



# Assessment of Transmural Dispersion of Repolarization in Children with Mitral Valve Prolapse

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## Abstract

**Background:** Children with mitral valve prolapse (MVP) may be prone to ventricular arrhythmias due to transmural dispersion of repolarization (TDR). This study aimed to assess alterations in ventricular repolarization in children with MVP and to investigate their relationships with the degree of mitral regurgitation.

**Methods:** Fifty children with MVP and 50 age- and sex-matched healthy children as controls were studied. Twelve-lead electrocardiography and echocardiography were performed in all the subjects. TDR parameters were QT and QTc intervals, QTc dispersion, Tp-e interval, Tp-e interval dispersion, Tp-e/QT, Tp-e/QTc, JTc, JTc dispersion, Tp-e/JT, and Tp-e/JTc.

**Results:** The mean age of the 50 patients with MVP was  $12.45 \pm 2.50$  years (F/M: 15/35). There were no significant differences in QT and QTc intervals between the 2 groups. QTc dispersion ( $P=0.001$ ), Tp-e dispersion interval ( $P=0.002$ ), Tp-e/QTc ( $P=0.001$ ), JTc dispersion ( $P=0.023$ ), Tp-e/JT ( $P=0.004$ ), and Tp-e/JTc ( $P=0.002$ ) were significantly higher in the patients with MVP than in the healthy controls. Positive correlations were found between Tp-e dispersion interval and Tp-e/QTc and an increase in the degree of mitral regurgitation ( $P=0.012$ ,  $r=0.42$  and  $P=0.004$ ,  $r=0.31$ , respectively). Additionally, positive correlations were detected between JTc dispersion and Tp-e/JTc and an increase in the degree of mitral regurgitation ( $P=0.032$ ,  $r=0.20$  and  $P=0.024$ ,  $r=0.42$ , correspondingly).

**Conclusion:** In this study, TDR was damaged in children with MVP and was positively correlated with an increase in the degree of mitral regurgitation. It appears that children with MVP are prone to life-threatening ventricular arrhythmias.

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**Keywords:** Arrhythmias, cardiac; Child; Mitral valve prolapse

## Introduction

Mitral valve prolapse (MVP) is not an unusual valvular heart disease during childhood. The prevalence of MVP is 2% to 3% among the general population.<sup>1</sup> MVP is defined as the superior displacement of at least 2 mm of 1 or both mitral

leaflets from the mitral annulus into the left atrium during the end-systolic phase with or without mitral leaflet thickening. MVP is divided into 2 types: classic and non-classic. The classic type is defined as a prolapse with the thickening of the leaflets greater than 5 mm, whereas the non-classic type is a prolapse with less than 5 mm of leaflet thickening.<sup>2</sup>

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The prognosis of MVP varies in previous studies. MVP usually has a good and benign prognosis. Nonetheless, it has been shown that MVP may increase the risk of sudden cardiac death due to ventricular arrhythmias.<sup>3, 4</sup> Indeed, in patients with MVP, the incidence of sudden cardiac death is approximately twice that of the general population.<sup>2, 5</sup> Structural changes in the papillary muscles, the MV, and the ventricular myocardium, in addition to an increase in autonomic tone, may be the cause of increased ventricular repolarization parameters. Moreover, the degree of regurgitation may influence the alterations of ventricular repolarization.

Life-threatening ventricular arrhythmias happen in patients with or without moderate-to-severe mitral regurgitation.<sup>5</sup> In patients with MVP, susceptibility to ventricular arrhythmias can be evaluated with 12-lead electrocardiography (ECG).<sup>6, 7</sup>

Transmural dispersion of repolarization (TDR) is one of the relatively new markers for the prediction of life-threatening ventricular arrhythmias. T-wave peak-to-end (Tp-e) interval, corrected QT (QTc), Tp-e/QT, Tp-e/QTc, and QTc dispersion can be used as the markers of TDR.<sup>8</sup>

In adult patients with MVP, increased Tp-e/QT and prolonged Tp-e interval are associated with an increased incidence rate of sudden cardiac death due to re-entrant ventricular arrhythmias.<sup>5-8</sup>

In this study, we sought to investigate alterations in TDR in children with MVP and to assess the relationships between TDR parameters and the degree of valvular regurgitation.

## Methods

The current cross-sectional study was conducted on children with MVP from April 2017 to April 2018. The study protocol was approved by the Research Ethics Committee of Arak University of Medical Sciences. Prior to study commencement, written informed consent was obtained from the parents of the children.

The total sample size was estimated at 100 through  $\alpha$  and  $\beta$  error of 0.05 and 0.2, respectively.<sup>9</sup> The intervention group was comprised of 50 children with MVP aged between 5 and 15 years and the control group consisted of 50 age- and sex-matched children with no structural heart disease. The patients of the MVP group were selected from children at our pediatric cardiac clinic, and the subjects of the control group were selected from the non-MVP children of the patients' families.

Physical examinations, ECG, and echocardiography were performed in all the subjects.

The exclusion criteria were hypertension, congenital heart disease, rheumatic heart disease, Marfan syndrome, ventricular dysfunction, arrhythmias with left and/or right heart failure, left and/or right ventricular hypertrophy, atrial fibrillation, and right or left bundle block.

Standard 12-lead ECG was performed using a recorder set at a paper speed of 25 mm/s and 1 mV/cm (CardiMax FX-7202). TDR parameters were measured. All the measurements (Tp-e and other surface ECG-related ones) were the mean values of 5 calculations. All TDR parameters were measured by using a ruler, a Vernier caliper, and a lens.

QT interval was defined as the time between the beginning of QRS complex to the end of T wave. QT interval was not measured when T wave was absent. QTc interval was calculated via the Bazett formula (QTc [ms]=QT measured/ $\sqrt{RR[s]}$ ). QT and QTc dispersions were calculated as the difference between maximum and minimum QT intervals. Five separate measurements of QT and QTc intervals were used to calculate QT and QTc dispersions.

JTc was defined as the interval between J (junction) points to the end of T wave, corrected by heart rate. JTc dispersion was defined as the difference between maximum and minimum JTc intervals.

Tp-e interval was defined as the interval between the peak (the highest point of T wave) and the end of T wave. Tp-e was defined as the line downward slope of T wave that disrupts the isoelectric line. All Tp-e measurements were taken using precordial leads. Tp-e/QT was calculated by using these measurements. The mean value of 5 calculations was used for Tp-e interval as well. Standard echocardiography was performed in all the subjects. Data were gathered via echocardiography as the average measurement of 3 to 5 consecutive beats. All the echocardiographic examinations were performed with a 3-7 MHz transducer (GE Vivid S6, Vingmed Ultrasound, USA).

Each echocardiogram was evaluated by a single pediatric cardiologist. Echocardiograms that were difficult to evaluate due to technical defects and the cases on which there was no consensus among the cardiologists were excluded from the study.

Left ventricular ejection fraction was determined by using M-mode echocardiography in the parasternal long-axis view. The measurements of left ventricular end-diastolic diameter, interventricular septum thickness, left ventricular posterior wall thickness at the end of diastole, and ejection fraction were obtained from M-mode echocardiographic tracings with 2D imaging. Measurements were determined via standard techniques in accordance with the recommendations of the American Society of Echocardiography.

MVP 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 view.

The mean $\pm$ standard deviation was calculated for all the data. The data were analyzed using SPSS software, version 23, (Armonk, NY: IBM Corp.). The quantitative variables were compared using the independent Student *t*-test. The Pearson correlation test was also applied to assess the correlation between the quantitative data. A P value of less

than 0.05 was considered statistically significant.

## Results

The demographic characteristics of the patients and the healthy controls are presented in Table 1. The mean age of

the patients with MVP was  $12.45 \pm 2.50$  years. Both groups were similar in terms of age, sex, height, weight, body mass index, systolic and diastolic blood pressures, and heart rate.

The M-mode echocardiographic parameters of the patients and their control subjects are depicted in Table 2. All the 50 patients with MVP had mitral regurgitation on color Doppler echocardiography.

Table 1. Demographic characteristics of the participants\*

|                          | Patients (n=50) | Controls (n=50) | P     |
|--------------------------|-----------------|-----------------|-------|
| Age (y)                  | 12.45±2.50      | 12.20±3.32      | 0.672 |
| Gender (M/F)             | 15/35           | 14/36           | 0.826 |
| Heart rate (bpm)         | 82.70±12.70     | 80.00±11.10     | 0.260 |
| BMI (kg/m <sup>2</sup> ) | 19.13±9.30      | 19.45±8.51      | 0.858 |
| SBP (mmHg)               | 108.11±10.64    | 107.13±10.14    | 0.638 |
| DBP (mmHg)               | 64.12± 8.65     | 64.43±7.98      | 0.853 |
| Mitral regurgitation     |                 |                 |       |
| Mild                     | 25 (0.5)        | -               | -     |
| Moderate                 | 15 (0.3)        | -               | -     |
| Moderate to severe       | 10 (0.2)        | -               | -     |

\*Data are presented as mean±SD or n(%)

MVP, Mitral valve prolapse; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

Table 2. Echocardiographic findings in the patients with MVP and the control subjects

|                              | Patients (n=50) | Controls (n=50) | P     |
|------------------------------|-----------------|-----------------|-------|
| IVSDd (mm)                   | 69.35±2.13      | 70.11±1.97      | 0.068 |
| LVDd (mm)                    | 40.15±6.17      | 40.23±5.93      | 0.947 |
| LVDs (mm)                    | 25.32±10.55     | 24.88±8.44      | 0.818 |
| LVPWDd (mm)                  | 73.82± 2.90     | 72.49±2.89      | 0.570 |
| EF (%)                       | 67.62±7.22      | 68.80±8.12      | 0.444 |
| Degree of MVP (mm)           | 5.20±2.10       | -               | -     |
| Thickness of MV leaflet (mm) | 4.90± 2.50      | -               | -     |

MVP, Mitral valve prolapse; IVSDd, Interventricular septum diastolic diameter; LVDd, Left ventricular end-diastolic diameter; LVDs, Left ventricular end-systolic diameter; LVPWDd, Left ventricular posterior wall diastolic diameter; EF, Ejection fraction

Table 3. Electrocardiographic parameters of the patients and controls

| Parameter                     | Patients (N=50) | Controls (N=50) | P     |
|-------------------------------|-----------------|-----------------|-------|
| QT (ms)                       | 395.01±42.43    | 390.12±33.18    | 0.522 |
| QTc (ms)                      | 370.61±38.53    | 368.75±21.09    | 0.765 |
| QT dispersion (ms)            | 40.69±17.10     | 38.55±12.38     | 0.475 |
| QTc dispersion (ms)           | 45.14±13.28     | 35.19±10.15     | 0.001 |
| Tp-e interval (ms)            | 80.83±13.17     | 79.74± 16.11    | 0.712 |
| Tp-e interval dispersion (ms) | 18.96±5.11      | 16.21±3.09      | 0.002 |
| Tp-e/QT                       | 0.39±0.13       | 0.38±0.08       | 0.644 |
| Tp-e/QTc                      | 0.27±0.05       | 0.20±0.02       | 0.001 |
| JTc (ms)                      | 370.85± 29.13   | 359.93±18.07    | 0.027 |
| JTc dispersion (ms)           | 32.15±10.85     | 27.02±11.42     | 0.023 |
| Tp-e/JT                       | 0.25±0.11       | 0.19±0.09       | 0.004 |
| Tp-e/JTc                      | 0.22±0.02       | 0.20±0.03       | 0.002 |

Tp-e, T-wave peak-to-end interval; QTc, Corrected QT; JTc, Corrected JT



The comparisons of the ECG features between the patients and the controls are given in Table 3. QTc dispersion was found to be significantly higher in the MVP group. Tp-e interval dispersion and Tp-e/QTc were higher in the MVP group than in the control group.

In the MVP group, positive correlations were found between Tp-e interval dispersion and Tp-e/QTc and an increase in the degree of mitral regurgitation ( $P=0.012$ ,  $r=0.42$  and  $P=0.004$ ,  $r=0.31$ , correspondingly). However, the degree of mitral regurgitation was not associated with the other parameters. Positive correlations were also detected between JTc dispersion and Tp-e/JTc and an increase in the degree of mitral regurgitation ( $P=0.032$ ,  $r=0.20$  and  $P=0.024$ ,  $r=0.42$ , respectively). Nevertheless, the degree of mitral regurgitation was not associated with the other parameters.

## Discussion

Increased atrial and ventricular arrhythmias have been reported in patients with MVP in comparison with the normal population. Prolonged transmural dispersion of ventricular repolarization may be the cause of ventricular arrhythmias and sudden cardiac death in patients with MVP.<sup>5</sup>

Patients with MVP may be more susceptible to ventricular arrhythmias and sudden cardiac death due to prolonged transmural dispersions of ventricular repolarization, including prolonged QTc dispersion and Tp-e interval, as well as increased Tp-e/QT and Tp-e/QTc.<sup>5, 7, 8</sup> Therefore, children with MVP, because of their longer life span, should be carefully examined for predisposing life-threatening arrhythmias.

In the present study, QT interval, QTc interval, and QT dispersion were similar in the 2 groups, but QTc dispersion was significantly different. Whereas QTc evaluates depolarization and repolarization times, JT and JTc assess only the repolarization time. We found that our 2 study groups were different in terms of JTc dispersion but not JTc. Our investigation also revealed similar findings concerning QTc dispersion and QTc, respectively. Also different between the MVP and control groups were QTC and JTc dispersion. Therefore, it appears that depolarization and repolarization times are inhomogeneous in patients with MVP.

Moreover, we found a positive correlation between JTc dispersion and an increase in the degree of mitral regurgitation, although the degree of regurgitation was not associated with the other parameters such as QT interval, QTc interval, QT dispersion, JTc, and JT interval.

Digeos-Hasnier et al.<sup>10</sup> reported an increase in QT and QTc dispersions among their patients with MVP. Yontar et al.<sup>7</sup> demonstrated prolonged QT interval durations among their adult patients with MVP, which is consistent with our findings.

In addition to QT and QTc dispersions, Tp-e interval and

Tp-e/QT have emerged as novel noninvasive ECG markers of the dispersion of ventricular repolarization.<sup>8, 10-12</sup>

In our study, we evaluated TDR parameters such as Tp-e interval, Tp-e/QT, and Tp-e/QTc among patients with MVP. Tp-e interval and Tp-e/QT were similar between our 2 study groups, while Tp-e interval dispersion and Tp-e/QTc were significantly different between the MVP group and the healthy children.

Yontar et al.<sup>7</sup> assessed Tp-e interval and Tp-e/QT in 2 groups of adult patients with and without MVP and found significantly higher Tp-e interval, Tp-e/QT, and Tp-e/QTc in the former group. Panikkath et al.<sup>12</sup> showed an association between the prolongation of Tp-e interval and Tp-e/QT and increased risk of ventricular arrhythmias and sudden cardiac death. In contrast to these results, we found that Tp-e interval and Tp-e/QT were not significantly higher in children with MVP than in controls. Still, our findings as regards Tp-e/QTc were different.

The results of the current study showed that the dispersions of the repolarization time, including JTc dispersion, Tp-e/JT, and Tp-e/JTc, were increased in children with MVP by comparison with healthy controls.

Several investigations have suggested that MVP patients with mitral regurgitation as compared with patients without it are more prone to ventricular arrhythmias.

Our study demonstrated that QTc dispersion, Tp-e interval, Tp-e/QTc, JTc dispersion, Tp-e/JT, and Tp-e/JTc were increased in children with MVP. We also found that Tp-e interval dispersion, Tp-e/QTc, JTc dispersion, and Tp-e/JTc were positively correlated with an increase in the degree of mitral regurgitation. Demiroglu et al.<sup>9</sup> observed a positive correlation between Tp-e/QTc and a rise in the degree of mitral regurgitation.

A notable limitation in the present study is that we could not perform a long-term follow-up of our patients with a view to not only detecting ventricular arrhythmias but also assessing the relationship between the mentioned parameters and future arrhythmic events. Accordingly, large prospective studies are needed to determine the correlations between these parameters and arrhythmic events in this group of patients. There is also a need for prospective studies with 24-hour ECG monitoring to evaluate the clinical efficiency of these parameters in children with MVP.

## Conclusion

The results of the present study, conducted on children with MVP, showed an increase in QTc dispersion, Tp-e interval dispersion, Tp-e/QTc, JTc dispersion, Tp-e/JT, and Tp-e/JTc. There were also positive correlations between Tp-e interval dispersion, Tp-e/QTc, JTc dispersion, and Tp-e/JTc and an increase in the degree of mitral regurgitation. Further, TDR was damaged in the children with MVP, which was positively



correlated with an increase in the degree of regurgitation. It appears that children with MVP are prone to life-threatening ventricular arrhythmias.

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