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Left bundle branch area pacing is associated with higher cardiac baroreflex sensitivity during orthostatic challenge

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Cardiac baroreflex function during orthostatic challenge remains poorly characterized in chronically paced patients. While conventional right ventricular (RV) pacing induces non-physiological activation, left bundle branch area pacing (LBBAP) restores near-normal ventricular activation. We compared their effects on cardiac baroreflex sensitivity (BRS) during standardized orthostatic challenge. We prospectively studied 100 patients with atrioventricular block—50 LBBAP, 50 RV pacing (25 apical pacing, 25 septal pacing). At 3 months, all underwent a standardized protocol (supine–tilt–recovery; 45°). Continuous beat-to-beat hemodynamics were recorded, and BRS was assessed using the sequence method alongside baroreflex effectiveness index (BEI). LBBAP was independently associated with significantly higher BRS compared to RV pacing across all phases (β = + 6.8 ms/mmHg; 95% CI + 3.9 to + 9.7; $p < 0.001$). At rest, BRS was significantly higher in LBBAP versus RV pacing (15.37 ± 6.05 vs. 8.19 ± 4.35 ms/mmHg). Both groups showed tilt-induced BRS reduction; however, during head-up tilt, BEI decreased in the RV pacing group ($p = 0.018$), while no significant within-group change was observed in the LBBAP group. A significant inverse ΔHR–ΔBRS association was observed only in LBBAP (ρ = − 0.43; $p = 0.0016$). No between-group differences in blood pressure or heart rate were observed. LBBAP is associated with higher baroreflex gain and preserved chronotropic–baroreflex coupling compared with RV pacing, despite comparable systemic hemodynamic responses. These findings suggest an association between ventricular activation pattern and autonomic cardiovascular regulation. The potential implications for arrhythmic risk and long-term outcomes require confirmation in dedicated outcome studies.

Keywords Left bundle branch area pacing, Baroreflex sensitivity, Autonomic regulation, Orthostatic challenge, Conduction system pacing

Permanent cardiac pacing remains the cornerstone of therapy for atrioventricular conduction disturbances[1–3]. Conventional right ventricular (RV) pacing, however, induces a non-physiological ventricular activation sequence with well-established electrical and mechanical consequences[4,5]. While pacing-induced ventricular dyssynchrony and its impact on left ventricular function have been extensively studied[6,7], the effects of different pacing strategies on autonomic cardiovascular control remain poorly characterized. Ventricular activation pattern may influence autonomic integration through electromechanical interactions affecting arterial loading conditions and baroreflex responsiveness[8].

Left bundle branch area pacing (LBBAP) has emerged as a physiological pacing strategy that enables near-normal ventricular activation[9–11]. It has demonstrated superiority in preserving electrical synchrony and mechanical efficiency[9,10,12], but its effect on spontaneous cardiac baroreflex control in humans remains unknown.

Cardiac baroreflex sensitivity (BRS) is a key mechanism of short-term cardiovascular regulation and a validated marker of cardiovagal integrity[13–15]. In healthy individuals, BRS is dynamically modulated during postural change, with attenuation during head-up tilt and recovery upon return to the supine position[14,16–18].

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Despite its physiological and clinical importance, baroreflex function has not been systematically evaluated in chronically paced patients without overt heart failure[19]. Although autonomic dysfunction has been linked to arrhythmic risk, heart failure progression, and adverse cardiovascular outcomes, autonomic endpoints have rarely been incorporated into pacing studies. Major clinical studies evaluating pacing strategies—including BLOCK-HF, BIOPACE, and more recently studies of conduction system pacing such as I-CLAS—have mainly focused on electrical synchrony, echocardiographic parameters, and clinical outcome measures, leaving the impact of pacing modality on autonomic cardiovascular regulation largely unaddressed[20–22].

To date and to our knowledge, no study has directly compared the dynamic modulation of baroreflex control across pacing modalities using a standardized orthostatic challenge.

In the present study, we investigated spontaneous cardiac baroreflex dynamics in patients with atrioventricular block under chronic ventricular pacing. We compared LBBAP and conventional RV pacing during supine rest, head-up tilt, and recovery to determine whether the ventricular activation pattern is associated with differences in autonomic cardiovascular regulation.

Results

Study population and electrophysiological characterization

The final study cohort comprised 100 patients (mean age 73.1 ± 6.5 years) with high-grade atrioventricular block, equally distributed between LBBAP (n = 50) and conventional RV pacing (n = 50; 25 RV apical pacing and 25 RV septal pacing). Lead position and pacing site classification were determined using standard fluoroscopic projections and corroborated by paced QRS morphology. Baseline clinical characteristics were comparable between groups (Table 1), including left ventricular ejection fraction (54.8 ± 7.6% vs. 55.0 ± 4.5%), beta-blocker use (38% vs. 34%), and calcium channel blocker use (32% vs. 36%). Mean paced QRS duration differed significantly across pacing sites ($p < 0.001$), being longest in RV apical pacing (164.1 ± 24.0 ms), intermediate in RV septal pacing (150.2 ± 30.7 ms), and shortest in the LBBAP group (116.3 ± 13.1 ms). Pairwise comparisons confirmed significantly shorter QRS duration in the LBBAP group compared with both RV pacing sites (both $p < 0.001$). All patients successfully completed the standardized 45° head-up tilt protocol.

Pacing strategy and cardiac baroreflex sensitivity

The primary endpoint, cardiac BRS, was significantly influenced by pacing strategy across all study phases. Linear mixed-effects modelling identified LBBAP as an independent predictor of higher BRS compared to conventional RV pacing (β = + 6.8 ms/mmHg; 95% CI + 3.9 to + 9.7; $p < 0.001$), independent of age, sex, and baseline pharmacological therapy. This association was consistent across both RV apical and septal pacing sites, with no evidence of site-specific effects (Fig. 1).

The primary association remained robust in a fully adjusted sensitivity analysis incorporating all available comorbidities (diabetes mellitus, arterial hypertension, dyslipidemia, obesity, renal disease), pharmacological therapy, LVEF, paced QRS duration, and resting hemodynamics (β = + 6.52 ms/mmHg, 95% CI + 4.16 to + 8.87, $p < 0.001$) (Supplementary Table S3).

At supine rest, BRS was nearly twofold higher in the LBBAP group compared with RV pacing (15.37 ± 6.05 vs. 8.19 ± 4.35 ms/mmHg). Both groups experienced the expected reduction in BRS during head-up tilt ($p < 0.001$), although LBBAP was associated with higher absolute values across all phases (Fig. 2; Table 2). No significant interaction between pacing strategy and study phase was observed ($p = 0.14$). Subgroup analysis confirmed higher BRS in LBBAP compared with both RV apical and septal pacing ($p < 0.001$), with no differences between RV pacing sites (Supplementary Fig. S1).

Variable †	RV pacing (n = 50)	LBBAP (n = 50)	*p*-value ‡
Age (years)	73.3 ± 5.8	72.9 ± 7.2	0.772
Male sex, n (%)	30 (60%)	28 (56%)	0.840
LVEF, %	54.8 ± 7.6	55.0 ± 4.5	0.874
Hypertension, n (%)	45 (90%)	47 (94%)	0.715
Diabetes mellitus, n (%)	17 (34%)	21 (42%)	0.537
Chronic Kidney Disease, n (%)	8 (16%)	12 (24%)	0.453
Dyslipidemia, n (%)	29 (58%)	41 (82%)	0.016 *
Obesity, n (%)	9 (18%)	12 (24%)	0.623
Beta-blockers, n (%)	19 (38%)	17 (34%)	0.835
Calcium channel blockers, n (%)	16 (32%)	18 (36%)	0.833
ACE inhibitors, n (%)	20 (40%)	17 (34%)	0.679
ARBs, n (%)	12 (24%)	14 (28%)	0.820
Diuretics, n (%)	29 (58%)	27 (54%)	0.840

Table 1. Baseline characteristics of the study population. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LBBAP, left bundle branch area pacing; LVEF, left ventricular ejection fraction; RV, right ventricular pacing. †Values are presented as mean ± standard deviation or n (%), as appropriate. ‡*P*-values refer to between-group comparisons using Student's t-test for continuous variables and Fisher's exact test for categorical variables. * $p < 0.05$.

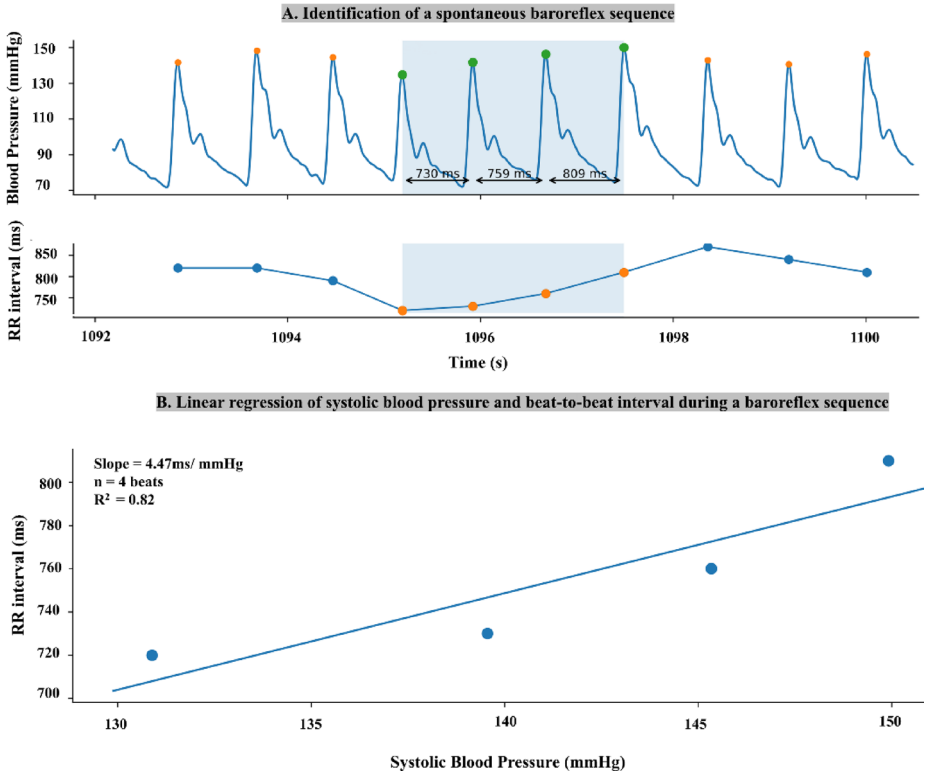


Fig. 1. Illustration of the sequence method for BRS. *Panel A*: Representative spontaneous baroreflex sequence showing concordant beat-to-beat changes in SBP and RR interval over at least three consecutive cardiac cycles. The shaded region highlights a representative sequence with progressive SBP increases accompanied by RR interval prolongation. *Panel B:* Linear regression between SBP and RR values derived from the selected sequence. Each point represents a cardiac cycle. The slope of the regression line (ms/mmHg) represents BRS, reflecting the magnitude of reflex chronotropic response to spontaneous blood pressure fluctuations; BRS, baroreflex sensitivity; SBP, systolic blood pressure.

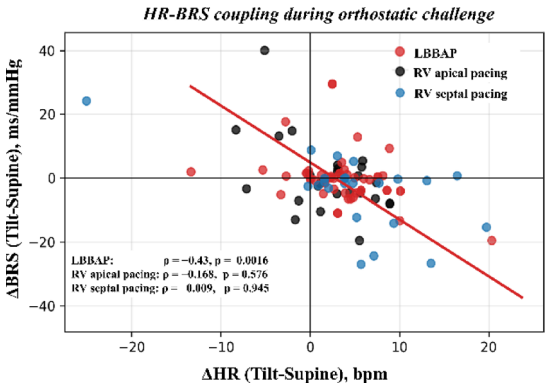


Fig. 2. Dynamic modulation of cardiac BRS during postural challenge according to pacing strategy. Mean BRS values during supine rest (S1), head-up tilt, and supine recovery (S2) in patients with LBBAP and conventional RV pacing. * $p < 0.05$ for LBBAP versus conventional RV pacing within the same study phase. † $p < 0.05$ for the within-group comparison between S1 and head-up tilt in patients undergoing LBBAP only. Shaded areas represent 95% confidence intervals around the mean. BRS, baroreflex sensitivity; LBBAP, left bundle branch area pacing; RV, right ventricular pacing.

Effect	β	95% CI	*p*-value
A: Inferential analysis[†]			
Group (LBBAP vs RV)	+ 6.8	+ 3.9 to + 9.7	< 0.001
Phase (Tilt vs S1)	− 2.4	− 3.4 to − 1.5	< 0.001
Phase (S2 vs S1)	+ 0.8	− 0.3 to + 1.9	0.14
Interaction (Group × Tilt)	− 1.2	− 2.8 to + 0.4	0.14
Interaction (Group × S2)	+ 0.87	− 1.24 to + 2.97	0.421
	Phase	**LBBAP (n = 50)**	**RV pacing (n = 50)**
B. Descriptive values by study phase[‡]			
BRS (ms/mmHg)	*S1*	15.37 ± 6.05	8.19 ± 4.35
	Tilt	12.29 ± 5.44	6.36 ± 4.58
	S2	15.04 ± 6.49	6.17 ± 4.27

Table 2. Cardiac baroreflex sensitivity (BRS) according to pacing strategy and study phase. [†] Fixed-effects estimates from the linear mixed-effects model accounting for repeated measurements within individuals, including the main effects of pacing group and study phase, as well as the Group × Phase interaction terms. Model: BRS ~ Pacing Group × Phase + Age + Sex + Beta-blocker use + Calcium channel blocker use + (1 | Subject). Reference categories: conventional RV pacing and S1 (supine rest). ‡ Phase-specific descriptive BRS values are presented as mean ± standard deviation. BRS, baroreflex sensitivity; CI, confidence interval; LBBAP, left bundle branch area pacing; RV, right ventricular pacing; S1, supine rest; S2, supine recovery.

Baroreflex effectiveness index

In contrast to BRS, the baroreflex effectiveness index (BEI) showed a phase-dependent pattern (Supplementary Table S1). Phase-specific BEI values were 5.80 ± 2.01%, 6.41 ± 2.47%, and 6.27 ± 2.31% in the LBBAP group and 6.19 ± 2.00%, 5.52 ± 1.94%, and 5.87 ± 2.04% in the RV pacing group during S1, Tilt, and S2, respectively. No significant overall between-group difference was observed. During head-up tilt, BEI decreased in the RV pacing group ($p = 0.018$), whereas no significant within-group change was observed in the LBBAP group ($p = 0.074$). A significant Group × S2 interaction was observed (β = + 0.78, 95% CI + 0.03 to + 1.53, $p = 0.044$), indicating higher BEI recovery in the LBBAP group during the post-tilt supine phase. This finding should be interpreted with caution given its exploratory nature.

Autonomic integration and hemodynamic profile

Autonomic (de)coupling was assessed as a prespecified mechanistic endpoint by examining the relationship between changes in heart rate (ΔHR) and baroreflex sensitivity (ΔBRS) during orthostatic challenge. A significant inverse association between ΔHR and ΔBRS during head-up tilt was observed in the LBBAP group (Spearman ρ = − 0.43; $p = 0.0016$), whereas no significant association was observed in RV apical pacing (ρ = − 0.168; $p = 0.576$) or RV septal pacing (ρ = 0.009; $p = 0.945$) (Fig. 3). Formal between-group comparison using Fisher's z-transformation did not reach statistical significance (LBBAP vs. RV combined: z = − 1.84, $p = 0.066$), although the confidence interval for the LBBAP correlation was entirely below zero, whereas those for both RV pacing subgroups spanned zero. SBP and HR trajectories during rest, head-up tilt, and recovery were comparable between pacing strategies ($p > 0.05$) (Supplementary Figure S2).

Discussion

Physiological pacing and autonomic integrity

The main finding of this study is that the ventricular activation pattern is closely associated with cardiac autonomic regulation in chronically paced patients. While conventional RV pacing has long been associated with electrical and mechanical dyssynchrony,[4,5] our data suggest that differences in ventricular activation pattern are associated with differences in the mechanisms involved in short-term cardiovascular regulation. Specifically, LBBAP was independently associated with higher cardiac BRS across all study phases compared with conventional RV pacing, with values nearly twofold higher at rest. This association remained significant independent of age, sex, and medical therapy and was consistent across physiological conditions, with no significant interaction between pacing strategy and study phase. The robustness of this association was further confirmed in a fully adjusted sensitivity model, in which adjustment for all available comorbidities, pharmacological therapy, ventricular function parameters, and resting hemodynamics yielded a consistent estimate. Notably, dyslipidemia—which was more prevalent in the LBBAP group (82% vs. 58%, $p = 0.016$)—was independently associated with lower BRS in the sensitivity model (β = − 3.68 ms/mmHg, $p < 0.001$). Adjustment for dyslipidemia—which was more prevalent in the LBBAP group—did not alter the primary association, confirming that the between-group differences did not confound the primary finding. Taken together, these findings suggest that pacing modality is associated with differences in complementary aspects of baroreflex function.

Although BEI did not differ between groups, BRS was consistently higher in the LBBAP group, suggesting a stronger reflex response once engaged. This pattern is consistent with higher cardiovagal gain in patients undergoing physiological pacing.

The observed differences in baroreflex gain may be related to differences in ventricular activation pattern. Physiological activation through LBBAP results in more synchronous ventricular depolarization and

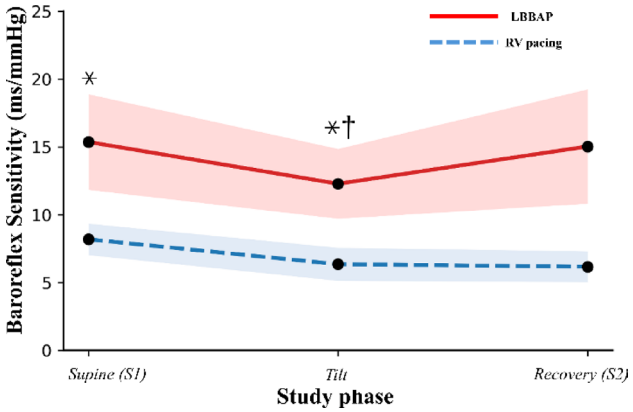


Fig. 3. Differential heart rate–baroreflex coupling during orthostatic challenge according to pacing strategy. Scatter plot illustrating the relationship between changes in heart rate (ΔHR) and baroreflex sensitivity (ΔBRS) from supine rest (S1) to head-up tilt. Each point represents an individual patient, stratified by pacing strategy (LBBAP, RV apical pacing, and RV septal pacing). The red regression line is shown for the LBBAP group only, as no statistically significant association was observed in either RV pacing subgroup. Spearman correlation coefficient for LBBAP: $\rho = -0.43$ (95% CI, −0.63 to −0.17; $p = 0.0016$). Formal between-group comparison using Fisher's z-transformation (LBBAP vs. combined RV pacing): $z = -1.84$, $p = 0.066$. HR, heart rate; BRS, baroreflex sensitivity; LBBAP, left bundle branch area pacing; RV, right ventricular pacing.

contraction, whereas conventional RV pacing induces electrical and mechanical dyssynchrony[4,5]. A plausible explanation is that differences in ventricular activation pattern may influence afferent cardiovascular signaling and baroreflex-mediated heart rate responses, potentially through changes in ventricular—arterial coupling and loading conditions[8,19]. Accordingly, higher BRS under LBBAP may be consistent with more effective autonomic regulation during orthostatic challenge, although this interpretation remains speculative.

BRS values in the LBBAP group were comparable to those reported in healthy individuals[16,23] and exceeded typical ranges observed in elderly populations, in whom spontaneous BRS often falls below 10 ms/mmHg[24]. In contrast, lower values were observed in the RV pacing group. These findings suggest that LBBAP may preserve cardiovagal function within ranges reported in healthy populations, although such comparisons should be interpreted cautiously given the differences in age, comorbidity burden, and chronic pacing status between the present cohort and published normative datasets. Furthermore, whether higher BRS values translate into improved clinical outcomes—including reduced arrhythmic risk or long-term survival benefit—cannot be determined from the present data and requires confirmation in prospective studies with long-term follow-up.

Orthostatic adaptation involves integrated autonomic responses, including cardiovagal withdrawal and sympathetic activation[25]. Although these components were not directly quantified, higher baroreflex gain under LBBAP may reflect more effective short-term cardiovascular regulation during orthostatic stress. While causality cannot be established, the consistent association between activation pattern and BRS suggests a physiologically plausible link between electrical synchrony and autonomic integrity[8,19]. Direct assessment of sympathetic activity, ventricular–arterial coupling, or autonomic neural signaling was beyond the scope of the present study. Future studies incorporating these measurements are necessary to elucidate the mechanisms underlying the observed associations.

Reflex gain vs. reflex effectiveness

Beyond baroreflex gain, reflex effectiveness assessed by BEI showed contrasting within-group responses during orthostatic stress. In the LBBAP group, BEI remained stable from supine rest to head-up tilt, whereas conventional RV pacing was associated with a reduction in reflex engagement during tilt. This pattern is consistent with more stable baroreflex engagement during orthostatic stress in the LBBAP group, in contrast to a more variable response with conventional RV pacing. These findings highlight the complementary nature of BRS and BEI, which reflect distinct physiological components of autonomic regulation: while BRS quantifies the magnitude of the chronotropic response once a sequence is engaged, BEI reflects the proportion of spontaneous blood pressure fluctuations that are accompanied by a detectable baroreflex sequence[26]. The absence of a significant between-group difference in BEI despite consistently higher BRS values suggests that reflex engagement was broadly preserved in both pacing groups, while reflex gain was substantially greater in patients undergoing LBBAP. This dissociation supports the concept that pacing modality may influence the strength of baroreflex-mediated cardiac responses without necessarily altering the frequency with which spontaneous blood pressure fluctuations are accompanied by a detectable baroreflex sequence.

Importantly, these differences were not accompanied by significant between-group differences in SBP or HR, indicating that alterations in reflex engagement may occur independently of global hemodynamic responses. This is consistent with prior observations that baroreflex indices capture aspects of autonomic regulation not reflected in conventional hemodynamic measures[13,14].

Integrated chronotropic-baroreflex coupling

As a prespecified mechanistic endpoint, autonomic (de)coupling was assessed by examining the relationship between changes in HR (ΔHR) and BRS (ΔBRS) during orthostatic challenge. In healthy individuals, orthostasis is characterized by sinus-mediated heart rate increase accompanied by baroreflex withdrawal[14,16,17]. In our cohort with high-grade atrioventricular block under atrial-sensed ventricular pacing, ventricular rate tracks sinus activity while ventricular activation remains paced, making HR–BRS coupling an informative marker of integrated autonomic control across pacing strategies.

A significant inverse HR–BRS association was observed in the LBBAP group but not in either RV pacing subgroup (Fig. 3), and formal between-group comparisons did not reach statistical significance. This pattern is consistent with more coordinated autonomic regulation under LBBAP, in which sinus—mediated chronotropic responses and baroreflex gain change in a physiologically coherent direction during orthostatic stress. The absence of such coupling in the RV pacing groups suggests attenuation of integrated autonomic control, which may reflect the downstream consequences of non—physiological ventricular activation on cardiovagal regulation, although this interpretation remains speculative.

Clinical relevance and future directions

Reduced cardiac BRS is a well-established marker of impaired autonomic regulation and has been consistently associated with increased arrhythmic vulnerability and sudden cardiac death[14,15,27,28]. The preservation of BRS and chronotropic-baroreflex coupling observed with LBBAP may have clinical implications, although these remain hypothesis-generating in the absence of longitudinal outcome data.

In our study, LBBAP was associated with higher BRS and preserved chronotropic—baroreflex coupling, whereas conventional RV pacing was associated with lower BRS values and absence of significant HR-BRS coupling. Impaired baroreflex function has been linked to heightened sympathetic activation and increased electrical instability, contributing to arrhythmogenesis[29–31]. These observations are consistent with emerging clinical data supporting a potential anti-arrhythmic benefit of conduction system pacing. In the I-CLAS study, LBBAP was associated with a reduced incidence of both atrial and ventricular arrhythmic events in patients with heart failure[22]. However, whether the observed differences in autonomic indices translate into clinical benefit requires evaluation in studies with long-term follow-up and pre-specified clinical endpoints.

Limitations

Several limitations should be considered. This was a single-center prospective study with a moderate sample size. Baroreflex assessment was based on spontaneous blood pressure and HR fluctuations. Although well validated, this approach is sensitive to inter-individual variability. Non-invasive beat-to-beat monitoring, while providing high-fidelity data, does not fully replicate invasive measurements. Finger cuff-based arterial pressure recording is subject to potential signal attenuation during peripheral vasoconstriction, particularly during head-up tilt, and may introduce absolute pressure offsets compared with intra-arterial measurements. However, both groups were assessed under identical conditions using the same device and protocol, such that any systematic measurement error would affect both equally and is unlikely to account for the observed between-group differences in BRS.

The 45° tilt angle represents a methodological limitation. The 45° protocol was not intended to induce vasovagal syncope but rather to elicit a reproducible orthostatic stimulus capable of engaging short-term cardiovascular regulatory mechanisms, including baroreflex-mediated chronotropic responses. This angle was selected to provide a standardized orthostatic stimulus while minimizing vasovagal reactions in an elderly, chronically paced population. An additional practical consideration was the maximum inclination supported by the tilt table available in our laboratory. Although higher tilt angles (60–70°) are commonly used in diagnostic tilt-testing protocols, in our study, the 45° protocol elicited consistent hemodynamic and baroreflex responses in both groups[32].

As ventricular activation was entirely device-mediated in all patients, the documented differences in BRS should be interpreted as associations between device-mediated activation pattern and cardiovagal reflex integrity. Pre-implant baroreflex assessment was not feasible in this population, given that all patients presented with high—grade atrioventricular block requiring immediate pacing. Moreover, the marked sympathetic activation and hemodynamic instability inherent to complete atrioventricular block at slow ventricular escape rates would have precluded valid baseline autonomic measurements and rendered any pre-implant comparison physiologically meaningless.

The non-randomized design is the primary methodological limitation of this study. Although formal randomization was not performed, pacing strategy was determined by bed allocation within the same ward: patients admitted under one operator's care received LBBAP, while those admitted under the second operator received conventional RV pacing. This allocation mechanism was not based on patient clinical characteristics and reduces, but does not eliminate, the likelihood of systematic selection bias; residual unmeasured confounding therefore cannot be excluded. However, patients were prospectively screened using predefined eligibility criteria, enrollment was completed before autonomic testing and outcome analysis, and baseline clinical characteristics and medical therapy were comparable between groups. Pharmacological therapy may nevertheless influence autonomic measurements. Beta-blockers and calcium channel blockers can affect heart rate responses and baroreflex indices. Although the prevalence of these medications was balanced between groups and the primary analyses were adjusted for baseline pharmacological therapy, residual medication—related confounding cannot be completely excluded. Confirmation of these findings in larger multicenter cohorts would be needed to establish the robustness and broader applicability of the observed associations.

Finally, the study reflects a single time-point assessment at 3 months post-implantation and does not address longitudinal autonomic adaptation, arrhythmia burden, pacing—induced cardiomyopathy, or other long—

term clinical outcomes. Accordingly, the link between preserved BRS and long-term clinical benefit remains hypothesis-generating.

Conclusions

LBBAP was associated with higher cardiac BRS and preserved chronotropic—baroreflex coupling during orthostatic challenge compared with conventional RV pacing. These findings identify a consistent association between ventricular activation pattern and cardiovagal reflex integrity, extending observations beyond established differences in mechanical synchrony.

The baroreflex—related autonomic coordination observed with LBBAP may have physiological relevance. Whether these autonomic differences translate into improved hemodynamic adaptation, reduced arrhythmic burden, or other clinical benefits requires evaluation in prospective studies with long-term follow-up and dedicated outcome assessment.

Materials and methods

Study design and patient selection

Patients were prospectively enrolled from a consecutive cohort of 534 pacemaker recipients between February and November 2025. Of these, 218 were excluded because they received single-chamber pacing systems and were therefore ineligible for the study protocol. Of the remaining 316 patients, 216 were excluded because of sinus node dysfunction (n = 174), persistent atrial arrhythmias (n = 34) or frequent supraventricular ectopy (n = 8). The remaining 100 patients met all eligibility criteria and were enrolled simultaneously into the two study groups (50 LBBAP and 50 conventional RV pacing). Enrollment continued until the predefined sample size for each group was reached and was completed before autonomic testing and outcome analysis were performed (Supplementary Figure S3).

In routine clinical practice at our center, pacing strategy reflected the operator-specific implantation pathway within the same ward. Specifically, patients admitted to beds assigned to one operator underwent LBBAP, while those admitted to beds assigned to the second operator received conventional RV pacing. Eligible patients were screened consecutively within each operator—specific admission pathway using predefined eligibility criteria. Pacing strategy was not randomized and reflected routine clinical practice at our institution. All patients were evaluated at a standardized 3-month follow-up visit.

Exclusion criteria included persistent atrial fibrillation, clinically significant sinus node dysfunction requiring atrial pacing or precluding reliable atrial sensing, pacing indications other than atrioventricular block, and inability to maintain stable atrial-sensed ventricular pacing (As/Vp) during the study protocol. All devices were programmed in DDD mode. The lower rate limit was set at 50 bpm and the upper tracking rate and sensor at 130 bpm. Rate—response functionality was disabled in all patients. Programmed sensed and paced AV delays were standardized at 120 ms and 150 ms, respectively. Rate-smoothing and other rate-adaptive algorithms were not activated. All patients included in the study demonstrated atrial—sensed ventricular—paced rhythm (As/Vp) with a ventricular pacing burden > 95%. Patients requiring atrial pacing were excluded from enrollment, resulting in an atrial pacing burden < 2% in the final study population. Patients with frequent supraventricular ectopy were also excluded from the study. Beat sequences containing ectopic beats, signal artefacts, or non-physiological blood pressure recordings were automatically excluded from baroreflex sequence analysis according to the predefined criteria of the sequence method.

All patients were in stable sinus rhythm (resting atrial rate > 50 bpm), allowing consistent As/Vp during testing. Patients were clinically stable and receiving chronic medical therapy. Medications with potential autonomic effects, including beta-blockers and calcium channel blockers were balanced between groups (Table 1), and analyses were adjusted for baseline pharmacological therapy.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania (approval number 530/5.02.2025). Written informed consent was obtained from all participants prior to enrollment in the study.

Implantation technique

Implantation procedures were performed using standard transvenous techniques. All patients were implanted with Medtronic/ Vitatron (*Minneapolis, MN, USA*) pacing systems. Venous access was obtained via the cephalic or subclavian vein according to anatomical considerations. As previously described[33], for LBBAP, a Medtronic 3830 lumenless pacing lead was delivered through a C315 His or C304 delivery sheath. Septal engagement and lead positioning were guided fluoroscopically using right anterior oblique (RAO 30°) and left anterior oblique (LAO 40°) projections using a Ziehm Imaging system (*Ziehm Imaging GmbH, Nuremberg, Germany*). Conventional RV pacing was achieved using standard active-fixation leads for septal positioning and passive-fixation leads for right ventricular apical pacing. In all patients, atrial leads were Medtronic passive-fixation leads positioned in the right atrium.

Electrical measurements

Electrical data were recorded intraprocedurally using the EP Tracer-2 system (*Schwarzer Cardiotek*, *Germany*). The procedural endpoint for physiological pacing was achievement of LBBAP, confirmed according to European Heart Rhythm Association (EHRA) consensus criteria[10]. The same system and standardized intraoperative 12-lead electrocardiographic monitoring were used during conventional RV pacing to document paced QRS morphology and electrical parameters, ensuring uniform assessment across pacing modalities.

Autonomic and hemodynamic assessment

Orthostatic challenge was performed using a standardized passive head-up tilt protocol on a motorized tilt table (*Trumpf Medical, Germany*). Following a 10-min stabilization period, the protocol consisted of three 10-min phases: supine rest (S1), 45° head-up tilt, and supine recovery (S2). Continuous non-invasive beat-to-beat arterial pressure waveforms were recorded using a finger cuff system based on the volume clamp method (*CNAP system, CNSystems, Graz, Austria*). The initial CNAP calibration sequence (~ 20 s) was excluded from analysis, with T0 defined as the first valid beat following calibration. Analysis included the entire recording following the initial CNAP calibration to capture both the instant and sustained autonomic responses to orthostatic challenge. Signals were recorded throughout all phases and used for the analysis of SBP, HR, and cardiac BRS.

Assessment of cardiac baroreflex sensitivity

Cardiac BRS was quantified using the sequence method, as previously described[13]. Before baroreflex analysis, all CNAP recordings were visually reviewed in LabChart (*ADInstruments, Sydney, Australia*) to verify signal quality, identify recording artefacts or interruptions, and confirm correct beat detection. Only recordings meeting predefined quality criteria were included in the final analysis. A baroreflex sequence was defined as a run of at least 3 consecutive cardiac cycles in which SBP and RR intervals changed in the same direction (concordant increases or decreases), with a minimum change of ≥ 1 mmHg per beat for SBP and ≥ 5 ms per beat for RR interval (Fig. 1). A dynamic time lag of up to three cardiac cycles between SBP and RR interval changes was applied to account for the physiological delay in the chronotropic baroreflex response. For each sequence, linear regression between SBP and RR interval values was performed, and the slope (ms/mmHg) was taken as an estimate of BRS. Only sequences with a Pearson correlation coefficient $r \geq 0.80$ were retained. Upward and downward sequences were analyzed separately. BRS was defined as the mean of upward and downward sequence slopes for each recording period. Group-level values are reported as mean ± SD. BEI was calculated as the proportion of spontaneous SBP ramps followed by identifiable baroreflex sequences. BEI values are expressed as percentages. These complementary metrics capture distinct aspects of baroreflex function and are not necessarily expected to change in parallel[26]. Quality-control metrics, including the number of valid upward, downward, and total baroreflex sequences per phase and group, are provided in Supplementary Table S2.

Study endpoints

The primary endpoint of the study was cardiac BRS, defined as the mean sequence slope for each phase of the study protocol. Secondary endpoints included BEI. A prespecified mechanistic endpoint assessed autonomic (de)coupling, defined as the relationship between changes in HR (ΔHR) and BRS (ΔBRS) across postural phases.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate based on the distribution of the data. Baroreflex parameters were analyzed using linear mixed-effects models with the following structure: BRS ~ PacingGroup × Phase + Age + Sex + Betablockers + Calcium channel blockers + (1 | Subject), where Pacing group (LBBAP vs. conventional RV pacing) and Phase (S1, Tilt, S2; with S1 as reference) were included as fixed effects along with their interaction term, and subject was included as a random intercept to account for within -subject correlation across phases. RV apical and RV septal pacing were first examined separately; the absence of significant site-specific differences at any phase (all pairwise comparisons $p > 0.80$ assessed using mixed-effects models including pacing site, orthostatic phase, and site-by-phase interaction terms) supported their pooling as a single comparator group. Confidence intervals for key contrasts were computed using the Wald method. No formal correction for multiple comparisons was applied across phases, as the primary contrast of interest was the main effect of pacing group averaged across phases. Model diagnostics including residual plots were examined to confirm adequate model fit.

The association between changes in HR (ΔHR) and BRS (ΔBRS) from supine rest to head-up tilt was assessed using Spearman's rank correlation, performed separately by pacing strategy. Between-group differences in correlation coefficients were assessed using Fisher's z-transformation. Statistical significance was defined as a two-sided p-value < 0.05. All statistical analyses were performed using R version 4.3.2 (*R Core Team, Vienna, Austria*) with the *lme4* (version 1.1–35) and *lmerTest* (version 3.1–3) packages. Satterthwaite-approximated degrees of freedom were used for inference. Full sensitivity analyses adjusting for diabetes, hypertension, diuretics, renal disease, LVEF, paced QRS duration, obesity, dyslipidemia and resting hemodynamics are presented in Supplementary Table S3.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Author contributions

I.T., R.I, I.P.P conceived and designed the study, performed patient enrollment and clinical evaluation, supervised data acquisition, performed data analysis and interpretation, and drafted the manuscript. I.I.C.E, I.P.P., M.S.C.H contributed to patient data collection, data organization, literature review, and manuscript revision. K.C., C.L. contributed to data interpretation, critical scientific revision of the manuscript, and methodological refinement.

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Declarations

Competing interests

The authors declare that there are no real, potential, or perceived conflicts of interest related to this study.

Additional information

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