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# New-onset atrial high-rate episodes in left bundle branch area pacing versus right ventricular pacing for patients with atrioventricular block

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**New-onset atrial high-rate episodes in left bundle branch area pacing versus right ventricular pacing for patients with atrioventricular block**

**Short title:** Atrial high-rate episodes in LBBAP vs. RVP

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**WHAT'S NEW?**

Left bundle branch area pacing (LBBAP) demonstrated a lower incidence of new-onset atrial high rate episodes (AHREs), and LBBAP was associated with a significantly reduced risk of new-onset AHREs by 73% compared with right ventricular pacing (RVP) among atrioventricular block (AVB) patients.

LBBAP showed stable left ventricular ejection fraction and decreased left atrial diameter compared with RVP at 1-year follow up.

**ABSTRACT**

**Background:** Left bundle branch area pacing (LBBAP) has demonstrated beneficial effects on clinical outcomes. Comparative data on the risk of atrial high-rate episodes (AHREs) between LBBAP and right ventricular pacing (RVP) are lacking.

**Aims:** This study aimed to investigate whether LBBAP can reduce the risk of new-onset AHREs compared with RVP in patients with atrioventricular block (AVB).

**Methods:** A total of 175 consecutive AVB patients undergoing dual-chamber pacemaker implantation (LBBAP or RVP) and with no history of atrial fibrillation were enrolled. Propensity score matching for baseline characteristics yielded 43 matched pairs. The primary outcome was new-onset AHREs detected on scheduled device follow-up. Changes in echocardiographic measurements were also compared between groups.

**Results:** New-onset AHREs occurred in 42 (24.0%) of all enrolled patients (follow-up 14.1 [7.5] months) and the incidence of new-onset AHREs in the LBBAP group was significantly lower than RVP (19.8% vs. 34.7%; *P* = 0.04). After propensity score matching, LBBAP still resulted in significantly lower incidence of new-onset AHREs (11.6% vs. 32.6%; *P* = 0.02), and a lower hazard ratio for new-onset AHREs compared with RVP (HR, 0.274; 95% CI, 0.113–0.692). At 1 year, LBBAP achieved preserved left ventricular ejection fraction (LVEF) (63.0 [3.2]% to 63.1 [3.1]%; *P* = 0.56), while RVP resulted in reduced LVEF (63.4 [4.9]% to 60.5 [7.3]%; *P* = 0.01]). Changes in LVEF were significantly different between 2 groups (2.6% [0.2 to 5.0]; *P* = 0.03).

**Conclusion:** LBBAP demonstrated a reduced risk of new-onset AHREs compared with RVP in patients with AVB.

**Key words:** atrial high-rate episodes, atrioventricular block, left bundle branch area pacing, right ventricular pacing

## INTRODUCTION

Conventional right ventricular pacing (RVP) induces ventricular electro-mechanical dyssynchrony and is associated with an increased risk of heart failure hospitalization, atrial fibrillation (AF) and mortality in patients with high pacing burden [1]. Conduction system pacing could achieve favorable ventricular synchrony [2], and both His-bundle pacing (HBP) and left bundle branch area pacing (LBBAP) have been shown to reduce the incidence of new-onset AF in bradycardia patients [3–5].

Since the presentation of AF may be asymptomatic and stored intracardiac electrograms are not always available, previous studies with clinical AF as the primary outcome should be interpreted with caution. Moreover, the patient population in previous studies was heterogeneous because it included patients with sinus node dysfunction and atrioventricular block (AVB). Atrial high-rate episodes (AHREs) represents continuous detection of atrial tachycardias by implanted cardiac devices and is strongly associated with clinical AF, elevated stroke risk and long-term mortality outcomes [6–8]. The present study was conducted to explore the effect of LBBAP on new-onset AHREs compared with RVP in patients with AVB.

## METHODS

### Study design and participants

This prospective observation study was conducted at the First Affiliated Hospital of Nanjing Medical University, Nanjing; and the Affiliated People's Hospital of Jiangsu University. Consecutive AVB patients with estimated VP >20% who underwent de novo successful dual-chamber pacemaker implantation were enrolled if they had no AF history between January 2019 and June 2022. The pacing strategies were determined by operators according to clinical practice, and it was not driven by the study. Patients were excluded if they (I) were younger than 18 years old; (II) had LVEF<50% at baseline; (III) had severe valvular disease, congenital heart disease, or hypertrophic cardiomyopathy; (IV) had myocardial infarction or open heart surgery within the past 3 months; (V) indicated for cardiac resynchronization therapy or implantable cardioverter defibrillator; (VI) combined serious diseases such as malignant tumor; (VII) had a previous history of hyperthyroidism; (VIII) were unavailable to be regularly followed up at the clinic visit. This study was approved by the institutional review board of both hospitals, and all patients provided written informed consent.

**Procedures**

LBBAP was performed using the Select Secure pacing lead (model 3830, 69 cm, Medtronic) delivered through a fixed curve sheath(C315HIS, Medtronic) as previously described [9]. The delivery sheath was inserted into the right ventricle over a long guide wire through the subclavian or axillary vein. The pacing lead was then advanced through the sheath to the tip of the catheter. In order to identify the potential screwing site, a His bundle electrogram was identified first, and the system was advanced 1.0–2.0 cm along an imaginary line between the His bundle and the right ventricular apex. Unipolar pacing was performed at an output of 2.0 v/0.4 ms before screwing, and the paced QRS complex in lead V1 always displayed a "W" morphology. The lead was then screwed into the interventricular septum by clockwise rotations until right bundle branch block morphology of the paced QRS complex was presented in electrocardiogram lead V1. Pacing stimulus to left ventricular activation time (LVAT) was measured at low (2.0 v/0.4 ms) and high (5.0 v/0.4 ms) outputs in lead $V_6$ repeatedly. LBBAP was considered successful if the unipolar paced QRS morphology presented with a right bundle branch block pattern along with demonstration of transition from nonselective to selective LBB/left ventricular septum during threshold testing, or shortest and constant LVAT at high and low output pacing (commonly ≤75 ms) or sudden increase in LVAT >10 ms at reduced pacing outputs. During right ventricular pacing, the right ventricular lead was inserted in standard fashion into the right ventricular septum or apex (RVA) based on operator preference.

Device programing was different between the two pacing modalities. In LBBAP group, for patients with complete AVB, the atrioventricular (AV) delay was set as 120/90 ms, whereas for patients with incomplete AVB, the AV delay was set 30 ms longer than the intrinsic AV interval if the patient had a normal intrinsic QRS complex, and 30 ms shorter than the intrinsic AV interval if the patient had baseline bundle branch block to possibly correct the electrical dyssynchronization. The automatic AV delay optimization algorithms were turned off. In RVP group, however, the AV delay was set as 150/120 ms for patients with complete AVB and 30 ms longer than the intrinsic AV interval for patients with incomplete AVB and the automatic AV delay optimization algorithms were routinely turned on to avoid unnecessary ventricular pacing for patients with intermittent AVB.

### Data collection and follow-up

Baseline demographics, comorbidities, prior medication history, electrocardiogram and echocardiographic parameters were collected. Patients underwent follow-up at 3, 6 and 12 months and annually after implantation. Pacing parameters were routinely documented. Ventricular pacing burden was recorded at the end of follow-up, censored to an early date if the primary outcome was reached. Echocardiographic evaluations were conducted at baseline and 12 months after the procedure, Biplane Simpson's method in two-dimensional transthoracic echocardiography was used for the evaluation of LVEF.

The primary outcome was new-onset AHREs detected on scheduled device follow-up. If no AHREs occurred during follow-up, patients would be censored at the last follow-up or death, once patients suffered from AHREs, the subjects were censored immediately. All data and follow-up dates were censored after June 30, 2023. AHREs was defined as events with an atrial frequency of ≥175 bpm and a duration of ≥5 min detected by pacemaker device [10]. All episodes of pacemaker-detected AHREs were documented and reviewed both by physicians and experts from the pacemaker manufacturing company.

### Statistical analysis

Continuous data are presented as mean (standard deviation), and categorical data are summarized as frequency (percentage). The $\chi^2$ or Fisher exact test was used to analyze categorical data. The Student's t-test was used to analyze continuous data. The Kaplan–Meier survival curve and log-rank test were employed to estimate cumulative event rates. The effect of individual variables on the risk of new-onset AHREs was investigated by using univariate Cox proportional hazard models applied to the whole study population. Baseline variables considered to be clinically relevant or univariate predictors with $P$ <0.1 were entered into multivariable Cox proportional hazard models.

Echocardiographic parameters were compared between groups with the analysis of covariance (ANCOVA), which took into account baseline values. To adjust for bias due to potential confounders, a propensity score was computed for eligible participants using binary logistic regression which incorporate pacing modality (LBBAP or RVP) as dependent variables and baseline variables including age, sex, heart failure, hypertension, coronary artery disease, diabetes, LVEF, left atrial diameter (LAD) and intrinsic QRS duration (QRSd) as independent variables. Then, patients were matched 1:1 with a caliper as 0.02. Analysis were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, US). Statistical significance was set at $P < 0.05$, all tests were 2 sided.

## RESULTS

### Baseline characteristics

A total of 175 consecutive patients were enrolled. LBBAP was successful in 126 patients, whereas 49 patients underwent successful RVP (30 and 19 paced from right ventricular septum and right ventricular apex, respectively) (Figure 1). In the unmatched cohort, several baseline characteristics (e.g., age, hypertension) differed significantly between the 2 groups. Because AVB was an inclusion criterion, the QRSd at baseline was slightly longer than normal values in both groups. Propensity score matching identified 43 pairs of patients with balanced baseline characteristics, which were used for the final analysis (Table 1).

### Electrophysiological and pacing characteristics

Compared with RVP, LBBAP showed lower pacing threshold, similar R wave amplitude and pacing impedance at implantation. During follow-up, the pacing threshold was comparable between the two groups, whereas better R wave amplitude and lower pacing impedance presented in the LBBAP group. LBBAP showed higher ventricular pacing percentage (VP%) (99.6 [1.0]% vs. 88.1 [20.9]%; $P = 0.001$), which maybe because the automatic AV delay optimization algorithms were turned off in this group. Paced QRSd was significantly narrower in the LBBAP group than in the RVP group (114.7 [12.2] ms vs. 167.1 [12.9] ms; $P$ <0.001). Pacing characteristics are listed in Table 2.

### Primary outcomes

During a mean follow-up duration of 14.1 (7.5) months, new-onset AHREs occurred in 42 (24.0%) of all enrolled patients and the incidence rate of new-onset AHREs in the LBBAP group was significantly lower than RVP (19.8% vs. 34.7%; $P$ = 0.04). *Table S1* in Supplementary material presents the univariate analysis of baseline characteristics and potential predisposing factors for new-onset AHREs. In multivariable analysis, LBBAP was independently associated with a lower risk of new-onset AHREs (HR, 0.368; 95% CI, 0.183–0.738; $P$ = 0.005), while age increased the risk of new-onset AHREs (Figure 2 and Figure 3). In the matched cohort, LBBAP group showed markedly longer follow-up duration than RVP: 16.0 (7.6) months and 11.8 (5.3) months, respectively ($P$ = 0.004). Nevertheless, new-onset AHREs occurred in 5 patients in the LBBAP group (11.6%), and 14 patients in the RVP group (32.6%) ($P$ = 0.02). Patients with LBBAP showed significantly higher AHREs-free survival than did patients with RVP (HR, 0.274; 95% CI, 0.113–0.692; $P$ = 0.007) (Figure 2).

### Echocardiographic measurements

Compared with baseline, LBBAP showed stable LVEF at the 1-year follow-up. On the contrary, RVP group showed decreased LVEF at the 1-year follow-up. Changes in LVEF were significantly different between treatment groups. The ANCOVA treatment effect was 2.6%, in favor of LBBAP (Table 3, Figure 4). The LAD showed a slight increase after 1 year of pacing in LBBAP group, and unchanged in RVP group, while there were no significant differences between groups. The LVEDD was nearly unchanged in both groups, and was not significantly different between groups.

## DISCUSSION

In this prospective observational study, we evaluated the differences between LBBAP and RVP on incidence of new-onset AHREs among AVB patients, and demonstrated a lower incidence of new-onset AHREs with LBBAP. LBBAP was associated with a 63% relative risk reduction compared with RVP. During a 1-year follow-up, LBBAP achieved preserved LVEF, while RVP resulted in reduced LVEF.

Previous studies have demonstrated that long-term RVP is associated with an increased risk of AF, heart failure hospitalization, and mortality [1, 11]. The risk of AF increased linearly with VP% in dual-chamber pacemaker group ([HR, 1.36; 95% CI, 1.09 – 1.69] for each 25% increase in VP%) [1]. HBP, as the most physiological pacing modality, could preserve or improve ventricular synchrony and has been associated with reduced risk of AF. Among patients with no history of AF, HBP demonstrated a lower risk of new-onset AF (HR, 0.53; 95% CI, 0.28–0.99) [3], and HBP also decreased the risk of persistent/permanent AF (HR, 0.28; 95% CI, 0.16–0.48) [12]. LBBAP, as one of the physiological pacing modalities, has been demonstrated to have obvious beneficial effect on clinical outcomes compared with RVP [13, 14]. Similar to HBP, LBBAP has been demonstrated to decrease the risk of new-onset AF, and this kind of effect seems to be more pronounced in patients with VP% ≥20% [4, 5].

Nowadays, AHREs could be continuously recorded by cardiac implantable electronic devices, with the goal of documenting episodes of AF and other atrial tachyarrhythmia. With AHREs as the primary outcome, the present study demonstrated significantly decreased incidence of new-onset AHREs compared with RVP in patients with AVB. Previous studies have showed that AHREs could increase the risk of clinical AF, ischemic stroke and mortality outcomes. In the meta-analysis by Mahajan et al. [6], patients with documented AHREs were 5.7 times more likely to have documented clinical AF during the follow-up period. An ancillary study of the MOde Selection Trial showed that the risk of death or stroke was increased by a factor of 2.5 in patients who had at least one episode of AHREs >5 min [15]. AHREs are commonly encountered in pacemaker patients without previous AF history [6], and it is of great importance to decrease the incidence of AHREs.

Factors that predispose patients to AHREs are not clear. In 2020, Witt et al. [16] found that left atrial emptying fraction and left atrial minimum volumes ($LA_{min}$) assessed by cardiac computed tomography were significantly associated with AHREs (HR, 0.95; 95% CI, 0.92–0.98, and HR, 1.02; 95% CI, 1.00–1.05). In the same year, Kishima et al. [17] found left ventricular stiffness assessed by diastolic wall strain was associated with AHREs in patients with a dual-chamber pacemaker. They speculated that increased left ventricular stiffness augmented left ventricular filling pressure, and further led to left atrial remodeling, which may then induce AHREs. Unfortunately, right ventricular pacing could result in left atrial remodeling and reduced atrial function, which may be related to elevated filling pressures and impairment of left ventricular systolic function [18]. This would explain why minimizing ventricular pacing could reduce AF incidence in patients with sinus-node disease.

However, generally minimizing ventricular pacing is not practical for patients with AVB, and physiological pacing modality may be the best option for such patients. As the most physiological pacing option for ventricular pacing, HBP resulted in a more physiological left ventricular electromechanical activation/relaxation and better left atrial function compared with RVP [19]. LBBAP has provided an alternative pacing site for lead implantation along the His–Purkinje system. Previous studies have demonstrated beneficial effect of LBBAP on cardiac function. LBBAP could preserve satisfactory left ventricular intraventricular synchrony and improve interventricular dyssynchrony compared with RVP [20]. Liu et al. [21] found increased left atrial myocardial elasticity and left atrial strain capacity with LBBAP. This present study also demonstrated an improved LVEF and decreased LAD after LBBAP when compared with RVP.

As conduction system pacing, both LBBAP and HBP has showed beneficial effect on clinical outcomes compared with RVP. However, there are some limitations with HBP. Studies have reported a gradually increased capture threshold and sensing issues, and the success rates for HBP varied between 65% and 92% [22–24]. LBBAP has been used for years in clinical practice, and it has been evaluated as a safe and feasible pacing modality. Su et al. [25] demonstrated success rate of 97.8% in patients undergoing

LBBAP with stable thresholds during a mean follow-up of 18.6 months. Particularly, LBBAP is safe and effective in patients ≥80 years old [26], and as AHREs may increase with aging [27, 28], older people may benefit more from LBBAP. Additionally, HBP was associated with a significantly higher risk of complications compared with LBBAP (8.6% vs. 1.3%; $P = 0.04$), mainly because of more lead-related complications, whereas LBBAP was associated with a risk of complications similar to that of RVP (3.5% vs. 1.3; $P = 0.36$) [29]. Thus, LBBAP may be more promising for patients with AVB.

## Study limitations

This present study had several limitations. It was a non-randomized controlled study with a relatively small sample size. Since significantly different baseline characteristics between the 2 study groups, we used propensity score matching to balance the cohorts; however, this resulted in discarding 50.9% of the original sample, which may lead to a decreased statistical precision in results. Nevertheless, statistical analysis before and after propensity score matching demonstrated consistent results, strengthening our conclusions.

By using a cutoff of >6 minutes, the rate of false-positive AHREs was 17.3% [8], which were subcategorized as noise, sensing of farfield R wave, or repetitive non-reentrant ventriculoatrial synchrony. Although each electrogram was reviewed by physicians, the accuracy of AHREs could not be fully guaranteed.

# CONCLUSIONS

The results of this observational study indicate that LBBAP was associated with a lower risk of new-onset AHREs compared with conventional RVP in patients with a high burden of VP%. Randomized trials with larger sample size are needed to further confirm these findings.

## Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

## Article information

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**Table 1.** Baseline characteristics of the general patients and the propensity score-matched cohort

| | General population | | | Propensity score matched | | |
|---|---|---|---|---|---|---|
| | LBBAP (n = 126) | RVP (n = 49) | *P*-value | LBBAP (n = 43) | RVP (n = 43) | *P*-value |
| Age, years | 68.3 (13.6) | 72.9 (10.0) | 0.02 | 75.0 (10.6) | 72.4 (10.0) | 0.24 |
| Male, n (%) | 74 (58.7) | 29 (59.2) | 0.96 | 28 (65.1) | 26 (60.5) | 0.66 |
| HF, n (%) | 36 (28.6) | 7 (14.3) | 0.049 | 11 (25.6) | 7 (16.3) | 0.29 |
| HTN, n (%) | 76 (60.3) | 38 (77.6) | 0.03 | 36 (83.7) | 33 (76.7) | 0.42 |
| CAD, n (%) | 32 (25.4) | 7 (14.3) | 0.11 | 11 (25.6) | 7 (16.3) | 0.29 |
| DM, n (%) | 33 (26.2) | 10 (20.4) | 0.43 | 13 (30.2) | 9 (20.9) | 0.32 |
| LVEF (%) | 63.0 (3.2) | 63.4 (4.9) | 0.54 | 62.2 (2.5) | 63.3 (5.2) | 0.24 |
| LAD, mm | 38.1 (4.6) | 37.8 (4.5) | 0.71 | 38.6 (5.0) | 38.1 (4.5) | 0.64 |

| | | | | | | |
|---|---|---|---|---|---|---|
| LVEDD, mm | 48.7 (4.7) | 49.1 (4.3) | 0.62 | 48.3 (5.2) | 49.2 (4.3) | 0.39 |
| Intrinsic QRSd, ms | 119.4 (30.3) | 110.3(26.6) | 0.07 | 116.3(26.2) | 113.1(27.2) | 0.58 |
| β blocker, n (%) | 32 (25.4) | 10(20.4) | 0.49 | 12(27.9) | 8(18.6) | 0.31 |
| ACEI/ARB, n (%) | 54 (42.9) | 27(55.1) | 0.15 | 29(67.4) | 23(53.5) | 0.19 |

Values are presented as mean (SD) or n (%)

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; QRSd, QRS duration; other — see Figure 1

**Table 2.** Pacing characteristics between LBBAP and RVP

| | LBBAP (n = 43) | RVP (n=43) | *P*-value |
|---|---|---|---|
| **Baseline** | | | |
| Sense, mV | 13.1 (5.5) | 11.5 (3.3) | 0.13 |
| Threshold, V/0.4 ms | 0.51 (0.12) | 0.84 (0.20) | <0.001 |
| Impedance, Ω | 825.2 (179.7) | 839.8 (201.8) | 0.73 |
| **Follow-up** | | | |
| Sense, mV | 14.5 (3.9) | 10.7 (3.9) | 0.001 |
| Threshold, V/0.4 ms | 0.70 (0.19) | 0.75 (0.23) | 0.33 |
| Impedance, Ω | 478.4 (75.8) | 553.5 (119.9) | 0.001 |

| | | | |
|---|---|---|---|
| Paced QRSd, ms | 114.7 (12.2) | 167.1 (12.9) | <0.001 |
| VP, % | 99.6 (1.0) | 88.1 (20.9) | 0.001 |

Values are presented as mean (SD)

Abbreviations: VP, ventricular pacing percentage; other — see Figure 1 and Table 1

**Table 3.** Changes of echocardiographic measurements between LBBAP and RVP

| | | LBBAP | RVP | ANCOVA effect | *P*-value |
|---|---|---|---|---|---|
| LVEF, % | Baseline | 63.0 (3.2) | 63.4 (4.9) | –2.6 (–5.0, –0.2) | 0.03 |
| | 1-year follow-up | 63.1 (3.1) | 60.5 (7.3)[a] | | |
| LAD, mm | Baseline | 38.1 (4.6) | 37.8 (4.5) | 0.2 (–1.1, 1.4) | 0.79 |
| | 1-year follow-up | 37.5 (4.2)[#] | 37.6 (4.4) | | |
| LVEDD, mm | Baseline | 48.7 (4.7) | 49.1 (4.3) | 1.0 (–0.3, 2.3) | 0.12 |
| | 1-year follow-up | 47.5 (4.0) | 48.5 (4.4) | | |

[a]Compared with baseline status, $P < 0.05$. Values are presented as mean (SD)

Abbreviations: other — see Figure 1 and Table 1

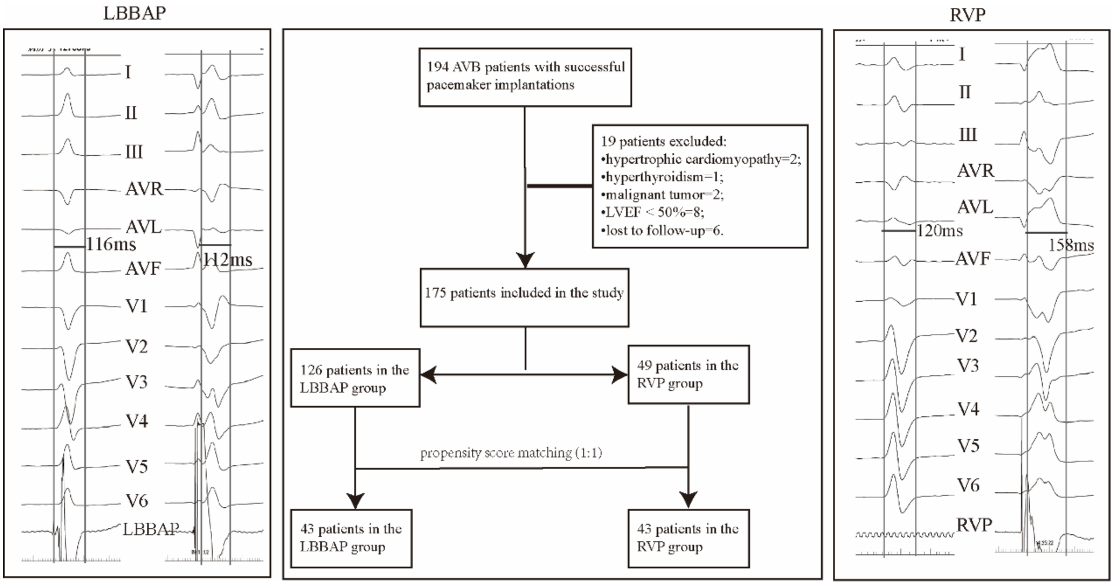


**Figure 1.** Flowchart of the study population enrollment

Abbreviations: LBBAP, left bundle branch area pacing; LVEF, left ventricular ejection fraction, RVP, right ventricular pacing

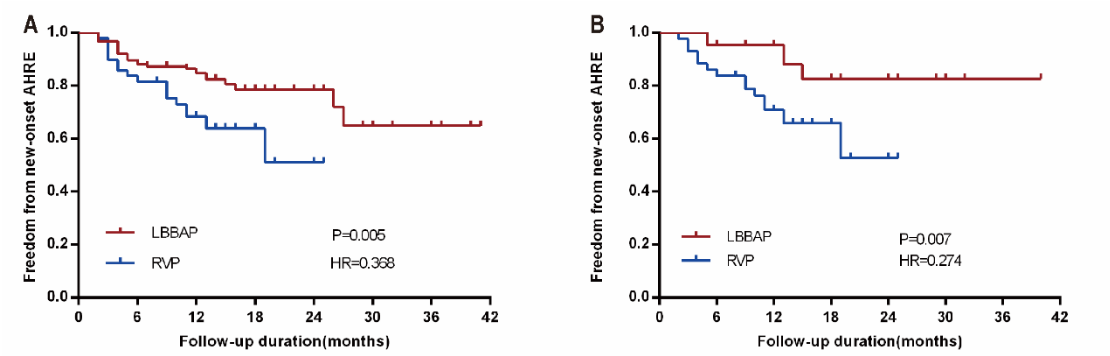


**Figure 2.** Comparison of new-onset AHREs between LBBAP and RVP groups. **A.** General patients. **B.** Propensity score matched cohort

Abbreviations: AHREs, atrial high rate episodes; other — see Figure 1

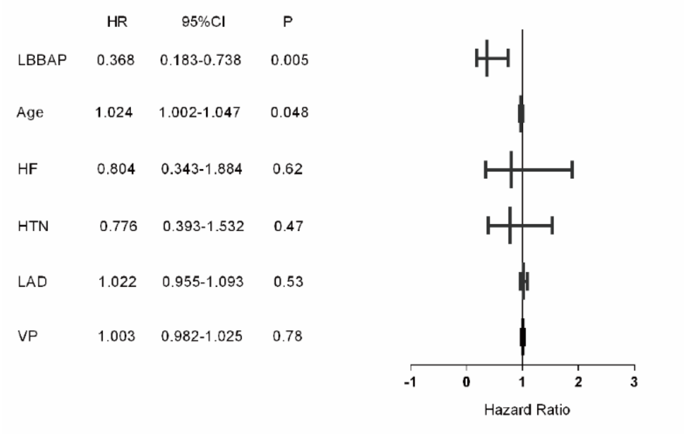


**Figure 3.** Multivariable Cox regression analysis of new-onset AHREs

Abbreviations: CI, confidence interval; HR, hazard ratio; other — see Figure 1 and Table 1 and 2

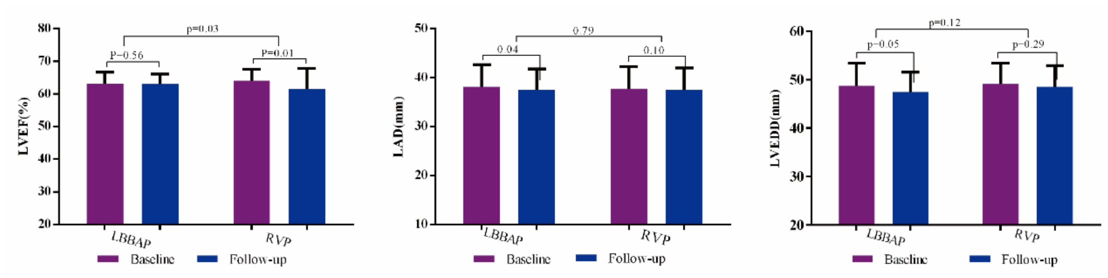


**Figure 4.** Comparison of echocardiographic measurements between LBBAP and RVP groups

Abbreviations: see Figure 1 and Table 1