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Incidence and predictors of pacemaker induced cardiomyopathy: A single-center experience

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ABSTRACT

Background: Pacemaker induced Cardiomyopathy (PICM) is an easily overlooked cause of heart failure with reduced ejection fraction. Data regarding this complication are sparse. Therefore, the aim of this study was to identify the incidence and predictors of PICM.
Methods: Between 2011 and 2017, 857 consecutive patients undergoing pacemaker (PM) implantation, were reviewed, and according to our inclusion criteria 173 individuals were enrolled in this retrospective single center study. All patients included had normal left ventricular ejection fraction (LVEF) before implantation, underwent single-chamber ventricular or dual-chamber PM implantation, had RV pacing burden ≥20%, and repeated echocardiogram was available ≥1 year after implantation. PICM was defined as deterioration LVEF ≥10%, resulting in LVEF <50%, which cannot be explained by other causes.
Results: During a mean follow-up of 39.9 ± 21.0 months, PICM occurred in 26 patients (16%). RV pacing percentage did not differ significantly between the both groups (76.5 vs 76.2%, $p = 0.65$). The PICM group patients were likely to be men ($p = 0.002$) and had a lower rate of arterial hypertension ($p = 0.01$). Multivariate analysis revealed male sex (HR 6.45, 0.95 CI 1.90–21.86, $p = 0.003$) and wider paced QRS complex (HR 1.04, 95% CI 1.02–1.07, $p < 0.001$) as predictors of PICM.
Conclusions: In patients with frequent RV pacing, the prevalence of PICM is not uncommon. Male sex and wider paced QRS complex are independent predictors of PICM and these patients may require closer follow-up.

Introduction

Pacemaker (PM) implantation for patients with bradyarrhythmia is widely used as recommended by current guidelines to reduce cardiac morbidity and mortality [1,2]. Right ventricular (RV) pacing percentage varies between patients and many patients tolerate high percentage RV pacing without complications [3,4]. However, chronic RV pacing may cause electrical and mechanical dyssynchrony which lead finally to reduce left ventricular ejection fraction (LVEF) [4,5]. This deterioration of LVEF has been defined as pacemaker induced cardiomyopathy (PICM) after all other causes of reduced LVEF could be excluded [4,6].

The incidence of PICM was described by many studies and was ranged between 10 and 26% [4–8]. This variation was related to the different definition used for PICM, different sample size (between 130 and 800 patients) and different follow-up period [4]. The predictors for PICM occurrence have not been well studied [4]. Some retrospective analysis tried to define the predictors of PICM [6,9,10]. For instance, QRS complex duration before implantation and baseline LVEF were defined as pre- implantation predictors [4,9]. RV pacing percentage and paced QRS (pQRS) complex duration were defined as post implantation predictors [9,10]. These studies were limited by variation in follow-up period and definition of PICM [4].

In this retrospective study, we therefore aimed to generate more data about the incidence and predictors of PICM in patients who underwent pacemaker implantation in our center.

Methods

We retrospectively screened a total of 857 patients who underwent a permanent single-chamber ventricular or dual-chamber PM implantation between 2011 and 2017. Implantable cardioverter-defibrillator and cardiac resynchronization therapy (CRT) patients were excluded. Individuals who have baseline transthoracic echocardiography (TTE) prior to PM implantation, normal LVEF ≥50% before implantation, repeated TTE ≥1 year after implantation and >20% RV pacing burden were included. A pacing cutoff of 20% was selected based on data from the

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MOST trial demonstrating increased incidence of heart failure above this level [11].

TTE was performed in all patients within 3 months prior to the procedure. LVEF was measured at our hospital using standard transthoracic echocardiographic technique according to modified biplane Simpson's Rule and analysed by a qualified experienced cardiologist. RV Pacing percentage was obtained from device interrogation at the time of follow-up TTE. Regarding pacing algorithm, rate response was activated if chronotropic incompetence was documented. Ventricular intrinsic preference (VIP) algorithm was activated if it was tolerated from the patients. Managed ventricular pacing (MVP) was also activated in patients with intermittent atrioventricular block (AV) type 1 or 2.

QRS complex duration before implantation was measured from 12-lead electrocardiogram (ECG) obtained within 1 day before implantation. Right or left bundle brunch block (RBBB or LBBB) were defined according to the criteria of the American Heart Association, American College of Cardiology and Heart Rhythm Society [6]. Paced QRS (pQRS) duration was measured from 12-lead ECG obtained at the time of follow-up TTE. The position of RV lead was determined from the 2-views chest X-ray (frontal and lateral) performed after implantation. Baseline clinical and demographic parameters were obtained from the electronic medical records.

PICM was defined as deterioration of LVEF ≥10%, resulting in LVEF <50% as previously reported, regardless of heart failure symptoms [4,6,10]. The first time of LVEF deterioration documented by follow-up TTE was considered as PICM. Other possible causes for LVEF deterioration like tachycardiomyopathy, uncontrolled hypertension, coronary artery disease progression, other kind of cardiomyopathy and progression of valvular disease were excluded. Frequent (>10%) premature ventricular contractions (PVCs) were also excluded from the analysis. Other possible causes were assessed by TTE, PM interrogation, Holter ECG, non-invasive stress imaging, or coronary angiogram depending on the clinical context. Patients were divided into PICM and control group. The study was in compliance with the principals outlined in the Declaration of Helsinki.

Statistical analysis

Continuous data are presented as mean ± standard deviation, skewed continuous parameters were expressed as median (interquartile range defined as Q1–Q3). Categorical data were summarized as frequencies and percentages and were compared using $\chi 2$ test. Comparisons between baseline characteristics were performed by independent Student's *t*-test, Mann–Whitney rank-sum, Fisher exact, or $\chi 2$ tests where appropriate. To analyze the association between baseline and procedural parameters on PICM, binary logistic regression analysis was used. Parameters that were found to be univariately associated with the outcome and those that show a slight association with the outcome with $p < 0.05$ were included in the final multivariable analysis. Cox regression analysis was performed to describe PICM. Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). A 2-tailed $p < 0.05$ was considered statistically significant.

Results

Of 857 initially screened patients, 173 patients were included in our final analysis. The other 684 patients were excluded due to missing data or other causes for LVEF deterioration (Fig. 1). The mean age of these 173 patients was 74.9 ± 11.4. No patient had a documented history of heart failure or AV block due to infiltrative cardiomyopathy. All patients had normal LVEF (58.5 ± 2.6) and normal QRS duration (92.1 ± 17.2) before PM Implantation. According to our study criteria, 26/173 patients (16%) developed PICM with post implantation LVEF of 38.6 ± 2.5% in patients with PICM vs 55.4 ± 7.4% in patients in the control group ($p < 0.001$).

Baseline characteristics of the study population are summarized in Table 1. The mean follow-up period was 44.4 ± 19 months in PICM and 39.1 ± 21.0 months in the control group ($p = 0.23$). RV pacing percentage was similar between both groups (76.5 ± 11.2 vs 76.2 ± 9.8%, $p = 0.65$).

The earliest time to PICM development was 12 month and the longest time was 72 months.

Among those with RV pacing percentages 20–39, 40–59, 60–79 and 80–100, the incidence of PICM was 2/22 (9%), 5/26 (19.2%), 4/21 (19.0%), and 15/104 (14.4%), respectively ($p = 0.58$ for comparison across groups). In our study, there was no association between RV pacing percentage and LVEF deterioration. Patients in the PICM group had a lower rate of hypertension (16/26 vs 121/147, $p = 0.016$), were likely to be men (23/26 vs 82/147, $p = 0.002$) and had a wider pQRS duration (148.2 ± 15.5 ms vs 134.7 ± 19.4 ms, $p = 0.001$).

Ten patients from PICM group presented with heart failure symptoms/signs (shortness of breath, fatigue, fluid retention, or any combination of these symptoms). All patients were treated with heart failure medications. Of those, 5 patients required CRT upgrade in addition to heart failure medications. Among all patients included in our final analysis 5 patients died during our follow-up. Three patients died in non PICM groups (2 patients due to severe Sepsis and 1 due to metastatic lung cancer) and two patients died in PICM group (1 due to severe decompensated heart failure and 1 due to metastatic prostatic cancer).

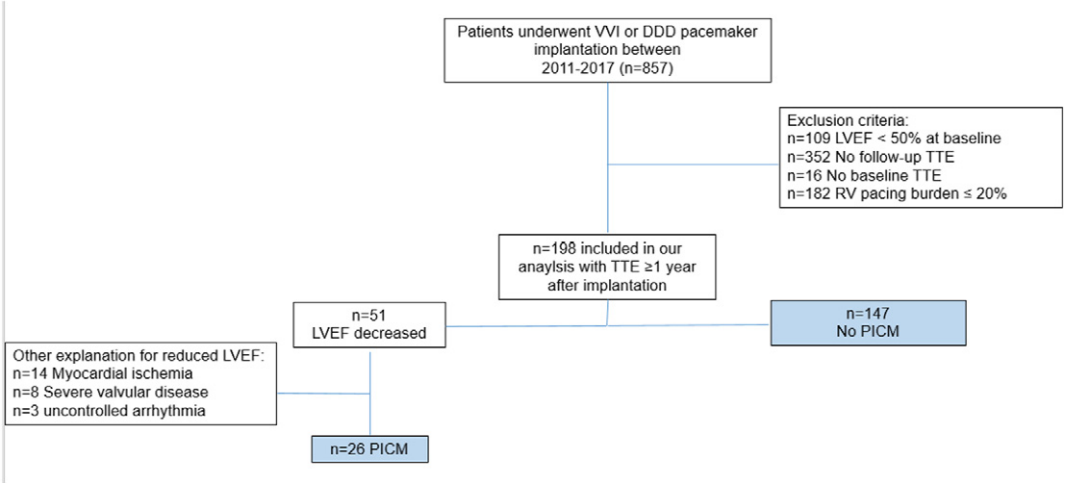

Fig. 1. Study flow-chart following pacemaker implantation and enrolment of the study patients.

Table 1
Baseline and procedural characteristics of study patients.

	PICM	No PICM	p value
Number of patients	26	147	
Age, years	71.85 ± 12.1	75.49 ± 11.2	0.73
Male	88.4% (23)	55.7% (82)	0.002
Pulse (/min)	58 ± 13	61 ± 15	0.38
BMI, kg/m^2	24.5 ± 4.82	26.2 ± 2.56	0.22
Hypertension	61.5% (16)	82.3% (121)	0.01
Diabetes mellitus	26.9% (7)	32.6% (48)	0.62
CAD	19.2% (5)	35.3% (52)	0.11
AF	30.7% (8)	42.8 (63)	0.24
Paroxysmal AF	26.9% (7)	21.7% (32)	0.56
Non paroxysmal AF	3.8% (1)	21% (31)	0.05
Baseline EF, %	58.77 ± 2.4	58.45 ± 2.7	0.36
Baseline QRS, ms	86.7 ± 12	93 ± 17	0.09
LBBB	7.6% (2)	6.8% (10)	0.86
RBBB	19.2% (5)	10.8% (16)	0.23
B-blocker	53.8% (14)	26.5% (92)	0.39
ACE inhibitors	65.3% (17)	76.1% (112)	0.24
Sick sinus syndrome	11.5% (3)	16.3% (24)	0.53
Tachy-brady syndrome	23.1% (6)	34.2% (51)	0.85
AV-block II	23% (6)	17.6% (26)	0.51
AV-block III	42.3% (11)	31.9% (47)	0.23
Dual chamber	84.6% (22)	83% (122)	0.55
Single ventricular chamber	15.4% (4)	17% (25)	0.55
RV apical lead	73.1% (19)	72.2% (106)	0.49
RV septal lead	26.9% (7)	27.8% (41)	0.49
QRS post-implant, ms	148.2 ± 15.5	134.7 ± 19.4	0.04
Follow-up (months)	44.4 ± 19	39.1 ± 21	0.23
RV pacing %	76.5 ± 11.2	76.2 ± 9.8	0.65

AF: atrial fibrillation. LBBB: left bundle brunch block. RBBB: right bundle brunch block. CAD: coronary artery disease. BMI: body mass index.

Multi variable regression analyses

Parameters that were found to be univariately significantly associated with PICM and those that show a slight association with PICM with $p < 0.05$ were included in the final multivariate logistic regression analysis. In multivariate analysis gender, hypertension, paced QRS were included to the model as these parameters had $p < 0.05$ in univariate analysis.

After multivariate analysis, male sex (HR 6.45, 0.95 CI 1.90–21.86, $p = 0.003$) and pQRS duration (HR 1.04, 0.95 CI 1.02–1.07, $p < 0.001$) solely remained as independent predictors of PICM occurrence (Table 2). In receiver operating characteristic curve analysis, pQRS duration ≥140 ms had the best sensitivity (84.5%) and specificity (62.6%) for development of PICM (AUC = 0.768).

Discussion

This retrospective analysis investigated the incidence and predictors of PICM. According to our study criteria, 16% of patients devolved PICM over a mean follow-up period of 39.9 ± 21.0 months. Male gender and a wide pQRS duration were found as predictors of occurrence of PICM.

Many studies reported that the risk of PICM is associated with a high burden of RV pacing [4,11,12]. For example, in the MOde Selection Trial (MOST), hospitalization risk due to heart failure was increased in patients with dual chamber pacing and RV pacing ≥20% compared to those with low RV pacing burden [11].

Table 2
Cox regression analysis.

	β	SE	Wald	df	Significance level	HR	CI 0.95 HR	
Male	2.129	0.691	9.477	1	0.003	6.45	1.90	21.86
pQRS	0.048	0.013	13.419	1	<0.001	1.04	1.02	1.07

SE: Standard error, df: degree freedom, HR: Hazard Ratio, CI: confidence interval, pQRS: paced QRS.

The incidence of PICM was investigated by some studies. Kiehl et al. reported an incidence of PICM of 12.3% for a follow-up period of 4.3 years [13]. Kiehl et al. included 823 patients with complete heart block and normal LVEF requiring permeant PM. PICM was defined as drop in post-implantation LVEF to <40% or the need to CRT upgrade.

Predictors of PICM were investigated by few single-center or small multi-center studies [4,6,14]. A total of 257 patients were enrolled in a retrospective single center study by Khurshid and his colleagues [6]. All patients included had normal LVEF before implantation and underwent single-chamber ventricular or dual-chamber PM implantation. In this study a drop in LVEF ≥10% resulting in LVEF <50% was used as a definition for PICM. A total of 50 patients (19.5%) developed PICM with a decrease in mean LVEF from 62.1% to 36.2% over a mean follow-up period of 3.3 years. PICM occurred in patients with a RV pacing burden of 20%. Multivariable analysis revealed male gender and wider native QRS duration as predictors for PICM [6].

Recently, a retrospective analysis included 234 patients without structural heart disease who required a permanent PM implantation due to sinus node dysfunction or atrioventricular block [9]. PICM was defined as a drop of >5% in LVEF with symptoms of heart failure, while other causes of heart failure were excluded. During a mean follow-up of 15.6 years, 20.5% of patients developed PICM. In multivariate analysis, elderly patients, high myocardial scar score (assessed by ECG), a higher percentage of RV pacing and wider pQRS duration were independent factors associated with the PICM development. pQRS duration >185 ms was 76% specific for the detection of PICM [9].

Very recently, Kim et al. enrolled 130 patients in multicenter retrospective analysis to assess the incidence and predictor of PICM. All patients underwent permanent PM implantation due to complete AV block. LVEF was available before and after implantation. PICM was defined as deterioration of LVEF ≥10%, resulting in LVEF <50% [10]. During a mean follow-up of 4.5 years, PICM was observed in 16.1% ($n = 21$) of all patients. Cox regression analysis revealed wider QRS duration before and after implantation as predictors for PICM. pQRS duration >140 ms was 95% sensitive for the detection of PICM while pQRS duration >167 was 90% specific for the occurrence of PICM.

In our analysis, the incidence of PICM was comparable with previous studies [4,7]. We aimed have more consistent study conditions compared to previous study by including patients with different indication for PM implantation. Moreover, follow-up TTE was available for all patients enrolled in our analysis. We also excluded all other etiologies of LVEF dysfunction.

According to the pacing site, some studies described a benefit of septal RV pacing over apical RV pacing which may have a more physiologic activation pattern and usually a narrower pQRS [14–16]. However, this finding has not been confirmed by recent studies [14,17,18].

In our analysis, we also did not find an association between PICM and RV pacing site.

Additionally, in our analysis, wider pQRS was a strong predictor for development of PICM regardless of pacing site. This finding is in accordance with by previous studies and may be due to electrical and mechanical dyssynchrony, which lead to LVEF deterioration [6,10]. Kim et al. have previously reported that PICM occurrence after long-term RV pacing could be predicted by wide pQRS, but not pacing site [10]. Our results suggest an added value of monitoring for PICM based on a pQRS duration. Similar finding has been reported regarding PVC induced cardiomyopathy based on QRS duration. QRS duration above 151 ms has been shown to have the best diagnostic accuracy for PVC induced cardiomyopathy [19]. Our findings suggest that these patients may require close TTE follow-up (once yearly) and eventually CRT-upgrade or His Pacing [4,19].

Interestingly, in our analysis male sex was an independent predictor for PICM. This finding was also reported by Khurshid et al. [6]. Moreover, gender was described as a risk factor for other cardiomyopathies (stress-induced and dilated cardiomyopathies) [20–21]. Further evaluation is required to understand the sex differences in PICM.

Additionally, some gray zones of PICM would appear and negative effects of RV pacing on LVEF are expected to be continuous. However, in our study population, there was no definite correlation between RV pacing percent and LVEF.

Interestingly, in our univariate analysis, presence of hypertension seems to be protective against PICM. Indeed, as we excluded patients with uncontrolled hypertension the "protective" effect of hypertension on PICM could be due to a selection bias. Furthermore, due to the retrospective design of our study, hypertension diagnosis was taken from our medical records with patients already on antihypertensive treatment. Especially angiotensin-converting-enzyme inhibitor and angiotensin II receptor blockers have been demonstrated to be protective in heart failure, which could be a second factor rendering hypertension protective in our cohort.

There are limitations of this study that need to be acknowledged. This analysis is retrospective in nature with a moderate number of patients. Therefore, it would be difficult to generalize our findings. Additionally, our study has a kind of selection and ascertainment bias due to exclusion of all patients without pre and post TTE and different period of follow-up. Moreover, our definition of PICM was based only on LVEF follow-up without clinical criteria. However, this definition was used by many previous studies. Furthermore, only using TTE as an imaging modality to evaluate LVEF after implantation could lead to LVEF underestimation due to pacing induced dysynchrony of LV contraction. Chest x-ray was the only used method to determine the lead position which is not always accurate in determining the lead position.

Conclusions

The prevalence of PICM is not uncommon in patients with high RV pacing burden. Male sex and wider pQRS are independent predictors of PICM. While the diagnosis of PICM is based on exclusion of other cardiac causes, special attention and closer follow-up is required for those patients with a high risk for development of PICM.

Declaration of competing interest

No conflict of interests.

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