



Effects of Mitral Valve Prolapse on Heart Rate Variability and the Autonomic Nervous System in Children

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Abstract

Background: Patients with mitral valve prolapse (MVP) may reveal symptoms of autonomic dysfunction and heart rate variability (HRV). We sought to explore the autonomic nervous system in children with MVP.

Methods: This cross-sectional study enrolled 60 children aged between 5 and 15 years with MVP and 60 age- and sex-matched healthy children as controls. Two cardiologists performed electrocardiography and standard echocardiography. HRV parameters were explored via 24-hour rhythm 3-channel Holter monitoring. The depolarization of ventricular and atrial parameters, comprising QT max and min, QTc intervals, QT dispersion, P maximum and minimum, and P-wave dispersion, was measured and compared.

Results: The mean age was 13.12 ± 1.50 years in the MVP group (F/M: 34/26) and 13.20 ± 1.81 years in the control group (F/M: 35/25). The maximum duration and P-wave dispersion in the MVP group were significantly different from the healthy children ($P < 0.001$). The longest and shortest QT dispersion values and QTc values were significantly different between the 2 groups ($P = 0.004$, $P = 0.043$, $P < 0.001$, and $P < 0.001$, respectively). The HRV parameters were significantly different between the 2 groups, too.

Conclusion: Decreased HRV and inhomogeneous depolarization showed that our children with MVP were prone to atrial and ventricular arrhythmias. Furthermore, P-wave dispersion and QTc could be used as prognostic markers of cardiac autonomic dysfunction before it is diagnosed by 24-hour Holter monitoring.

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Introduction

Mitral valve prolapse (MVP) is characterized by the superior displacement of 1 or both leaflets of the mitral

valve from the mitral valve annulus to the left atrium during the systole, not triggered by a secondary cause. In general, MVP prognosis is benign, although problems such as ventricular arrhythmias and sudden death have been

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reported in some patients.¹

In 12-lead electrocardiography (ECG), P-wave parameters, such as P-wave dispersion (PWD) and maximal P-wave duration (P-max), are considered the noninvasive predictors of intermittent and inhomogeneous propagation of sinus impulses. Elevated PWD could be attributed partly to increased sympathetic activity, which might increase the risk of arrhythmias.²

QT dispersion is the difference between the longest and shortest QT durations in ECG derivations. QT dispersion is thought to occur as regional differences in cardiac repolarization. In studies on adults, augmented QT dispersion in patients with MVP, as opposed to QT length, is linked to ventricular arrhythmias.³

Heart rate variability (HRV), measured by 24-hour rhythm Holter monitoring, is used to evaluate the autonomic functions of the heart. Low HRV is linked to ventricular arrhythmias.^{3, 4} A study on children with MVP reported declining parasympathetic action and disruptive sympathovagal balance in HRV.⁵ Nonetheless, the results of studies on HRV in patients with MVP are controversial.^{6, 7} Previous research has shown transmural dispersion of repolarization in children with MVP is positively correlated with an increase in the degree of mitral regurgitation (MR). It appears that children with MVP are prone to life-threatening ventricular arrhythmias.⁹

The present study aimed to investigate the effects of MVP on HRV and the autonomic nervous system in children.

Methods

From April 2016 through April 2017, the current cross-sectional research was conducted on children with MVP. The Research Ethics Committee of the University of Medical Sciences approved the research protocol. The children's parents were requested to sign informed consent for their child's involvement in the research before it began. Sixty pediatric patients have admitted to the Pediatric Cardiology Outpatient Clinic with a diagnosis of primary MVP and 60 healthy children met the requirements to be included in this study. The sample size was calculated using the Stata 11 software at 95% levels of the confidence interval and a power of 80% based on the results of a similar study.¹⁰ Inclusion criteria were age between 5 and 15 years, appropriate echocardiography views, the displacement of the anterior and posterior mitral leaflets more than 2 mm from the mitral annulus, normal heart structure and function without congenital heart diseases, no history of cardiac arrhythmias, and no treatment with antiarrhythmic drugs. Patients whose MVP was linked to secondary causes such as Marfan syndrome, rheumatic heart disease, Ehlers-Danlos syndrome, infective endocarditis, cardiomyopathy, atrial septal defect, and anorexia nervosa and patients

who consumed antiarrhythmic drugs or had prolonged QT intervals were excluded from the study.

Standard 12-lead ECG was conducted using a recorder set at a paper speed of 25 mm/s and 1 mV/cm (CardiMax, FX-7202). ECGs were then examined for parameters such as speed, rhythm, atrial enlargement, QRS axis, ventricular hypertrophy, and ST-T change. Two pediatric cardiologists, blind to the patients, interpreted the ECGs in both groups.

The duration of the P wave, is defined as the interval between the starting point of the P wave (the junction between the isoelectric line and the outset of deflection) and the offset of the P wave (the junction between the end of P-wave deflection and the isoelectric line), was measured in milliseconds (ms). P-wave duration was computed at 3 consecutive cardiac cycles for each lead, and the mean value was used for the analysis. P-max and P-min were defined as the longest and shortest 12 leads, and P minimum was defined as the shortest duration. The difference between the maximum and minimum durations of the P wave was considered PWD.

QT interval was defined as the interval between the beginning of the QRS complex and the end of the T wave. At least 2 or 3 QRS-T complexes were examined in each derivation, and the average QT period was measured in milliseconds. The subjects for whom QT measurement could be performed in at least 9 derivations participated in the study. Thereafter, the longest and shortest QT intervals on 12-derivation ECG were selected, and their difference was recorded as QT dispersion. QT interval corrected for heart rate (QTc) was computed via the Bazett formula. The recording was done with 24-hour 3-channel rhythm Holter monitoring devices. Moreover, basal rhythm, the lowest and highest heart rates, average heart rate, ventricular premature beat (VPB), supraventricular premature beat, ventricular tachycardia, supraventricular tachycardia, pause interval, and HRV measurements were studied.

Among the time domain measurements of HRV, average normal RR intervals (mean RR), the standard deviation of all normal sinus RR intervals (SDNN), the standard deviation of RR intervals in all 5-minute segments (SDANN), the average standard deviation of RR intervals in all 5-minute segments during 24-hour periods (SDNN index), the square root of the average squares of differences between consecutive RR intervals (RMSSD), and the percentage of consecutive RR intervals with a variance of more than 50 ms between the recorded parameters (pNN50) were computed.

Standard echocardiography was conducted for all the subjects. Data were collected during echocardiography as a mean measurement of 3 to 5 consecutive beats. The echocardiographic examinations were carried out with a 3–7 MHz transducer (Vivid 6s GE, Vingmed Ultrasound, USA) by 2 echocardiographers, who concurred on the patients' conditions. Echocardiograms were excluded if they were difficult to assess due to technical defects and if cardiologists

could not reach an agreement about them. Via the parasternal long-axis view of M-mode echocardiography, the left ventricular ejection fraction was calculated. Additionally, via M-mode echocardiography with 2D imaging, the left ventricular end-diastolic diameter, the interventricular septum thickness, the left ventricular posterior wall thickness at the end of the diastole, and the ejection fraction were determined. All the standard echocardiography calculations were based on the mean of 3 cycles. The measurements were performed using standard techniques and guidelines proposed by the American Society of Echocardiography. In our study, MVP was defined as the superior displacement of the anterior and posterior mitral leaflets more than 2 mm from the mitral annulus to the left atrium in the parasternal long-axis view. The extent of MR was evaluated in keeping with the existing guidelines, and the degree of valvular regurgitation was recorded.¹¹

Statistical analysis was conducted using the SPSS 23 software (Armonk, NY: IBM Corp; 2015). Descriptive statistics, including the mean±standard deviation and percentage ratios, were performed for all the data. First, the distribution normality of the information was assessed via the Kolmogorov–Smirnov test. The quantitative values of the 2 groups were compared using the Student test-test, and the comparison of the qualitative values was carried out using the χ^2 test. The relationship between the parameters was examined using the Spearman correlation test for data with normal distributions and the Pearson test for data with abnormal distributions. A P value of 0.05 was considered statistically significant in all the cases.

Results

We designed a cross-sectional study with 60 children between 5 and 15 years of age with MVP and 60 age- and sex-matched healthy children as controls. The mean age was 13.12±1.50 years in the MVP group (F/M: 34/26) and 13.20±1.81 years in the control group (F/M: 35/25).

Table 1 shows the demographic and clinical characteristics

of the intervention and control groups. Age, sex, height, weight, body mass index (BMI), systolic and diastolic blood pressures, and heart rate did not vary significantly between the 2 groups. The M-mode echocardiographic parameters are depicted in Table 2. The thickness of the MV leaflet had significant differences between the 2 groups ($P<0.001$).

In the patients with MVP, PWD and the maximum duration of P wave were significantly different from those in healthy children (Table 3). P maximum and PWD had significant differences between the 2 groups, respectively ($P<0.001$).

The results also showed that PWD was not associated with age, BMI, systolic and diastolic blood pressures, thickness, leaflet displacement, and M-mode echocardiographic parameters. Further, no correlations were found between MR and P-wave parameters, including P maximum ($r=0.081$, $P=0.679$), P minimum ($r=0.06$, $P=0.899$), and PWD ($r=0.112$, $P=0.329$).

The QT measurements are shown in Table 4. The longest and shortest QTs had significant differences between the MVP and control groups ($P=0.004$ and $P=0.043$, respectively). Moreover, QT dispersion and QTc were significantly different between the 2 groups ($P<0.001$).

Statistically significant differences were also observed between the MVP and control groups in terms of QT dispersion and QTc interval. A positive correlation was detected between the QT dispersion interval and the increased degree of MR ($r=0.401$; $P<0.050$). However, the degree of MR was not correlated with the longest QT ($r=0.012$, $P=0.880$), the shortest QT ($r=0.078$, $P=0.679$), and QTc ($r=0.090$, $P=0.629$).

During the 24-hour Holter monitoring, no VPB was observed in 30 patients, uniform rare VPB ($<30/s$) was observed in 10 patients, frequent uniform VPB ($>30/s$) was recorded in 8 patients, multiform VPB was observed in 7 patients, and repetitive VPB with couplet was recorded in 7 patients. Furthermore, non-sustained or sustained ventricular tachycardia was not found in any of the patients. All HRV parameters were significantly different between the patients in the MVP group and the controls (Table 5).

Table 1. Demographic and clinical characteristics of the MVP and control groups*

	Patients (n=60)	Controls (n=60)	P
Age (y)	13.12±1.50	13.20±1.81	0.793
Sex (M/F)	26/34	25/35	0.853
Mean heart rate (bpm)	83.34±13.87	81.22±13.10	0.391
BMI (kg/m ²)	19.13±8.11	19.45±8.59	0.834
SBP (mmHg)	110.12±11.54	109.12±11.94	0.642
DBP (mmHg)	65.12±11.65	64.89 ±11.96	0.915
Mitral regurgitation (n, %)			
Mild	25 (42.0%)	-	-
Moderate	20 (33.0%)	-	-
Severe	15 (25.0%)	-	-

*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 results of the MVP and control groups*

	Controls (n=60)	Patients (n=60)	P
IVSDd (mm)	71.11±1.96	71.15±1.93	0.911
LVEDd (mm)	40.73±5.73	41.25±5.97	0.627
LVEDs (mm)	24.58±8.84	25.61±9.55	0.541
LVPWd (mm)	7.61±2.83	7.81±2.77	0.696
EF (%)	67.55 ±7.51	68.67±7.52	0.416
Thickness of MV leaflet (mm)	4.21±1.03	6.40± 1.90	<0.001

*Data are presented as mean±SD.

MVP, Mitral valve prolapse; IVSDd, Interventricular septum diastolic diameter; LVEDd, Left ventricular end-diastolic diameter; LVEDs, Left ventricular end-systolic diameter; LVPWd, Left ventricular posterior wall diastolic diameter; EF, Ejection fraction

Table 3. Measurements of P-wave parameters in the mitral valve prolapse and control groups*

	Control (n=60)	Patients (n=60)	P
P maximum (ms)	82.89 ± 9.34	87.34 ± 9.81	0.001
P minimum (ms)	45.62 ± 11.89	43.54 ± 11.23	0.327
P-wave dispersion (ms)	31.88 ± 9.45	44.13 ± 8.97	<0.001

*Data are presented as mean±SD.

MVP, Mitral valve prolapse

Table 4. Measurements of QT parameters in the mitral valve prolapse and control groups*

	Control (n=60)	Patients (n=60)	P
QT, the longest (ms)	349.32±23.15	368.12±43.14	0.004
QT, the shortest (ms)	301.19±42.11	318.24±49.01	0.043
QT dispersion (ms)	45.46±16.18	60.01±18.11	<0.001
QTc (ms)	421.56±18.79	439.23±31.09	<0.001

*Data are presented as mean±SD.

MVP, Mitral valve prolapse; QTc, QT corrected for heart rate

Table 5. Heart rate variability parameters in the MVP and control groups*

	Control (n=60)	Patients (n=60)	P
Mean RR (ms)	734.78±56.08	709.89±63.23	0.023
SDNN (ms)	166.42±28.50	150.51±32.11	0.004
SDANN (ms)	158.75±34.43	140.76±38.88	0.007
SDSD (ms)	48.97±15.43	40.65±18.42	0.009
SDNNI (ms)	74.59±12.98	66.65±13.59	<0.001
RMSSD (ms)	68.91±15.35	60.80±16.65	0.006
pNN50 (%)	17.29±15.91	23.15±14.62	0.025

*Data are presented as mean±SD.

MVP, Mitral valve prolapse; RR intervals, Average time between heartbeats; SDNN, Standard deviation of all normal sinus RR intervals; SDANN, Standard deviation of RR intervals in all 5-minute segments; SDSD, Standard deviation of successive RR interval differences; SDNNI, The average standard deviations of RR intervals in all 5-minute segments during 24-hour periods; RMSSD, The square root of the average squares of differences between consecutive RR intervals; pNN50, The percentage of consecutive RR intervals with a variance of more than 50 ms between the recorded parameters

Discussion

A small percentage of individuals with MVP exhibit autonomic dysfunction, including decreased parasympathetic activity and increased adrenergic tone, according to clinical and biochemical investigations. HRV measurement, as a yardstick of autonomic nervous system function, which constitutes an integral part of routine clinical examinations in adults, is seen as a key factor in the examination of children and adolescents, too. HRV findings in patients with MVP have been inconsistent. Electrophysiological heterogeneity could be triggered by variations in the sympathovagal balance of patients with MVP.

Amplified dispersion indicates electrophysiological heterogeneity within the atrial myocardium, which could be attributed to modified sympathovagal balance in patients with MVP. Alterations in the autonomic tone, owing to its effect on the atrial conduction velocity, may influence the duration of the P wave. Tuñek et al¹² reported that intensified sympathetic activity could induce a significant growth in PWD. Intermittent and inhomogeneous propagation of sinus impulses across the atrium was revealed by PWD.

We assessed PWD in terms of the presence of MR in the MVP group; hence, we managed to evaluate the effects of regurgitation on PWD. According to the results, PWD had increased significantly in the MVP group compared with the

control group. The significant drop in minimum values could justify the elevated PWD in the MVP group. This could be the earliest prognostic marker of parasympathetic dysfunction in patients with MVP. We observed that the minimum P-wave duration remained relatively unchanged without any significant variation. There was, however, a statistically significant increase in P-max, which could be attributed to the dominance of sympathetic activation in children with MVP. This supports the assumption that PWD prolongation might be associated with an amplified sympathetic tone. This finding is not consistent with the results reported by Babaoglu et al.²

We did not observe any correlation between acute MR and P-wave parameters. It could be explained by the fact that the majority of our patients had mild or moderate regurgitation, as indicated by Gunduz et al⁷ and Babaoglu et al.²

QT interval exhibits the sum of repolarization and ventricular depolarization duration. The elevated QT dispersion in children with MVP may serve as a marker for evaluating ventricular arrhythmias.

ST-T changes with a prevalence rate of 30% were reported in children with primary MVP. Likewise, Ebru Yalın İmamoğlu et al¹⁰ reported that the rate of ST-T changes in their patients was 28.5%. In the present study, however, we did not assess ST-T changes. The aforementioned increase in QT dispersion may be a valuable marker for assessing imminent ventricular arrhythmias in children with primary MVP. In this research, QT characteristics, such as QT dispersion and QTc, were substantially different between the MVP and control groups. In addition, we found a correlation between T dispersion and primary MVP in children. We discovered higher QT dispersion and QTc in children with primary MVP. Moreover, autonomic function tests showed synchronic parasympathetic and sympathetic disorders in our patients.

Many reasons have been proposed for ventricular arrhythmia development in primary MVP, including prolonged QT interval and elevated QT dispersion, which are caused by repolarization and autonomic dysfunction changes.¹³ In studies on adults, a close relationship has been reported between QT and JT dispersion and the echocardiographic degree of MVP and mitral leaflet thickness.¹³

Cetinkaya et al,¹⁴ in their study on 37 children with primary MVP and 26 healthy children, reported elevated QT dispersion in the children with MVP compared with the healthy children. Nonetheless, there was no significant difference between the subjects in the intervention and control groups in terms of QTc. It contradicts the findings of the current research, which found that QTc in children with primary MVP was greater than that in healthy children. Moreover, they reported a ventricular arrhythmia frequency of 18.9% in children with primary MVP using 24-hour rhythm Holter monitoring, introducing VPB as

the most common ventricular arrhythmias. Nevertheless, they found no association between ventricular arrhythmias and QT dispersion. The frequency of complex ventricular arrhythmias was lower in children with primary MVP as opposed to adults.

According to Ebru Yalın İmamoğlu et al,¹⁰ children with primary MVP and subjects in the control group were significantly different concerning HRV. Furthermore, there was no significant difference between the patient group split by the number of VPBs recorded during 24-hour Holter monitoring and the existence of complicated ventricular arrhythmias and the control group. They assumed that elevated QT dispersion might occur in children with primary MVP without disturbing HRV measurements.

Demiro M et al¹⁵ observed that QT dispersion and QTC dispersion were significantly higher in patients with MVP. Still, they reported no significant differences between the groups in terms of QT and QTc. Their results also suggested that QT and QTC were not correlated with the increased degree of MR. These results are not consistent with our findings.

Yontar et al¹⁶ observed that QT and QTc were significantly higher in patients with MVP. In their study, the 2 groups had similar echocardiographic findings; however, mitral valve thickness was significantly higher in MVP patients. These findings are in agreement with our findings. In a study by Han et al¹⁷ on 67 children with primary MVP aged between 6 and 18 years, the intervention group had a lower HRV than the control group. The authors contended that sympathovagal balance was disrupted in the MVP group in terms of lower parasympathetic action.

We observed that HRV parameters in patients with MVP were significantly different from those in the control subjects. Moreover, the 2 groups were significantly different in terms of the parameters of 24-hour Holter monitoring.

We revealed that increased QT dispersion and impaired HRV occur in children with primary MVP. This does not chime in with the findings reported by Ebru Yalın İmamoğlu et al.¹⁰ Moreover, QTc and QT dispersion were increased with a rise in the extent of ventricular arrhythmias, but the difference was not statistically significant. We believe that controversial results concerning QT interval could be attributed to the application of diverse measurement techniques in various studies and the difficulty of determining the end of the T wave.

HRV results have been inconsistent among patients with MVP. Han et al¹⁷ reported that the time-domain and frequency-domain indicators of HRV in children with MVP were lower than those of subjects in the control group, and there were no significant differences between symptomatic and asymptomatic patients.

Significant differences were observed between patients with MVP and control subjects in terms of HRV parameters. Frisinghelli et al¹⁸ revealed that the presence of MR in



patients with MVP was associated with elevated vagal tone.

Gunduz et al⁷ suggested that time-domain HRV parameters were not different in adult patients with MVP who were either MR positive or MR negative. Babaoglu et al² indicated that children with MVP were not significantly different in terms of time-domain HRV parameters, which is not consistent with the findings of this study. Nonetheless, many studies have shown that HRV parameters remain unchanged in patients with MVP.^{7, 19} Moreover, Tacoy et al²⁰ revealed that time-domain indices in symptomatic patients with MVP were significantly lower than those in control subjects.

Eventually, our study demonstrated that inhomogeneous depolarization in atrial and ventricular cardiac tissues of children with MVP and also decreased HRV showed enhanced sympathetic overdrive and decreased vagal activity. Elevated QT dispersion and QTC exhibit symptoms of ventricular arrhythmias in children with MVP, and elevated PWD suggests proniging to atrial arrhythmias in this group of children. Furthermore, HRV and the autonomic nervous system exhibited conflicts in the MVP group. Therefore, this study showed the effects of MVP on cardiac autonomic function.

The current investigation has several limitations. Firstly, we did not follow up with our patients to detect ventricular arrhythmias and assess the relationship between the abovementioned parameters and future arrhythmic events for a long time. As a result, large prospective studies are needed to investigate the link between these variables and arrhythmic events in patients with MVP. Secondly, we did not investigate ST-T alterations in primary MVP, and we were unable to show a link between these measures and symptoms. Accordingly, further studies with a larger sample size are required to indicate any relationship between elevated parameters and symptoms and between severity measurements and HRV parameters.

Conclusion

The results of the present study suggested that HRV parameters were significantly different between the MVP and control groups, with PWD being significantly higher in the former group. According to these findings, P wave and QT parameters as the depolarization index could be used as prognostic markers, warning about cardiac autonomic dysfunction in children with MVP before parasympathetic and sympathetic dysfunction is diagnosed via other autonomic function tests.

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