Risk factors of pacing-induced cardiomyopathy—Insights from lead position

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Abstract

Background
Mid-right ventricular septum (mid-RVS) pacing is challenging to implant a lead in the intended position, and its effectiveness for preventing pacing-induced cardiomyopathy (PICM) remains controversial. This study aimed to elucidate the predictors of PICM among the patients with the confirmed lead position.

Methods
This retrospective multicenter observational study enrolled patients who underwent pacemaker implantation with lead in right ventricular apex (RVA) or mid-RVS and underwent follow-up transthoracic echocardiography (TTE). The position of mid-RVS leads were confirmed by computed tomography. PICM was defined as a left ventricular ejection fraction decrease to <40% at the follow-up TTE. We investigated the predictors of PICM among those patients.

Results
Among 172 enrolled patients (76±11 years and 88 men), 18 (10.5%) experienced PICM. The paced QRS duration of the mid-RVS pacing was significantly shorter than that of the RVA pacing (RVAP; 140±12 ms vs. 158±18 ms, P<.001); however, there was no significant difference in the incidence of PICM between the two groups (log-rank test, P=.17). The preoperative left ventricular end-systolic diameter (pre-LVESD) and paced QRS duration were independent predictors of PICM in multivariate analyses (hazard ratio, 1.12; 95% confidence interval, 1.03–1.22; P=.01 and hazard ratio 1.03; 95% confidence interval 1.004–1.06; P=.02, respectively).

Conclusion
Mid-RVS pacing reduced the QRS duration compared with RVAP, but the lead position was not a predictor of PICM. The paced QRS duration and pre-LVESD may be useful indicators for predicting PICM.
INTRODUCTION

Implantation of a permanent pacemaker (PM) for bradycardia is an effective treatment associated with extended longevity and improved quality of life.1,2 It has been increasingly recognized that chronic right ventricular (RV) pacing may lead to compromised left ventricle (LV) function.3 The decrease of LV systolic function in post-RV pacing without an alternative identifiable trigger is termed pacing-induced cardiomyopathy (PICM). The reported predictors of PICM include age, male gender, intrinsic QRS duration, baseline LV ejection fraction (LVEF), history of atrial fibrillation (AF), paced QRS duration, and percentage of RV pacing.4-7

The right ventricular apex (RVA) is a common site for ventricular lead implantation because of the simplicity of these procedures. Right ventricular septum (RVS) pacing, which provides a shorter paced QRS duration than that for RVA pacing (RVAP), has been performed to prevent PICM.8 However, it remains controversial that RVS pacing (RVSP) is superior to RVAP in protecting left ventricular function.9 Additionally, in RVSP, it has been reported that it is difficult to accurately implant leads in the RV. It is common to place leads in the RV with fluoroscopy guidance.10 However, a previous study using computed tomography (CT) revealed that among leads placed in the RVS with fluoroscopy guidance, many of them were placed in the right ventricular free wall or the anterior edge of the septum instead of the true RVS.11 Previous reports examining the difference in the incidence of PICM between RVAP and RVSP did not verify that the leads were accurately placed in the RVS.

We previously demonstrated that mid-RVSP results in the shortest-paced QRS duration in the RV.12 The present study investigated the predictors of PICM among the patients who underwent PM implantation with lead in RVA or mid-RVS confirmed by CT. This study aimed to elucidate the potential difference in the incidence of PICM between RVAP and "true" mid-RVSP and to identify factors that could predict PICM.

METHODS

Study population

This retrospective multicenter observational study included 604 consecutive patients who were referred to our institutions (Osaka City University Graduate School of Medicine and Osaka City General Hospital) for PM implantation between January 2008 and January 2018. Patients were excluded if the LVEF was <50% at device implantation, if only atrial lead implantation was done, if His bundle pacing (HBP) was performed, or if a leadless pacemaker was implanted. In addition, those without echocardiographic follow-up, those who developed myocardial infarction, those who underwent open-heart surgery, and those with a ventricular pacing rate of <20% during the follow-up period were excluded. Furthermore, in the surgical records, patients who had implanted the leads in RVS, but who did not undergo a chest CT scan after PM implantation or those in whom lead position was not the mid-RVS on a chest CT scan were also excluded. The CT scans were analyzed in the axial and short-axis views reconstructed on a workstation (ZIO M900 QUADRA; Amin CO., Ltd., Tokyo, Japan). All RVA lead positions were verified by chest radiography. Figure 1 presents representative cases. 12-lead electrocardiogram (ECG) and chest radiograph of a patient with leads implanted in RVA are shown in Figure 1A. ECG and CT data of the axial and short-axis views of the RV of a patient with leads implanted in mid-RVS are shown in Figure 1B. This study was approved by the institutional review boards of both hospitals.

Outcome measures

The primary outcome was the occurrence of PICM, defined as an LVEF decrease to <40% at the latest follow-up echocardiography.5 Transthoracic echocardiograms (TTE) were performed in all patients within 1 month before device implantation and at 4.1±2.7 years after device implantation. The LVEF was calculated using modified Simpson’s method. Baseline clinical data at the time of PM implantation, comorbidities, oral medication at follow-up, and echo data were collected from medical records. ECG was performed before and after PM implantation in all patients. The paced QRS duration was measured by Stim-QRSend in all leads of a 12-lead ECG. All patients were classified into the PICM and non-PICM groups, and each factor was compared between the two groups to determine those that could predict PICM and to elucidate whether the lead placement site was related to the onset of PICM.

Implantation technique

Devices were implanted in the electrophysiology laboratory or operating room using a local anesthetic agent and conscious sedation. Using standard implant techniques, the leads were inserted through the left or right subclavian veins. We used active fixation leads for ventricular pacing in all patients.

Lead implantation was performed under fluoroscopic guidance, with the site determined at the physician’s discretion. When the lead was implanted in the mid-RVS, the fluoroscopic criterion for mid-RVS implantation was that the lead tip resided in the middle of the cardiac silhouette in the right anterior oblique 30° view, with the lead tip head oriented rightward in the left anterior oblique 40° view.10

Statistical analyses

In this study, continuous variables were expressed as mean±SD values, whereas categorical variables were expressed as
percentages. Categorical variables were compared using Fisher’s exact tests. Furthermore, Mann–Whitney U tests were used to compare continuous variables. A comparison of the probability of freedom from the primary endpoint between the two groups was performed using Kaplan–Meier survival analysis. Univariate and multivariate Cox proportional hazard models were constructed to evaluate the predictors of PICM using the following variables for adjustment in the multivariate analysis according to the literature: gender, preoperative left ventricular end-systolic diameter (pre-LVESD), and paced QRS duration. Statistical significance was defined as $P < .05$.

3 | RESULTS

3.1 | Baseline characteristics

From January 2008 to January 2018, 604 patients were assessed for eligibility. Patient selection performed according to the exclusion criteria described in Section 2 resulted in the exclusion of 432 patients. Therefore, this study enrolled a total of 172 patients (Figure 2). The LVEF on TTE before PM implantation was $65.6 \pm 6\%$, and the QRS duration before PM implantation was $115 \pm 27$ ms. The number of patients with the mid-RVSP and RVAP was 106 and 66, respectively. In the mid-RVSP group, 92 patients had an atrioventricular block, five patients had sick sinus syndrome, and the remaining nine had AF bradycardia, whereas in the RVAP group, 53 patients had an atrioventricular block, eight patients had sick sinus syndrome, and the remaining five had AF bradycardia. There was no significant difference in the indication for pacemaker implantation between the mid-RVSP and RVAP groups (AVB $86.8\%$ vs $80.3\%$, $P = .29$; SSS $4.7\%$ vs $12.1\%$, $P = .08$; AF bradycardia $8.5\%$ vs $7.6\%$, $P = 1.0$). We observed no significant differences in the percentage of cumulative VP ($95 \pm 16\%$ vs $90 \pm 21\%$, $P = .07$), QRS duration before PM implantation ($113 \pm 26$ ms vs $117 \pm 29$ ms, $P = .57$), and LVEF ($65 \pm 6\%$ vs $65 \pm 6\%$, $P = .66$) between the mid-RVSP and RVAP groups. The paced QRS duration was significantly shorter in the mid-RVSP than that in the RVAP ($140 \pm 17$ ms vs $158 \pm 18$ ms, $P < .001$).

3.2 | Follow-up data

Follow-up TTE performed at $4.1 \pm 2.7$ years after implantation revealed PICM in 18 patients ($10.5\%$). The clinical characteristics are summarized in Table 1. There was no significant difference in the percentage of cumulative ventricular pacing between the PICM and non-PICM groups ($93 \pm 18\%$ vs $99 \pm 3\%$, $P = .70$). The lead position did not differ significantly between the PICM and non-PICM groups ($72\%$ vs $60\%$, $P = .44$). Kaplan–Meier analysis showed that mid-RVSP was not associated with the incidence of PICM compared with RVAP (log-rank test, $P = .17$) (Figure 3A). A comparison of the PICM and
non-PICM groups showed that preoperative ECG findings, preoperative EF, age, BMI, comorbidities, VP rate, and AF burden did not differ significantly between the two groups. The paced QRS duration was significantly longer in the PICM group than that in the non-PICM group (160 ± 18 ms vs 145 ± 16 ms, \( P = .002 \)). Furthermore, the LVEDD and LVESD before implantation were significantly larger in the PICM group than those in the non-PICM group (52 ± 9 mm vs 46 ± 6 mm, \( P = .001 \), 34 ± 8 mm vs 28 ± 5 mm, \( P = .002 \), respectively).

In univariate Cox proportional regression analysis, male gender, pre-LVEDD, pre-LVESD, and paced QRS duration were significantly associated with the incidence of PICM. Pre-LVESD and paced QRS duration remained significant in multivariate analyses (HR, 1.12; 95% CI, 1.03–1.22; \( P = .01 \), HR 1.03; 95% CI 1.004–1.06; \( P = .02 \) (Table 2).

Receiver operating characteristic (ROC) curve analysis revealed cutoff values for pre-LVESD and paced QRS duration of 33 mm (area under the ROC curve [AUC] = 0.74; 84% sensitivity and 63% specificity) and 153 ms (AUC = 0.74; 70% sensitivity and 78% specificity), respectively. Kaplan–Meier analysis showed that a pre-LVESD of \( \geq 33 \) mm was associated with the incidence of PICM compared with a pre-LVESD of \(< 33 \) mm (log-rank test, \( P < .001 \)) (Figure 3B).

Kaplan–Meier analysis also showed that a paced QRS duration of \( > 150 \) ms was associated with the incidence of PICM compared with a paced QRS duration of \( \leq 150 \) ms (log-rank test \( P < .001 \)) (Figure 3C). Kaplan–Meier analysis showed that PICM could not be prevented in cases with a paced QRS duration of \( > 150 \) ms, even with leads in mid-RVS confirmed by CT. (Figure 4).

4 | DISCUSSION

The major findings of this study were as follows: (1) the incidence of PICM did not differ between mid-RVSP confirmed by CT and RVAP and (2) the predictors of PICM were paced QRS duration and pre-LVESD.

Among the previously reported predictors of PICM, the factors that operators can intervene in are the percentage of RV pacing and paced QRS duration. The development of PM algorithms has allowed the suppression of unwanted ventricular pacing. On the other hand, the paced QRS duration is reportedly shorter in the mid-RVSP than that in the RVAP. 

Kaye et al. randomly assigned patients with severe atrioventricular block to RVAP or RV high septum (RVHS) pacing groups and followed them for 2 years, reporting no significant difference in left ventricular function between the two groups. In that study, the lead placement site was the RVHS rather than the mid-RVS, and the authors did not report the paced QRS duration in both groups. Mizukami et al. reported that there was no significant difference in the incidence of all-cause mortality or heart failure hospitalization between the RVSP and RVAP groups in their retrospective cohort study with propensity matching. As above, previous studies have not shown the effectiveness of RVSP in protecting left ventricular function. The difficulty of accurately implanting the lead in the RVS may have influenced these results.

Hattori et al. reported that only 37 (16%) of the 228 leads presumed to be implanted in the RVS according to conventional fluoroscopic criteria were confirmed to be in that location by CT. Previous studies comparing RVSP and RVAP provided no evidence that the leads in the RVSP group were correctly implanted; thus, RVAP and RVSP could not be compared properly. Therefore, the present study enrolled the patients with the confirmed mid-RVS lead location by CT and investigated the potential difference in the incidence of PICM between RVAP and true mid-RVSP. To our knowledge, no other data have been reported evaluating the predictor of PICM using mid-RVSP with the validated lead location.
In this study, consistent with previous reports, the paced QRS duration of mid-RVSP was significantly shorter than that of RVAP; however, the paced QRS duration, not the lead position, was an independent predictor of PICM. This result may seem paradoxical but may indicate that it is reasonable to implant a lead in mid-RVSP to shorten the QRS duration for the purpose of preventing PICM, but PICM could not be prevented in the cases with long paced QRS duration, even if those leads accurately implanted in mid-RVSP.

Figure 4 shows that the group of patients with a paced QRS duration of >150 ms had a significantly higher occurrence of PICM, even if those leads were implanted in mid-RVSP, where the QRS duration was shortest in the RV.

In this study, pre-LVESD was also an independent predictor of PICM. These results may indicate that PICM onset may be associated with LV remodeling, probably caused by myocardial damage present at the time of implantation. Therefore, we speculate that changing the pacing site in the RV cannot prevent the occurrence of PICM for these patients.

The present study included more men in the group who developed PICM compared with that in the group who did not, similar to previous reports.

In recent years, conduction system pacing (CSP), which includes HBP and pacing of the distal conduction system (pacing the left bundle branch via an intra-septal approach), has received attention.
Abdelrahman et al. reported that the de novo placement of an HBP was associated with a significantly reduced composite endpoint of death, hospitalization due to heart failure, or upgrade to a CRT system, as compared to a standard dual-chamber PM. However, HBP has some limitations, such as elevated pacing thresholds leading to lead revisions and/or premature battery depletion, sensing problems, and the use of certain device algorithms that were never intended for use with HBP. Pacing the distal conduction system (often referred to as left bundle branch pacing or left bundle branch area pacing) is attracting attention because it has the potential to overcome these limitations. Zhang et al. reported patients with heart failure with reduced EF and LBBB who underwent LBB pacing, which significantly shortened the QRS duration, LV activation time, interventricular mechanical delay, and intraventricular LV dyssynchrony.

During a mean follow-up of 6.7 months, pacing significantly improved the New York Heart Association (NYHA) functional class, the plasma level of B-type natriuretic peptide, LVESD, and LVEF. However, there are many unclear points such as the long-term prognosis and whether this method can be safely performed when lead extraction is required. Hence, it remains controversial whether CSP should be performed in all cases expected to have high ventricular pacing rates. The identification of the group of patients who are likely to show a deterioration of LV function by conventional RV pacing may allow the selection of patients who should undergo CSP. The pre-LVESD and paced QRS duration that we derived in this study may be useful for this selection. Further studies are needed to confirm this hypothesis.

This study had some limitations. First, the study population and the number of events were small. Second, this was a retrospective

FIGURE 3 Kaplan–Meier survival analysis of pacing-induced cardiomyopathy. (A) Mid-RVSP was not associated with the incidence of PICM compared to RVAP. (B) A pre-LVESD of ≥33 mm was associated with the incidence of PICM as compared to a pre-LVESD of <33 mm. (C) A paced QRS duration of >150 ms was associated with the incidence of PICM as compared to a paced QRS duration of ≤150 ms.

TABLE 2 Predictors of PICM

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR                  | 95% CI                | p value | HR                  | 95% CI                | p value |
| Age                       | 1.01                | 0.97–1.05             | .555    | 2.07                | 0.51–8.38             | .31     |
| Male gender               | 3.91                | 1.28–11.9             | .017    | 2.07                | 0.51–8.38             | .31     |
| Atrial fibrillation burden (%) | 0.99            | 0.98–1.01             | .348    |                    |                      |         |
| Percentage of cumulative VP (%) | 1.06          | 0.96–1.16             | .235    |                    |                      |         |
| Intrinsic QRS duration    | 1.01                | 0.99–1.03             | .378    |                    |                      |         |
| Preoperative LVESD        | 1.14                | 1.05–1.23             | .002    |                    |                      |         |
| Preoperative EF           | 0.94                | 0.88–1.02             | .119    |                    |                      |         |
| Mid-RVS implant           | 2.05                | 0.72–5.86             | .179    |                    |                      |         |
| Paced QRS duration        | 1.04                | 1.02–1.07             | .001    | 1.03                | 1.004–1.06            | .02     |

Note: Data are expressed as mean ± SD.

Abbreviations: CI, confidence interval; EF, ejection fraction; HR, hazard ratio; LVESD, left ventricular end-systolic diameter; PICM, pacing-induced cardiomyopathy; RVAP, right ventricular apex pacing; RVSP, right ventricular septum pacing.
study rather than a randomized, prospective study. A prospective randomized study with a large cohort is needed to ensure that RVSP is not superior to RVAP for preventing PICM. However, it is expected that CSP will continue to develop, and it may be impractical for such studies to be conducted. Finally, this retrospective observational study did not demonstrate cardiac MRI findings and evaluated ventricular dyssynchrony using speckle tracking. Evaluation of ventricular dyssynchrony is crucial to predicting LV remodeling, and cardiac MRI is useful for evaluating myocardial damage. Further studies are needed to evaluate these parameters.

5 | CONCLUSIONS

The incidence of PICM did not differ between mid-RVSP confirmed by CT and RVAP. The paced QRS duration and pre-LVESD may be useful indicators for predicting the incidence of PICM in patients with RV pacing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest for this article.

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