QT dispersion and ventricular arrhythmias in children with primary mitral valve prolapse

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Abstract

Aim: To investigate ventricular arrhythmias in children with primary mitral valve prolapse and to evaluate its relation with QT length, QT dispersion, autonomic function tests and heart rate variability measurements.

Material and Methods: Forty two children with mitral valve prolapse and 32 healthy children were enrolled into the study. Twelve-lead electrocardiograms, autonomic function tests, echocardiography and 24-hour rhythm Holter tests were performed. Electrocardiograms were magnified digitally. The QT length was corrected according to heart rate. The patients were grouped according to the number of premature ventricular contractions and presence of complex ventricular arrhythmia in the 24-hour rhythm Holter monitor test. Heart rate variability measurements were calculated automatically from the 24-hour rhythm Holter monitor test. Orthostatic hypotension and resting heart rate were used as autonomic function tests.

Results: The mean age was 13.9 ± 3.3 years in the patient group and 14.6 ± 3.1 years in the control group ($p > 0.05$). Thirty four of the patients (81%) were female and eight (19%) were male. Twenty five of the control subjects (78%) were female and seven (22%) were male. The QT dispersion and heart rate corrected QT interval were found to be significantly increased in the children with primary mitral valve prolapse when compared with the control group (56 ± 16 ms vs. 43 ± 11 ms, $p = 0.001$; 426 ± 25 ms vs. 407 ± 26 ms, $p = 0.002$, respectively). In 24-hour rhythm Holter monitor tests, ventricular arrhythmias were found in 21 out of 42 patients (50%) and 6 out of 32 control subjects (18.8%) ($p = 0.006$). QT dispersion was found to be significantly increased in patients with premature ventricular contractions ≥ 10 /day and/or complex ventricular arrhythmias compared to the control group without ventricular premature beats ($p = 0.002$). There was no significant difference in autonomic function tests and heart rate variability measurements between the patient and control groups.

Conclusions: The noted increase in QT dispersion may be a useful indicator for the clinician in the evaluation of impending ventricular arrhythmias in children with primary mitral valve prolapse. (Turk Pediatri Ars 2016; 51: 135-41)

Keywords: Arrhythmia, children, primary mitral valve prolapse, QT dispersion

Introduction

Primary mitral valve prolapse (MVP) is defined as ballooning extending of one or both leaflets of the mitral valve from the mitral valve annulus towards the left atrium during systole in the absence of a secondary cause (1, 2). Primary MVP mostly has a benign prognosis, but problems including mitral regurgitation (MR), infective endocarditis, brain emboly, orthostatic hypotension, ventricular arrhythmias and sudden death may be observed in some patients (3, 4).

QT dispersion is defined as the difference between the longest and shortest QT periods in electrocardiogram

(ECG) derivations (5, 6). It is thought that QT dispersion reflects regional differences in ventricular repolarization. In studies involving adults, it has been proposed that increased QT dispersion in patients with MVP is associated with ventricular arrhythmias, but QT length is not associated with ventricular arrhythmias (7-9). Heart rate variation examination is a method which is measured on 24-hour rhythm Holter monitoring and used in evaluation of the autonomic functions of the heart (10, 11). It has been proposed that reduction in heart rate variability is related with ventricular arrhythmias especially in individuals with heart disease (12). The results which have been reported in studies related with heart rate variability in individuals with MVP are

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controversial (13-15). In a study involving children, it was shown that parasympathetic action decreased and sympatovagal balance was disrupted in examination of the heart rate variability of 67 children with MVP (16).

There exists no study in which QT measurements, heart rate variability measurements and autonomic function tests have been evaluated in association based on the pathogenesis of ventricular arrhythmias in children with primary MVP.

In this study, it was aimed to investigate ventricular arrhythmias in children with primary MVP and to evaluate the relationship of ventricular arrhythmias with QT dispersion, QT length, heart rate variability and autonomic function tests.

Material and Methods

Patients: Fourty two pediatric patients who were being followed up with a diagnosis of primary MVP in İstanbul University, Cerrahpaşa School of Medicine, Pediatric Cardiology Outpatient Clinic and 32 healthy children were included in this study. Patients who had MVP related with secondary causes (rheumatic heart disease, Marfan syndrome, Ehlers-Danlos syndrome, cardiomyopathy, infective endocarditis, atrial septal defect, anorexia nervosa etc.) and patients who were using drugs which prolong QT interval or antiarrhythmic drugs were not included in the study. The patient and control groups were asked to avoid caffeinated drinks during the study. Height and weight measurements were performed and the body mass index was calculated using the formula of kg/height^2 .

The study was approved by the ethics committee of Istanbul University, Cerrahpaşa School of Medicine (Ethics committee decision number: 30315). Written informed consent was obtained from the children aged above 12 years in the patient and control groups and from all parents.

Electrocardiogram and QT measurements: Twelve-derivation ECG (Hewlett Packard, XLI) was performed following a 10-minute rest in the supine position. All ECGs were transferred to the digital media by scanning with an optical scanner (Hewlett Packard PSC 1510). Electrocardiograms were examined in terms of rhythm, speed, QRS axis, atrial enlargement, ventricular hypertrophy and ST-T change. The values were compared with the normal values reported by Davignon et al. (17). All mea-

surements were performed by an experienced investigator who did not know which group the subjects belonged to. The QT interval was measured. The QT interval was considered as the distance between the starting point of the QRS complex and the end of the T wave. The criteria defined by Lepschkin and Surawicz (18) were used in determining the end of the T wave and in differentiation of the U wave. At least two or three QRS-T complexes were evaluated in each derivation and the mean QT period was calculated as millisecond. The subjects for whom QT measurement could be performed in at least nine derivations were included in the study. The longest and shortest QT distances on 12-derivation ECG were selected and the difference between them was recorded as QT dispersion. The QT interval corrected for heart rate (QTc) was calculated using the Bazett formula.

QT corrected for heart rate (QTc)=QT/√RR

In measurement of QT, the intraobserver coefficient of variation which is calculated by dividing the standard deviation of two measurements performed at different times to the mean value was found to be 2.1%, 3% and 4.6%, respectively, for the longest QT, shortest QT and QT dispersion in 20 subjects.

Autonomic function tests: Basal blood pressure measurements were performed following a 10-minute rest in the supine position. Afterwards, the subjects were asked to stand motionless with the arms and legs adjoined for 10 minutes and presence of orthostatic hypotension was evaluated by measuring the blood pressure at the end of these 10 minutes. Reductions of more than 20 mmHg in the systolic blood pressure were considered abnormal. The resting heart rate was calculated from the RR interval on ECG. Among cardiac autonomic function tests, orthostatic hypotension was used to investigate the sympathetic system and resting heart rate was used to investigate the parasympathetic system.

Echocardiography: The echocardiographic examinations of the patient and control groups were performed by an experienced cardiologist using Vivid 3 device (General Electrics) and 3 MHz probe. Diagnostic echocardiographic examination was performed from all echocardiographic windows using M-mode, two-dimensional, colored Doppler, 'pulse-wave' Doppler and 'continuous-wave' Doppler. On two-dimensional echocardiographic examination, partial or complete displacement of the anterior and posterior leaflets from the mitral annulus level towards the left atrium above 2 mm was considered the diagnostic criterion for MVP (1, 2).

The degree of mitral regurgitation was evaluated according to the recommendations of the American Heart Association (19). A vena contracta of <3 mm was recorded mild regurgitation, a vena contracta of $\geq 3 - 7$ mm was recorded moderate regurgitation and a vena contracta of ≥ 7 mm or more was recorded significant regurgitation.

Twenty-four hour-rhythm Holter examination and heart rate variability: Twenty four-hour recording was performed using three channel rhythm Holter device (Del Mar Reynolds Impresario Solo). The basal rhythm, the highest and lowest heart rates, mean heart rate, supra-ventricular premature beat, ventricular premature beat (VPB), supraventricular tachycardia, ventricular tachycardia, pause interval and heart rate variability measurements were examined.

The ventricular arrhythmias in the recordings were evaluated according to the modified Lown criteria (20). Accordingly, the classes were grouped as follows: class 0: no VPB, class 1: uniform rare VPB (<30/s), class 2: uniform frequent VPB (>30/s), class 3: multiform VPB, class 4: repetitive VPB [4a: couplet, 4b: ventricular tachycardia]. The ventricular arrhythmias in class 2 were considered complex ventricular arrhythmia.

Among the time domain measurements of heart rate variability, the mean of all normal RR intervals (mean RR), standard deviation of all normal sinus RR intervals (SDNN), standard deviation of the RR intervals in all 5-minute segments (SDANN), the mean of the standard deviations of the RR intervals in all 5-minute segments throughout 24 hours (SDNN index), the square root of the mean of the squares of the differences between consecutive RR intervals (RMSSD) and the percentage of the number of consecutive RR intervals with a difference of more than 50 ms between each other throughout the recording (pNN50) were calculated.

Statistical analysis

Statistical Package for the Social Science 15.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. The measurements were expressed as mean $\pm$ standard deviation and %. The quantitative values between the two groups were compared using t-test and the qualitative values were compared using χ^2 test. Kruskal Wallis test was used, when there were more than two groups and the measurements which were found to be different were evaluated using post hoc Dunn test. A p value of <0.05 was considered statistically significant.

Results

Thirty four (81%) of 42 patients with a diagnosis of primary MVP were female and eight (19%) were male. The mean age of the patients was 13.9 ± 3.3 years ranging between 6.5 years and 18 years. In the control group, 25 (78.1%) of 32 healthy children were female and seven (21.9%) were male. The mean age was 14.6 ± 3.1 years ranging between 6.3 years and 18 years. No significant difference was found between the groups in terms of age and gender ($p > 0.05$ and $p > 0.05$). No significant difference was found between the patient and control groups in terms of height and weight, whereas the body mass index of the patient group (17.6 ± 3.1 kg/m²) was found to be lower compared to the control group (19.8 ± 2.7 kg/m²) ($p = 0.003$).

No significant difference was found between the patient group (115.5 ± 11.6 mmHg and 65.5 ± 9.2 mmHg) and control group (117.2 ± 11 mmHg ve 65.1 ± 8 mmHg) in terms of systolic and diastolic blood pressure ($p > 0.05$). Orthostatic hypotension was found in seven patients (16.7%) in the patient group and in one child (3.1%) in the control group ($p > 0.05$). The mean resting heart rate was found to be 84 ± 15 /min in the patient group and 85 ± 17 /min in the control group ($p > 0.05$).

Electrocardiogram findings: The electrocardiograms of the patient and control groups all showed sinus rhythm and QRS axes. PR and QRS intervals were within the normal limits for age. Atrial enlargement finding and criteria indicating ventricular enlargement were not found in any ECG. ST-T changes were found in 12 (28.5%) of the patients. ST-T change was not found in the control group. Ventricular premature beat was found in one patient with primary MVP.

QT dispersion and QTc were increased in the patient group compared to the control group (56 ± 16 ms, 43 ± 11 ms, $p = 0.001$ and 426 ± 25 ms, 407 ± 26 ms, $p = 0.002$) (Table 1).

Echocardiogram findings: Tricuspid valve prolapse was also found in 15 (35.7%) of the patients. MR was ab-

Table 1. Electrocardiogram findings of the patients with primary mitral valve prolapse and the control group

	Patients	Control	p
QT the longest ms	371 $\pm$ 66	358 $\pm$ 33	>0.05
QT the shortest ms	315 $\pm$ 59	314 $\pm$ 32	>0.05
QT dispersion ms	56 $\pm$ 16	43 $\pm$ 11	0.001
QTc (ms)	426 $\pm$ 25	407 $\pm$ 26	0.002

QTc: QT corrected for heart rate

Table 2. Classification of the ventricular arrhythmias of the patients with primary mitral valve prolapse and control group by modified Lown criteria

Classes	Patients (n)	Control (n)
Class 0	21	26
Class 1	16	6
Class 2	1	0
Class 3	0	0
Class 4 ^a	1	0
Class 4 ^b	3	0

n: number of subjects

sent in 11 patients (26.2%), 26 patients (61.9%) had mild MR and five patients (11.9%) had moderate MR. Severe MRI was not found.

Twenty four-hour rhythm Holter examination and heart rate variability findings: Ventricular arrhythmia was found in 21 (50%) of 42 patients and in 6 (18.8%) of 32 controls. The frequency of ventricular arrhythmia was found to be statistically significantly higher in the patient group compared to the control group ($p=0.006$).

Sixteen (38%) of 42 patients had class 1 ventricular arrhythmia, one had class 2 ventricular arrhythmia, one had class 4a ventricular arrhythmia and three had class 2 b ventricular arrhythmia (Table 2). Complex ventricular arrhythmia above class 2 was found in four patients (9%). Ventricular arrhythmias found in six children in the control group were class 1 ventricular arrhythmias (low number of VPBs).

The findings of the patients were evaluated by dividing the findings into subgroups by the number of VPBs in addition to complex ventricular arrhythmia, because complex ventricular arrhythmias were found only in four patients and a low number of VPBs may be observed on 24-hour rhythm Holter monitorization in healthy children (six subjects in the control group who were found to have VPB were excluded from the group, group 1: patients without VPB, group 2: patients with a VPB number of <10 and group 3: patients with a VPB number of ≥ 10 and/or presence of complex ventricular arrhythmia). It was found that QT dispersion and QTc increased, as the degree of ventricular arrhythmias increased (Table 3). It was found that QT dispersion was statistically significantly increased in group 3 patients who had a VPB number of 10 and higher and/or who had complex ventricular arrhythmias compared to the control group (excluding the ones with VPBs) ($p=0.002$) (Table 3).

No statistically significant difference was found both between all patients and the control group ($p>0.05$) and between the patient subgroups divided by ventricular arrhythmias and the controls who had no VPBs in terms of heart rate variability measurements (Table 3).

Supraventricular premature beats were found in 10 children in the control group and in 17 patients in the patient group.

Discussion

It is known that ventricular arrhythmias are common in patients with primary MVP (21-26). In studies involving adults, the frequency of ventricular arrhythmia in patients with primary MVP has been reported with a rate ranging between 49% and 89% depending on the patient group and MVP diagnostic criteria (21-23). Kavey et al. (25) found ventricular arrhythmia in 43 (41.7%) of 103 children with primary MVP and complex ventricular arrhythmia above class 2 in 19 (18.5%) with 24-hour rhythm Holter monitoring. In this study, ventricular arrhythmia was found in 21 (50%) of 42 patients with primary MVP and in six (18.8%) of 32 healthy children; the frequency of ventricular arrhythmia was found to be increased in the patient group.

Various causes have been proposed in formation of ventricular arrhythmias in primary MVP. These include stretching of the papillary muscles with ballooning prolapse of mitral leaflets (27), mechanical stimulation of the endocardium by thickened chordate (28), coronary emboly caused by accumulation of platelets and fibrin as a result of endocardial friction (29), autonomic dysfunction (30, 31) and repolarization changes characterized by prolongation in QT interval and increase in QT dispersion (7-9).

In studies involving adults, a close relation between ventricular arrhythmias and QT dispersion which is a criterion for regional differences in the ventricular repolarization period has been reported (7-9). In the study of Kulan et al. (7) which involved 64 adult patients with primary MVP and 80 healthy individuals, it was shown that QT dispersion increased in the patient group and there was a correlation between the increase in QT dispersion and complex ventricular arrhythmias. In the study of Ülgen et al. (8) which compared 58 adult patients with primary MVP with 60 healthy individuals, it was shown that QT dispersion increased in the patient group and there was a correlation between the increase in QT dispersion and ventricular arrhythmias; these investigators proposed that variability in ventricular re-

Tablo 3. QT measurements and heart rate variability in the patients who were divided into groups by the number of ventricular premature beats in 24-hour rhythm Holter and presence of complex ventricular arrhythmia and in the control group who had no ventricular premature beats

	Control ^a	Group 1: VPB (-)	Group 2: VPB<10	Group 3: VPB≥10, CVA	p ^b
Number of patients sayısı	26	21	10	11	
QT the longest (ms)	358±32	353±88	387±34	390±17	0.019
QT the shortest (ms)	314±32	302±78	330±33	326±21	0.463
QT dispersion (ms)	43±11	51±17	57±12	63±18	0.002
QTd (ms)	407±26	421±23	431±30	433±24	0.040
Mean RR (ms)	718±78	722±126	735±75	719±88	0.841
SDNN (ms)	163±41	167±53	170±31	158±46	0.884
SDANN (ms)	150±40	149±51	151±27	141±42	0.696
SDSD (ms)	44±21	54±36	47±24	41±28	0.750
SDNNI (ms)	63±19	68±26	66±22	59±23	0.801
RMSSD (ms)	57±26	70±44	61±29	53±35	0.965
pNN50 (%)	19±11	22±14	21±9	17±14	0.838

CVA: complex ventricular arrhythmia; mean RR: mean of all normal RR intervals; pNN50: percentage of the number of consecutive RR intervals with a difference of more than 50 ms between; RMSSD: squareroot of the mean of the squares of the differences between consecutive RR intervals; SDANN: standard deviation of the mean of the RR intervals in all 5-minute segments; SDNN: standard deviation of all normal sinus RR intervals; SDNN index: mean of the standard deviations of the RR intervals in all 5-minute segments; VPB: ventricular premature beat All values were given as mean ± standard deviation.

Control: the children in the control group who did not have ventricular premature beats Kruskal Wallisb.

Post hoc: QT dispersion, control-group 3 p=0.002

polarization could contribute to development of ventricular arrhythmia and increased QT dispersion could indicate the risk of ventricular arrhythmia. In the study of Çetinkaya et al. (32) which involved 37 children with primary MVP and 26 healthy children, it was found that QT dispersion was increased in the children with MVP compared to the healthy children.

They found that the frequency of ventricular arrhythmias was 18.9% in children with primary MVP using 24-hour rhythm Holter monitoring and they reported that the most common ventricular arrhythmia was VPB. However, they could not show a correlation between ventricular arrhythmias and QT dispersion.

Ventricular premature beats may also be observed in healthy children. In the study of Nagashima et al. (33) in which 24-hour Holter monitoring was performed in 360 healthy children, VPBs were found in 18% of newborns, in 6% of infants, in 8% of children aged between 4 and 6 years, in 14% of children aged between 9 and 12 years and in 27% of children aged between 13 and 15 years. The number of VPBs in healthy children is generally below 10 per hour. Complex ventricular arrhythmias are observed with a lower frequency in children with primary MVP in contrast to adults (32). Complex ventricular arrhythmia was found in only

four of our patients on 24-hour Holter monitoring. Therefore, we divided our patients into three groups as the ones who had no VPB, who had less than 10 VPBs and who had more than 10 VPBs and/or who had complex ventricular arrhythmias on 24-hour Holter monitoring and compared these groups with healthy children. We found that QT dispersion and QTc increased as the degree of ventricular arrhythmias increased and QT dispersion was significantly higher in the group who had more than 10 VPBs in 24 hours and/or who had complex ventricular arrhythmias compared to healthy children who had no VPBs. Different results have been reported in studies related with QT interval in adults with primary MVP (7, 8). Kulan et al. (7) found no significant difference between adult patients with MVP and healthy controls in terms of QTc. In the study of Ülgen et al. (8) which involved 58 adult patients with primary MVP and 60 healthy individuals, it was shown that QTc was increased in the patient group. In the study of Çetinkaya et al. (32) which involved 37 children with primary MVP and 26 healthy children, no significant difference was found between the patients and the control group in terms of QTc. In this study, QTc was found to be increased in children with primary MVP compared to healthy children. In addition, QTc was also found to be increased as well as QT dispersion, as the degree of ventricular

arrhythmias increased, but a statistically significant difference could not be demonstrated. We think that controversial results related with QT interval may have arisen from use of different measurement techniques in different studies and the difficulty in determining the end of the T wave. In this study, all ECGs were transferred to the digital media by scanning with optical scanner. The criteria defined by Lepeschkin and Surawicz (18) were used to define the end of the T wave and to differentiate U wave.

QT interval reflects the sum of the ventricular depolarization period and repolarization period. When Bekheit et al. (34) examined the ECGs of adult patients with primary MVP, they found ST-T changes which are among the other repolarization disorders in addition to QT prolongation in 50% of the patients. Kavey et al. (35) reported ST-T changes with a rate of 31% in children with primary MVP. Similarly, this rate was found to be 28.5% in our patients.

It has been proposed that autonomic dysfunction is present in adult patients with primary MVP and this might be related with ventricular arrhythmias (30, 31). In this study, no significant difference was found between the patient and control groups in terms of resting heart rate and orthostatic hypotension. It was thought that the increase in QT dispersion and QTc in children with primary MVP occurred before parasympathetic and sympathetic disorders were detected in these patients with autonomic function tests.

The results reported in studies in which heart rate variability was examined in adult patients with primary MVP are controversial (13-15). In the study of Han et al. (16) which involved 67 children with primary MVP aged between 6 and 18 years, heart rate variability measurements were found to be lower in the patients compared to the control group and it was proposed that sympathovagal balance was disrupted in children with MVP because of decreased parasympathetic action. In this study, no significant difference was found between the children with primary MVP and the control group in terms of heart rate variability. In addition, no significant difference was found between the three patient groups divided by the number of VPBs on 24-hour Holter monitoring and presence of complex ventricular arrhythmias and the control group. It was thought that increase in QT dispersion may occur in children with primary MVP without impairment in heart rate variability measurements.

In conclusion, increase in QT dispersion in children with MVP may be a helpful indicator in evaluating ventricular arrhythmias. This study is the first study in which the correlation between QT dispersion and ventricular arrhythmias was demonstrated in children with primary MVP.

Ethics Committee Approval: Ethics committee approval was received for this study from İstanbul University Cerrahpaşa School of Medicine Ethic Committee.

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

Peer-review: Externally peer-reviewed.

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