ORIGINAL RESEARCH

Pressure-Volume Analysis Demonstrates Short- and Long-Term Hemodynamic Effects of Atrioventricular Interval Modulation Therapy in Hypertension

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ABSTRACT

BACKGROUND Prior studies show that atrioventricular interval modulation (AVIM) therapy provides immediate, substantial, and sustained clinically meaningful reductions in ambulatory and office systolic blood pressures (SBPs) in hypertensive patients with pacemakers.

OBJECTIVES The goal of this study was to assess the acute and chronic mechanisms by which AVIM therapy reduces blood pressure and assess the impact of lead location on these mechanisms.

METHODS Acute hemodynamic effects were assessed by invasive pressure-volume (PV) analysis in hypertensive subjects (N = 16) with intact atrioventricular (AV) conduction. The impact of standard right ventricular pacing (RVp) vs left bundle branch area pacing (LBBAp) was also evaluated. Chronic effects of AVIM therapy were assessed by using noninvasive PV analysis with data from a subgroup of subjects (n = 32) from the MODERATO II study (NCT02837445).

RESULTS Acutely studied subjects had average office SBP of 144 ± 25 mm Hg despite antihypertensive medications. AVIM therapy significantly reduced end-diastolic volume (–12.6 ± 14.0 mL with RVp [$P = 0.003$]; –18.6 ± 16.2 mL with LBBAp [$P < 0.001$]) and effective arterial elastance (–0.23 ± 0.39 mm Hg/mL with RVp [$P = 0.032$]; –0.31 ± 0.55 mm Hg/mL with LBBAp [$P = 0.037$]), leading to significant SBP reductions (–17.1 ± 10.1 mm Hg with RVp [$P < 0.001$]; –19.2 ± 12.6 mm Hg with LBBAp [$P < 0.001$]). Neither left ventricular (LV) end-systolic nor end-diastolic properties were significantly affected by AVIM therapy at either pacing site. Noninvasive PV analysis showed similar reductions in SBP (–11.7 ± 21.8 mm Hg; $P = 0.023$) and reductions of end-diastolic volume (–21.5 ± 19.2 mL; $P = 0.005$ vs control) indicative of reverse remodeling.

CONCLUSIONS AVIM therapy acutely reduces SBP by decreasing preload and effective arterial elastance unrelated to lead location without affecting LV end-systolic or end-diastolic function. Chronic AVIM therapy reduces SBP and end-diastolic volume indicative of favorable reverse LV remodeling. (JACC Clin Electrophysiol. 2025;■:■–■)
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ABBREVIATIONS AND ACRONYMS

aSBP = ambulatory systolic blood pressure

AV = atrioventricular

AVIM = atrioventricular interval modulation

CSP = conduction system pacing

DBP = diastolic blood pressure

E_a = arterial elastance

EDV = end-diastolic volume

E_{es} = end-systolic elastance

EF = ejection fraction

ESV = end-systolic volume

ESPVR = end-systolic pressure-volume relationship

HTN = hypertension

LBBA = left bundle branch area

LV = left ventricular

oSBP = office systolic blood pressure

PV = pressure-volume

RV = right ventricular

SBP = systolic blood pressure

V_o = volume axis intercept of ESPVR

More than 1 million individuals undergo implantation or replacement of a pacemaker every year; approximately 70% of these individuals have coexisting hypertension (HTN).[1] The high prevalence of HTN in this group is representative of the elderly pacemaker population and is accompanied by other significant cardiovascular comorbidities such as arterial disease, stroke, heart failure, and atrial fibrillation.[2] Not surprisingly, the majority of pacemaker recipients have isolated systolic HTN, a difficult-to-treat form of HTN.[3] Consistent with other populations of patients with HTN, there is a high rate of uncontrolled HTN in the pacemaker population despite pharmacologic therapy.[4] Accordingly, an algorithm to treat HTN contained in an implanted pulse generator offers an attractive risk-benefit profile in patients who are already clinically indicated for a pacemaker. In the MODERATO I and II studies,[5,6] atrioventricular (AV) interval modulation (AVIM) therapy consisting of a sequence of variably timed short and longer AV intervals immediately and substantially reduced systolic blood pressure (SBP) with a durable effect over years of therapy delivery (**Central Illustration**).

The long-term efficacy and safety of AVIM therapy as a treatment for uncontrolled HTN in patients indicated for a dual-chamber pacemaker are currently being investigated in the BACKBEAT (Bradycardia Pacemaker With AV Interval Modulation for Blood Pressure Treatment) Investigational Device Exemption Study (NCT06059638). In this study, AVIM therapy, incorporated into Astra and Azure dual-chamber pacemakers (Medtronic) through a RAM-ware download, delivers a repeating sequence of 8 to 13 beats with short A-V intervals (20-80 milliseconds), followed by 1 to 3 beats with longer A-V intervals (100-180 milliseconds). The mechanisms by which AVIM therapy reduces blood pressure include reducing ventricular preload volume during the short

A-V intervals (decreasing left ventricular [LV] pressure generation according to the Frank-Starling mechanism) and modulating arterial resistance by intermittent exposure of the baroceptors to increased blood pressure pulses approximating baseline during the longer A-V intervals. Assessments of the acute and chronic effects of AVIM therapy on ventricular preload, ventricular function, ventricular structure, and ventricular-vascular coupling are fundamental to understanding how to optimize the long-term benefits and minimize potential adverse effects of AVIM therapy. It is important to note that prior studies showing proof of concept, and supporting the efficacy and safety of AVIM therapy, were conducted before the widespread adoption of conduction system pacing (CSP) involving the placement of the ventricular lead in the left bundle branch area (LBBA). How CSP modifies and influences the effects of AVIM therapy is currently unknown, but a comprehensive understanding can be provided through ventricular pressure-volume (PV) analysis. PV analysis through invasive means is most suited to elucidating the acute effects of AVIM therapy, whereas noninvasive PV analysis is most suited for studying the chronic effects.

The primary purpose of the current study was to provide a comprehensive hemodynamic assessment of the acute and chronic effects of AVIM therapy using PV analysis. Hemodynamic assessments were made using 2 different patient cohorts: acute data from a cohort of patients scheduled to undergo pacemaker implantation and chronic data from subjects enrolled in the MODERATO II study (NCT02837445). A secondary assessment analyzed the impact of right ventricular (RV) pacing vs CSP on these effects.

METHODS

ACUTE EFFECTS OF AVIM THERAPY ON BLOOD PRESSURE AND LV FUNCTION WITH DIFFERENT LEAD LOCATIONS. The acute hemodynamic effects of AVIM therapy were assessed at Na Homolce Hospital using PV analysis in 16 subjects with HTN

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CENTRAL ILLUSTRATION Acute and Chronic Effects of Atrioventricular Interval Modulation Therapy

AVIM Therapy Uses a Dual-Chamber Pacemaker to Deliver Repeated Sequences of Short and Longer AV Intervals
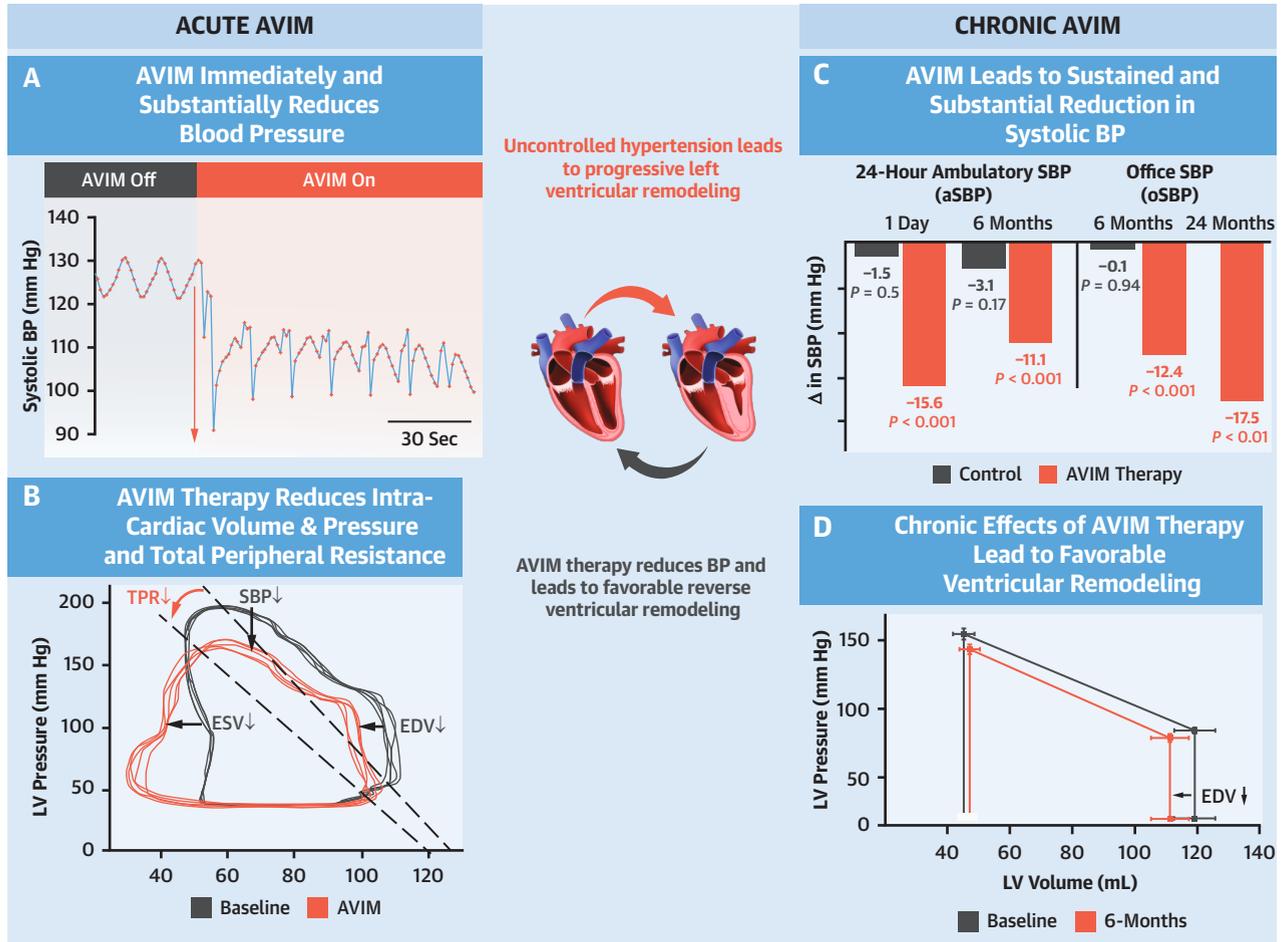
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(A) Immediate and substantial reduction in systolic blood pressure (SBP) is seen upon activation of atrioventricular (AV) interval modulation (AVIM) therapy. Each orange dot reflects a measure of SBP during a single cardiac cycle.[15] (B) Pressure-volume loop shows a reduction in SBP, end-systolic volume (ESV), end-diastolic volume (EDV), and total peripheral resistance (TPR) during delivery of AVIM therapy. (C) Results of the MODERATO II study exhibit a sustained as well as a substantial reduction in both ambulatory SBP (aSBP) and office SBP (oSBP) at 6 and 24 months, respectively.[5] (D) Chronic noninvasive pressure-volume loop data showing the effects of AVIM therapy and favorable ventricular remodeling at 6 months, with reductions in left ventricular (LV) volumes and pressures.

scheduled to undergo pacemaker implantation with placement of LBBA leads. Subjects without intrinsic 1:1 AV conduction were excluded from this acute study to allow for each subject to serve as their own control. The study was approved by the ethics committee, and all patients provided written informed consent.

After placing the right atrial lead in a standard fashion, 2 ventricular pacing leads were temporarily placed: one in a standard non-LBBA position (in the right ventricle) and a second in the LBBA confirmed using standard methods. The leads were then connected to a pacemaker capable of delivering AVIM therapy. The pacemaker was programmed to pace the

atrium at a rate of approximately 5 beats/min above the intrinsic sinus rate and allow intrinsic AV conduction.

PV loops were measured under 5 pacing conditions, allowing for 5-minute stabilization periods at each setting: 1) atrial pacing alone (with intrinsic conduction); 2) AV sequential (DDD) pacing with AV delay = 130 milliseconds; 3) return to baseline atrial pacing; 4) AVIM therapy pacing; and 5) final return to atrial pacing. The second lead was then connected to the pacemaker and the sequence repeated (Supplemental Figure 1). The order in which AVIM vs AV sequential pacing, and the order in which lead location (right ventricle vs LBBA) were tested in this sequence, were randomly varied to prevent systematic bias. After completion of the protocol, the RV lead was removed, leaving the LBBA lead for use in the permanent pacemaker system. PV loops were calibrated and analyzed as detailed in the following sections.

ACUTE INVASIVE PV LOOPS. PV loops were obtained by using a previously described conductance catheter (CD Leycom).[7] In brief, a pigtail catheter with a solid-state pressure sensor in the middle of an array of 12 equally spaced electrodes (10 mm spacing) was placed in the left ventricle. A high-frequency alternating electrical current of known amperage was passed between the most proximal and most distal electrodes, creating an electric field within the left ventricle. Voltage drops measured between successive pairs of electrodes are inversely proportional to the cross-sectional LV area at the level of the electrode pair; segmental volumes were estimated by the product of the cross-sectional area and the known, fixed distance between electrodes. Total estimated ventricular volume was calculated by summing the segmental volumes of each electrode pair within the LV chamber. The raw time-varying signal was calibrated by determining a gain factor (α) and an offset factor (ie, the parallel conductance), which were determined based on preprocedural echocardiographic measurements of LV ejection fraction (EF) and end-diastolic volume (EDV).[8]

After calibration, PV loops were analyzed to yield EDV and end-systolic volume (ESV) and end-diastolic and end-systolic pressures. LV end-systolic PV relationships (ESPVRs) were determined from single-beat methods from which end-systolic elastance (E_{es}; a measure of LV contractility) and V_0 (the ESPVR volume axis intercept) were determined.[9,10] Similarly, end-diastolic PV relationships were also determined from single-beat methods.[11,12] Effective arterial elastance (E_a) was determined as the ratio

| TABLE 1 Demographic Characteristics of Subjects in the Acute Invasive PV Loop Study (N = 16)	
Age, y	71.7 ± 10.4
Male	7 (44)
Height, cm	168.6 ± 10.2
Weight, kg	80.8 ± 16.6
LVEF, %	63.4 ± 4.9
Pacemaker indication[a]	
Sick sinus syndrome	19
AV block I	1
AV block II	7
AV block III	0
Other	1
Blood pressure	
Office SBP, mm Hg	144.0 ± 25.0
Office DBP, mm Hg	70.7 ± 11.9
Office heart rate, beats/min	70.5 ± 16.7
Medication use, no.	2.3 ± 1.1
Potassium-sparing diuretic	9
Beta-blocker	4
ACE inhibitor	13
ARB	0
CCB	7
Centrally acting agent	3
Medical history	
Diabetes	4
Coronary artery disease	4
Prior atrial fibrillation	2
Stroke	1

Values are mean ± SD or n (%) unless otherwise indicated. [a]Subjects may have more than one indication for a pacemaker implant.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AV = atrioventricular; CCB = calcium-channel blocker; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; PV = pressure-volume; SBP = systolic blood pressure.

between end-systolic pressure and stroke volume. All beats chosen for analysis were obtained at end-expiration.

CHRONIC (6-MONTH) EFFECTS OF AVIM THERAPY ON BLOOD PRESSURE, LV FUNCTION, AND LV STRUCTURE. The chronic effects of AVIM therapy on noninvasive PV loops were assessed by comparing 6-month follow-up data vs baseline data obtained from subjects in the MODERATO II study. Details of the inclusion criteria, follow-up measurements, and study endpoints have been previously described in detail.[5] In brief, MODERATO II was a prospective, multicenter (13 European centers), double-blind study investigating the efficacy of therapy in subjects with uncontrolled HTN and an indication for implantation or replacement of a dual-chamber pacemaker. Subjects were required to be taking a stable antihypertensive medical regimen for HTN for at least 6 weeks, with average daytime ambulatory

FIGURE 1 Example of Hemodynamic Response to AVIM Therapy
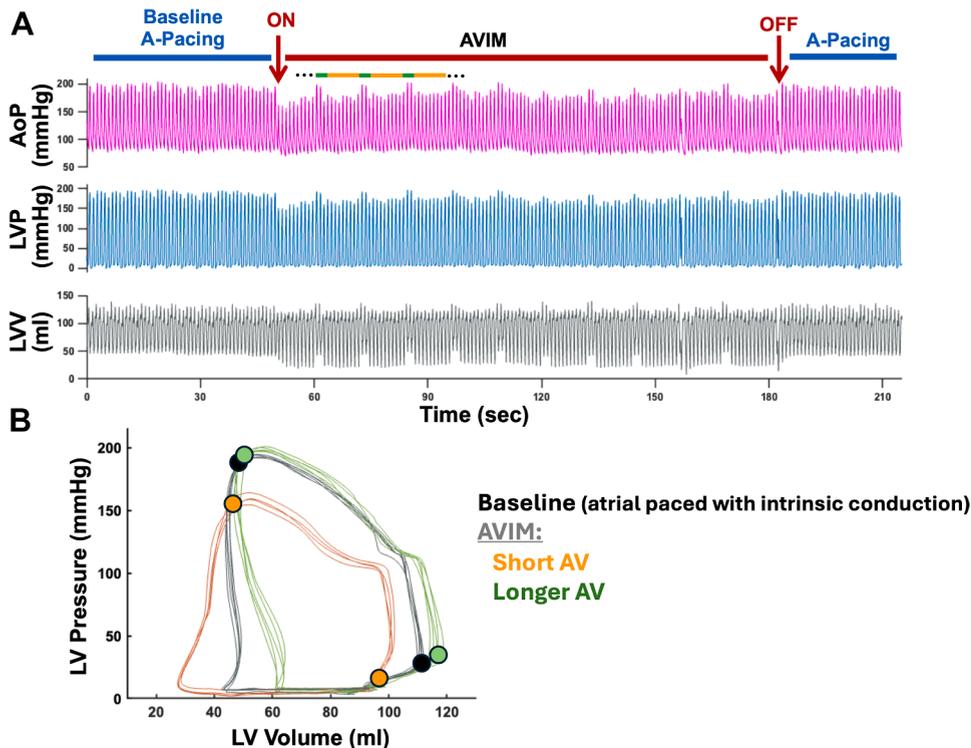
(A) Continuous left ventricular (LV) pressure (LVP), LV volume (LVM), and aortic pressure (AoP) tracings during atrial pacing (A-Pacing) with intrinsic conduction, during atrioventricular (AV) interval modulation (AVIM) therapy, and during resumption of A-Pacing. In this example, AVIM therapy consisted of 10 beats with a short AV interval (orange bars) and 2 beats with a longer AV interval (green bars). (B) Concomitantly measured pressure-volume loops from intrinsic AV conduction beat during A-Pacing (black), from a long AV interval beat during AVIM therapy (green), and from a short AV interval beat during AVIM therapy (orange). As detailed in the text, the loops measured during longer AV interval beats were similar to those during normal A-Pacing with intrinsic conduction. Loops measured during short AV interval beats had reduced preload and, accordingly, generated less pressure. End-diastolic and end-systolic points of each curve are shown by the dots at the bottom right and top left of each loop, respectively.

systolic blood pressure (aSBP) ≥130 mm Hg and office systolic blood pressure (oSBP) ≥140 mm Hg. Subjects with LV EF <50% and/or symptoms of heart failure (NYHA functional class II or higher) were excluded, and both groups continued with prerandomization medical therapy. Follow-up was conducted at 1, 3, and 6 months after randomization for assessment of primary and secondary endpoints. A subgroup of subjects (n = 32) agreed to be evaluated after 12 months of AVIM therapy. Echocardiographic images and blood pressure measurements were collected at each time point with AVIM therapy turned off and on (in both groups) so that both the sonographer and the echocardiographic core laboratory were blinded to group assignment.

NONINVASIVE PV ANALYSIS. As described previously,[13,14] noninvasive PV loops were constructed from 3 points on the PV plane estimated from the brachial SBP and diastolic blood pressure (DBP), LV EDV, and ESV. LV end-diastolic pressure was estimated from Doppler measures of E and e' waves: LV end-diastolic pressure $\approx 11.96 + 0.596 \cdot$ E/e'. E_a, a measure of ventricular afterload imposed by the arterial system, was quantified by dividing the estimated LV end-systolic pressure by stroke volume.

STATISTICAL ANALYSIS. For the acute study, an average of volume and pressure parameters from 3 to 5 cardiac cycles with intrinsic AV conduction was compared vs the average obtained using the specific

FIGURE 2 Example Pressure-Volume Loops During Pacing and AVIM Therapy
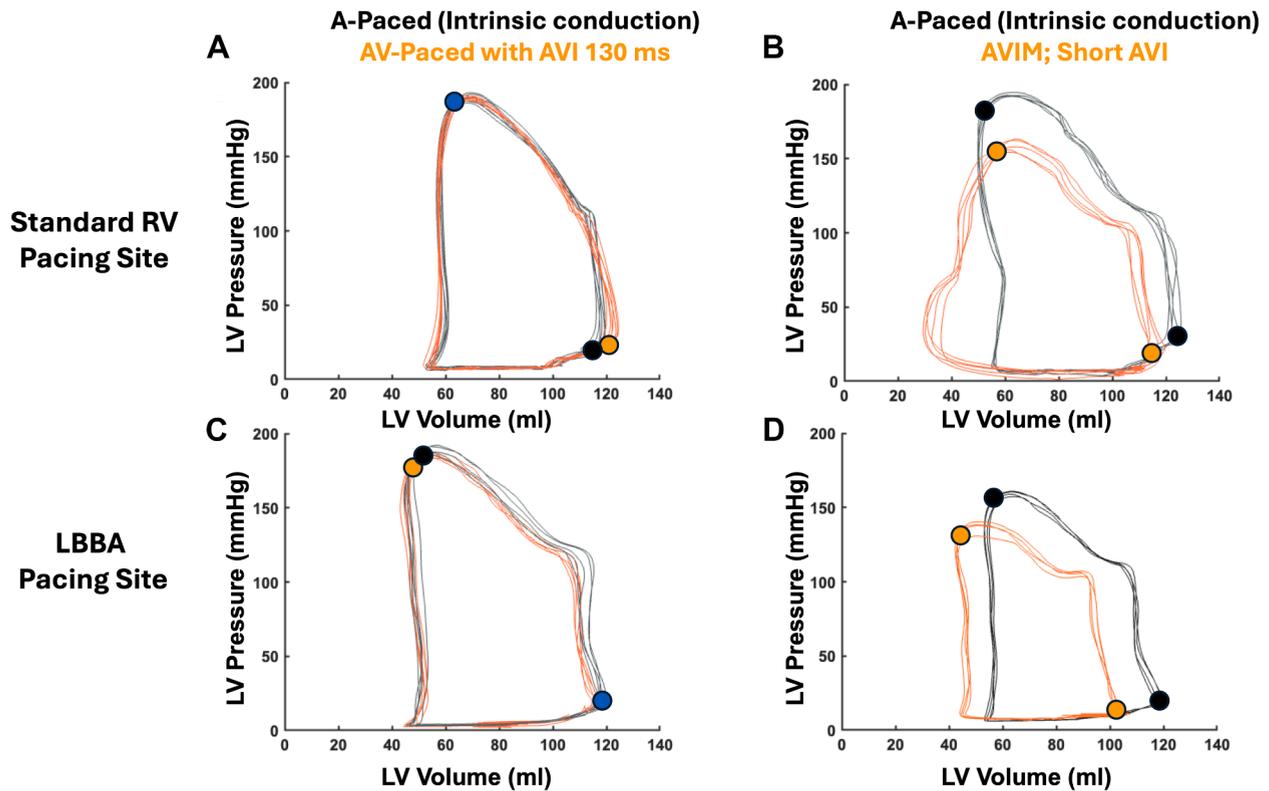
Invasive pressure-volume loops comparing ventricular mechanics during steady pacing from the atrium (with intrinsic conduction), pacing from a standard right ventricular (RV) site (A and B), and pacing from the left bundle branch area (LBBA) (C and D). Panels A and C compare loops measured during steady A-Pacing with intrinsic AV conduction vs those measured during AV sequential pacing with an AV interval (AVI) of 130 milliseconds from RV and LBBA sites, respectively. Panels B and D compare loops measured during steady A-Pacing with intrinsic AV conduction vs those measured during the short AVI beats (50 milliseconds) during AVIM therapy from RV and LBBA sites. End-diastolic and end-systolic points of each curve are shown by the dots at the bottom right and top left of each loop (note: blue dots indicate points where the pressure-volume points of 2 loops on a particular graph are coincident). Abbreviations as in **Figure 1**.

pacing modality and lead position. Sixteen subjects had a full set of data comparing baseline vs AVIM therapy in both lead positions, and 14 of the 16 subjects had a full set of data comparing baseline vs standard pacing. For the chronic study, all patients who had paired baseline and 6-month data (n = 32 [11 control and 21 treatment]) were included in the primary analysis of 6-month results. For an additional supplemental analysis of longer term effects, all patients who had data at 6 months and 12 months and received AVIM therapy for a full 12 months were included (n = 14). For all cohorts, descriptive statistics (means, medians, SDs, and percentages) were used to summarize findings.

Data are presented as mean ± SD, and comparisons were made with paired two-sided Student *t*-tests. *P* values <0.05 were considered statistically significant. No corrections were made for multiple comparisons. A sample size of 16 subjects enabled the

detection of a >10 mm Hg reduction in pressure with 80% power (*P* = 0.05).

Evaluation of the long-term effects of AVIM therapy included all subjects with paired data at baseline and 6 months (32 subjects), allowing comparison of changes in the evaluated parameters using paired Student *t*-tests. Descriptive statistics were used.

RESULTS

ACUTE EFFECTS OF AVIM THERAPY ON BLOOD PRESSURE AND LV FUNCTION FROM DIFFERENT LEAD LOCATIONS. Baseline characteristics of subjects who participated in the acute invasive PV loop study are summarized in **Table 1**. Patients averaged 71 years of age, had an average oSBP of 144 mm Hg despite taking an average of 2.3 antihypertensive medications, had normal LV function, were receiving a first-time pacemaker implant (ie, no replacement

devices), and had numerous comorbid conditions typical of the pacemaker patient population.

Figure 1A shows tracings of aortic pressure, LV pressure, LV volume, and simultaneously measured PV loops (Figure 1B) during atrial pacing with intrinsic conduction, with the onset of AVIM therapy and with cessation of AVIM therapy and resumption of atrial pacing with intrinsic conduction. In this example, compared with baseline, SBP decreased by approximately 23 mm Hg on the 10 beats with a short AV delay during AVIM therapy. On the 2 beats with longer AV delays, SBP approximates the pressures seen during baseline atrial pacing.

Comparable effects are also noted in the LV volume signal: reduced EDV during the short AV delay beats and EDVs approximating baseline values during beats with a longer AV delay. The effects are clearly evident on the corresponding PV loops (Figure 1B). It is worth noting that as seen on the time-domain plots, the blood pressure reduction with initiation of AVIM therapy is immediate, substantial, and stable, returning to baseline without an overshoot upon resumption of intrinsic conduction. This observation (lack of overshoot) indicates that during AVIM therapy, there is no baroreflex activation in response to the significant reduction of blood pressure during the short AV interval, as would typically be expected to occur without the autonomic nervous system modulation achieved through the intermittent introduction of the longer AV interval.[12]

The impact of lead location on AV sequential pacing and AVIM therapy is shown as an example in the PV loops of Figure 2. Figures 2A and 2C present examples of PV loops with atrial pacing (with intrinsic AV conduction) compared with AV sequential pacing (with a 130-millisecond AV interval) with standard RV lead location (Figure 2A) and LBBA lead position (Figure 2C). There is no significant impact on the PV loops between atrial and ventricular pacing with either lead location. Detailed comparisons of the atrial pacing (with intrinsic AV conduction) to RV pacing (with both standard and LBBA lead locations) on LV chamber properties are summarized in Table 2 (n = 14). Except for a nonsignificant approximately 3 mm Hg average reduction of aortic SBP with LBBA pacing, there was no significant impact of ventricular pacing at either site on ventricular pressures, volumes, contractility (indexed by single beat estimates of E_{es} and V_O), stroke work, or PV area, which correlates to myocardial oxygen consumption.

PV loops measured during beats with a short AV interval are similarly affected with standard and LBBA pacing locations. In both cases, preload and

TABLE 2 Hemodynamic and PV Loop Parameters Derived From Steady-State Pacing Comparing A-Pacing vs RV Pacing With Lead Position Either in a Standard Location or With LBBA Location: Results From the Acute Hemodynamic Study (n = 14)
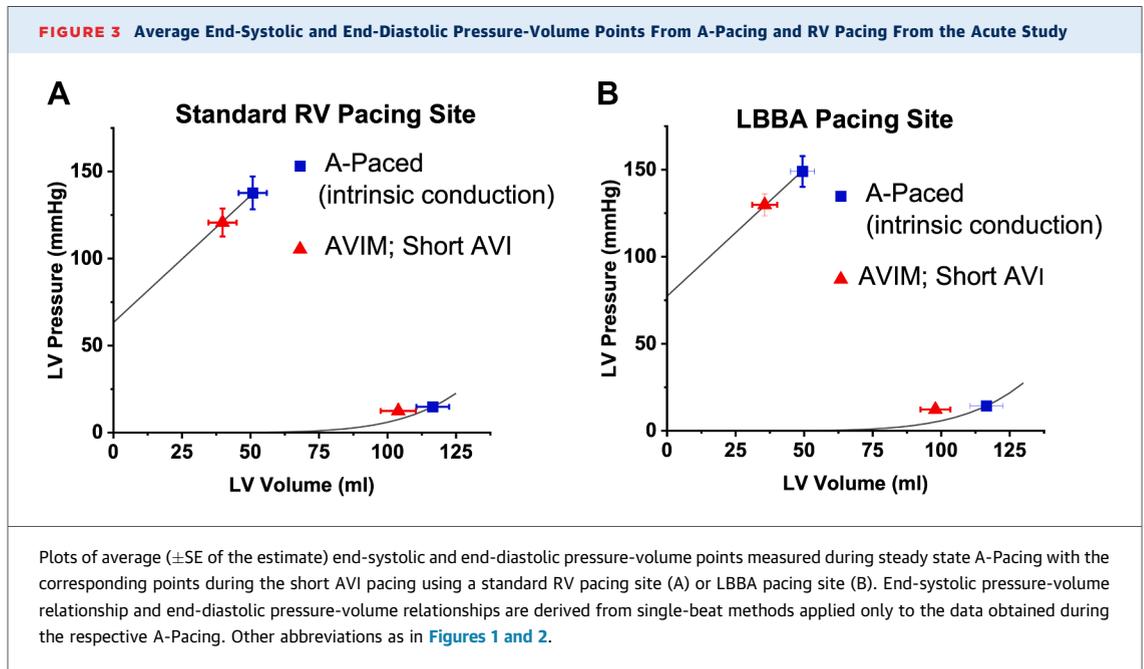
	A-Pacing	RV Pacing	Difference	P Value
Standard RV pacing site				
Aortic SBP, mm Hg	136.4 ± 35.6	134.7 ± 36.8	−1.7 ± 5.1	0.236
EDV, mL	125.6 ± 22.8	124.0 ± 26.3	−1.6 ± 16.8	0.721
ESV, mL	51.7 ± 18.2	53.8 ± 19.3	2.1 ± 12.0	0.528
EDP, mm Hg	9.6 ± 5.5	9.9 ± 5.5	0.3 ± 2.4	0.659
E_{es}, mm Hg/mL	1.03 ± 0.31	1.05 ± 0.32	0.02 ± 0.2	0.696
V_O, mL	−76.6 ± 36.2	−74.4 ± 42.8	2.3 ± 22.9	0.714
E_a, mm Hg/mL	1.94 ± 0.93	1.98 ± 1.0	0.04 ± 0.45	0.726
SW, mm Hg · mL	9,440 ± 3,336	9,398 ± 4,303	−42 ± 1692	0.927
PVA, mm Hg · mL	17,900 ± 6,782	17,593 ± 8,295	−1,564 ± 5,554	0.727
LBBA pacing				
Aortic SBP, mm Hg	138.5 ± 28.6	135.5 ± 27.1	−3.0 ± 4.1	0.016
EDV, mL	122.0 ± 22.3	121.4 ± 24.7	−0.6 ± 17.9	0.895
ESV, mL	53.2 ± 21.8	54.9 ± 23.2	1.6 ± 8.8	0.499
EDP, mm Hg	9.8 ± 4.2	9.5 ± 4.9	−0.3 ± 2.9	0.718
E_{es}, mm Hg/mL	1.31 ± 0.59	1.31 ± 0.63	−0.01 ± 0.4	0.945
V_O, mL	−44.2 ± 94.1	−46.6 ± 72.9	−2.4 ± 45.5	0.805
E_a, mm Hg/mL	2.06 ± 0.74	2.04 ± 0.86	−0.03 ± 0.47	0.823
SW, mm Hg · mL	9,291 ± 2,496	8,606 ± 3,006	−685 ± 1,729	0.162
PVA, mm Hg · mL	15,704 ± 6,902	14,807 ± 5,728	−897 ± 2,887	0.266

A-Pacing = atrial pacing; E_a = effective arterial elastance; EDV = end-diastolic volume; EDP = end-diastolic pressure; ESV = end-systolic pressure; E_{es} = end-systolic elastance, which is the slope of the end-systolic pressure-volume relationship; LBBA = left bundle branch area; PVA = pressure-volume area; RV = right ventricular; SW = stroke work; V_O = volume axis intercept of end-systolic pressure-volume relationship; other abbreviations in Table 1.

TABLE 3 Hemodynamic and PV Loop Parameters on the Short AV Delay Beats During AVIM Pacing Compared With Steady-State Beats During A-Pacing: Results From the Acute Hemodynamic Study

	Steady-State A-Pacing	AVIM	Change	P Value
RV pacing AVIM				
Aortic BP, mm Hg	137.7 ± 37.7	120.7 ± 31.7	−17.1 ± 10.1	<0.001
EDV, mL	116.5 ± 23.9	103.9 ± 25.6	−12.6 ± 14.0	0.003
ESV, mL	50.8 ± 20.5	39.8 ± 20.4	−11.0 ± 11.4	0.002
EDP, mm Hg	14.8 ± 5.6	12.4 ± 5.8	−2.3 ± 3.9	0.031
E_{es}, mL/mm Hg	1.48 ± 0.48	1.46 ± 0.63	−0.02 ± 0.41	0.858
Vo, mL	−42.1 ± 31.7	−44.9 ± 33.8	−2.8 ± 15.6	0.481
E_a, mL/mm Hg	2.14 ± 0.67	1.91 ± 0.71	−0.23 ± 0.39	0.032
SW, mm Hg · mL	8,066 ± 3,176	6,470 ± 3,360	−1596 ± 1934	0.005
PVA, mm Hg · mL	14,258 ± 6,006	11,138 ± 5,044	−3120 ± 2918	<0.001
LBBA pacing AVIM				
Aortic SBP, mm Hg	149.0 ± 35.4	129.8 ± 25.5	−19.2 ± 12.6	<0.001
EDV, mL	116.5 ± 23.9	97.9 ± 21.7	−18.6 ± 16.2	<0.001
ESV, mL	49.6 ± 17.5	35.6 ± 18.2	−14.1 ± 14.6	0.002
EDP, mm Hg	14.3 ± 5.7	12.2 ± 5.3	−2.13 ± 3.9	0.045
E_{es}, mL/mm Hg	1.47 ± 0.36	1.49 ± 0.39	0.02 ± 0.28	0.795
Vo, mL	−54.3 ± 29.6	−52.4 ± 31.5	1.88 ± 18.0	0.682
Ea, mL/mm Hg	2.32 ± 0.68	2.01 ± 0.50	−0.31 ± 0.55	0.037
SW, mm Hg · mL	9,077 ± 4,102	7,207 ± 3,667	−1,870 ± 2,051	0.002
PVA, mm Hg · mL	16,705 ± 7,378	12,589 ± 5,865	−4,116 ± 3,297	<0.001

Abbreviations as in Tables 1 and 2.

FIGURE 3 Average End-Systolic and End-Diastolic Pressure-Volume Points From A-Pacing and RV Pacing From the Acute Study

Plots of average (±SE of the estimate) end-systolic and end-diastolic pressure-volume points measured during steady state A-Pacing with the corresponding points during the short AVI pacing using a standard RV pacing site (A) or LBBA pacing site (B). End-systolic pressure-volume relationship and end-diastolic pressure-volume relationships are derived from single-beat methods applied only to the data obtained during the respective A-Pacing. Other abbreviations as in Figures 1 and 2.

pressure generation are significantly decreased, as shown in **Figures 2B and 2D**. Average results are summarized in **Table 3** (n = 16). Independent of lead location, the hemodynamic effects of AVIM therapy are comparable in all parameters, including the almost 20% reduction in SBP. Importantly, similar to AV sequential pacing, delivery of short AV intervals and AVIM therapy from either the RV or LBBA locations had no significant impact on LV contractility (indexed by E_{es} and V_0).

To further summarize this key finding visually, we plotted the average end-systolic and end-diastolic PV points measured during steady-state atrial pacing with the corresponding points during the short AV interval pacing with the 2 different sites of ventricular pacing (**Figure 3**). The ESPVR and end-diastolic PV relationship displayed on these graphs are derived from single beat methods applied during atrial pacing. As seen in the graphs, on average, AVIM therapy reduces preload volume and pressure and end-systolic volume and pressure generation, without a significant change in LV contractility. In addition, there was a significant reduction in E_a, indicative of a reduction in total peripheral resistance and ventricular afterload. Finally, stroke work and PV area were significantly reduced by approximately 20% with the short AV delay, signifying a reduction in myocardial oxygen consumption; this

effect was observed without a significant impact on stroke volume.

CHRONIC (6-MONTH) EFFECTS OF AVIM THERAPY ON BLOOD PRESSURE AND LV FUNCTION. From the original cohort of subjects who participated in the MODERATO II study, echocardiograms were available for 32 subjects: 11 from the control arm and 21 from the treatment arm. Nineteen (60%) subjects received the Moderato system as a new implant and 13 (40%) as a replacement device. There were no significant differences between treatment and control arm subjects in terms of baseline characteristics (**Table 4**). The cohort was 56% male, had normal LV EF (59.4% ± 5.9%), an average oSBP of 151.9 ± 14.3 mm Hg, and aSBP of 136.4 ± 11.1 mm Hg despite being prescribed an average of 3 antihypertensive medications. Notably, isolated systolic HTN was present in approximately 88% of subjects.

Group-averaged noninvasive PV loops at baseline and after 6 months' follow-up are shown in **Figure 4**; quantitative details are provided in **Table 5**. In patients receiving AVIM therapy, SBP decreased by 11.7 mm Hg (158.2 ± 19.1 mm Hg vs 146.5 ± 16.6 mm Hg; $P = 0.02$), and EDV was lowered by 7.5 mL (118.1 ± 30.3 mL vs 110.6 ± 27.9 mL; $P = 0.096$) when comparing baseline vs 6-month follow up. This indicates a leftward shift of the end-diastolic

pressure volume relationship (ie, reverse remodeling) (Central Illustration). Concomitantly, LVEF decreased by 4.3% ± 6.1% (from 63.7% ± 6.4% to 59.4% ± 6.2%; $P = 0.004$).

As further summarized in Table 5 and evident in Figure 4, while SBP decreased by 11.7 ± 21.8 mm Hg ($P = 0.023$), end-systolic volume did not change significantly, signifying a small reduction in LV contractility. Estimated end-diastolic pressure did not change (18.9 ± 3.4 vs 18.5 ± 2.3 mm Hg; $P =$ not significant). In control subjects, there was no change in blood pressure, and LV EDV increased significantly (111.0 ± 12.4 mL vs 125.0 ± 19.8 mL; $P = 0.03$), indicating progressive remodeling. The change in EDV was significantly different between the control and treatment groups ($P = 0.005$). There were no changes in any of the other hemodynamic parameters assessed, and, importantly, the changes observed occurred with minimal change in antihypertensive therapy in either group (Table 6).

A subset of treatment subjects had echocardiographic images that were suitable for analysis at 12-month follow-up (n = 14). As summarized in Supplemental Table 1, all of the hemodynamic benefits observed at 6 months were maintained in this subgroup, including the reductions in oSBP and EDV.

DISCUSSION

The current study examined the acute and chronic effects of AVIM therapy on LV size and function via PV analyses. In the acute setting, PV loops measured with the conductance catheter confirmed that the main mechanism of blood pressure reduction is a reduction in LV preload volume. Prior findings showing that AVIM therapy reduces blood pressure without increasing ventricular afterload as indexed by E_a[15] were also reconfirmed. This is significant in that in contrast to AVIM therapy, with simple short AV pacing without intermittently interspersed beats with longer AV intervals, reductions in blood pressure are counteracted by acute activation of the sympathetic system; it was therefore inferred that AVIM reduces blood pressure without activation of the sympathetic nervous system. As also shown in our subjects with normal EF, there was no acute impact of RV pacing on LV contractility, neither from a standard RV site nor from LBBA. Acute AVIM therapy was equally effective at reducing blood pressure with pacing delivered using a standard RV lead location or an LBBA site. Because CSP using leads in the LBBA continues to gain prominence clinically, these data provide important details on the

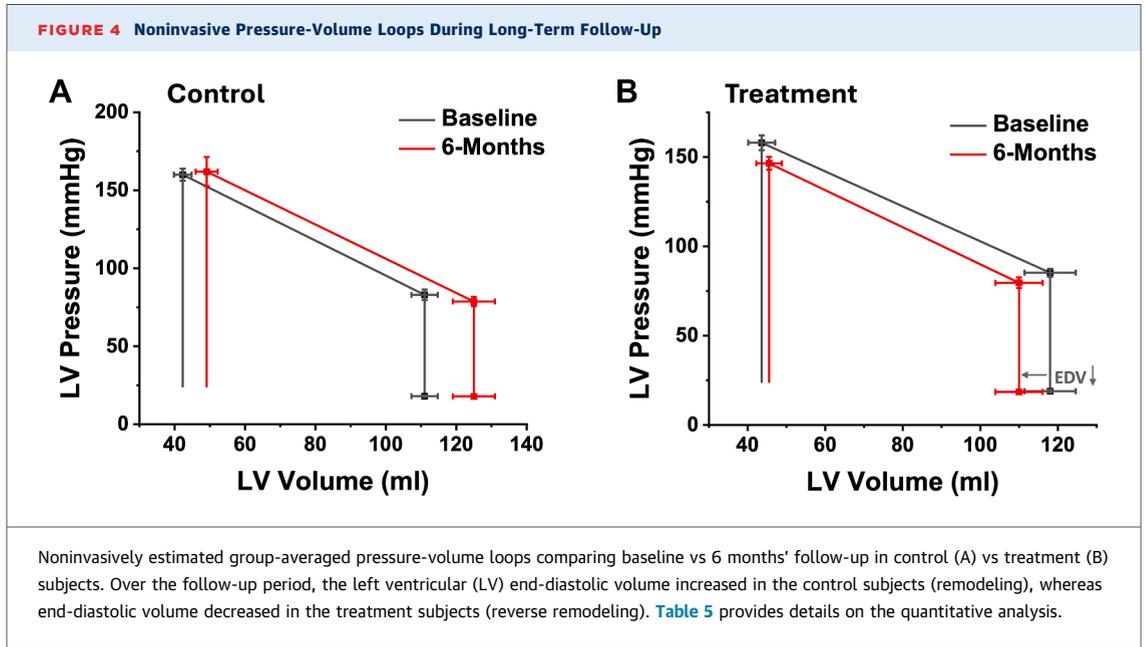| TABLE 4 Baseline Demographic Characteristics of Subjects Included in the Chronic (6-Month Follow-Up) Noninvasive PV loop Substudy of the MODERATO II Study				
	All (N = 32)	Control (n = 11)	Treatment (n = 21)	P Value
Age, y	73.2 ± 9.0	73.4 ± 9.8	73.0 ± 8.8	0.927
Male sex	18 (56)	7 (64)	11 (52)	0.712
Height, cm	168.4 ± 9.8	165.9 ± 8.1	169.7 ± 10.6	0.311
Weight, kg	85.3 ± 17.2	84.7 ± 19.2	85.6 ± 16.5	0.898
LVEF, %	59.4 ± 5.9	57.5 ± 3.9	60.3 ± 6.6	0.210
Pacemaker				
New implant	19 (59)	7 (64)	12 (57)	1.000
Replacement	13 (41)	4 (36)	9 (43)	
Indication				
Sick sinus syndrome	9 (28)	4 (36)	5 (24)	0.681
Bradycardia	6 (19)	2 (18)	4 (19)	1.000
AV block I	5 (16)	2 (18)	3 (14)	1.000
AV block II	12 (38)	3 (27)	9 (43)	0.465
AV block III	3 (9)	1 (9)	2 (10)	1.000
Other	2 (6)	1 (9)	1 (5)	1.000
Baseline blood pressures				
Office SBP, mm Hg	151.9 ± 14.3	152.0 ± 16.0	151.9 ± 13.7	0.993
Office DBP, mm Hg	80.3 ± 11.7	77.0 ± 13.5	82.0 ± 10.6	0.256
Office heart rate, beats/min	64.8 ± 9.1	63.7 ± 9.5	65.3 ± 9.2	0.645
aSBP, mm Hg	136.4 ± 11.1	137.5 ± 14.1	136.4 ± 9.6	0.795
aDBP, mm Hg	73.8 ± 6.2	74.8 ± 5.9	73.3 ± 6.4	0.529
aHR, beats/min	71.9 ± 9.2	67.9 ± 9.9	73.9 ± 8.3	0.078
Isolated systolic HTN	28 (88)	8 (73)	20 (95)	0.110
Medications, n	3.0 ± 1.4	2.7 ± 1.3	3.2 ± 1.5	0.399
Loop diuretic	18 (56)	5 (45)	13 (62)	0.465
Potassium-sparing diuretic	3 (9)	1 (9)	2 (10)	1.000
Beta-blocker	11 (34)	2 (18)	9 (43)	0.248
ACE inhibitor	20 (63)	9 (82)	11 (52)	0.140
ARB	11 (34)	2 (18)	9 (43)	0.250
CCB	20 (63)	6 (55)	14 (67)	0.703
Alpha-agonist	3 (9)	1 (9)	2 (10)	1.000
Centrally acting agent	3 (9)	2 (18)	1 (5)	0.266
Medical history				
Diabetes	12 (38)	3 (27)	9 (43)	0.465
Prior atrial fibrillation	5 (16)	3 (27)	2 (10)	0.310
Coronary artery disease	12 (38)	5 (45)	7 (33)	0.703
Stroke	1 (3)	0 (0)	1 (5)	1.000

Values are mean ± SD or n (%) unless otherwise indicated.

aSBP = average 24-hour ambulatory systolic blood pressure; aDBP = average 24-hour ambulatory diastolic blood pressure; aHR = average 24-hour heart rate; HTN = hypertension; other abbreviations as in Tables 1 and 2.

acute hemodynamic effects of LBBA pacing as related to delivery of AVIM therapy.

In the acute study using invasive PV measurements, we found that LV contractility in subjects with normal EF was not significantly impaired by RV pacing, whether from a standard RV region or from LBBA compared with atrial pacing. This was the case for both standard pacing and pacing with short AV intervals during AVIM therapy. With longer term exposure, there was an approximately 4% (absolute) reduction in LV EF. Noninvasive PV loops suggest that there may be a reduction in LV contractility as

FIGURE 4 Noninvasive Pressure-Volume Loops During Long-Term Follow-Up

Noninvasively estimated group-averaged pressure-volume loops comparing baseline vs 6 months' follow-up in control (A) vs treatment (B) subjects. Over the follow-up period, the left ventricular (LV) end-diastolic volume increased in the control subjects (remodeling), whereas end-diastolic volume decreased in the treatment subjects (reverse remodeling). Table 5 provides details on the quantitative analysis.

LV pressure generation decreased by 11.7 mm Hg, whereas end-systolic volume remained the same. Importantly, the changes in contractility occurred with a significant reduction in LV EDV and no increase in estimated LV EDP, indicating beneficial reverse ventricular remodeling, and this suggests that the reduction of contractility is not clinically meaningful. Comparing the effects in the AVIM therapy treatment group vs those of the control group, which represents the natural progression of adverse remodeling (progressive LV dilatation), underscores the beneficial impact of AVIM therapy on cardiac remodeling.

Using a noninvasive approach to PV analysis, long-term AVIM therapy exerts beneficial effects on LV size. As shown in the control group of the MODERATO II study, LV EDV increased during the 6-

TABLE 5 Summary of PV Loops Hemodynamics of Subjects Participating in the Chronic Noninvasive PV Loop Substudy

	Baseline	6 Months	Change	P Value Baseline vs 6 Months	P Value Treatment vs Control
Treatment (n = 21)					
Office SBP, mm Hg	158.2 ± 19.1	146.5 ± 16.6	−11.7 ± 21.8	0.023	0.147
Office DBP, mm Hg	85.2 ± 10.3	79.6 ± 13.8	−5.6 ± 14.2	0.087	0.800
EDV, mL	118.1 ± 30.3	110.6 ± 27.9	−7.5 ± 19.8	0.096	0.005
ESV, mL	43.6 ± 15.9	45.5 ± 15.1	1.9 ± 10.9	0.431	0.233
EF, %	63.7 ± 6.4	59.4 ± 6.2	−4.3 ± 6.1	0.004	0.175
E/e'	11.7 ± 5.7	11.0 ± 3.9	−0.71 ± 3.9	0.415	0.916
eEDP, mm Hg	18.9 ± 3.4	18.5 ± 2.3	−0.42 ± 2.3	0.414	0.915
E_a, mm Hg/mL	2.0 ± 0.6	2.1 ± 0.5	0.10 ± 0.53	0.424	0.359
Control (n = 11)					
Office SBP, mm Hg	160.2 ± 12.8	162.5 ± 30.9	2.2 ± 30.8	0.814	
Office DBP, mm Hg	83.1 ± 11.2	78.7 ± 9.8	−4.4 ± 7.8	0.090	
EDV, mL	111.0 ± 12.4	125.0 ± 19.8	14.0 ± 18.1	0.028	
ESV, mL	42.3 ± 8.3	49.1 ± 10.4	6.8 ± 10.9	0.064	
EF, %	62.1 ± 4.8	60.9 ± 4.0	−1.2 ± 6.2	0.547	
E/e'	10.5 ± 2.3	10.0 ± 4.1	−0.54 ± 5.24	0.741	
eEDP, mm Hg	18.2 ± 1.4	17.9 ± 2.4	−0.32 ± 3.12	0.547	
E_a, mm Hg/mL	2.1 ± 0.3	2.0 ± 0.7	−0.11 ± 0.7	0.612	

EF = ejection fraction; E/e' = ratio of Doppler-derived peak E and e' waves; other abbreviations as in Tables 2 and 4.

TABLE 6 Number of Medication Changes (Any Increase or Decrease in Dose) Between Baseline and 6-Month Follow-Up by Study Group and Drug Class (for All Subjects Included in the Chronic PV Loop Study)

	Treatment		Control	
Subjects with a change in medications	3 (14%)		2 (18%)	
	Increase	Decrease	Increase	Decrease
Diuretic	3	2	1	1
ACE inhibitor	0	1	1	1
ARB	1	1	0	1
Beta-blocker	1	1	0	0
Potassium-sparing diuretics	1	0	0	0
CCB	0	1	1	0
Sum of all changes	6	6	3	2

Abbreviations as in Table 1.

month follow-up period. Such a change is referred to as ventricular remodeling and is, in part, a consequence of progressively increased wall stress imposed on the myocardium with chronic pressure overload, one of the adverse consequences of persistent uncontrolled HTN. In the MODERATO II treatment group, remodeling was not only prevented but was reversed, a phenomenon known as reverse remodeling (Central Illustration). The primary focus of the MODERATO II study was to examine the impact of AVIM therapy on blood pressure and safety. The study showed an average 12.4 mm Hg reduction in oSBP and a 11.1 mm Hg reduction in aSBP despite nearly constant antihypertensive therapies with no safety concerns. The effects on oSBP were maintained throughout 24 months of follow-up. The current analysis extends these findings by looking at the short- and long-term mechanisms associated with the clinical effects seen.

STUDY LIMITATIONS. In the acute studies of invasive studies of PV loops, E_{es} and V_O were determined by the widely used single-beat method.[9,10] A more accurate means of assessing these parameters involves use of transient inferior vena cava occlusion. This would require obtaining additional vascular access and result in longer procedure times; it was therefore deemed unjustifiable for the purposes of the current study. Furthermore, many of the relevant findings are evident by examining the configuration of the PV loops without the need to resort to evaluation of the PV relations. For example, it is worth noting the minimal changes in the contour of the PV loop comparing atrial vs ventricular pacing from either the RV or LBBA (Figures 2A and 2C). Nevertheless, it could be that a more accurate means of assessing E_{es} and V_O would have been more sensitive in detecting pacing site-related changes on contractility. In addition, the impact of 6-month exposure to AVIM therapy on LV size and function are from a subset of MODERATO II subjects with technically suitable echocardiographic images, resulting in an unbalanced number of control and treatment patients. Nevertheless, there were no significant differences in baseline characteristics between the included control and treatment subjects. The chronic study relied on noninvasive assessments of PV loops based on echocardiographic measurement of volumes, which are subject to variability due to different angles of the imaging plane. Finally, in the chronic setting, we examined AVIM delivered only through

RV pacing; delivery of AVIM through LBBA pacing may have obviated the small reduction in LV EF and contractility noted by noninvasive PV analysis.

CONCLUSIONS

In this acute study using invasive PV analysis, we showed that the predominant mechanism by which AVIM therapy reduces blood pressure is reduction of LV preload and afterload without compensatory sympathetic activation. AVIM therapy is equally effective in the acute setting whether delivered from a standard RV lead location or from LBBA (CSP). Furthermore, in these subjects with normal EF, RV pacing from either a standard lead location or LBBA did not have a significant acute effect on LV contractility compared with that measured during atrial pacing with intrinsic conduction. In a separate cohort, noninvasive PV analysis revealed that long-term AVIM therapy not only prevented but reversed the progressive increase of LV volume seen in the control group (ie, AVIM therapy induced ventricular reverse remodeling). Data from these acute and chronic PV loop studies support the mechanism of action and show a favorable impact of AVIM therapy on cardiovascular hemodynamics. The ongoing BACKBEAT pivotal study will include patients receiving AVIM through both RV pacing and CSP to further elucidate the long-term impact of pacing site on AVIM therapy and LV function.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A large proportion of patients with a pacemaker have HTN that is poorly controlled despite medical therapy. With increased duration of exposure to high blood pressures, myocardial mass increases and the LV chamber increases in size, a process called remodeling. AVIM therapy is a pacemaker-based approach that reduces blood pressure through delivery of repeating sequences of short and longer AV intervals. Over a 6-month period, the blood pressure reductions achieved with delivery of AVIM therapy were statistically and clinically significant, sustained in nature, and reversed LV chamber enlargement, a process called "reverse" remodeling.

TRANSLATIONAL OUTLOOK: An ongoing prospective, randomized, double blind, pivotal study (the BACKBEAT trial) is investigating the safety and efficacy of AVIM therapy as a treatment for HTN in patients with a guideline indication for a dual-chamber pacemaker.

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APPENDIX For a supplemental figure and table, please see the online version of this article.