FULL LENGTH ARTICLE

Three-dimensional echocardiography with left ventricular strain analyses helps earlier prediction of right ventricular pacing-induced cardiomyopathy

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Background and objectives: Right ventricular (RV) pacing can lead to progressive ventricular dysfunction over a certain period. This pacemaker-induced cardiomyopathy (PiCMP) may be more common than previously reported. Speckle tracking imaging is a recent development in echocardiography that can identify left ventricular (LV) dysfunction even before the LV ejection fraction (LVEF) value decreases. Three-dimensional (3D) echocardiography has made more accurate assessment of LVEF possible. The objectives of this study are to study the incidence of RV PiCMP using 3D echocardiography and LV strain analysis over a follow-up of 6 months, and to identify its predictors.

Methods: This is an observational study of consecutive patients without structural heart disease and with a baseline EF of more than 45% who received a permanent pacemaker. They were observed over a 6-month period. PiCMP was defined as a decrease in LVEF by 10 percentage points or a decrease in LV strain by 15% from baseline in the absence of other known causes of cardiomyopathy. PiCMP incidence and its associations were analyzed over a 6-month period.

Results: The incidence of PiCMP was not only significant over a period of 6 months but also at 24 hours. Significant drops in 3D EF were noted in one (2.8%) patient at 24 hours and in another four (11.1%) patients at 6 months. A significant decrease in LV global longitudinal strain was noted in 23 (63.9%) patients by 6 months. In seven of these patients, there was significant decrease in global longitudinal strain 24 hours after implantation. In analyzing longitudinal strain, the parameter significantly influencing a decrease was a pacing percentage of $\geq$20% ($p = 0.023$).

Conclusions: PiCMP is not uncommon in patients undergoing pacemaker implantation and is associated with RV pacing. PiCMP was associated with a ventricular pacing percentage of $\geq$20%. 3D echocardiography with LV strain analysis plays a vital role in identifying LV dysfunction at an earlier stage compared to EF. PiCMP, if picked up and intervened upon early, can help impede its progression.

Keywords: Ejection fraction, Incidence, Pacing induced cardiomyopathy, Predictors, Three-dimensional echocardiography

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Introduction

Implantable cardiac pacing devices are the only effective treatment for symptomatic bradyarrhythmias, and right ventricular (RV) apex has been the traditional site of pacing because of ease of implantation and lead stability. However, RV pacing can lead to progressive ventricular dysfunction by causing electrical and mechanical dyssynchrony. This pacemaker-induced cardiomyopathy (PiCMP) may be more common than previously reported. PiCMP has been variably defined based on decrease in left ventricular ejection fraction (LVEF) as assessed by two-dimensional echocardiography. One accepted definition is a decrease in LVEF by 10 percentage points. The recent development of speckle tracking echocardiography (STE) to measure LV strain has facilitated detection of LV systolic dysfunction before a perceptible change in EF occurs. Three-dimensional (3D) echocardiography has also made assessment of LVEF more accurate. In this observational study, our intent was to estimate the incidence of PiCMP as assessed both by LV strain and LV 3D ejection fraction (3D EF) and identify the factors predicting its incidence.

Methods

After institutional review board approval was obtained, consecutive patients undergoing permanent pacemaker implantation in our institution were recruited over a 6-month period, and each patient was followed up for a minimum of 6 months. Informed written consent was taken from all patients included in our study. The inclusion criteria were adult patients with permanent pacemaker implantation [VVI (R)/DDD (R)/VDD (R)] and normal EF (more than 45% by two-dimensional Simpson's method) at the time of implantation. The exclusion criteria were patients undergoing implantable cardioverter defibrillator implantation or cardiac resynchromization therapy, structural heart disease defined as the presence of congenital cardiac disease (shunt lesions and complex cyanotic and acyanotic heart diseases), valvular heart disease, or cardiomyopathies, and patients with arrhythmias such as atrial fibrillation, frequent ventricular ectopics, or any incessant tachycardia that can produce LV dysfunction. A total of 36 patients were recruited during the study period.

All patients underwent echocardiography at baseline prior to pacemaker implantation, and at 24 hours and 6 months after implantation. Echocardiography was performed by the primary investigator using Vivid E9 (GE Healthcare System, Horten, Norway) ultrasound system with 4V-D transducer (volume phased matrix array with a frequency range of 1.5–4.0 MHz). LV strain was calculated using 4D Auto LVQ software (GE Healthcare system, GE Vingmed Ultrasound A/S, Horten, Norway) offline. A standard 12-lead surface electrocardiogram at 25 mm/s was done immediately after implantation, and paced QRS width and axis were determined using standard criteria. The site of RV pacing was determined by chest X-ray in both posteroanterior and lateral views. In lateral view, lead position was divided as apical and nonapical. RV lead-tip position in the posteroanterior view was classified as RV outflow tract (RVOT), RV high-septum (RVHS), RV mid-septum (RVMS), RV apex (RVA), and RV free wall (RVFW) as described previously by Thebault et al. [1]. For analysis RVOT, RVHS, and RVMS were grouped together, and RVFW and RVA were considered together. Pacemaker interrogation was done immediately after implantation and at 6 months. PiCMP was defined as decrease in LVEF by 10 percentage points or a decrease LV global longitudinal strain (GLS) by 15% from baseline (not the absolute decrease in GLS value) in the absence of other known causes of LV dysfunction. This is assessed at 24 hours and at 6 months.

Abbreviations

3D	three-dimensional
EF	ejection fraction
GLS	global longitudinal strain
LV	left ventricular
PiCMP	pacemaker induced cardiomyopathy
RVOT	right ventricular outflow tract
RVHS	right ventricular high-septum
RVMS	right ventricular mid-septum
RVA	right ventricular apex
RVFW	right ventricular free wall
STE	speckle tracking echocardiography

Statistical methods

All the categorical variables such as sex, type of pacemaker, ventricular lead position, paced QRS axis quadrant, and ventricular pacing percentage were summarized as frequency and percentage (%). All continuous variables such as age, QRS duration EF, and longitudinal strain were examined for normality and summarized as

mean ± standard deviation. Independent *t* tests were used to compare continuous variables. Patients were grouped according to their decrease in longitudinal strain (more than or less than 15% decrease by 6 months) with independent *t* tests used to compare continuous variables and chi-square *t* test or Fisher's exact test (in the presence of small numbers) for the categorical variables. One-way repeated-measures analysis of variance with the pairwise comparison test was used to test the significant change between the time points for EF and longitudinal strain. Fischer's exact test was used for categories that had numbers less than five. Univariate logistic regression analysis was done for all variables with PiCMP as the outcome. For all the analysis, 5% level of significance was considered to be significant. All statistical analyses were done using Stata/ic software Version 13.1 (statacorp 4905, lakeway drive college station, Texas 77845, USA, 800-STATA PC).

Results

There were 25 (69.4%) males, and 11 (30.6%) patients were females. Their mean age was 62.0 years. Ten (27.8%) patients underwent single chamber pacemaker (VVI/VVIR), and the rest underwent dual chamber pacing (DDD(R)/VDD). The baseline characteristics of the patients are shown in Table 1. The mean QRS duration was 137.72 milliseconds. The QRS axis was superior in 27 patients (75%) and inferior in the rest. Ventricular lead position was apical or free wall in 29 patients (80.6%), and septal position in the remaining patients. The majority of our patients had pacing from the RVA.

Table 1. Baseline characteristics.

Baseline parameters	
Age (y)	62.03 ± 13.37
Sex	
Males	25 (69.4)
Females	11 (30.6)
Type of pacemaker	
Dual chamber	26 (72.2)
Single chamber	10 (27.8)
QRS duration (ms)	137.72 ± 27.96
Ventricular lead position	
Apical and free wall	29 (80.6)
Septal	7 (19.4)
Axis quadrant	
Superior	27 (75)
Inferior	9 (25)
Ejection fraction	57.38 ± 5.70
Longitudinal strain	17.73 ± 3.11
Ventricular pacing	
<20%	11 (30.6)
≥20%	25 (69.4)
Ventricular lead threshold (V)	0.82 ± 0.25

Data are reported as *n* (%) for categorical variables and Mean ± standard deviation for continuous variables.

The incidence of PiCMP as defined in this study occurred in 23 (63.9%) patients over a period of 6 months. A clinically significant decrease in 3D EF (defined as >10% decrease from baseline) was noted in only four (11.1%) patients by 6 months, of which one patient had significant decrease within 24 hours. As a group, there was statistically significant decrease in the mean 3D EF from baseline to 6 months ($p < 0.001$). However, the decrease in mean EF was only 3.3 percentage points (57.8% prior to implantation vs. 54.5% at 6 months) with both values in the normal range (Fig. 1A). The 3.3 percentage drop is less than the test variability [2] A significant decrease in LV GLS (defined as >15% decrease from baseline) was noted in 23 (63.9%) patients by 6 months ($p < 0.001$). In seven of these patients, there was significant decrease in GLS at 24 hours after implantation with $p < 0.001$ (Fig. 1B). There was progressive drop in GLS over 6 months (17.97 prior to implantation vs. 13.92 at 6 months) with significant decrease noted even at 24 hours (17.97 prior to implantation vs. 16.31 at 24 hours). However, unlike the decrease in EF, there was a discernible decrease in GLS (4.05 at 6 months). A drop in GLS of 4.05 is more than the variability in the measurement of GLS [2].

In univariate analysis for predicting the drop in longitudinal strain considering pacing percentage as a parameter, the odds ratio of getting the event is 5.542 (1.196–25.682) times higher with ≥20% pacing as compared to that of <20% pacing ($p = 0.029$). With reference to pacing mode, the odds of getting the event is 4.071 (0.879–18.868) times higher with dual chamber pacing as compared to single chamber pacing. Considering QRS duration, the odds of getting the event is 1.019 (0.994–1.046) as the duration progresses (Table 2); meanwhile, other factors did not reach statistical significance: age ($p = 0.275$), sex ($p = 0.630$), QRS axis quadrant ($p = 0.161$), QRS duration ($p = 0.143$), change in QRS duration from baseline ($p = 0.471$), site of pacing ($p = 0.500$), and ventricular pacing threshold ($p = 0.410$). However, in multivariate analysis, the pacing percentage was not found significant ($p = 0.169$) when adjusted to paced QRS duration.

Discussion

RV pacing can lead to LV systolic dysfunction and heart failure. The detrimental effects on cardiac structure may be related to the abnormal

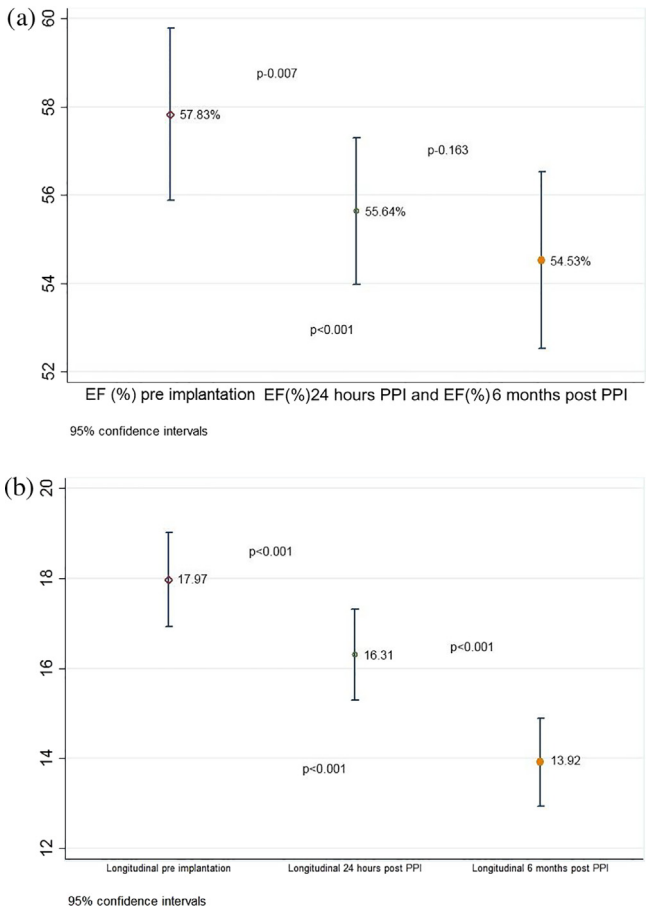

Figure 1. Statistical significance for drop in EF and strain values. (A) Significant drop in EF. (B) Significant drop in longitudinal strain. EF = ejection fraction; PPI = permanent pacemaker implantation.

Table 2. Univariate analysis.

Predictors	Longitudinal strain decrease <15% (N = 13)	Longitudinal strain decrease ≥15% (N = 23)	p
Age	65.31 ± 12.01	60.17 ± 13.99	0.275
Sex			
Males	9 (69.23)	16 (69.57)	0.630
Females	4 (30.77)	7 (30.43)	
Paced QRS duration	128.54 ± 27.02	142.91 ± 27.71	0.143
Delta QRS	11.54 ± 29.19	19.52 ± 32.82	0.471
Axis quadrant			
Superior	8 (61.54)	19 (82.61)	0.161
Inferior	5 (38.46)	4 (17.39)	
Pacemaker type			
Single chamber	6 (46.15)	4 (17.39)	0.064
Dual chamber	7 (53.85)	19 (82.61)	
Lead position			
Apical and free wall	11 (84.62)	18 (78.26)	0.500
RVOT and septum	2 (15.38)	5 (21.74)	
Lead threshold	0.87 ± 0.28	0.80 ± 0.24	0.410
Ventricular pacing percentage			
<20%	7 (53.85)	4 (17.39)	
≥20%	6 (46.15)	19 (82.61)	0.029

Data are reported as n (%) or mean ± standard deviation.
RVOT = right ventricular outflow tract.

electrical and mechanical activation pattern of the ventricles caused by RV pacing. This abnormal activation pattern of the ventricles can result in changes in perfusion, cardiac metabolism, contractility, and hemodynamics. Some of these can result in acute deterioration of LV function. Experimental studies have demonstrated that long-term RV apical pacing induces abnormal histologic changes with myofibrillar disarray and wall thinning. Acute and long-term effects of RV pacing have been explained by Tops et al. [3].

The criteria for defining PiCMP vary in different studies. Khurshid et al. [4] included patients with LVEF of more than 50% and defined PiCMP as a decrease of 50% or more in the EF of the left ventricle, resulting in an EF of less than 50%. It was variably defined as a fall in EF by a certain percentage point to a value below 45–50%. The incidence of PiCMP—as defined by an LVEF $\leq$ 45%—has been reported to be 9% 1 year after implantation [5]. Zhang et al. [6] reported new onset heart failure in 26% patients with frequent RV pacing over 7.8 years median follow-up. Kiehl et al. [7] reported a 20% prevalence of PiCMP over a decade. Kiehl et al. [7] reported 12.3% incidence of PiCMP in a cohort of patients undergoing pacemaker implantation over 4.3 ± 3.9 years follow-up. PiCMP developed as early as 1 month and as late as 15 years after pacemaker implantation [8]. However, the use of LVEF has important limitations. First, the measurement of LVEF has large interpersonal and intrapersonal variability and also depends on the technique used. Second, the reduction in LVEF is often a late phenomenon. Once LVEF is decreased, despite intervention there is failure of recovery of systolic function in up to 58% of patients. Hence, there is a role for an imaging modality that is relatively inexpensive and that can pick up early PiCMP.

In recent times, a reduction in LV strain has emerged as a sensitive and early marker of LV dysfunction. Current acquisition and measurement techniques of LV strain are fairly automated, thereby decreasing inter- and intrapersonal variability. Therefore, we used strain echocardiography as a modality for assessment of PiCMP with the intention to detect early LV systolic dysfunction. A meta-analysis [9] of normal reference values for LV strain based on STE reported normal values of GLS varied with a mean of 19.7% (95% confidence interval, 20.4–18.9%). According to Thavendiranathan et al. [10], the thresholds of change in GLS values to predict chemotherapy induced cardiotoxicity have ranged from 10% to 15% decrease using STE, and a study by Stoodley et al. [11] considered significant strain values as a fall in more than 10% from baseline values. We extrapolated these criteria to define the fall in strain value of $\geq$15% from baseline value to define PiCMP and found that significant decrease in LV GLS (defined as $\geq$15% decrease from baseline) was noted in 23 (63.9%) patients by 6 months and seven patients by 24 hours. A fall in strain values might predict future risk of developing clinical heart failure in individuals undergoing pacemaker implantation.

As only a subset of patients develops PiCMP following RV pacing, the predictors of its incidence remain undefined. Susceptibility to different varieties of cardiomyopathies has been shown to differ by sex [12–14]. Previous studies showed men to be at increased risk for PiCMP. The pacing parameters including duration and location of pacing lead also predict the occurrence of PiCMP [15]. Kim et al. [16] emphasized the role of paced QRS axis on PiCMP and showed that normal QRS axis correlated with preserved LV function. In our study, age, sex, location of pacing lead, and the paced QRS axis did not influence the incidence of PiCMP. This was probably because of the small sample size. Khurshid et al. [17] showed longer follow-up paced QRS duration to be associated with the presence of PiCMP. Our study, being of short duration, failed to show this association. For obvious reasons, the percentage RV pacing is a predictor of PiCMP. Khurshid et al. [17] and Kiehl et al. [7] have shown increased incidence of PiCMP with RV pacing of $\geq$20% of the time. In our study also ventricular pacing percentage was shown to influence the incidence of PiCMP ($p = 0.023$) at 6 months.

The commonly preferred site for endocardial transvenous ventricular lead implantation is the RVA owing to the ease of placement and stability. However, theoretically RV apical pacing has been implicated in the development of PiCMP by producing wider QRS than alternate sites such as para-Hisian tissue, the mid and or the RVOT septum. Most short-term studies found significantly better hemodynamic parameters in RVOT pacing [18–20]. Larger studies such as PROTECT-PACE (Protection of Left Ventricular Function during Right Ventricular Pacing), in which apical pacing showed no significant effect on LV function, did not corroborate this [21]. In our study, also, the lead position was not a significant predictor of PiCMP.

There are several limitations to our study. The sample size is small and duration of follow-up is short. In addition, we did not assess clinical endpoints. In conclusion, we have shown that

subclinical PiCMP is more common than studies previously suggested, and it can occur in a short time after pacemaker implantation. By detecting the onset of PiCMP early, we can intervene more quickly so as to impede its progression.

Conclusion

PiCMP associated with RV pacing is more common than previously thought; however, the role of the pacing site being responsible is still debatable. 3D echocardiography with LV strain analysis plays an important role in identifying LV dysfunction at an earlier stage compared to EF. PiCMP, if diagnosed and intervened upon early, can improve long-term prognosis.

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