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Original Article

Assessment of ventricular repolarization inhomogeneity in patients with mitral valve prolapse: value of T wave peak to end interval

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Abstract: Mitral valve prolapse (MVP) has been long known for causing susceptibility for ventricular arrhythmogenesis, and this risk was evaluated by various methods, mostly by using QT interval related measurements on surface electrocardiogram. T wave peak to end (Tp-e) interval is a relatively new marker for ventricular arrhythmogenesis and repolarization heterogeneity. Prolongation of this interval represents a period of potential vulnerability to re-entrant ventricular arrhythmias. However, there is no information available assessing the Tp-e interval and related calculations in patients with MVP. The aim of this study was to assess ventricular repolarization in patients with MVP by using QT, corrected QT (QTc) and Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. Electrocardiogram of consecutive 72 patients, who were followed by outpatient clinic because of mitral valve prolapse, were obtained and scanned. Electrocardiograms of age and sex matched 60 healthy control individuals were also gained for comparison. QT, QTc, Tp-e/QT and Tp-e/QTc were calculated. Baseline characteristics were similar in both groups. QT (405.1±64.3 vs. 362.1±39.1; p<0.001), QTc (457.6±44.4 vs. 428.3±44.7; p<0.001), Tp-e (100.2±22.1 vs. 74.6±10.2; p<0.001) and Tp-e/QT (0.24 vs. 0.20; p<0.001) and Tp-e/QTc (0.21 vs. 0.17; p<0.001) were significantly worse in MVP group. Our study revealed that Tp-e interval and Tp-e/QT ratio were increased in MVP patients. Tp-e interval and Tp-e/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to ventricular arrhythmias in patients with MVP.

Keywords: Prolapse, T wave peak to end, arrhythmogenesis

Introduction

The most frequently diagnosed form of valvular heart disease in community is mitral valve prolapse (MVP) [1]. It is commonly accepted that MVP shows a good prognosis [2] due to low incidence of natural complications. However, there are some serious complications [3] which would affect many individuals because of MVP's high incidence in community [4]. Endocarditis, cerebrovascular events and sudden death due to ventricular arrhythmogenesis are some of those serious complications. Of our concern, ventricular arrhythmias and sudden death are major complications and carry an incidence of 0.5% [3-5]. MVP has been long known for causing susceptibility for ventricular arrhythmogenesis, and this risk was evaluated by various methods, mostly by using surface electrocardiogram [6-9].

T wave peak to end (Tp-e) interval is a relatively new marker for ventricular arrhythmogenesis and repolarization heterogeneity [10-12]. Prolongation of this interval represents a period of potential vulnerability to re-entrant ventricular arrhythmias. Prolonged Tp-e has been associated with increased risk of mortality in the congenital and acquired long QT syndromes [13], hypertrophic cardiomyopathy [14] and also in patients undergoing primary PCI for myocardial infarction [15].

However, there is no information available assessing the Tp-e interval and related calculations in patients with MVP. The aim of this study was to assess ventricular repolarization in patients with MVP by using QT, corrected QT (QTc) and Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

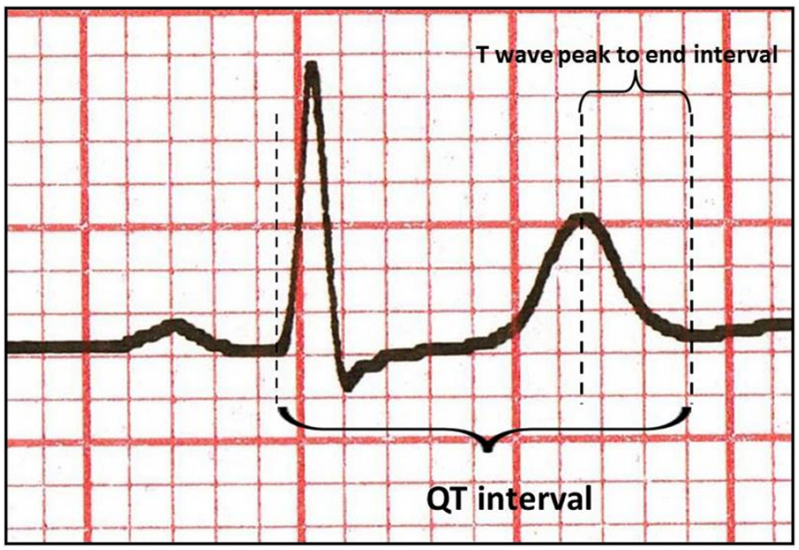

Figure 1. Demonstration of T wave peak to end and QT intervals.

Methods

Study participants

Patient records of Bursa Postdoctorate Training and Research Hospital were retrospectively analyzed. Electrocardiogram of consecutive 72 patients, who were followed by outpatient clinic because of mitral valve prolapse, were obtained and scanned. Electrocardiograms of age and sex matched 60 healthy control individuals were also gained for comparison. Patients with critical coronary stenosis, moderate or severe valve disease, left and/or right heart failure, hypertension, left and/or right ventricle hypertrophy, atrial fibrillation, right or left bundle block or patients who got pacemaker or cardioverter/defibrillator implanted were excluded.

Measurement of Tp-e, QT and QRS intervals from the 12-lead ECG

All ECGs were scanned. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave (**Figure 1**). Measurements of Tp-e interval were performed from precordial leads as it was described [16]. T wave peak to end interval, QT and RR intervals were measured by an engineer with a computer program. By using a ruler, vernier caliper or any other manual measuring tool; getting measurements off from ECG papers could be either inaccurate or slow. Therefore ECG papers were scanned and this made gathering measurements possible in digital environment. These measurements are done by a program which is generated with MATLAB (MathWorks, Natick, Massachusetts, U.S.A.) codes that written by an engineer. These codes are based on image manipulation principles.

Image manipulation method could be divided into three subdivisions: image processing, image analysis and image understanding. Image analysis is the technique that should be used to gather measurement data from ECG. Running the written code imports the image file first and then, by choice, allows user to pick points that need to be picked to get measurements or generates a matrix that consists of a dedicated numeric value of each pixel's color. Creating a matrix gives user the flexibility of using functions which predefined by program. In spite of this, hand picking is easier and has a simple interface especially for beginner level users. Algorithms are developed and used to get excellent measurements in order to tolerate differences: such are tilting during scanning process, different scanning resolutions and using different ECG.

The QT interval was defined as extending from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline. When a U wave interrupted the T wave before returning to baseline, the QT interval was measured to the nadir of the curve between the T and U waves. The QTc interval was calculated using the Bazett formula: QTc (ms) = QT measured/$\sqrt{}$RR (sec).

All measurements (Tp-e and other surface ECG related ones) were mean value of three calculations. All the measurements were double checked by a blinded engineer.

Echocardiography

Mitral valve prolapse was defined as a systolic excursion of any leaflet that exceeded 3 mm from the mitral valve annulus proximally in the

Table 1. Echocardiographic and electrocardiographic parameters between the patient group with the control group

Parameters	Patients (n = 72)	Controls (n = 60)	*P*-value
LVEDD (mm)	46.5±3.3	46.9±3.5	0.538
LVESD (mm)	27.4±6.1	27.8±5.7	0.720
LVEF (%)	62.8±4.0	62.2±4.7	0.405
Mitral valve thickness (mm)	6.1±0.8	1.5±0.6	<0.001
QT (msec)	405.1±64.3	362.1±39.1	<0.001
QTc (msec)	457.6±44.4	428.3±44.7	<0.001
Tp-e (msec)	100.2±22.1	74.6±10.2	<0.001
Tp-e/QT ratio	0.24±0.0	0.20±0.0	<0.001
Tp-e/QTc ratio	0.21±0.0	0.17±0.0	<0.001

LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVEF, left ventricle ejection fraction; Tp-e, T wave peak to end interval; mm, millimeter; msec, millisecond; QTc, corrected QT; Data are presented as means ± SD.

Table 2. The ROC analysis of ECG variables and their area under the curve values, confidence intervals and *p*-values

Variables	Area	*p* value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
QT (msec)	.702	.000	.610	.794
QTc (msec)	.647	.005	.546	.748
Tpe (msec)	.860	.000	.794	.926
Tpe/QT	.810	,000	.731	.889
Tpe/QTc	.853	.000	.784	.922

Tp-e, T wave peak to end interval; msec, millisecond; QTc, corrected QT.

parasternal long axis and apical 4-chamber windows [17]. Each echocardiogram was evaluated by 2 experienced cardiologists. Echocardiograms that were difficult to evaluate due to technical defects, and the cases in which the cardiologists could not agree, were excluded from the study.

Statistical analysis

SPSS 13.0 statistical software was utilized. Independent-samples T test and Pearson's chi-square tests were used for univariate case-control comparisons of continuous and categorical variables for all cases vs. controls, respectively. A *P*-value of <0.05 value was accepted statistically significant for our analyses in our study.

Results

Mean age for patients with MVP was 38.6±12.8 and for control group was 39.4±12.8 (*P* = 0.723). Group MVP included 24 male patients (33.3%) whereas there were 21 male patients (35.0%) in control group (*P* = 0.841). Echocardiographic measurements except mitral valve thickness were similar in both groups. Groups were compared for calculated Tp-e, QT and QTc intervals and Tp-e/QT and Tp-e/QTc ratios. All calculations were significantly higher in MVP group (**Table 1**).

The ROC curve showed significant results about relationship between MVP and QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc (**Table 2**; **Figure 2**). Cut-off values and sensitivity-specificity ratios were as follows for all ECG variables: QT interval cut off: 372.5, sensitivity: 70%, specificity: 59%; QTc interval cut off: 432.8, sensitivity: 72%, specificity: 52%; Tp-e interval cut off: 80.5, sensitivity: 83%, specificity: 77%; Tp-e/QT ratio cut off: 0.21, sensitivity: 88%, specificity: 70%, Tp-e/QTc ratio cut off: 0.18, sensitivity: 80%, specificity: 82%.

Discussion

The present study showed that Tp-e interval and Tp-e/QT ratio were prolonged in patients with MVP when compared to the control group.

MVP is one of the most common valvular heart disorders. Increased ventricular arrhythmias and sudden death have been demonstrated in patients with MVP in previous studies [4, 18]. There are several reports of repolarization abnormalities such as prolongation of the QT interval and QT dispersion in MVP [6-9]. Recently Guven et al. speculated that MVP patients with QT dispersion values greater than 55 ms are more likely to be primary MVP than rheumatic MVP [19].

Myocardial repolarization has been evaluated by various methods including QT dispersion (QTd), corrected QT dispersion (cQTd), and transmural dispersion of repolarization. Recent studies indicated that Tp-e interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), can be used

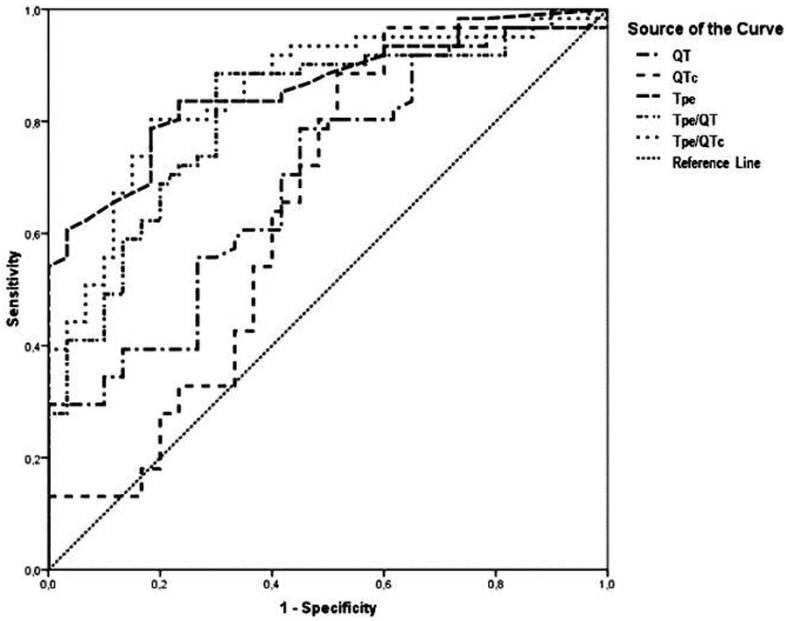

Figure 2. The ROC Curve. Tp-e, T wave peak to end interval; msec, millisecond; QTc, corrected QT.

as an index of total (transmural, apico-basal, and global) dispersion of repolarization [20, 21]. Also, increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality [22]. Recently, a new index, the Tp-e/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to QTd, cQTd, and Tp-e intervals which is independent of alterations in heart rate [23]. Also, these markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death [16, 20]. Previous studies showed that prolongation of Tp-e interval was associated with increased mortality in Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, and in patients who suffered myocardial infarction [16, 24, 25]. The novel repolarization indexes Tp-e interval and Tp-e/QT ratio, is not studied in these patients before.

Several mechanisms have been proposed for the etiopathogenesis of increased QT dispersion, complex ventricular arrhythmias and sudden death in patients with MVP, including papillary muscle traction resulting mitral leaflet displacement and autonomic dysfunction [26-28]. Also recent studies showed high circulating catecholamines, increased responsiveness to catecholamines, abnormal catecholamine regulation and baroreflex modulation, and activation of atrial natriuretic peptide in patients with MVP [29, 30]. Indeed, investigations have shown that enhanced adrenergic activity in MVP patients is associated with repolarization abnormalities and the occurrence of ventricular arrhythmias [6, 30, 31]. Thus, changes in autonomic neural tone may be another reason for the increase of Tp-e interval and Tp-e/QT ratio in patients with MVP.

When 2 groups were compared in our study, QT, QTc, Tp-e interval and Tp-e/QT and Tp-e/cQT ratio of the patients MVP were significantly higher than control groups. Further studies are required to determine the relation between Tp-e interval and Tp-e/QT ratio and ventricular arrhythmia and MVP. We have shown for the first time that patients with MVP have higher Tp-e interval, Tp-e/QT and Tp-e/QTc ratio compared to controls.

In conclusion, the measurement of Tp-e interval and Tp-e/QT ratio may be used to indicate increased risk of MVP-related adverse cardiovascular events. According to current study findings, the risk of development of ventricular arrhythmia might be increased in MVP due to myocardial voltage gradients resulting from heterogeneity of repolarization.

The most important restriction of our study is the limited number of patients. Another limitation we did not assess the association between ventricular arrhythmias with Tp-e interval and Tp-e/QT ratio. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Large-scale prospective studies are needed to determine the predictive value of prolonged Tp-e interval and increased Tp-e/QT ratio in this population.

Our results may contribute to pathophysiological mechanisms of increased prevalence of

ventricular arrhythmias and cardiovascular mortality risk by indicating increased ventricular repolarization heterogeneity in these patients. Increased the frequency of ventricular arrhythmia and sudden cardiac death might be explained with prolonged transmural dispersion in MVP patients.

Our study revealed that Tp-e interval, Tp-e/QTc and Tp-e/QT ratio were increased in MVP patients. Tp-e interval and Tp-e/QTc and Tp-e/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to ventricular arrhythmias in patients with MVP.

Disclosure of conflict of interest

None.

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