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Original Research / Orijinal Araştırma

Paced Corrected QT İnterval is Associated with Lv Diastolic Dysfunction in Patients With Permanent Pacemakers and Preserved Left Ventricular Ejection Fraction

Paced Düzeltilmiş QT İntervali Kalıcı Kalp Pili Olan Sol Ventrikül Ejeksiyon Fraksiyonu Korunmuş Hastalarda Sol Ventrikül Diyastolik Disfonksiyonu ile İlişkilidir

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ABSTRACT

Objective: Although chronic right ventricular apex (RVA) pacing is usually well tolerated in patients with normal cardiac function, recent studies report that not only left ventricular (LV) systolic function but also diastolic function is adversely affected. The aim of the present study was to detect the relationship between paced QRS, paced corrected QT (pQTc) duration, and echocardiographic parameters of LV diastolic dysfunction to examine the effects of RVA pacing in patients with preserved LV ejection fraction (LVEF).

Methods: We included 74 patients with LVEF>50% and DDD(R) pacemakers implanted for atrioventricular block (45 men and 29 women; mean age 64.9±11.6 years). Patients were included to the study at least 6 months after battery implantation. Patients with RVA pacing rate <70% were excluded from the study. Patients were classified into two groups according to the left atrial (LA) volume index.

Results: pQTc was associated with LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e' velocity, and mitral E/e' ratio in bivariate analysis. The cut-off value of pQTc obtained by receiver operating characteristic curve analysis was 512 ms for prediction of increased (>34 mL/m^2) LA volume index (sensitivity: 88.0% and specificity: 79.6%). The area under the curve was 0.848 (p<0.001).

Conclusion: pQTc duration was found to be significantly associated with the echocardiographic parameters of LV diastolic dysfunction. We suggest that pQTc be used as a marker to predict the risk of diastolic dysfunction after permanent pacemaker implantation in patients with preserved LVEF. It can also be used to optimize the RV pacing area with intraoperative measurements.

Keywords: Paced QT interval, cardiac pacing, paced qrs width

ÖZ

Amaç: Kronik sağ ventrikül apikal pacing, normal kardiyak fonksiyonlu hastalarda genellikle iyi tolere edilse de, son çalışmalarda sadece sol ventrikül sistolik fonksiyonunda değil diastolik fonksiyonda da olumsuz etkilenme saptanmıştır. Ejeksiyon fraksiyonu korunmuş hastalarda sağ ventrikül pacingin etkilerini incelemek için paced QRS, paced QTc süresi ve sol ventrikül diyastolik disfonksiyonunun ekokardiyografik parametreleri arasındaki ilişkiyi saptamayı amaçladık.

Yöntemler: Sol ventrikül EF>%50 olan ve AV blok nedeniyle DDD(R) kardayak pacemaker implante edilmiş olan 74 hasta (45 erkek, 29 kadın; ortalama yaş 64,9±11,6 yıl) çalışmaya dahil edildi. Hastalar, pacemaker implantasyonundan en az 6 ay sonra çalışmaya dahil edildi. Sağ ventrikül apikal pacing oranı <%70 olan hastalar çalışma dışı bırakıldı. Hastalar sol atriyum hacim endeksine göre iki gruba ayrıldı.

Bulgular: Paced QTc, bivariate analizde sol atriyum hacim endeksi, sol atriyum hacmi, sol atriyum diyastolik son çapı, E dalga deselerasyon zamanı, septal anüler e' hızı ve mitral E/e' oranı ile ilişkiliydi. ROC eğrisi analizi ile elde edilen artmış (>34mL/m2) sol atriyum hacim endeksi için pQTc'nin cut-off değeri 512 ms olarak bulundu (duyarlılık: %88,0, özgüllük: %79,6). Eğri altındaki alan 0,848 idi (p<0.001).

Sonuç: Paced QTc süresinin, sol ventrikül diyastolik disfonksiyonunun ekokardiyografik parametreleri ile anlamlı derecede ilişkili olduğu bulundu. Sol ventrikül EF korunmuş hastalarda kalıcı pacemaker implantasyonundan sonra diyastolik disfonksiyon riskini öngörmek için pQTc'nin bir belirteç olarak kullanılabileceğini öneriyoruz. Ayrıca intraoperatif ölçümlerle sağ ventrikül pacing alanını optimize etmek için de kullanılabileceği düşünülmektedir.

Anahtar kelimeler: Paced QT interval, kardiyak pacemaker, paced QRS genişliği

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INTRODUCTION

Right ventricular (RV) pacing has been demonstrated to have detrimental effects on cardiac hemodynamics and is associated with a reduction in left ventricular (LV) function (1). It is thought that approximately 25% of patients receiving RV pacing for sick sinus syndrome and complete heart block experience "pacemaker syndrome" with symptoms of shortness of breath, dizziness, palpitations, abnormal pulsations, or chest pain (2). Chronic RV apex (RVA) pacing is usually well tolerated in patients with normal cardiac function; however, recent studies report that not only LV systolic function but also diastolic function is adversely affected (3, 4). These adverse effects may cause deterioration on the left atrial (LA) structure and function and trigger new-onset atrial arrhythmias.

The aim of the present study was to detect the relationship between paced QRS (pQRS), paced corrected QT (pQTc) duration, and echocardiographic parameters of LV diastolic dysfunction to examine the effects of RVA pacing in patients with preserved LV ejection fraction (LVEF).

METHODS

Study Protocol and Study Population

We included 74 patients with LVEF>50% and DDD(R) pacemakers implanted for atrioventricular (AV) block (45 men and 29 women; mean age 64.9±11.6 years). Patients were included to the study at least 6 months after battery implantation. Patients with RVA pacing rate <70% were excluded from the study. To eliminate the negative effects on LV diastolic function in patients with permanent atrial fibrillation, congenital heart disease, history of coronary artery disease, primary pulmonary hypertension, hypertension, diabetes, renal insufficiency (serum creatinine level>1.5 mg/dl), respiratory diseases (pulmonary embolism and chronic obstructive pulmonary disease), isolated right heart failure (HF), and moderate and severe aortic and mitral valve diseases were excluded from the study. Complete blood count, N-terminal pro-B-type natriuretic peptide, uric acid, serum lipids, serum electrolytes, and renal function tests were performed. Patients were classified into two groups according to the LA volume index. All statistical analyses were made between the two groups. The local ethics committee approved the study protocol. Written informed consent was obtained from each participant.

Echocardiographic and Electrocardiographic Parameters of the Study Population

Echocardiography was performed using a 2.5-3.5 MHz transducer (Philips HD11 Ultrasound System; Bothell, USA). LV transverse axis dimensions from M-mode recordings were measured according to the recommendations of the American Society of Echocardiography (5). Simpson's equation was used to compute LVEF. Peak E-wave velocity, peak A-wave velocity, mitral valve (MV) E/A ratio, MV deceleration time, and isovolumetric relaxation time were calculated with PW Doppler. Lateral annular e' velocity, septal annular e' velocity, and mitral E/e' ratio were determined with PW and color tissue Doppler. Indices of LA volumes for body surface area were also calculated. The AV delay of DDD(R) pacemakers was at factory setting (130-170 ms). The pQRS duration was measured in the lead with the widest QRS complex. The interval between the earliest onset of the QRS complex and the end of the T-wave was determined as the QT interval. The corrected QT was calculated using Bazett's formula (6).

Statistical Analysis

Variables were divided into two groups as categorical and continuous. Categorical data were expressed as numbers and percentages and compared with the chi-square test. Continuous variables were expressed as mean±SD. Normal distribution of continuous variables was calculated by the Shapiro-Wilk test. Normally distributed continuous variables were compared with independent sample t-test. Non-normally distributed variables were compared using Mann-Whitney U test. Multivariate logistic regression analysis was performed with variables that are found to be significant in univariate analysis. Results were expressed as the p-value and odds ratio in 95% confidence interval. Receiver operating characteristic (ROC) curve analysis was made to determine the cut-off value of pQTc to detect increased LA volume index. Statistical analysis were conducted using SPSS (Statistical Package for Sociel Sciences) Version 20.0 (IBM Corp.; Armonk, NY, USA). A $p<0.05$ was considered statistically significant.

RESULTS

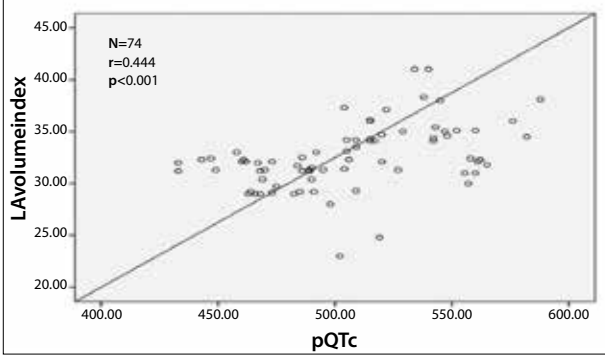
Comparison of Baseline Clinical and Laboratory Parameters in Patients with and without Increased (>34 mL/m^2) LA Volume Index

Table 1 shows a comparison of the baseline clinical and laboratory parameters. There were no significant differences between the two groups ($p>0.05$, for all).

Comparison of Electrocardiographic and Echocardiographic Parameters in Patients with and without Increased (>34 mL/m^2) LA Volume Index

LA end-diastolic diameter, LA volume, LA volume index, diastolic filing, and pQTc were significantly higher; lateral and septal annular e' velocity was significantly lower ($p<0.05$, for all) in patients with increased (>34 mL/m^2) LA volume index (Table 2). pQRS width was higher in patients with increased (>34 mL/m^2) LA volume index, but there was no statistically significant difference ($p = 0.092$).

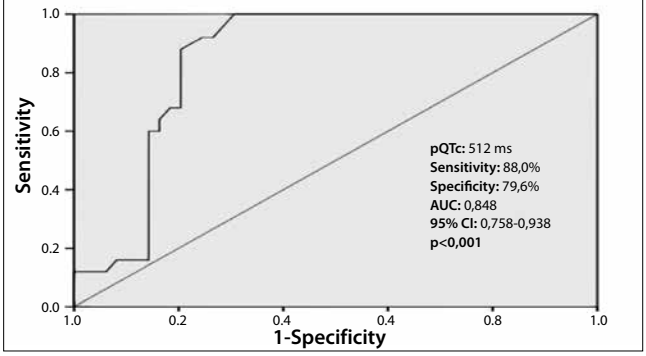
Figure 1. Scatter plot diagram of the relationship between pQTc and LA volume index. LA, left atrial



Bivariate Relationships of pqtc and pqrs Duration

pQTc was associated with LA volume index (r=0.444, p<0.001), LA volume (r=0.350, p=0.002), LA end-diastolic diameter (r=0.373, p=0.001), E-wave deceleration time (r=0.293, p=0.011), septal annular e' velocity (r=0.267, p=0.022), and mitral E/e'ratio (r=0.260, p=0.025) in bivariate analysis. Figure 1 shows a scatter plot diagram of the relationship between pQTc and LA volume index. pQRS duration was not found to be associated with LA volume index (p=0.67), LA volume (p=0.70), LA end-diastolic diameter (p=0.90), E-wave deceleration time (p=0.88), septal annular e'velocity (p=0.30), lateral annular e'velocity (p=0.30), and mitral E/e'ratio (p=0.16).

Figure 2. ROC curve analysis to determine the predictive value of pQTc for increased (>34 mL/m^2) LA volume index. ROC, receiver operating characteristic; LA, left atrial



Tablo 1. Comparison of baseline clinical and laboratory parameters in patients with and without increased (>34 mL/m2) LA volume index

	Normal LA volume index (≤34 mL/m^2)	Increased LA volume index (>34 mL/m^2)	
	n=49	n=25	p
Age (years)	65.9±12.0	62.9±10.8	0.319
Gender (male, %)	31 (63)	14 (56)	0.545
Smoking status (n, %)	20 (41)	7 (28)	0.279
Baseline NYHA (I/II)	12/37	2/22	0.206
Hemoglobin (g/dL)	11.7±1.6	11.1±1.5	0.189
BUN (mg/dl)	45.3±72	43.5±7.6	0.324
Creatinine (mg/dL)	0.94±0.23	0.98±0.28	0.528
LDL cholesterol (mg/dL)	124.3±31.4	127.1±30.0	0.717
HDL cholesterol (mg/dL)	48.8±7.9	48.2±7.6	0.591
Triglycerides (mg/dL)	136.5±31.1	129.5±32.1	0.369
NT-proBNP (pg/mL)	319±84	349±99	0.225
Uric acid (mg/dL)	6.0±1.5	5.9±1.6	0.790

LA: left atrial, NYHA: New York Heart Association, BUN: blood urea nitrogen, LDL: low-density lipoprotein, HDL: high-density lipoprotein, NT-proBNP: N-terminal pro-B-type natriuretic peptide

ROC Curve Analysis to Determine Predictive Value of pqtc for Increased (>34 mL/m^2) LA Volume Index

The cut-off value of pQTc obtained by ROC curve analysis was 512 ms for prediction of increased (>34 mL/m^2) LA volume index (sensitivity: 88.0% and specificity: 79.6%). The area under the curve was 0.848 (p<0.001) (Figure 2).

DISCUSSION

To the best of our knowledge, the present study was the first to reveal a significant association between pQTc interval and LV diastolic functions in patients with preserved LV systolic function and permanent pacemakers. The main findings of the present study were that (1) pQTc>512 ms predicted increased (>34 mL/m^2) LA volume index with 88.0% sensitivity and 79.6% specificity and (2) pQTc was associated with echocardiographic parameters of LV diastolic function such as LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e'velocity, and mitral E/e'ratio in bivariate analysis.

Patients with permanent cardiac pacemakers are rising every day with increased life expectancy. In general practice, among different ventricular pacing sites, RVA pacing is most commonly

Tablo 2. Comparison of the baseline electrocardiographic and echocardiographic features of the study population

	Normal LA volume index (≤34 mL/m^2)	Increased LA volume index (>34 mL/m^2)	
	n=49	n=25	p
Paced QRS width (ms)	164.3±21.1	173.0±19.0	0.092
Paced QTc (ms)	491.4±35.3	536.1±23.3	**<0.001**
LV end-diastolic diameter (mm)	50.1±5.4	51.8±6.8	0.254
LV end-systolic diameter (mm)	34.7±4.4	35.4±4.4	0.511
LVEF (%)	56.9±4.9	55.5±4.5	0.225
LVEDV (mL)	109.0±23.4	108.9±26.3	0.992
LVESV (mL)	46.3±8.8	48.0±11.0	0.467
Peak E-wave velocity (cm/s)	53.5±17.9	48.2±16.3	0.219
Peak A-wave velocity (cm/s)	41.1±11.4	41.8±15.0	0.832
MV E/A ratio	1.31±0.25	1.18±0.33	0.066
Lateral annular e'velocity (cm/s)	11.9±2.0	10.0±2.8	**0.004**
Septal annular e'velocity (cm/s)	9.1±1.4	7.4±2.4	**0.003**
Mitral E/e'ratio	5.1±1.5	6.0±3.0	0.094
MV deceleration time (ms)	183.0±33.6	203.4±39.4	**0.033**
IVRT (ms)	80.0±9.8	74.2±13.6	0.066
LA end-diastolic diameter (mm)	34.7±2.6	39.1±3.1	**<0.001**
LA volume (mL)	44.6±4.8	53.4±7.7	**<0.001**
LA volume index (mL/m^2)	30.8±1.9	35.9±2.0	**<0.001**

LA: left atrial, LV: left ventricular, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVEDV: left ventricular end-diastolic volume, IVRT: isovolumetric relaxation time, MV: mitral valve

used owing to its stability for lead positioning, safety, easy accessibility, and cost-effectiveness (7, 8). However, RVA pacing was shown to be associated with cardiac dysfunction and an increased rate of rehospitalizations in previous studies (9-13). Negative effects of chronic RVA pacing are more significant in certain populations such as patients with a high rate of RVA pacing. Thus, there is a need for parameters to predict possible deterioration in LV systolic and diastolic functions to evaluate the early risks posed to patients who are expected to have high rate of RVA pacing in order to optimize the pacing strategy.

A longer pQRS duration indicates more myocardium tissue to be activated by muscle to muscle conduction before the pacing activation front enters the normal conduction system, whereas a relatively shorter pQRS duration indicates earlier entry of pacing activation front to His-Purkinje system and a more physiological conduction. Previous studies showed that prolonged pQRS duration is associated with LV systolic function (14, 15). In a study conducted by Miyoshi et al. (14), prolonged pQRS duration is found to be associated with impaired LV systolic function in patients with AV block. Pan et al. (15) also demonstrated that pQRS duration is correlated with the structure and systolic function of the left ventricle. However, LV systolic function of most of the patients with preserved EF did not decrease after permanent pacemaker implantation. Nevertheless, HF symptoms can develop in these patients due to diastolic dysfunction, not systolic dysfunction. To our knowledge, there are no studies that investigated the association of pQRS duration with LV diastolic function. In our study, we found pQRS duration to be associated with none of the echocardiographic parameters of LV diastolic function.

There have been many data about the clinical implications of intrinsic QTc interval in the general population and populations such as hypertrophic cardiomyopathy, coronary artery disease, and HF. These studies investigated the association of QTc with the risk of ventricular tachyarrhythmia or sudden cardiac (16-19). In the study by Lee et al. (20), patients with more pQTc prolongation were found to have higher mortality rate than those with less pQTc prolongation. In their study, Cho et al. (21) revealed a significant association between the development of new LV systolic dysfunction and cardiac death and the degree of pQTc interval after permanent cardiac pacemaker implantation in patients with preserved LVEF. In our study, we found pQTc interval to be associated with echocardiographic parameters of LV diastolic function such as LA volume index, LA volume, LA end-diastolic diameter, E-wave deceleration time, septal annular e'velocity, and mitral E/e'ratio.

The present study has some limitations. The sample size is relatively small, and our results need to be confirmed in future large multicenter prospective trials. Owing to the observational nature of our study, we did not make modifications on pacemakers of patients such as AV delay optimization. Therefore, we did not have the chance to evaluate the effects of pacemaker modifications on LV diastolic function. Since our study was not a follow-up study, we could not determine the change of LV systolic and diastolic functions in time and its association with pQTc. We did not use long-term Holter electrocardiogram monitoring to detect atrial arrhythmias; thus, we did not have the chance to detect the association of pQTc with atrial arrhythmias such as atrial fibrillation.

pQTc duration was found to be significantly associated with the echocardiographic parameters of LV diastolic function. We suggest that pQTc be used as a marker to predict the risk of diastolic dysfunction after permanent pacemaker implantation in patients with preserved LVEF. It can also be used to optimize the RV pacing area with intraoperative measurements. Larger and long-term studies are needed to determine the relationship between pQTc and prognostic parameters after permanent pacemaker implantation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Çukuruva University (Decision Date: 2017).

Informed Consent: Informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

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