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Paced QT interval as a risk factor for new-onset left ventricular systolic dysfunction and cardiac death after permanent pacemaker implantation

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ABSTRACT

Background: Prolongation of corrected QT (QTc) interval reflects an increased risk of fatal arrhythmia and cardiac death in various populations. However, it is not clear whether the paced-QTc (p-QTc) interval is associated with new-onset left ventricular systolic dysfunction (new-LVSD) or cardiac death.
Methods: In 491 consecutive patients (64 ± 14 years) with preserved LV ejection fraction (64 ± 7%), the p-QTc interval was measured within 2 weeks after PPM implantation. We assessed the rates of new-LVSD and cardiac death based on the degree of p-QTc interval.
Results: During the follow-up period (78 ± 51 months), new-LVSD and cardiac death were identified in 53 (10.8%) and 26 (5.3%) patients, respectively. Patients with new-LVSD had more frequent atrioventricular block ($P = 0.041$), a higher percentage of ventricular pacing ($P = 0.005$), a longer p-QRS duration ($P < 0.001$), and more prolonged p-QTc interval ($P < 0.001$) compared to those without new-LVSD. There was a graded increase in the rates of new-LVSD ($P < 0.001$) and cardiac death ($P = 0.001$) from the patients in the lowest to those in the highest tertile of the p-QTc interval. Additionally, the incidence of cardiac death was significantly elevated especially in the patients with new-LVSD and wider p-QTc interval. In Cox regression analyses, the p-QTc interval was independently associated with new-LVSD and cardiac death even after adjusted with various relevant confounding factors.
Conclusions: Prolonged p-QTc interval was closely associated with new-LVSD and cardiac death after PPM implantation in patients with preserved LV systolic function. The rate of cardiac death significantly increased especially in patients who showed more p-QTc widening along with new-LVSD.

1. Introduction

Permanent pacemaker (PPM) implantation is the only safe and effective treatment for patients with symptomatic sinus node dysfunction or atrioventricular block (AVB). However, long-standing right ventricular (RV) pacing is frequently associated with deterioration of left ventricular (LV) function and heart failure (HF) in selected patients [1,2]. Several risk factors have been suggested for the adverse outcomes such as preexisting LV dysfunction, RV apical pacing location, pacing-induced LV dyssynchrony represented by prolonged paced-QRS duration (p-QRSd), and high percentage of RV pacing (RVp%) [3–6].

On the other hand, prolonged corrected QT (QTc) interval was often found in patients with advanced chronic HF and shown to be a powerful predictor of ventricular arrhythmia and mortality in this patient group [7–9]. However, the relation of paced-QTc (p-QTc) interval to new-onset LV systolic dysfunction (new-LVSD) and cardiac death following PPM implantation has never been evaluated. Therefore, the purpose of this study is to assess whether the prolonged p-QTc interval is associated with the development of new-LVSD or cardiac death after PPM implantation in patients with preserved LV systolic function.

2. Methods

2.1. Study population

In all patients undergoing PPM implantation at the Samsung Medical Center (Seoul, Korea), routine clinical, electrocardiographic, echocardiographic, and pacing parameters are prospectively collected and entered into our PPM database. To focus our analysis on the development of new-LVSD and cardiac death after the PPM implantation, patients with baseline LV ejection fraction (EF) <50% were excluded. Patients with lack of p-QRS complex on the 12-lead ECG, implantable cardioverter-defibrillator, or biventricular pacemaker were also excluded. Finally, for the present study we enrolled 491 consecutive patients who underwent PPM implantation with preserved LV systolic function between January 1995 and February 2013. The study protocol was

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approved by the institutional review board of the Samsung Medical Center and the requirement for written informed consent was waived.

2.2. Measurement of electrocardiographic and echocardiographic parameters

Standard 12-lead ECGs were obtained with an optimal low-pass filter setting (filter range, 0.15–100 Hz; alternating current filter, 60 Hz, 25 mm/s, 10 mm/mV; GE Marquette, Milwaukee, WI). All intervals of intrinsic or paced rhythms were manually measured from 12-lead ECG tracings without premature beats or significant baseline wander within 2 weeks (4.2 ± 4.7 days) after PPM implantation. In the presence of atrial fibrillation, at least 3 intrinsic or paced ventricular beats were used for averaging [10]. The QT interval was taken from the earliest onset of the QRS complex to the end of the T-wave, where a line drawn following the down-sloping limb of the T-wave intersected the baseline. The QT was corrected for heart rate according to the Bazett's formula [10]. All ECG tracings were reviewed by 2 cardiologists blinded to clinical outcomes. In the measurement of p-QT interval, the interobserver mean relative error was 7.6% and the intraobserver mean relative errors were 5.2% and 3.3%, respectively.

Comprehensive transthoracic echocardiography (M-mode, 2-D, and Doppler) was performed using commercially available equipment (Vivid 7, GE Medical system, Milwaukee, WI or Acuson 512, Siemens Medical Solutions, Mountain View, CA or Sonos 5500, Philips Medical System, Andover, Mass, USA). Various echocardiographic parameters were obtained such as LV EF, LV end diastolic and systolic diameters, and left atrial diameter.

2.3. Follow-up and clinical outcomes

Serial recordings of standard 12-lead ECG (1 day, 2 weeks, 3 months, and every 6 months) and device analysis (3 months, and every 6 months) were performed after the PPM implantation. Pacemaker programming was adjusted on an individual basis to minimize the RVp% during every visits to the cardiac device clinic. The RVp% analyzed at 3 month follow-up was used as a baseline value for the present study. Echocardiographic examinations were carried out prior to, 1 year after the procedure, and at any time when a patient reported new-onset symptoms suggesting HF.

The primary endpoint was new-LVSD which was defined as LV EF < 40% or LV ESD > 40 mm if LV EF was measured 40 to 50% on follow-up echocardiography. Secondary endpoints were cardiac mortality, which included deaths attributable to heart failure or cardiac arrest. Other deaths were considered as cardiac mortality as well when no documented evidence showing a clear noncardiac origin was available. The survival status was ascertained by review of medical records, device analysis data, and prescription refill. Only for a minority of patients, structured telephone interview was used.

2.4. Statistical analyses

Continuous variables were listed as means with standard deviations (SD) and were compared using the Student t-test. Categorical variables were presented as frequencies and percentages and were assessed using the χ^2 test or Fisher's exact test. Correlations between the degree of p-QTc interval and the rates of new-LVSD or cardiac death were evaluated using linear-by-linear association and Spearman's rho test for trend. Event-free survival depending on the degree of p-QTc interval was estimated by Kaplan–Meier analysis and the log-rank test was applied to evaluate differences between survival curves. To assess independent determinants of the development of new-LVSD or cardiac death, Cox regression analyses were performed after the proportional hazards assumption was tested based on correlations between survival rankings and Schoenfeld residuals. For multivariate analysis, statistically significant variables in univariate analysis and other important clinical variables irrespective of their univariate *P*-value were included into the model. The discriminative power of p-QTc interval and p-QRSd for predicting new-LVSD were assessed with receiver-operating characteristic (ROC) curve. All reported *P*-values were two-sided, and a *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics 18 software for Microsoft (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population and baseline characteristics

Mean (±SD) age of the 491 patients was 64 ± 14 years. Proportions of patients with male gender and hypertension were 48 and 44%, respectively. Mean (±SD) value of LV EF was 64 ± 7%. A total of 491 patients with sinus node dysfunction (n = 262, 53%), complete AVB (n = 196, 40%), or other forms of AVB (n = 33, 7%) were treated by pacemakers with DDD/DDDR (n = 261, 53%), VVI/VVIR (n = 210, 43%), or VDD (n = 20, 4%) mode.

3.2. Comparison between the patients with and without new-onset LV systolic dysfunction

During the mean follow-up of 78 ± 51 months, 53 (11%) patients were identified to develop new-LVSD (new-LVSD group) whereas the remaining 438 (89%) patients did not show new-LVSD (no-LVSD group).

There was no significant difference between the new-LVSD and no-LVSD groups regarding the baseline demographic characteristics and medications except for a higher proportion of male gender in the new-LVSD group (Table 1). Although the new-LVSD group showed a numerically greater LV ESD and a lower LV EF than the no-LVSD group, the measured values of LV ESD (30 ± 5 and 34 ± 6 mm) and EF (64 ± 7 and 59 ± 8%) in the both groups fell within normal ranges. However, patients in the new-LVSD group had more frequent AVB as an indication for PPM implantation ($P = 0.041$) and a greater RVp% ($P = 0.005$). In addition, the p-QRSd and p-QTc interval were more significantly prolonged in the new-LVSD compared to the no-LVSD group ($P < 0.001$) whereas intrinsic QTc interval was not significantly different between the two groups.

3.3. New-onset LVSD and cardiac death depending on the degree of p-QTc interval

To assess the development of new-LVSD (n = 53, 11%) or cardiac death (n = 26, 5%) depending on the degree of p-QTc prolongation, we divided the 491 patients into 3 groups; the lowest (p-QTc ≤ 450 ms; n = 160), mid (450 < p-QTc ≤ 490 ms; n = 166), and the highest tertile (p-QTc > 490 ms; n = 165). In classifying the patients into 3 groups based upon the p-QTc interval measurement, the kappa value was 0.859 showing a very good interobserver agreement. As the degree of p-QTc prolongation was augmented, there was a stepwise increase in the rates of new-LVSD ($P < 0.001$), cardiac death ($P = 0.001$), or new-LVSD/cardiac death ($P < 0.001$, Table 2). Unadjusted Kaplan–Meier survival curves depending on the degree of p-QTc prolongation are presented in Fig. 1. Being the highest tertile was independently associated with the new-LVSD, cardiac death, and new-LVSD/cardiac death in various multivariable Cox models adjusted with age, sex, coronary artery disease, baseline LV EF, post-PPM heart rate, p-QRSd, presence of AVB, PPM lead location, RVp%, and ACEI/ARB use (Table 2 and Supplemental Table 1). Additionally, p-QTc interval, when incorporated as a continuous variable into multivariate analysis, still maintained an independent association with new-LVSD ($P = 0.039$), cardiac death ($P = 0.007$), or new-LVSD/cardiac death ($P = 0.044$, Supplemental Table 2). Even if Fridericia formula was used for the correction of p-QT interval, a consistent result was obtained showing increasing rates of