77.0±10.7	82.3±11.4	0.092	81.6±12.4	82.9±10.7	0.706
oHeart rate, beats per min	66.8±10.5	66.9±7.8	66.8±11.4	0.987	66.5±10.9	67.1±12.1	0.847
Response to acute CNT activation, mm Hg					–15.0±10.2	–15.2±9.6	0.955

Values are mean±SD or number (percentage). aDBP indicates ambulatory diastolic blood pressure; aSBP, ambulatory systolic blood pressure; BP, blood pressure; CNT, cardiac neuromodulation therapy; ISH, isolated systolic hypertension; oDBP, office diastolic blood pressure; and oSBP, office systolic blood pressure.

As detailed above, aSBP decreased similarly in control and treatment patients during the run-in study phase (when devices were programmed in pacing-only mode without CNT).

Twenty-four hours following randomization, aSBP decreased by 15.6±10.7 mm Hg (95% CI, –20.1 to –11.2 mm Hg) in the treatment group compared with a 1.5±10.1- mm Hg (95% CI, –6.3 to 3.2 mm Hg) decrease in the control group, yielding a net aSBP reduction of 14.1±10.4 mm Hg (95% CI, –20.4 to –7.8 mm Hg) (P<0.001). At 6 months following randomization (primary end point), aBP measurements were available in all treatment patients and in 19 of 21 control patients; 1 control patient died before the 6-month follow-up and measurements were technically unsuccessful in another patient despite 2 attempts. At this 6-month time point, aSBP was 11.1±10.5 mm Hg (95% CI, –15.4 to –6.9 mm Hg) lower than prerandomization in the treatment group compared to 3.1±9.5 mm Hg (95% CI, –7.7 to 1.5 mm Hg) lower in control patients, yielding a net treatment effect of an 8.1±10.1 mm Hg (95% CI, –14.2 to –1.9 mm Hg) (P=0.012) reduction of aSBP. Similarly, results of ANCOVA analysis, which accounted for baseline values of aSBP, yielded a –7.7±9.8 mm Hg (95% CI, –13.7 to –1.7 mm Hg) between-group treatment effect (P=0.013). The substitution of missing values in the control group with the worst result of the group did not alter primary efficacy conclusions.

Results at intermediate time points are summarized in Figure 2A. When summarizing results in terms of a responder analysis (detailed in Data S1), 85% of the patients in the treatment group had a decrease in aSBP compared with 63% in the control group (P=0.03); 54% of treatment patients versus 37% of control patients had a decrease >10 mm Hg (P=0.03). Fan plots, which provide a graphical means of comparing BP changes between groups are provided in Figure S3.

Antihypertension medical therapies were tracked during the 6-month study period. As summarized in Table 3, there were relatively few prescribed medication changes in the treatment group and these were reasonably balanced between the number of dose increases and dose decreases within each drug class. In contrast, there were twice as many prescribed drug dose increases than decreases in the control group, suggesting that the observed change in aSBP may have underestimated the true treatment effect. Indeed, there were 14 control and 23 treatment patients who had no prescribed medication changes; in these patients, the between-group difference in aSBP at 6 months was 11.2±10.0 mm Hg (95% CI, –18.3 to –4.2 mm Hg) (P=0.003).

Between-group differences in oSBP paralleled those obtained with aSBP (Figure 3A), with 5.1±14.2 mm Hg (95% CI, –13.5 to 3.3 mm Hg), 14.6±15.9 mm Hg (95% CI, –24.0 to –5.2 mm Hg), and 12.3±16.9 mm Hg (95% CI, –22.4 to –2.2 mm Hg) net reductions in favor of the treatment group at 1, 3, and 6 months, respectively (Figure 3B). Additionally, changes in orthostatic BPs from preactivation to the 6-month visit did not differ between groups (P=0.20) and no patient reported symptoms related to hypotension in either group.

Ambulatory and office DBPs in the randomized cohort did not differ between the control and treatment groups (Table S2). Furthermore, DBPs did not change in either group during the follow-up period (Table S2).

Primary Safety Analysis

There were only 3 protocol-prespecified primary safety end point events in 2 patients, both in the control group. One patient experienced angina pectoris leading to right coronary angioplasty and stenting and later died as a result of a newly diagnosed disseminated adenocarcinoma. A second patient experienced persistent atrial fibrillation requiring cardioversion. Other serious adverse events (summarized in Table S3) also occurred only in the control group (7 events in 4 patients, including the 3 events noted above).

Table 3. Number of Medication Changes (Any Increase or Decrease in Dose) Between Baseline and 6-Month Follow-Up by Study Group and by Drug Class

Patients With a Change in Medications, n (%)	Treatment		Control	
	3 (11.5%)		7 (33.0%)	
	Increase	Decrease	Increase	Decrease
Diuretic	3	2	4	2
ACEI	0	1	3	1
ARB	1	1	0	1
β-Blocker	1	1	2	0
Potassium-sparing diuretics	1	0	1	1
CCB	0	1	1	1
Sum of all changes	6	6	11	6

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

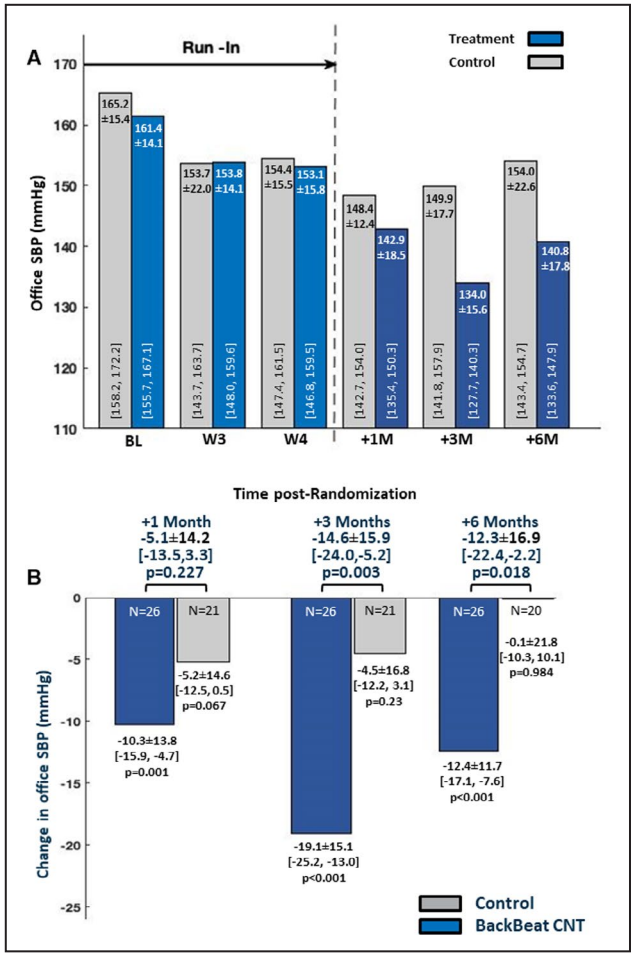

Figure 3. Office blood pressure results.
A, Comparison of office systolic blood pressure (oSBP) between groups over the entire course of the study. **B**, Between-group comparisons of change in oSBP relative to the 3-week prerandomization values. CNT indicates cardiac neuromodulation therapy; and SBP, systolic blood pressure.

Echocardiographic Assessments

Echocardiographic parameters were measured in a blinded core laboratory. There were no differences in changes in LV end-diastolic volumes (+9.2±16.2 mL in controls versus –2.3±26.1 mL in treatment, *P*=0.16), LV ejection fraction (–1.3%±5.4% in controls versus –5.4%±7.5% in treatment, *P*=0.09), left atrial dimension (+1.5±3.3 mm in controls versus 2.7±3.3 in treatment, *P*=0.22), or right atrial dimension (0.5±6.1 mm in controls versus 3.4±5.6 mm in treatment, *P*=0.13). Right ventricular size and function were graded qualitatively; no significant differences were found in either group between baseline and 6 months.

Other Assessments

Additional evaluations included DBPs, assessment of heart rate from Holter recordings (Table S4, no significant change), assessment of heart rate from ambulatory pressure recordings (Table S5, no significant change), changes in supraventricular and ventricular ectopy from Holter recordings (Table S6, no significant change), and blood tests focused on assessment of renal function (Table S7, no significant change).

DISCUSSION

CNT is a pacemaker-based therapy that takes advantage of the fact that: (1) ventricular pressure generation is preload dependent; (2) preload can be manipulated by reducing atrioventricular pacing intervals; and (3) periodic, orchestrated variations of systolic BP achieved by a repeating sequence of alternating short and longer atrioventricular intervals can suppress sympathetic activation ordinarily accompanying reductions in BP. The randomized double-blind design of the present pilot study reinforces results of prior unblinded studies[4,5] showing that pacemaker-based CNT is effective in reducing BP.

More specifically, compared with a control group, CNT decreased average 24-hour aSBP (the primary end point) by an average of 8.1 mm Hg from prerandomization values following 6 months of treatment. These findings were paralleled by a between-group difference of 12.3 mm Hg in oSBP. Importantly, during follow-up, there were more instances where antihypertensive drug doses were decreased rather than increased in the treatment group, compared with more instances when drug doses were increased rather than decreased in the control group. Thus, the observed between-group reductions in BP in the treatment group could not be attributed to changes in background medical therapy. On the contrary, such medication changes likely contributed to the finding that the between-group difference in aSBP was greater during the first 24 hours following randomization (14.1 mm Hg, Figure 2B) compared with 6 months (8.1 mm Hg) since medication changes are not likely to occur during the first 24 hours following randomization. Furthermore, between-group differences in both aSBP and oSBP at 6 months were larger after excluding patients in whom medication prescriptions were changed during follow-up.

The population targeted in the current study had a clinical indication for a pacemaker and an average age of 74 years, which is significantly older than patients generally enrolled in hypertension studies. Not surprisingly, there was also a higher prevalence of comorbid conditions and ISH (81%). It is therefore noteworthy that the significant reductions in SBP observed in the present study were achieved by CNT

in a population that is particularly challenging to treat.[2,7-9]

DBP was not influenced by CNT, most likely because of the fact that 81% of patients had ISH, meaning that their DBP values were in the normal range. Importantly, this is a group of patients in whom reductions of DBP could be detrimental.

This study focused on assessing the efficacy of CNT. Data concerning safety were collected, and no CNT-related adverse events were noted. Among potential safety concerns that will be addressed in larger and longer studies is that related to chronic right ventricular pacing, which has been associated with increased heart failure events.[10-12] However, such observations have primarily been limited to patients with underlying LV dysfunction and appear to be less of a concern in patients with normal LV function especially when evaluated in comparison to a control group.[13] In this regard, it is noteworthy that during the 6-month CNT treatment, no patients developed heart failure and that LV end-diastolic volumes decreased in the CNT treatment group compared with controls, which is opposite of what would have been observed with the development of heart failure.

Persistently elevated BPs above guideline-recommended levels despite multidrug regimens has encouraged the development and testing of several device-based therapies. These include baroreceptor activation therapy,[14-16] renal denervation,[6,17-23] arteriovenous shunting,[24,25] carotid body resection or denervation,[26,27] and mechanical stimulation of the baroreceptors.[28] Prior reports have provided overviews and comparisons of these different approaches.[29,30] Of these, the most widely studied approach is renal denervation. The most notable randomized controlled studies included the SYMPLICITY HTN-3 (which showed no significant between-group difference in aSBP),[6] SPYRAL HTN-OFF MED Pivotal study (which showed 4.0-mm Hg greater reduction of aSBP in treatment versus control in patients with hypertension in whom hypertension medications were withheld),[19] SPYRAL HTN-ON MED pilot study (which showed a 7.4-mm Hg greater reduction of aSBP in treatment versus control patients),[20] and the RADIANCE-HTN (A Study of the ReCor Medical Paradise System in Clinical Hypertension) SOLO study (which showed a 4.1-mm Hg between-group difference).[17] Three very recent meta-analyses of randomized trials have arrived at similar conclusions regarding the net treatment effect of renal denervation on aSBP: Dahal et al,[31] 3.45 mm Hg; Stavropoulos et al,[32] 3.62 mm Hg; and Syed et al,[33] 3.55 mm Hg. Most recently, Mahfoud et al[22] reported an average aSBP reduction of 8.9 mm Hg at 3 years of follow-up among several subgroups of patients considered to be at high risk for cardiovascular events and a reduction of 10.4 mm Hg in patients with resistant hypertension; this was a registry study without a control group. The current finding of an average 8.1-mm Hg between-group CNT-associated reduction of aSBP treatment is favorable in light of these findings with other technologies. In addition, 80% of the patients in the present Moderato II study had ISH, a particularly difficult group to treat,[2,21,24] which was excluded from the SPYRAL and RADIANCE studies. Finally, because the mechanisms are fundamentally different, CNT and renal denervation and other technologies have the potential to be used in combination in patients whose BPs remain above guideline recommendations with one or the other therapy.

Limitations

Despite protocol specifications to the contrary, physicians or patients may choose to modify medical therapies based on BP values observed during the follow-up period. Medication modifications are a well-known confounding effect in therapeutic trials of hypertension.[6,19,34] Our assessment of medical compliance was based on patient and physician reporting rather than blood and urine tests, as have been implemented in some recent studies.[19,20,35] However, in a randomized double-blind study of a therapy that is truly effective, more medication uptitrations would be expected in the control group. As noted above, this is exactly what was observed.

Second, while many efforts were taken to maintain blinding (including that the unblinded site clinician had no part in study-related clinical evaluations and signed an agreement to maintain confidentiality), there is a possibility of unblinding that could have occurred during unscheduled office visits. There was no attempt to formally assess for unblinding. However, any change in patient or physician behavior in response to unblinding would arguably have had to be mediated by greater uptitration of antihypertensive medications, which was not the case.

Third, despite the small number of patients in this study, statistically significant reductions in BP were identified in this double-blind pilot study relative to a control group. While the data provide preliminary evidence of safety, longer-term follow-up from a larger number of patients is needed to completely rule out potential safety concerns discussed above.

CONCLUSIONS

This pilot study provides important evidence that hypertension treatment with a pacemaker-based device that delivers CNT, a repeating sequence of variably timed short and longer atrioventricular intervals, can

meaningfully reduce SBP over 6 months of follow-up. There was a high rate of response to the therapy. No safety concerns emerged and patients did not experience any adverse sensations associated with the short atrioventricular delay beats. As in prior studies, the current study included patients who required pacemaker implantation or replacement; thus, the need to undergo the implantation procedure was independent of their need for additional hypertension therapy. This dissociates the risks associated with the implant procedure from those of CNT. With further proof of safety and efficacy in larger studies of longer duration, such a therapy could potentially be expanded to include patients not requiring a pacemaker.

ARTICLE INFORMATION

Received January 9, 2021; accepted April 1, 2021.

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Acknowledgments

A full list of the MODERATO II study investigators is provided in the Supplemental Material.

Sources of Funding

This study was supported by Backbeat Medical, Inc., a wholly owned subsidiary of Orchestra BioMed Inc.

Disclosures

Dr Merkely reports consultancy agreements with Biotronik, Abbott, AstraZeneca, Boehringer Ingelheim, and Novartis. Dr Mitkowski reports consultancy fees from Abbott, Biotronik, Boston Scientific and Medtronic. Dr Sokol reports consultancy agreements with BackBeat, Biotonik, Medtronic, and Boston Scientific. Dr Pluta reports consultancy agreements with BSCI, Medtronic, and Biotronik. Dr Getter reports consultancy agreements with Biotronik, Medtronic, Abbott, Boston Scientific, and Vitatron. Dr Osztheimer reports receiving consulting fees from Backbeat Medical, Biotronik, Medtronic, Abbott, and Boston Scientific. Dr Mika is an employee of BackBeat Medical and has equity in Orchestra Biomed. Dr Evans is a consultant to BackBeat Medical and has equity in Orchestra Biomed. Dr Hastings is a consultant to BackBeat Medical. Dr Burkhoff is a consultant to BackBeat Medical and has equity in Orchestra Biomed. Dr Kuck has no disclosures to report.

Supplementary Material

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Supplemental Material

Data S1.

STUDY ORGANIZATION AND CONDUCT

This trial was sponsored by BackBeat Medical, an Orchestra BioMed company. The protocol, a synopsis of which is provided below, was designed by the investigators in collaboration with the sponsor. The protocol was approved by the ethics committee at each participating center, and all the patients provided written informed consent. The sponsor participated in site selection and management and in data analysis. Source documents of primary and secondary endpoints were 100% monitored to ensure integrity of the data. The principal investigators had unrestricted access to the data, wrote the manuscript, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

All collected data were confirmed by independent monitors. Blood tests, echocardiograms, 24-hours ambulatory blood pressure and 24-hour Holter recordings were evaluated by blinded core labs. Adverse events were reviewed by an independent events adjudication committee (EAC) which ascribed severity and device- and procedure-relatedness. An independent data safety monitoring board (DSMB) monitored aggregate safety data during the study. EAC and DSMB memberships are detailed below.

Data Safety Monitoring Board and Events Adjudication Committee

(Chair): Prof. Marc Klapholz, Chair, Department of Medicine Rutgers, New Jersey Medical School

Dr. Jose Dizon, Associate Professor of Medicine at CUMC, New York-Presbyterian/Columbia

Dr. Sam Hanon, Associate Professor of Medicine, Cardiology, The Mount Sinai Hospital

Non-voting statistician

Dr. Harold M Hastings, Division of Science, Mathematics and Computing, Bard College at Simon's Rock, Great Barrington MA and Department of Physics and Astronomy, Hofstra University, Hempstead NY (Professor Emeritus)

List of Centers and Principal Investigators who screened patients

Country	City	Hospital	PI
Austria	Linz	Krankenhaus der Elisabethinen	Prof. Josef Aichinger
	Vienna	Medical University of Vienna, Vienna General Hospital	Prof. Thomas Pezawas
Belgium	Aalst	OLV Hospital Aalst	Dr. Riet Dierckx
Czech Republic	Prague	Na Homolce Hospital	Prof. Petr Neuzil
Hungary	Budapest	Semmelweis University Heart and Vascular Center	Prof. Bela Merkely
Latvia	Riga	P. Stradins Clinical University Hospital	Prof. Andrejs Erglis
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	Prof. Germanas Marinskis
Poland	Gdansk	Medical University of Gdansk	Prof. Krzysztof Narkiewicz
	Poznan	Szpital Kliniczny Przemiemienia Panskiego	Prof. Przemysław Mitkowski
	Szczecin	Pomeranian Medical University Hospital no. 2	Prof. Jaroslaw Kazmierczak
	Warsaw	I Katedra i Klinika Kardiologii Samodzielny Publiczny Centralny Szpital	Prof. Marcin Grabowski
	Zabrze	Silesian Center for Heart Diseases	Prof. Zbigniew Kalarus
UK	London	St. Thomas' Hospital	Prof. Aldo Rinaldi

Supplemental Methods

Methods for measuring blood pressure

Office blood pressure measurements were performed consistent with the Standard Joint National Committee VII, European Society of Hypertension and European Society of Cardiology recommendations.[1,2] Office blood pressure was based on the average of three measurements. Office blood pressures were measured using the automatic Omron blood pressure monitor (model number 705, Omron Corporation, Kyoto). All centers were provided with the devices to unify the measurements. If systolic blood pressure values were more than 15 mmHg apart on any pair of these readings, measurements were repeated, and the final value was based on the last three consecutive consistent (<15 mmHg differences) readings. 24-Hour ambulatory blood pressure monitoring tests were performed with an oscillometric Spacelabs 90207-1 monitor (Spacelabs Healthcare, Hertford, UK), with readings recorded every 10 minutes during the day (7am to 10pm) and every 20 minutes at night. Measurements were deemed acceptable if at least 30 readings during the day-time period and 9 readings during the night-time period were successfully recorded. One repeat of the 24-hour ambulatory measurement was permitted in case the number of readings did not meet specified minimum recordings.

Moderato device and CNT Description

The Moderato device and CNT therapy has been described in detail previously.[3] In brief, the CNT pacing sequence consists of 8-13 beats with a shorter AV delay followed by 1-3 beats with a longer AV delay. The CNT algorithm has atrial rate tracking, meaning that its rate automatically adjusts to an average of 4-to-5 beat/min above the native heart rate in patients whose heart rate is determined by the intrinsic atrial rate. The device connects to the heart with any commercially available IS-1 bipolar endocardial lead. An external device programmer allows clinicians to program device parameters and download diagnostic information. The device implantation or exchange procedures were performed according to local standard dual-chamber pacemaker implantation protocols; no special implantation instructions beyond those used for standard pacemakers were needed. A typical blood pressure response to activation of CNT pacing is shown in Fig. S1.

Efforts to Minimize Placebo and Hawthorne Effects

The nature of the Moderato system and the patient population to which it applies allowed for a novel study design to account for placebo and Hawthorne effects. Specifically, in addition to hypertension, all study subjects had a clinical indication for a pacemaker for treatment of bradyarrhythmia. Accordingly, patients could receive the device implant and be observed during a significant time period prior to randomization. In this manner, patients whose adherence with medical therapies or lifestyle behaviors resulted in improved control of blood pressure could be withdrawn from the study prior to randomization. This is not possible with other technologies whose putative anti-hypertensive effects are in effect at the moment of application. Indeed, Hawthorne effects have interfered with the ability to effectively quantify treatment effects in prior studies of renal denervation. Of the original 68 patients enrolled in our study, blood pressure fell below the study inclusion criterion in 21 (31%) during the initial 30-day observation period without any changes in prescribed therapies. Blood pressure also dropped in most subjects who remained in the study, but their final pre-randomization values were still in a range requiring additional treatment.

Exploratory Endpoints

A series of additional exploratory endpoints included between group differences in the change (from baseline to 6 months) of oSBP and diastolic blood pressure (DBP), average night-time SBP, average daytime SBP and 24-hour average DBP; the percentage of patients who had decreases in ambulatory blood pressure, the percentage of patients with a reduction of 5 mmHg or more in their ambulatory pressure and the percentage of patients having a super response of 10mmHg or more. Analyses of echocardiographic data focused on between-group differences in changes

of end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF). Analyses of blood test focused on changes of creatinine, BUN, eGFR.

Supplemental Results

Diastolic blood pressures

As detailed in Table 2 of the main text, aDBP in the randomized cohort averaged 73.3±6.8 mmHg and did not differ between control and treatment groups. Furthermore, aDBP did not change in either group during the follow-up period (Table S3).

Heart Rate

Average heart rate was assessed from 24-hour ambulatory blood pressure recordings and 24-hour Holter recordings. Results (detailed in Table S5 and S6) show a ~3-4 beat per minute higher heart rate in Treatment compared to Control, which is fully explainable by the atrial rate tracking feature of the IPG. This is an intrinsic feature of the CNT algorithm in order to ensure capture of both the atria and ventricles to achieve precise control of the AV interval.

Holter

Twenty-four hour Holter recordings were performed pre-randomization and at 6 months and were analyzed for ventricular and supraventricular arrhythmic burden. As detailed in Table S7, there was a very low overall arrhythmia burden which did not change significantly in either group.

Blood Sample Analysis

Blood sample analysis focused on changes in renal function. As detailed in Table S8, there were minimal changes in blood urea nitrogen, serum creatinine or estimated glomerular filtration rate (eGFR) over the 6-month study period in both Treatment and Control groups.

MODERATO II STUDY SYNOPSIS

Study Title	**Clinical Evaluation of Safety and Effectiveness of the BackBeat Medical Moderato System in Patients with Hypertension: A Double-Blind Randomized Trial.**
Study code	CS-03 (Version 1.1, October 26, 2015)
Name of the Device	Moderato System
Intended Use	The Moderato System is indicated for patients with hypertension who also require a dual chamber pacemaker, in order to reduce their blood pressure.
Study Design	This will be a randomized, double-blind study in which patients are randomized to either a cohort that will receive active treatment with the Moderato System delivering hypertension therapy plus continued medical therapy or to a cohort that will have the Moderato System in pacemaker only mode and receive continued medical therapy.
Patient Population / Sample Size	A total of 50* subjects will be enrolled from up to 30 sites; a majority of sites will be from countries within the European Union. The maximum number of subjects enrolled per site will be 40. Patients who dropout during the "Run-In Phase" will be replaced.
Duration of the investigation	Each subject will be followed for approximately 7 months, consisting of a 1 month "Run-In Phase" after device implantation, followed by a 6-month observation period. It is expected to take approximately 20 months to recruit the subjects, so the total duration of the study will be approximately 20 + 7 = 27 months.
Study Rationale	Pacemaker technology is well established, with well-defined hardware, firmware and logic algorithms. The Moderato System leverages existing technology to deliver a novel pacing therapy to treat Hypertension (HTN). The device has undergone rigorous bench and preclinical animal testing to confirm its safety and performance and has been implanted in 35 patients in a pilot clinical study aimed to evaluate the safety and functionality of the system. Pilot study interim results indicate that the device functions as expected and suggest that there is a significant decrease in blood pressure in both ambulatory and office measurements after device activation. The goal of this study is to confirm the effects of the Moderato System on blood pressure in a controlled, randomized, double-blinded study. Hypertension (HTN) ultimately affects 1 in 3 adults in most cultures and is one of the most important factors contributing to cardiovascular morbidity and mortality. Medications are frequently effective in controlling blood pressure. However, >40% of HTN patients remain with unacceptably high blood pressure. Unacceptably high blood pressure is defined as systolic pressure >140 mmHg in the absence of other cardiovascular risk factors, or >130 mmHg in the presence of other risk factors. According to the United States National Heart, Lung and Blood Institute (NHLBI), about 69% of people presenting with their first heart attack, 77% presenting with their first stroke and 74% presenting with congestive heart failure have a systolic blood pressure higher than 140 mmHg. Cardiovascular risk doubles for every 10 mmHg increase in systolic blood pressure.

	Although there are several medications that are helpful in controlling blood pressure, one of their major limitations is the notoriously low rate of compliance. Thus, many medically responsive patients have high pressures simply because they do not take their medications. This is sometime due to unpleasant side effects. In addition, there are many patients who have persistently elevated blood pressure despite compliance with medical therapies. Accordingly, investigators have turned to alternate strategies to treat HTN, in particular device-based therapies. Percutaneous renal denervation is one example that, in early studies, achieved significant success in a population with medically refractory HTN (i.e., systolic pressure >160 mmHg despite the use of at least 3 antihypertensive drugs). Symplicity-3, a randomized, sham-controlled blinded study, however, revealed no significant difference between the renal denervation and sham groups (1). Another device therapy for hypertension utilizes Baroreflex Activation Therapy (BAT) to electrically stimulate the carotid sinus using an implanted pulse generator (Rheos). The Rheos pivotal trial (baroreceptor stimulation) enrolled 265 patients with a systolic BP >160mmHg and an average ambulatory BP >135mmHg (2); 42% of treated patients achieved blood pressure control during long-term follow-up (3). However, there was a 25% procedural complication event rate, an approximately 10% device-related complication event rate and a 13% device safety complication rate. Thus, additional treatments are needed. BackBeat Medical has developed a family of cardiac pacing algorithms that have been shown in pre-clinical studies to safely reduce blood pressure. They have also been shown to be safe and reduce blood pressure in acute studies performed in patients with HTN. Preliminary data from an ongoing long-term study in patients who require a pacemaker has also shown significant blood pressure-lowering effects with no adverse impact on cardiac function. These Cardiac Neuromodulation Therapy (CNT) pacing algorithms use standard dual-chamber pacing signals and involve alterations of the timing at which these signals are delivered. Accordingly, they have been incorporated as an added feature into a standard pacemaker that connects to the heart with standard, commercially available pacing leads. The present study will enrol subjects who have hypertension despite a stable anti-HTN medical regimen for greater than one month who either require implantation of a dual chamber pacemaker or have a pre-existing pacemaker that requires a pulse generator exchange. Subjects who require a new pacemaker implant or a pacemaker exchange will be exposed to the well-established risks of pacemaker implantation and pacing therapy, independent of whether they receive the Moderato System. Therefore, the risks associated with participating in this study and of using the Moderato System are restricted to those risks associated with use of the specific BackBeat-CNT therapy pacing algorithm. To enhance its safety profile, the BackBeat-CNT therapy pacing algorithm is programmed according to the needs of each individual subject and the therapy can be turned off at any time.
Description of System Components	1. Moderato IPG: A sterile Pacemaker that, in addition to standard pacemaker capabilities and features, also incorporates the BackBeat-CNT pacing algorithms to reduce blood pressure for use as a treatment for hypertension. 2. Any commercially available, IS-1 BI compatible, bipolar endocardial pacing leads; 3. Moderato Programmer: An external device programmer capable of communicating with the Moderato IPG through the skin to program device parameters.

Follow-up Schedule	The details of the study flow are detailed in the protocol along with a flow diagram (Figure S2). After screening, the study will be conducted in two phases: a 4 weeks Run-In Phase and a 6-month Randomized Phase. **Pre-screening and Screening:** After signing an informed consent, subjects will be screened for blood pressure and hypertension treatments to determine eligibility. This will consist of an office visit to document medical therapies for hypertension (including drug name, daily dose and duration of treatment), to measure blood pressure and to obtain a 24-hour recording of ambulatory blood pressure. Subjects will also undergo an Echo study, blood samples will be collected and evaluated to determine GFR. ECG will be performed and, if applicable, the subject will undergo a pregnancy test. Subjects will be eligible for inclusion in the study if the average daytime (7AM to 10PM) ambulatory systolic pressure is ≥130 mmHg and an office blood pressure ≥140 mmHg. All subjects meeting this screening criterion and all other study inclusion/exclusion criteria (detailed below) will undergo implant of the Moderato IPG. **Run-In Period** Following implantation, the normal pacing functions of the device will be programmed as per the needs of the patient. The day of implantation will be considered Day 0 of the study from which the timing of future study visits will be determined. The patient will be seen in the office at the end of study week 3 and will have an office BP check, medical history and medications will be recorded, a 24 hour Holter to provide a baseline assessment of the amount of ambient ectopy, and a repeat 24-hour ambulatory blood pressure recording; this blood pressure will be considered the pre-randomization Baseline ambulatory blood pressure. Patients will be seen in the office at the end of study week 4, the results of the prior 24-hour ambulatory pressure recording will be reviewed. Patients will be eligible to move to the Randomized Phase of the study (detailed in the next section) if their average daytime (7AM-10PM) ambulatory systolic pressure is ≥125 mmHg. Patients eligible for randomization will undergo the final pre-randomization Baseline testing (echocardiogram, office blood pressure, blood tests) these tests will be used as the pre-randomization Baseline for evaluating the effect of BackBeat-CNT therapy on these tests. Patients who do not meet the criteria to be randomized will be followed according to the same study visit schedule as for randomized patients for 6 months and will be followed mainly for safety evaluation. These patients (the Non-Randomized Cohort), in collaboration with their primary physician, can choose to have the BackBeat-CNT hypertension treatment algorithm activated (e.g., if their office blood pressure is persistently elevated). However, efficacy results will not be included in the primary analysis of blood pressure effects. In addition, these patients will be replaced, so that a total of 170 patients enter the Randomized Phase of the study. **Randomized Phase** After the 4-week Run-In phase, all subjects eligible for the Randomized Phase will undergo a BackBeat-CNT therapy optimization procedure. This consists of measuring blood pressure while varying BackBeat-CNT therapy algorithm parameters to determine the parameters that provide the best therapy. Following this optimization procedure, patients will be randomized into one of two groups: Group 1 (active treatment group) will have continued medical therapy plus the BackBeat-CNT Therapy activated; Group 2 (control group) will continue with the standard

	pacing regimen and continued medical therapy. Both the patients and the physicians will be blinded to group assignment. At each center, there will be one "unblended" physician who will handle all pacemaker evaluations and treatments. Patients in both groups will be seen at 1, 3, and 6 months post randomization and will undergo a review of the interim medical history, an office measurement of BP (each visit), echocardiograms (at 1 and 6 months), blood tests including ANP and BNP (at 1 and 6 months) and a 24-hour ambulatory blood pressure recording (at 1 and 6 months). An ECG and Holter monitor recording will also be performed at the 6 month visit post-randomization. The study will be considered complete for the primary endpoint after all randomized subjects have completed the 6-month follow-up tests. At the end of the 6-month BackBeat-CNT Therapy period (post randomization), subjects in Group 1 (the active group) will have the option to continue with the BackBeat-CNT therapy activated; subjects in Group 1 opting for active treatment will have office visits at months 12, 18 and 24 post randomization. Subjects in Group 2 (the control group) will have the option to have the BackBeat-CNT therapy activated; patients opting for active treatment will be followed at 1, 3 and 6 months post activation (months 7, 9 and 12 post randomization) and every 6 months thereafter for a total of 2 years. At the 1, 3 and 6 months post activation (months 7, 9 and 12 post randomization), subjects who were in group 2 will repeat the tests and evaluations as described under the visits 1, 3, and 6 months post randomization. Subjects in the Non-Randomized Cohort who have opted to activate the BackBeat-CNT treatment algorithm will be seen at 1, 3, 6, 12, 18 and 24 months with the same tests as the study patients. Non-randomized Cohort subjects who do not have active treatment or subjects in groups 1 or 2 who decide not to activate the BackBeat-CNT treatment at the end of the 6-month post randomization visit will be followed every 6 months through a total of 2 years follow-up for the interrogation of the Moderato pacemaker and modification of the standard pacemaker parameters in case needed.
Inclusion Criteria	**1)** Subject is ≥ 18 years of age **2)** Subject requires the implant or replacement of a dual chamber pacemaker **3)** Subject has stable (for prior 1 month) hypertension treatment with at least 1 antihypertensive drug, which is anticipated to be able to be maintained without changes for 7 months. **4)** Subject has an average day-time (7AM to 10PM) ambulatory systolic blood pressure of ≥ 130mmHg and office systolic blood pressure ≥140 mmHg **5)** Subject lives in the proximity of the study center, which will permit compliance with study visits for at least 7 months.
Exclusion Criteria	**1)** Subject has a known secondary cause of HTN **2)** Subject with average ambulatory or office systolic BP >195 mmHg **3)** Subject has permanent atrial fibrillation

	4) Subject has a history of significant paroxysmal atrial fibrillation/flutter burden (defined as >25% of beats). Fibrillation/flutter burden will be determined by pacemaker interrogation (for those already having a pre-existing pacemaker) or, otherwise, by patient history. **5)** Subject has ejection fraction <50% **6)** Subject has symptoms of heart failure, NYHA Class II or greater **7)** Subject has hypertrophic cardiomyopathy, restrictive cardiomyopathy or interventricular septal thickness ≥15 mm **8)** Subject is on dialysis **9)** Subject has estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m² **10)** Subject has prior neurological events (stroke or TIA) within the past year or an event at any prior time that has resulted in residual neurologic deficit **11)** Subject has known carotid artery disease **12)** Subject has known autonomic dysfunction **13)** Subject has a history of clinically significant untreated ventricular tachyarrhythmia or has experienced sudden death **14)** Subject has had previous active device-based treatment for hypertension **15)** Subject has an existing implant, other than a pacemaker that needs replacing **16)** Subject is pregnant or has the possibility of becoming pregnant during the conduct of the study and is not willing to use a means of contraception during the study. **17)** Subject cannot or is unwilling to provide informed consent.
Analysis of Clinical Effectiveness	The Moderato System will be considered to be effective if the mean change of the average 24-hour ambulatory systolic blood pressure (6 months' average – pre-randomization Baseline average) in the active treatment group (Group 1) is significantly greater than the mean change (6 month average – Pre-randomization Baseline average) in the control group (Group 2) (Note: The Baseline pre-randomization 24-hour blood pressure is the mean ambulatory blood pressure measured at the 3 week visit during the Run-In Phase.)
Safety	The Moderato System will be considered safe if the rate of major adverse cardiac events [including: heart failure, clinically significant arrhythmias (e.g., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke, heart failure and renal failure and/ or other related safety events that result in death] does not differ between groups.
Other Analyses	Changes in the following parameters will be analyzed (6 months versus pre-randomization [Baseline]) and compared between groups using descriptive statistics to provide additional information about the safety and effectiveness of the therapy: • Holter recording to confirm proper functioning of the BackBeat-CNT treatment algorithm and to assess changes in the incidence of ventricular and supraventricular events • Average day-time blood pressures from 24-hour ambulatory monitoring • Average night-time blood pressures from 24-hour ambulatory monitoring • Office systolic and diastolic blood pressure measurements • Echocardiograms: Ejection fraction, left ventricular end-diastolic and end-systolic volumes • Blood tests: ANP, BNP, Creatinine • Overall type and rate of adverse events

*Note: the original protocol called for 170 patients and was designed as a pivotal study with sample size based on results from a prior unblinded study. However, it was decided that results from the first 50 patients would be analyzed to provide a better assessment of the rate of safety events and changes of blood pressure (particularly in the blinded control group) for more accurate estimation of sample size for the pivotal study powered for both safety and efficacy.

Table S1. Study Schedule of Visits and Tests.

			All visits after implantation have a window of±1 week						
			Run-In Period			Randomized Phase			Post-Study**
	Pre-Screening	Screening	Moderato IPG Implant	3 Wk F/U	4 Wk F/U	+1 Mo F/U	+3 Mo F/U	+6 Mo F/U	Post-Study F/U: every 6 Months through 2 years
Informed Consent	X								
Office Visit / Medical History		X		X	X	X	X	X	X
Medications		X		X	X	X	X	X	X
Office Blood Pressure Check		X		X	X	X	X	X	X
Electrocardiogram		X						X	
Pregnancy test (if applicable)		X							
24 Hour Holter Monitor				X				X	
24 Hour Ambulatory Blood Pressure Monitor		X		X	X	X		X	
Eligibility Determination		X			X				
Echocardiogram		X*			X▲	X▲		X▲	X▲
Blood tests		X			X	X		X	
Basic chemistry panel and hematology		X			X	X		X	
Estimated GFR		X *			X	X		X	
MR pro ANP and NT Pro BNP		X			X	X		X	
Moderato IPG Implant			X						
Randomization and BackBeat-CNT Therapy optimization					X				
Moderato IPG interrogation				X	X	X[a]	X[a]	X[a]	X[a]
Adverse Events (as needed)		X	X	X	X	X	X	X	X

**Subjects in the control arm who agree to be activated with the Moderato-CNT therapy at the end of the study (+6 months F/U) will repeat the F/U schedule of +1 month to + 6 months in the post study and every 6 months through 2 years

*) GFR and Echocardiography will be also evaluated by the institution for the determination of the inclusion/exclusion criteria.

▲) Echocardiography will be done twice, with Moderato-CNT therapy ON and OFF

[a]) Moderato-CNT Therapy optimization as required

Table S2. Summary of ambulatory and office diastolic blood pressure at the follow-up time points.

	Ambulatory Diastolic BP				Office Diastolic BP			
	Pre-Randomization	+1 Day	+1 Month	+6 Months	Pre-Randomization	+1 Month	+3 Months	+6 Months
Treatment	74.0±6.9	71.9±6.9	74.3±8.4	73.2±5.4	83.0±10.8	83.3±9.6	79.0±9.2	82.1±9.3
Control	72.6±6.7	72.5±8.0	71.1±7.0	70.7±6.9	81.6±12.4	79.6±11.2	80.3±11.8	80.8±8.5
Difference	1.4	0.58	3.1	2.5	1.34	3.7	-1.3	1.2
p-value	0.670	0.800	0.179	0.178	0.693	0.227	0.684	0.643

Treatment/Control values are mean±SD.

Table S3. Summary of adverse events.

Subject	Group	EVENT
A	Control	Anemia
B	Control	Unstable angina leading to RCA stent
		Metastatic prostate cancer
C	Control	Pneumonia
D	Control	Atrial fibrillation requiring cardioversion
		Hyponatremia
		Gastroenteritis
		Dislocated RV pacing lead

Table S4. Heart rate based on Holter analysis.

		Week 3 Pre-Randomization	+6 Months	Change +6M–W3
Treatment	Mean	74.00	76.81	2.81
	SD	9.70	10.52	7.55
	N	26	26	26
Control	Mean	71.19	70.65	-1.05
	SD	9.16	8.60	4.44
	N	21	20	20

Table S5. Heart rate based on ambulatory blood pressure monitor results.

		Baseline	Week 3	+1 Day	+1 Month	+6 Months	Change +1D–W3	Change +1M–W3	Change +6M–W3
Treatment	Mean	64.13	69.57	74.85	73.10	72.63	4.92	3.53	3.06
	SD	8.02	9.50	9.43	8.46	10.14	4.33	6.06	6.63
	N	25	26	25	26	26	25	26	26
Control	Mean	64.69	68.43	68.26	69.46	67.70	0.24	1.04	-1.59
	SD	12.48	8.46	9.24	9.10	7.80	2.83	2.93	4.19
	N	21	21	20	21	19	20	21	19

Table S6. Holter monitor analysis of ventricular and supraventricular arrhythmia burden. No significant difference noted between treatment and control groups.

Parameter			Week 3	+6 Months	Change +6M – W3
TREATMENT	**SVE**	Mean±SD	0.92±2.3	0.49±0.9	-0.44±2.5
		Median (IQR)	0.06 (0.01, 0.46)	0.01 (0.01, 0.61)	-0.01 (-0.14, 0.05)
	PVC	Mean±SD	0.85±2.2	0.70±1.5	-0.16±1.6
		Median (IQR)	0.13 (0.04, 0.43)	0.1 (0.02, 0.39)	-0.01 (-0.16, 0.12)
CONTROL	**SVE**	Mean±SD	0.38±0.9	0.82±2.3	0.42±2.5
		Median (IQR)	0.01 (0.00, 0.13)	0.02 (0.01, 0.31)	0.00 (-0.05, 0.02)
	PVC	Mean±SD	1.04±3.0	0.27±0.46	-0.82±3.1
		Median (IQR)	0.14 (0.02, 0.63)	0.13 (0.02, 0.28)	0.00 (-0.39, 0.06)

IQR, interquartile range; SVE, percentage of all beats that are supraventricular ectopic beats; PVC, percentage of all beats that are premature ventricular contractions.

Table S7. Blood tests related to renal function.

	Blood tests	baseline	Week 4	+1 Month	+6 Months	Change +1M – W4	Change +6M – W4
Treatment	BUN (mmol/l)	5.8±1.6	6.0±1.7	6.1±1.5	6.3±1.2	0.10±1.3	0.29±1.3
	Creatinine (μmol/l)	77.5±16.4	76.7±12.8	81.2±15.6	82.7±20.5	3.9±12.0	5.9±17.9
	eGFR (ml/min/1.73m²)	80.5±19.1	79.0±16.9	76.0±18.0	75.3±22.1	-2.7±13.7	-3.7±16.0
Control	BUN (mmol/l)	7.2±3.7	6.9±2.2	6.9±2.3	6.6±2.0	0.11±1.1	-0.41±1.8
	Creatinine (μmol/l)	97.4±24.5	92.6±20.5	92.1±20.5	94.3±19.6	0.5±7.0	2.3±15.2
	eGFR (ml/min/1.73m²)	65.4±20.6	68.1±19.3	68.8±17.3	66.8±21.0	-0.71±6.8	-1.8±9.6

Values are mean±SD.

Figure S1. Study design and randomization scheme.

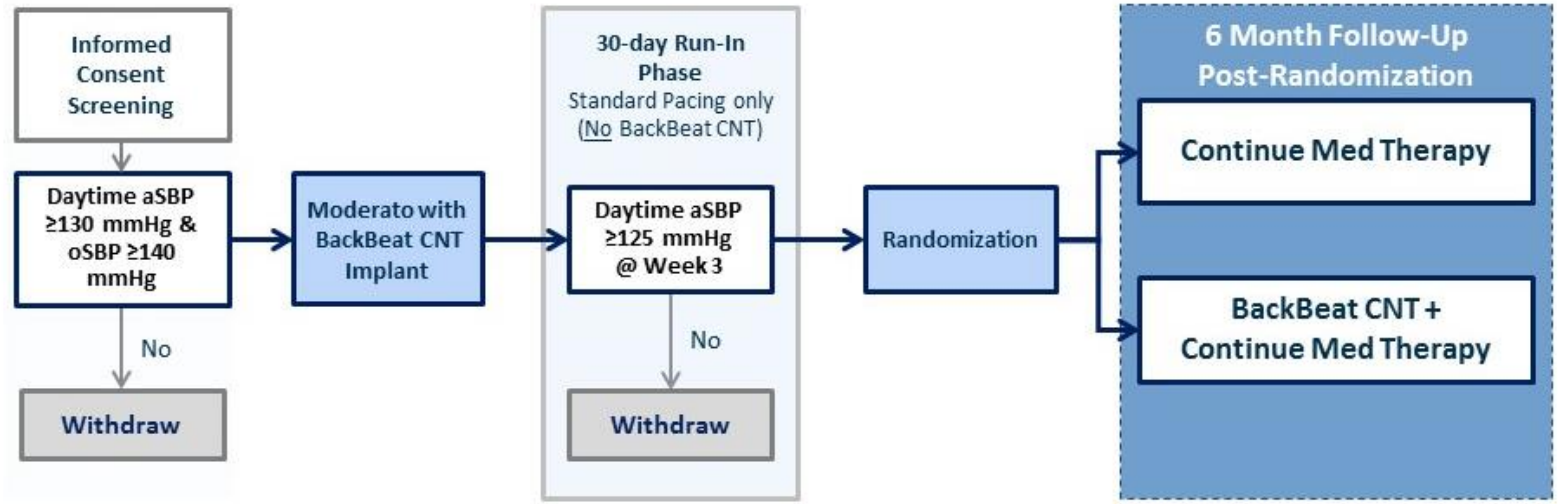

Figure S2. Red dots show systolic blood pressure (SBP) on each beat; sinusoidal variation due to respiration. Cardiac Neuromodulation therapy (CNT) pacing initiated as indicated by the bar. SBP on short AV delay paced beats drops significantly. SBP increases on the two beats with longer AV delays (red arrows) and then drops significantly with resumption of short AV delay pacing. When CNT pacing is suspended, blood pressure increases gradually back towards the original baseline, suggesting that total peripheral resistance was decreased during the period on CNT pacing through modulation of autonomic nervous system activity by SBP variations.

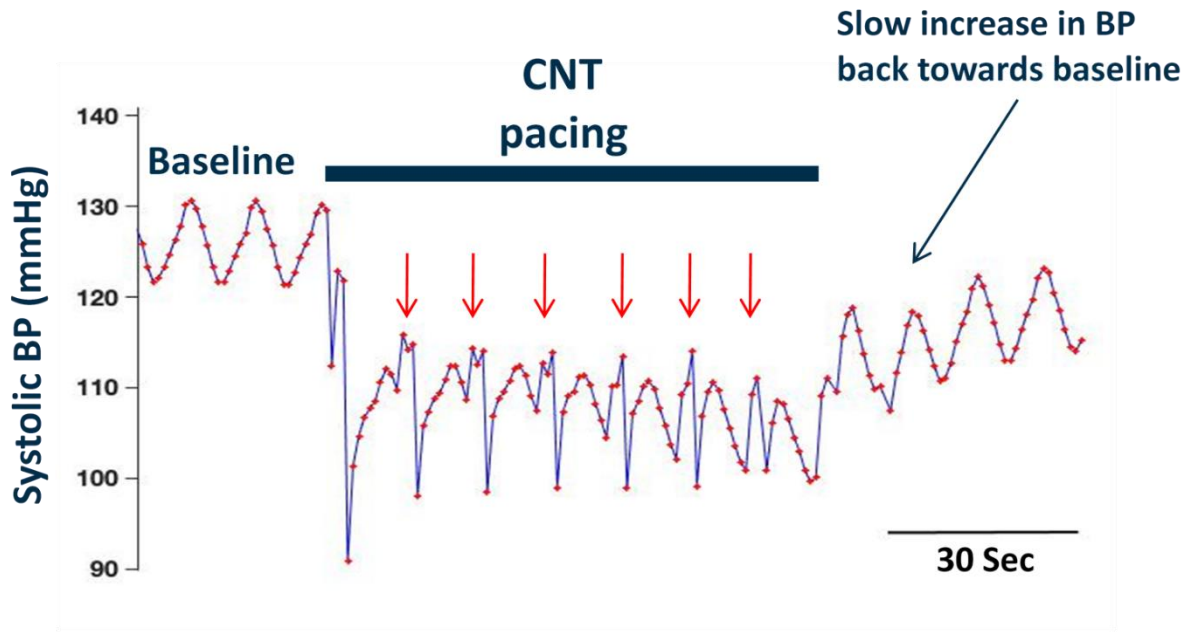

Figure S3. Fan plots showing changes in ambulatory systolic blood pressure (aSBP) from pre-randomization (week 3) in treatment and control groups. In this "responders' analysis", orange lines show instances when aSBP increased compared to pre-randomization; grey lines show instances when aSBP decreased.