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ORIGINAL ARTICLE

Prolonged Tp–e Interval and Tp–e/QT Ratio in Children with Mitral Valve Prolapse

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Abstract Although it is considered to be a benign condition, previous studies have shown that a subset of patients with mitral valve prolapse (MVP) may be at risk of ventricular arrhythmia and sudden cardiac death (SCD). Previous studies have suggested that the interval between the peak and the end of the T wave (Tp–e) can be used as a marker for the transmural dispersion of repolarization. Increased Tp–e interval and Tp–e/QT ratio are associated with ventricular arrhythmias and SCD. The aim of this study was to assess alterations in ventricular repolarization by using the Tp–e interval and Tp–e/QT ratio in children with MVP and to investigate their relationships with the degree of valvular regurgitation. This study prospectively investigated 110 children with MVP and 107 age- and sex-matched healthy control subjects. Tp–e interval, Tp–e/QT ratio, and QT and QTc dispersions were measured from a 12-lead electrocardiogram and compared between groups. QT and QTc dispersions, Tp–e interval, and Tp–e/QTc ratio were found to be significantly higher in patients with MVP. A positive correlation was found between Tp–e/QTc ratio and increase in the degree of mitral regurgitation (MR) ($p < 0.05$; $r = 0.2$). However, the degree of MR was not associated with QT, QTc, or Tp–e intervals; QT, QTc, or Tp–e dispersions; or Tp–e/QT ratio (all p values >0.05). Individuals with MVP may be more prone to ventricular arrhythmias due to prolonged QTd, QTcd, and Tp–e interval and increased Tp–e/QT and Tp–e/QTc ratios. Therefore, due to their longer life expectancy, children with MVP should be followed up on regarding life-threatening arrhythmias.

Keywords Tp–e interval · Tp–e/QT ratio · Tp–e/QTc ratio · Mitral valve prolapse

Introduction

Mitral valve prolapse (MVP) has been reported to be the most common valvular heart disease, with the prevalence of 2–3 % among the general population [1]. It is characterized by the superior displacement of the mitral valve leaflets more than 2 mm into the left atrium during systole [2, 3]. Although it is considered to be a benign condition, previous studies have showed that a subset of patients with MVP may be at risk of ventricular arrhythmia and sudden cardiac death (SCD) [4–6]. The exact mechanisms causing ventricular arrhythmias remain elusive. Structural abnormalities of the mitral valve leading to mechanical triggering and abnormalities of the autonomic nervous system are considered to be the underlying conditions of ventricular arrhythmias [7–10].

An increased SCD incidence rate of about 0.2–0.4 % per year has been reported in cases of MVP, approximately twice that of the general population [2, 11]. Although some previous studies demonstrate an association between life-threatening ventricular arrhythmias and moderate to severe mitral regurgitation, life-threatening ventricular arrhythmias also occur in patients with MVP in the absence of mitral regurgitation (MR) [11–14]. By using a 12-lead surface electrocardiogram (ECG), researchers have demonstrated susceptibility to ventricular arrhythmogenesis in patients with MVP [15, 16]. T wave peak-to-end

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(Tp–e) interval, which refers to the interval between the peak and the end of the T wave on electrocardiogram (ECG), can be used as a marker of the transmural dispersion of repolarization (TDR). Also, the Tp–e/QT and Tp–e/QTc ratios are used as an index of arrhythmogenesis [17, 18]. The prolongation of the Tp–e interval and increased Tp–e/QT ratio were found to be associated with SCD in various clinical conditions [19, 20].

Alterations of ventricular repolarization have been demonstrated in adult patients with MVP due to increased QT, Tp–e interval, QT dispersion, and Tp–e/QT ratio [16]. However, to the best of our knowledge, Tp–e interval and Tp–e/QT ratio have not been evaluated in children with MVP. The aim of this study is to assess alterations in ventricular repolarization by using Tp–e interval and Tp–e/QT ratio in children with MVP and to investigate their relationships with the degree of valvular regurgitation.

Methods

Study Population

A total of 110 consecutive patients who were followed up or newly diagnosed with MVP in our pediatric cardiology outpatient clinic between January 2015 and November 2015 were prospectively reviewed. One hundred and seven age- and sex-matched children diagnosed with innocent murmur without any structural heart disease were also enrolled as a control group. All of the participants underwent electrocardiographic and echocardiographic examinations. Personal data and medical histories were recorded. Patients with additional congenital heart disease, history, or echocardiographic evidence of rheumatic heart disease, Marfan's syndrome, ventricular dysfunction, arrhythmia, or any medication that could affect ECG parameters were excluded. The study was approved by the ethics committee of Behcet Uz Children's Hospital.

Electrocardiography

Standard 12-lead ECG recordings with a sweeping rate of 25 mm/s and an amplitude of 1 mV/cm while in the supine position were made. ECG recordings were scanned and transferred to a personal computer. After 400× zooming in Adobe Photoshop software, measurements were performed directly from these ECG tracings by a pediatric cardiologist who was blinded to the patients' data. The QT interval was defined as the time between the beginning of the QRS complex and the end of the T wave. In the presence of the U wave, the nadir point between the T and U waves was measured. The QT interval was not measured if the T wave was absent. The QTc interval was calculated by using Bazzett's formula [21]. An ECG recording was considered to be analyzable when the QT interval could be measured in more than eight leads. The QT dispersion was calculated in at least eight available leads. These leads usually included leads I, II, and V5. QT and QTc dispersions were calculated as the difference between the maximum and minimum QT intervals. At least three separate measurements of the QT and QTc intervals were used to calculate the QT and QTc dispersions [22].

The Tp–e interval was defined as the distance from the T peak (the highest point of the T wave) to the T end. We defined Te as the intersection point of the tangent to the downward slope of the T wave and the isoelectric line. All Tp–e measurements were taken using precordial leads. The U wave was not taken into consideration. The Tp–e/QT ratio was calculated using these measurements [16]. The mean value of three calculations was used for the Tp–e interval as well.

Echocardiography

A Vivid 3 Pro Ultrasound System (GE Medical Systems, NE) with 3- and 5-MHz transducers was used for the echocardiographic examinations. Mitral valve prolapse was defined as the superior displacement of the anterior and posterior mitral leaflets over 2 mm from the mitral annulus into the left atrium in the parasternal long-axis and apical four-chamber views [2, 3]. The degree of mitral regurgitation was assessed via the current guidelines recommendations, and the degree of valvular regurgitation was recorded [23].

Statistical Analysis

SPSS 18.0 was used (SPSS Inc., Chicago, IL, USA) for statistical analysis. The distribution pattern of the data was evaluated via the Kolmogorov–Smirnov test. Values are expressed as mean ± SD or median (interquartile range) where appropriate. A Student's *t* test was used for normally distributed data, and the Mann–Whitney *U* test was used for abnormally distributed data. Chi-square analysis was used for the comparison of categorical variables. The associations between parameters were assessed using Spearman's correlation test for normally distributed data and Pearson's test for abnormally distributed data. A p value <0.05 was considered statistically significant.

Results

The demographic characteristics of the patients and healthy controls are given in Table 1. The mean age and heart rates of the patients with MVP were 12 ± 3.5 years and

Table 1 Demographic characteristics of both groups and degree of mitral regurgitation of the patients

	Patients with MVP ($n = 110$)	Controls ($n = 107$)	p value
Age (years)[a]	12 ± 3.5	10.2 ± 3.3	0.7
Gender (M/F)	34/73	47/63	0.3
Mean heart rate (bpm)	80.7 ± 12.5	82.0 ± 12.2	0.4
Mitral regurgitation (n, %)			
Mild	44 (41.1)	–	
Moderate	7 (6.5)	–	
Moderate to severe	5 (4.6)	–	

bpm beat per minute, *n* number of the subjects

[a] Data are expressed as mean ± SD

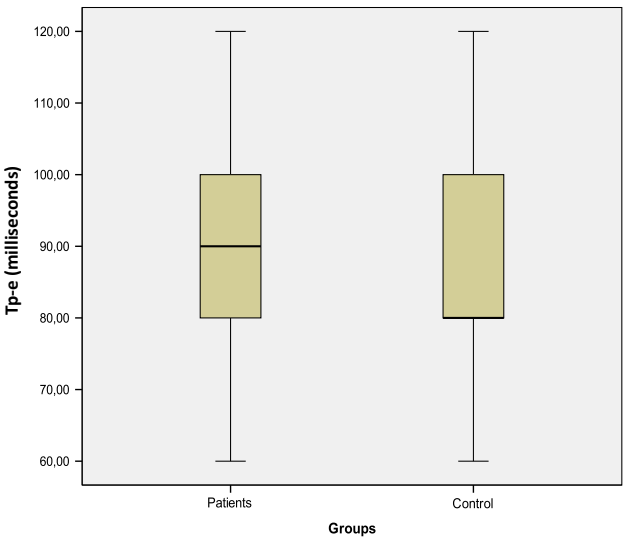

Fig. 1 Tp–e interval in patients with MVP and control groups

80.7 ± 12.5 beat/min, respectively. Both groups were similar in terms of age, gender, and mean resting heart rate ($p > 0.05$). Fifty-six of the patients with MVP (52.3 %) had mitral regurgitation on color Doppler echocardiography. The mitral regurgitation was mild in 44 (41.1 %), moderate in 7 (6.5 %), and moderate to severe in 5 (4.6 %) cases. The comparison of the electrocardiographic features of the patients and controls is given in Table 2. QT, QTc, and Tp–e dispersions were found to be significantly higher in the MVP group ($p < 0.001$). The patients had greater Tp–e intervals, Tp–e/QT ratios, and Tp–e/QTc ratios than the healthy controls (p values of 0.02, 0.001, and <0.001, respectively). There were no differences in QT and QTc intervals between the two groups ($p > 0.05$). The differences in Tp–e interval and Tp–e/QTc ratio between the groups are shown in Figs. 1 and 2, respectively.

A positive correlation was found between Tp–e/QTc ratio and increase in the degree of MR ($p < 0.05$; $r = 0.2$). However, the degree of MR was not associated with QT, QTc, or Tp–e intervals; QT, QTc, or Tp–e dispersions; or Tp–e/QT ratio (all p values >0.05).

Discussion

This prospective study demonstrated that QT and QTc dispersions; Tp–e interval; and Tp–e/QT and Tp–e/QTc ratios are increased in children with MVP. It also demonstrated that these parameters are positively correlated with an increase in the degree of regurgitation. Although Tp–e interval and Tp–e/QT ratio have been studied in adult patients [16], and QT and QTc dispersions have been studied in children with MVP previously [24], Tp–e interval and Tp–e/QT and Tp–e/QTc ratios have not been evaluated before, and this study is the first concerning the pediatric age group to assess the parameters of transmural dispersion of repolarization, Tp–e interval, and Tp–e/QT and Tp–e/QTc ratios with a large number of patients with MVP.

Increased atrial and ventricular arrhythmias have been reported in patients with MVP as compared to the normal

Table 2 Electrocardiographic parameters of patients and controls

Parameters	Patient group ($n = 110$)	Control group ($n = 107$)	p value
QT (ms)[a]	340 (40)	320 (40)	0.46
QTc (ms) (mean ± SD)	388 ± 25.8	390 ± 25.1	0.85
QT dispersion (ms)[a]	40 (20)	20 (20)	<0.001
QTc dispersion (ms)[a]	20 (30)	10 (10)	<0.001
Tp–e interval (ms)[a]	90 (20)	80 (20)	0.02
Tp–e interval dispersion (ms)[a]	40 (20)	40 (10)	<0.001
Tp–e/QT[a]	0.26 (0.04)	0.25 (0.05)	0.001
Tp–e/QTc (mean ± SD)	0.23 ± 0.03	0.21 ± 0.03	<0.001

ms milliseconds, *n* number of the subjects

[a] Data are expressed as median with interquartile range in parentheses

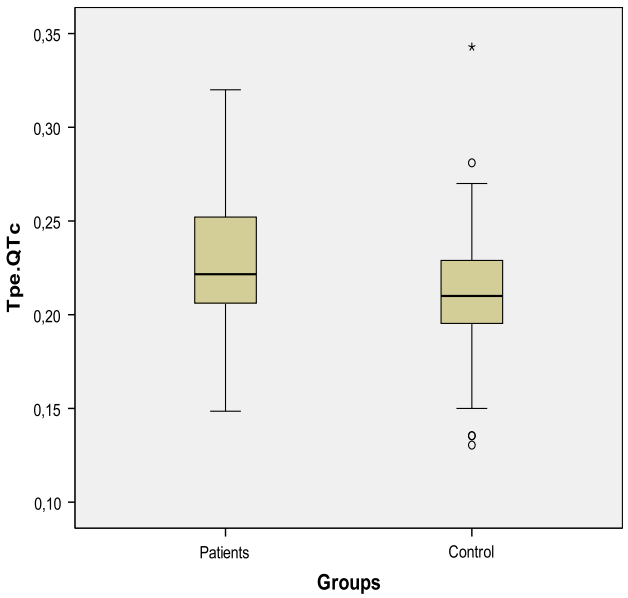

Fig. 2 Tp–e/QTc ratio in MVP patients and control groups

population [25]. In a community-based study, Narayanan et al. [10] evaluated 729 cases of sudden cardiac arrest (SCA) and reported that MVP was observed in 2.3 % of these cases. Similar to this study, the prevalence of MVP in the SCA population was found to be 2.4 % [26]. In another study, Basso et al. [27] reported that MVP was observed in 10 % of the SCA population. The underlying mechanisms of ventricular arrhythmias and SCD in MVP patients have not been fully understood. Various potential mechanisms have been put forward. Thickened and prolapsed leaflets, traction of the papillary muscles, and endocardial lesions in the inferobasal LV wall may play a role in ventricular arrhythmias [8, 27]. Increased autonomic tone is another proposed mechanism of ventricular arrhythmias, as are abnormal catecholamine regulation, increased catecholaminergic state, and baroreflex modulation in patients with MVP [27, 28]. Previous studies have shown increased catecholaminergic activity to be associated with repolarization abnormalities and ventricular arrhythmias [9].

Several reports showed alterations in ventricular repolarization, such as increased QT and QTc dispersions, in MVP patients [29, 30]. In addition, the prolongation of QT dispersion was found to be associated with the degree of prolapse and thickness of the leaflets [31]. In a study of pediatric patients, QT dispersion values >55 ms were found to be more likely in cases of primary MVP than in cases of rheumatic MVP [24]. Some previously reported studies showed that patients with MVP have prolonged QT interval durations [16]. In contrast to this study, Turker et al. did not find any difference in QT and QTc intervals in MVP patients with ventricular arrhythmias as compared to those without ventricular arrhythmias.

In addition to QT and QTc dispersions, Tp–e interval, which is the interval between the peak and the end of the T wave on ECG, and Tp–e/QT ratio have emerged as novel noninvasive electrocardiographic markers of dispersion of ventricular repolarization [17–19]. Previous studies have suggested that the Tp–e interval and Tp–e/QT ratio are increased in hypertrophic cardiomyopathy with long QT and Brugada syndrome [20, 32, 33]. Increased Tp–e interval and Tp–e/QT ratio are found to be associated with ventricular arrhythmias and SCD [19]. Unlike Tp–e interval, Tp–e/QT ratio is not influenced by the heart and has been found to be an accurate marker in predicting ventricular arrhythmogenesis and SCD [18]. Recently, Yontar et al. [16] evaluated adult patients with MVP, and they found that Tp–e interval and Tp–e/QT and Tp–e/QTc ratios were significantly higher in MVP patients as compared to controls. Similar to these findings, in the current study, we found significantly higher QT and QTc dispersions; Tp–e interval; and Tp–e/QT and Tp–e/QTc ratios in children with MVP as compared to controls. Our results showed that the indices of total dispersion of repolarization were increased in children with MVP as compared to healthy controls. Some studies suggested that MVP patients with MR are more prone to ventricular arrhythmias than those without MR. In a study that evaluated the predictors of ventricular arrhythmias in patients with MVP, the authors speculated that the only independent predictor of ventricular arrhythmia was the occurrence of moderate to severe MR [12]. In another study, patients with complex ventricular arrhythmias frequently had MR [34]. However, some studies had contradictory results. They did not find any correlation between the degree of regurgitation and the occurrence of arrhythmia [14]. In our study, a positive correlation was found only between Tp–e/QTc ratio and increase in the degree of MR. Structural changes in the mitral valve, papillary muscle, and ventricular myocardium, together with increased autonomic tone, may lead to increased ventricular repolarization parameters. Also, the degree of regurgitation may have an additional role in the alteration of ventricular repolarization. The results of the current study may contribute to understanding of the potential link between MVP and a predisposition toward ventricular arrhythmogenesis/SCD. The tendency toward ventricular arrhythmias and SCD in patients with MVP may resulted from the prolonged transmural dispersion of ventricular repolarization.

Due to the increased risk of adverse outcomes, such as arrhythmias and SCD, follow-up of children with MVP is important. We suppose that the frequency of clinical follow-up should be based on symptoms, arrhythmias, and the degree of MR. Asymptomatic patients without any evidence of arrhythmias generally have good prognoses. We suggest yearly echocardiographic examination to check for

the progression of the disease, and we also suggest initial 24-h Holter monitoring for any atrial and ventricular arrhythmias, as well as repeat monitoring if any symptoms develop in the follow-up period. However, we suggest close follow-ups for symptomatic patients who have palpitations, tachycardia, syncope, chest pain, or moderate to severe MR to prevent ventricular arrhythmias and SCD. If patients have sustained ventricular arrhythmias and moderate to severe MR, we recommend an echocardiographic examination and 24-h Holter monitoring every 6 months.

The present study has some limitations that must be considered. We did not evaluate the correlations between prolonged Tp–e interval, Tp–e/QT and Tp–e/QTc ratios, and PVCs. Also, we could not follow up the study population prospectively for ventricular arrhythmias; thus, we could not evaluate these parameters in terms of future arrhythmic events. Large prospective studies are needed to demonstrate correlations between these parameters and arrhythmic events in this population.

In conclusion, our results show that QT and QTc dispersions, Tp–e interval, Tp–e/QT and Tp–e/QTc ratios are increased in children with MVP and that Tp–e/QTc ratio is correlated with increase in the degree of MR. Individuals with MVP may be more prone to ventricular arrhythmias due to prolonged QTd, QTcd, and Tp–e intervals and increased Tp–e/QT and Tp–e/QTc ratios. Therefore, due to their longer life expectancy, children with MVP should be followed up in terms of life-threatening arrhythmias. Furthermore, prospective studies with 24-h ECG monitoring are needed to demonstrate the clinical usefulness of these parameters in children with MVP.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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