Prognostic factors of pacing-induced cardiomyopathy

Hong Zhang[1], Yu-Jie Zhou[2], Yu-Jie Zeng[1]

[1]Emergency and Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China;
[2]Department of Cardiology, 12th Ward, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Clinical Center for Coronary Heart Disease, Capital Medical University, Beijing 100029, China.

Abstract

Background: The detrimental outcomes of right ventricular pacing on left ventricular electromechanical function ultimately result in heart failure, a phenomenon termed pacing-induced cardiomyopathy (PICM) in clinical research. This study aimed to validate prognostic factors that can be used to identify patients with higher susceptibility to progress to the stage of cardiomyopathy before pacemaker implantation.

Methods: This observational analysis enrolled 256 patients between January 2013 and June 2016, 23 (8.98%) of whom progressed to PICM after 1 year of follow-up. A Cox proportional hazard model was used to analyze the prognostic factors associated with PICM. Dose-response analysis was used to evaluate the relationship between significant indicators in multifactor analysis and PICM.

Results: The mean values of left ventricular ejection fraction before and after pacemaker implantation in 23 patients diagnosed with PICM were 62.3% and 42.7%, respectively. Univariate analysis showed that sex, atrio-ventricular block, paced QRS duration, and ventricular pacing percentage were significantly associated with PICM. In the multivariate analysis, male sex (hazard ratio: 1.20, 95% confidence interval [CI]: 1.09–1.33, $P < 0.005$), paced QRS duration (hazard ratio: 1.95 per 1 ms increase, 95% CI: 1.80–2.12, $P < 0.001$), and ventricular pacing percentage (hazard ratio: 1.65 per 1% increase, 95% CI: 1.51–1.79, $P < 0.001$) were independent prognostic factors associated with the development of PICM. The ventricular pacing percentage and paced QRS duration level defined by the dose-response analysis were positively associated with PICM ($P < 0.05$).

Conclusions: Our findings indicated that paced QRS duration and ventricular pacing percentage were the most sensitive prognostic factors for PICM.

Keywords: Right ventricular pacing; Pacing-induced cardiomyopathy; Heart failure

Introduction

As a type of cardiac implantable electrical devices (CIEDs), pacemakers are currently the most useful method for bradycardia treatment. The Chinese Heart Rhythm Society reported that approximately 76,717 patients underwent their first pacemaker implantation in 2017. Traditionally, the goal of pacemaker follow-up is to ensure appropriate device conditions and assess patients' health status.[1] Previous studies have demonstrated decreased post-procedure complications attributed to CIED implantation between 2002 and 2005.[2,3] However, the most common and under-recognized long-term complication of pacemaker implantation is pacing-induced cardiomyopathy (PICM) due to left ventricular (LV) electrical and mechanical desynchronization.[4-6] In 2018, Kaye and colleagues[7] reported that the incidence of PICM ranged from 5.9% to 39% according to the definition of PICM. Patients who underwent pacemaker implantation are at risk of PICM and are often hospitalized with higher mortality. Based on current evidence and literature, no available method or mechanism yet exists to identify pacemaker-implanted (including single-chamber and dual-chamber pacemakers) patients who will eventually progress to PICM. Furthermore, none of the guidelines advise alternative pacing methods such as cardiac resynchronization therapy (CRT) for patients with normal LV ejection fraction (LVEF). Khurshid *et al*[8] proposed that patients with higher PICM susceptibility should receive CRT to potentially enhance LV systolic function while mitigating or averting re-operation rates; however, this opinion remains controversial. This retrospective study was aimed to identify and validate the prognostic factors within the pre-implantation phase for patients at increased risk of progressing to PICM.

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Correspondence to: Dr. Yu-Jie Zhou, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
E-Mail: azzyj12@163.com

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Methods

Ethical approval

All enrolled patients provided written informed consent after receiving detailed explanations before the operation. The research protocol was supervised and authorized by the Capital Medical University Ethics Committee (No. 2020008X).

Study population

This observational analysis continually reviewed 363 pacemaker-implanted cases admitted in Beijing Anzhen Hospital, Capital Medical University between January 2013 and June 2016. A total of 256 patients met the inclusion criteria, while 107 patients were excluded during the data review due to abnormal LVEF (<55%) pre-operation, inadequate data, or other causes. Among the included patients, presence of LVEF (≥55%) before implantation was considered as normal; under the standard clinical protocol, the patients were administered a routine echocardiogram 1 year after the procedure. The indications for pacemaker implantation were based on the criteria published by the Heart Rhythm Society (HRS) and European Heart Rhythm Society. Patients who received an implantable cardioverter-defibrillator or CRT were excluded, as were patients underwent pulse generator changes. Patients with native left or right bundle branch blocks before pacemaker implantation were also excluded. The standard definition of left or right bundle branch blocks was based on the guidelines from the American College of Cardiology, American Heart Association (AHA), and HRS.[9]

The enrolled patients received 228 double-chamber pacemakers and 28 single-chamber pacemakers, and all implanted pacemakers had rate response function. The patients were assessed at our center and complied with the follow-up schedule, in which the patients were required to visit the clinic every 6 months for routine evaluation at 1 year after implantation. The left or right cephalic vein was the primary choice for lead entry access; however, if this failed, ipsilateral axillary vein, or subclavian vein punctures with or without contrast were alternative entry method. None of the patients in this study underwent thoracotomy for lead implantation. The database development and quality control were completed by professional data entry personnel using double-random entries.

Demographic baseline, echocardiogram, electrocardiogram, and pacing data burden

The baseline demographic data were acquired from medical database of Beijing Anzhen Hospital. The parameters of LVEF were synthesized and controlled by a validated and standardized protocol at Beijing Anzhen Hospital, Capital Medical University. Data on QRS duration were obtained from electrocardiograms performed during admission and follow-up in the outpatient department. Interrogation was performed by the assigned electrophysiology clinician to determine the burden (percentage) of ventricular pacing. The confounding factors included age, sex, body mass index, hypertension, diabetes, coronary artery bypass grafting, and clinical serum indicators. The endpoint was the occurrence of PICM.

Definition of PICM

The diagnosis of PICM was based on the exclusion of other known causes of cardiomyopathy. In this study, PICM was defined as LVEF less than 45% or a decline in LVEF greater than 10% after pacemaker implantation compared with normal baseline LVEF pre-operation. Prior to PICM diagnosis in the enrolled patients, patients' medical records were evaluated to exclude alternative causes of cardiomyopathy including chronic myocardial ischemia, myocardial infarction, frequent (>20%) ventricular premature depolarizations, severe valvular heart disease, severe uncontrolled hypertension, alcohol addiction, and severe metabolic disorders. If the etiology could not be defined, the clinician consulted the cardiac pacing specialist to address any concerns regarding the study protocol.

Statistical analysis

Normal quantitative data were expressed as mean ± standard deviation (SD), while qualitative data were expressed as percentage frequency (%). Chi-squared and Student's *t* tests were performed to analyze qualitative and quantitative data, respectively, for differences between groups. We used Cox proportional hazard model to analyze the risk factors associated with PICM development. Variables that showed significant correlations with PICM in univariate tests were evaluated using multivariate models. To determine which prognostic factors could better detect the occurrence of PICM, dose-response analysis was used to evaluate the relationship between significant indicators in multifactor analysis for PICM. Based on the results of the dose-response curve, a stratified analysis was used in this study. Statistical significance was set at $P < 0.05$. Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Table 1 shows the significant differences in sex, pacemaker type, indication, paced QRS duration, and ventricular pacing percentage between the PICM and non-PICM groups ($P < 0.05$). No significant differences in the other evaluated variables were observed between the two groups.

The univariate analysis showed that sex, atrio-ventricular (AV) block, paced QRS duration, and ventricular pacing percentage were prognostic factors of PICM [Table 2]. The multivariate analysis included all significant variables from the univariate analysis in the regression model and found that male sex (hazard ratio: 1.20, 95% confidence interval [CI]: 1.09–1.33, $P < 0.005$), paced QRS duration (hazard ratio: 1.95 per 1 ms increase, 95% CI: 1.80–2.12, $P < 0.001$), and ventricular pacing percentage (hazard ratio: 1.65 per 1% increase, 95% CI: 1.51–1.79, $P < 0.001$) were independently associated with the development of PICM.

The mean differences in LVEF between pre-implantation and post-implantation in 23 patients diagnosed with PICM

Table 1: Baseline characteristics of patients stratified by PICM development.

Variables	PICM ($n=23$)	Non-PICM ($n=233$)	χ^2/t	P
Sex			3.95	0.047
Female	7 (30.43)	122 (52.36)		
Male	16 (69.57)	111 (47.64)		
Age (years)	65.8 ± 7.4	67.6 ± 11.9	−0.72	0.473
BMI (kg/m^2)	23.3 ± 3.0	25.0 ± 15.9	−0.50	0.615
Pacemaker type			4.37	0.037
Single chamber	6 (26.09)	22 (9.44)		
Double chamber	17 (73.91)	211 (90.56)		
Pre-operation QRS duration (ms)	82.0 ± 11.1	85.8 ± 11.0	1.48	0.141
Indication			13.94	0.003
AF with ventricular pause	5 (21.7)	22 (9.4)		
Sick sinus syndrome	2 (8.7)	112 (48.1)		
AVB (II degree type 2 or advanced)	5 (21.7)	36 (15.5)		
AVB (III degree)	11 (47.8)	63 (27.0)		
Ventricular lead position			0.86	0.354
Right ventricular apex	16 (69.6)	139 (59.7)		
Right ventricular septum	7 (30.4)	94 (40.3)		
Algorithm to avoid ventricular pacing	10 (43.5)	121 (51.9)	0.60	0.439
Paced QRS duration (ms)	153.4 ± 11.5	141.7 ± 13.4	4.04	< 0.001
Ventricular pacing percentage	60.6 ± 25.6	38.2 ± 31.5	3.29	0.001
Baseline left ventricle ejection fraction, %	62.3 ± 4.8	63.8 ± 4.6	1.49	0.138
Coronary artery bypass grafting	1 (4.4)	16 (6.9)	0	0.981
Diabetes	3 (13.0)	47 (20.2)	0.30	0.584
Hypertension	8 (34.8)	68 (29.2)	0.31	0.575
Hemoglobin (g/L)	138.3 ± 21.5	134.7 ± 17.1	0.97	0.332
HS-CRP (mg/L)	5.0 ± 4.6	5.2 ± 5.7	−0.09	0.927
Uric acid (μmol/L)	327.2 ± 114.2	337.9 ± 114.2	−0.43	0.670
Homocysteine (μmg/L)	14.3 ± 8.5	14.06 ± 8.7	0.13	0.901
Urea (mmol/L)	80.0 ± 21.1	88.0 ± 54.7	−0.69	0.489
ACEI use	7 (30.4)	51 (21.9)	0.87	0.350

Values are n (%) or mean ± standard deviation. PICM: Pacing-induced cardiomyopathy; BMI: Body mass index; AF: Atrial fibrillation; AVB: Atrioventricular conduction block; ACEI: Angiotensin converting enzyme inhibitor; HS-CRP: high sensitive C reaction protein.

ranged from 9% to 46%, while the means and medians of LVEF for pre-implantation and post-implantation were 62.3% and 63.0%, and 42.7% and 45.0%, respectively [Figure 1].

The occurrence of PICM sharply increased with increasing paced QRS duration. According to the data aggregation, QRS duration was divided into three groups (<140, 140–160, and ≥160 ms) to determine its association with PICM.

The occurrence of PICM also increased sharply with increasing ventricular pacing percentage. According to the data aggregation, ventricular pacing percentages were divided into three groups (<27.2, 27.2–87.2, and ≥87.2) to distinguish its association with PICM [Figure 2].

There were statistically significant differences in the occurrence of PICM at different levels of paced QRS duration and ventricular pacing percentage between the two groups [Table 3].

Finally, there were statistically significant differences in paced QRS duration levels (hazard ratio: 1.45 per 1 ms increase, 95% CI: 1.21–1.74, $P < 0.001$) and ventricular pacing percentage level (hazard ratio: 1.87 per 1% increase, 95% CI: 1.72–2.03, $P < 0.004$) in the Cox regression multivariate analysis after adjusting for age, sex, and body mass index.

Discussion

In the past two decades, right ventricular (RV) pacing has demonstrated poor outcomes due to LV electromechanical dysfunction, ultimately leading to heart failure (HF), a phenomenon termed PICM. In this consecutive retrospective study, all included patients underwent pacemaker implantation with normal LVEF. We investigated the prognostic factors that identified patients with increased risk to progress to PICM before pacemaker implantation. The results of our study indicate that paced QRS duration and ventricular pacing percentage were the most sensitive prognostic factors for PICM. This finding suggests that more attention should be paid to paced QRS duration and ventricular pacing percentage after pacemaker implantation.

The incidence of PICM was 8.98% at 1 year after the procedure, which is comparable to that reported by Yu et al[10] (9%). Currently, the exact incidence of PICM remains unclear and varies due to studies using different

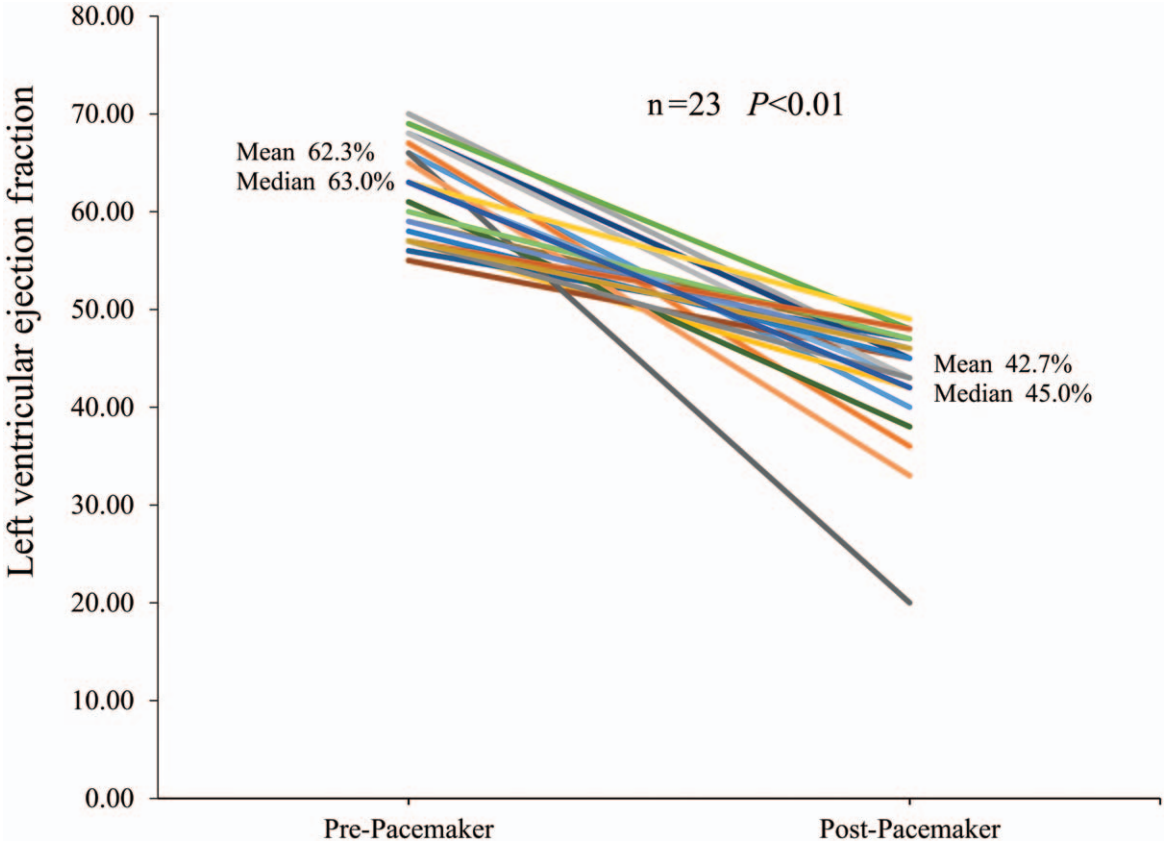

Figure 1: Left ventricular ejection fraction decreased in patients diagnosed with pacing-induced cardiomyopathy.

Table 2: Univariate and multivariate Cox regression analysis of PICM.

	Univariate			Multivariate		
Variables	**Hazard ratio**	**95% CI**	***P***	**Hazard ratio**	**95% CI**	***P***
Gender						
Female	1.00					
Male	1.50	1.36–1.66	0.003	1.20	1.09–1.33	0.003
Age (per 1 year increase)	0.99	0.96–1.02	0.491			
BMI (per 1 kg/m^2 increase)	0.91	0.78–1.07	0.270			
Pacemaker type						
Single chamber	1.00					
Double chamber	1.71	0.65–4.52	0.277			
Indication						
AF with ventricular pause	1.00			1.00		
Sick sinus syndrome	2.11	0.96–4.65	0.063	0.89	0.19–4.24	0.884
AVB (II degree type 2 or advanced)	0.20	0.07–0.60	0.004	0.39	0.09–1.67	0.203
AVB (III degree)	1.39	0.63–3.06	0.411	1.40	0.38–5.11	0.542
Ventricular lead position						
Right ventricular apex	1.00					
Right ventricular septum	1.22	0.78–1.90	0.379			
Algorithm to avoid ventricular pacing	1.17	0.77–1.76	0.462			
Paced QRS duration (per 1 ms increase)	2.12	1.92–2.34	0.007	1.95	1.80–2.12	<0.001
Ventricular pacing percentage (per 1% increase)	1.99	1.72–2.32	<0.001	1.65	1.51–1.79	<0.001
Baseline left ventricle ejection fraction (per 1% increase)	0.91	0.29–2.84	0.632			

PICM: Pacing-induced cardiomyopathy; CI: Confidence interval; BMI: Body mass index; AF: Atrial fibrillation; AVB: Atrio-ventricular conduction block.

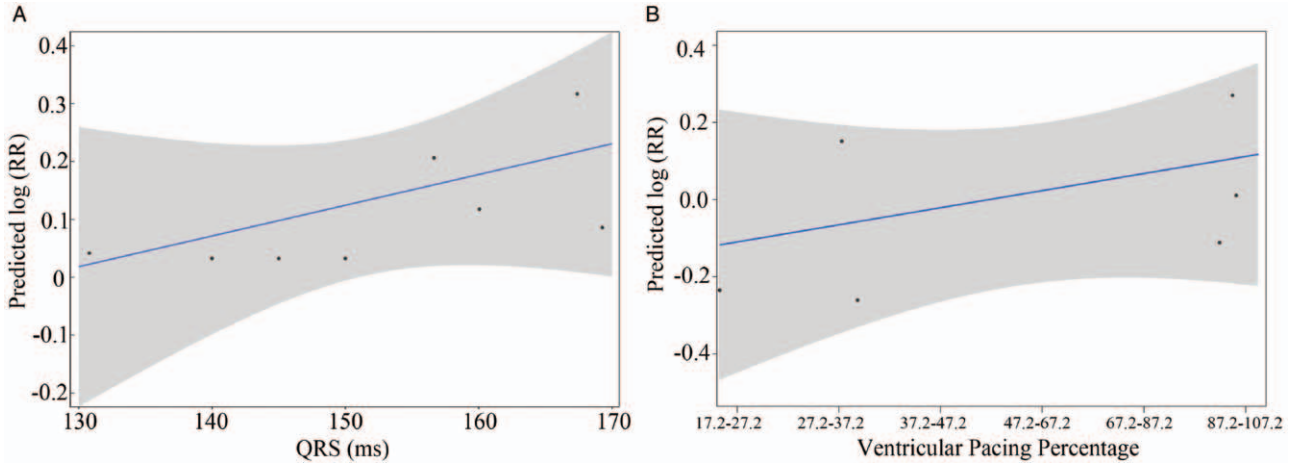

Figure 2: The relationship between pacing-induced cardiomyopathy and paced QRS duration (A), ventricular pacing percentage (B) in the dose-response relationship diagram.

Table 3: Univariate analysis of PICM occurrence at different levels of paced QRS duration and ventricular pacing percentage.

Variables	PICM ($n = 23$)	Non-PICM ($n = 233$)	χ^2	P
Paced QRS duration level			28.92	<0.001
<140 ms	2 (8.7)	151 (64.8)		
140–160 ms	15 (65.2)	51 (22.0)		
≥160 ms	6 (26.1)	31 (13.3)		
Ventricular pacing percentage level			10.78	0.005
<27.2%	4 (17.4)	113 (48.5)		
27.2–87.2%	13 (56.5)	92 (39.5)		
≥87.2%	6 (26.1)	28 (12.0)		

Values are presented as *n* (%). PICM: pacing-induced cardiomyopathy. Adjusted for age, sex, and BMI. PICM: Pacing-induced cardiomyopathy.

definitions of PICM. Leeand colleagues[11] reported a 20.5% incidence of PICM after a mean follow-up period of 15.6 years in a cohort of 234 patients. They defined PICM as a greater than 5% drop in LVEF from baseline or attributed to HF symptoms. Kiehl *et al*[12] used a borderline definition for PICM to diagnose patients based on either an LVEF decrease ≤40% or meeting the indications for upgrading to CRT for HF management in an 823-patient cohort with normal baseline LVEF (>50%) before permanent pacemakers were implanted as complete AV conduction block. Their final results showed a PICM incidence of 12.3% after a mean follow-up period of 4.3 years. Additionally, the Pacing to Avoid Cardiac Enlargement (PACE) study randomly divided 177 enrolled patients with normal LVEF at baseline into biventricular (CRT) pacing or RV groups. The enrolled patients' mean LVEF was 61.7%. After 1 year, the mean LVEF of the RV pacing group was 54.8%; by contrast, the LVEF in the CRT pacing cohort remained stable at 62.2% ($P < 0.001$). In the RV group, the LV systolic volume increased significantly, accompanied by a drop in LVEF. After a mean follow-up of 4.8 years, the PACE study observed a 23.9% incidence of HF-related hospitalization in the RV pacing group

The Mode Select Trial observed an increased probability of hospitalization due to HF and three times atrial fibrillation occurrence for RV pacing burdens greater than 40% compared to those for pacing percentage values below 40%. The Dual Chamber and VVI Implantable Defibrillator Trial is a cohort trial in which patients with impaired LV function met the indication for defibrillator implantation.[13] This study demonstrated a >30% cumulative death or HF hospitalization incidence at 18 months in patients with RV pacing >40% compared with the <10% cumulative death or HF hospitalization incidence in those with RV pacing burden of <40%. The Multicenter Automatic Defibrillator Implantation Trial II study, another similar study conducted in patients eligible for defibrillator implantation, reported a nearly two-fold increase in the incidence of new-onset HF or HF exacerbation after a 3-year follow-up. This finding derived from the percentage of RV pacing more than 50%, and the outcomes were judged by the investigator on the grounds of patients' symptoms or need for augmentation with pharmacological therapy.[14] A single-center study in Germany enrolled 791 patients with normal LVEF (>55%) at baseline. After a mean follow-up of 44.2 months, only 5% of patients had a LVEF of <40%. Therefore, the investigators concluded that the RV pacing percentage was not a unique predictor of decreased LV function. This finding suggested that various risk factors play complex roles in PICM development.[15] Khurshid *et al*[8] reported that the RV pacing burden for PICM

progression may be below the conventionally accepted pacing burden of 40%. Among patients undergoing pacing burden changes from 20% to 40%, about 13% were diagnosed with PICM. A study of 12 patients after implantation of dual-chamber pacemakers who were interrogated a relatively shorter AV delay compared with the physiological AV conduction time, resulted in a forced RV pacing, and then the patients underwent gated blood pool scans to evaluate for LVEF, decreased LVEF was observed within 2 h (60.3% *vs*. 66.5% at baseline, $P < 0.0002$). A reduction in LV pump function lasted for 7 days, while RV pacing stopped. Although LVEF increased after RV pacing stopped, it remained impaired compared with baseline LVEF for over 24 h after the electro-ventricular activation pattern returned to normal. This finding suggests that the outcomes of impair LV performance in patients after RV pacing are not completely dependent on electrical dys-synchrony. Thus, the relationship between PICM and ventricular pacing percentage remains unclear, and further studies are needed. Aggregate data evidence indicated that not all patients who underwent pacemaker implantation were susceptible to PICM, even those with a higher RV pacing burden. The exact mechanism of this phenomenon is not completely understood. Chen and colleagues[16] reported that 286 pacemaker-implanted patients who had undergone AV junction ablation procedure resulted in a relatively higher frequency of RV pacing. After a mean follow-up of 20 months, no significant decrease in LVEF was observed, and only 8% of the cohort experienced HF-related hospitalization after 10 years.

Additionally, male patients tend to show a higher susceptibility to PICM as well as progression to hypertrophic, stress-induced, dilated cardiomyopathies, and myocarditis.[17-19] To date, it remains unclear which mechanisms were implicated in the observed sex differences or why men are prone to developing cardiomyopathy. Furthermore, RV apex (RVA) pacing has traditionally been thought to negatively impact synchronous ventricular activation and is mainly attributed to decreased basal LV and apical rotation and delayed rotation in LV apical-basal, resulting in LV pump function disability.[20]. Alternative pacing positions such as RV outflow and inter-ventricular septum once showed promise to prevent the clinical outcomes such as RVA pacing. Randomized controlled studies have evaluated the effects of these alternative pacing positions, particularly the chronic side effects on LVEF. Domenichini *et al*[21] reported that RV septum pacing confers no advantage in relation to ventricular function compared with RVA pacing. The PROTECT-PACE study enrolled 240 patients diagnosed with high-grade AV block and anticipated an RV pacing frequency greater than 90%, while the baseline LVEF was greater than 50%. The patients were randomized to the RV apex pacing or high septal region groups. No significant differences were observed in terms of the burden of atrial fibrillation, mortality, plasma brain natriuretic peptide levels, and HF hospitalization.[22]

The exact timing for PICM occurrence remains an active area of research. Several studies have indicated that PICM may develop within 1 to 4 years. However, clinical observations suggest that it may occur even earlier. The PACE study observed a discernible decrease in LVEF after 1 year. Their outcomes showed a decrease from 61.5% at baseline to 54.8% in the RV pacing group. In our study, the earliest case developed PICM within 24 h after pacemaker implantation. Currently, the mechanism of PICM is mainly attributed to aberrant electrical and mechanical activation compared to the physiological heart activation sequence. Inter-ventricular dys-synchrony due to RV pacing subsequently leads to delayed activation at the lateral and basal LV walls, and then the myocardial strain is redistributed, especially around the pacing site, showing early shortening during the systolic period resulting in inadequate myocardial function and impaired contractile activity.[23] Myocardial strain redistribution also leads to aberrant metabolism at the cardiac cellular level and leads to regional myocardial perfusion abnormalities. Electromechanical dysfunctions were also linked to some myocardial mitochondrial enzymes such as mitochondrial DNA of respiratory chain subunits and mitochondrial bioenergetic enzymes, and apoptotic remodeling was found in patients with PICM.[24]

Some clinicians and researchers have suggested that cardiac magnetic resonance scan should be administrated before pacemaker implantation to classify patients at higher risk of progressing to PICM. However, according to the 2018 ACC/AHA/HRS guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay, only disease-specific advanced imaging should be administered for suspected structural heart disease not confirmed by other diagnostic modalities (class of recommendation IIa, level of evidence C). Therefore, it is not reasonable for all patients to undergo cardiac magnetic resonance scan before pacemaker implantation. Additionally, current data and evidence did not show an acceptable proof that cardiac magnetic resonance scan is highly sensitive and specific for the purpose of predicting PICM before pacemaker implantation.

To overcome the detrimental outcomes of RV pacing, biventricular pacing was considered as the most effective pacing form for a long time and as an alternative to RV pacing. However, this method had poor clinical results in patients with non-left bundle branch block (LBBB).[25] In recent days, some scholars and clinicians offer an attractive opinion of His bundle pacing (HBP), which is closest to physiological ventricular pacing. Deshmukh *et al*[26] reported that about 12 of 18 patients had a successful HBP after AV nodal ablation procedure while developed chronic atrial fibrillation and HF. In this cohort, a positive outcome was observed from an improvement in LVEF from $20 \pm 9\%$ to $31 \pm 11\%$ ($P < 0.01$), although some small randomized trials have confirmed the safety and applicability of HBP, long-term studies and randomized trials are still warranted.

Limitations

This study has several limitations. First, the sample size was relatively small. Second, the duration of follow-up was relatively short compared to those in other studies. Finally, we could not verify the actual lead position without echocardiography or cardiac computed tomography.

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Conflicts of interest

None.

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