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ORIGINAL ARTICLE

The Prevalence of Pacing-Induced Cardiomyopathy (PICM) in Patients With Long Term Right Ventricular Pacing – Is it a Matter Of Definition?

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Background Chronic right ventricular pacing may contribute to deterioration in left ventricular ejection fraction (LVEF). The aim of the study was to identify the prevalence of pacing-induced cardiomyopathy (PICM) in patients with chronic right ventricular pacing.

Methods Patients attending a pacemaker clinic were retrospectively identified as having had transthoracic echocardiographic LVEF measurement during the 12 months prior to device implantation. Those with cardioverter-defibrillators or biventricular devices were excluded. The remaining patients were invited back for a repeat echocardiogram. Three (3) different definitions of PICM were employed: 1) follow-up LVEF of ≤40% if baseline LVEF was ≥50%, or an absolute reduction in LVEF ≥5% if baseline LVEF was <50%; 2) follow-up LVEF of ≤40% if baseline LVEF was ≥50%, or an absolute reduction in LVEF ≥10% if baseline LVEF was ≤50%; 3) absolute reduction in LVEF ≥10% irrespective of baseline LVEF. Alternate causes of cardiomyopathy were excluded following a chart review.

Results The study cohort of 118 included 67 males (mean age 77.8 ± 10.5 years) and 51 females (mean age 76.8 ± 11.2 years). The mean time between baseline and follow-up echocardiograms was 3.5 + 1.4 years (range 1.5–6.4 years). The prevalence of PICM ranged from 5.9 to 39.0% depending on PICM definition. Multivariate analysis found that PICM was significantly associated with ventricular pacing burden ($p = 0.013$).

Conclusions The prevalence of pacing induced cardiomyopathy is dependent on current accepted clinical definitions. A clear definition of PICM is required for a better understanding of the clinical implications of right ventricular pacing.

Keywords Right ventricular pacing • Cardiomyopathy • Pacing induced cardiomyopathy • Prevalence

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Introduction

Although right ventricular apex (RVA) pacing is a mature and successful long-term therapy, experimental and clinical data suggest that it may contribute to a decrease in left ventricular systolic function [1,2]. A combination of abnormal ventricular activation (electrical dyssynchrony) and resultant abnormal ventricular contraction patterns (mechanical dyssynchrony) appears to result in adverse left ventricular remodelling promoting heart failure, atrial fibrillation and increasing mortality [3–5]. Deterioration in left ventricular systolic function purely related to pacing with no other identifiable cause is generally referred to as pacing-induced cardiomyopathy (PICM). There is currently no internationally accepted definition and previous studies have variably defined PICM as a reduction in baseline left ventricular ejection fraction (LVEF) from normal (≥55%) to follow-up of ≤40%, or an absolute reduction in LVEF ≥10% resulting in an LVEF of ≤50% [6,7]. Importantly, there have been no major prospective multi-centre randomised studies and much of our current knowledge is based upon retrospective studies which have shown a wide variation in PICM prevalence of between 3 and 30% [4,6–9].

The aim of the current study was to determine the prevalence of PICM in patients with chronic right ventricular pacing using differing definitions of reduced left ventricular function.

Methods

Study Population

The pacemaker database (Paceart, Medtronic Inc, Minneapolis, MN, USA) at the Princess Alexandra Hospital, Brisbane, Australia was cross-referenced against the echocardiography database to identify patients who had undergone a transthoracic echocardiogram within the 12 months preceding device implantation. Patients with an implantable defibrillator, resynchronisation device or a single chamber atrial pacemaker were excluded.

Baseline demographics, medical co-morbidities including diabetes mellitus, body mass index (BMI), systemic hypertension (HTN), a history of prior myocardial infarction, known coronary artery disease, and current smoking were collected from a review of the medical records. Other possible causes of progressive left ventricular deterioration such as known ischaemic or non-ischaemic cardiomyopathy, severe valvular or congenital heart disease or a strong family history of known genetic cardiomyopathy were identified from chart review. The percentage of ventricular pacing and the aetiology of the presenting bradyarrhythmias were recorded from the hospital pacing database.

All chest X-rays were reviewed to confirm pacing lead position which was defined as RVA if the lead was pointing inferiorly or horizontally in the anteroposterior chest X-ray and non-RVA if the lead was pointing superiorly, as described in previous publications [6].

Echocardiography

All patients had undergone standard 2D transthoracic echocardiographic studies prior to device implant and this was repeated at study follow-up. Patients were imaged after lying in the resting state for a minimum of 5 minutes to ensure data were gathered under basal conditions. Images were recorded using either an iE33, (Philips Healthcare, Andover, MA, USA; Vivid 7, E9) or Vivid I, (GE Medical Systems, Milwaukee, WI, USA). All recordings were made in end-tidal expiration, to ensure consistency in the face of haemodynamic variations due to breathing and to minimise the effect of movement of the imaging plane. All image clips were recorded over three consecutive cardiac cycles, and ectopic and post-ectopic beats were excluded. Left ventricular ejection fraction was calculated using the Simpson's biplane method [10]. All echocardiograms were reviewed by three experienced operators who were blinded to the clinical and pacing data of the study.

Definition of Pacing Induced Cardiomyopathy

Latest European Society of Cardiology (ESC) guidelines defined heart failure with reduced ejection fraction as ≤40% [11]. Current European Association of Echocardiography suggests test-retest reliability of LVEF was an absolute ±5% difference [12,13].

In the present analysis, the authors adopted three definitions:

- **Definition 1:** PICM was defined as a follow-up LVEF of ≤40% if baseline LVEF was ≥50%, or an absolute reduction in LVEF ≥5% if baseline LVEF was <50%;

A follow-up LVEF ≤40% was chosen as the authors felt that this level of LVEF would likely trigger a clinical intervention such as addition of medical therapy or upgrade to cardiac resynchronisation therapy (CRT). In addition, it is also the ESC clinical definition of heart failure with reduced ejection fraction. An absolute reduction in LVEF ≥5% was chosen due to the test-retest reliability of LVEF as stated above.

- **Definition 2:** PICM was defined as a follow-up LVEF of ≤40% if baseline LVEF was ≥50%, or an absolute reduction in LVEF ≥10% if baseline LVEF was ≤50%.

For this definition, an absolute reduction in LVEF ≥10% was chosen as it was considered clinically more significant.

- **Definition 3:** an absolute reduction in LVEF ≥10% irrespective of baseline LVEF.

This definition was also considered clinically relevant as it has been used in previous publications.

The project was reviewed in line with the National Statement on Ethical Conduct and Human Research (2007) and considered to be exempt from requiring formal ethical review.

Statistical Analysis

Continuous variables in the relationship between PICM and demographic characteristics, lead position and co-morbidities were tested using the Mann-Whitney U-test. Categorical variables were analysed using Pearson Chi-square test or Fisher's exact test. As the prevalence of PICM is dependent on definition, the authors identified independent determinants of the change in LVEF which would not be directly influenced by the definition of PICM. A linear mixed model with a diagonal covariance structure was used with significant univariables included as covariates in order to identify independent determinants for the change in LVEF. Statistical significance was established if p-value was <0.05. The analysis was performed using SPSS Statistics version 23 (IBM Corp. Armonk, NY, USA).

Results

Database Analysis

Of 2,500 patients in the pacing database only 142 patients were identified as having had a pre-implantation echocardiogram within the preceding 12 months. After a review of the clinical charts, 24 were excluded, 17 due to moderate to severe valvular heart disease, 1 with complex congenital heart disease, 5 due to known cardiomyopathy and 1 with significant (three vessel) coronary artery disease. One hundred and eighteen patients (118), overall mean patient age 77.4 ± 10.8 years, were included in the analysis of whom 67 were males (mean age 77.8 ± 10.5 yrs) and 51 females (mean age 76.8 ± 11.2 yrs). Dual chamber pacemakers were implanted in 107 patients (90.7%). Patient comorbidities are presented in Table 1.

Presenting Cardiac Rhythm

The rhythm at device implant was high grade atrioventricular block (AVB) in 77 patients (65.3%), sinus node disease in 21 (17.8%) and tachy-brady syndrome in 20 (16.9%).

Prevalence of PICM

The mean interval between baseline echocardiogram and device implant was 34 ± 69 days and the mean time between baseline and follow-up echocardiograms was 3.4 + 1.4 years (range 1.5–6.4 yrs). There was a significant decline in LVEF from baseline to follow-up (62.3 ± 11.1 vs $56.0 \pm 9.7\%$, $p < 0.001$) in the entire study cohort. A total of 15 patients (12.7%) had impaired LVEF (<50%) at baseline.

Based on PICM definition 1; 11 of 118 patients had PICM giving a prevalence of 9.3%. The mean baseline LVEF of the PICM and non-PICM groups was $55.5 \pm 12.1\%$ and $63.0 \pm 10.9\%$ respectively ($p = 0.045$) and at follow-up was $35.5 \pm 6.7\%$ and $58.2 \pm 7.0\%$ respectively ($p < 0.001$).

Based on PICM definition 2; 7 of 118 patients had PICM giving a prevalence of 5.9%. The mean baseline LVEF of the PICM and non-PICM groups was $62.0 \pm 9.2\%$ and $62.3 \pm 11.3\%$ respectively ($p = 0.84$) and at follow-up was $33.9 \pm 7.2\%$ and $57.4 \pm 8.0\%$ respectively ($p < 0.001$).

Based on PICM definition 3; 46 of 118 patients had PICM giving a prevalence of 39.0%. The mean baseline LVEF of the PICM and non-PICM groups was $69.8 \pm 7.9\%$ and $57.4 \pm 10.2\%$ respectively ($p < 0.001$) and at follow-up was $51.7 \pm 10.2\%$ and $58.8 \pm 8.3\%$ respectively ($p < 0.001$). However, of these 46 patients, 31 patients still had a LVEF $\geq$50% on follow-up.

In addition, 10 patients (8.5%) had a >10% improvement in LVEF at follow-up compared to baseline.

Ventricular Pacing Burden

Based on PICM definition 1, the mean percentage pacing burden in the PICM and non-PICM groups were $68.6 \pm 37.5\%$ and $59.6 \pm 41.3\%$ respectively ($p = 0.65$).

For definition 2; the mean percentage pacing burden in the PICM and non-PICM groups were $82.3 \pm 28.5\%$ and $59.1 \pm 41.2\%$ respectively ($p = 0.19$).

Table 1 **Patient characteristics (n = 118) for the total group included in the study.**

Comorbidities	Total Number	Percentage
Diabetes	32	27.1
Coronary artery disease	36	30.5
Previous myocardial infarction	17	14.4
Hypertension	87	73.7
Hyperlipidaemia	57	48.3
Obstructive sleep apnoea	9	7.6
Current smoking	8	6.9 (n = 116)
Mean Body Mass Index – BMI (kg/m^2)	29.2 ± 6.6 (n = 117)	
Pre-implant medications:		
Beta blockers		21.7%
ACE inhibitors		34.8%
ARB		23.2%
Aldosterone antagonist		7.3%

Abbreviations: BMI, body mass index; ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker.

For definition 3; the mean percentage pacing burden in the PICM and non-PICM groups were 70.7 ± 36.6% and 53.9 ± 42.3% respectively (p = 0.025).

When ventricular pacing burden was arbitrarily dichotomised into >40% or <40%, patients with ≥40% ventricular pacing burden appeared to show a greater decline in LVEF with RVA lead position compared to non-RVA, although overall patient numbers were small (Figure 1).

There was no difference in the pacing burden between patients with reduced LVEF at baseline (<50%) versus those with preserved LVEF at baseline (LVEF > = 50%), (52.6 ± 40.1 vs. 61.6 ± 41.0%, p = 0.419 by Mann Whitney U test).

The mean pre-pacing QRS width for the group as a whole was 120.5 ± 27.7 ms (n = 81) and the mean post-pacing QRS width was 147.1 ± 32.9 ms (n = 95).

Ventricular Lead Position

There were no statistical differences between RVA versus non-RVA pacing position in patients with and without PICM regardless of PICM definition: definition 1 (p > 0.99), definition 2 (p = 0.46) or definition 3 (p = 0.26).

Co-Morbidities

There were no significant differences in the prevalence of active smokers, diabetes or HTN between the PICM and non-PICM groups regardless of PICM definition (all p > 0.05). There were no significant gender differences between the PICM and non-PICM groups regardless of definition of PICM: definitions 1 (p = 0.35), 2 (p = 0.70) or 3 (p = 0.85).

Multivariate Analysis

As shown in the results above, the prevalence of PICM appears dependent on its definition. Therefore, identifying independent determinants of prevalence of PICM by multiple logistic regression would be inappropriate. In contrast, identifying independent determinants of the change in LVEF is not affected by PICM definition. Thus, linear mixed modelling was used to identify determinants of the change in LVEF on follow-up. On univariable analysis, the change in LVEF on follow-up was correlated with age (p = 0.003), BMI (p = 0.025) and ventricular pacing burden (p = 0.002). There was no difference between RVA versus non-RVA pacing position (p = 0.34) nor was there any correlation with pacing duration (p = 0.34). On multivariable analysis, age, BMI, pacing burden were included in the linear mixed model. The only independent predictor of change in LVEF on follow-up was ventricular pacing burden (p = 0.013). Figure 2 shows that there is a gradual progressive development of PICM over time irrespective of the definition of PICM.

Discussion

The results of this study show that if definition 1 and 2 are adopted, where left ventricular function is reduced to a degree associated with a clinically accepted definition of a cardiomyopathy, the prevalence of PICM varies between 5.9 and 9.3%. In contrast, if definition 3 is accepted where there is a reduction in left ventricular function from baseline, but not to a level where a clinical definition of cardiomyopathy would be generally accepted, then the prevalence is much higher at 39%. We feel definitions 1 and 2 are more likely to represent the true prevalence and that definition 3 over estimates its value. We suggest that the criteria in definition 3 could be re-characterised as a *pacing induced reduction* in left ventricular function.

There is a wide variation in the published prevalence of PICM [4,6–9]. Although this may be related to study design and relatively small patient numbers a major cause is the

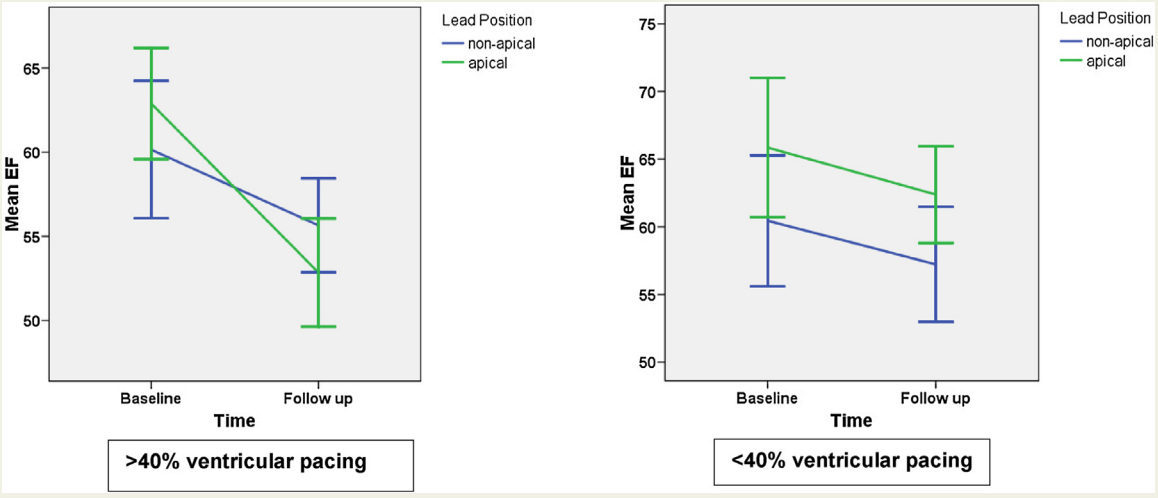

Figure 1 In patients with ventricular pacing burden >40% (*left panel*), there was a trend towards greater decline in LVEF on follow-up with RVA pacing compared to RVNA pacing (change in LVEF 10.0 ± 14.2 vs. 4.5 ± 12.6%, p = 0.075). In patients with ventricular pacing burden <40% (*right panel*), there was no difference in the change in LVEF between RVA versus RVNA pacing (3.5 ± 10.1 vs. 3.2 ± 8.8%, p = 0.93).
Abbreviations: LVEF, left ventricular ejection fraction; RVA, right ventricular apex; RVNA, right ventricular non-apical.

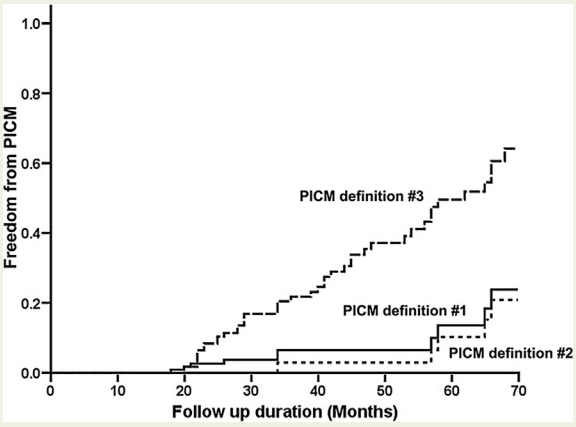

Figure 2 Freedom from pacing-induced cardiomyopathy (PICM) over time, in months. The solid line is PICM definition 1, dotted line is definition 2 and dashed line is definition 3.

variability in definition. Retrospective studies have inherent and fundamental limitations. In the two major published studies a majority of paced patients were excluded due to failure to achieve study entry criteria. For example, Khurshid's group noted that of 1,750 patients in their pacing database, 1,473 were excluded from analysis, the majority due to an absence of a follow-up echocardiogram [6]. In Kiehl's study, a total of 823 patients were analysed and 28.2% of patients were excluded from analysis [7]. These highly selected groups may not, therefore, be representative of the pacing population from which the cohort was drawn, suggesting potential selection bias. In addition PICM is variably defined: either a >10% decrease in LVEF, with resultant LVEF <50% or a post-pacemaker LVEF <40%, or the requirement for CRT upgrade [6–8]. Of the two largest published studies the incidence of PICM was 12.3% and 19.5% respectively [4,6,7]. Our results suggest a lower prevalence. We believe this to be due to both the study design, where all patients were followed-up with echocardiography regardless of clinical indication and the different definitions of PICM. The more purposive prospective methodology of our study overcomes the issue of missing echo follow-up data inherent in retrospective database analyses. However, a disadvantage is that relatively small patient numbers were enrolled and may have under- or overestimated the true prevalence. Only a large scale, multi-centre prospective study with long follow-up will provide a definitive determination of the prevalence of PICM and consensus on the appropriate PICM definition would be mandatory before such a study is undertaken. The importance of defining the size of the problem has significant health care implications. Currently more than 1,000,000 new pacemakers are implanted worldwide each year and, as populations age, this number will continue to increase [14]. In addition, although every patient paced from the right ventricle is exposed to both electrical and mechanical dyssynchrony only a relative minority develop clear evidence of PICM [6,7,15]. The ability to accurately predict which paced patient will develop clinical heart failure has important implications and might allow more targeted pacing modes from the time of presentation [16].

A robust statistical finding in our study was an association with pacing burden, irrespective of the definition of PICM. This has also been a consistent finding in a number of publications and meta-analyses [6,18]. Kiehl noted that a pacing burden greater than 20% was an important determinant as well as a lower pre-pacemaker implantation LVEF whereas other studies suggest >40% burden is relevant [7,8,17,18]. In the Mode Selection Trial (MOST) an increase in pacing burden of 10% translated to an increased hospitalisation rate of 20% [3]. An increased burden of ventricular pacing therefore appears to be a risk factor for developing PICM.

Outcomes from meta-analyses also suggest that PICM is more likely to develop when baseline LV function is impaired [17,18,21]. The majority of our patients had preserved LV function prior to enrolment and LVEF was not deemed a risk factor on multivariate analysis although overall patient numbers were small. However, our data study does concur with others studies in finding an increase in the frequency of PICM over time. Although PICM has been described as rarely occurring within one month of pacemaker implantation, often it takes years to develop [6,7,17,21]. Very long-term follow-up, up to 19 years, in children does suggest ongoing deleterious effects of right ventricular pacing [19,20].

Another potential risk factor for PICM cited in literature is right ventricular pacing lead position. Septal pacing has been suggested as an alternative to RVA pacing but comparative studies have provided variable results [17,18,21,22]. A number of studies have reported no significant difference between RVA and non-RVA pacing in the development of PICM [6,7,23]. We have found the same but also note that, in terms of pacing lead position, RVA pacing may be associated with greater falls in LVEF over time compared to non-RVA pacing. A similar result has been noted in two meta-analyses [17,18]. Data from various studies support the concept that high ventricular pacing burden, a lower baseline LVEF and RV apical pacing combine to increase the risk of PICM. An interesting and unique observation in the present study was that a small percentage of patients (8.5%) had an improvement in ejection fraction. The cause of this is not evident. It may be related to variation in the error inherent in measuring LVEF with echocardiography or perhaps to change of medical therapy during the follow-up period, not determined from the database. More work is required to establish whether this is a genuine pacing related effect or not.

Our study raises a number of clinically important issues specifically that only small numbers of patients underwent echocardiography prior to device implant. Most patients requiring a pacemaker are admitted urgently, may not have had any prior cardiac evaluation and many do not undergo echocardiography at the time of the implant. In addition, even though there is concern about the long-term effect of right ventricular pacing few patients undergo regular surveillance [6]. None of the patients in our study presented with clinical

signs of left ventricular impairment and the latter only came to light with a repeat echocardiogram suggesting that waiting for patients to present with clinical symptoms implies left ventricular impairment may already be advanced.

Our study results and others would support periodic and even regular echocardiographic surveillance, the frequency dictated by currently known risk factors such as pacing burden and baseline left ventricular function. Monitoring of LV function may enable pre-emptive intervention in those who are at risk of LVEF decline. An alternative is to await clinical events, i.e. when patients present with symptoms or signs of heart failure, rather than invest time and expense in repeat echocardiography. Regular monitoring allows early introduction of optimal medical therapy which may delay or prevent further deterioration possibly negating the need for upgrade. It might also enable recognition of other causes of left ventricular deterioration not evident at the time of presentation for pacing [24]. Although current guidelines on the use of echocardiography do not support regular surveillance unless there is a change in clinical status [25], we advocate for surveillance of paced patients becoming an integral part of clinical management. The frequency could be determined by the two factors of LV function at presentation and the pacing burden. Where baseline LV function is preserved, surveillance should be recommended every 2, or perhaps 3 years, and if LVEF falls <50% or by more than 10%, then annual echocardiography would be prudent with introduction of medical therapy.

Study Limitations

This study was performed in a single centre with relatively small numbers and represents a highly selected patient group. Although extensive measures were taken to review cases for other causes of impaired LV function rather than purely pacing, these causes may not have been identified or even known at this stage. Although pre-implant IVCD/Bundle branch block and use of medications (BB, ACE-I, ARB, aldosterone antagonists) may have an influence on PICM, these were not explored in detail due to incomplete data. In addition, selection bias may have inadvertently been introduced in that patients with impaired or poor left ventricular function at device implantation may have preferentially undergone pre-implantation echocardiograms and/or septal lead positioning.

Overall, however, the study participants were observed over a reasonable follow-up period and represent a real world group of patients. Finally, although the database was retrospectively reviewed to identify patients who had undergone echocardiography within 12 months of device implant, these patients were prospectively invited to undergo a repeat echocardiogram. As far as we are aware, this is the only such study of this design in this area.

Conclusions

We interpret the true prevalence of PICM between 5.9 and 9.3%. However, a reduction in LVEF with pacing occurs in a significant proportion of patients (39.0%). On multivariate analysis the only significant risk factor for development of PICM is high ventricular pacing burden. We recommend that all patients should have baseline echocardiograms at the time of implantation. Regular surveillance should be performed in all patients with right ventricular pacing: those with preserved LVEF at baseline and with a high pacing burden (>40%) should have echocardiograms every 2 years and those with impaired baseline LVEF (<50%), annually.

Conflict of Interest

None.

Funding Source

None.

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