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Paced QRS duration is a Major Determinant for the Occurrence of Pacing-Induced Cardiomyopathy in Complete AV Block: A Multi-Center Observation over a 15-Year Period

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Running title: major determinant for pacing-induced cardiomyopathy

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Abstract

Objectives The predictors of pacing-induced cardiomyopathy (PICM) for complete atrioventricular (AV) block (CAVB) have not yet been defined. The aim of this study was to investigate the major determinant for the occurrence of PICM.

Setting Multi-center retrospective analysis of CAVB from tertiary referral centers in Deajeon, South Korea

Participant A cohort of 900 consecutive patients with an implanted pacemaker was collected from December 2001 to August 2015. Of these, a total of 130 CAVB patients with pacing-dependent rhythm who underwent ECG and echocardiogram before and after implantation were analyzed for the occurrence of PICM.

Outcome Measures Cox proportional hazards models evaluated the determinant of PICM by ECG, device parameters and echocardiogram over a mean of 4.5 (IQR 4.8–7.2) years.

Results PICM was observed in 16.1% (n=21) of all patients with CAVB (age, 64±11 years; male, 36.2%). The pre-implant left ventricular (LV) ejection fraction (66±9% vs. 66±8%) and non-apical pacing (40.4% vs. 33.3%) were similar; however, the native QRS duration (nQRSd) (124±34 ms vs. 149±32 ms) and the paced QRS duration (pQRSd) (139±29 ms vs. 167±28 ms) were significantly different between the two groups. The post-implant LV ejection fraction (61±7% vs. 31±8%) was also significantly different at the end of follow-up. A pQRSd significantly correlated with PICM (HR 1.05, 95% CI 1.02 to 1.09, p=0.001). A pQRSd above 140 ms was cut-off value with a sensitivity of 95%, while pQRSd above 167 ms was cut-off with a specificity of 90% for PICM.

Conclusion In CAVB patients with pacing-dependent rhythm, regardless of the pacing site, the pQRSd is a major determinant for occurrence of PICM.

Keywords: complete AV block, pacemaker, cardiomyopathy

Strengths and limitations of this study

- Our study enrolled only CAVB patients with pacing-dependent rhythm and pre-implant normal LV function, and excluded all patients with potentially confounding, alternative causes (pre-existing persistent/permanent AF, coronary artery disease, cardiac surgery and LV dysfunction) for heart failure at pre-implant state.

- A pQRSd was significantly associated with the occurrence of PICM during follow-up regardless of the pacing site. In addition, patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. A pQRSd should be monitored for the timely exact evaluation and management of patients at risk of PICM to reduce cardiac adverse events.

- CAVB patients without pre-implant or post-implant echocardiogram were excluded for analysis and appropriate universal definition of PICM is needed.

INTRODUCTION

Pacemakers have been a definite treatment tool for symptomatic brady-arrhythmia to reduce cardiac morbidity and mortality[1]. However, chronic right ventricular (RV) pacing has a potentially deleterious effect on left ventricular (LV) function[1-4]. This deleterious effect of chronic RV pacing on LV function is known as pacing-induced cardiomyopathy (PICM). Pacing induced electrical dyssynchrony with different pacing burden[5] develop mechanical dyssynchrony of the LV, subsequently causing PICM[1 4-6]. Several studies have suggested that RV apical pacing may be more likely to cause PICM than non-apical pacing[3]. However, a randomized trial showed that RV non-apical pacing does not confer any protective effect on LV function compared to RV apical pacing[7]. In addition, a 20-40% increase in RV pacing burden is associated with a greater risk of heart failure[8]; however, another study showed that a reduction of ventricular pacing did not improve clinical outcomes[9]. Until now, available data on the relationship between chronic RV pacing and PICM are still inconclusive. Pacing site, pacing burden and pre-implant LV function are considered risk factors for the occurrence of PICM in patients with chronic RV pacing[1 3 7 10]. In particular, complete atrioventricular block (CAVB) patients who have pacing-dependent rhythm seem to be at higher risk of developing PICM. If predictors for the occurrence of PICM could be identified among CAVB patients, then patients at high risk for the occurrence of PICM could receive timely management, thereby potentially preventing the development of cardiac morbidity and mortality. However, because PICM does not occur in all CAVB patients with chronic RV pacing, timely and proper evaluation should be considered for those who most likely have pacing-dependent rhythm-associated PICM[10]. Therefore, we retrospectively analyzed a large cohort to identify the major determinants of the occurrence of PICM in CAVB patients with pacing-dependent rhythm over a long period of time.

METHODS

Study population

Consecutive patients with an implanted pacemaker were retrospectively collected from three different tertiary referral centers, Eulji University, Chungnam National University, and Catholic Saint Hospital, which are located in Daejeon, South Korea from December 2001 to August 2015. Among a total of 900 patients with an implanted

pacemaker, patients with sick sinus syndrome, paroxysmal and advanced AV block (n=482), persistent/permanent atrial fibrillation (n=140) and pre-implant LV dysfunction (n=148) combined with ischemic heart disease, including acute coronary syndrome, other proven cardiomyopathy or severe valvular disease at the pre-implant period were excluded from the study. Our investigators excluded pre-existing persistent/permanent atrial fibrillation and significant coronary artery disease, which are considered risk factors for the occurrence of heart failure and could influence the relationship between CAVB and PICM. Thus, CAVB patients (n=130) with documented pre- and post-implant LV ejection fraction (LVEF) were analyzed in this study (Supplemental Figure). All patients provided informed consent, and institutional review board approval was acquired from each center and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

LVEF was measured at Eulji and Chungnam University Hospital using standard echocardiographic techniques. Pre-implant and post-implant (at least 1 day after the index implant) echocardiograms were performed and interpreted by two experienced cardiologists who were echocardiogram specialists (Professor. JY Chin at Eulji University Hospital and Professor. HJ Park at Chungnam University Hospital). None of the patients developed myocardial infarction during the follow-up period, and the baseline clinical and demographic data, ECG and echocardiographic data, and medication data were acquired from the electronic medical records. Baseline ECG parameters were acquired from the ECG that was performed closest to the pre-implant period using the standard criteria established by the American Heart Association (AHA) and HRS Expert Consensus[11]. Pacemaker data were also acquired at regular intervals (at least six months), and the pacing burden (atrial and ventricular pacing %) was recorded at the time of follow-up and PICM diagnosis.

ECG and definition of PICM

Native QRS duration (nQRSd) and paced QRS duration (pQRSd) were measured from the surface ECG within 7 days pre-implant and post-implant as well as during the follow-up period. PICM was defined as more than a 10% decrease in LVEF with a resultant LVEF less than 50%, as previously reported[10], regardless of heart failure symptoms[12]. The time of PICM occurrence was considered the date of the first decrease in LVEF determined by echocardiogram during the follow-up period.

Statistical analysis

Baseline clinical, ECG, echocardiogram and device interrogation data of the enrolled patients were compared between those without PICM and with PICM using independent t-test and chi-square. To determine independent predictors of PICM occurrence, the multivariate Cox regression hazard model was used for PICM. An ROC curve was plotted to identify the cut-off value with the best sensitivity and specificity for the occurrence of PICM, and a Kaplan-Meier curve was plotted for free-from-PICM survival. Analyses were performed with the MedCalc software (version 17.0, USA). P values <0.05 were considered to be statistically significant.

RESULTS

Comparison of baseline characteristics between patients without with and without PICM

Among all patients, 130 CAVB patients with implanted pacemakers (dual chamber: 84.6%) were suitable for the analysis of PICM in this study. The average age (64±11 years vs. 62±11 years), the proportion of men (36.7% vs. 33.3%) and the occurrence of atrial fibrillation (AF) (14.6% vs. 14.2%) was detected among patients without PICM and with PICM during the follow-up period, and the mean duration of follow-up (4.8±3.5 years vs. 4.2±3.5 years) was similar between patients without PICM and with PICM. Other baseline clinical characteristics, except for diabetics and previous stroke, were also similar between patients without PICM and with PICM. Among the laboratory data, hemoglobin and total bilirubin levels, which are associated with heart failure, were similar between patients without PICM and with PICM at pre-implant and post-implant stages (Table 1).

Comparison of ECG data between patients with and without PICM

Among the 130 patients, 109 patients maintained normal LV function until the end of follow-up. The remainder of the CAVB patients (n=21, 16.1%) were considered to have PICM, with a decrease in LVEF from 65±10% at baseline to 37±8%. The follow-up ventricular pacing burden was similar between the patients without PICM and with PICM (85±18% vs. 85±17%). Compared to the patients without PICM, the patients who developed

PICM had a significantly wider nQRSd (124±34 ms vs. 149±32 ms, p=0.004), QTc interval (466±54 ms vs. 495±44 ms, P=0.035), and pQRSd (139±29 ms vs. 167±28 ms, p<0.001) (Table 2).

Comparison of medications between patients with and without PICM

Unlike the patients without PICM, the patients with PICM more frequently took angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) medication before implantation and β-blockers and diuretics after implantation, as shown in Table 4.

Predictors of PICM occurrence

Multivariate Cox regression analysis showed that nQRSd had a hazard ratio (HR) of 1.01 and a 95% confidence interval (CI) of 1.00–1.03 with a P value of 0.051 and that pQRSd had an HR of 1.05 and a 95% CI of 1.02–1.09 with a P value <0.001 (Table 3). Receiver operating characteristic curve analysis showed that a pQRSd above 140 ms had the combined the best sensitivity (95%) with specificity (36%) and pQRS above 167 ms had the combined sensitivity (52%) with the best specificity (90%) for predicting the occurrence of PICM with statistical significance (Figure 1). In the Kaplan-Meier curve, both pQRSd 140ms (Figure 2-1) and 167 ms (Figure 2-2) was significantly associated with the occurrence of PICM (log rank, p=0.03 vs. p<0.001).

DISCUSSION

In our study, among the CAVB patients with normal LV function at the pre-implant period, PICM occurred in 16.1% of the patients with pacing-dependent rhythm over a mean follow-up duration of 4.7±3.5 years. A pQRSd was significantly associated with the occurrence of PICM. In particular, a pQRSd wider than 140ms had a sensitivity of 95% and 167 ms had a specificity of 90% for predicting the occurrence of PICM.

Our result for the incidence of PICM over a long-term follow-up period is comparable to that from previous reports, ranging from 9% to 26% depending on the population investigated and the length of the follow-up[4 10]. We also defined PICM as more than a 10% decrease in LVEF with a resultant LVEF less than 50% at least 1 day after the index implant. The time to the diagnosis of PICM was defined as the period from the date of

implantation to the date of the first documented decrease in LVEF.

PICM have been widely considered as the pacing-associated heart failure[1 10]. The significance of PICM has been established for an increased risk in AF, heart failure hospitalization and cardiac mortality[8]. Independent predictors of PICM have been considered to be the pacing site, increased pacing burden, pre-implant LV dysfunction and QRS duration[1-4 10 13].

First, with regard to the pacing site, recent meta-analysis has suggested that the LVEF is higher in patients with RV non-apical pacing than those with RV apical pacing. However, this conclusion is still debated due to conflicting results[3 14]. In the PROTECT-PACE study, among patients with a high-grade AV block and preserved LV function, RV non-apical pacing did not have a protective effect on LV function compared to RV apical pacing over a 2-year period[7]. Our multi-center study also showed no significant difference between RV apical and non-apical pacing for the occurrence of PICM (40.4% vs. 33.3%, p=0.546) among CAVB patients with pacing-dependent rhythm over a long-term follow-up period. Our data suggest a simply measured parameter as a predictor to justify QRS duration rather than anatomical pacing site for PICM.

Second, pacing burden has been considered a better predictor for the occurrence of PICM, and previous studies have shown heterogeneous percentages of pacing burden[2]. In our study, in CAVB patients who required a high burden of permanent pacing, the confounding factor was minimized using homogeneous percentages of RV pacing (85% vs. 85%, p=0.860) when analyzing the predictors of PICM.

Third, with regard to pre-implant LV dysfunction, previous studies had baseline pre-existing heart failure associated with coronary artery disease and AF[4 10], and in the PREDICT-HF trial, pre-existing heart failure was highly associated with pQRSd. Other studies have also found pQRSd to be an important predictor of heart failure among patients with chronic RV pacing[15-17]. In our study, all CAVB patients without pre-existing heart failure, with a baseline normal LVEF (66±9% vs. 65±10%), were included, and our results were reliable enough to include the analysis of PICM compared to previous studies.

Fourth, pacing-induced electrical dyssynchrony developed mechanical dyssynchrony; thus, the pQRSd could be a strong and independent determinant for the occurrence of PICM[6]. Our data also show that the pQRSd related to LV mechanical dyssynchrony has been confirmed to be significantly associated with LV remodeling

(representative of the dyssynchrony index with strain in the 2- or 3-dimensional parameters), resulting in the occurrence of PICM by echocardiogram.

Pap et al. reported that nQRSd could be positively correlated with pQRSd, although the escape nQRSd is influenced by the level of antegrade block on the His-Purkinje system during AV block[18]. In addition, an nQRSd above 115 ms was highly specific (90%) for the occurrence of PICM as reported in a single-center study[19]. A single-center study by Khurshid et al. also suggested that the nQRSd (HR=1.03 per ms; p<0.001) is an independent predictor of PICM occurrence[15]. In comparison, our study reported an nQRSd above 115 ms in patients without PICM and with PICM (55% vs. 74%) (Table 2). However, the incidence of PICM was similar between the patients with nQRSd narrower than 115 ms and wider than 115 ms over a long period of time. The nQRSd (HR=1.02; p=0.010) was slightly significant in our univariate analysis and exhibited a positive trend (HR=1.01; p=0.051) in the multivariate analysis of the occurrence of PICM (Table 3). It is implicated that a wider nQRS suggests that there may be predisposition to cardiomyopathy. In particular, among CAVB patients with normal LV function before implant, wider nQRSd may reflect more pathological electrical His-Purkinje conduction.

Miyoshi et al. also proposed that a pQRSd wider than 190 ms suggested a greater morbidity rate than a pQRSd below 190 ms[20]. However, the enrolled patients had ischemic heart disease, valvular heart disease and other causes of cardiomyopathy, whereas our study did not. Chen et al. prospectively showed in 194 CAVB patients without heart failure over a 3-year follow-up that clinical heart failure events were higher and the LVEF was lower among patients with a wider pQRSd. In addition, a pQRSd of 165 ms had the best specificity (67%) for predicting heart failure[16], and a single-center study by Kurshid et al. also proposed that a pQRSd of 150 ms was a sensitive marker for PICM; however, those enrolled patients also had pre-existing AF, coronary artery disease and unknown cardiomyopathies[15].

Taken together, a wider pQRSd could be a major determinant of the occurrence of PICM. We also found that delayed signs and symptoms of heart failure reduce the early detection of PICM in the patients with pacing-dependent rhythm and that not all patients with PICM meet the clinical criteria for heart failure despite a significant reduction of LVEF. This is consistent with previous studies showing only low sensitivity for the diagnosis of heart failure with reduced LV function. Therefore, a more sensitive and specific marker for PICM

occurrence may be required for patients with pacing-dependent rhythm.

Our study analyzed a contemporary cohort of CAVB patients and provided a detailed characterization of the clinical, electrocardiographic, laboratory and echocardiographic data at both pre-implant and post-implant periods as well as at the end of the long-term follow-up. Our multi-center study showed that a pQRSd was significantly associated with the occurrence of PICM during the long-term follow-up regardless of the pacing site. In addition, patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. Therefore, even though pQRSd correlates with occurrence of PICM, pQRSd <140 ms could exclude occurrence of PICM and pQRSd >167 ms could not exclude non-PICM state for follow-up.

We suggested major determinant, wider pQRSd, thus enabling the identification of occurrence of PICM that theoretically could be a reason for using echocardiogram and reversed with preventive His-bundle pacing or biventricular pacing before clinical manifestation.

Our study has several limitations. First, our study was a retrospective study with unmeasured selection bias. Especially, patients without pre-implant or post-implant echocardiogram were excluded for analysis. Second, this was a multi-center study, and thus, the influence of different physicians on clinical decision-making may also influence the clinical variables associated with heart failure. Third, the definition of PICM was defined only with LVEF based on anecdotal evidence from a previous study. An appropriate universal definition of PICM is needed. Fourth, it is unlikely that patients with subclinical PICM may undergo incidental follow-up echocardiograms at an out-patient clinic. Fifth, while we excluded all potential etiologies of heart failure, it is speculated that a wider nQRSd is associated with the occurrence of PICM because it reflects cardiomyopathy with normal LV function at pre-implant stage. The nQRSd was not significantly predictive for the occurrence of PICM in the multivariate analysis, but univariate analysis of the nQRSd showed that it was a significant predictor. This could be the reason why the nQRSd is likely to affect the pQRSd in patients with chronic RV pacing. Thus, more detailed studies on the relationship between the nQRSd and an electrical pathology or substrate in CAVB patients with normal LV function are needed. Sixth, the ability to upgrade to biventricular pacing or Hi-bundle pacing for a pQRSd over 150 ms was limited in patients with PICM in our study because of the strict coverage of the national health insurance.

Early detection and preventive management of PICM are challenging in patients with pacing-dependent rhythm because there are few data to guide clinicians in identifying subclinical and clinical PICM in the subsequent months to years after pacemaker implantation.

CONCLUSION

The occurrence of PICM in patients with pacing-dependent rhythm seems to be common but cannot be reliably diagnosed based on the conventional heart failure criteria. The pQRSd, which was higher than the nQRSd, is associated with the occurrence of PICM. In particular, a patient with a pQRSd above 140ms had the best sensitivity and above 167ms had the best specificity of occurrence for PICM. Regardless of the pacing site, the pQRSd should be monitored for the timely evaluation and proper management of patients at high risk of PICM to reduce cardiac morbidity and mortality over a long follow-up period.

Contributorship Statement

Dr. Ki-Woon Kang designed the study and revised the manuscript in the final version.

Dr. Jun Hyung Kim, Dr. Yu Jeong Choi, and Dr. Tae-Seok Kim collected and analyzed the clinical characteristic, ECG and pacemaker interrogation data.

Dr. Jung Yeon Chin and Dr. Jae-Hyeong Park collected and analyzed the echocardiogram data.

Conflict of Interest

The authors have no conflict of interest to declare.

No funding

Ethics approval:

The study was approved by the institutional review board approval of each center in South Korea

No data sharing

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Figure Legends

Figure 1. ROC curve analysis showing the pQRSd had correlated with PICM occurrence and two rectangular black marks showing the best sensitivity (pQRS 140ms) and specificity (pQRS 167ms) with statistical significance.

Figure 2. Kaplan-Meier curve analysis showing free-from PICM survival with a pQRSd (cut-off value of 140ms and 167 ms).

Supplemental Figure. Flow chart of the stratified study population.

Table 1. Baseline characteristics between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Age, y	64±11	64±11	62±11	0.472
Male, n (%)	47 (36.2)	40 (36.7)	7 (33.3)	0.768
Hypertension, n (%)	75 (57.7)	58 (53.2)	16 (76.2)	0.146
Diabetes, n (%)	31 (24.0)	30 (27.5)	1 (5.0)	0.030*
IHD, n (%)	15 (11.5)	11 (10.1)	4 (19.0)	0.239
Stroke or TIA, n (%)	9 (6.9)	5 (4.6)	4 (19.0)	0.017*
Alcohol, n (%)	16 (12.3)	13 (11.9)	3 (13.3)	0.763
Smoking, n (%)	18 (13.8)	16 (14.7)	2 (9.5)	0.531
Hemoglobin, g/L	12.3±2.1	12.1±1.9	12.4±2.6	0.660
Total bilirubin, mg/dL	1.0±0.8	1.0±0.6	1.0±0.8	0.556

IHD: ischemic heart disease; * statically significant.

Table 2. Comparison of ECG parameters between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
Ejection fraction, n (%)	65±10	66±9	65±10	0.607
Left atrial diameter, mm	39±9	38±7	40±8	0.552
Heart rate, bpm	60±30	57±18	60±12	0.550
PR interval, ms	190±81	170±115	213±130	0.203
QRS duration, ms	136±26	124±34	149±32	0.004*
QTc interval, ms	480±37	466±54	495±44	0.035*
Post-implant				
Dual chamber, n (%)	110 (84.6)	90 (82.5)	20 (95.2)	0.142
Ejection fraction, n (%)	45±8	61±7	37±8	<0.001*
Left atrial diameter, mm	40±7	39±7	40±6	0.266
Occurrence of AF, n (%)	19 (14.6)	16 (14.6)	3 (14.2)	0.962
Heart rate, bpm	68±30	69±14	67±9	0.616
PR interval, ms	178±81	168±80	187±62	0.337
Paced QRS duration, ms	149±26	139±29	167±28	<0.001*
Paced QRS axis, degree	2±78	2±78	1±91	0.971
Paced QTc interval, ms	490±37	484±46	496±36	0.254
Non-apical pacing, %	51 (39.1)	44 (40.4)	7 (33.3)	0.546
Atrial pacing, %	23±22	23±23	22±22	0.954

Ventricular pacing, %	85±17	85±18	85±17	0.860

AF: atrial fibrillation; * statistically significant.

Table 3. Cox Regression Analysis for the Occurrence of PICM

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, per year	1.01	0.97-1.06	0.371			
Gender, male	0.90	0.35-2.30	0.833			
Diabetes mellitus	0.29	0.03-2.26	0.297			
nQRSd, per ms	1.02	1.00-1.04	0.010*	1.01	1.00-1.03	0.051
nQTc interval, per ms	1.00	0.99-1.08	0.195			
pQRSd, per ms	1.05	1.03-1.08	<0.001*	1.05	1.02-1.09	0.001*
Non-apical pacing	0.35	0.11-1.10	0.074			

HR: hazard ratio; CI: confidence interval; ms: millisecond * statistically significant.

Table 4. Comparison of medications between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
ACEI or ARB, n (%)	50 (38.5)	37 (33.9)	13 (61.9)	0.016*
Beta-blocker, n (%)	16 (12.3)	11 (10.1)	5 (23.8)	0.080
CCB, n (%)	26 (20.0)	22 (20.2)	4 (19.0)	0.905
Diuretics, n (%)	30 (23.1)	22 (20.2)	8 (38.1)	0.074
Post-implant				
ACEI or ARB, n (%)	58 (44.6)	45 (41.3)	13 (61.9)	0.082
Beta-blocker, n (%)	22 (16.9)	15 (13.8)	7 (33.8)	0.029*
CCB, n (%)	31 (23.8)	28 (25.7)	3 (14.3)	0.262
Diuretics, n (%)	32 (24.6)	23 (21.1)	9 (42.9)	0.034*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensinogen receptor blocker;

CCB: calcium channel blocker; * statistically significant.

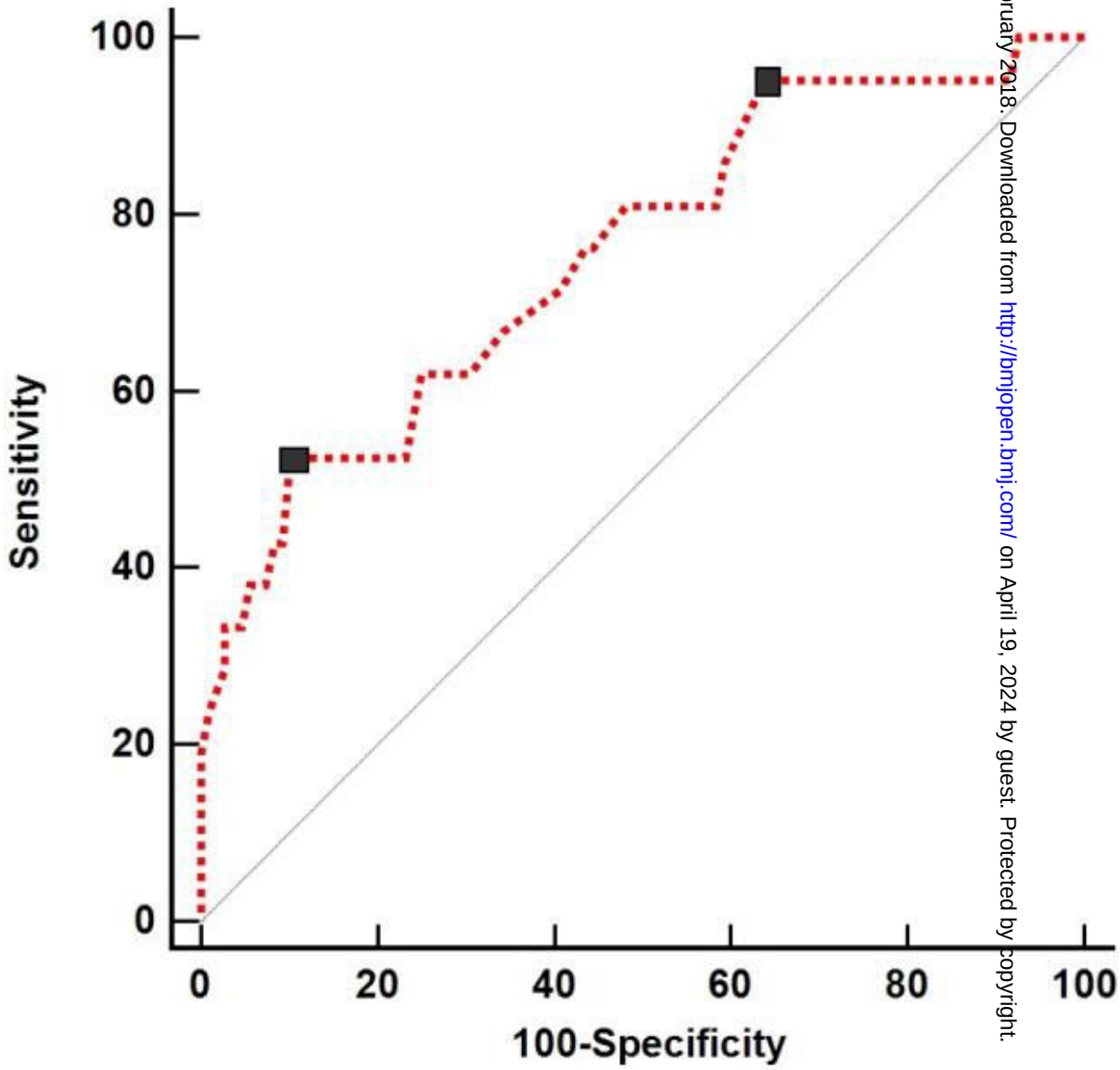


Figure 1

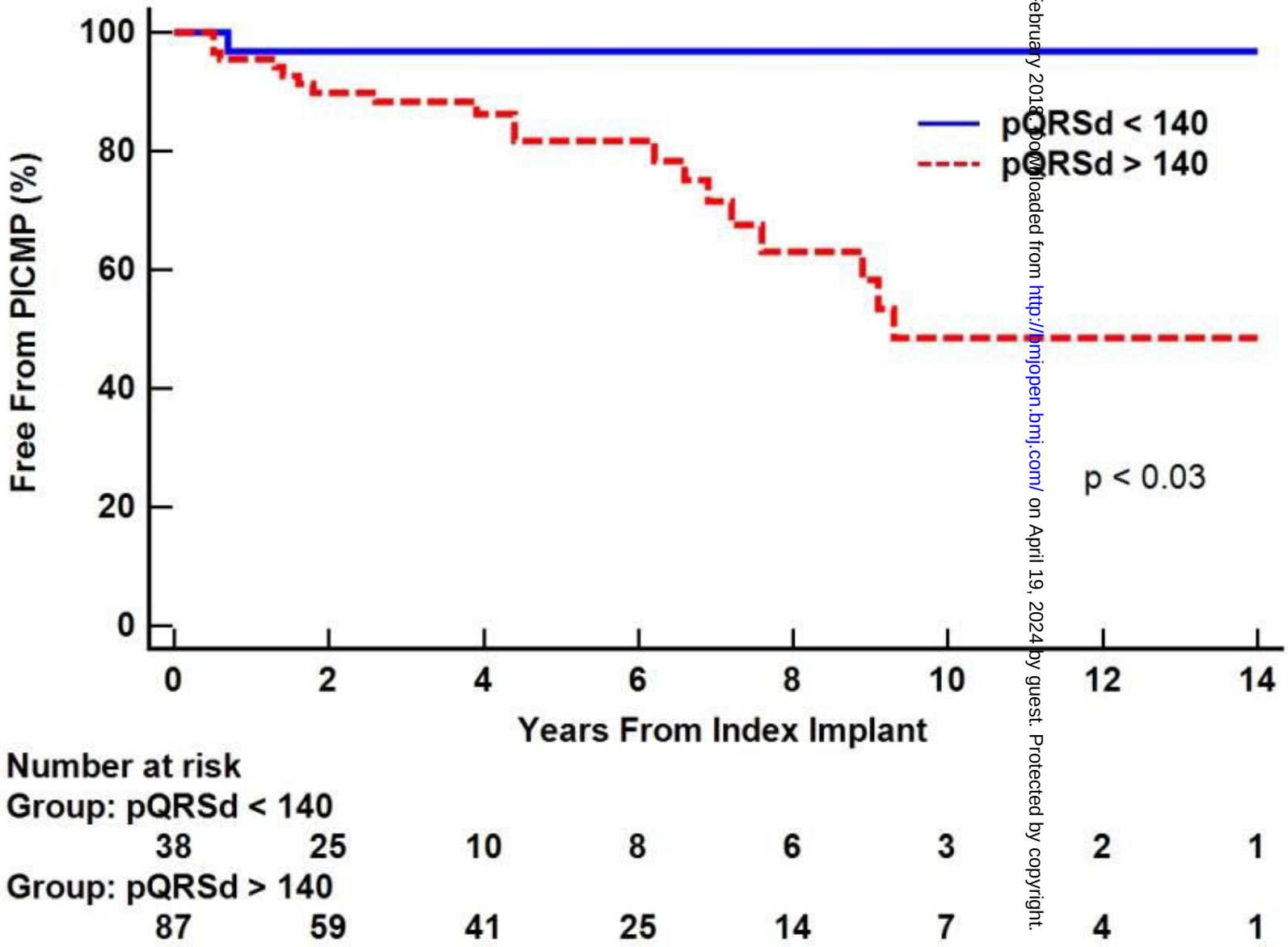


Figure 2-1

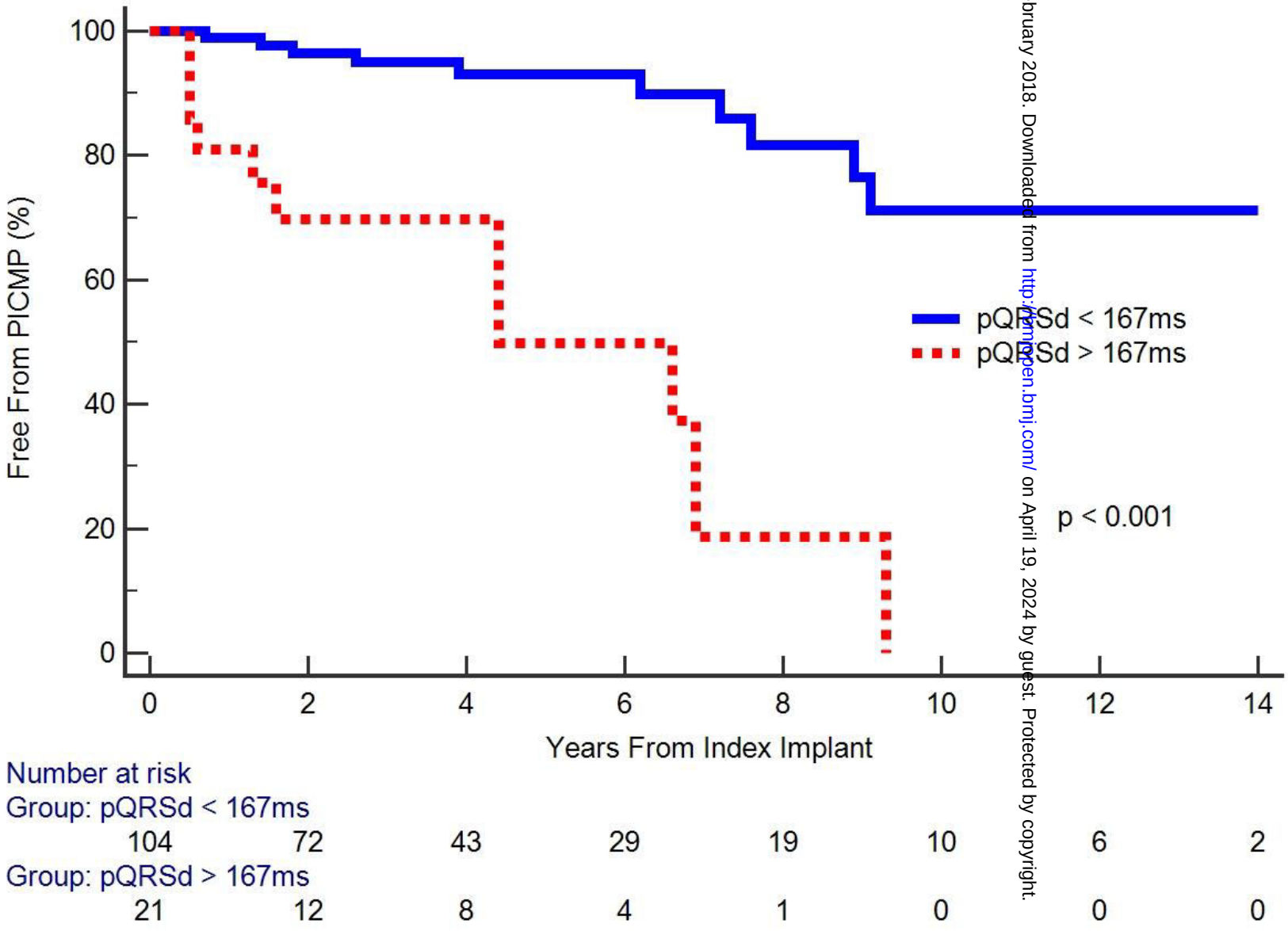
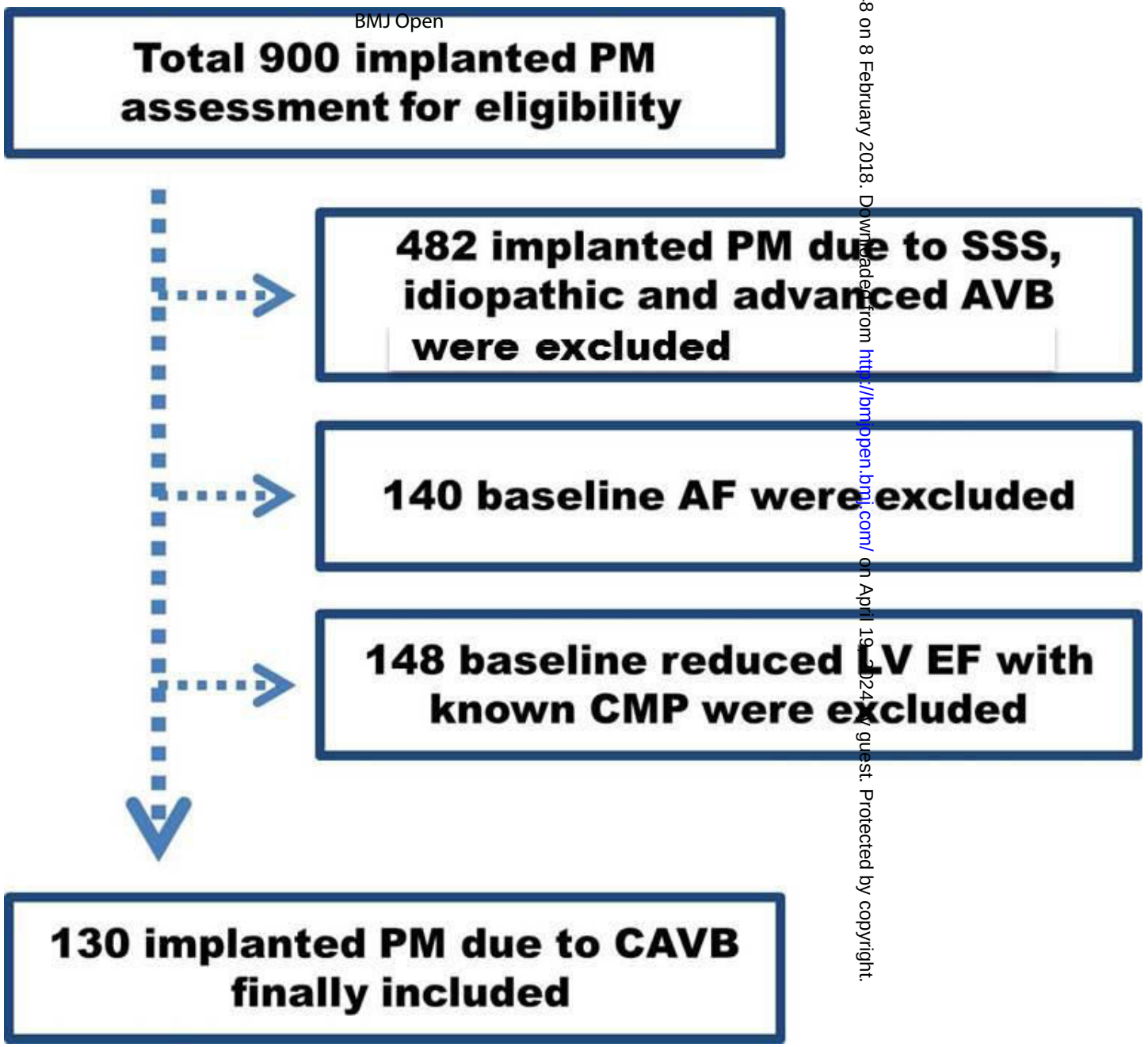


Figure 2-2



Supplemental Figure

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4-5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4-5
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	5
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
	10c	V	For validation, describe how the predictions were calculated.	6
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	6
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	7
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	7
	15b	D	Explain how to the use the prediction model.	7
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	7
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	7
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	8
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	10
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	10
Other information0				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	0
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	20

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Paced QRS duration is a Major Determinant for the Occurrence of Pacing-Induced Cardiomyopathy in Complete AV Block: A Multi-Center Observation over a 15-Year Period

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Paced QRS duration is a Major Determinant for the Occurrence of Pacing-Induced Cardiomyopathy in Complete AV Block: A Multi-Center Observation over a 15-Year Period

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Running title: major determinant for pacing-induced cardiomyopathy

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Abstract

Objectives The predictors of pacing-induced cardiomyopathy (PICM) for complete atrioventricular (AV) block (CAVB) have not yet been defined. The aim of this study was to investigate the major determinant for the occurrence of PICM.

Setting Multi-center retrospective analysis of CAVB from tertiary referral centers in Deajeon, South Korea

Participant A cohort of 900 consecutive patients with an implanted pacemaker was collected from December 2001 to August 2015. Of these, a total of 130 CAVB patients with pacing-dependent rhythm who underwent ECG and echocardiogram before and after implantation were analyzed for the occurrence of PICM.

Outcome Measures Cox proportional hazards models evaluated the determinant of PICM by ECG, device parameters and echocardiogram over a mean of 4.5 years.

Results PICM was observed in 16.1% (n=21) of all patients with CAVB (age, 64±11 years; male, 36.2%). The pre-implant left ventricular (LV) ejection fraction (66±9% vs. 66±8%) and non-apical pacing (40.4% vs. 33.3%) were similar; however, the native QRS duration (nQRSd) (124±34 ms vs. 149±32 ms) and the paced QRS duration (pQRSd) (139±29 ms vs. 167±28 ms) were significantly different between the two groups. The post-implant LV ejection fraction (61±7% vs. 31±8%) was also significantly different at the end of follow-up. A pQRSd significantly correlated with PICM (HR 1.05, 95% CI 1.02 to 1.09, p=0.001). A pQRSd above 140 ms was cut-off value with a sensitivity of 95%, while pQRSd above 167 ms was cut-off with a specificity of 90% for PICM.

Conclusion In CAVB patients with pacing-dependent rhythm, regardless of the pacing site, the pQRSd is a major determinant for occurrence of PICM.

Keywords: complete AV block, pacemaker, cardiomyopathy

Strengths and limitations of this study

- Our study enrolled only CAVB patients with pacing-dependent rhythm and pre-implant normal LV function, and excluded all patients with potentially confounding, alternative causes (pre-existing persistent/permanent AF, coronary artery disease, cardiac surgery and LV dysfunction) for heart failure at pre-implant state.

- A pQRSd was significantly associated with the occurrence of PICM during follow-up regardless of the pacing site. In addition, patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. A pQRSd should be monitored for the timely exact evaluation and management of patients at risk of PICM to reduce cardiac adverse events.

- CAVB patients without pre-implant or post-implant echocardiogram were excluded for analysis and appropriate universal definition of PICM is needed.

INTRODUCTION

Pacemakers have been a definite treatment tool for symptomatic brady-arrhythmia to reduce cardiac morbidity and mortality[1]. However, chronic right ventricular (RV) pacing has a potentially deleterious effect on left ventricular (LV) function[1-4]. This deleterious effect of chronic RV pacing on LV function is known as pacing-induced cardiomyopathy (PICM)[1 4-6]. Several studies have demonstrated that pacing anatomical site, pacing burden and pre-implant LV dysfunction make difference of effect on the occurrence of PICM and its subsequent clinical outcomes[1 3 7-9]. In particular, recognition of predictors for occurrence of PICM may lead to better identification of patients at high risk in the complete atrioventricular block (CAVB) with pacing-dependent rhythm. However, because PICM does not occur in all CAVB patients with chronic RV pacing, timely and proper evaluation should be considered for those who most likely have pacing-dependent rhythm-associated PICM[7]. Therefore, we retrospectively analyzed a large cohort to identify the major determinants of the occurrence of PICM in CAVB patients with pacing-dependent rhythm over a long period of time.

METHODS

Study population

Consecutive patients with an implanted pacemaker were retrospectively collected from three different tertiary referral centers, Eulji University, Chungnam National University, and Catholic Saint Mary's Hospital, which are located in Daejeon, South Korea from December 2001 to August 2015. Among a total of 900 patients with an implanted pacemaker, patients with sick sinus syndrome, paroxysmal and advanced AV block (n=482), persistent/permanent atrial fibrillation (n=140) and pre-implant LV dysfunction (n=148) combined with ischemic heart disease[10], including acute coronary syndrome, other proven cardiomyopathy or severe valvular disease at the pre-implant period were excluded from the study. Our investigators excluded pre-existing persistent/permanent atrial fibrillation and significant coronary artery disease, which are considered risk factors for the occurrence of heart failure and could influence the relationship between CAVB and PICM. Thus, CAVB patients (n=130) with documented pre- and post-implant LV ejection fraction (LVEF) were analyzed in this study (Supplemental Figure 1). All patients provided informed consent, and institutional review board approval

was acquired from each center and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

LVEF was measured at Eulji, Chungnam University and St Mary's Hospital using standard echocardiographic techniques. Pre-implant and post-implant (at least 1 day after the index implant) echocardiograms were performed and interpreted by two experienced cardiologists who were echocardiogram specialists (Professor. JY Chin at Eulji University Hospital and Professor. HJ Park at Chungnam University Hospital). None of the patients developed myocardial infarction during the follow-up period, and the baseline clinical and demographic data, ECG and echocardiographic data, and medication data were acquired from the electronic medical records.

ECG parameters, pacemaker data and definition of PICM

Baseline ECG parameters were acquired from the ECG that was performed closest to the implant period using the standard criteria established by the American Heart Association (AHA) and HRS Expert Consensus[11]. RV pacing-leads sites were reviewed using the standard X-ray (Supplemental Figure 2). Pacemaker data were also acquired at regular intervals (at least six months), and the pacing burden (atrial and ventricular pacing %) was recorded at the time of follow-up and PICM diagnosis. Native QRS duration (nQRSd) was measured within 7 days at pre-implant state and paced QRS duration (pQRSd) was also measured within 7 days at the post-implant state from the surface 12 lead ECG.

PICM was defined as more than a 10% decrease in LVEF with a resultant LVEF less than 50%, as previously reported[7], regardless of heart failure symptoms[4 12 13] (Supplemental Video 1 and 2). The time of PICM occurrence was considered the date of the first decrease in LVEF determined by echocardiogram with documented ECG at the time during the follow-up period.

Statistical analysis

Baseline clinical, ECG, echocardiogram and device interrogation data of the enrolled patients were compared between those without PICM and with PICM using independent t-test and chi-square. To determine independent predictors of PICM occurrence, the multivariate Cox regression hazard model was used for PICM. An ROC

curve was plotted to identify the cut-off value with the best sensitivity and specificity for the occurrence of PICM, and a Kaplan-Meier curve was plotted for free-from-PICM survival. Analyses were performed with the MedCalc software (version 17.0, USA). P values <0.05 were considered to be statistically significant.

RESULTS

Comparison of baseline characteristics between patients without with and without PICM

Among all patients, 130 CAVB patients with implanted pacemakers (dual chamber: 84.6%) were suitable for the analysis of PICM in this study. The average age (64±11 years vs. 62±11 years), the proportion of male (36.7% vs. 33.3%) and the occurrence of atrial fibrillation (AF) (14.6% vs. 14.2%) were detected among patients without PICM and with PICM during the follow-up period, and the mean duration of follow-up (4.8±3.5 years vs. 4.2±3.5 years) was similar between patients without PICM and with PICM. Other baseline clinical characteristics, except for diabetics and previous stroke, were also similar between patients without PICM and with PICM. Among the laboratory data, hemoglobin and total bilirubin levels, which are associated with heart failure, were similar between patients without PICM and with PICM at pre-implant and post-implant stages (Table 1).

Comparison of ECG data between patients with and without PICM

Among the 130 patients, 109 patients maintained normal LV function until the end of follow-up. The remainder of the CAVB patients (n=21, 16.1%) were considered to have PICM, with a decrease in LVEF from 65±10% at baseline to 37±8%. The follow-up ventricular pacing burden was similar between the patients without PICM and with PICM (85±18% vs. 85±17%). Compared to the patients without PICM, the patients who developed PICM had a significantly wider nQRSd (124±34 ms vs. 149±32 ms, p=0.004), QTc interval (466±54 ms vs. 495±44 ms, P=0.035), and pQRSd (139±29 ms vs. 167±28 ms, p<0.001) (Table 2).

Comparison of medications between patients with and without PICM

Unlike the patients without PICM, the patients with PICM more frequently took angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) medication before implantation and β-blockers and

diuretics after implantation, as shown in Table 3.

Predictors of PICM occurrence

Multivariate Cox regression analysis showed that nQRSd had a hazard ratio (HR) of 1.01 and a 95% confidence interval (CI) of 1.00–1.03 with a P value of 0.051 and that pQRSd had an HR of 1.05 and a 95% CI of 1.02–1.09 with a P value <0.001 (Table 4). Receiver operating characteristic curve analysis showed that a pQRSd above 140 ms had the combined the best sensitivity (95%) with specificity (36%) and pQRS above 167 ms had the combined sensitivity (52%) with the best specificity (90%) for predicting the occurrence of PICM with statistical significance (Figure 1). In the Kaplan-Meier curve, both pQRSd 140ms and 167 ms was significantly associated with the occurrence of PICM (log rank, p=0.03 vs. p<0.001, Figure 2).

DISCUSSION

In our study, among the CAVB patients with normal LV function at the pre-implant period, PICM occurred in 16.1% of the patients with pacing-dependent rhythm over a mean follow-up duration of 4.7±3.5 years. A pQRSd was significantly associated with the occurrence of PICM. In particular, a pQRSd wider than 140ms had a sensitivity of 95% and 167 ms had a specificity of 90% for predicting the occurrence of PICM.

Our result for the incidence of PICM over a long-term follow-up period is comparable to that from previous reports, ranging from 9% to 26% depending on the population investigated and the length of the follow-up[4 7]. We also defined PICM as more than a 10% decrease in LVEF with a resultant LVEF less than 50% after the index implant. The time to the diagnosis of PICM was defined as the period from the date of implantation to the date of the first documented decrease in LVEF.

PICM have been widely considered as the pacing-associated heart failure[1 7]. The significance of PICM has been established for an increased risk in AF, heart failure hospitalization and cardiac mortality[9]. Independent predictors of PICM have been considered to be the pacing site, increased pacing burden, pre-implant LV dysfunction and QRS duration[1-4 7 14].

First, with regard to the pacing site, recent meta-analysis has suggested that the LVEF is higher in patients with

RV non-apical pacing than those with RV apical pacing. However, this conclusion is still debated due to conflicting results[3 15]. In the PROTECT-PACE study, among patients with a high-grade AV block and preserved LV function, RV non-apical pacing did not have a protective effect on LV function compared to RV apical pacing over a 2-year period[8]. In addition, Chan et al. has previously reported that LV volumes and systolic function after long term RV pacing could be predicted by pQRSd, but not pacing site[16]. Our multi-center study also showed no significant difference between RV apical and non-apical pacing for the occurrence of PICM (40.4% vs. 33.3%, p=0.546) among CAVB patients with pacing-dependent rhythm over a long-term follow-up period.

Second, pacing burden has been considered a better predictor for the occurrence of PICM, and previous studies have shown heterogeneous percentages of pacing burden[2]. In our study, in CAVB patients who required a high burden of permanent pacing, the confounding factor was minimized using homogeneous percentages of RV pacing (85% vs. 85%, p=0.860) when analyzing the predictors of PICM.

Third, with regard to pre-implant LV dysfunction, previous studies had baseline pre-existing heart failure associated with coronary artery disease and AF[4 7], and in the PREDICT-HF trial, pre-existing heart failure was highly associated with pQRSd. Other studies have also found pQRSd to be an important predictor of heart failure among patients with chronic RV pacing[13 17 18]. In our study, all CAVB patients with pre-existing LV systolic dysfunction (with or without heart failure) were excluded, and our results were reliable enough to include the analysis of PICM compared to previous studies.

Fourth, pacing-induced electrical dyssynchrony developed mechanical dyssynchrony; thus, the pQRSd could be a strong and independent determinant for the occurrence of PICM[6]. Our data also show that the pQRSd related to LV mechanical dyssynchrony has been confirmed to be significantly associated with LV remodeling (representative of the dyssynchrony index with strain in the 2- or 3-dimensional parameters, Supplemental Video 3 and 4), resulting in the occurrence of PICM by echocardiogram.

Pap et al. reported that nQRSd could be positively correlated with pQRSd, although the nQRSd as escape rhythm is influenced by the level of antegrade block on the His-Purkinje system during AV block[19]. In addition, a nQRSd above 115 ms was highly specific (90%) for the occurrence of PICM as reported in a single-center

study[20]. A single-center study by Khurshid et al. also suggested that the nQRSd (HR=1.03 per ms; p<0.001) is an independent predictor of PICM occurrence[13]. In comparison, our study demonstrated that proportion of patients with a nQRSd above 115 ms is higher in patients with PICM than those without PICM (74% vs. 55%). In particular, the nQRSd (HR=1.02; p=0.010) was slightly significant in our univariate analysis and exhibited a positive trend (HR=1.01; p=0.051) in the multivariate analysis of the occurrence of PICM (Table 4). It is implicated that a wider nQRSd may be predisposition to cardiomyopathy. In particular, among CAVB patients with normal LV function before implant, wider nQRSd may reflect more pathological electrical His-Purkinje conduction.

Miyoshi et al. also proposed that a pQRSd wider than 190 ms suggested a greater morbidity rate than a pQRSd below 190 ms[21]. However, the enrolled patients had ischemic heart disease, valvular heart disease and other causes of cardiomyopathy, whereas our study did not. Chen et al. prospectively showed in 194 CAVB patients without heart failure over a 3-year follow-up that clinical heart failure events were higher and the LVEF was lower among patients with a wider pQRSd. In addition, a pQRSd of 165 ms had the best specificity (67%) for predicting heart failure[17], and a single-center study by Kurshid et al. also proposed that a pQRSd of 150 ms was a sensitive marker for PICM; however, those enrolled patients also had pre-existing AF, coronary artery disease and unknown cardiomyopathies[13].

Taken together, a wider pQRSd could be a major determinant of the occurrence of PICM. We also found that delayed signs and symptoms of heart failure reduce the early detection of PICM in the patients with pacing-dependent rhythm and that not all patients with PICM meet the clinical criteria for heart failure despite a significant reduction of LVEF. This is consistent with previous studies showing only low sensitivity for the diagnosis of heart failure with reduced LV function[22]. Therefore, a more sensitive and specific marker for PICM occurrence may be required for patients with pacing-dependent rhythm.

Our study analyzed a contemporary cohort of CAVB patients and provided a detailed characterization of the clinical, electrocardiographic, laboratory and echocardiographic data at both pre-implant and post-implant periods as well as at the end of the follow-up. In particular, it could be noteworthy that a multicenter study with a longer follow-up duration distinguish it from previous studies as well as complement the previous studies[13 14].

Patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. Therefore, even though pQRSd correlates with occurrence of PICM, pQRSd <140 ms could exclude occurrence of PICM and pQRSd >167 ms could not exclude non-PICM state for follow-up.

We suggested major determinant, wider pQRSd, thus enabling the identification of occurrence of PICM that theoretically could be a reason for using echocardiogram and reversed with preventive His-bundle pacing or biventricular pacing before clinical manifestation[23 24].

Our study has several limitations. First, our study was a retrospective study with unmeasured selection bias and patients without pre-implant or post-implant echocardiogram were excluded for analysis. Our study suffers from a small number of PICM patients due to low incidence of PICM and lack of associations may be raised due to power issues. In addition, the prevalence of PICM seems to be overestimated since patients with heart failure are more likely to get referred for echocardiograms and thus more likely to be included in the analysis. Second, this was a multi-center study, and thus, the influence of different physicians on clinical decision-making may also influence the clinical variables associated with heart failure. Third, the definition of PICM was defined only with LVEF based on anecdotal evidence from a previous study. An appropriate universal definition of PICM is needed[25]. Fourth, it is unlikely that patients with subclinical PICM may undergo incidental follow-up echocardiograms at an out-patient clinic. Fourth, while we excluded all potential etiologies of heart failure, it is speculated that a wider nQRSd is associated with the occurrence of PICM because it reflects cardiomyopathy with normal LV function at pre-implant stage. Thus, more detailed studies on the relationship between the nQRSd and an electrical pathology or substrate in CAVB patients with normal LV function are needed. Fifth, the ability to upgrade to biventricular pacing or Hi-bundle pacing for a pQRSd over 150 ms was limited in patients with PICM in our study because of the strict coverage of the national health insurance.

Early detection and preventive management of PICM are challenging in patients with pacing-dependent rhythm because there are few data to guide clinicians in identifying subclinical and clinical PICM in the subsequent months to years after pacemaker implantation.

CONCLUSION

The occurrence of PICM in patients with pacing-dependent rhythm seems to be common but cannot be reliably

diagnosed based on the conventional heart failure criteria. The pQRSd, which was higher than the nQRSd, is associated with the occurrence of PICM. In particular, a patient with a pQRSd above 140ms had the best sensitivity and above 167ms had the best specificity of occurrence for PICM. Regardless of the pacing site, the pQRSd should be monitored for the timely evaluation and proper management of patients at high risk of PICM to reduce cardiac morbidity and mortality over a long follow-up period.

Contributorship Statement

Dr. Ki-Woon Kang designed the study and revised the manuscript in the final version.

Dr. Jun Hyung Kim, Dr. Yu Jeong Choi, and Dr. Tae-Seok Kim collected and analyzed the clinical characteristic, ECG and pacemaker interrogation data.

Dr. Jung Yeon Chin and Dr. Jae-Hyeong Park collected and analyzed the echocardiogram data.

Conflict of Interest

The authors have no conflict of interest to declare.

No Funding

Ethics approval:

The study was approved by the institutional review board approval of each center in South Korea

No data sharing

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Figure Legends

Figure 1. ROC curve analysis showing the pQRSd had correlated with PICM occurrence and two rectangular black marks showing the best sensitivity (pQRS 140ms) and specificity (pQRS 167ms) with statistical significance**.**

Figure 2. Kaplan-Meier curve analysis showing free-from PICM survival with a pQRSd (cut-off value of 140ms and 167 ms).

Supplemental Figure1. Flow chart of the stratified study population

Supplemental Figure 2. Non-apical ventricular pacing leads at the high sepum (left) and mid septum (right) in the X-ray

Supplemental Video 1. A case of the pre-implant echocardiogram before occurrence of PICM.

Supplemental Video 2. A case of the post-implant follow-up echocardiogram after occurrence of PICM.

Supplemental Video 3. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (parasternal long axis).

Supplemental Video 4. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (apical short axis).

Table 1. Baseline characteristics between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Age, y	64±11	64±11	62±11	0.472
Male, n (%)	47 (36.2)	40 (36.7)	7 (33.3)	0.768
Hypertension, n (%)	75 (57.7)	58 (53.2)	16 (76.2)	0.146
Diabetes, n (%)	31 (24.0)	30 (27.5)	1 (5.0)	0.030*
IHD, n (%)	15 (11.5)	11 (10.1)	4 (19.0)	0.239
Stroke or TIA, n (%)	9 (6.9)	5 (4.6)	4 (19.0)	0.017*
Alcohol, n (%)	16 (12.3)	13 (11.9)	3 (13.3)	0.763
Smoking, n (%)	18 (13.8)	16 (14.7)	2 (9.5)	0.531
Hemoglobin, g/L	12.3±2.1	12.1±1.9	12.4±2.6	0.660
Total bilirubin, mg/dL	1.0±0.8	1.0±0.6	1.0±0.8	0.556

IHD: ischemic heart disease; * statically significant.

Table 2. Comparison of ECG parameters between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
Ejection fraction, n (%)	65±10	66±9	65±10	0.607
Left atrial diameter, mm	39±9	38±7	40±8	0.552
Heart rate, bpm	60±30	57±18	60±12	0.550
PR interval, ms	190±81	170±115	213±130	0.203
QRS duration, ms	136±26	124±34	149±32	0.004*
QTc interval, ms	480±37	466±54	495±44	0.035*
Post-implant				
Dual chamber, n (%)	110 (84.6)	90 (82.5)	20 (95.2)	0.142
Ejection fraction, n (%)	45±8	61±7	37±8	<0.001*
Left atrial diameter, mm	40±7	39±7	40±6	0.266
Occurrence of AF, n (%)	19 (14.6)	16 (14.6)	3 (14.2)	0.962
Heart rate, bpm	68±30	69±14	67±9	0.616
PR interval, ms	178±81	168±80	187±62	0.337
Paced QRS duration, ms	149±26	139±29	167±28	<0.001*
Paced QRS axis, degree	2±78	2±78	1±91	0.971
Paced QTc interval, ms	490±37	484±46	496±36	0.254
Non-apical pacing, %	51 (39.1)	44 (40.4)	7 (33.3)	0.546
Atrial pacing, %	23±22	23±23	22±22	0.954

Ventricular pacing, %	85±17	85±18	85±17	0.860

AF: atrial fibrillation; * statistically significant.

Table 3. Comparison of medications between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
ACEI or ARB, n (%)	50 (38.5)	37 (33.9)	13 (61.9)	0.016*
Beta-blocker, n (%)	16 (12.3)	11 (10.1)	5 (23.8)	0.080
CCB, n (%)	26 (20.0)	22 (20.2)	4 (19.0)	0.905
Diuretics, n (%)	30 (23.1)	22 (20.2)	8 (38.1)	0.074
Post-implant				
ACEI or ARB, n (%)	58 (44.6)	45 (41.3)	13 (61.9)	0.082
Beta-blocker, n (%)	22 (16.9)	15 (13.8)	7 (33.8)	0.029*
CCB, n (%)	31 (23.8)	28 (25.7)	3 (14.3)	0.262
Diuretics, n (%)	32 (24.6)	23 (21.1)	9 (42.9)	0.034*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensinogen receptor blocker;

CCB: calcium channel blocker; * statistically significant.

Table 4. Cox Regression Analysis for the Occurrence of PICM

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, per year	1.01	0.97-1.06	0.371			
Gender, male	0.90	0.35-2.30	0.833			
Diabetes mellitus	0.29	0.03-2.26	0.297			
nQRSd, per ms	1.02	1.00-1.04	0.010*	1.01	1.00-1.03	0.051
nQTc interval, per ms	1.00	0.99-1.08	0.195			
pQRSd, per ms	1.05	1.03-1.08	<0.001*	1.05	1.02-1.09	0.001*
Non-apical pacing	0.35	0.11-1.10	0.074			

HR: hazard ratio; CI: confidence interval; ACEI; angiotensin converting enzyme; ARB: angiotensin receptor blockr; ms: millisecond * statistically significant.

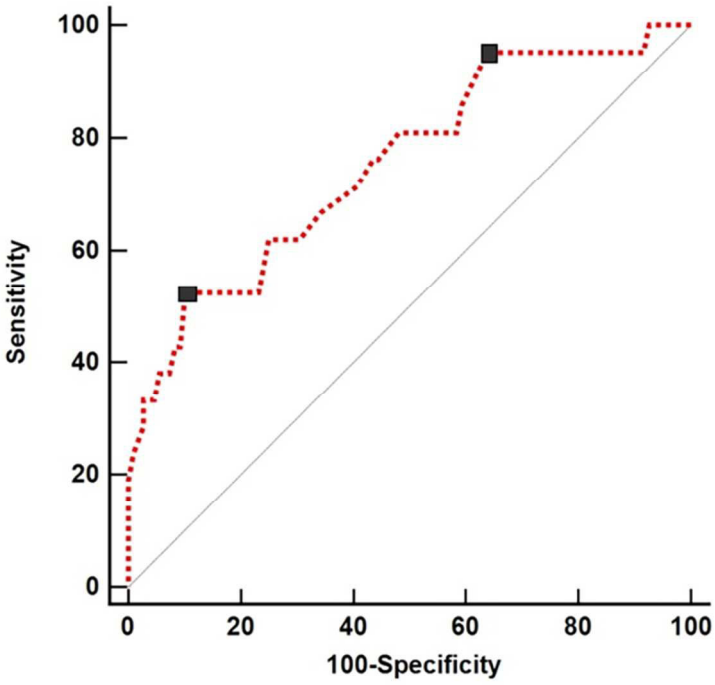

Figure 1

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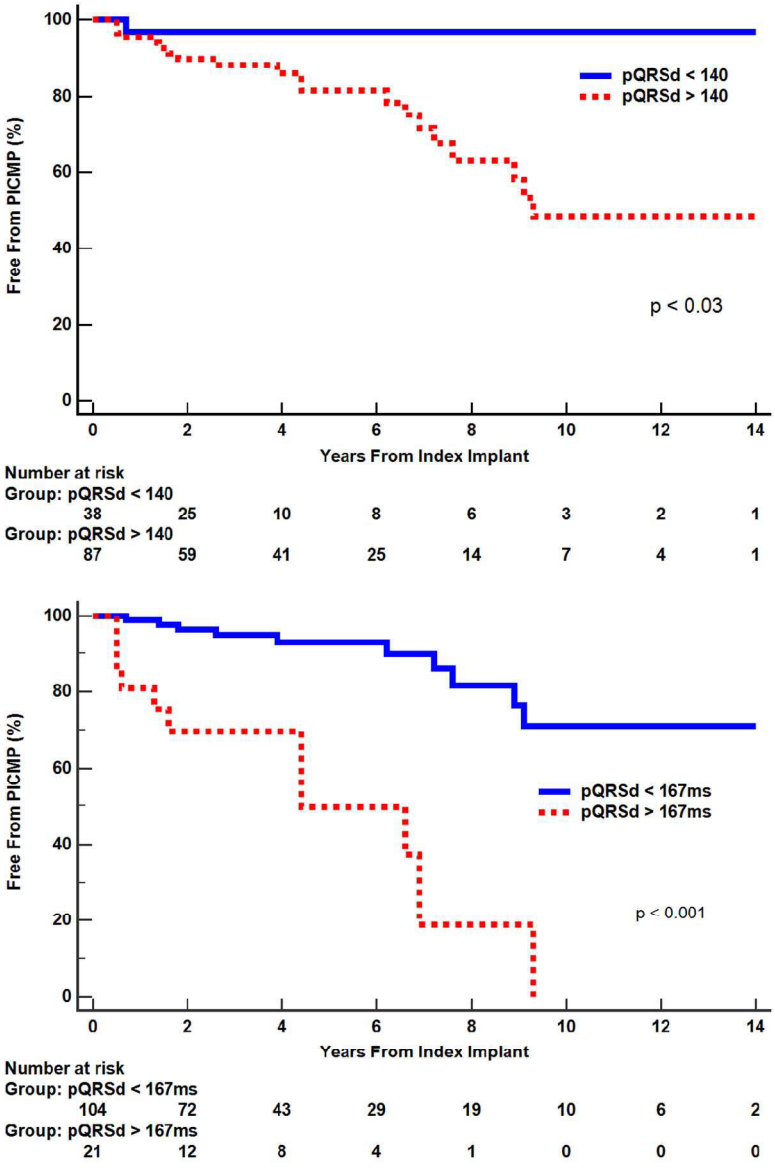

Figure 2

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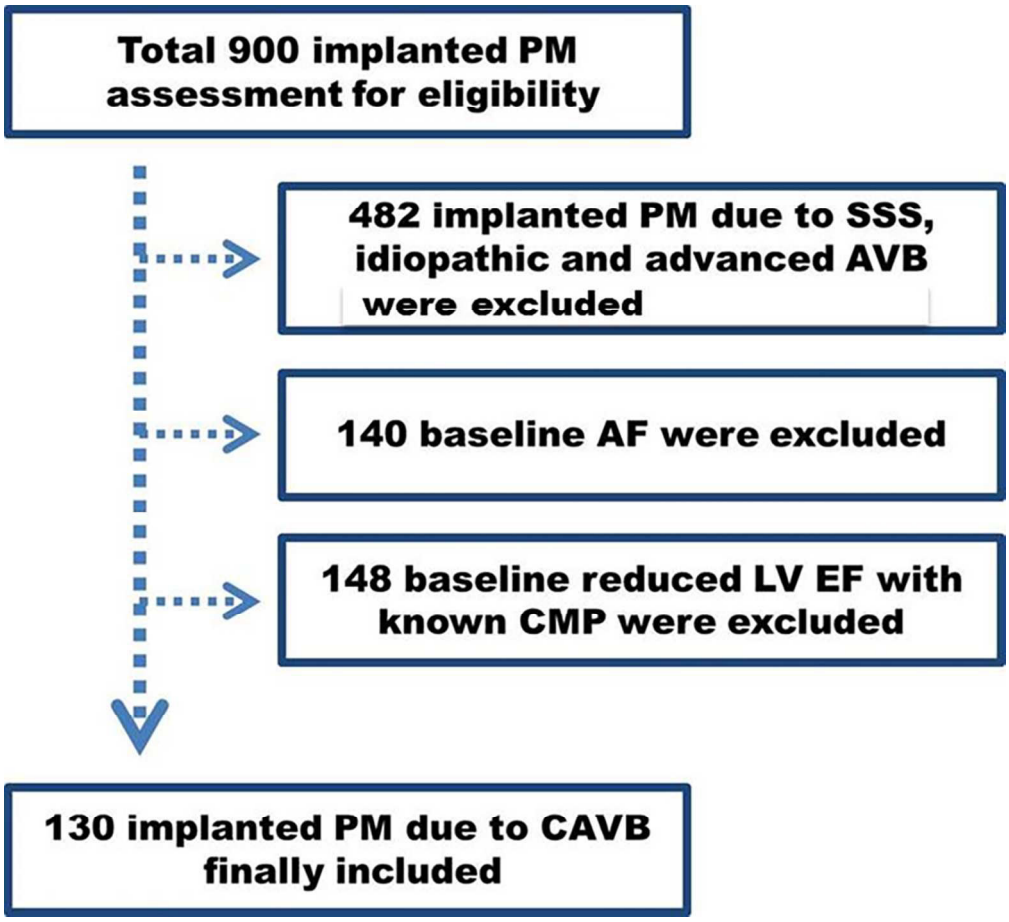

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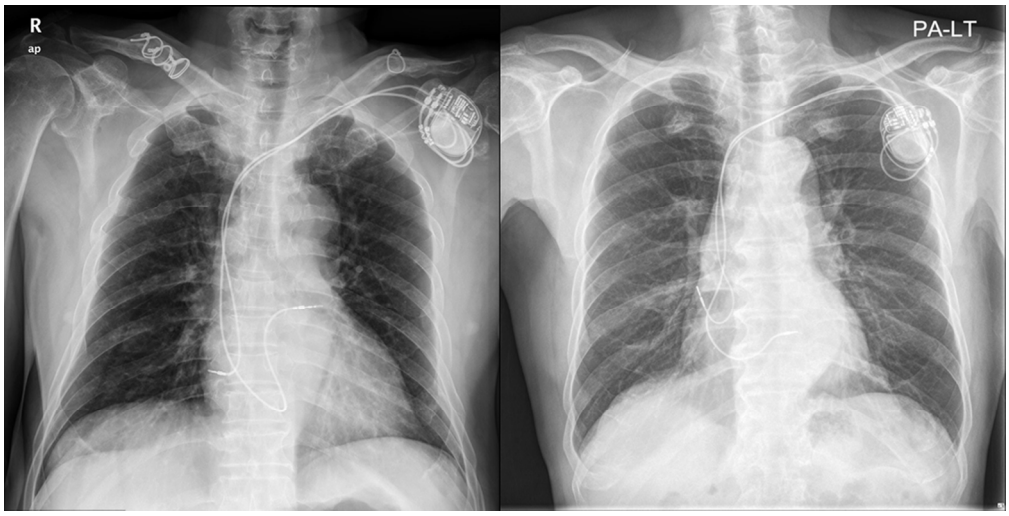

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Paced QRS duration is a Major Determinant for the Occurrence of Pacing-Induced Cardiomyopathy in Complete AV Block: A Multi-Center Observation over a 15-Year Period

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Paced QRS duration is a Major Determinant for the Occurrence of Pacing-Induced Cardiomyopathy in Complete AV Block: A Multi-Center Observation over a 15-Year Period

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Running title: major determinant for pacing-induced cardiomyopathy

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Abstract

Objectives The predictors of pacing-induced cardiomyopathy (PICM) for complete atrioventricular (AV) block (CAVB) have not yet been defined. The aim of this study was to investigate the major determinant for the occurrence of PICM.

Setting Multi-center retrospective analysis of CAVB from tertiary referral centers in Deajeon, South Korea

Participant A cohort of 900 consecutive patients with an implanted pacemaker was collected from December 2001 to August 2015. Of these, a total of 130 CAVB patients with pacing-dependent rhythm who underwent ECG and echocardiogram before and after implantation were analyzed for the occurrence of PICM.

Outcome Measures Cox proportional hazards models evaluated the determinant of PICM by ECG, device parameters and echocardiogram over a mean of 4.5 years.

Results PICM was observed in 16.1% (n=21) of all patients with CAVB (age, 64±11 years; male, 36.2%). The pre-implant left ventricular (LV) ejection fraction (66±9% vs. 66±8%) and non-apical pacing (40.4% vs. 33.3%) were similar; however, the native QRS duration (nQRSd) (124±34 ms vs. 149±32 ms) and the paced QRS duration (pQRSd) (139±29 ms vs. 167±28 ms) were significantly different between the two groups. The post-implant LV ejection fraction (61±7% vs. 31±8%) was also significantly different at the end of follow-up. A pQRSd significantly correlated with PICM (HR 1.05, 95% CI 1.02 to 1.09, p=0.001). A pQRSd above 140 ms was cut-off value with a sensitivity of 95%, while pQRSd above 167 ms was cut-off with a specificity of 90% for PICM.

Conclusion In CAVB patients with pacing-dependent rhythm, regardless of the pacing site, the pQRSd is a major determinant for occurrence of PICM.

Keywords: complete AV block, pacemaker, cardiomyopathy

Strengths and limitations of this study

- Our study enrolled only CAVB patients with pacing-dependent rhythm and pre-implant normal LV function, and excluded all patients with potentially confounding, alternative causes (pre-existing persistent/permanent AF, coronary artery disease, cardiac surgery and LV dysfunction) for heart failure at pre-implant state.

- A pQRSd was significantly associated with the occurrence of PICM during follow-up regardless of the pacing site. In addition, patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. A pQRSd should be monitored for the timely exact evaluation and management of patients at risk of PICM to reduce cardiac adverse events.

- CAVB patients without pre-implant or post-implant echocardiogram were excluded for analysis and appropriate universal definition of PICM is needed.

INTRODUCTION

Pacemakers have been a definite treatment tool for symptomatic brady-arrhythmia to reduce cardiac morbidity and mortality[1]. However, chronic right ventricular (RV) pacing has a potentially deleterious effect on left ventricular (LV) function[1-4]. This deleterious effect of chronic RV pacing on LV function is known as pacing-induced cardiomyopathy (PICM)[1 4-6]. Several studies have demonstrated that pacing anatomical site, pacing burden and pre-implant LV dysfunction make difference of effect on the occurrence of PICM and its subsequent clinical outcomes[1 3 7-9]. In particular, recognition of predictors for occurrence of PICM may lead to better identification of patients at high risk in the complete atrioventricular block (CAVB) with pacing-dependent rhythm. However, because PICM does not occur in all CAVB patients with chronic RV pacing, timely and proper evaluation should be considered for those who most likely have pacing-dependent rhythm-associated PICM[7]. Therefore, we retrospectively analyzed a large cohort to identify the major determinants of the occurrence of PICM in CAVB patients with pacing-dependent rhythm over a long period of time.

METHODS

Study population

Consecutive patients with an implanted pacemaker were retrospectively collected from three different tertiary referral centers, Eulji University, Chungnam National University, and Catholic Saint Mary's Hospital, which are located in Daejeon, South Korea from December 2001 to August 2015. Among a total of 900 patients with an implanted pacemaker, patients with sick sinus syndrome, paroxysmal and advanced AV block (n=482), persistent/permanent atrial fibrillation (n=140) and pre-implant LV dysfunction (n=148) combined with ischemic heart disease[10], including acute coronary syndrome, other proven cardiomyopathy or severe valvular disease at the pre-implant period were excluded from the study. Our investigators excluded pre-existing persistent/permanent atrial fibrillation and significant coronary artery disease, which are considered risk factors for the occurrence of heart failure and could influence the relationship between CAVB and PICM. Thus, CAVB patients (n=130) with documented pre- and post-implant LV ejection fraction (LVEF) were analyzed in this study (Supplemental Figure 1). All patients provided informed consent, and institutional review board approval

was acquired from each center and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

LVEF was measured at Eulji, Chungnam University and St Mary's Hospital using standard echocardiographic techniques. Pre-implant and post-implant (at least 1 day after the index implant) echocardiograms were performed and interpreted by two experienced cardiologists who were echocardiogram specialists (Professor. JY Chin at Eulji University Hospital and Professor. HJ Park at Chungnam University Hospital). None of the patients developed myocardial infarction during the follow-up period, and the baseline clinical and demographic data, ECG and echocardiographic data, and medication data were acquired from the electronic medical records.

ECG parameters, pacemaker data and definition of PICM

Baseline ECG parameters were acquired from the ECG that was performed closest to the implant period using the standard criteria established by the American Heart Association (AHA) and HRS Expert Consensus[11]. RV pacing-leads sites were reviewed using the standard X-ray (Supplemental Figure 2). Pacemaker data were also acquired at regular intervals (at least six months), and the pacing burden (atrial and ventricular pacing %) was recorded at the time of follow-up and PICM diagnosis. Native QRS duration (nQRSd) was measured within 7 days at pre-implant state and paced QRS duration (pQRSd) was also measured within 7 days at the post-implant state from the surface 12 lead ECG.

PICM was defined as more than a 10% decrease in LVEF with a resultant LVEF less than 50%, as previously reported[7], regardless of heart failure symptoms[4 12 13] (Supplemental Video 1 and 2). The time of PICM occurrence was considered the date of the first decrease in LVEF determined by echocardiogram with documented ECG at the time during the follow-up period.

Statistical analysis

Baseline clinical, ECG, echocardiogram and device interrogation data of the enrolled patients were compared between those without PICM and with PICM using independent t-test and chi-square. To determine independent predictors of PICM occurrence, the multivariate Cox regression hazard model was used for PICM. An ROC

curve was plotted to identify the cut-off value with the best sensitivity and specificity for the occurrence of PICM, and a Kaplan-Meier curve was plotted for free-from-PICM survival. Analyses were performed with the MedCalc software (version 17.0, USA). P values <0.05 were considered to be statistically significant.

RESULTS

Comparison of baseline characteristics between patients without with and without PICM

Among all patients, 130 CAVB patients with implanted pacemakers (dual chamber: 84.6%) were suitable for the analysis of PICM in this study. The average age (64±11 years vs. 62±11 years), the proportion of male (36.7% vs. 33.3%) and the occurrence of atrial fibrillation (AF) (14.6% vs. 14.2%) were detected among patients without PICM and with PICM during the follow-up period, and the mean duration of follow-up (4.8±3.5 years vs. 4.2±3.5 years) was similar between patients without PICM and with PICM. Other baseline clinical characteristics, except for diabetics and previous stroke, were also similar between patients without PICM and with PICM. Among the laboratory data, hemoglobin and total bilirubin levels, which are associated with heart failure, were similar between patients without PICM and with PICM at pre-implant and post-implant stages (Table 1).

Comparison of ECG data between patients with and without PICM

Among the 130 patients, 109 patients maintained normal LV function until the end of follow-up. The remainder of the CAVB patients (n=21, 16.1%) were considered to have PICM, with a decrease in LVEF from 65±10% at baseline to 37±8%. The follow-up ventricular pacing burden was similar between the patients without PICM and with PICM (85±18% vs. 85±17%). Compared to the patients without PICM, the patients who developed PICM had a significantly wider nQRSd (124±34 ms vs. 149±32 ms, p=0.004), QTc interval (466±54 ms vs. 495±44 ms, P=0.035), and pQRSd (139±29 ms vs. 167±28 ms, p<0.001) (Table 2).

Comparison of medications between patients with and without PICM

Unlike the patients without PICM, the patients with PICM more frequently took angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) medication before implantation and β-blockers and

diuretics after implantation, as shown in Table 3.

Predictors of PICM occurrence

Multivariate Cox regression analysis showed that nQRSd had a hazard ratio (HR) of 1.01 and a 95% confidence interval (CI) of 1.00–1.03 with a P value of 0.051 and that pQRSd had an HR of 1.05 and a 95% CI of 1.02–1.09 with a P value <0.001 (Table 4). Receiver operating characteristic curve analysis showed that a pQRSd above 140 ms had the combined the best sensitivity (95%) with specificity (36%) and pQRS above 167 ms had the combined sensitivity (52%) with the best specificity (90%) for predicting the occurrence of PICM with statistical significance (Figure 1). In the Kaplan-Meier curve, both pQRSd 140ms and 167 ms was significantly associated with the occurrence of PICM (log rank, p=0.03 vs. p<0.001, Figure 2).

DISCUSSION

In our study, among the CAVB patients with normal LV function at the pre-implant period, PICM occurred in 16.1% of the patients with pacing-dependent rhythm over a mean follow-up duration of 4.7±3.5 years. A pQRSd was significantly associated with the occurrence of PICM. In particular, a pQRSd wider than 140ms had a sensitivity of 95% and 167 ms had a specificity of 90% for predicting the occurrence of PICM.

Our result for the incidence of PICM over a long-term follow-up period is comparable to that from previous reports, ranging from 9% to 26% depending on the population investigated and the length of the follow-up[4 7]. We also defined PICM as more than a 10% decrease in LVEF with a resultant LVEF less than 50% after the index implant. The time to the diagnosis of PICM was defined as the period from the date of implantation to the date of the first documented decrease in LVEF.

PICM have been widely considered as the pacing-associated heart failure[1 7]. The significance of PICM has been established for an increased risk in AF, heart failure hospitalization and cardiac mortality[9]. Independent predictors of PICM have been considered to be the pacing site, increased pacing burden, pre-implant LV dysfunction and QRS duration[1-4 7 14].

First, with regard to the pacing site, recent meta-analysis has suggested that the LVEF is higher in patients with

RV non-apical pacing than those with RV apical pacing. However, this conclusion is still debated due to conflicting results[3 15]. In the PROTECT-PACE study, among patients with a high-grade AV block and preserved LV function, RV non-apical pacing did not have a protective effect on LV function compared to RV apical pacing over a 2-year period[8]. In addition, Chan et al. has previously reported that LV volumes and systolic function after long term RV pacing could be predicted by pQRSd, but not pacing site[16]. Our multi-center study also showed no significant difference between RV apical and non-apical pacing for the occurrence of PICM (40.4% vs. 33.3%, p=0.546) among CAVB patients with pacing-dependent rhythm over a long-term follow-up period.

Second, pacing burden has been considered a better predictor for the occurrence of PICM, and previous studies have shown heterogeneous percentages of pacing burden[2]. In our study, in CAVB patients who required a high burden of permanent pacing, the confounding factor was minimized using homogeneous percentages of RV pacing (85% vs. 85%, p=0.860) when analyzing the predictors of PICM.

Third, with regard to pre-implant LV dysfunction, previous studies had baseline pre-existing heart failure associated with coronary artery disease and AF[4 7], and in the PREDICT-HF trial, pre-existing heart failure was highly associated with pQRSd. Other studies have also found pQRSd to be an important predictor of heart failure among patients with chronic RV pacing[13 17 18]. In our study, all CAVB patients with pre-existing LV systolic dysfunction (with or without heart failure) were excluded, and our results were reliable enough to include the analysis of PICM compared to previous studies.

Fourth, pacing-induced electrical dyssynchrony developed mechanical dyssynchrony; thus, the pQRSd could be a strong and independent determinant for the occurrence of PICM[6]. Our data also show that the pQRSd related to LV mechanical dyssynchrony has been confirmed to be significantly associated with LV remodeling (representative of the dyssynchrony index with strain in the 2- or 3-dimensional parameters, Supplemental Video 3 and 4), resulting in the occurrence of PICM by echocardiogram.

Pap et al. reported that nQRSd could be positively correlated with pQRSd, although the nQRSd as escape rhythm is influenced by the level of antegrade block on the His-Purkinje system during AV block[19]. In addition, a nQRSd above 115 ms was highly specific (90%) for the occurrence of PICM as reported in a single-center

study[20]. A single-center study by Khurshid et al. also suggested that the nQRSd (HR=1.03 per ms; p<0.001) is an independent predictor of PICM occurrence[13]. In comparison, our study demonstrated that proportion of patients with a nQRSd above 115 ms is higher in patients with PICM than those without PICM (74% vs. 55%). In particular, the nQRSd (HR=1.02; p=0.010) was slightly significant in our univariate analysis and exhibited a positive trend (HR=1.01; p=0.051) in the multivariate analysis of the occurrence of PICM (Table 4). It is implicated that a wider nQRSd may be predisposition to cardiomyopathy. In particular, among CAVB patients with normal LV function before implant, wider nQRSd may reflect more pathological electrical His-Purkinje conduction.

Miyoshi et al. also proposed that a pQRSd wider than 190 ms suggested a greater morbidity rate than a pQRSd below 190 ms[21]. However, the enrolled patients had ischemic heart disease, valvular heart disease and other causes of cardiomyopathy, whereas our study did not. Chen et al. prospectively showed in 194 CAVB patients without heart failure over a 3-year follow-up that clinical heart failure events were higher and the LVEF was lower among patients with a wider pQRSd. In addition, a pQRSd of 165 ms had the best specificity (67%) for predicting heart failure[17], and a single-center study by Kurshid et al. also proposed that a pQRSd of 150 ms was a sensitive marker for PICM; however, those enrolled patients also had pre-existing AF, coronary artery disease and unknown cardiomyopathies[13].

Taken together, a wider pQRSd could be a major determinant of the occurrence of PICM. We also found that delayed signs and symptoms of heart failure reduce the early detection of PICM in the patients with pacing-dependent rhythm and that not all patients with PICM meet the clinical criteria for heart failure despite a significant reduction of LVEF. This is consistent with previous studies showing only low sensitivity for the diagnosis of heart failure with reduced LV function[22]**.** Therefore, a more sensitive and specific marker for PICM occurrence may be required for patients with pacing-dependent rhythm.

Our study analyzed a contemporary cohort of CAVB patients and provided a detailed characterization of the clinical, electrocardiographic, laboratory and echocardiographic data at both pre-implant and post-implant periods as well as at the end of the follow-up. In particular, it could be noteworthy that a multicenter study with a longer follow-up duration distinguish it from previous studies as well as complement the previous studies[13 14].

Patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. Therefore, even though pQRSd correlates with occurrence of PICM, pQRSd <140 ms could exclude occurrence of PICM and pQRSd >167 ms could not exclude non-PICM state for follow-up.

Our findings suggest that patients with a wider pQRSd are at higher risk for developing PICM, and therefore these patients may benefit from routine echocardiographic screening for PICM and possibly a lower threshold for early biventricular or His-bundle pacing[23 24].

Our study has several limitations. First, our study was a retrospective study with unmeasured selection bias and patients without pre-implant or post-implant echocardiogram were excluded for analysis. Our study suffers from a small number of PICM patients due to low incidence of PICM and lack of associations may be raised due to power issues. In addition, the prevalence of PICM seems to be overestimated since patients with heart failure are more likely to get referred for echocardiograms and thus more likely to be included in the analysis. Second, this was a multi-center study, and thus, the influence of different physicians on clinical decision-making may also influence the clinical variables associated with heart failure. Third, the definition of PICM was defined only with LVEF based on anecdotal evidence from a previous study. An appropriate universal definition of PICM is needed[25]. Fourth, it is unlikely that patients with subclinical PICM may undergo incidental follow-up echocardiograms at an out-patient clinic. Fourth, while we excluded all potential etiologies of heart failure, it is speculated that a wider nQRSd is associated with the occurrence of PICM because it reflects cardiomyopathy with normal LV function at pre-implant stage. Thus, more detailed studies on the relationship between the nQRSd and an electrical pathology or substrate in CAVB patients with normal LV function are needed. Fifth, the ability to upgrade to biventricular pacing or Hi-bundle pacing for a pQRSd over 150 ms was limited in patients with PICM in our study because of the strict coverage of the national health insurance.

Early detection and preventive management of PICM are challenging in patients with pacing-dependent rhythm because there are few data to guide clinicians in identifying subclinical and clinical PICM in the subsequent months to years after pacemaker implantation.

CONCLUSION

The occurrence of PICM in patients with pacing-dependent rhythm seems to be common but cannot be reliably

diagnosed based on the conventional heart failure criteria. The pQRSd, which was higher than the nQRSd, is associated with the occurrence of PICM. In particular, a patient with a pQRSd above 140ms had the best sensitivity and above 167ms had the best specificity of occurrence for PICM. Regardless of the pacing site, the pQRSd should be monitored for the timely evaluation and proper management of patients at high risk of PICM to reduce cardiac morbidity and mortality over a long follow-up period.

Contributorship Statement

Dr. Ki-Woon Kang designed the study and revised the manuscript in the final version.

Dr. Jun Hyung Kim, Dr. Yu Jeong Choi, and Dr. Tae-Seok Kim collected and analyzed the clinical characteristic, ECG and pacemaker interrogation data.

Dr. Jung Yeon Chin and Dr. Jae-Hyeong Park collected and analyzed the echocardiogram data.

Conflict of Interest

The authors have no conflict of interest to declare.

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Ethics approval:

The study was approved by the institutional review board approval of each center in South Korea

No data sharing

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Figure Legends

Figure 1. ROC curve analysis showing the pQRSd had correlated with PICM occurrence and two rectangular black marks showing the best sensitivity (pQRS 140ms) and specificity (pQRS 167ms) with statistical significance**.**

Figure 2. Kaplan-Meier curve analysis showing free-from PICM survival with a pQRSd (cut-off value of 140ms and 167 ms).

Supplemental Figure1. Flow chart of the stratified study population

Supplemental Figure 2. Non-apical ventricular pacing leads at the high sepum (left) and mid septum (right) in the X-ray

Supplemental Video 1. A case of the pre-implant echocardiogram before occurrence of PICM.

Supplemental Video 2. A case of the post-implant follow-up echocardiogram after occurrence of PICM.

Supplemental Video 3. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (parasternal long axis).

Supplemental Video 4. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (apical short axis).

Table 1. Baseline characteristics between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Age, y	64±11	64±11	62±11	0.472
Male, n (%)	47 (36.2)	40 (36.7)	7 (33.3)	0.768
Hypertension, n (%)	75 (57.7)	58 (53.2)	16 (76.2)	0.146
Diabetes, n (%)	31 (24.0)	30 (27.5)	1 (5.0)	0.030*
IHD, n (%)	15 (11.5)	11 (10.1)	4 (19.0)	0.239
Stroke or TIA, n (%)	9 (6.9)	5 (4.6)	4 (19.0)	0.017*
Alcohol, n (%)	16 (12.3)	13 (11.9)	3 (13.3)	0.763
Smoking, n (%)	18 (13.8)	16 (14.7)	2 (9.5)	0.531
Hemoglobin, g/L	12.3±2.1	12.1±1.9	12.4±2.6	0.660
Total bilirubin, mg/dL	1.0±0.8	1.0±0.6	1.0±0.8	0.556

IHD: ischemic heart disease; * statically significant.

Table 2. Comparison of ECG parameters between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
Ejection fraction, n (%)	65±10	66±9	65±10	0.607
Left atrial diameter, mm	39±9	38±7	40±8	0.552
Heart rate, bpm	60±30	57±18	60±12	0.550
PR interval, ms	190±81	170±115	213±130	0.203
QRS duration, ms	136±26	124±34	149±32	0.004*
QTc interval, ms	480±37	466±54	495±44	0.035*
Post-implant				
Dual chamber, n (%)	110 (84.6)	90 (82.5)	20 (95.2)	0.142
Ejection fraction, n (%)	45±8	61±7	37±8	<0.001*
Left atrial diameter, mm	40±7	39±7	40±6	0.266
Occurrence of AF, n (%)	19 (14.6)	16 (14.6)	3 (14.2)	0.962
Heart rate, bpm	68±30	69±14	67±9	0.616
PR interval, ms	178±81	168±80	187±62	0.337
Paced QRS duration, ms	149±26	139±29	167±28	<0.001*
Paced QRS axis, degree	2±78	2±78	1±91	0.971
Paced QTc interval, ms	490±37	484±46	496±36	0.254
Non-apical pacing, %	51 (39.1)	44 (40.4)	7 (33.3)	0.546
Atrial pacing, %	23±22	23±23	22±22	0.954

Ventricular pacing, %	85±17	85±18	85±17	0.860

AF: atrial fibrillation; * statistically significant.

Table 3. Comparison of medications between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
ACEI or ARB, n (%)	50 (38.5)	37 (33.9)	13 (61.9)	0.016*
Beta-blocker, n (%)	16 (12.3)	11 (10.1)	5 (23.8)	0.080
CCB, n (%)	26 (20.0)	22 (20.2)	4 (19.0)	0.905
Diuretics, n (%)	30 (23.1)	22 (20.2)	8 (38.1)	0.074
Post-implant				
ACEI or ARB, n (%)	58 (44.6)	45 (41.3)	13 (61.9)	0.082
Beta-blocker, n (%)	22 (16.9)	15 (13.8)	7 (33.8)	0.029*
CCB, n (%)	31 (23.8)	28 (25.7)	3 (14.3)	0.262
Diuretics, n (%)	32 (24.6)	23 (21.1)	9 (42.9)	0.034*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensinogen receptor blocker;

CCB: calcium channel blocker; * statistically significant.

Table 4. Cox Regression Analysis for the Occurrence of PICM

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, per year	1.01	0.97-1.06	0.371			
Gender, male	0.90	0.35-2.30	0.833			
Diabetes mellitus	0.29	0.03-2.26	0.297			
nQRSd, per ms	1.02	1.00-1.04	0.010*	1.01	1.00-1.03	0.051
nQTc interval, per ms	1.00	0.99-1.08	0.195			
pQRSd, per ms	1.05	1.03-1.08	<0.001*	1.05	1.02-1.09	0.001*
Non-apical pacing	0.35	0.11-1.10	0.074			

HR: hazard ratio; CI: confidence interval; ACEI; angiotensin converting enzyme; ARB: angiotensin receptor blockr; ms: millisecond * statistically significant.

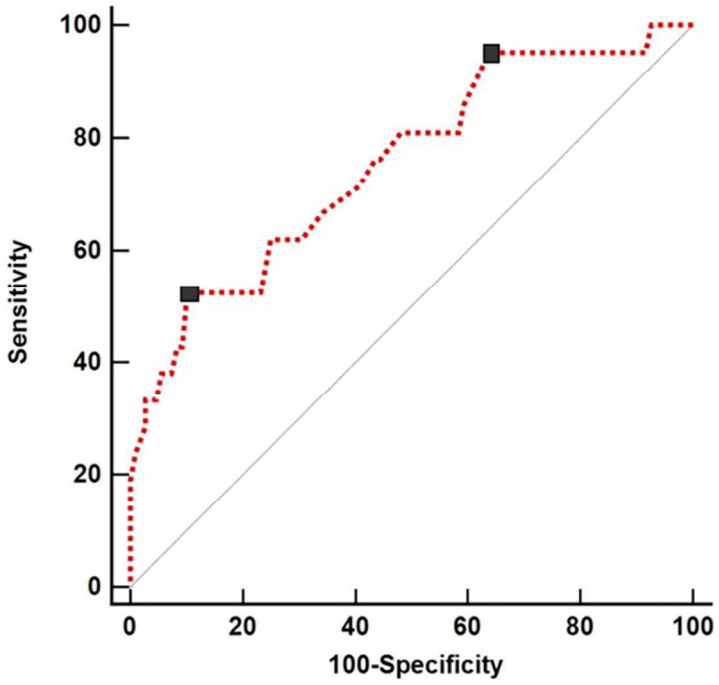

Figure 1

104x78mm (300 x 300 DPI)

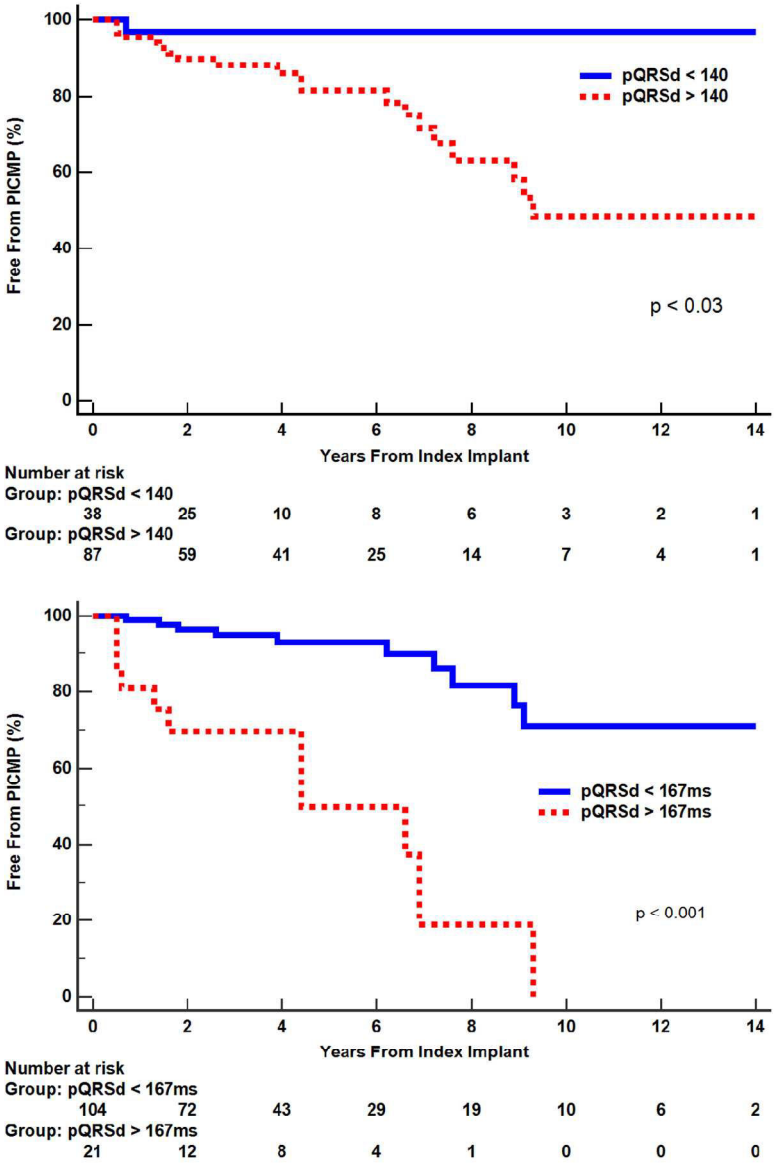

Figure 2

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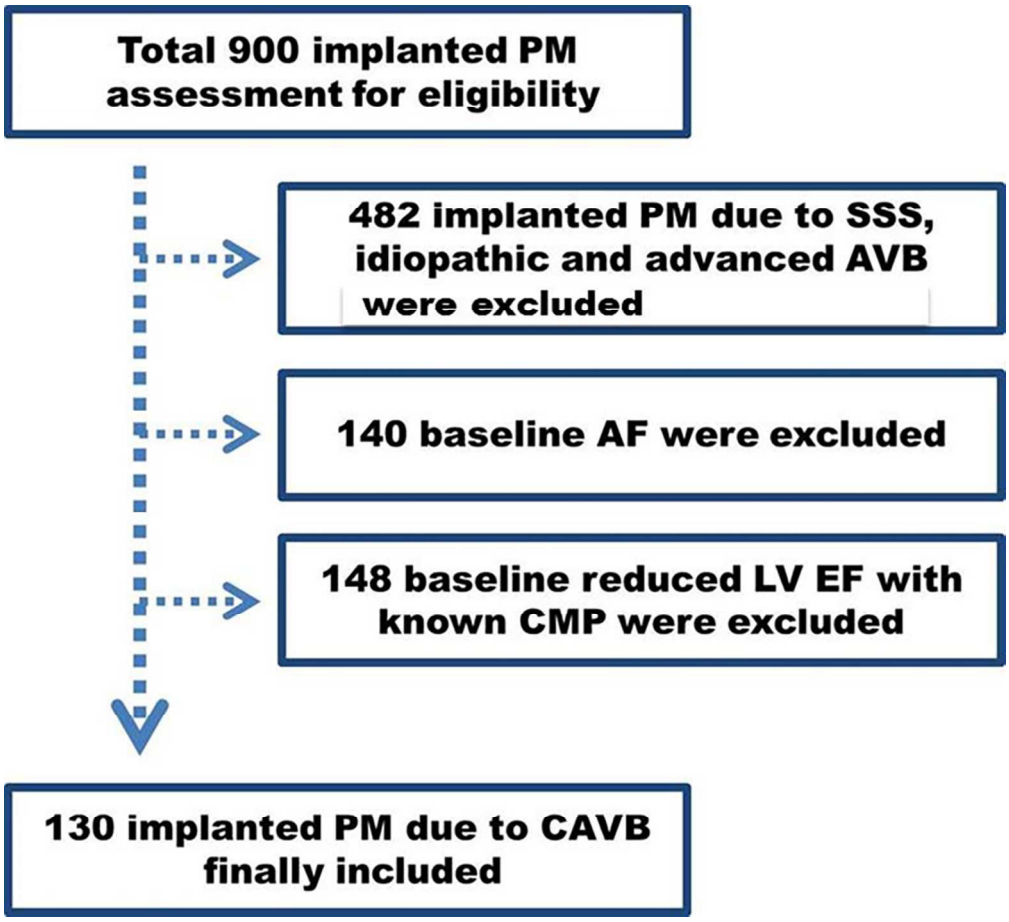

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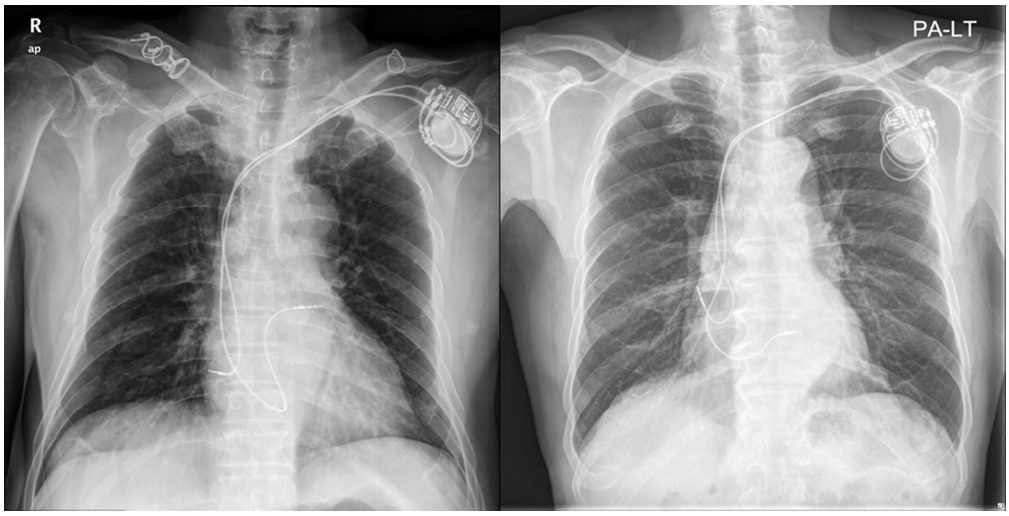

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	4
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	4
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	6
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	6
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	7
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	7
	15b	D	Explain how to the use the prediction model.	7
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	7
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	7
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	10
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	8
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	8
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	9
Other information0				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	0
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	12

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Major determinant for the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: a multicenter retrospective analysis over a 15-year period in South Korea

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Keywords:	complete AV block, pacemaker, Cardiomyopathy < CARDIOLOGY

Major determinant for the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: a multi-center retrospective analysis over a 15-year period in South Korea

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Running title: major determinant for pacing-induced cardiomyopathy

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Abstract

Objectives The predictors of pacing-induced cardiomyopathy (PICM) for complete atrioventricular (AV) block (CAVB) have not yet been defined. The aim of this study was to investigate the major determinant for the occurrence of PICM.

Setting Multi-center retrospective analysis of CAVB from tertiary referral centers in Deajeon, South Korea

Participant A cohort of 900 consecutive patients with an implanted pacemaker was collected from December 2001 to August 2015. Of these, a total of 130 CAVB patients with pacing-dependent rhythm who underwent ECG and echocardiogram before and after implantation were analyzed for the occurrence of PICM.

Outcome Measures Cox proportional hazards models evaluated the determinant of PICM by ECG, device parameters and echocardiogram over a mean of 4.5 years.

Results PICM was observed in 16.1% (n=21) of all patients with CAVB (age, 64±11 years; male, 36.2%). The pre-implant left ventricular (LV) ejection fraction (66±9% vs. 66±8%) and non-apical pacing (40.4% vs. 33.3%) were similar; however, the native QRS duration (nQRSd) (124±34 ms vs. 149±32 ms) and the paced QRS duration (pQRSd) (139±29 ms vs. 167±28 ms) were significantly different between the two groups. The post-implant LV ejection fraction (61±7% vs. 31±8%) was also significantly different at the end of follow-up. A pQRSd significantly correlated with PICM (HR 1.05, 95% CI 1.02 to 1.09, p=0.001). A pQRSd above 140 ms was cut-off value with a sensitivity of 95%, while pQRSd above 167 ms was cut-off with a specificity of 90% for PICM.

Conclusion In CAVB patients with pacing-dependent rhythm, regardless of the pacing site, the pQRSd is a major determinant for occurrence of PICM.

Keywords: complete AV block, pacemaker, cardiomyopathy

Strengths and limitations of this study

- **This is a multicenter retrospective data analysis over a 15-year period in the complete atrioventriucular block.**
- **This study included relatively small sized patients in the three referral centers in South Korea and may limit the generalisation of the results.**

INTRODUCTION

Pacemakers have been a definite treatment tool for symptomatic brady-arrhythmia to reduce cardiac morbidity and mortality[1]. However, chronic right ventricular (RV) pacing has a potentially deleterious effect on left ventricular (LV) function[1-4]. This deleterious effect of chronic RV pacing on LV function is known as pacing-induced cardiomyopathy (PICM)[1 4-6]. Several studies have demonstrated that pacing anatomical site, pacing burden and pre-implant LV dysfunction make difference of effect on the occurrence of PICM and its subsequent clinical outcomes[1 3 7-9]. In particular, recognition of predictors for occurrence of PICM may lead to better identification of patients at high risk in the complete atrioventricular block (CAVB) with pacing-dependent rhythm. However, because PICM does not occur in all CAVB patients with chronic RV pacing, timely and proper evaluation should be considered for those who most likely have pacing-dependent rhythm-associated PICM[7]. Therefore, we retrospectively analyzed a large cohort to identify the major determinants of the occurrence of PICM in CAVB patients with pacing-dependent rhythm over a long period of time.

METHODS

Study population

Consecutive patients with an implanted pacemaker were retrospectively collected from three different tertiary referral centers, Eulji University, Chungnam National University, and Catholic Saint Mary's Hospital, which are located in Daejeon, South Korea from December 2001 to August 2015. Among a total of 900 patients with an implanted pacemaker, patients with sick sinus syndrome, paroxysmal and advanced AV block (n=482), persistent/permanent atrial fibrillation (n=140) and pre-implant LV dysfunction (n=148) combined with ischemic heart disease[10], including acute coronary syndrome, other proven cardiomyopathy or severe valvular disease at the pre-implant period were excluded from the study. Our investigators excluded pre-existing persistent/permanent atrial fibrillation and significant coronary artery disease, which are considered risk factors for the occurrence of heart failure and could influence the relationship between CAVB and PICM. Thus, CAVB patients (n=130) with documented pre- and post-implant LV ejection fraction (LVEF) were analyzed in this study (Supplemental Figure 1). All patients provided informed consent, and institutional review board approval

was acquired from each center and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

LVEF was measured at Eulji, Chungnam University and St Mary's Hospital using standard echocardiographic techniques. Pre-implant and post-implant (at least 1 day after the index implant) echocardiograms were performed and interpreted by two experienced cardiologists who were echocardiogram specialists (Professor. JY Chin at Eulji University Hospital and Professor. HJ Park at Chungnam University Hospital). None of the patients developed myocardial infarction during the follow-up period, and the baseline clinical and demographic data, ECG and echocardiographic data, and medication data were acquired from the electronic medical records.

ECG parameters, pacemaker data and definition of PICM

Baseline ECG parameters were acquired from the ECG that was performed closest to the implant period using the standard criteria established by the American Heart Association (AHA) and HRS Expert Consensus[11]. RV pacing-leads sites were reviewed using the standard X-ray (Supplemental Figure 2). Pacemaker data were also acquired at regular intervals (at least six months), and the pacing burden (atrial and ventricular pacing %) was recorded at the time of follow-up and PICM diagnosis. Native QRS duration (nQRSd) was measured within 7 days at pre-implant state and paced QRS duration (pQRSd) was also measured within 7 days at the post-implant state from the surface 12 lead ECG.

PICM was defined as more than a 10% decrease in LVEF with a resultant LVEF less than 50%, as previously reported[7], regardless of heart failure symptoms[4 12 13] (Supplemental Video 1 and 2). The time of PICM occurrence was considered the date of the first decrease in LVEF determined by echocardiogram with documented ECG at the time during the follow-up period.

Statistical analysis

Baseline clinical, ECG, echocardiogram and device interrogation data of the enrolled patients were compared between those without PICM and with PICM using independent t-test and chi-square. To determine independent predictors of PICM occurrence, the multivariate Cox regression hazard model was used for PICM. An ROC

curve was plotted to identify the cut-off value with the best sensitivity and specificity for the occurrence of PICM, and a Kaplan-Meier curve was plotted for free-from-PICM survival. Analyses were performed with the MedCalc software (version 17.0, USA). P values <0.05 were considered to be statistically significant.

RESULTS

Comparison of baseline characteristics between patients without with and without PICM

Among all patients, 130 CAVB patients with implanted pacemakers (dual chamber: 84.6%) were suitable for the analysis of PICM in this study. The average age (64±11 years vs. 62±11 years), the proportion of male (36.7% vs. 33.3%) and the occurrence of atrial fibrillation (AF) (14.6% vs. 14.2%) were detected among patients without PICM and with PICM during the follow-up period, and the mean duration of follow-up (4.8±3.5 years vs. 4.2±3.5 years) was similar between patients without PICM and with PICM. Other baseline clinical characteristics, except for diabetics and previous stroke, were also similar between patients without PICM and with PICM. Among the laboratory data, hemoglobin and total bilirubin levels, which are associated with heart failure, were similar between patients without PICM and with PICM at pre-implant and post-implant stages (Table 1).

Comparison of ECG data between patients with and without PICM

Among the 130 patients, 109 patients maintained normal LV function until the end of follow-up. The remainder of the CAVB patients (n=21, 16.1%) were considered to have PICM, with a decrease in LVEF from 65±10% at baseline to 37±8%. The follow-up ventricular pacing burden was similar between the patients without PICM and with PICM (85±18% vs. 85±17%). Compared to the patients without PICM, the patients who developed PICM had a significantly wider nQRSd (124±34 ms vs. 149±32 ms, p=0.004), QTc interval (466±54 ms vs. 495±44 ms, P=0.035), and pQRSd (139±29 ms vs. 167±28 ms, p<0.001) (Table 2).

Comparison of medications between patients with and without PICM

Unlike the patients without PICM, the patients with PICM more frequently took angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) medication before implantation and β-blockers and

diuretics after implantation, as shown in Table 3.

Predictors of PICM occurrence

Multivariate Cox regression analysis showed that nQRSd had a hazard ratio (HR) of 1.01 and a 95% confidence interval (CI) of 1.00–1.03 with a P value of 0.051 and that pQRSd had an HR of 1.05 and a 95% CI of 1.02–1.09 with a P value <0.001 (Table 4). Receiver operating characteristic curve analysis showed that a pQRSd above 140 ms had the combined the best sensitivity (95%) with specificity (36%) and pQRS above 167 ms had the combined sensitivity (52%) with the best specificity (90%) for predicting the occurrence of PICM with statistical significance (Figure 1). In the Kaplan-Meier curve, both pQRSd 140ms and 167 ms was significantly associated with the occurrence of PICM (log rank, p=0.03 vs. p<0.001, Figure 2).

DISCUSSION

In our study, among the CAVB patients with normal LV function at the pre-implant period, PICM occurred in 16.1% of the patients with pacing-dependent rhythm over a mean follow-up duration of 4.7±3.5 years. A pQRSd was significantly associated with the occurrence of PICM. In particular, a pQRSd wider than 140ms had a sensitivity of 95% and 167 ms had a specificity of 90% for predicting the occurrence of PICM.

Our result for the incidence of PICM over a long-term follow-up period is comparable to that from previous reports, ranging from 9% to 26% depending on the population investigated and the length of the follow-up[4 7]. We also defined PICM as more than a 10% decrease in LVEF with a resultant LVEF less than 50% after the index implant. The time to the diagnosis of PICM was defined as the period from the date of implantation to the date of the first documented decrease in LVEF.

PICM have been widely considered as the pacing-associated heart failure[1 7]. The significance of PICM has been established for an increased risk in AF, heart failure hospitalization and cardiac mortality[9]. Independent predictors of PICM have been considered to be the pacing site, increased pacing burden, pre-implant LV dysfunction and QRS duration[1-4 7 14].

First, with regard to the pacing site, recent meta-analysis has suggested that the LVEF is higher in patients with

RV non-apical pacing than those with RV apical pacing. However, this conclusion is still debated due to conflicting results[3 15]. In the PROTECT-PACE study, among patients with a high-grade AV block and preserved LV function, RV non-apical pacing did not have a protective effect on LV function compared to RV apical pacing over a 2-year period[8]. In addition, Chan et al. has previously reported that LV volumes and systolic function after long term RV pacing could be predicted by pQRSd, but not pacing site[16]. Our multi-center study also showed no significant difference between RV apical and non-apical pacing for the occurrence of PICM (40.4% vs. 33.3%, p=0.546) among CAVB patients with pacing-dependent rhythm over a long-term follow-up period.

Second, pacing burden has been considered a better predictor for the occurrence of PICM, and previous studies have shown heterogeneous percentages of pacing burden[2]. In our study, in CAVB patients who required a high burden of permanent pacing, the confounding factor was minimized using homogeneous percentages of RV pacing (85% vs. 85%, p=0.860) when analyzing the predictors of PICM.

Third, with regard to pre-implant LV dysfunction, previous studies had baseline pre-existing heart failure associated with coronary artery disease and AF[4 7], and in the PREDICT-HF trial, pre-existing heart failure was highly associated with pQRSd. Other studies have also found pQRSd to be an important predictor of heart failure among patients with chronic RV pacing[13 17 18]. In our study, all CAVB patients with pre-existing LV systolic dysfunction (with or without heart failure) were excluded, and our results were reliable enough to include the analysis of PICM compared to previous studies.

Fourth, pacing-induced electrical dyssynchrony developed mechanical dyssynchrony; thus, the pQRSd could be a strong and independent determinant for the occurrence of PICM[6]. Our data also show that the pQRSd related to LV mechanical dyssynchrony has been confirmed to be significantly associated with LV remodeling (representative of the dyssynchrony index with strain in the 2- or 3-dimensional parameters, Supplemental Video 3 and 4), resulting in the occurrence of PICM by echocardiogram.

Pap et al. reported that nQRSd could be positively correlated with pQRSd, although the nQRSd as escape rhythm is influenced by the level of antegrade block on the His-Purkinje system during AV block[19]. In addition, a nQRSd above 115 ms was highly specific (90%) for the occurrence of PICM as reported in a single-center

study[20]. A single-center study by Khurshid et al. also suggested that the nQRSd (HR=1.03 per ms; p<0.001) is an independent predictor of PICM occurrence[13]. In comparison, our study demonstrated that proportion of patients with a nQRSd above 115 ms is higher in patients with PICM than those without PICM (74% vs. 55%). In particular, the nQRSd (HR=1.02; p=0.010) was slightly significant in our univariate analysis and exhibited a positive trend (HR=1.01; p=0.051) in the multivariate analysis of the occurrence of PICM (Table 4). It is implicated that a wider nQRSd may be predisposition to cardiomyopathy. In particular, among CAVB patients with normal LV function before implant, wider nQRSd may reflect more pathological electrical His-Purkinje conduction.

Miyoshi et al. also proposed that a pQRSd wider than 190 ms suggested a greater morbidity rate than a pQRSd below 190 ms[21]. However, the enrolled patients had ischemic heart disease, valvular heart disease and other causes of cardiomyopathy, whereas our study did not. Chen et al. prospectively showed in 194 CAVB patients without heart failure over a 3-year follow-up that clinical heart failure events were higher and the LVEF was lower among patients with a wider pQRSd. In addition, a pQRSd of 165 ms had the best specificity (67%) for predicting heart failure[17], and a single-center study by Kurshid et al. also proposed that a pQRSd of 150 ms was a sensitive marker for PICM; however, those enrolled patients also had pre-existing AF, coronary artery disease and unknown cardiomyopathies[13].

Taken together, a wider pQRSd could be a major determinant of the occurrence of PICM. We also found that delayed signs and symptoms of heart failure reduce the early detection of PICM in the patients with pacing-dependent rhythm and that not all patients with PICM meet the clinical criteria for heart failure despite a significant reduction of LVEF. This is consistent with previous studies showing only low sensitivity for the diagnosis of heart failure with reduced LV function[22]. Therefore, a more sensitive and specific marker for PICM occurrence may be required for patients with pacing-dependent rhythm.

Our study analyzed a contemporary cohort of CAVB patients and provided a detailed characterization of the clinical, electrocardiographic, laboratory and echocardiographic data at both pre-implant and post-implant periods as well as at the end of the follow-up. In particular, it could be noteworthy that a multicenter study with a longer follow-up duration distinguish it from previous studies as well as complement the previous studies[13 14].

Patients with PICM mostly showed a prolonged pQRS >140ms while those without PICM rarely show a prolonged pQRSd >167 ms. Therefore, even though pQRSd correlates with occurrence of PICM, pQRSd <140 ms could exclude occurrence of PICM and pQRSd >167 ms could not exclude non-PICM state for follow-up.

Our findings suggest that patients with a wider pQRSd are at higher risk for developing PICM, and therefore these patients may benefit from routine echocardiographic screening for PICM and possibly a lower threshold for early biventricular or His-bundle pacing[23 24].

This study included relatively small sized patients in the three referral centers in South Korea and may limit the generalisation of the results due to several limitations. First, our study was a retrospective study with unmeasured selection bias and patients without pre-implant or post-implant echocardiogram were excluded for analysis. Our study suffers from a small number of PICM patients due to low incidence of PICM and lack of associations may be raised due to power issues. In addition, the prevalence of PICM seems to be overestimated since patients with heart failure are more likely to get referred for echocardiograms and thus more likely to be included in the analysis. Second, this was a multi-center study, and thus, the influence of different physicians on clinical decision-making may also influence the clinical variables associated with heart failure. Third, the definition of PICM was defined only with LVEF based on anecdotal evidence from a previous study. An appropriate universal definition of PICM is needed[25]. Fourth, it is unlikely that patients with subclinical PICM may undergo incidental follow-up echocardiograms at an out-patient clinic. Fourth, while we excluded all potential etiologies of heart failure, it is speculated that a wider nQRSd is associated with the occurrence of PICM because it reflects cardiomyopathy with normal LV function at pre-implant stage. Thus, more detailed studies on the relationship between the nQRSd and an electrical pathology or substrate in CAVB patients with normal LV function are needed. Fifth, the ability to upgrade to biventricular pacing or Hi-bundle pacing for a pQRSd over 150 ms was limited in patients with PICM in our study because of the strict coverage of the national health insurance.

Early detection and preventive management of PICM are challenging in patients with pacing-dependent rhythm because there are few data to guide clinicians in identifying subclinical and clinical PICM in the subsequent months to years after pacemaker implantation.

CONCLUSION

The occurrence of PICM in patients with pacing-dependent rhythm seems to be common but cannot be reliably diagnosed based on the conventional heart failure criteria. The pQRSd, which was higher than the nQRSd, is associated with the occurrence of PICM. In particular, a patient with a pQRSd above 140ms had the best sensitivity and above 167ms had the best specificity of occurrence for PICM. Regardless of the pacing site, the pQRSd should be monitored for the timely evaluation and proper management of patients at high risk of PICM to reduce cardiac morbidity and mortality over a long follow-up period.

Contributorship Statement

Dr. Ki-Woon Kang designed the study and revised the manuscript in the final version.

Dr. Jun Hyung Kim, Dr. Yu Jeong Choi, and Dr. Tae-Seok Kim collected and analyzed the clinical characteristic, ECG and pacemaker interrogation data.

Dr. Jung Yeon Chin and Dr. Jae-Hyeong Park collected and analyzed the echocardiogram data.

Conflict of Interest

The authors have no conflict of interest to declare.

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Ethics approval:

The study was approved by the institutional review board approval of each center in South Korea

No data sharing

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Figure Legends

Figure 1. ROC curve analysis showing the pQRSd had correlated with PICM occurrence and two rectangular black marks showing the best sensitivity (pQRS 140ms) and specificity (pQRS 167ms) with statistical significance**.**

Figure 2. Kaplan-Meier curve analysis showing free-from PICM survival with a pQRSd (cut-off value of 140ms and 167 ms).

Supplemental Figure1. Flow chart of the stratified study population

Supplemental Figure 2. Non-apical ventricular pacing leads at the high sepum (left) and mid septum (right) in the X-ray

Supplemental Video 1. A case of the pre-implant echocardiogram before occurrence of PICM.

Supplemental Video 2. A case of the post-implant follow-up echocardiogram after occurrence of PICM.

Supplemental Video 3. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (parasternal long axis).

Supplemental Video 4. A case of occurrence of LV dyssynchrony at the post-implant 1 day echocardiogram (apical short axis).

Table 1. Baseline characteristics between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Age, y	64±11	64±11	62±11	0.472
Male, n (%)	47 (36.2)	40 (36.7)	7 (33.3)	0.768
Hypertension, n (%)	75 (57.7)	58 (53.2)	16 (76.2)	0.146
Diabetes, n (%)	31 (24.0)	30 (27.5)	1 (5.0)	0.030*
IHD, n (%)	15 (11.5)	11 (10.1)	4 (19.0)	0.239
Stroke or TIA, n (%)	9 (6.9)	5 (4.6)	4 (19.0)	0.017*
Alcohol, n (%)	16 (12.3)	13 (11.9)	3 (13.3)	0.763
Smoking, n (%)	18 (13.8)	16 (14.7)	2 (9.5)	0.531
Hemoglobin, g/L	12.3±2.1	12.1±1.9	12.4±2.6	0.660
Total bilirubin, mg/dL	1.0±0.8	1.0±0.6	1.0±0.8	0.556

IHD: ischemic heart disease; * statically significant.

Table 2. Comparison of ECG parameters between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
Ejection fraction, n (%)	65±10	66±9	65±10	0.607
Left atrial diameter, mm	39±9	38±7	40±8	0.552
Heart rate, bpm	60±30	57±18	60±12	0.550
PR interval, ms	190±81	170±115	213±130	0.203
QRS duration, ms	136±26	124±34	149±32	0.004*
QTc interval, ms	480±37	466±54	495±44	0.035*
Post-implant				
Dual chamber, n (%)	110 (84.6)	90 (82.5)	20 (95.2)	0.142
Ejection fraction, n (%)	45±8	61±7	37±8	<0.001*
Left atrial diameter, mm	40±7	39±7	40±6	0.266
Occurrence of AF, n (%)	19 (14.6)	16 (14.6)	3 (14.2)	0.962
Heart rate, bpm	68±30	69±14	67±9	0.616
PR interval, ms	178±81	168±80	187±62	0.337
Paced QRS duration, ms	149±26	139±29	167±28	<0.001*
Paced QRS axis, degree	2±78	2±78	1±91	0.971
Paced QTc interval, ms	490±37	484±46	496±36	0.254
Non-apical pacing, %	51 (39.1)	44 (40.4)	7 (33.3)	0.546
Atrial pacing, %	23±22	23±23	22±22	0.954

Ventricular pacing, %	85±17	85±18	85±17	0.860

AF: atrial fibrillation; * statistically significant.

Table 3. Comparison of medications between patients with and without PICM

	All patients	Without PICM	With PICM	*P*
	N=130	N=109	N=21	
Pre-implant				
ACEI or ARB, n (%)	50 (38.5)	37 (33.9)	13 (61.9)	0.016*
Beta-blocker, n (%)	16 (12.3)	11 (10.1)	5 (23.8)	0.080
CCB, n (%)	26 (20.0)	22 (20.2)	4 (19.0)	0.905
Diuretics, n (%)	30 (23.1)	22 (20.2)	8 (38.1)	0.074
Post-implant				
ACEI or ARB, n (%)	58 (44.6)	45 (41.3)	13 (61.9)	0.082
Beta-blocker, n (%)	22 (16.9)	15 (13.8)	7 (33.8)	0.029*
CCB, n (%)	31 (23.8)	28 (25.7)	3 (14.3)	0.262
Diuretics, n (%)	32 (24.6)	23 (21.1)	9 (42.9)	0.034*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensinogen receptor blocker;

CCB: calcium channel blocker; * statistically significant.

Table 4. Cox Regression Analysis for the Occurrence of PICM

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, per year	1.01	0.97-1.06	0.371			
Gender, male	0.90	0.35-2.30	0.833			
Diabetes mellitus	0.29	0.03-2.26	0.297			
nQRSd, per ms	1.02	1.00-1.04	0.010*	1.01	1.00-1.03	0.051
nQTc interval, per ms	1.00	0.99-1.08	0.195			
pQRSd, per ms	1.05	1.03-1.08	<0.001*	1.05	1.02-1.09	0.001*
Non-apical pacing	0.35	0.11-1.10	0.074			

HR: hazard ratio; CI: confidence interval; ACEI; angiotensin converting enzyme; ARB: angiotensin receptor blockr; ms: millisecond * statistically significant.

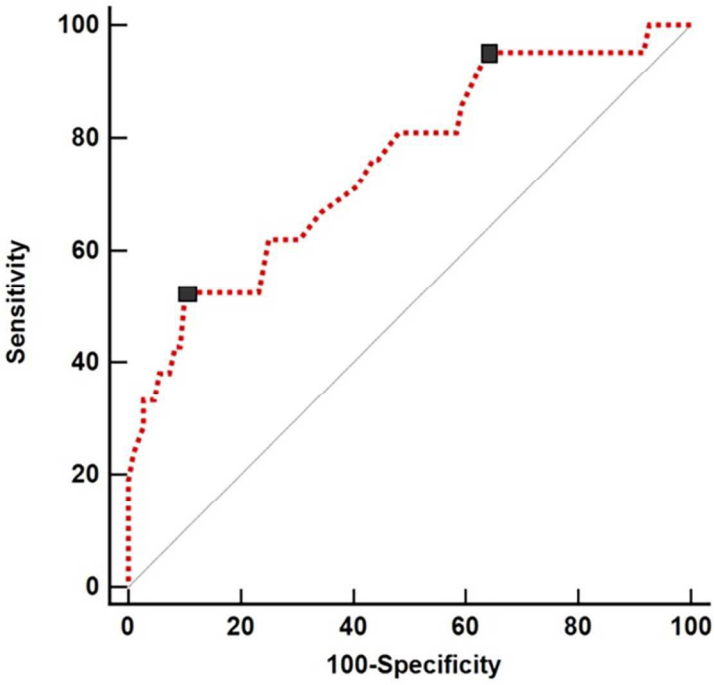

Figure 1

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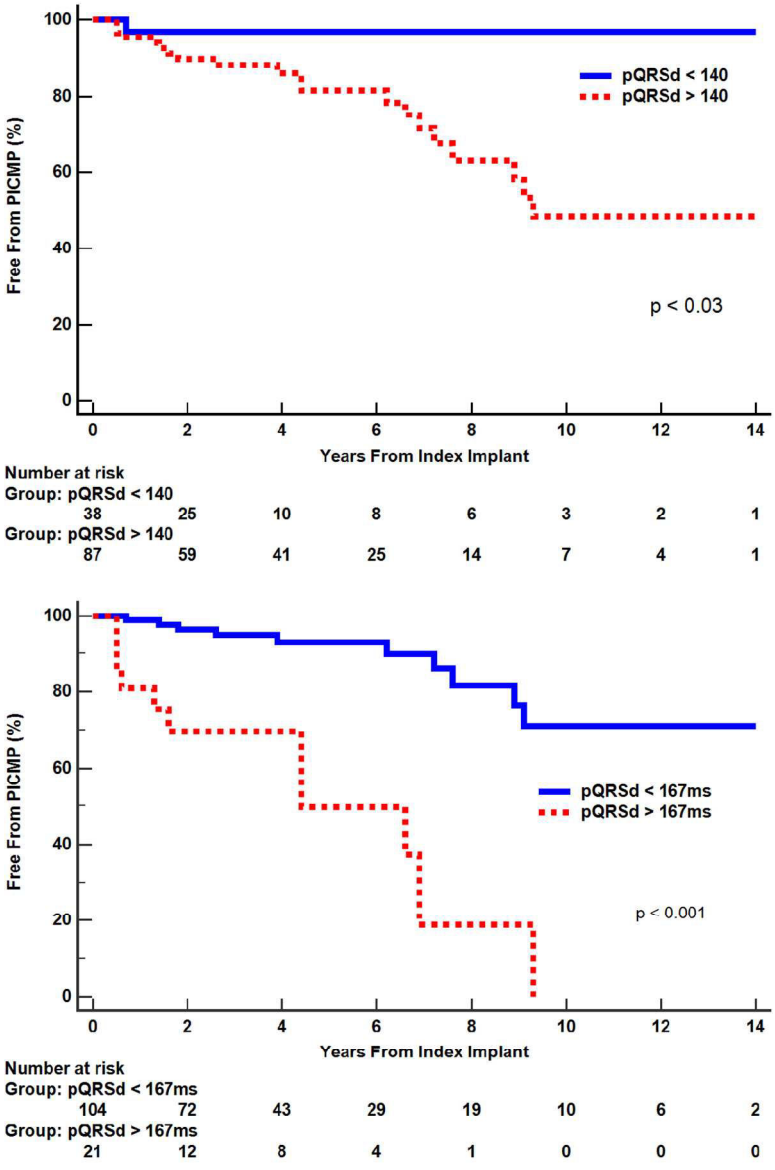

Figure 2

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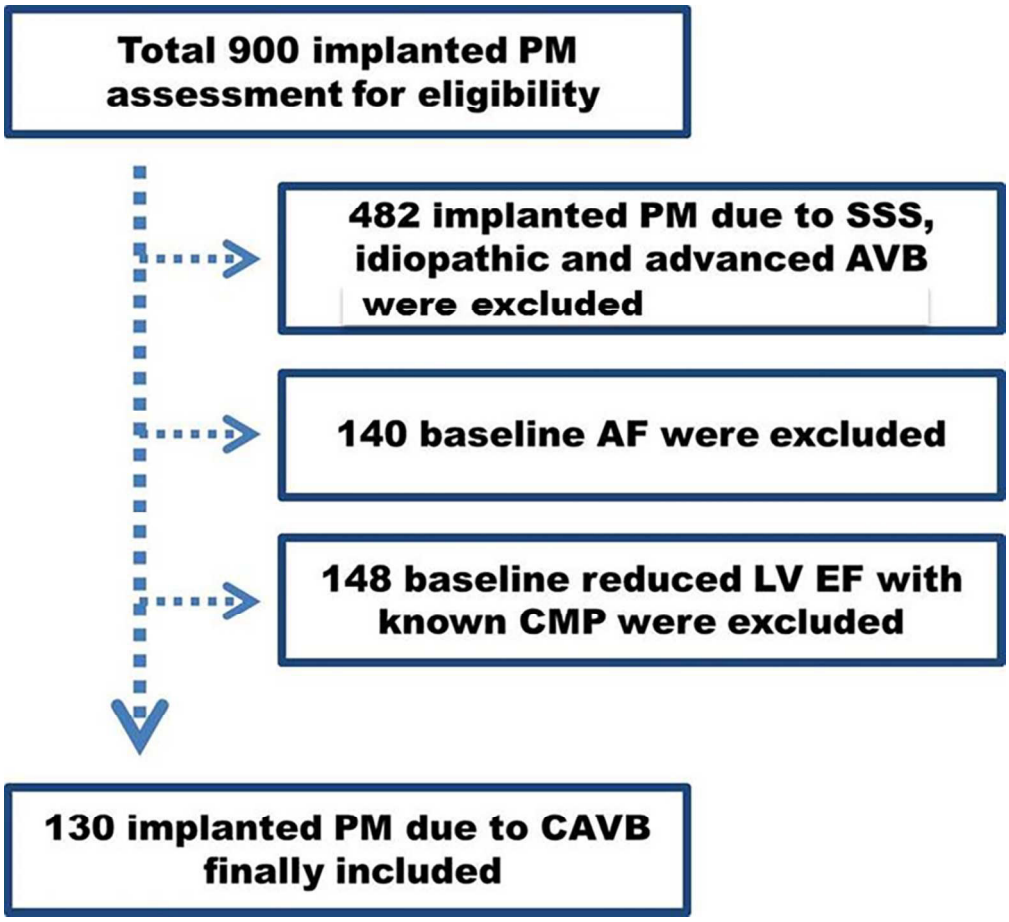

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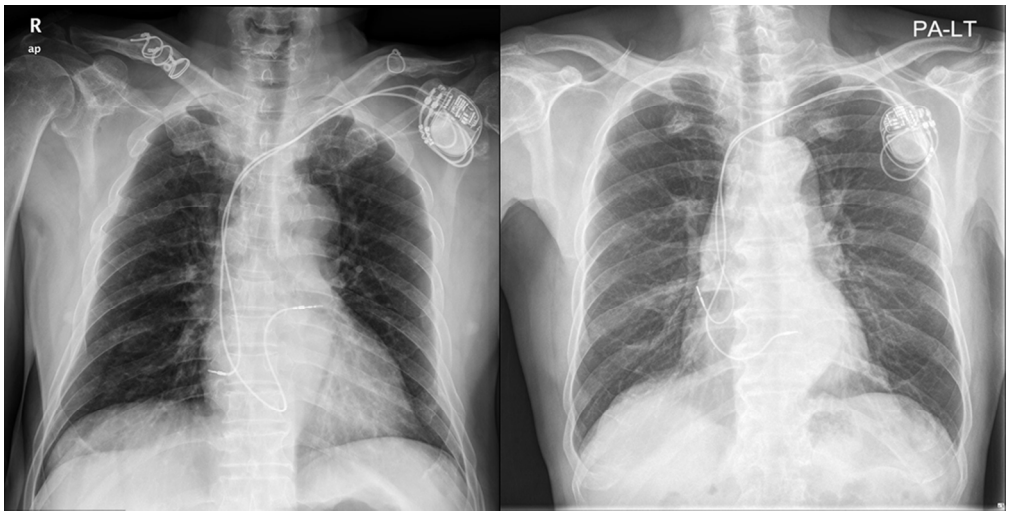

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (page 4)
Methods		
Study design	4	Present key elements of study design early in the paper (page 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 4)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (page 4)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed (page 5)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (page 5)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (page 5)
Bias	9	Describe any efforts to address potential sources of bias (page 5)
Study size	10	Explain how the study size was arrived at (page 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 5)
Statistical methods (page 5-6)	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (page 4, supplemental table)
		(b) Give reasons for non-participation at each stage (page 4)
		(c) Consider use of a flow diagram (supplemental table)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (page 17)
		(b) Indicate number of participants with missing data for each variable of interest (page 17, page 18)
		(c) Summarise follow-up time (eg, average and total amount) (page 17, page 18)
Outcome data	15*	Report numbers of outcome events or summary measures over time (Figure 2)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Table 4)

		(*b*) Report category boundaries when continuous variables were categorized (Table 1, Table 2)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 7)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 10)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (page 8, page 9)
Generalisability	21	Discuss the generalisability (external validity) of the study results (page 9)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 12)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.