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Research Article

Rationale and evidence for the development of a durable device-based cardiac neuromodulation therapy for hypertension

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Abstract

We assessed the feasibility of achieving acute, sustained blood pressure reductions through the use of cardiac pacing algorithms delivered via standard dual-chamber pacing based on introducing short atrio-ventricular (AV) delays (SAVD). Eighteen hypertensive subjects (57.3 ± 9.8 years old; 10 male and 8 female) with average initial systolic and diastolic blood pressures of 151.2 ± 17.6/92.2 ± 12.7 mmHg already scheduled to undergo an invasive electrophysiology procedure were included in this study. Pacing sequences were applied for ~1-minute intervals with AV delays of 80, 40, 20 and 2 ms, while making high fidelity blood pressure measurements. Average reductions of 19.6 ± 7.7 mmHg in systolic pressure and 4.3 ± 3.8 mmHg in diastolic pressure ($P < .001$ each) were demonstrated with 2 ms AV delay pacing. Initial SBP reductions were followed by rebound effects which diminished the SBP reducing effects of SAVD pacing, likely due to baroceptor activation causing increased peripheral resistance. This effect was eliminated by intermittent introduction of longer AV delay pacing which modulated the baroreflexes. These findings provide the rationale and evidence underlying recent data showing significant and long-term blood pressure reductions in response to this cardiac neuromodulation therapy in hypertensive patients despite medical therapy. J Am Soc Hypertens 2018;12(5):381–391.

Keywords: Blood pressure; pacemaker; baroreceptor; autonomic nervous system.

Introduction

Hypertension (HTN) affects 1 in 3 adults in the United States, Europe, and China[1] and is a major factor contributing to cardiovascular morbidity and mortality.[2–4] Cardiovascular risk doubles for every 10 mmHg increase in systolic blood pressure (SBP).[2] Medications are usually effective in controlling blood pressure (BP). However, more than 10% of HTN patients are refractory to medical therapy, meaning they remain with BP above accepted

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target values despite prescription of appropriate medical therapies.[2,5] Another major issue with medications is low compliance in many patients.[6] Because of these factors, investigators have turned to alternate strategies to treat HTN, in particular device-based therapies. Percutaneous renal denervation,[7–9] baroreflex stimulation,[10,11] and arterial-venous shunts[12] are such examples. Although early studies of these approaches applied to patients with medically refractory HTN achieved certain levels of success, results in controlled trials have been more ambiguous and none has yet proven efficacy in reducing BP in randomized pivotal studies.[13–15] The recent SPYRAL HTN-OFF MED study,[16] which tested renal denervation in HTN patients without taking anti-HTN medications, showed, in comparison to sham controls, a 10-mmHg reduction in office SBP and a 5.5-mmHg reduction in average 24-hour ambulatory SBP at the end of 3 months' follow-up. Although these results are encouraging, the magnitude of the effect indicates that new, more potent therapies are needed.

We developed and tested a new therapeutic concept that employs novel cardiac pacing algorithms to reduce BP.[17] These algorithms use standard dual-chamber pacing impulses that employ short atrioventricular delay (SAVD) pacing with periodically introduced beats with longer AV delays. Prior studies showed that continuous SAVD pacing provides only short-term BP reduction, likely due to autonomic nervous system activation and compensation.[18,19] However, our recent study showed that use this novel programmable hypertension control (PHC) pacing algorithm based on repeated sequences of SAVD and longer AV delay pacing could achieve sustained reductions of BP over follow-up periods extending through 2 years.[17]

The purpose of the present study was to describe the acute kinetics of BP changes following introduction and withdrawal of SAVD pacing and how periodic introduction of beats with longer AV delays provides a means of quenching autonomic nervous system activation. Studies were performed in patients with HTN (SBP $>$ 140 mmHg) scheduled to undergo an electrophysiologic diagnostic or therapeutic procedure. The results clarify the theory and provide the initial experimental verification thereof, for this novel device-based approach to HTN therapy.

Material and Methods

Study Subjects

This was an exploratory single-arm, unblinded, treatment-only feasibility study conducted in 18 patients already scheduled to undergo an invasive electrophysiology procedure at a single center (The First Affiliated Hospital of Nanjing Medical University, Nanjing, China). This study was approved by the hospital ethics committee, and informed consent was obtained before any study-related procedures. The study was registered on www.clinicaltrials.gov (NCT02382484).

To be included in the study, patients were required to have systolic pressures greater than 140 mmHg despite at least one antihypertensive medication, as well as have a clinical indication and electrophysiology study involving the introduction of transvenous electrophysiology catheters into the right atrium and right ventricle. Eligible patients also needed to be at least 18 years of age, willing, and able to provide informed consent. Patients were excluded from the study for any of the following reasons: (1) atrial fibrillation at the time of the study; (2) ejection fraction (EF) less than 45%; (3) history of symptomatic heart failure, regardless of EF; (4) undergoing an ablation procedure for a bypass tract; or (5) history of resuscitation from ventricular fibrillation or sustained ventricular tachycardia. Although 19 patients were initially consented, one patient developed atrial fibrillation before the start of the study and was excluded.

Study Procedures

On the day of the study, the patient was brought to the electrophysiology laboratory, prepared and draped in sterile fashion according to standard hospital procedure. Catheter-based bipolar electrode leads were generally used and introduced via a femoral vein. In each case, one lead was positioned in the right atrium and a second lead positioned in the right ventricular (RV) apex. Femoral arterial access was used for the insertion of a solid-state pressure sensor (Millar Instruments, Houston, Texas) to continuously monitor aortic BP; this signal was digitized simultaneously with the ECG for offline analysis. In a subgroup comprising the first four patients, an extra femoral venous access sheath was used to introduce an OptiQ catheter for measuring cardiac output (Hospira; Q2 and Q2 Plus CCO/SO2 System), pulmonary artery (PA) pressure, and mixed venous oxygen saturation (SvO_2).

After placement, the leads were connected to a modified pacing system (MPS) capable of delivering pacing signals with a wide range and patterns of AV delays. The MPS allowed measurement of lead impedances, sensing (mV), and pacing thresholds (V). First, the heart was paced in DDD mode (i.e., dual chamber pacing, dual chamber sensing and dual chamber pacing inhibition), with the atrial rate set $\sim$10% greater than the intrinsic heart rate with a long AV delay that permitted native ventricular activation (baseline). The MPS was then programmed to deliver pacing signals in two phases. In phase 1, AV pacing was performed using SAVDs of 80, 40, 20, and 2 ms, for periods of $\sim$1 minute followed by a period of several minutes of pacing with a longer AV delay to characterize the kinetics of BP responses to initiation and withdrawal of SAVD pacing.

After phase 1, phase 2 of the study was performed in which the pacing paradigm was modified to include a repeating sequence of 8–25 beats of SAVD pacing with AV delay 2–80 ms, followed by introduction of 1–4 beats with longer AV delays ranging between 60 and 300 ms; multiple combinations were tested. Each test was preceded and followed by a baseline period consisting of atrial pacing at a rate 10% greater than the intrinsic heart rate.

The overall duration for the tests after instrumentation was approximately 45 minutes.

Assessment of Safety

Safety was evaluated by the number and severity of adverse events that occurred during or after the study. Furthermore, changes in cardiac output, SvO_2 (mixed venous oxygen saturation), PA pressure, and incidences of sensation or discomfort were monitored.

Statistical Analysis

This was a feasibility study with a physiologic primary endpoint, namely changes in BP. Based on prior clinical studies, we anticipated an average starting BP of 145 mmHg with a standard deviation of 12 mmHg. It was desired to be able to detect an average of at least a 10-mmHg reduction of SBP. For the final sample size calculation, we assumed that the standard deviation of the *change* of SBP would also be 12 mmHg. Based on these assumptions, and aiming for a 2-sided alpha level of 5% with at least 80% power, it was estimated that a total of 18 patients would be sufficient for this study.

Descriptive statistics were used to summarize values for SBP, DBP, and mean BP; pulmonary vein systolic and diastolic pressures; and cardiac output at each pacemaker setting. Data from all patients were pooled and expressed as means and standard deviations. Differences in values between baseline and pacing conditions were compared with Student's *t*-test.

Time Course of Changes of BP

Temporal changes in BP in response to the initiation (onset) and termination (offset) of SAVD pacing were fit with a single exponential decay using nonlinear fitting toolbox (MATLAB; The MathWorks Inc). As will be detailed in Results, upon initiation of SAVD pacing, SBP drops initially and then increases according to an exponential growth curve. Accordingly, the time course of BP changes following the onset of SAVD pacing was fit with the function: $P(t) = P_{ini} + \Delta P \cdot (1 - e^{-t/\tau})$, where P(t) is systolic pressure at time t, P_{ini} is the initial, minimum SBP pressure on the first few beat following initiation of SAVD pacing, ΔP is the final magnitude of the pressure recovery achieved from start to end of the pacing period, and τ is the time constant of pressure change. Following termination of SAVD pacing, pressure increases above the initial baseline value and returns to baseline according to an exponential decay. Accordingly, changes in pressure following SAVD termination were fit with the following function: $P = P_{ini} + \Delta P \cdot (e^{-t/\tau})$, where the terms are as defined previously.

Results

Baseline characteristics of the study population are summarized in Table 1. The average age was 56 ± 10 years, 10 men and 8 women. EF averaged 61 ± 10%. Average wall thickness was within normal range but was greater than 12 mm in 28% (5/18) of the patients. 28% had diabetes; a smaller proportion had coronary artery disease (17%). There was no prior history of renal dysfunction. The reason for electrophysiological studies included: evaluation of ventricular tachycardia (n = 3), ventricular tachycardia ablation procedure (n = 2), supraventricular tachycardia ablation procedure (n = 7), ablation procedure for atrial fibrillation (n = 6).

The average initial SBP and diastolic blood pressure (DBP) were 151.2 ± 17.6 and 92.2 ± 12.7 mmHg, respectively. Antihypertensive medications are summarized in Table 2. Nine subjects were treated with angiotensin-converting enzyme inhibitors, six were treated with angiotensin receptor blockers, four were treated with beta-blockers, five were treated with calcium channel blockers, and one with diuretics. Two subjects were treated for HTN with a combination of three drugs; seven were treated with two drugs; and the rest were taking one drug. The average number of drugs was 1.71.

Effects of Short AV Pacing on BP

Figure 1A shows a typical continuous high-fidelity recording of aortic BP when pacing was switched from pacing with the normal AV delay to AV pacing with a delay of 2 ms (green arrow) and then back to A-pacing with natural AV delay (red arrow). Note that heart rate is kept constant throughout this entire recording period by atrial pacing. Figure 1B and 1C shows the initiation and withdrawal of SAVD pacing at an enlarged time scale so individual heart beats can be viewed. The red dots indicate the SBP on each heartbeat, whereas the black X's indicate the DBP for each beat. Normal sinusoidal BP variations due to respiration and autonomic reflexes are readily appreciated throughout the entire course of these tracings; these variations amount to ~20 mmHg in systole and ~5 mmHg in diastole. At baseline, average SBP was ~150 mmHg. Upon initiation of SAVD pacing, SBP dropped immediately by ~35 mmHg to ~115 mmHg and started to increase according to an exponential growth curve, reaching a new steady-state pressure of ~140 mmHg (10 mmHg below

Table 1
Baseline characteristics of study subjects

Subject	Age (years)	Weight (kg)	Gender	LV EF (%)	Diabetes	CAD	Procedure
1	53	75	M	66	N	N	EP Study
2	47	80	M	68	Y	N	SVT ablation
3	41	88	M	61	N	N	VT ablation
4	45	68	M	61	N	N	EP Study
5	64	75	M	58	N	Y	VT Ablation
6	57	62	M	62	N	N	SVT Ablation
7	72	67	F	68	Y	Y	SVT Ablation
8	45	91	M	61	N	N	Afib Ablation
9	46	70	M	61	N	N	SVT Ablation
10	53	75	F	62	N	N	Afib Ablation
11	62	77	F	63	Y	Y	Afib Ablation
12	56	79	M	61	N	N	SVT Ablation
13	70	71	F	65	Y	N	EP Study
14	68	49	F	66	Y	N	Afib Ablation
15	64	60	F	70	N	N	Afib Ablation
16	63	51	F	25	N	N	SVT Ablation
17	45	70	F	64	N	N	SVT Ablation
18	54	77	M	61	N	N	Afib Ablation
Mean or N	56	71	10 M	61	5 Y	3 Y	
Standard deviation or N	10	11	8 F	10	13 N	15 N	

CAD, coronary artery disease; LV EF, left ventricular ejection fraction; EP, electrophysiological study; SVT, supraventricular tachycardia; VT, ventricular tachycardia; Afib, atrial fibrillation; M, male; F, female.

the initial baseline). When SAVD pacing was withdrawn, there was an immediate rise in SBP by ~20 mmHg, overshooting the original baseline value, which was then followed by an exponential decay back to baseline with a rate that appeared more rapidly than the rise following initiation of SAVD. The likely mechanism underlying these transients of BP is baroreceptor-mediated activation of the sympathetic nervous system[17,20] that will be discussed below. Overall, changes in DBP followed a similar time courses of change in the SBP but with a lower magnitude.

Table 2
Antihypertensive medications

Patient	ACE-I	ARB	BB	CaB	Diuretic	Number of Drugs
1	Y	N	N	N	N	1
2	N	Y	N	N	N	1
3	N	Y	Y	N	N	2
4	Y	N	N	Y	N	2
5	Y	N	Y	Y	N	3
6	Y	N	N	Y	N	2
7	Y	N	N	N	N	1
8	Y	N	N	Y	N	2
9	Y	N	N	N	Y	2
10	N	Y	Y	N	N	2
11	Y	N	Y	N	N	2
12	N	N	Y	N	N	1
13	n.a.	n.a.	n.a.	n.a.	n.a.	
14	N	Y	N	N	N	1
15	N	Y	N	N	N	1
16	N	Y	N	N	N	1
17	Y	N	N	N	N	1
18	Y	N	Y	Y	N	3
					Average	1.6

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CaB, calcium channel blocker.

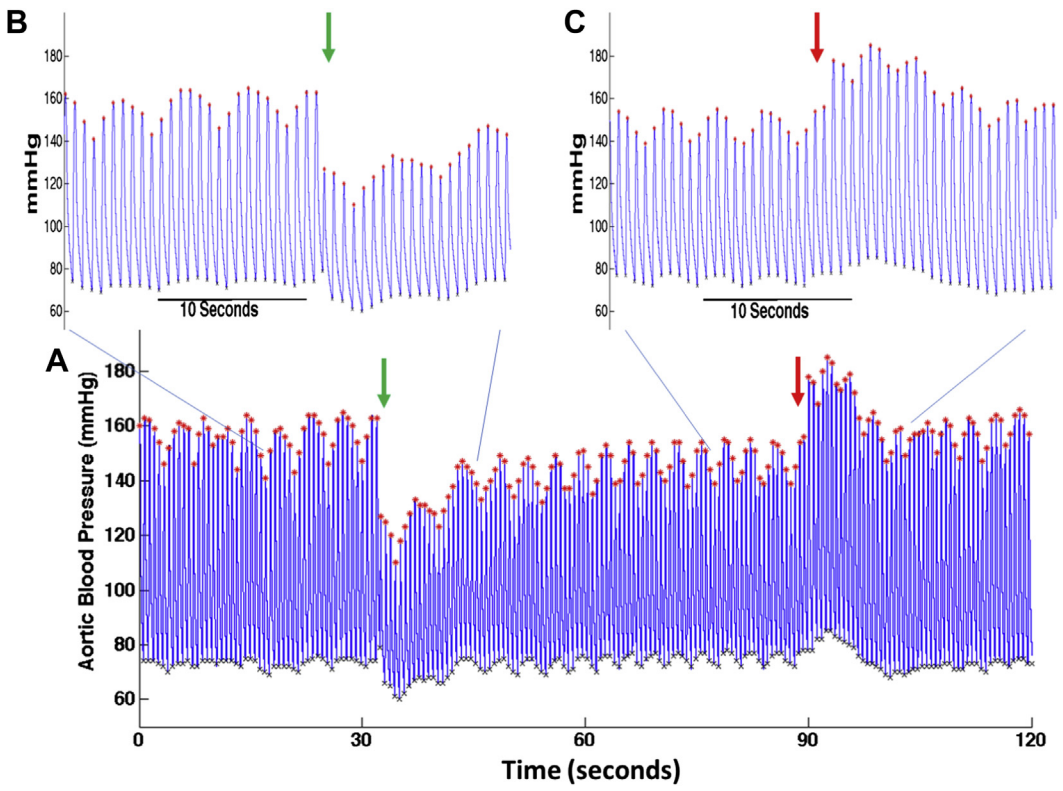

Figure 1. (A) Blood pressure recordings before, during, and after termination of SAVD pacing as indicated by the *green and red arrows*. (B) Higher time-resolution tracing of signals at the onset of SAVD pacing. (C) Higher time-resolution tracing of signals at the termination of SAVD pacing. The red dots indicate the detection of the SBP on each heartbeat, whereas the black X's indicate the DBP for each beat. DBP, diastolic blood pressure; SAVD, short atrioventricular delay; SBP, systolic blood pressure.

The pattern seen with SAVD pacing characterized by a rapid drop in pressure followed by an exponential increase toward baseline and an overshoot following termination, followed by a return to baseline was seen in each of the 18 patients. Table 3 summarizes the effect of pacing with SAVD of 2 ms on SBP and DBP. Data represent effects measured ~1 minute after switching to pacing with the 2-ms AV delay. SBP was consistently reduced by more than 11 mmHg in all patients resulting with an average reduction of 19.7 ± 7.4 mmHg ($P < .001$). DBP was significantly reduced by an average of 4.3 ± 3.7 mmHg ($P < .001$).

Effect of AV Delay on the BP Changes

The magnitude of the initial BP drop could be modulated by varying AV delay as shown in Fig. 2 where SAVD pacing with delays of 2, 20, 40, and 80 ms are shown. Note that the greater the BP drop, the greater the pressure rebound during the SAVD pacing period and the greater the overshoot in pressure when pacing with normal AV delay is restored. Average results obtained from all 18 patients are summarized in Fig. 3; data represent effects measured ~1 minute after switching to pacing with the specified AV delay. The decrease in systolic pressure was statistically significant at each of the AV delays tested, ranging from 20 mmHg with the 2-ms delay and 7 mmHg at 80 ms. In contrast, diastolic pressure decreased a statistically significant 5 mmHg with 2-ms AV delay but was negligible at AV delays greater than 20 ms. There was no impact of background medical therapy or starting BP on the impact of SAVD on BP reduction.

Temporal Behavior of the Changes in Blood Pressure

Figure 4 shows the changes in SBP over time when SAVD pacing of 2 ms was initiated and withdrawn. The time course of changes of systolic pressure following initiation of SAVD pacing in this case could be fit to a single exponential function [ie, $P(t) = P_{ini} + \Delta P \cdot (1 - e^{-t/\tau})$], where $P_{ini} = 114.8$ mmHg, $\Delta P = 22.7$ mmHg, and $\tau = 15.6$ seconds (τ for this period will be referred to as τ_{on}). The decay of SBP after the initial jump following cessation of SAVD pacing in this case could be fit with a single exponential function [ie, $P(t) = P_{ini} + \Delta P \cdot e^{-t/\tau}$], where $P_{in} = 186.3$ mmHg, $\Delta P = -31.3$ mmHg, and $\tau_{off} = 4.98$ seconds (τ for this period will be referred to as τ_{off}). The same temporal behavior of SBP in response

Table 3
Systolic and diastolic pressures in response to sequential AV pacing using 2-ms AV delay in individual subjects

Subject	Baseline		Short AV delay (2 ms)		Change in Systolic Pressure	Change in Diastolic Pressure
	Systolic	Diastolic	Systolic	Diastolic		
1	165.5	90.6	141.9	85.3	−23.6	−5.3
2	162.1	86.9	148.3	78.9	−13.8	−8.0
3	147.3	94.5	136.0	92.0	−11.3	−2.5
4	159.9	104.4	130.7	89.6	−29.2	−14.8
5	181.8	104.8	168.1	102.6	−13.7	−2.2
6	182.9	93.7	160.5	90.7	−22.3	−3.0
7	185.4	95.9	165.2	92.3	−20.2	−3.6
8	140.2	83.5	122.8	77.6	−17.4	−5.9
9	149.2	86.0	137.9	83.3	−11.3	−2.7
10	144.8	76.4	103.9	67.2	−40.9	−9.2
11	153.6	85.3	129.7	78.5	−23.9	−6.8
12	147.7	90.1	132.4	85.5	−15.3	−4.6
13	157.6	72.2	133.7	68.4	−23.9	−3.8
14	163.0	72.3	144.5	72.0	−18.5	−0.3
15	154.1	88.4	136.6	88.2	−17.5	−0.2
16	159.5	97.0	147.8	96.0	−11.7	−1.0
17	171.6	119.4	148.7	115.9	−22.9	−3.5
18	159.4	89.9	142.5	90.3	−16.9	0.4
Mean	**160.3**	**90.6**	**140.6**	**86.4**	**−19.7**	**−4.3**
STD	**13.2**	**11.7**	**15.3**	**12.0**	**7.4**	**3.7**
P value					**.00000**	**.00015**

AV, atrioventricular.

Changes represent the difference between the pressure before the delivery of pacing with an AV delay of 2 ms and the steady-state pressure after 1 minute of pacing.

to initiation and cessation of SAVD pacing was observed in all studied patients. On average, initiation of SAVD pacing at 2 ms was associated with response to pacing with a ΔP of 24 ± 9.2 mmHg and a time constant of τ_{on} = 13.6 ± 9.6 seconds. On average, cessation of SAVD pacing was associated with a ΔP of −28.7 ± 14.7 mmHg and a τ_{off} of 4.4 ± 1.8 seconds. Importantly, note the physiologically and statistically significant difference ($P = .003$) between τ_{on} and τ_{off}.

Modulation of the Baroreflex

In 14 of the patients, we tested the hypothesis that baroreflex activation during SAVD pacing can be modulated

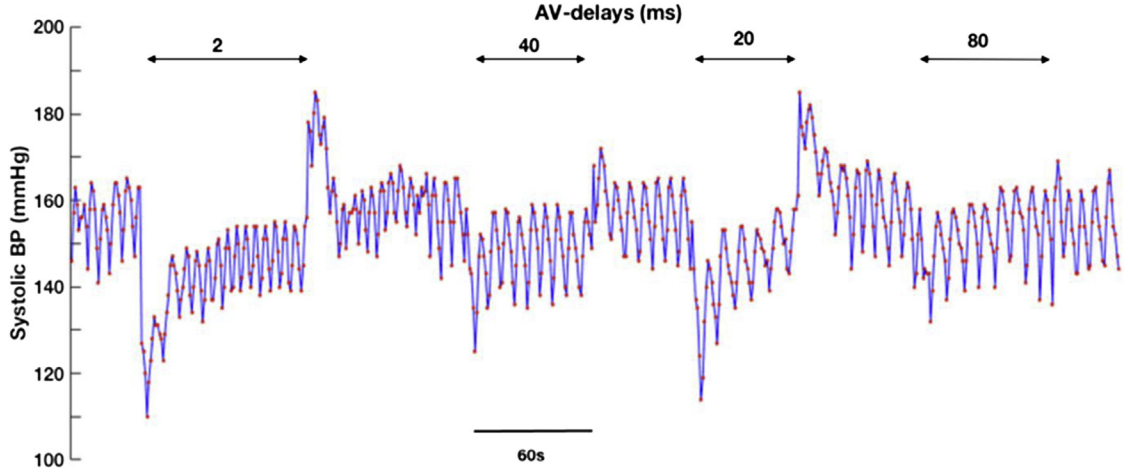

Figure 2. Recording of SBP with four serial tests at varying AV delays. The effect on BP was dependent on the value of AV delay, with greater degrees of SBP reduction and higher overshoots attained the shorter the AV delay. The order of AV durations was randomly generated during tests. AV, atrioventricular; BP, blood pressure; SBP, systolic blood pressure.

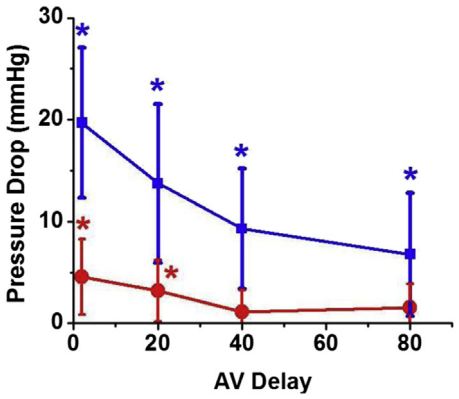

Figure 3. Average reductions in systolic (*blue*) and diastolic (*red*) pressures relative to control levels as a function of AV delay. The drop in systolic pressure was significant across the range of AV delays shown, whereas reductions in diastolic blood pressure were only significant at AV delays of 2 and 20 ms. Means and standard deviations are based on 18 subjects. AV, atrioventricular.

through the use of pacing sequences that included intermittent introduction of beats with longer AV delays. We termed these pacing sequences programmable hypertension control (PHC). A PHC pacing sequence was characterized by four parameters: (1) the AV delay during the SAVD pacing period (AVD_{short}); (2) the number of SAVD-paced beats (N_{short}); (3) the AV delay during the longer AV delay pacing period (AVD_{long}); and (4) the number of beats with the longer AV delay (N_{long}). Based on the magnitudes and kinetics of BP responses observed with SAVD pacing from prior preclinical work in a canine model, combined with mathematical simulations, it was anticipated that N_{short} values of 8–13 beats and N_{long} values of 1–3 beats, combined with AVD_{short} values between 2 and 60 ms and AVD_{long} values of 100–140 ms, would be effective in suppressing baroreceptor activation. Only a limited number of the near-infinite possible combinations of these parameters were explored in these 14 patients, and slightly different combinations were used in different patients.

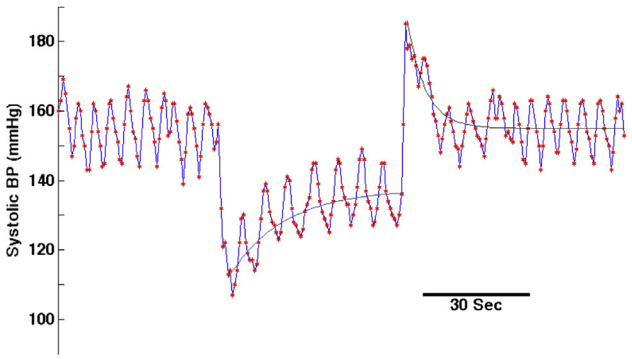

Figure 4. Beat-by-beat systolic blood pressure during initiation and termination of SAVD pacing illustrating respiratory variation, large drop in SBP upon initiation of SAVD pacing, exponential rise toward a new level (solid line shows exponential fit), overshoot of SBP above original baseline upon termination of SAVD pacing, and the exponential return to the original baseline value (solid line shows exponential fit). SAVD, short atrioventricular delay; SBP, systolic blood pressure.

Fig. 5 shows typical examples from a single patient, illustrating how the time course of pressure change is influenced by different combinations of PHC parameters. Fig. 5A shows the changes in SBP during a 60-second episode of simple, continuous SAVD pacing with a 2-ms AV delay; prominent, normal respiratory variations are appreciated. As in the prior examples (Figs. 1, 2, and 4), the immediate changes in SBP following initiation and termination of SAVD pacing were followed by transient changes back toward the original baseline value. Fig. 5B shows the changes in SBP measured in the same patient during 60 seconds of PHC pacing with the following parameter values: $N_{short} = 12$, $AVD_{short} = 2$ ms, $N_{long} = 3$ beats, and $AVD_{long} = 180$ ms. As anticipated, SBP on the three beats of longer AV delays was higher than that on the SAVD-paced beats. A transient rise of the pressure was still evident from one PHC sequence to the next; SBP on the AVD_{long}-paced beats exceeded the original baseline value, suggesting sympathetic activation. Similarly, there was a transient decline of SBP once this PHC sequence was withdrawn. Yet, note that the magnitude of the pressure overshoot was less compared with the tracings of Fig. 5A. Fig. 5C shows another pattern in which AVD_{long} was decreased to 120 ms. SBP overshoots on the AVD_{long}-paced beats still exceeded the original baseline levels, and transient SBP reductions were still evident following withdrawal of PHC, though the magnitudes of these overshoots were decreased compared with Fig. 5A and 5B. Finally, data of Fig. 5D were obtained when AVD_{long} was shortened further. In this case, there is no evidence of an increase in pressure during the PHC pacing period and no overshoot when PHC is discontinued. Thus, with this combination of PHC parameters, SBP was reduced, but there was no evidence (at least in the short time frame of this experiment) of baroreceptor activation.

In the 14 patients studied, it was always possible to identify a combination of parameters that resulted in abolition of the transient changes when PHC pacing was discontinued. Best results were obtained when the SAVD was ~2 ms and the longer AV delay was ~150 ms.

Safety

There were no serious adverse events during the study period. One patient who was consented for participation developed atrial fibrillation during the scheduled procedure and was promptly cardioverted. This patient was excluded from participation in this study per the protocol and never received any SAVD or PHC pacing.

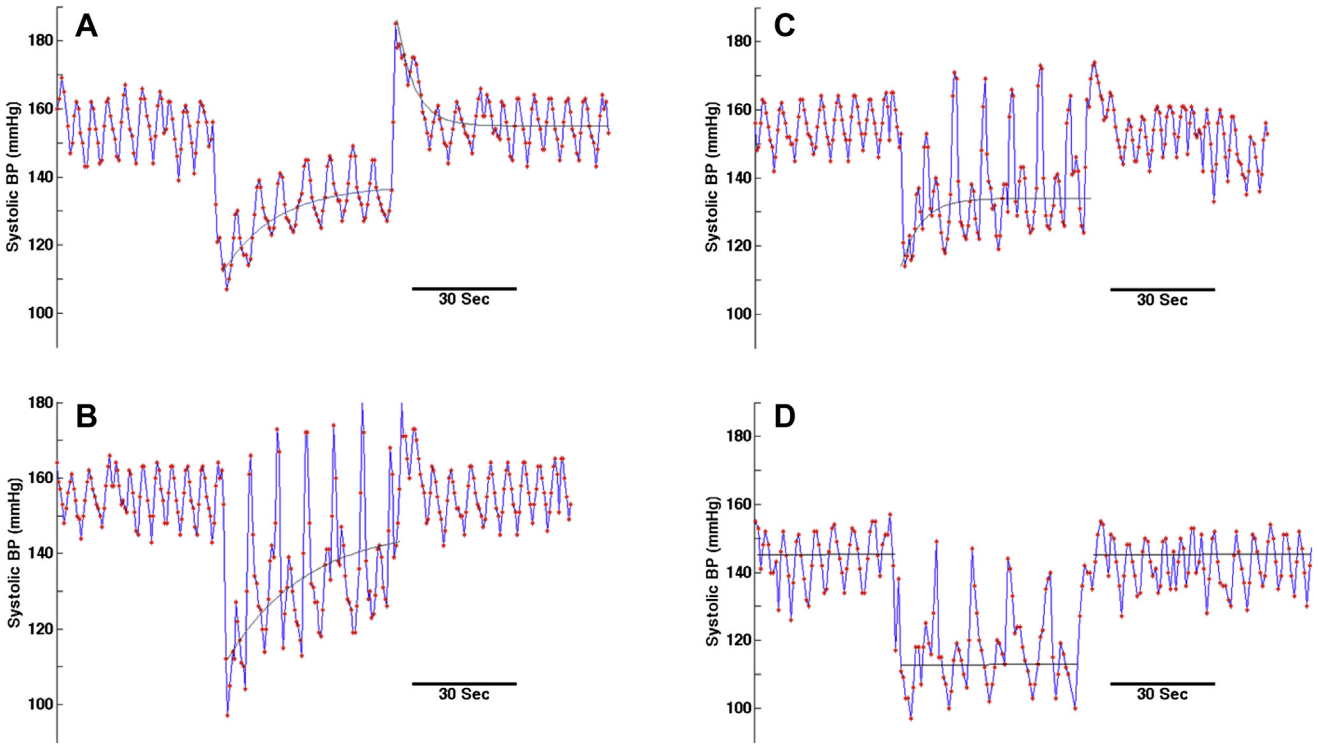

Figure 5. Modulation of transient changes in SBP upon initiation of short AV delay pacing (2 ms) alone (A) or with PHC pacing (B, C, and D). (A) Activation of simple SAVD pacing with an AV delay of 2 ms. (B) Sequence of eight SAVD-paced beats followed by three beats with AV delay 180 ms. (C) Sequence of eight SAVD-paced beats followed by three beats with AV delay 120 ms. Note that the magnitudes of pressure rebound and overshoot following initiation and termination of this pacing sequence are reduced compared with tracing in (B). (D) Sequence of eight SAVD-paced beats followed by 2 beats with AV delay 80 ms. Note that in this case, there is no appreciable pressure rebound or overshoot upon initiation and termination of this pacing sequence. AV, atrioventricular; PHC, programmable hypertension control; SAVD, short atrioventricular delay; SBP, systolic blood pressure.

Short periods with premature ventricular beats were observed in eight subjects during positioning of catheters used during this study. The events were anticipated and resolved by repositioning the catheters.

There were no events of sensation or discomfort encountered during the pacing signal delivery.

There were no significant changes in hemodynamic parameters obtained from right heart catheterization as measured in the first four patients. Specifically, there were no significant acute changes in cardiac output (4.3 ± 1.5 vs. 4.8 ± 1.9 L/min, $P = .4$) or changes in PA systolic or diastolic pressures (22 ± 5 vs. 19 ± 3 mmHg and 16 ± 2 vs. 18 ± 2, $P = .7$, respectively) during SAVD pacing.

Discussion

The acute effects of SAVD pacing on BP were studied in hypertensive patients already scheduled to undergo a clinically indicated invasive electrophysiology test. Upon switching to continuous SAVD pacing, average BPs dropped significantly (systolic: −20 mmHg average; diastolic: −5 mmHg average) and trended to return toward baseline with a time constant that was significantly longer than the time constant upon termination of the SAVD ($\tau_{on} = 13.6 \pm 9.6$ seconds vs. τ_{off} of 4.4 ± 1.8 second). The reductions of SBP were dependent on the AV delay; the shorter the AV delay, the greater the reduction. The transient changes seen with the onset and termination of SAVD pacing are due to reflex-mediated changes in autonomic tone (discussed further below). The difference in the time constants gave rise to a hypothesis that the baroreflex responses could be manipulated to cause a sustained reduction in BP when 2–3 beats with longer AV delays were periodically interspersed within a sequence of beats with SAVDs (ie, PHC pacing) and that the transient changes of SBP observed with initiation and termination of PHC pacing could be blunted and even eliminated; the data obtained in this study and in the recent pilot clinical study[17] support this hypothesis. Because PHC pacing appears to work largely by regulating autonomic tone, we consider this treatment as a cardiac neuromodulation therapy for HTN.

There are at least two mechanisms contributing to the transient changes in BP observed when AV delay is

abruptly shortened. These include (1) reductions in left ventricular (LV) filling due to the atria contracting against partially closed mitral and tricuspid valves causing an immediate decrease in BP and (2) activation of baroreflexes due to the reduction in BP and causing a return toward the baseline BP. The results of the present study suggest that the main mechanism of the immediate reduction of BP is due to reduced ventricular filling. A potential contributing mechanism could also be LV dyssynchrony due to RV pacing; however, results of the recent clinical pilot study that evaluated LV function during long-term follow-up suggest that this is not an important contributing factor.[17]

The Frank-Starling Law of the heart describes the natural mechanism by which ventricular pressure generation is regulated by preload. Its short-term effects are evident in the significant variations of arterial pressure during respiration (Fig. 1) due to changes in venous return and ventricular filling. BP reductions due to SAVD pacing are a manifestation of the same phenomenon.

Regarding the BP effects, the data presented here suggest a primary role of baroreflex activation due to the initial drop in BP from the SAVD pacing, which then acts to increase total peripheral resistance. The overshoot in the pressure upon returning to intrinsic, longer AV delays further supports this hypothesis. This same explanation has been provided in prior studies of the BP effects of SAVD pacing.[20]

The PHC pacing described herein (alternating shorter and longer AV delay sequences) is intended to be applied to patients with long-standing HTN (typically associated with LV hypertrophy and normal LV contractility) without any history of heart failure. As noted previously, the available evidence suggests that dyssynchrony does not play a significant role in the short-term BP effects. Nevertheless, the impact of long-term PHC pacing, in which the right ventricle is paced, is being examined in a controlled study that has already been initiated (www.clinicaltrials.gov NCT02837445). A majority of prior studies investigating the clinical effects of RV pacing have been performed in patients with reduced EF.[21–25] For example, results of some studies suggest that RV pacing leads to reduction of LV EF[21] and a greater incidence of heart failure.[21,24] In addition, AV sequential pacing has been associated with a higher incidence of atrial fibrillation.[22,23] On the other hand, results of one meta-analysis comparing an RV pacing strategy to a biventricular pacing strategy following AV node ablation in patients with symptomatic atrial fibrillation revealed that after 6–20 months of continuous pacing, EF increased in both groups and there was only a 2% (absolute) difference in EF between groups favoring the biventricular paced group. Another meta-analysis comparing atrial-based pacing with RV-based pacing for patients with bradycardias showed no difference in overall mortality or development of heart failure, but a higher incidence of atrial fibrillation.[23] As already noted, because of the marked difference in cardiac substrate, it is unknown if any of these results will apply to PHC pacing in patients with normal EF. Furthermore, all prior studies evaluating the effect of RV pacing on ventricular function were not performed in concert with the potentially beneficial effects that PHC pacing was seen to confer in the pilot study[17]: decreased preload (decrease in LV volumes, thereby decreasing wall tension) and decreased afterload (decrease in BP). Importantly, there is already evidence of lack of EF reduction during 3 months of PHC pacing[17]; as noted previously, a large, randomized study is underway to evaluate the longer-term effects on EF and other safety parameters.

Baroreflex-mediated increases in heart rate, contractility, and total peripheral resistance decrease the magnitude of BP reductions achievable by SAVD pacing alone as has been seen in prior studies where acute BP reductions due to simple SAVD were not sustained.[18,19] The differential time constants of baroreflex-mediated activation (~15 seconds) and inactivation (~5 seconds) observed in the present study led us to explore a unique pacing paradigm (eg, intermittent SAVD pacing) that aimed to minimize baroreflex activation. Based on this observation, we refer to this class of treatment as cardiac neuromodulation therapy for HTN.

Limitations

A limitation of the present study is that it is an unblinded, treatment-only study performed at a single center. Furthermore, it is limited in scope in that we investigated only very brief periods of PHC pacing with the primary goal of elucidating the magnitude of BP effects that could reasonably be achieved with this strategy. As noted previously, there are several important aspects of long-term safety and efficacy that need to be clarified, even beyond those already demonstrated in the pilot trial.[17] In addition, it will be important to understand the long-term impact on sympathetic tone and to determine whether a pacing paradigm of intermittent SAVD and long AV delay pacing can avoid causing any untoward effects.

The present study enrolled patients with mild-to-moderate BP who were not maximally medicated. However, the goal of the study was to demonstrate the basic means by which BP could be regulated and baroreceptor responses could be modulated, and the results of the present study do not rely on studies in patients with so called ‘‘refractory’’ HTN that have been in recent studies. The mechanisms underlying the findings in this study are fundamental to the cardiovascular system and are expected to be present in all subjects, whether or not they are taking maximal medications and their degree of BP elevation.

Conclusions

Acute delivery of sequential atrial and ventricular pacing with repeating sequence of SAVD and longer AV delay

significantly reduces SBP and DBP in patients with HTN, SBP > 140 mmHg despite treatment with at least one medication for BP control. The ability to modulate compensatory baroreflex responses was demonstrated acutely by using PHC pacing, which is a repeating sequence of SAVD pacing with periodic introduction of a few beats with longer (more normal) AV delays. Parameters of this PHC pacing algorithm were identified that modulated baroreflex responses to the reduction of BP. The ability to modulate the baroreflex response in this fashion appears to be due to the fact that the time constant of baroreceptor response is longer in response to a decrease on BP than to an increase of BP. The initial safety and efficacy of this form of therapy has been provided in a pilot study[17]; more definitive evidence is currently being sought in a prospective, double-blind study of PHC therapy in patients with persistent HTN (www.clinicaltrials.gov NCT02837445).

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References

1. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet 2017;390:2549–58.
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146–603.
3. Clark D 3rd, Guichard JL, Calhoun DA, Ahmed MI. Recent advancements in the treatment of resistant hypertension. Postgrad Med 2012;124:67–73.
4. Centers for Disease C and Prevention. Vital signs: awareness and treatment of uncontrolled hypertension among adults–United States, 2003-2010. MMWR Morb Mortal Wkly Rep 2012;61:703–9.
5. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension 2004;43:10–7.
6. Feig PU, Roy S, Cody RJ. Antihypertensive drug development: current challenges and future opportunities. J Am Soc Hypertens 2010;4:163–73.
7. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–81.
8. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010;376:1903–9.
9. Esler MD, Krum H, Schlaich M, Schmieder RE, Bohm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation 2012;126:2976–82.
10. Scheffers IJ, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. J Am Coll Cardiol 2010;56:1254–8.
11. Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the rheos pivotal trial. J Am Soc Hypertens 2012;6:152–8.
12. Ott C, Lobo MD, Sobotka PA, Mahfoud F, Stanton A, Cockcroft J, et al. Effect of Arteriovenous anastomosis on blood pressure reduction in patients with isolated systolic hypertension compared with combined hypertension. J Am Heart Assoc 2016;5.
13. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370:1393–401.
14. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol 2011;58:765–73.
15. Chen C, Upadhyay A. Renal denervation for uncontrolled hypertension: critical review of the evidence. Curr Opin Nephrol Hypertens 2017;26:114–22.
16. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al; Bohm M and investigators* SH-OMt. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017;390:2160–70.
17. Neuzil P, Merkely B, Erglis A, Marinskis G, de Groot JR, Schmidinger H, et al. Pacemaker-mediated programmable hypertension control therapy. J Am Heart Assoc 2017;6:1–18.
18. Schaefer J, Schwarzkopf HJ, Pape C. Reduction of elevated systolic blood pressure values associated with bradycardic disturbances of rhythm by increasing

heart rate via permanent pacing (author's transl). Klin Wochenschr 1974;52:198–9.
19. Schaefer J, Schwarzkopf HJ, Pape C, Schottler M. Permanent cardiac pacing as a possible adjunct for the treatment of hypertensive heart disease with bradycardia. Johns Hopkins Med J 1974;135: 143–51.
20. Manisty CH, Al-Hussaini A, Unsworth B, Baruah R, Pabari PA, Mayet J, et al. The acute effects of changes to AV delay on BP and stroke volume: potential implications for design of pacemaker optimization protocols. Circ Arrhythm Electrophysiol 2012;5:122–30.
21. Nahlawi M, Waligora M, Spies SM, Bonow RO, Kadish AH, Goldberger JJ. Left ventricular function during and after right ventricular pacing. J Am Coll Cardiol 2004;44:1883–8.
22. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003;42:614–23.
23. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA, et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation 2006;114:11–7.
24. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288: 3115–23.
25. Wilkoff BL, Kudenchuk PJ, Buxton AE, Sharma A, Cook JR, Bhandari AK, et al; Investigators DI. The DAVID (dual chamber and VVI implantable defibrillator) II trial. J Am Coll Cardiol 2009;53:872–80.