ORIGINAL RESEARCH

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Pacemaker-Mediated Programmable Hypertension Control Therapy

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***Background*—**Many patients requiring a pacemaker have persistent hypertension with systolic blood pressures above recommended levels. We evaluated a pacemaker-based Programmable Hypertension Control (PHC) therapy that uses a sequence of variably timed shorter and longer atrioventricular intervals.

***Methods and Results*—**Patients indicated for dual-chamber pacing with office systolic blood pressure (oSBP) >150 mm Hg despite stable medical therapy were implanted with a Moderato™ pulse generator that delivers PHC therapy. Patients were followed for 1 month (Run-In period) with conventional pacing; those with persistent oSBP >140 mm Hg were included in the study and had PHC therapy activated. The co-primary efficacy end points were changes in 24-hour ambulatory systolic blood pressure and oSBP between baseline and 3 months. Safety was assessed by tracking adverse events. Thirty-five patients met the initial inclusion criteria and underwent Moderato implantation. At 1 month, oSBP was <140 mm Hg in 7 patients who were excluded. PHC was activated in the remaining 27 patients with baseline office blood pressure 166±11/80±10 mm Hg despite an average of 3.2 antihypertensive medications. During the Run-In period, oSBP and 24-hour ambulatory systolic blood pressure decreased by 8±13 and 5±12 mm Hg (P<0.002), respectively. Compared with pre-PHC activation measurements, oSBP decreased by another 16±15 mm Hg and 24-hour ambulatory systolic blood pressure decreased by an additional 10±13 mm Hg (both P<0.01) at 3 months. No device-related serious adverse effects were noted.

***Conclusions*—**In pacemaker patients with persistent hypertension despite medical therapy, oSBP and 24-hour ambulatory systolic blood pressure are decreased by PHC therapy. Initial indications are that this therapy is a safe and promising therapy for such patients.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02282033. **(*J Am Heart Assoc*. 2017;6: e006974. DOI: 10.1161/JAHA.117.006974.)**

Key Words: Hypertension • Pacing • AV Delay • Isolated Systolic Hypertension

Recent efforts to address the problem of persistent hypertension despite prescription of appropriate multidrug regimens have included the development and investigation of device-based therapies. Factors contributing to the inability to achieve guideline-recommended blood pressures through pharmacologic means, which include ineffectiveness of medical therapies in some patients and/or inability to maintain long-term compliance, have the potential to be overcome by device-based therapies.

Pressure generation by the heart, which is a primary factor in determining arterial blood pressure, is highly dependent on left ventricular (LV) preload according to the well-known

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Clinical Perspective

What Is New?

- This study introduces a new class of hypertension therapy using standard pacemaker hardware and a novel pacing algorithm that introduces a repeating sequence of a variable number of beats with short and longer atrioventricular delays.
- Patients treated with this pacing algorithm showed sustained blood pressure reductions for 2 years and no significant safety concerns.
- A larger randomized controlled blinded study is currently under way.

What Are the Clinical Implications?

- Many patients with hypertension have blood pressures above guideline recommendations despite being prescribed multiple drugs, either because of lack of effectiveness or lack of compliance with medications.
- This pacemaker therapy could provide a safe and effective nonpharmacological alternative for patients with refractory hypertension and cardiac implanted devices.

Frank-Starling Law of the Heart.[1] For patients in normal sinus rhythm, up to 15% of ventricular filling is determined by atrial contraction.[2] For patients with normal sinus rhythm, variations in atrioventricular delay are known to modulate LV filling.[3,4] We therefore hypothesized that regulation of LV preload by reducing the atrioventricular interval may be an effective means of reducing blood pressure as a therapy for hypertension.

One important consideration for this as a long-term approach to reducing blood pressure is the response of the autonomic reflexes.[5] Reductions in blood pressure mediated by a reduced atrioventricular interval may invoke baroreflex-mediated neuronal and hormonal responses aimed at restoring blood pressure to what the system deems as "normal" by increasing sympathetic activity with potential increases in heart rate, peripheral resistance, and myocardial contractility. Accordingly, it is important to be able to modulate such baroreflex responses in order to achieve long-term blood pressure reductions. Preliminary preclinical studies and acute clinical studies have shown that by alternating between a shorter and a longer atrioventricular delay, blood pressure can be reduced chronically without sympathetic activation or habituation to the therapy.

Here, we report the results of the first multicenter study of this pacemaker-based therapy for hypertension. Changes in 24-hour ambulatory systolic blood pressure (SBP) and office-based measurements of SBP were the co-primary efficacy end points. Device functionality and safety were also assessed.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patient Population

The Moderato-HTN Study was an open-label, single-arm, multicenter, prospective trial investigating the safety and efficacy of a pacemaker-based Programmable Hypertension Control (PHC) device in patients with persistent hypertension indicated for implantation or replacement of a dual-chamber pacemaker. Patients were screened at 8 centers in Europe and 1 center in Chile. Eligible patients had to be at least 18 years of age, indicated for implantation or replacement of a dual-chamber permanent pacemaker where no lead extraction was necessary, and in whom the office SBP (oSBP) measurement on 2 separate days averaged $\geq$150 mm Hg despite a stable (for at least 2 months) regimen of 2 or more tolerated antihypertension medications. Patients were excluded if they had a known secondary cause of hypertension, systolic BP >190 mm Hg, a history of persistent atrial fibrillation or clinically significant paroxysmal atrial fibrillation, LV ejection fraction (LVEF) <50%, symptoms of heart failure greater than or equal to New York Heart Association functional class II, hypertrophic or restrictive cardiomyopathy, were on dialysis or had an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, prior neurological events, known carotid artery disease, known autonomic dysfunction, or had an existing cardiac implant other than a pacemaker. Patients who were pregnant or of childbearing potential during the conduct of the study, or who were unwilling to provide informed consent or were currently participating in another clinical study were also excluded. The study was approved by the ethics committees at each participating site. All patients provided written informed consent. This study was registered on clinicaltrials.gov (NCT02282033).

Device Description and Implantation

The Moderato System (BackBeat Medical, New Hope, PA), is a dual-chamber, rate-responsive pacemaker implantable pulse generator (IPG), which incorporates PHC algorithms that pace the heart with a series of variably timed, alternating shorter (eg, 20–80 ms) and longer (eg, 100–180 ms) atrioventricular intervals. Details of PHC therapy optimization are discussed below; in general, the pacing sequence consists of 8 to 13 beats with the shorter atrioventricular delay followed by 1 to 3 beats with the longer atrioventricular delay. The device is active 24 h/d and paces the right ventricle on nearly every beat. The device interfaces with any commercially available

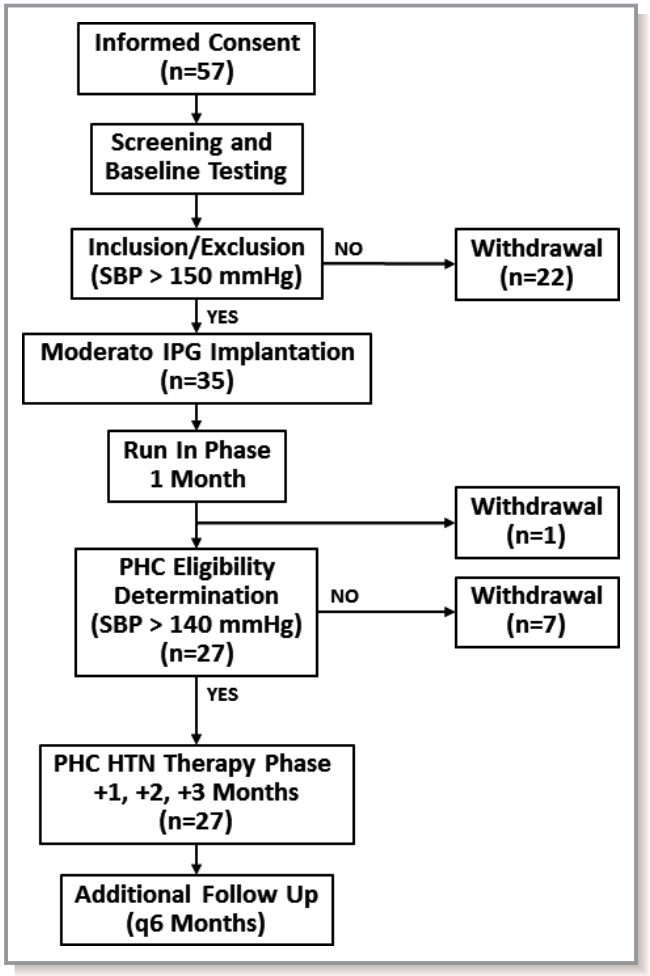

Figure 1. CONSORT flow chart showing number of patients coursing through the various stages of the protocol. CONSORT indicates Consolidated Standards of Reporting Trials; HTN, hypertension; IPG, implantable pulse generator; PHC, programmable hypertension control; SBP, systolic blood pressure.

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.

Study Procedures

The overall study design is summarized in Figure 1. Following informed consent, patients indicated for the implantation of a dual-chamber pacemaker (either as a primary implant or an implantable pulse generator exchange or upgrade from a single-chamber pulse generator) were screened for hypertension medications and blood pressure measurements in the office on 2 separate days (1–7 days apart) to determine eligibility. Patients in whom systolic pressure was >140 mm Hg on both visits and averaged ≥150 mm Hg were considered potentially eligible. These patients also underwent echocardiography, 24-hour ambulatory systolic blood pressure (24hASBP) measurement, and blood tests for renal function.

After all inclusion criteria and the absence of exclusion criteria were confirmed, patients underwent Moderato IPG implantation. The pacemaker parameters were programmed as per the normal clinical needs of the patient; the PHC algorithm was not activated at this time. The patients were followed for 1 month in a Run-In phase with standard pacemaker programming during which blood pressure stability was assessed; patients who met the blood pressure inclusion criteria (oSBP >140 mm Hg at 2 and 4 weeks) during the Run-In phase were enrolled into the 3-month therapy phase during which PHC therapy was active. The day on which PHC therapy was activated served as the study start date (time=0).

During the Run-In phase, patients were seen in the office 2 weeks after device implantation (corresponding with time point −2 weeks relative to the study start date) for a blood pressure check, device interrogation, and a 24-hour Holter monitor to confirm proper functioning of the pacemaker and provide a baseline level of arrhythmic events. Approximately halfway through enrollment into the study, ambulatory blood pressure monitoring was added at this visit to enable assessment of changes in ambulatory blood pressure attributable to participation in the study (ie, Hawthorne effect[6]); this was added after the results of the Renal Denervation in Patients with Uncontrolled Hypertension – SYMPLICITY HTN-3 study[7] unexpectedly showed that in addition to office blood pressure, even the more objective ambulatory blood pressure measurements decreased significantly in the control group. Patients were seen again 4 weeks after device implantation for a final office BP check, before PHC therapy activation. Patients in whom oSBPs remained >140 mm Hg on both the week 2 and week 4 visits were eligible for continuation to the PHC Hypertension Therapy phase of the study. These patients also underwent an echocardiogram and repeat blood tests. Patients not eligible for continuation were withdrawn from the treatment phase of the study.

Patients eligible for continuation had the Moderato PHC therapy activated and were followed for an additional 3 months for the primary safety and efficacy analysis. On the day of activation (which was designated time 0 for the study), the parameters of the PHC pacing algorithm were optimized. For this optimization, blood pressure was measured using a noninvasive continuous blood pressure measurement system (Finapres Medical Systems, Amsterdam, The Netherlands) and the changes in pressure in response to PHC stimulation were recorded and analyzed. The PHC therapy parameters, specifically the values for the shorter and the longer atrioventricular intervals and the number of beats with each atrioventricular interval, were adjusted until a significant and sustained reduction in SBP of at least 5 mm Hg was

achieved. Immediately following the optimization procedure, a 24-hour ambulatory blood pressure monitoring test was initiated. The patients were then seen at 1, 2, and 3 months of PHC therapy (designated as time points +1, +2, and +3 months, respectively). Assessments included office BP measurements at all visits, 24-hour Holter monitor at +1 month, and 24-hour ambulatory blood pressure monitoring, echocardiography, and blood tests at +3 months. Echocardiographic images were obtained simultaneously with an ECG. During follow-up, at each echocardiographic evaluation, echocardiograms were obtained both with PHC off and with PHC active. When PHC therapy was in active mode, measurements were taken from echocardiographic images obtained during the shorter atrioventricular paced beats.

Approximately halfway through enrollment into the study, ambulatory blood pressure measurements and blood tests were added to the +1-month visit, and blood tests were added to the +2-month visit. These, and the extra ambulatory blood pressure measurement at 2 weeks following implantation described above, were added in order to provide better definition of the time course of changes in these parameters.

At the end of the +3-month follow-up period, PHC therapy could be continued and, if so, patients were followed at 6-month intervals for safety, device functionality (by pacemaker interrogation), office blood pressure measurements, blood tests, and echocardiography through 24 months.

The study was monitored by an independent Data Safety Monitoring Board that adjudicated all serious adverse events and reviewed aggregate safety data throughout the study.

Blood Pressure Monitoring

Office blood pressure measurements were performed consistent with the Standard Joint National Committee VII, European Society of Hypertension, and European Society of Cardiology recommendations.[8,9] Office blood pressure was designated as the average of 3 measurements. If SBP values were >15 mm Hg apart on any pair of these readings, measurements were repeated and the final value based on the last 3 consecutive consistent (<15 mm Hg differences) readings. Twenty-four-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 (7 AM to 9 PM) and every 20 minutes at night. Measurements were deemed acceptable if at least 70% of readings during the 24-hour period were successfully recorded.

End Points

The co-primary efficacy end points of this study were based on changes in SBP assessed by 24hASBP measurements and in-office sphygmomanometry. For the 24hASBP measurements, the end point was the average change in SBP between baseline and 3 months postactivation of PHC therapy. For the office blood pressure measurements, the end point was the average change in SBP between preactivation and 3 months postactivation of PHC therapy; the preactivation value was the average of the measurements made at the 2- and 4-week visits during the Run-In phase. For both end points, an intention-to-treat analysis was applied for all patients who qualified for initiation of PHC therapy after the initial Run-In phase. Moderato system functionality was assessed through analysis of 24-hour Holter monitoring recordings. Finally, safety of the device and PHC therapy were assessed by determining the incidence of periprocedural device and treatment-related serious adverse events. Additional safety assessments included changes in ambient atrial and ventricular ectopy (assessed by Holter monitoring), changes in LV and left atrial sizes and function, and changes in renal function.

Statistical Analysis

All efficacy assessments consisted of comparisons between baseline and 3-month follow-up tests. Descriptive statistics were used to summarize these findings. The Anderson-Darling test was used to confirm normality of data distribution; this being the case, data are presented as means, SDs, and percentages when appropriate. Paired *t* tests were used to assess statistical significance of changes in continuous variables. It was anticipated that ≈25 patients would qualify to proceed from the Run-In phase to the PHC Hypertension Therapy phase and complete the study. With an assumed 15 mm Hg SD of changes observed in prior studies,[7,10] the study was able to detect a mean reduction of 9 mm Hg or greater in 24hASBP with a power of ≈80%. To compare the incidences of atrial fibrillation between observed on 24-hour Holter monitoring between baseline and 1 month, a 2-sided McNemar test for the difference between correlated proportions was used.

Results

Patients

A total of 57 patients provided written informed consent and underwent baseline testing. Among these, 35 patients satisfied the criteria for Moderato IPG implantation (Figure 1). The baseline characteristics of these patients are summarized in Table. Patients were distributed equally between males and females, had an average age of 73 years, a mean body mass index of 29 kg/m^2, heart rate of 64 beats/min, and normal LVEF. Approximately one third had diabetes mellitus and ≈20% had coronary artery disease, peripheral vascular

Table. Baseline Demographic Data

	All Implanted Patients (n=35)*	Patients Continuing to Hypertension Treatment Phase (n=27)	Patients Not Meeting BP Criteria to Continue (n=7)
Age, y	73±7.2	72±6.8	75.0±6.9
Sex	17 M/18 F	14 M/13 F	2 M/5 F
Physical exam			
Height, cm	168.0±10.3	168.3±10.8	166.6±9.8
Weight, kg	82.3±17.3	84.3±17.8	78.4±13.1
Heart rate, bpm	64.1±12.1	62.9±12.7	67.4±9.7
Body mass index	29.1±5.5	29.7±5.7	28.2±3.6
LV ejection fraction, %	62.9±5.2	62.7±5.3	65±3.4
Past medical history			
Diabetes mellitus	10 (29)	8 (29)	2 (29)
History of AF	2 (6)	2 (7)	0 (0)
Cardiovascular disease	1 (3)	1 (4)	0 (0)
Peripheral vascular disease	3 (9)	2 (7)	1 (14)
Renal dysfunction	2 (6)	1 (4)	1 (14)
Pacemaker indication			
Sick sinus syndrome	13 (37)	10 (37)	3 (43)
Brady-/tachy-syndrome	7 (20)	3 (11)	3 (43)
II° AV block	12 (34)	8 (30)	4 (57)
III° AV block	4 (11)	4 (15)	0 (0)
Other	7 (20)	6 (22)	1 (14)
HTN medications			
Average number	3.2	3.3	3.1
Medication classes			
Diuretic	27 (77)	20 (71)	7 (100)
K-sparing diuretic	4 (11)	3 (11)	1 (14)
β-Blocker	11 (31)	8 (29)	2 (29)
ACE-I	20 (57)	16 (57)	4 (57)
ARB	12 (34)	10 (36)	2 (29)
Calcium channel blocker	21 (60)	18 (64)	3 (43)
α-Adrenergic antagonist	9 (26)	6 (21)	2 (29)
Ang-II antagonist	1 (3)	0 (0)	1 (14)
Blood pressure (office)			
Screening			
Systolic BP, mm Hg	165.6±11.6	165.6±11.1	162.1±8.7
Diastolic BP, mm Hg	79.8±9.4	80.4±9.9	76.6±7.4
Preactivation			
Systolic BP, mm Hg	152.3±15.9	156.4±14.4	136.4±10.9
Diastolic BP, mm Hg	79.9±9.5	81.3±10.0	74.3±2.9

Continued

Table. Continued

	All Implanted Patients (n=35)*	Patients Continuing to Hypertension Treatment Phase (n=27)	Patients Not Meeting BP Criteria to Continue (n=7)
Pacemaker implantation			
New implant, n (%)	25 (71)	17 (64)	7 (100)
Replacement, n (%)	10 (29)	10 (36)	0 (0)

Values are mean±SD or n (%). ACE-I indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; Ang-II, angiotensin II; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; bpm, beats per min; brady/tachy, bradycardia/tachycardia; HTN, hypertension; K, potassium; LV, left ventricular.
*One patient died during the Run-In phase and his data are only included in the first data column.

disease, or renal dysfunction. The main indications for a pacemaker were sick sinus syndrome, and second- and third-degree atrioventricular block. Patients were prescribed an average of 3.2 antihypertensive medications with >50% of patients taking diuretics, calcium channel blockers, β-blockers, and angiotensin-converting enzyme inhibitors. A significant number of patients were also taking α-adrenergic antagonists.

Blood Pressure During Run-In Phase

Office blood pressure at the time of screening (just before IPG implantation) averaged 165.6±11.6/78.8±10.3 mm Hg. The IPG was a first-time implant in 25 patients and a replacement (9 patients) or upgrade from a VVI device (1 patient) in the other 10 patients.

At the end of the Run-In phase (before PHC therapy activation), oSBP averaged 152.3±15.9/79.8±9.3 mm Hg, dropping by an average of 12.0±15.6 mm Hg from preimplantation screening values. However, in 7 patients, oSBP was <140 mm Hg on the 2- and/or 4-week visit. SBP had dropped in these patients by 28.4±12.5 mm Hg to an average of 136.4±10.9/74.3±2.9 mm Hg. These patients did not progress to the PHC phase of the study. In contrast, blood pressure averaged 156.4±14.4/81.3±10.0 mm Hg in the 27 patients in whom oSBP remained ≥140 mm Hg at both the 2- and 4-week visit, with an average drop in blood pressure of only 7.8±13.5 mm Hg (P=0.005). As summarized in the Table, other than blood pressure, there were no significant differences in clinical characteristics between patients who did and those who did not qualify to progress to the PHC phase of the study.

PHC Parameters Optimization

An example of noninvasively acquired beat-by-beat SBP values (using Finapres) from a patient undergoing PHC therapy optimization (Figure 2) illustrates both of the proposed mechanisms of action defined above. First, consider the effects of simple, sustained short atrioventricular delay pacing (Figure 2A). The first 30 s shown on this graph serve as baseline blood pressure measurements. Note the slow periodic fluctuations in blood pressure (on the order of ≈10 mm Hg) that are because of respiration. At time 0.5 minutes (green arrow), pacing was initiated with an atrioventricular delay of 40 ms and an immediate ≈40 mm Hg drop in blood pressure was observed. However, this was followed by a relatively rapid, beat-by-beat exponential rise of blood pressure that reached a new steady level after ≈35 s that was only ≈5 mm Hg below the initial baseline value. This secondary increase of pressure represents baroreflex-mediated sympathetic activation that increases peripheral vascular resistance. This interpretation is supported by the fact that when atrioventricular delay was returned to its original longer value after ≈1 minute (red arrow), SBP jumped immediately, overshooting the initial baseline value. The degree of pressure overshoot provides an index of the degree to which vascular resistance was increased during the period of short atrioventricular pacing. In response to this increase of pressure, reflex-mediated vasodilation was next observed, evidenced by the fast beat-by-beat blood pressure decline back to the initial baseline value. In contrast to the ≈35 s it took for pressure to stabilize with the initiation of short atrioventricular delay pacing, it is important to note that the time course of blood pressure decline during this phase is relatively fast, returning to baseline values in <10 s. These differential responses of blood pressure kinetics to increases versus decreases in blood pressure, which was observed in all patients, suggested an asymmetric response of the baroreflex to increases and decreases in blood pressure. Specifically, the response to an increase of pressure is faster than a decrease in pressure.

The PHC algorithm takes advantage of this asymmetry to reduce blood pressure in a manner that does not increase sympathetic tone, as illustrated in Figure 2B (same patient as in Figure 2A). With initiation of short atrioventricular delay pacing (green arrow), blood pressure decreases as in Figure 2A. In this case, however, after 10 beats pacing with

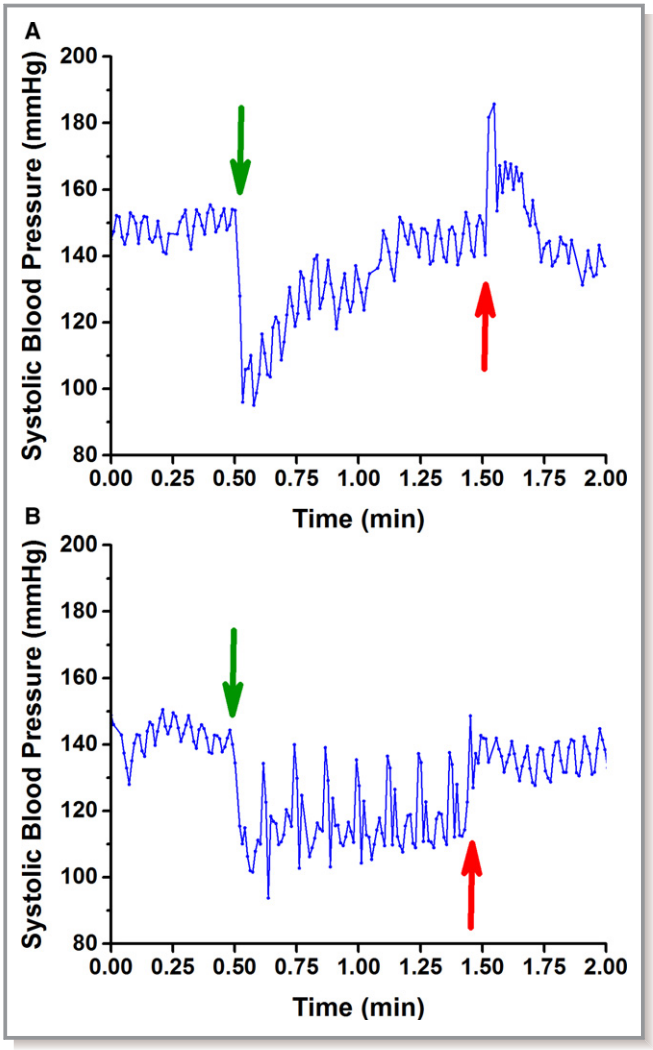

Figure 2. A, Beat-by-beat measurements of systolic blood pressure (by Finapres device) in response to a change of pacing from normal AV delay to pacing with an AV delay of 40 ms (green arrow). Note initial large drop and subsequent exponential rise of pressure to a new steady level only ≈5 mm Hg less than the original baseline. When normal AV delay pacing is resumed (red arrow), there is an initial overshoot of pressure followed by a more rapid return to baseline. B, When a repeating sequence of 10 short AV paced beats (at 40 ms) and 2 beats with longer AV delays (140 ms) is initiated (green arrow), there are no significant transients in blood pressure changes, even when constant, long AV delay pacing is resumed (red arrow). This repeating sequence, which is PHC pacing therapy, prevents sympathetic activation despite reduction of systolic blood pressure. AV indicates atrioventricular; PHC, programmable hypertension control.

a 40-ms atrioventricular delay (few enough beats so that there was minimal pressure rebound), 2 beats are introduced with an atrioventricular delay of 140 ms. Pressure on these 2 beats was increased, but still slightly below the starting baseline value. Upon resumption of 40-ms atrioventricular delay pacing, blood pressure dropped again. As seen, upon repeated application of this 10-beat/2-beat sequence of shorter/longer atrioventricular delay pacing, the pressures during each phase did not change significantly over time. Furthermore, and importantly, when normal pacing with the (constant) longer atrioventricular delay was resumed (red arrow), no blood pressure overshoot was observed. This indicates that reducing blood pressure in this manner did not invoke a sympathetic response despite the fact that the average pressure was significantly lower than at baseline.

More generally, the differences in the time constants of blood pressure changes observed with onset and cessation of short atrioventricular delay pacing (Figure 2A) suggested that the optimal sequence of short and long atrioventricular delay pacing consists of 8-to-13 beats with short atrioventricular delay (in the range of 20–80 ms) followed by 1-to-3 beats with longer atrioventricular delay (in the range of 100–180 ms). A specific, effective combination of atrioventricular delay and number of beats for each phase can be easily identified for each patient by directly observing blood pressure responses in a short optimization procedure.

Changes in Medical Therapies During Study Period

Over the 3-month study period, 1 patient had an increase in calcium channel blocker dose, 3 had an increase in loop diuretic dose, and 1 had an increase in potassium-sparing diuretic dose. In contrast, 2 patients had a decrease in calcium channel blocker dose, 2 had a decrease in angiotensin-converting enzyme inhibitor dose, 2 had a decrease in loop diuretic dose, 1 had a decrease in alpha adrenergic inhibitor dose, 2 had decreases in angiotensin receptor blocker dose, and 1 had a reduction in imidazoline I_1 receptor blocker dose. Thus, on balance, there were more instances in which drug doses were decreased than increased during the study period.

Blood Pressure During Study Period

Histograms showing the distribution of SBP during 24 hours, recorded from a typical patient, are provided in Figure 3A. In this example, baseline SBP varied over a large range throughout the day (between 95 and 184 mm Hg) with a mean value of 153.8±14.5 mm Hg. The distribution remained similarly broad at +3 months, but it was significantly shifted towards lower pressures, ranging between 90 and 168 with a mean value of 126.7±16.5 mm Hg.

The group average 24hASBP of the 27 patients treated with PHC is shown in Figure 3B. 24hASBP dropped from an average of 136.7±9.2 mm Hg at baseline to 119.8±9.1 mm Hg the day following activation of the therapy, a reduction of 16.9±10.6 mm Hg (P<0.001). Average 24hASBP remained reduced at 122.5±11.3 mm Hg +3 months after activation of

PHC therapy, a reduction of 14.2±9.8 mm Hg (P<0.001) compared with baseline. There was no significant difference between the average systolic pressure immediately after the activation and +3-months postactivation (120±9 versus 123±11, P=0.19). In patients who were followed according to the modified protocol with 2 measurements made before PHC therapy activation and 3 made after PHC therapy activation (Figure 3C, blue), average 24hASBP dropped by 5.3±11.7 mm Hg from the first to the second measurement (P=0.09); this change indicates the impact of the patients' participation in the study. There was an additional, immediate 11.6±10.1 mm Hg drop (P<0.001 versus the −2 weeks average) detected in 24hASBP recorded on the day of PHC therapy activation. This reduction stayed relatively constant during the Hypertension Therapy phase of the study such that by the +3-month follow-up, average 24hASBP had dropped by 10.1±13.0 mm Hg to 122.5±11.3 mm Hg (P=0.007 versus −2 week measurement, and P<0.001 versus baseline). For 11 patients who were followed according to the original protocol with readings at baseline, immediately postimplantation and at +3 months (Figure 3C, red) the data at common time points were not different from those of the rest of the subgroup (Figure 3C, blue).

In addition to SBP, diastolic and mean blood pressures were also tracked during the Hypertension Therapy phase of the study. Twenty-four-hour ambulatory diastolic blood pressure was 70.2±7.6 mm Hg at baseline and did not change during the course of the study, having a value of 69.8±7.1 mm Hg at the +3-month study end point. Twenty-four-hour ambulatory average blood pressure decreased from 92.3±6.4 mm Hg at baseline to 87.7±5.3 mm Hg immediately after PHC activation (P=0.001) and remained decreased at 87.3±7.5 mm Hg at the +3-month time point (P<0.001 versus baseline).

Finally, reductions in average daytime 24hABP (14±11 mm Hg) were similar to the reductions in average nighttime 24hASBP (13±12 mm Hg).

Absolute values of oSBP measured in the 27 patients who participated in the PHC phase of the study are summarized in Figure 4A. During the Run-In phase, oSBP (the average of week 2 and week 4 relative to the average of screening and baseline) dropped significantly by an average of 7.8±13.5 mm Hg, from 165.2±10.2 to 157.4±11.3 mm Hg (P=0.006). oSBP dropped further and remained lower during the Hypertension Therapy phase, decreasing by an additional 16.1±15.1 mm Hg to 141.4±14.2 mm Hg (P<0.001) at the +3-month follow-up visit. There were no significant changes in diastolic blood pressure during the study, having a mean value of 81.3±9.7 mm Hg at preactivation and 79.8±8.7 mm Hg at +3 months (P=0.325). Mean office blood pressure decreased from 106.9±9.2 mm Hg pre-PHC signal activation to 100.3±9.3 mm Hg at the +3-month follow-up visit.

These effects on oSBP were maintained in patients who were followed for up to 2 years (Figure 4B). Since follow-up is still ongoing, not all patients have reached the 24-month time point. Reductions in SBP were 13.5 mm Hg at 18 months and 20 mm Hg at 24 months.

Responders Analysis

Figure 5A presents the individual changes in 24hASBP from *baseline* to +3-month follow-up visit for all 27 study patients. As can be seen, 24hASBP decreased in 25 patients and increased in only 2. Overall, 23 of the 27 patients (85%) had a reduction of >5 mm Hg in their ambulatory blood pressure. The analysis based on changes of 24hASBP from *pre-PCH activation* to +3 months (Figure 5B) from the 16 study patients enrolled after the addition of the preactivation measurement similarly showed that pressure decreased in 14 of 16 patients (87.5%) and increases in only 2 patients (12.5%). In 11 of the 16 patients (69%), systolic 24hASBP decreased by >5 mm Hg.

oSBP decreased in all but 3 patients when analyzed both as changes from baseline to +3 months (Figure 5C) and changes from pre-PHC activation to +3 months (Figure 5D). oSBP decreased by 5 mm Hg or more from baseline in 85.2% of patients and by 5 mm Hg from pre-PHC activation in 81.5% of patients, indicating a high responder rate.

Echocardiographic Assessment of Heart Size and Function

Compared with preactivation values, LV end-diastolic volume decreased by 13.3±24.8 (median decrease of 6.0, with interquartile range [IQR] of 23) mL by the +3-month measurement (109.9±36.8 mL versus 98.3±22.0 mL, P=0.02), and there were no significant changes in end-systolic volume (43.2±17.1 mL versus 41.1±12.9 mL), LVEF (61.4±3.9% versus 59.7±5.5%), or left atrial diastolic dimension (39.8±5.0 mm versus 41.6±5.3 mm).

Heart Rate and Rhythm

Holter monitoring was performed 2 weeks before and +1 month after activation of PHC hypertension therapy. Recordings examined from each patient confirmed that the device performed as intended by delivering ventricular and atrial pacing spikes with alternating sequences of longer and shorter atrioventricular intervals. The percentage of ventricular ectopic beats had a median value of 0.08% (IQR 0.60%) at baseline, which did not change significantly at +1 month, having a median value of 0.06% (IQR 0.35%, W=145, P=0.14 by Wilcoxon signed-ranks test). The percentage of supraventricular ectopic beats had a median value of 0.05% (IQR

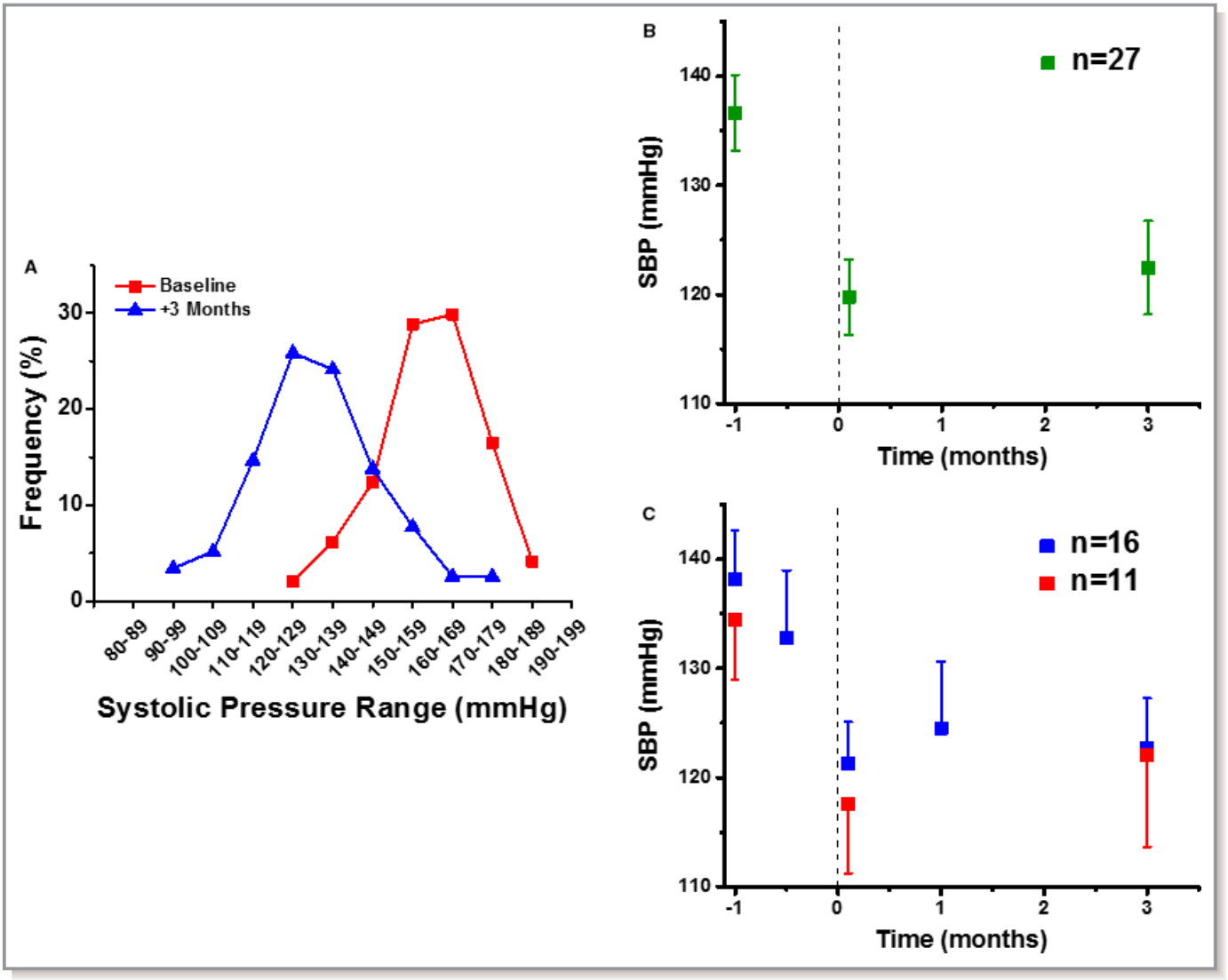

Figure 3. A, Example of a histogram of systolic blood pressure distribution obtained from 24-h ambulatory blood pressure monitoring before and +3 months after activation of programmable hypertension control (PHC) therapy. B, Mean±95% confidence intervals of 24-hour ambulatory systolic pressures at baseline, immediately after activation, and +3 months of PHC therapy from the 27 patients included in the Hypertension Therapy phase of the study. C, Sixteen of the patients were enrolled after a protocol modification that allowed additional measurements of 24-hour ambulatory blood pressures (shown in blue). These measurements showed a 5.3±11.7 mm Hg (P=0.09) reduction in SBP from baseline to 2 weeks (−0.5 months) during the Run-In phase. Results from the first 11 patients in whom measurements were made at baseline, just after and at +3 months (shown in red), show similar results at common time points. SBP indicates systolic blood pressure.

0.65%) at baseline, which also did not change significantly +1 month, having a median value of 0.03% (IQR 0.19%, P=0.11). There was also no significant change in the incidence of atrial fibrillation from 2 weeks before PCH activation (5.9%) to (0%) at +1 month (P=0.5).

The PHC algorithm tracks the intrinsic atrial rate and paces the atria a few beats above that value. Accordingly, the average heart rate increased after initiation of PHC therapy from 68.9±9.4 to 73.5±10.1 beats/min (P=0.002). However, during the course of treatment, the average heart rate decreased and was not significantly different from the baseline value (71.3±9.6 beats/min, P=0.06). These findings regarding heart rate measured with the office blood pressure measurements were consistent with measurements made on the 24hASBP, in which average heart rate increased by 4.0±8.6 beats/min (P<0.001) from preactivation to immediately after activation (as a result of the PHC atrial rate tracking algorithm). Subsequently, the average heart rate decreased by 4.1±6.8 beats/min (P=0.004) on the +3-months measurement, back to the preactivation level.

Renal Function

Blood tests for creatinine and estimates of glomerular filtration rate showed that renal function was stable during the treatment period. Average estimated glomerular filtration

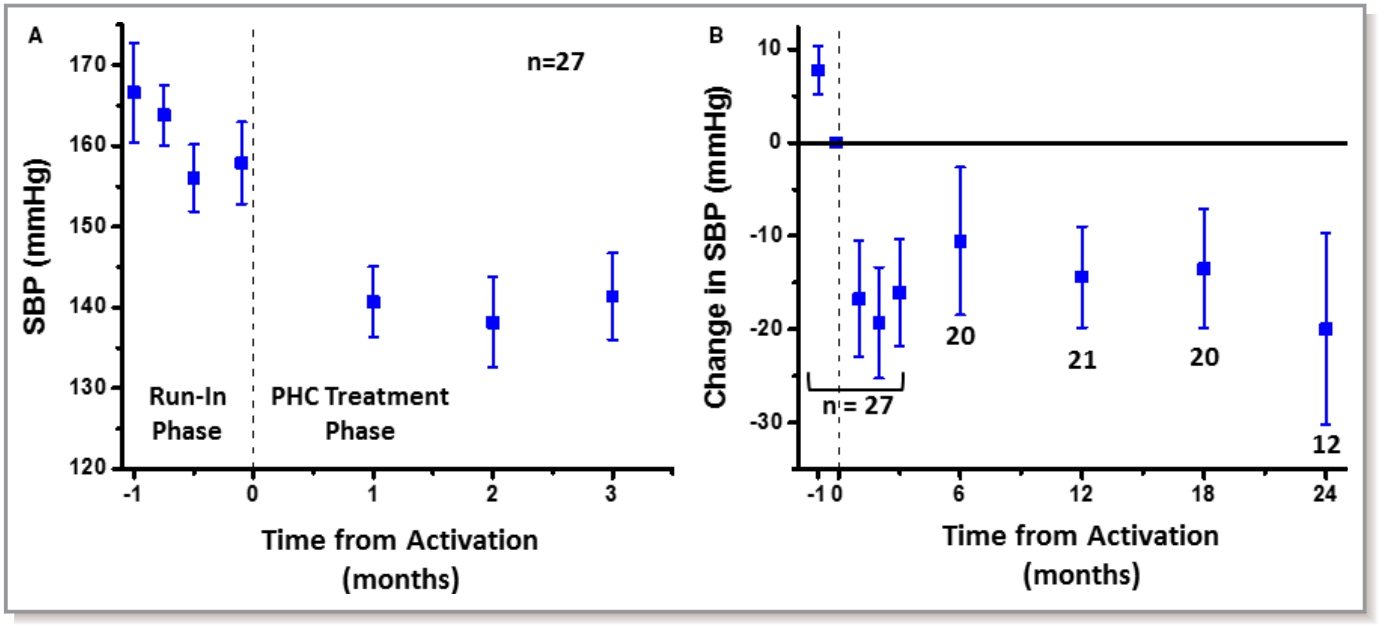

Figure 4. A, Office systolic blood pressure (SBP) measurements (means±95% confidence intervals) from the 27 patients included in the hypertension study. B, Changes in office SBP (means±95% confidence intervals) compared with preactivation, for all available time points following activation of programmable hypertension control (PHC) therapy. Numbers below or above error bars denote numbers of patients available for SBP measurement at the respective time point (all patients who reached the specific time point were included).

rate was 72±16 mL/min per 1.73 m^2 at baseline, 74±18 mL/min per 1.73 m^2 before activation, and 71±18 mL/min per 1.73 m^2 +3 months after activation (*P*=ns between time points).

Safety

There were 3 periprocedural adverse events considered to be related to the implantation procedure, including a pleural effusion, a pocket hematoma, and a pneumothorax. One patient died during the Run-In phase before the activation of the PHC therapy because of witnessed respiratory arrest, which was deemed unrelated to device or therapy by the investigator and the study's Data Safety Monitoring Board; this patient's data are included in the baseline characteristics of the 35 patients but were not included in either subgroup in the Table.

There were 11 serious adverse events in 5 patients during the PHC phase of the therapy. Events adjudicated as being not related to the PHC therapy included diaphragmatic fasciculation, dyspnea, urinary tract infection, pericardial effusion because of lead perforation, apical dyskinesis (transient Takotsubo cardiomyopathy), atrial flutter, and coronary artery stenosis with chest pain. Events that were adjudicated as being possibly related to the PHC therapy included cardiac asthma, prolonged atrial fibrillation requiring direct-current cardioversion, and ambulatory myocardial infarction with subsequent symptoms of heart failure. Based on these data, the study met its predefined safety end point.

Discussion

There is growing appreciation for the relatively high incidence and socioeconomic impact of persistent hypertension despite appropriate medical therapy. This has motivated the investigation of nonpharmacologic approaches.[7,10–12] The present study investigated the safety and efficacy of a pacemaker-based therapy that takes advantage of the fact that ventricular pressure generation is preload dependent and that preload can be manipulated by altering atrioventricular pacing delay. With this approach, it was demonstrated that average SBP assessed by 24-hour ambulatory monitoring was decreased by a clinically meaningful and statistically significant 14 mm Hg from baseline following 3 months of pacemaker-based treatment using the PHC therapy, a sequence of pacing signals with variably timed shorter and longer atrioventricular intervals. In the subset of patients in whom ambulatory blood pressure was also measured during the 1-month Run-In phase, there was an initial 5.3 mm Hg decline in SBP (possibly Hawthorne effect[6]) followed by an additional, statistically significant 10 mm Hg reduction after 3 months of therapy. These findings were paralleled by changes in office-based blood pressure measurements; mean SBP decreased by 7.8 mm Hg from baseline during the Run-In phase. SBP further decreased by 16.1 mm Hg from preactivation to +3 months of therapy, which corresponded to a 23.8 mm Hg drop from baseline values. The reductions in blood pressure were maintained throughout the 3-month study period. These results have extended to longer follow-up,

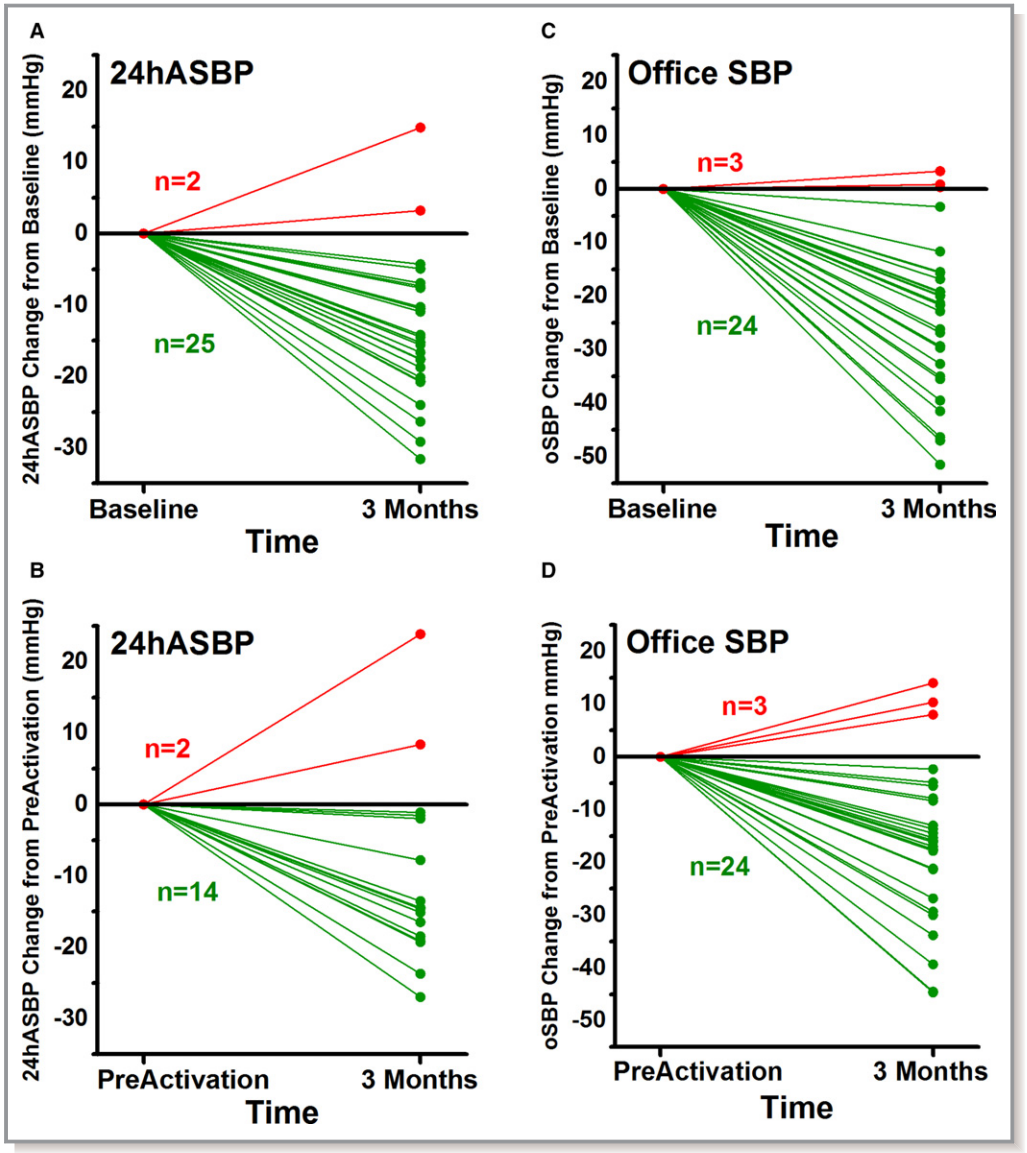

Figure 5. Changes in 24-h ambulatory systolic blood pressure (24hASBP) and office systolic blood pressure (oSBP) from baseline (A and C) and from pre-PHC activation (B and D). Numbers quantify number of patients whose SBP decreased (in green) and those whose SBP did not decrease (in red). PHC indicates programmable hypertension control.

which has reached 2 years in some patients. The individual results demonstrated a high response rate compared with other device therapies.

The mechanisms by which PHC controls blood pressure involves at least 2 components: (1) dual-chamber pacing with a short delay in order to reduce ventricular filling, which decreases pressure generation according to the Frank-Starling Law of the heart; and (2) intermittent imposition of beats with longer atrioventricular delays to create a blood pressure pattern that modulates the baroreceptors in a manner that prevents sympathetic activation in response to the reduced blood pressure during the short atrioventricular delay pacing. Importantly, during the follow-up period, there were more instances in which drug doses were *decreased* than *increased*, indicating that the observed reductions in blood pressure are not caused by changes in background medical therapy.

There are 2 lines of evidence for lack of sympathetic activation by PHC therapy: first, heart rate decreases during long-term therapy; second, changes in blood pressure with initiation/cessation of simple short atrioventricular delay pacing (Figure 2A) and lack of such changes with initiation/termination of PHC pacing therapy (Figure 2B) suggest that PHC therapy does not induce baroceptor-mediated changes in vascular resistance. These observations and interpretations are fully consistent with results presented by Manisty et al,[13] who showed transient responses in blood pressure and other hemodynamic parameters to abrupt changes in

atrioventricular interval, which they demonstrated to be caused by reflex-mediated changes in vasomotor tone. Accordingly, lack of such changes in BP during PHC therapy suggests that the sympathetic tone is not increased.

Other possible mechanisms may contribute to mechanisms of PHC therapy on long-term blood pressure control and autonomic modulation. For example, some studies indicate that long-term pacing has effects on the balance between sympathetic and parasympathetic activation.[14] This may, in part, be related to the effects on the intrinsic cardiac nervous system that is composed of an interconnected network of ganglia and local circuit neurons.[15,16] While it is known that this network communicates with the central nervous system and regulates myocardial properties, less is known about its influence on blood pressure regulation. However, the fact that blood pressure reduction is not a standard consequence of standard long-term dual-chamber pacing suggests this mechanism may not be important for the PHC effect; PHC uses standard pacing pulses and it is only the unique timing of those pulses that results in blood pressure control.

Recent interest in device-based therapies for hypertension has been fueled by the large percentage of patients exhibiting persistent blood pressure elevations above guideline-recommended levels. These studies have suggested that lack of blood pressure control in a large proportion of these patients is caused by poor compliance with prescribed therapies. This has been highlighted in the SIMPLICITY HTN-3 study of renal denervation, which enrolled 535 patients with presumed medically refractory hypertension.[7] In the sham group of that study, oSBP fell by 11.7±25.9 mm Hg and systolic 24hASBP fell by 4.8±17.3 mm Hg at 6 months compared with baseline. These reductions were similar to what we observed during the Run-In phase of the current study. Thus, although the current study was not randomized, this 1-month Run-In phase allowed us to observe the impact of study participation (Hawthorne effect) on blood pressure and demonstrated marked PHC therapy-mediated changes in office and 24hASBP in addition to those observed during the Run-In period. This offered 2 major study design advantages for ensuring realistic assessment of the treatment effect: (1) we excluded patients whose blood pressures decreased into the guideline-recommended range, and (2) we were able to use the blood pressure at the end of the Run-In phase as the baseline comparative value for assessing the impact of therapy. In addition, we relied on the objective measure of 24hASBP and not only on office blood pressure as the primary measure of treatment success.

As noted above, persistent blood pressures above guideline-recommended levels in patients with hypertension despite multidrug regimens has encouraged the development and testing of several device-based therapies. These include baroreceptor activation therapy,[17–19] renal denervation,[7,20] arteriovenous shunting,[10,21] carotid body resection or denervation,[12,22] and mechanical stimulation of the baroreceptors.[23] Prior review articles have provided overviews and comparisons of these different approaches and will not be repeated here,[24,25] other than to say that treatment of isolated systolic hypertension (ie, patients with office diastolic blood pressure <90 mm Hg), which is characterized by increased vascular stiffness, has proved to be particularly challenging for some of these approaches, with such patients excluded from the recently complete SPYRAL HTN-OFF MED study.[19,26] It is therefore noteworthy that 78% of patients in the present study had isolated systolic hypertension with an excellent response rate.

There are several potential advantages of PHC therapy compared with other device-based therapies for hypertension. First is the ability to adjust and "tune" the PHC therapy when needed, enabling tailored control of blood pressure. The ability to immediately observe the acute blood pressure responses (including the presence or absence of a blood pressure overshoot when PHC pacing is suspended) provides a powerful tool for adjusting the magnitude of blood pressure reduction and for gauging the impact on sympathetic activation (at least in the acute setting). This contrasts with other therapies where the treatment is "all or none" and, in some instances, the effects may not be evident for some time. Second, the mechanism involves modulation of both ventricular filling and the baroreflexes, suggesting that PHC therapy mimics the effect of multiple classes of drugs and has the potential to treat patients with isolated systolic hypertension.

One potential consequence of long-term right ventricular pacing may be the development of heart failure. Clinical symptoms of heart failure have been observed in up to 26% of patients who have a normal or reduced LVEF and who subsequently underwent pacemaker implantation with a high percentage of right ventricular pacing.[27–29] However, most of those studies did not have a control group matched for age and cardiovascular comorbid conditions. One study that did have an appropriate control group showed no significant impact of right ventricular pacing on the occurrence of heart failure or other cardiovascular adverse effects.[30] It is therefore noteworthy that during the 3-month PHC treatment phase of the current study, there was a reduction in LV end-diastolic volume and no significant change in LVEF. While there was no suggestion of LV structural or functional changes observed in the present study, the short duration of follow-up and small number of patients require that this potential effect be studied further.

One potential consequence of short atrioventricular interval pacing is increased left and right atrial stress (because of atrial contraction against a partially closed mitral valve). This could result in left and right atrial enlargement and an

increase in the occurrence of atrial tachycardias. Thus far there has been no evidence of either effect. Echocardiographic data from the patients followed for up to 2 years are similar to those reported at 3 months, with no significant changes in LVEF. However, it is recognized that longer follow-up of more patients will be required in order to demonstrate the safety of this therapy.

Limitations

The main limitations of the present first-in-human study are the nonrandomized study design, the small number of included patients, and the relatively short duration of follow-up. The acceptable safety profile and strong efficacy signal observed in the present study support further investigation of the technology to address these limitations. Such a study is has been initiated (www.clinicaltrials.gov NCT02837445). In addition, the potential impact of PHC pacing on exercise tolerance has not been evaluated but should also be considered in future studies.

Conclusions

This first-in-human study provides initial evidence that hypertension treatment with a pacemaker-based device that paces the heart with variably timed shorter and longer atrioventricular intervals appears safe and effective at intermediate-term follow-up. The current study included patients already having or requiring implantation of a pacemaker. This approach markedly improves the safety profile of the therapy since these patients would have been exposed to the risks associated with pacemaker implantation or replacement regardless of their participation in this study or use of PHC pacing therapy. Another advantage of this therapy compared with other device-based therapies is the ability to adjust and "tune" the PHC therapy when needed, enabling tailored control of blood pressure. The evidence available thus far indicates that this therapy results in intermediate-term reductions in blood pressure without evidence of sympathetic activation. Factors requiring further clarification in longer-term randomized studies include assessments of safety (impact on LV size and function, atrial size and arrhythmias), and the impact on sympathetic nervous activation and efficacy. With further proof of safety and efficacy, such a therapy could potentially be expanded to include patients not requiring a pacemaker.

Appendix

BackBeat Study Investigators: Filip Malek, Jaroslav Simon, Libor Dujka, Libor Machalek, Ákos Király, Levente Molnár, Attila Kovács, Marianna Szabó, Kaspars Kupics, Ieva Ansaberga, Janis Ansabergs, Nikolajs Nesterovics, Jurate Barysiene, Marc van Cruijsen, Mindel M. Schellevis, Thomas Pezawas, Emilio Flores, Demian Fullerton, Martine M.A. Beeftink, Matthias Meine.

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Data Safety Monitoring Board: Deborah D. Ascheim, MD (Chair), Jose Dizon, MD, Samuel Hanon, MD, Harold Hastings, PhD (statistician).

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Disclosures

Neuzil has received a research grant from Backbeat Medical. Merkely has personal fees from Boston Scientific, personal fees from Biotronik, personal fees from Medtronic, and personal fees from St. Jude Medical, outside the submitted work. de Groot has received grants from St. Jude Medical, grants from Atricure Europe Inc, personal fees from Atricure Europe Inc, personal fees from Daiichi Sankyo International, personal fees from Pfizer, and personal fees from Boehringer Ingelheim, outside the submitted work. Gellér has received personal fees from St Jude Medical, personal fees from Medtronic, and personal fees from Biotronik, outside the submitted work. Osztheimer has received personal fees from BackBeat Medical, during the conduct of the study; personal fees and nonfinancial support from Biotronik, personal fees and nonfinancial support from St. Jude Medical, personal fees and nonfinancial support from Medtronic, and nonfinancial support from Boston Scientific, outside the submitted work. Mika is an employee of BackBeat Medical; he has received personal fees from Backbeat Medical, during the conduct of the study; personal fees from Backbeat Medical, outside the submitted work; in addition, Mika has a patent Methods and Systems for Lowering Blood Pressure through Reduction of Ventricle Filling (9008769) issued, a patent Methods and Systems for Lowering Blood Pressure Through Reduction of Ventricle Filling (9333352) issued, and a patent Methods and Systems For Controlling Blood Pressure By Controlling Atrial Pressure (9370662) issued. There are additional patents submitted in the United States and multiple countries that are pending. The full list can be provided upon request. Evans serves as a consultant to BackBeat Medical. Burkhoff serves as a consultant to BackBeat Medical; he has received personal fees from Backbeat Medical, during the conduct of the study; in addition, Burkhoff has a patent Methods and Systems for Lowering Blood Pressure through Reduction of Ventricle Filling (9008769) issued, a patent Methods and

Systems for Lowering Blood Pressure Through Reduction of Ventricle Filling (9333352) issued, and a patent Methods and Systems For Controlling Blood Pressure By Controlling Atrial Pressure (9370662) issued. Kuck has received personal fees from Medtronic, personal fees from Biosense Webster, personal fees from Boston-Scientific, and personal fees from St. Jude Medical, outside the submitted work. Erglis, Marinskis, Schmidinger, Rodriguez Venegas, Voskuil, Sturmberger, Petru, Jongejan, Aichinger, Kamzola, Aidietis, and Mraz declare no relationships with industry.

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Pacemaker–Mediated Programmable Hypertension Control Therapy

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