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Incidence, Risk Factors, and Outcomes of Left Atrial Enlargement in Patients Requiring Right Ventricular Pacing: A Retrospective Study of 461 Cases from 2012 to 2020

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Statistical Analysis C
Data Interpretation D
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Background: Long-term right ventricular (RV) pacing has been linked to left atrial enlargement (LAE). The incidence and risk factors associated with significant LAE after RV pacing remain unknown. This retrospective study included 461 patients requiring RV pacing at 2 centers between 2012 and 2020 and aimed to evaluate the incidence, risk factors, outcomes, and complications of LAE.

Material/Methods: A total of 461 patients with normal-sized pre-implant left atrial dimension and dual-chamber pacing pacemaker implantation for complete atrioventricular block were enrolled. Patients were grouped based on a ≥20% increase from their baseline left atrial dimension by echocardiography, indicating significant LAE, and initial characteristics, echocardiographic data, and outcomes were compared.

Results: During a mean 7.0±4.9 years follow-up period, 96 patients (20.8%) developed significant LAE, whereas 365 patients did not. In multivariate logistic regression analysis, smaller pre-implant left atrial dimension (OR, 0.776; 95% CI, 0.728-0.828; *P*<0.001), lower post-implant left ventricular ejection fraction (OR, 0.976; 95% CI, 0.957-0.995; *P*=0.014), post-implant development of moderate to severe mitral regurgitation (OR, 2.357; 95% CI, 1.172-4.740; *P*=0.016), and RV pacing duration ≥3.3 years (OR, 1.576; 95% CI, 1.039-2.646; *P*=0.045) were independent predictors of significant LAE after RV-dependent pacing. There was a significant difference in the incident stroke events between patients without and with significant LAE (9.9% vs 17.7%; log-rank *P*=0.047).

Conclusions: Long-term RV pacing was linked to significant LAE in 20.8% of patients with complete atrioventricular block, with those affected experiencing a higher stroke rate during follow-up.

Keywords: **Atrioventricular Block • Stroke • Forney Robinson Pascoe Syndrome • Heart Atria • Cardiac Pacing, Artificial**

Abbreviations: **RV** – right ventricular; **LAE** – left atrial enlargement; **OR** – odds ratio; **CI** – confidence interval; **PPM** – permanent pacemaker; **LV** – left ventricular; **PICM** – pacing-induced cardiomyopathy; **HF** – heart failure; **EF** – ejection fraction; **CAVB** – complete atrioventricular block; **LVESV** – left ventricular end systolic volume; **LVEDV** – left ventricular end diastolic volume; **ROC** – receiver operating characteristic; **MR** – mitral regurgitation

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Introduction

Owing to an aging society and increasing survival rate in the elderly, the need for permanent pacemaker (PPM) placement increases with age, with an estimated 70% to 80% of all PPMs being implanted in patients aged 65 years or older [1-3]. Right ventricular (RV) apical pacing is a common method used in cardiac pacing, in which the pacing lead is placed in the apex of the RV. This technique is utilized for various indications, such as bradyarrhythmia and conduction block, in which it helps maintain an adequate heart rate and improve cardiac function [4]. However, recent guidelines also discuss the potential drawbacks of long-term RV apical pacing and the importance of considering alternative pacing sites or strategies to minimize adverse effects [5,6]. Long-term RV pacing can contribute to left ventricular (LV) dysfunction and atrial enlargement [7,8]. RV pacing-induced cardiomyopathy (PICM) develops in 10% to 20% of individuals requiring frequent conventional RV pacing, and the risk factors for PICM include male sex, wider native and paced QRS durations, and a higher RV pacing percentage [9,10]. The progression of PICM is significantly associated with the ventricular pacing burden (>40% ventricular pacing) [11]. A paced QRS length ≥163 msec can lead to PICM and is associated with a 3.506-fold increase in heart failure (HF) hospitalization [12]. Therefore, long-term RV pacing leads to LV systolic dysfunction and HF events, owing to the development of mechanical dyssynchrony of LV and increased fibrosis in the LV myocardium [13,14]. When comparing single-chamber atrial pacing with single-chamber or dual-chamber ventricular pacing, an increase in left atrial dimension was observed in patients with ventricular pacing, and this left atrial enlargement (LAE) can contribute to higher incidences of HF and atrial fibrillation [15-18]. LAE has been identified as an independent predictor of stroke/systemic embolic events in patients with atrial fibrillation [19,20]. Furthermore, after adjusting for LV dimensions and LV ejection fraction (LVEF), LAE was found to be significantly more prevalent in patients with complete atrioventricular block (CAVB) than in those with sick sinus syndrome [21]. Therefore, RV pacing-related LAE cannot be solely attributed to pacing-related LV dysfunction. However, there have been limited reports focusing on the change in LA size and clinical outcomes related to LAE following long-term RV-dependent pacing. Therefore, we conducted this retrospective study to investigate the incidence and risk factors of significant LAE after long-term RV-dependent pacing in patients with CAVB and to observe the clinical impact of significant LAE.

This retrospective study included 461 patients requiring RV pacing at 2 centers between 2012 and 2020 and aimed to evaluate the incidence, risk factors, outcomes, and complications of LAE.

Material and Methods

Patient Population

Between January 2012 and December 2020, a total of 1048 patients with CAVB who underwent PPM implantation in the PPM registry of 2 medical centers (Kaohsiung Chang Gung Memorial Hospital and Chi Mei Medical Center) were enrolled. Patients without baseline echocardiographic parameters, severe valvular heart disease, HF with mildly reduced or reduced ejection fraction, dilated left atrial dimension, or preexisting atrial fibrillation before PPM implantation, and pacing percentage <50% were excluded.

This resulted in the recruitment of 461 patients with CAVB and RV-dependent pacing and a normal-sized LA before implantation. The pacing method used was dual-chamber pacing systems, overseen by electrophysiologists from 2 medical centers (Kaohsiung Chang Gung Memorial Hospital and Chi Mei Medical Center). During the follow-up period, 365 patients without significant LAE were compared with 96 patients with significant LAE. Patients were assessed and compared based on demographics, comorbidities, initial and subsequent echocardiographic measurements, and health outcomes, distinguishing those with and without significant LAE.

Ethics Statement

This retrospective study adhered to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Committees of Kaohsiung Chang Gung Memorial Hospital (approval date: 2020/12/30; number: 202002623B0) and Chi Mei Medical Center (approval date: 2023/09/07; number: 11209-07) for Human Research. The institutional review board waived the requirement for written informed consent, owing to the retrospective nature of the study.

Echocardiography

Echocardiographic assessments were conducted using advanced ultrasound systems (GE Vivid 9, Philips IE33, Philips EPIQ 7) to measure key parameters such as left atrial dimension, LVEF, and LV volumes at systole and diastole. The measurements used M-mode and were refined with the 2-dimensional biplane Simpson's method. Regular echocardiographic monitoring, which was suggested biennially barring clinical incidents, is crucial for patients to track cardiovascular health.

Definitions

LAE was defined as a left atrial diameter of 41 mm or greater in men or 39 mm in women [22]. Patients with atrial fibrillation exhibited an average left atrial dimension of 47 mm,

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Table 1. Baseline characteristics between patients without and with significant LAE.

	Without significant LAE	With significant LAE	P value
Number	365	96	
General demographics			
Age (years)	71±11.9	70±15.9	0.486
Male sex (%)	183 (50.1)	53 (55.2)	0.422
BMI (kg/m^2)	23.12±6.54	22.68±7.06	0.562
Comorbidities			
Hypertension (%)	261 (71.5)	70 (72.9)	0.899
DM (%)	140 (38.4)	31 (32.3)	0.288
CAD (%)	64 (17.5)	14 (14.6)	0.544
Hyperlipidemia (%)	81 (22.2)	12 (12.5)	0.045
ESRD (%)	18 (4.9)	5 (5.2)	0.912
Prior stroke (%)	46 (12.6)	15 (15.6)	0.498
Mean of CHA2DS2-VASc score at baseline	3.3±1.7	3.3±1.7	0.870
Paced QRS duration (msec)	166.98±17.65	164.75±21.32	0.376
RV lead position			0.363
Lower septum or apex (%)	60 (16.4)	20 (20.8)	
High septum or near RVOT region (%)	305 (83.6)	76 (79.2)	
Medication			
ACEI/ARB (%)	271 (74.2)	71 (74.0)	0.954
β-blocker (%)	59 (16.2)	13 (13.5)	0.636
Statin (%)	119 (32.6)	23 (24.0)	0.108
F/U period (years)	6.7±4.9	8.0±4.6	0.019

Data are expressed as mean (standard deviation) or as number (percentage). LAE – left atrial enlargement; DM – diabetes mellitus; BMI – body mass index; CAD – coronary artery disease; ESRD – end-stage renal disease; RV – right ventricle; RVOT – right ventricular outflow tract; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; F/U – follow-up.

which is at least 20% larger than the upper normal limit and contrasts with those in sinus rhythm [19,20]. Accordingly, significant LAE was characterized by an increase of 20% or more from the baseline measurement, surpassing the normal size threshold in this study by echocardiography. PICM was defined as a ≥10% decrease in the LVEF, with a resultant LVEF <50% in the absence of other alternative diagnoses [23]. Stroke events encompassed both ischemic and hemorrhagic types of cerebrovascular incidents. HF episodes were identified by the necessity for hospitalization and treatment for symptoms corresponding to New York Heart Association functional classes II to IV. Cardiovascular mortality referred to sudden deaths due to arrhythmias, HF, or heart attacks. All-cause mortality included deaths from any reason.

Study Endpoint

The study focused on key endpoints, such as HF-related hospitalizations, stroke incidents, deaths due to cardiovascular causes, and overall mortality during the observation period.

Statistical Analyses

Data were summarized using means±standard deviations, medians with interquartile ranges for skewed distributions, or counts (percentages). The study groups' clinical features were analyzed using either the *t* test or Mann-Whitney U test for continuous data, and the chi-square or Fisher exact test for categorical data. Receiver operating characteristic (ROC) curve

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Table 2. Baseline and follow-up echocardiographic parameters between patients without and with significant LAE.

	Without significant LAE	With significant LAE	P value
Number	365	96	
Baseline			
LA dimension (mm)	35.2±3.7	31.1±4.5	<0.001
LVEF (%)	69.5±8.4	69.1±10.1	0.715
LVESV (mL)	32.6±15.2	29.4±13.5	0.064
LVEDV (mL)	107.7±32.7	99.1±33.0	0.022
MR grade			
No or trivial MR (%)	159 (43.6)	49 (51.0)	0.206
Mild MR (%)	206 (56.4)	47 (49.0)	0.206
Follow-up			
LA dimension (mm)	35.6±5.0	41.8±5.8	<0.001
LVEF (%)	61.4±13.4	57.9±12.8	0.022
PICM (EF ≤50%) (%)	73 (20.0)	23 (24.0)	0.399
LVESV (mL)	48.3±15.1	49.4±19.6	0.620
LVEDV (mL)	116.0±43.4	113.5±40.6	0.774
MR grade			
No and trivial (%)	118 (32.6)	19 (19.8)	0.015
Mild (%)	211 (57.8)	56 (58.3)	0.926
Moderate to severe (%)	36 (9.9)	21 (21.9)	0.003
Pacing duration (years)	3.0 (2.6-3.3)	4.3 (3.3-5.7)	0.002
Median dimension in the change of LA (mm)	1.0 (0-1.7)	10.0 (9.0-11.0)	<0.001
Percentage of LAE (%)	2.7 (0-4.9)	32.3 (30.0-35.5)	<0.001
Median dimension of LA enlargement/year (mm/y)	0.2 (0-0.4)	2.3 (1.9-3.0)	<0.001
Percentage of pacing ≥3.3 years (%)	181 (49.6)	60 (62.5)	0.029

Data are expressed as mean (standard deviation) or median (interquartile range) or as number (percentage). LAE – left atrial enlargement; LVEF – left ventricular ejection fraction; LVESV – left ventricular end systolic volume; LVEDV – left ventricular end diastolic volume; MR – mitral regurgitation; PICM – pacing-induced cardiomyopathy.

analysis was used to determine the area under the curve of pacing years for LAE after RV-dependent pacing in terms of sensitivity and specificity. To identify factors associated with LAE, both univariate and multivariate logistic regression analyses were conducted, presenting correlations as odds ratios (ORs) with 95% confidence intervals (CIs). Kaplan-Meier curves depicted stroke events over time. Propensity score matching adjusted for baseline differences, ensuring comparable groups. Analyses were conducted using IBM SPSS Statistics, version 22.0, with significance determined at $P<0.05$.

Results

Baseline Characteristics and Demographics Between Patients without and with Significant LAE

Over a mean follow-up period of 7.0±4.9 years, 96 patients (20.8%) developed an increase of ≥20% from the baseline left atrial dimension, whereas 365 patients did not. We categorized the study population into 2 groups: those with significant LAE and those without significant LAE. In the group without significant

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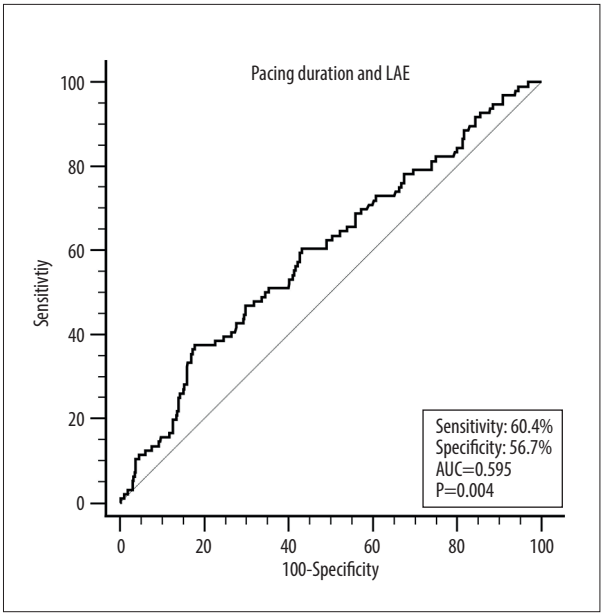

Figure 1. Receiver operating characteristic (ROC) curves of pacing years and an increase of ≥20% from the baseline left atrial dimension. The optimal cut-off point of an increase of ≥20% from the baseline left atrial dimension was 3.3 years, as it demonstrated the best sensitivity (60.4%) and specificity (56.7%), and the area under the curve was 0.595 (*P*=0.004). LAE – left atrial enlargement.

LAE, the average age was 71 years, with about half being male (50.1%). Conversely, in the group with significant LAE, the average age was slightly lower at 70 years, and male patients constituted a slightly higher percentage, at 55.2% (**Table 1**). Age and sex distribution did not significantly differ between the 2 patient groups. However, a higher prevalence of hyperlipidemia was observed in the patients without significant LAE than in those with significant LAE (22.2% vs 12.5%; *P*=0.045). There were no significant differences of other comorbidities, including hypertension, type 2 diabetes mellitus, coronary artery disease, end-stage renal disease, and prior stroke, between the 2 groups. There were no significant differences between the groups in baseline CHA2DS2-VASc scores, duration of paced QRS, positioning of the RV lead, or use of medications. However, patients with significant LAE had a longer follow-up period than did those without significant LAE (8.0±4.6 vs 6.7±4.9 years; *P*=0.019).

Baseline and Follow-Up Echocardiographic Parameters Between Patients without and with significant LAE

Baseline and follow-up left atrial dimension and LV parameters are presented in **Table 2**. At baseline, the left atrial dimension (35.2±3.7 mm vs 31.1±4.5 mm; *P*<0.001) and LV volumes at diastole (107.7±32.7 mL vs 99.1±33.0 mL; *P*=0.022) were significantly larger in patients without significant LAE than in patients with significant LAE. However, the LVEF, LV volumes at systole, and the prevalence of mild mitral regurgitation (MR) did not differ between the 2 groups. At the final follow-up, patients with significant LAE exhibited a larger left atrial dimension than did those without significant LAE (41.8±5.8 mm vs 35.6±5.0 mm; *P*<0.001). The median dimension of LAE/year was significantly larger in patients with significant LAE than in patients without significant LAE. Additionally, patients without significant LAE had a higher LVEF than did those with significant LAE (61.4±13.4% vs 57.9±12.8%; *P*=0.022). However, the prevalence of PICM did not differ between the 2 groups. The incidence of development of moderate to severe MR was higher in patients with significant LAE than in patients without significant LAE (21.9% vs 9.9%; *P*=0.003). Moreover, the total duration of RV pacing was significantly longer in patients with significant LAE than in patients without significant LAE (4.3 [3.3-5.7] vs 3.0 [2.6-3.3]; *P*=0.002).

ROC Curves of RV Pacing Duration (Years) and Significant LAE

ROC curves were plotted to analyze the relationship between RV pacing duration and an increase of ≥20% from the baseline left atrial dimension (significant LAE). The optimal cut-off point of an increase of ≥20% from the baseline left atrial dimension (significant LAE) was found to be 3.3 years of RV pacing, as it demonstrated the best sensitivity and specificity. The area under the curve was 0.595 (*P*=0.004), sensitivity was 60.4%, and specificity was 56.7% (**Figure 1**).

Incidence of Significant LAE and Change of Left Atrial Dimension During Follow-Up Between Patients with RV Pacing <3.3 years and ≥3.3 years

Patients with RV pacing for more than 3.3 years showed a higher incidence of significant LAE than did those with pacing for less than 3.3 years (24.9% vs 16.4%, *P*=0.029; **Figure 2A**). Furthermore, patients with RV pacing duration ≥3.3 years exhibited a higher mean change in left atrial dimension (3.3±6.2 mm vs 1.6±5.5 mm; *P*=0.002) and a higher mean percentage of change in left atrial dimension (11.1±19.7% vs 5.6±16.8%; *P*=0.001) than did patients with RV pacing duration <3.3 years (**Figure 2B, 2C**).

Univariate and Multivariate Logistic Regression Analyses of Predictors of Significant LAE After PPM Implantation

In univariate analysis, hyperlipidemia, smaller pre-implant left atrial dimension, lower pre-implant LV volumes at diastole, lower post-implant LVEF, post-implant development of moderate to severe MR, longer RV pacing years, and RV pacing duration ≥3.3 years were significant predictors of significant LAE after implantation (**Table 3**). However, in multivariate logistic regression analysis, only RV pacing duration ≥3.3 years (OR, 1.576; 95% CI, 1.039-2.646; *P*=0.045), smaller pre-implant left atrial dimension (OR, 0.776; 95% CI, 0.728-0.828;

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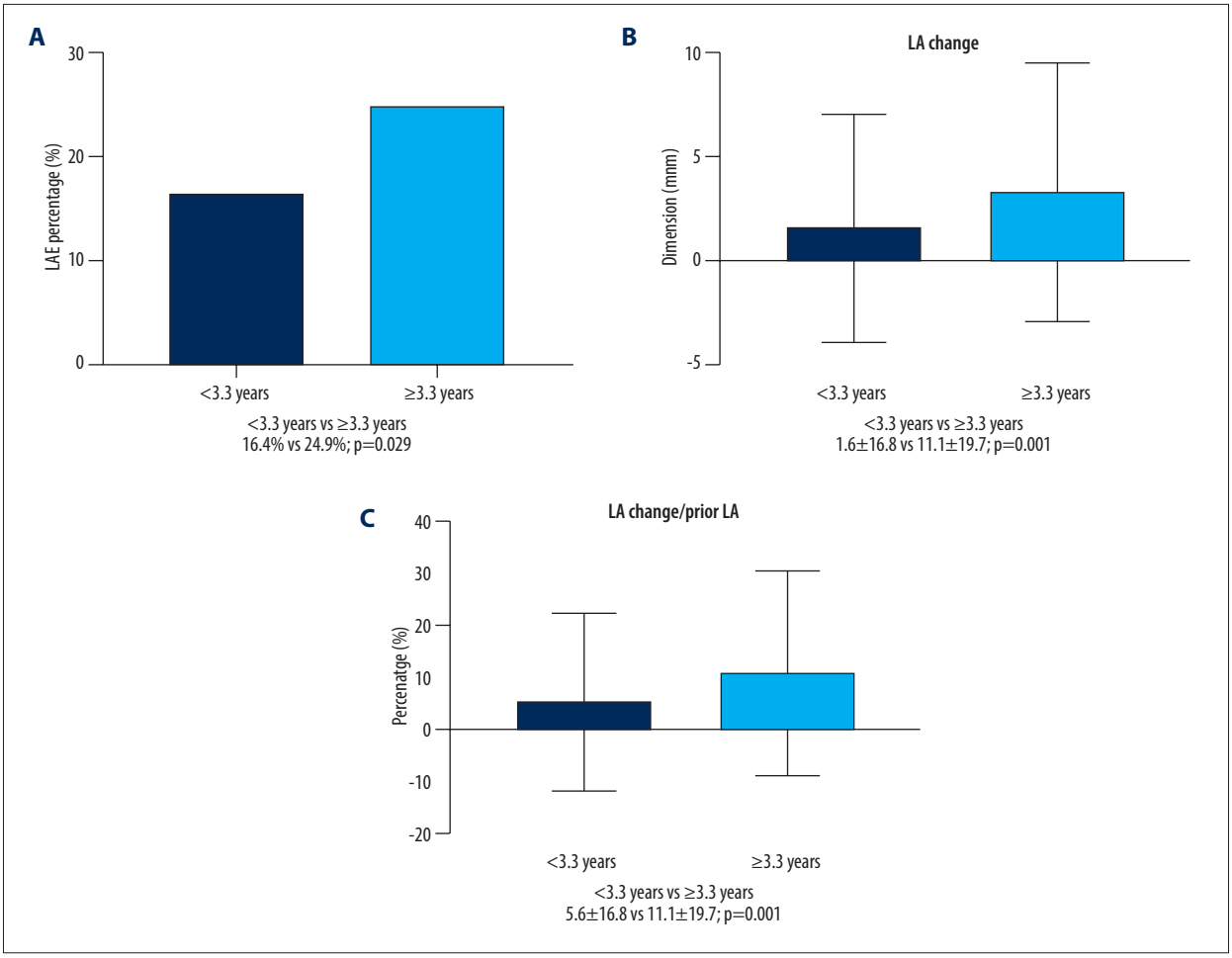

Figure 2. The incidence of an increase of ≥20% from the baseline left atrial dimension and the change of left atrial dimension between the patients with pacing <3.3 years and ≥3.3 years. (**A**) The difference in the incidence of an increase of ≥20% from the baseline left atrial dimension between patients with pacing duration <3.3 years and those with pacing duration ≥3.3 years was statistically significant (16.4% vs 24.9%; *P*=0.029). (**B**) Patients with pacing duration ≥3.3 years exhibited a higher mean change in left atrial dimension than did patients with pacing duration <3.3 years (3.3±6.2 mm vs 1.6±5.5 mm; *P*=0.002). (**C**) Patients with pacing duration ≥3.3 years exhibited a higher mean percentage of change in left atrial dimension than did patients with pacing duration <3.3 years (11.1±19.7% vs 5.6±16.8%; *P*=0.001). LAE – left atrial enlargement; LA – left atrium.

P<0.001), lower post-implant LVEF (OR, 0.976; 95% CI, 0.957-0.995; *P*=0.014), and post-implant development of moderate to severe MR (OR, 2.357; 95% CI, 1.172-4.740; *P*=0.016) were identified as independent predictors of significant LAE after PPM implantation in the patients with RV-dependent pacing.

Clinical Outcomes Between Patients without and with Significant LAE

A higher incidence of developing new-onset atrial fibrillation was observed in patients with significant LAE than in patients without significant LAE, although the difference did not reach statistical significance (**Table 4**). **Figure 3** showed the Kaplan-Meier curve of incident stroke events, with a trend toward higher incidence of stroke events in patients with significant LAE than in patients without significant LAE at the 3.3-year follow-up (10.4% vs 7.1%; log-rank *P*=0.325). However, a significant difference in the incident stroke events (mainly ischemic stroke) between patients with and without significant LAE (17.7% vs 9.9%; log-rank *P*=0.047) was observed at the 10-year follow-up (**Figure 3, Table 4**). There were no differences in HF events, cardiovascular mortality, or all-cause mortality between the 2 groups (**Table 4**).

Comparison of Clinical Outcomes Between Patients without and with Significant LAE After Propensity Score Matching

Following propensity score matching, there were no significant differences between the 2 groups in terms of age, sex, follow-up duration, baseline characteristics, initial left atrial dimension, and LVEF (**Table 5**). However, compared with patients without

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Table 3. Univariate and multivariate logistic regression analyses of predictors of significant LAE.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Male	0.816	0.519-1.281	0.377			
Age (per 10 years)	0.941	0.793-1.116	0.486			
BMI	0.990	0.959-1.023	0.562			
Hypertension	1.073	0.648-1.776	0.785			
Diabetes mellitus	0.766	0.476-1.235	0.275			
Hyperlipidemia	0.501	0.261-0.963	0.038	0.661	0.245-1.779	0.412
Coronary artery disease	0.803	0.429-1.504	0.493			
End stage renal disease	1.059	0.383-2.930	0.912			
Prior stroke or TIA	1.284	0.683-2.415	0.438			
Pre-implant LA	0.792	0.746-0.840	<0.001	0.776	0.728-0.828	<0.001
Pre-implant LVEF	0.995	0.970-1.021	0.714			
Pre-implant LVEDV	0.991	0.983-0.999	0.021	0.997	0.985-1.010	0.676
Pre-implant LVESV	0.982	0.964-1.001	0.060	0.992	0.963-1.021	0.580
Post-implant LVEF	0.981	0.965-1.007	0.023	0.976	0.957-0.995	0.014
PICM	1.260	0.739-2.150	0.396			
Post-implant LVEDV	0.997	0.993-1.004	0.620			
Post-implant LVESV	1.001	0.994-1.007	0.773			
Post-implant development of moderate to severe MR	2.559	1.413-4.634	0.002	2.357	1.172-4.740	0.016
Pacing QRS duration	0.994	0.979-1.008	0.375			
Lead position at lower septum and apex	1.338	0.760-2.354	0.313			
Pacing years (per year)	1.088	1.030-1.149	0.003			
≥3.3 years	1.694	1.068-2.687	0.025	1.576	1.039-2.646	0.045
New-onset atrial fibrillation after implantation	1.484	0.913-2.411	0.111	1.089	0.489-2.426	0.835
ACEI/ARB	0.985	0.590-1.645	0.954			
β-blocker	0.812	0.425-1.552	0.529			
Statin	0.651	0.388-1.093	0.104	0.896	0.401-2.002	0.788

OR – odds ratio; CI – confidence interval; BMI – body mass index; TIA – transient ischemic attack; LA – left atrium; LAE – left atrial enlargement; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; PICM – pacing-induced cardiomyopathy; MR – mitral regurgitation; ACEI – angiotensin-converting-enzyme inhibitor; ARB – angiotensin II receptor blocker.

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Table 4. Clinical outcomes between patients without and with significant LAE.

	Without significant LAE	With significant LAE	P value
Number	365	96	
New-onset atrial fibrillation	92 (25.2)	32 (33.3)	0.121
HF event (%)	22 (6.0)	6 (6.3)	0.935
Stroke event (%)	36 (9.9)	17 (17.7)	0.032
Ischemic stroke (%)	33 (33/36; 91.7)	17 (17/17; 100)	0.543
Hemorrhagic stroke (%)	3 (3/36; 8.3)	0 (0/17; 0)	0.543
Cardiovascular mortality (%)	12 (3.3)	2 (2.1)	0.744
All-cause mortality (%)	48 (13.2)	11 (11.5)	0.734

Data are expressed as number (percentage). LAE – left atrial enlargement; HF – heart failure.

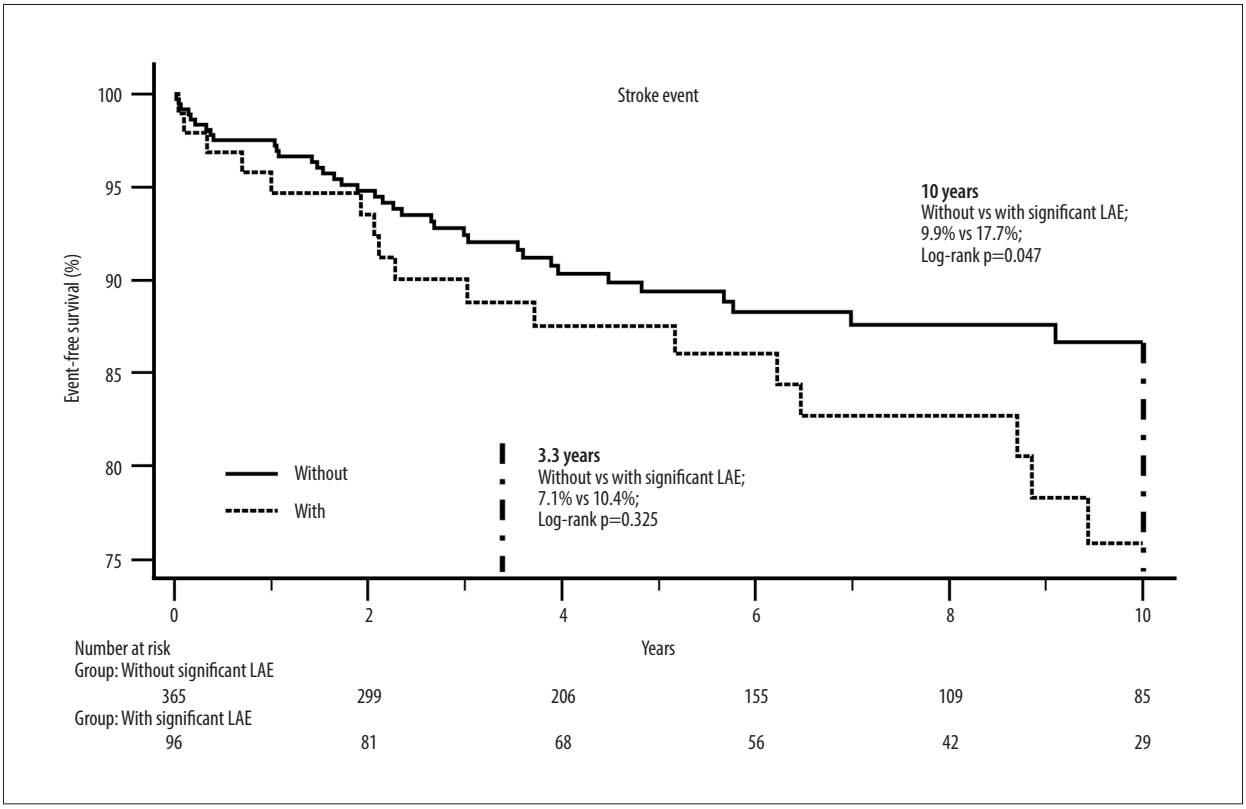

Figure 3. A Kaplan-Meier curve of long-term stroke events. There was no significant difference in stroke events at the 3.3-year follow-up between patients with and without an increase of ≥20% from the baseline left atrial dimension (10.4 vs 7.1%; log-rank *P*=0.325). However, a significant difference in stroke events between patients with and without an increase of ≥20% from the baseline left atrial dimension was observed at the 10-year follow-up (17.7 vs 9.9%; log-rank *P*=0.047). LAE – left atrial enlargement.

significant LAE, patients with significant LAE had larger left atrial dimension (42.4±5.5 mm vs 35.3±4.8 mm; *P*<0.001), reduced LVEF (57.7±13.0% vs 62.4±13.0%; *P*=0.016), higher prevalence of moderate to severe MR (22.2% vs 6.7%; *P*=0.005), higher incidence of new-onset atrial fibrillation (33.3% vs 16.7%; *P*=0.015), and higher incidence of stroke events (18.9% vs 3.3%; *P*=0.001).

Discussion

In this study, we showed that in patients with normal LA size before PPM implantation and without history of HF, moderate-to-severe valvular heart disease, or preexisting atrial fibrillation before PPM implantation, RV-dependent pacing duration

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Table 5. The comparison of clinical outcomes between patients without and with significant LAE after propensity score matching.

	Without significant LAE	With significant LAE	P value
Number	90	90	
General demographics			
Age (years)	70±13.7	70±14.7	0.758
Male sex (%)	47 (52.2)	50 (55.6)	0.765
BMI (kg/m^2)	23.4±5.0	23.0±6.8	0.645
Comorbidities			
DM (%)	35 (38.9)	30 (33.3)	0.535
CAD (%)	12 (13.3)	14 (15.6)	0.832
Hyperlipidemia (%)	10 (11.1)	12 (13.3)	0.821
F/U period (years)	7.9±5.2	8.1±4.6	0.841
Baseline			
LA dimension (mm)	32.6±3.7	31.7±4.0	0.096
LVEF (%)	70.1±8.0	69.4±10.0	0.652
Follow-up			
LA dimension (mm)	35.3±4.8	42.4±5.5	<0.001
LVEF (%)	62.4±13.0	57.7±13.0	0.016
Moderate to severe MR (%)	6 (6.7)	20 (22.2)	0.005
Pacing duration (years)	5.3±2.2	5.5±2.3	0.759
Percentage of pacing ≥3.3 years (%)	55 (61.1)	56 (62.2)	1.000
Clinical outcomes			
New-onset atrial fibrillation (%)	15 (16.7)	30 (33.3)	0.015
HF event (%)	5 (5.6)	6 (6.7)	1.000
Stroke event (%)	3 (3.3)	17 (18.9)	0.001
Cardiovascular mortality (%)	1 (1.1)	2 (2.2)	1.000
All-cause mortality (%)	7 (7.8)	11 (12.2)	0.457

Data are expressed as mean (standard deviation) or as number (percentage). LAE – left atrial enlargement; BMI – body mass index; DM – diabetes mellitus; CAD – coronary artery disease; F/U – follow-up; LA – left atrium; LVEF – left ventricular ejection fraction; MR – mitral regurgitation; HF – heart failure.

of ≥3.3 years resulted in the development of significant LAE in 20.8% (96/461) of patients and was associated with a 1.576-fold increase in the risk of development of significant LAE after PPM implantation. In addition, smaller pre-implant left atrial dimension, lower post-implant LVEF, and post-implant development of moderate-to-severe MR were also independent predictors of development of significant LAE after long-term RV-dependent pacing. Patients with significant LAE following RV-dependent pacing experienced a notably higher rate of stroke events over a 10-year monitoring period. Even after propensity score matching, patients with significant LAE continued to show a higher rate of new-onset atrial fibrillation and stroke events. Despite no differences in HF events following propensity score matching, patients with significant LAE exhibited a lower LVEF during follow-up than did patients without significant LAE. RV pacing leads to LAE and has been shown to impair left atrial ejection force, a finding supported by animal models of CAVB with RV pacing [24].

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Clinical Impact of LAE

LAE is a crucial contributor to mortality and is closely associated with LV diastolic dysfunction, atrial tachyarrhythmia, and stroke risk [25]. The LA plays a major role in cardiac physiology by collecting blood during systole and modulating LV filling during diastole, which can lead to overloading of LA pressure or volume, due to diastolic dysfunction or MR [26,27]. The common method for assessing LA size is to measure its anteroposterior linear dimension using M-mode or 2-dimensional echocardiography in the parasternal long-axis view by transthoracic echocardiography [28]. Although the anteroposterior diameter of the LA is considered inaccurate and may not fully represent the actual LA size, this assessment method is widely used and is highly reproducible [29]. The size of the LA, whether measured by volume, area, or diameter, can be a significant predictor of cardiovascular outcomes and can reflect underlying conditions and complicate the patient's cardiovascular health [22,30,31]. The prognostic implications of LA size have been demonstrated in general and high-risk populations with coronary artery disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, and patients undergoing valve replacement for mitral valve disease [29,32-35]. One meta-analysis showed that with every 10-mm increase in left atrial dimension, the odds of stroke increase by 24% [36]. LAE is a risk marker that only indirectly reflects one or a combination of risk factors of stroke.

Association Between LAE and RV-Dependent Pacing Following AVB

In an animal model, chronic AVB led to progressive LA dilatation [37]. LA dysfunction and fibrosis were observed following RV pacing in an AVB animal model [24]. The mechanism of LA enlargement in patients with long-term RV pacing is related to loss of AV synchrony [21]. In our study involving patients with RV-dependent pacing, pacing duration of ≥3.3 years resulted in insignificant LAE in 20.8% (96/461) of patients, and patients with significant LAE may have exhibited an increased long-term risk of stroke. We have reported that post-pacemaker implant QRS duration ≥163 msec was the most important predictor of HF admission [12]. However, no significant differences were observed in paced QRS duration between patients with significant LAE and patients without significant LAE (**Table 1**). This finding might account for the no differences in HF events between patients with and without significant LAE (**Table 4**). RV apical pacing, an alternative to natural ventricular activation via the His-Purkinje system, can adversely affect heart function [38]. Emerging strategies for physiological pacing not only enhance LVEF but can also inadvertently increase stress on the LA myocardium and affect left atrial ejection force [39].

Post-Implant Lower LVEF and Development of MR After RV-Dependent Pacing

PPM-induced worsening of MR was associated with the mechanical dyssynchrony of LV, which improved after upgrading to resynchronization therapy [40,41]. In our study, we observed that post-implantation development of moderate-to-severe MR was a strong predictor of significant LAE after RV-dependent pacing; however, the paced QRS duration did not influence the development of pacing-related LAE. A lower LVEF leads to increased LV filling pressure and impaired LV relaxation, resulting in impaired LA emptying function and, consequently, LA [25]. In our study, we found that a higher post-implantation LVEF was a negative predictor of significant LAE.

Study Limitations

This study has several limitations that should be acknowledged. First, this study was retrospective and non-randomized, with a relatively small participant group but extended follow-up. Efforts were made to mitigate potential biases and confounding factors, yet the possibility of selection bias cannot be entirely eliminated. Second, the assessment of LA size relied on left atrial dimension measurements using M-mode and 2-dimensional echocardiography, which can have certain limitations, even though this method has been used worldwide. Third, the study population comprised a relatively older cohort, which contributed to a relatively high all-cause mortality rate despite the difference in the development of left atrial dimension. Additionally, echocardiographic examinations were conducted every 1 to 2 years for patients without new events, potentially introducing variations in data collection intervals. Fourth, patients without baseline or follow-up echocardiographic examinations were excluded, which may have affected the generalizability of the findings to the entire patient population. Fifth, this study enrolled patients with CAVB and RV-dependent pacing who had a normal-sized LA prior to PPM implantation. Consequently, the clinical events observed in this study may not be comparable to those of other studies. Sixth, an analysis of baseline diastolic dysfunction and subsequent changes in the grade of diastolic dysfunction was not specifically conducted in this study. Seventh, data on B-type natriuretic peptide levels at baseline and during follow-up were not specifically examined in this study. Despite these limitations, our study provides valuable insights for clinical practice, particularly regarding the incidence and risk factors of significant LAE after long-term RV-dependent pacing in patients with normal pre-implant LA size. Future prospective studies are needed to further understand the long-term effects of physiological pacing on changes in left atrial dimension.

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Conclusions

Long-term RV pacing was linked to significant LAE in 20.8% of patients with CAVB, with those affected experiencing a higher stroke rate during follow-up.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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