

The Prevalence and Short-Term Outcomes of Ventricular Dyssynchrony after Right Ventricular Pacing

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Abstract

Objective: Long-term right ventricular pacing has been associated with an increased risk of heart failure and cardiomyopathy. The pathophysiology of cardiomyopathy associated with right ventricular pacing remains unclear. We aim to evaluate the burden and short-term outcomes of ventricular dyssynchrony after immediate permanent pacemaker implantation. **Materials and Methods:** This prospective cohort study examined consecutive patients who had permanent pacemaker implantation at Vajira Hospital in 2019. Left ventricular systolic function, specifically left ventricular ejection fraction (LVEF) and echocardiographic ventricular dyssynchrony parameters were assessed. The endpoints included the prevalence of ventricular dyssynchrony, new-onset cardiomyopathy, heart failure, and death. The correlation between QRS complex duration, the burden of ventricular pacing, and echocardiographic ventricular dyssynchrony was measured. **Results:** Thirty-six consecutive patients underwent pacemaker implantation. The prevalence of mechanical ventricular dyssynchrony was 22.2% using the interventricular conduction delay method, 41.7% using LV pre-ejection period method, and 11.1% using the septal posterior wall motion abnormality method. Electrical ventricular dyssynchrony was 86.1% and new-onset cardiomyopathy was 17.1% after 3 months of permanent pacemaker implantation. The right ventricular pacing of more than 20% was significantly associated with cardiomyopathy ($p < 0.022$) and heart failure (log-rank, $p = 0.049$) within 3 months. But heart failure was not associated with mechanical ventricular dyssynchrony parameters (log-rank, $p = 0.610$; hazard ratio [HR], 1.53; 95% confidence interval [CI], 0.29 - 7.96; $p =$

0.613 for IVMD and log-rank, $p = 0.398$; HR, 0.04; 95% CI, 0.01 - 3316.7 for SPWMD). Conclusion: Mechanical and electrical ventricular dyssynchrony are common findings in right ventricular pacing. High-burden right ventricular pacing after 3 months of permanent pacemaker implantation is often associated with cardiomyopathy and heart failure, but mechanical and electrical ventricular dyssynchrony does not predict a short-term decline in left ventricular systolic function and heart failure.

Keywords

Right Ventricular Pacing, Ventricular Dyssynchrony, Predictor, Correlation, Heart Failure, Cardiomyopathy, Left Ventricular Ejection Fraction Decline

1. Background

Symptomatic bradycardia and conduction block are common problems detected in elderly people. The standard treatment for symptomatic bradycardia is permanent pacemaker implantation (PPM) [1] [2]. Chronic right ventricular (RV) pacing has been associated with a deterioration in left ventricular (LV) systolic function [3]. Right ventricular pacing may produce mechanical and electrical ventricular dyssynchrony by activating the right ventricle to contract before the left ventricle (interventricular dyssynchrony) or the septum to contract before the lateral cardiac walls (intraventricular dyssynchrony). Asynchronous electrical activation of the ventricle causes left bundle branch block in traditional electrocardiography [4]. Septal and lateral wall out-phase contractions reduce stroke work and cause energy transfer from the contracting wall to the opposite relaxed wall. A deterioration in left ventricular function after chronic right ventricular pacing is known as pacing-induced cardiomyopathy (PICM). PICM has been recognized as a cause of heart failure in a patient with atrioventricular (AV) block [5]. A high rate of left ventricular pacing had been associated with left ventricular systolic dysfunction, frequently reported as PICM [6] [7]. Nonetheless, chronic RV pacing with preserved LV function may also be observed [8] [9].

Biventricular pacing or cardiac resynchronization therapy (CRT) is the coordination of right and left ventricular contractions. CRT is a proven treatment that improves congestive symptoms, quality of life and reduces mortality in patients with severe chronic heart failure with poor left ventricular systolic function [10]. Effective treatment for PICM is resynchronization of the right and left ventricle. A retrospective observational study of patients with PICM showed the reversal of cardiomyopathy with CRT [11].

Electrical ventricular dyssynchrony is indicated by a wide QRS complex duration, while mechanical ventricular dyssynchrony, lack of synchronization of both ventricles, can be detected by echocardiography. The prevalence of ventricular dyssynchrony in normal left ventricular systolic function and clinical cor-

relation in the short-term is not well established. Left ventricular systolic dysfunction and heart failure following permanent pacemaker implantation are controversial, especially in patient with good left ventricular systolic function. The primary objectives of this study are to evaluate the prevalence of mechanical and electrical dyssynchrony using simple echocardiography and electrocardiogram and to identify the short-term clinical effects following permanent pacemaker implantation in patients with preserved left ventricular systolic function.

2. Materials and Methods

2.1. Study Design

A prospective cohort study determines the prevalence of mechanical and electrical dyssynchrony using simple echocardiography parameters and QRS complex duration correlation.

All participants provided written informed consent. Study protocols were approved by the institutional review board from the Navamindradhiraj University and conducted in accordance with the ethical principles set out in the Declaration of Helsinki and the Good Clinical Practice Guidelines.

2.2. Study Population

We prospectively enrolled consecutive patients who had undergone single- or dual-chamber pacemaker implantation at a single tertiary care hospital located in Bangkok, Thailand, between February 2019 and November 2019. The inclusion criteria were as follows: 1) Of 18 years of age or older; 2) On permanent right ventricular pacing therapy; 3) Has a left ventricular ejection fraction (LVEF) of more than 35%. Patients who received biventricular pacing therapy were excluded from the trial.

2.3. Clinical Data and Measurement

Patients who met all the eligibility criteria were assessed by electrocardiography and echocardiography. The electrocardiography was performed before and after permanent pacemaker implantation to measure QRS complex duration and called QRS complex duration at pre-pacing and post-pacing periods; the left ventricular systolic function, specifically left ventricular ejection fraction (LVEF) was assessed at baseline and 3 months after device implantation. Mechanical dyssynchrony was measured and validated by the consensus of two cardiologists. Standard 12-lead electrocardiogram was recorded at 25 mm/s and 1 mV/cm with the PageWriter TC30 Cardiograph (Philips, the Netherlands). Intrinsic and paced QRS complex duration measurements were performed in digital format from the beginning of the Q wave to the end of the S wave.

Collected clinical data was assessed, including patient demographic characteristics, previous disease before permanent pacemaker implantation, electrocardiographic and echocardiographic findings before permanent pacemaker im-

plantation, indications for permanent pacemaker implantation, procedural outcomes after permanent pacemaker implantation, post-permanent pacemaker implantation follow-up device diagnostics, and electrocardiographic and echocardiographic findings during right ventricular pacing after permanent pacemaker implantation.

Heart failure within 3 months were collected for survival analysis. Heart failure was categorized into outpatient care (up-titrating diuretic due to clinical heart failure or starting a new loop diuretic due to clinical heart failure) or hospitalization.

3. Definition

3.1. Mechanical Dyssynchrony

Mechanical dyssynchrony can be evaluated by echocardiography as outlined below.

Interventricular dyssynchrony was measured by a discordance between the time of RV and LV contraction. On the other hand, pulse-wave doppler images of aortic and pulmonary flow velocities were utilized to measure interventricular mechanical delay (IVMD). IVMD included a recording of the LV outflow tract from an apical five-chamber view and the RV outflow tract from a parasternal short-axis view of the pulmonary artery. The time differences were utilized between electrocardiogram-derived Q wave onset and the onset of LV outflow and the time between the Q wave onset and the onset of RV outflow [12] [13].

Intraventricular mechanical dyssynchrony is considered dyssynchrony within the LV. M-mode septal to posterior wall motion abnormality (SPWMD) was calculated as the difference in the timing of both septal and posterior wall contractions. The M-mode cursor was positioned perpendicular to the septum and posterior wall at the base of the LV in a parasternal axis view. SPWMD was the calculated difference between the time from onset of the electrocardiogram-derived Q wave to the peak posterior displacement of the septum; it is also known as the time from the onset of QRS to the peak systolic displacement of the posterior wall [13] [14] [15].

3.2. Electrical Dyssynchrony

Electrical dyssynchrony was defined as a QRS complex duration of >130 msec.

3.3. Pacemaker-Induced Cardiomyopathy

Pacemaker-induced cardiomyopathy after permanent pacemaker implantation was defined as a decline LVEF from baseline more than 10%.

3.4. Trial Endpoints

The primary endpoint was the prevalence of electrical and mechanical dyssynchrony. The secondary outcomes were the association of ventricular dyssynchrony and adverse clinical outcomes (heart failure and new-onset LV systolic

dysfunction) at 3 months, the correlation between the burden of RV pacing and adverse clinical outcomes (heart failure and new-onset left ventricular systolic dysfunction), and the correlation between electrical and mechanical dyssynchrony.

3.5. Statistical Analysis

Continuous variables were reported as mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for variables with a non-normal distribution. Categorical data were presented as frequencies and percentages. Independent t-tests, Pearson's correlation coefficient, and the Mann-Whitney U test were used as appropriate. A p-value of <0.05 was considered statistically significant. Survival analysis time-to-event outcomes were presented as cumulative events (Kaplan-Meier estimate for endpoints including new-onset LV dysfunction and heart failure). Data was analyzed using SPSS software version 22 for Windows (SPSS Inc., Chicago).

4. Results

Forty-four patients were enrolled in this study, and five were lost to follow-up. Thirty-nine patients were admitted for permanent pacemaker implantation. The three patients were excluded due to an incomplete 3-month follow-up. Total patients with completed the follow-up were 36 patients (81.1%). The baseline characteristics of patients were listed in **Table 1**. More than half of the 36 participants included in the analysis were male (51.2%) and mean age 69.89 ± 15.72 years. A total of 33.3% of patients had diabetes mellitus, 72.2% with hypertension, 69.4% with dyslipidemia, 44.4% with atrial arrhythmia, 27.8% with ischemic heart disease, and 30.6% with chronic kidney disease. Eighteen patients (43.9%) were found to have sinus node dysfunction and 16 patients (39%) with AV nodal disease.

The prevalence of mechanical dyssynchrony estimated by IVMD, LV pre-ejection period (LVPEP), and SPWMD was at 22.2%, 41.7%, and 11.1%, respectively. Electrical dyssynchrony estimated by a QRS complex duration of more than 130 msec occurred in 86.1% of patients.

Six patients (16.7%) developed PICM. Patients with PICM had a significant reduction in LVEF compared with non-PICM group ($16.4\% \pm 5.8\%$ vs. $0.5\% \pm 0.9\%$, respectively; $p = 0.001$; **Table 2**). LVEF before implantation was not significantly different between patients in the PICM and non-PICM groups ($66.1\% \pm 9.7\%$ vs. $66.2\% \pm 13.4\%$; $p = 0.993$). The PICM group had a higher percentage for RV pacing (98.5%, IQR = 89.0% - 100.0% vs. 11.3%, IQR = 1.6% - 97.0%; $p = 0.022$). High-burden RV pacing (>20%) was found to be significantly correlated with PICM. LVEF in patients in the PICM group significantly changed at 1 month ($p = 0.024$) and 3 months ($p = 0.049$) after implantation. However, the indications for permanent pacemaker implantation were not associated with PICM (sinus node dysfunction, $p = 0.67$; AV nodal dysfunction, $p = 0.18$). The

Table 1. Baseline characteristics of study participants.

Variables	Total (n = 36)	Non-PICM (n = 30)	PICM (n = 6)	p-value
Postprocedural CHB	14 (38.9%)	10 (33.3%)	4 (66.7%)	0.181
Age (years)	71.4 ± 15.4	71.1 ± 15.7	72.5 ± 15.0	0.851
Sex: Male	20 (55.6%)	16 (53.3%)	4 (66.7%)	0.672
Diabetes mellitus	12 (33.3%)	11 (36.7%)	1 (16.7%)	0.640
Hypertension	26 (72.2%)	22 (73.3%)	4 (66.7%)	1
Dyslipidemia	25 (69.4%)	21 (70.0%)	4 (66.7%)	1
Atrial arrhythmia	16 (44.4%)	13 (43.3%)	3 (50.0%)	1
Ischemic heart disease	10 (27.8%)	7 (23.3%)	3 (50.0%)	0.317
Chronic kidney disease	11 (30.6%)	10 (33.3%)	1 (16.7%)	0.643
Intrinsic QRS duration (msec)	107.9 ± 24.8	106.4 ± 25.9	121.7 ± 21.1	0.187
Paced QRS duration (msec)	151.6 ± 35.0	154.4 ± 27.0	150.7 ± 19.1	0.750
Pacemaker mode				
DDD	25 (69.4%)	21 (70.0%)	6 (66.7%)	1
VVI	11 (30.6%)	9 (30.0%)	2 (33.3%)	1
Rate adaptative	12 (33.3%)	10 (33.3%)	2 (33.3%)	1
Atrial pacing rate (%)	30.6 (6.0 - 49.5)	32.9 (6.0 - 53.0)	18.0 (5.0 - 31.5)	0.603
RV paced (%)	50.2 (2.0 - 98.0)	11.3 (1.6 - 97.0)	98.5 (89.0 - 100.0)	0.022

Values are presented as mean ± standard deviation (SD) or median (IQR) and n (%). The p-value corresponds to the independent t-test or Mann-Whitney U test and Fisher's exact test.

Table 2. Post-ventricular pacing characteristics.

Variables	Total (n = 36)	Non-PICM (n = 30)	PICM (n = 6)	p-value
Electrical dyssynchrony				
QRS duration ≥130 ms	31 (86.1%)	26 (86.7%)	5 (83.3%)	0.829
Mechanical dyssynchrony				
IVMD ≥40 ms	8 (22.9%)	6 (20.7%)	2 (33.3%)	0.516
LVPEP ≥140 ms	15 (42.9%)	11 (37.9%)	4 (66.7%)	0.207
SPWMD ≥130 ms	4 (11.8%)	2 (7.1%)	2 (33.3%)	0.071
RV paced (%)				
≥20% RV paced	20 (55.6%)	14 (46.7%)	6 (100.0%)	0.024
≥40% RV paced	18 (50.0%)	12 (40.0%)	6 (100.0%)	0.019
Pre-procedural LVEF	65.2 ± 13.0	66.2 ± 13.4	66.1 ± 9.7	0.993
Post-procedural LVEF at 3 months	63.0 ± 15.0	65.6 ± 14.7	49.7 ± 8.1	0.015
Post-procedural LVEF <55%	9 (25.0%)	5 (16.7%)	4 (66.7%)	0.025
Difference between pre and post LVEF	3.1 ± 8.4	0.5 ± 5.9	16.4 ± 5.8	<0.001
Heart failure	10 (27.8%)	7 (23.3%)	3 (50.0%)	0.317

Values are presented as mean ± standard deviation (SD) or median (IQR) and n (%). The p-value corresponds to the independent t-test or the Mann-Whitney U test and Fisher's exact test.

pacemaker mode was not associated with PICM (**Table 1**).

All ventricular dyssynchrony parameters from echocardiography and electrocardiography were not found to be associated with PICM (**Table 2**). The electrical dyssynchrony, specifically wide QRS complex duration of more than 130 msec was 83.3% in the PICM group and 86.7% in the non-PICM group. The electrical dyssynchrony rate tended to be higher in PICM but there was no statistical significance associated with PICM ($p = 0.829$). In approximately one-third of patients with PICM showed interventricular mechanical delay (IVMD) more than 40 msec (PICM group, 33.3% vs. non-PICM group, 20.7%; $p = 0.516$). While a Left Ventricular Pre-Ejection Period (LVPEP) more than 140 msec was almost twice as common in patient with PICM than non-PICM (PICM group, 66.7% vs. non-PICM group, 37.9%; $p = 0.207$). Similarly, septal posterior wall dyssynchrony (SPWMD) >130 msec was four times more common in PICM group than in the non-PICM group. (PICM group, 33.3% vs. non-PICM group, 7.1%; $p = 0.071$).

During RV pacing, ventricular dyssynchrony was observed. Electrical dyssynchrony was significantly changed after RV pacing (intrinsic QRS duration = 102.0 msec, IQR = 91.0 - 124.0 msec vs. paced QRS duration = 157.5 msec, IQR = 140.5 - 171.5 msec; $p < 0.001$). Interventricular conduction delay changed significantly after RV pacing (mean pre-pacing IVMD, 8.0 ± 23.6 vs. mean post-pacing IVMD, 23.7 ± 26.1 ; $p < 0.01$). LVPEP and SPWMD were not significantly different after RV pacing. The QRS complex during RV pacing correlated with IVMD and LVPEP ($r = 0.361$, $p = 0.024$ and $r = 0.315$, $p = 0.028$; **Figure 1**).

A Kaplan-Meier survival curve of cumulative heart failure demonstrated a clinically association between heart failure and a high-burden of right ventricular pacing more than 20% within 3 months (log-rank, $p = 0.086$; **Figure 2**). Mechanical dyssynchrony was estimated using IVMD, LVPEP, and SPWMD and was not significantly associated with heart failure (log-rank, $p = 0.610$ for IVMD; $p = 0.112$ for LVPEP; $p = 0.398$ for SPWMD). Pacing-induced cardiomyopathy was associated with clinical heart failure but was not significantly different between patients in the PICM and non-PICM groups (23.3% vs. 50%; $p = 0.317$).

5. Discussion

Ventricular dyssynchrony was common in the RV pacing and may contribute to the worsening of LV systolic function. Because of the small number of study participants and the short follow-up period, mechanical and electrical dyssynchrony parameters could not predict short-term heart failure, cardiomyopathy and the correlation between ventricular dyssynchrony and ventricular systolic dysfunction.

From our study, the patients with a LVEF of more than 35% and high-burden RV pacing demonstrated new-onset cardiomyopathy and heart failure within a 3-month follow-up after permanent pacemaker implantation. Patients with a LVEF of 35% or lower were excluded due to strong recommendation for biventricular pacing. While LVEF is between 35% to 50%, right ventricular pacing or

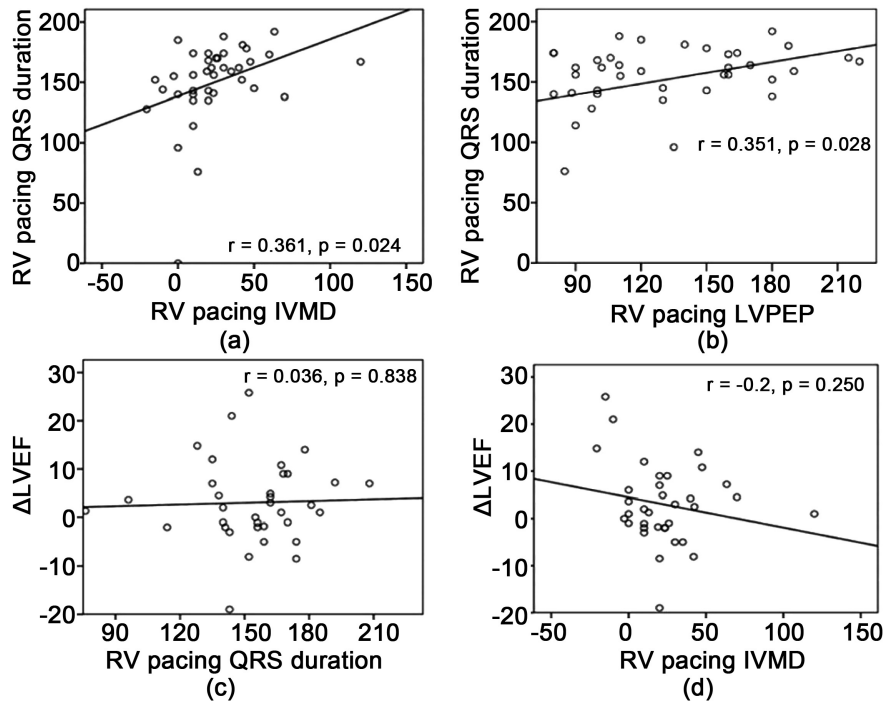


Figure 1. The correlation between mechanical, electrical ventricular dyssynchrony and difference in left ventricular systolic function at 3 months after permanent pacemaker implantation. (a) The correlation between RV pacing QRS complex duration and inter-ventricular mechanical delay (IVMD). (b) The correlation between RV pacing QRS complex duration and Left Ventricular Pre-Ejection Period (LVPEP). (c) The correlation between RV pacing QRS complex duration and pre and post PPM difference in left ventricular ejection fraction (LVEF) implantation. (d) The correlation between pre and post PPM implantation difference in left ventricular ejection fraction (LVEF) and interventricular mechanical delay (IVMD).

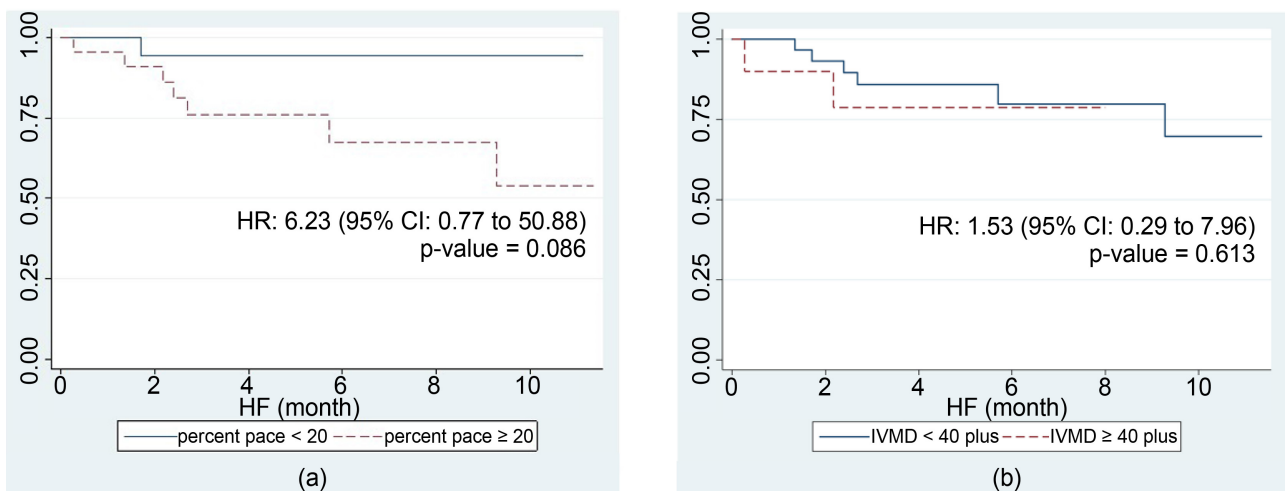


Figure 2. Cumulative incidence of heart failure. Kaplan-Meier curves show the cumulative incidence of heart failure with (a) Burden of RV pacing. (b) Mechanical ventricular dyssynchrony, particularly interventricular mechanical delay (IVMD).

biventricular pacing were therapeutic options. This data reveals the prevalence and time course of PICM and heart failure in the presence of high-burden RV

pacing, suggesting that the adverse clinical effects of PICM and heart failure may occur quickly.

Several studies have reported that RV pacing is significantly related to PICM and heart failure. For example, the Pacing to Avoid Cardiac Enlargement trial randomized 86 patients to an RV pacing group. In this group, mean LVEF decreased from 61.5% to 54.8% ($p < 0.01$) at 12 months. In contrast, in the biventricular pacing group, LVEF and ventricular volumes remained stable when compared with baseline [16]. Acute deterioration of LV systolic function was detected in the other study. Twelve participants with a dual chamber pacemaker implantation, normal LV function and physiological AV nodal conduction were examined using the serial gait blood pool technique. LVEF decreased from $66.5\% \pm 4.5\%$ to $52.9\% \pm 8.3\%$; ($p < 0.0001$) after 1 week of RV pacing. After cessation of pacing at 32 hours, LVEF increased to $62.9\% \pm 7.6\%$ ($p = 0.11$) compared with baseline [17]. These findings were similar to our results showing the occurrence of PICM within a short follow-up period. The threshold of RV pacing also observed in our study, in an analysis of patients receiving a permanent pacemaker from 2000 to 2014 for complete heart block with a LVEF of $>50\%$, 823 patients (12.3%) developed PICM over a mean follow-up period of 4.3 ± 3.9 years. The PICM group was significantly associated with the RV pacing of more than 20% [18]. From Merchant Faisal M and et al., acute heart failure after RV pacing was reported in the group with complete AV block within 6 months (HR = 1.62, 95% CI 1.48 - 1.79; $p < 0.001$) [19]. Accordingly, these studies supported our results. RV pacing might be contributing to acute adverse hemodynamic events, which in turn result in PICM and acute heart failure. Multiple clinical trials have demonstrated reverse remodeling after resynchronized right and left ventricular stimulation. CRT showed improved morbidity, congestive heart failure, and mortality [20]. Thus, physiologic pacing, such as His-bundle pacing or biventricular pacing, has been recommended for high-burden RV pacing to avoid PICM and heart failure [2].

RV pacing did not affect some patients in this study. On the other hand, a previous cohort study reported infrequent development of left ventricular systolic dysfunction in pacemaker recipients with predominantly normal LVEF [21]. Many factors cause PICM and heart failure, one of which is high-burden RV pacing. After multivariable data analysis, we did not detect a significant correlation between cardiomyopathy and other factors. Considering that the sample size was small and follow-up duration short, the multivariate analysis was limited. In this study, the PICM group had a higher rate of ischemic heart disease compared with the non-PICM group (50% vs. 23.3%) but not statistically significant. Ischemic heart disease accelerates or precipitates LV systolic dysfunction and heart failure. Atrial fibrillation, age, gender, and pre-existing valvular dysfunction were not associated with early onset heart failure and PICM in our study, although the real impact of RV pacing is difficult to detect due to many confounding factors. Additional studies are needed to identify individuals most

susceptible to the adverse effects of RV pacing and to determine who might benefit from biventricular pacing.

6. Study Limitations

Our study has several important limitations that should be noted. This study had a small sample size that could limit the power of multivariate analysis. Due to the short follow-up duration, the low rates of adverse events, such as left ventricular systolic dysfunction and heart failure, made it impossible to differentiate ventricular dyssynchrony. We suggested further study should be longer follow up. Due to small sample size and short duration follow-up time, the heart failure patients in this study were defined with first onset heart failure. The quality of life such as functional class, six-minute walk test, and pulmonary hypertension parameters should be collected as evidence of heart failure. Our study did not record other echocardiographic information about left ventricular remodeling, such as diastolic and systolic left ventricular internal diameter or global longitudinal strain pattern, which could represent the severity of cardiac remodeling. Echocardiographic strain patterns were not included in our study due to facility limitations, which might have been helpful in detecting LV dyssynchrony early and with good specificity.

7. Clinical Implications

Ventricular dyssynchrony is common after permanent pacemaker implantation. Early ventricular systolic dysfunction can occur in a short duration. If a patient is clinically suspected of having LV systolic dysfunction, such as dyspnea or clinical heart failure, LV systolic function assessment should be carried out. In high-risk groups, an evaluation of LV systolic function may be beneficial for PICM. Upgrading to CRT can reverse ventricular systolic dysfunction.

8. Conclusion

Mechanical and electrical dyssynchrony is a common finding after RV pacing. New-onset cardiomyopathy is significantly associated with high-burden RV pacing (>20%) within 3 months after implantation. High-burden RV pacing is also found to be contributing to heart failure. Future studies should look into identifying individuals most susceptible to the adverse effects of RV pacing, a way to determine which patients might benefit from biventricular pacing or his bundle pacing.

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Potential Conflicts of Interest

The authors declare no conflict of interest.

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