Association Between QT Dispersion Prolongation and Mitral Valve Prolapse: Case-Control Study

Mitral Kapak Prolapsusu ve QT Dispersiyonu Uzaması Arasındaki İlişki: Olgu-Kontrol Çalışması

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ABSTRACT Objective: Mitral valve prolapse (MVP) is a commonly recognized syndrome with an apparent prevalence of approximately 4-6%. The incidence of ventricular arrhythmias and sudden death appears to be high in this patient group. It was also claimed that the prolonged QT or QT dispersion intervals in MVP cases could be related to arrhythmia and sudden death. The aim of the present study was to determine the electrocardiographic features (including QT dispersion) in MVP cases. **Material and Methods:** We studied 37 patients with MVP and 30 healthy control subjects. In all subjects, transthoracic 2-dimensional and Doppler echocardiographic examinations were performed. Classic MVP was defined as superior displacement of mitral leaflets of more 2 mm during systole and as a maximal leaflet thickness of at least 5 mm during diastole and non-classic prolapse was defined as displacement of more than 2 mm, with a maximal leaflet of 5 mm. Electrocardiographic (ECG) parameters including QT dispersion of patients with mitral valve prolapse (MVP) were statistically compared with the parameters of healthy control subjects. Correlations of ECG parameters between themselves and their correlations with age were observed. **Results:** PR interval, QRS complex duration and QTc duration of MVP cases were shorter than those control cases but these findings were statistically insignificant. QT and QTc dispersions of MVP cases were significantly longer than of control cases (42.9±15 and 47.5±17 ms). QT interval and QT dispersion were correlated with age among MVP cases. Compared with control group, nonspecific ST segment changes and dysrhythmia were found to be more frequent within MVP cases. Among MVP cases, QT dispersions of cases with ST segment changes were also significantly longer than MVP subjects with normal ECG findings (58.6±14.3 vs 38.6±12.6 ms). **Conclusion:** QT dispersion prolongation, ST segment changes and dysrhythmias are commonly observed among subjects with MVP, which may explain increased incidence of sudden death in this population. QT interval and QT dispersion should be followed clinically as a routine procedure in the management of MVP. Furthermore, It is advisable to consider whether there is MVP or not in a patient with ischemic like changes such as ST segment changes or dysrhythmia.

Key Words: Mitral valve prolapse; electrocardiography; QT-dispersion

ÖZET Amaç: Mitral kapak prolapsusu (MKP) yaklaşık %4-6 sıklık oranında görülmesi ile tanınan bir sendromdur. Bu grup hastalarda ventriküler aritmi ve ani ölüm görülme insidansı yüksek olabilir. MKP vakalarında uzamış QT ve QT dispersiyonu intervalinin aritmi ve ani ölüm ile ilişkili olduğu iddia edilmiştir. Bu çalışmanın amacı MKP vakalarında elektrokardiyografik (QT dispersiyonu içeren) özellikleri belirlemekti. **Gereç ve Yöntemler:** MKP'lu 37 hasta çalışma grubu ve 30 sağlıklı birey kontrol grubu olarak belirlendi. Bütün olgulara 2 boyutlu transtorasik ve Doppler ekokardiyografik inceleme yapıldı. Klasik MKP sistol sırasında mitral yaprakçıkların 2 mm fazla atriuma doğru bombeleşmesi ve diastolde yaprakçık kalınlığının en az 5 mm üzerinde olması şeklinde tanımlanırken, non-klasik prolapsus maksimum yaprakçıkta 5 mm kalınlaşma ile 2 mm'den fazla bombeleşme olarak tanımlandı. MKP'lu hastaların QT dispersiyonunu içeren elektrokardiyografi parametreleri sağlıklı kontrol grubunun parametreleri ile karşılaştırıldı. Elektrokardiyografik parametrelerinin kendi içindeki ilişkileri ve yaş ile olan ilişkileri incelendi. **Bulgular:** MKP'lu olgularda PR intervali, QRS süresi ve QTc süresi kontrol bireylerden kısa idi fakat bulgular istatistiksel olarak önemsizdi. MKP'lu olgularda QT ve QTc dispersiyonları kontrol grubundan önemli derece uzundu (42.9±15 ve 47.5±17 ms). MKP'lu olgular arasında QT intervali ve QT dispersiyonu ile yaş arasında korelasyon saptandı. Kontrol grubu ile karşılaştırıldığında MKP'lu olgular içerisinde daha sık non-spesifik ST dalgası değişikliği ve disritmi tespit edildi. MKP'lu hastalar arasında, ST segment değişiklikli olgulardaki QT dispersiyonu, normal elektrokardiyografi'li kişilerdeki QT dispersiyonundan önemli derecede uzundu (58.6±14.3 ve 38.6±12.6 ms). **Sonuç:** Mitral kapak prolapsus'lu kişiler arasında ki bu popülasyonda ani ölüm insidansı artışını açıklayabilen, uzamış QT dispersiyonu, ST segment değişikliği ve disritmi genellikle gözlenmiştir. Mitral kapak prolapsusu tedavisinde rutin prosedürde klinik olarak QT dispersiyonu ve QT intervali takip edilmelidir. Dahası, ST segment değişikliği ve disritmi gibi iskemik benzeri değişiklik bulunan hastalarda MKP'nun olup olmadığının düşünülmesi tavsiye edilmektedir.

Anahtar Kelimeler: Mitral kapak prolapsusu; elektrokardiyografi; QT-dispersiyon

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As probably every physician know mitral valve prolapse (MVP) is a frequently reported cardiovascular finding all over the world.[1] Some studies have reported that ischemic-like ST segment changes, arrhythmia, QT dispersion differences and pre-excitation syndromes were more frequent in subjects with MVP than normal population.[2]

Association of Wolff-Parkinson-White syndrome and arrhythmia with sudden death has been pointed in some articles.[2] Although sudden death in MVP is a very important problem, certain criteria have not been described yet. Most of these subjects are younger women with thickened valves and long QT intervals.[3] Furthermore, there are studies that found that, instead of a prolonged QT interval increase, intrinsic QT dispersion can be related to arrhythmia in these cases. Various arrhythmias, from atrial to complex ventricular arrhythmias, have been reported in MVP cases.[4-8]

Ischemia-like ECG changes in MVP cases during exercise have also been reported. To determine the mechanism of this change in cases with normal coronary angiograms, treadmill exercise tests and coronary haemodynamic studies were prospectively performed. These changes were related to the coronary micro vascular dysfunction rather than altered cardiac metabolism.[9,10]

The aim of our study was to determine the electrocardiographic changes (including QT dispersion) in MVP cases comparing with normal subjects, observe the correlations between these parameters and evaluate of results for clinical usefulness.

MATERIAL AND METHODS

This was a case-control, observational and analytical study. We studied 37 patients with MVP and 30 healthy control subjects. Those patients who had disorders such as ischemic or rheumatic heart disease, systemic and/or pulmonary hypertension, diabetes mellitus, electrolyte abnormalities, hyperthyroidism, stenotic valvular heart disease, severe mitral regurgitation were excluded. Those patients whose clinical condition and finding evoked suspicion of a disease and who were taking QT prolonging drugs were excluded. All patients gave written informed consent, and the study was approved by the local ethics committee.

All individuals underwent M-mode; two-dimensional and color-Doppler examinations with a commercially available system (Toshiba core-vision pro machine with a 2.5 MHz probe). The measurements were carried out according to the standards of the American Society of Echocardiography[11], using the parasternal long axis and apical 4-chamber windows. Classic MVP was defined as superior displacement of mitral leaflets of more 2 mm during systole and as a maximal leaflet thickness of at least 5 mm during diastole and non-classic prolapse was defined as displacement of more than 2 mm, with a maximal leaflet of 5 mm.

For all subjects, 12-derivation ECG was performed at 50 mm/sec (Nihon Kohden, Japan). While they were allowed to breathe at a normal rate during ECG, they were prevented from any movement and speaking. PR segment distances; QRS times and QT intervals were recorded. QT intervals were measured from the beginning of the QRS complex to the end of the T wave where isoelectric line began again. Ending point of T wave was accepted as the nadir between the T and U waves where U wave followed T wave. The derivations on which the ends of T waves couldn't be identified were excluded. QT values were corrected considering the effect of heart rate by using Bazzet's formula ($QTc=QT/\sqrt{RR}$). QT intervals were measured in every derivation by digital caliper (Which provides 0.01 mm measurement). The consecutive three measurements were recorded and mean values were used for each derivation. Similarly, QT dispersions were also calculated as the differences in ms between the minimum and maximum QT intervals. The procedure was repeated for corrected QT intervals and QTc dispersions were also calculated. As QT dispersion results, Patients were divided into two main groups: First, 49 ms and lesser, Second, greater than 49 ms.[12]

Electrocardiographic signs were classified as normal, dysrhythmia (determined at least on two separate ECG analyses), short PR interval (less than

0.12 ms) and ST segment depression (at rest) according to their main significant features in repetitive records in different times.

We also classified dysrythmia as supraventricular tachycardia, supraventricular extrasystol or ventricular extrasystol as well. ST segments depressions were nearly 1 mm at rest and on inferior derivations every time. Further ST segment changes during procedure were observed in order to evaluate these changes by treadmill's effort test whether they were specific or not. Maximal effort capacity with no further ST segment collapse was accepted as treadmill negative and otherwise (without reaching maximal capacity for any reason and significant ST subsidement on the procedure) as positive according to the report of cardiologist.

ST segment changes were evaluated by performing Treadmill's effort test. Electrocardiographic features of the control cases were also classified in a similar manner. Cardiologist was blinded with ECG results of patients and the staff who performed ECG and measurements was blinded with Echocardiography results.

STATISTICAL ANALYSIS

ST segment changes of the cases were classified as treadmill positive and treadmill negative. Nonspecific ST segment changes, dysrhythmias seen in mitral valve prolapse (Generally), short PR interval (cases with PR distance shorter than 0.12 second on ECG) were statistically compared with control group by 2x2 tables chi-square test and Binary Logistic regression. A P value of less than 0.05 was considered significant. PR segment distances, QRS durations, QT intervals and QT dispersions were also compared among patient groups and among QT interval, QT dispersion groups. Differences in the means of continuous measurements were tested by unpaired t-test. We also performed multivariate analyses among age, PR, QRS, QT and QT dispersion. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were in the 95% CI and performed on a personal computer.

RESULTS

In this study, we evaluated totally 42 patients with MVP, five of which were excluded after all (one for beta-blocking using, two for hypocalcaemia and two for hypomagnesemia). Thirty-seven MVP patients and thirty control subjects were enrolled. Of MVP patients, 31 (83%) were female and 6 (16%) were male with an average age of 38.6 ± 8.4 years. The control group comprised asymptomatic healthy volunteers, in whom neither clinical evaluation nor echocardiographic examination could detect any kind of valvular prolapse; there were 26 females (86%) and four (13%) males with an average age of 32 ± 7.5 years. From the view-point of age and sex, statistically there was no significant difference between the patient and control groups. Of the 37 patients with MVP detected by echocardiography, 29 (78%) had prolapse of the anterior leaflet, three (8%) had prolapse of the posterior leaflet and five (10%) had prolapse of both anterior and posterior leaflet. All patients had mitral regurgitation on color Doppler echocardiography. The mitral regurgitation was mild in 35 (95%), moderate in two (5%) patients. All patients had normal left ventricular systolic function and there were no significant differences among groups regarding left ventricular dimensions, and ejection fraction. Comparison of echocardiographic parameters of the control cases and patients MVP were expressed in Table 1.

Of mitral valve prolapse cases, 18 of them were within the normal electrocardiographic ranges. Other features were dysrythmia (6 cases), short PR intervals (7 cases) and ST segment changes (6 cases) as well. In control group, we observed normal ECG within 29 of them (Table 2). ST segment changes and dysrhtmia of MVP cases were found to be more frequent than control group (Chi-square; p= 0.029).

Dysrhythmias were Supraventricular tachycardia (33.3 percent), Supraventricular extra systole (33.3 percent) and Ventricular extra systole (33.3 percent) as well.

Treadmill's effort tests were performed to subjects with ST segment change displayed no further subsidement while reaching maximal effort capa-

TABLE 1: Comparisons of demographic and echocardiographic parameters between MVP and Control cases

	Groups		
	MVP (37)	Control (30)	p
Age (year)	38.6±8.4	32±7.5	NS
Male/Female, n	6/31	4/26	NS
LVEDD (cm)	4.4±0.3	4.3±0.3	NS
LVESD (cm)	2.7±0.3	2.7±0.2	NS
EF (%)	65±4	64±2	NS
LAD (cm)	3.5±0.4	3.4±0.3	NS
AMLT (mm)	3.9±0.9	1.4±0.3	< 0.0001
PMLT (mm)	3.51±0.53	1.2±0.2	< 0.0001

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; LAD, left atrial diameter; AMLT, anterior mitral leaflet thickness; PMLT, posterior mitral leaflet thickness; NS, not significant.
Values were given as mean ± standart deviation.

city. As a consequence, these features were accepted as nonspecific changes.

PR interval, QRS complex duration and QTc duration of MVP cases were shorter than those control cases but these findings were statistically insignificant (Table 3). However, QT dispersions and QTc dispersions of MVP cases were significantly longer than of control cases. Statistical analyses were calculated within 95% confidence interval. We performed Factorial ANOVA analysis for correction of possible effects of age among groups. We observed statistical significance in the correction model (p< 0.001).

QTc dispersions of cases with "ST segment change" were significantly longer than MVP cases with Normal ECG (Mann-Whitney U test, p< 0.001) and cases with short PR interval (Mann-Whitney U, p= 0.037) (Table 4).

TABLE 2: Major electrocardiographic features of MVP and Control cases.

	ECG features				
Groups	Normal	Dysrhythmia	Short PR	ST segment change	Total
MVP	18	6	7	6	37
Control	29	0	1	0	30

Values in semicolons display percents of features within every category.

TABLE 3: Comparisons of electrocardiographic parameters between MVP and control cases

	Groups		
ECG parameter	MVP (37)	Control (30)	p
PR interval(ms)	141.9 ± 22.2	145.7 ± 21.5	NS
QRS duration(ms)	87.4 ± 10.8	88 ± 7.5	NS
QT interval(ms)	372.6 ± 36.7	371 ± 27.5	NS
QT interval(ms) (Corrected)	399.2 ± 23.3	399.5 ± 17.8	NS
QT dispersion(ms)	42.9 ± 15	22.4 ± 11	< 0.001
QT dispersion(ms) (Corrected)	47.5 ± 17	25 ± 13.8	< 0.001

NS, not significant.
Values were given as mean ± standart deviation.

We observed the percentages of QT dispersion higher than 49 ms among subjects (MVP= 17 cases, 46 percent; Control= 2 cases, 7 percent). We detected significant difference for QT dispersion groups (49 ms and less and higher than 49 ms) among case and control groups by Binary Logistic regression.

We have observed positive correlations between age and QT / QTC intervals among MVP cases. (Pearson correlation = 0.444, 0.328 n=37 p= 0.006, 0.048). In the control group, we never observed any correlation statistically.

TABLE 4: Comparisons of electrocardiographic parameters between ECG groups of MVP cases.

	Groups				
ECG parameters	Normal (18)	Dysrhythmia (6)	Short PR (7)	ST segment change (6)	p
PR interval (ms)	146.3 ± 17	156.7 ± 18.8	109.7 ± 5	151.3 ± 17.2	< 0.001
QRS duration (ms)	87 ± 10	82 ± 5	90.3 ± 17	90.7 ± 8.3	NS
QT interval (ms)	377.4 ± 21.8	368.7 ± 30.3	363.4 ± 72.6	372.7 ± 25.2	NS
QT interval (ms) (Corrected)	399.5 ± 17.6	395.5 ± 18.7	396.3 ± 39.3	405 ± 15.6	NS
QT dispersion (ms)	38.6 ± 12.6	49.9 ± 12	34.6 ± 13.5	58.6 ± 14.3	0.013
QT dispersion (Corrected) (ms)	41.5 ± 12.7	57 ± 18.2	38.9 ± 10.4	65.8 ± 18.6	0.014

NS, not significant.
Values were given as mean ± standart deviation.

DISCUSSION

COMPARISONS WITH PREVIOUS FINDINGS

In previous articles, It has been reported that ventricular pre-excitation syndromes and dysrhytmias observed in mitral valve prolapse were more frequent than normal population.[2,13] Ischemia-like ECG changes in MVP cases during exercise have also been reported. These changes were related to coronary micro vascular dysfunction.[9,10] In our study, we observed ishaemic-like ST segment changes during rest and all of them were within inferior derivations. Also we observed that "dysrhythmia" was more frequent than those control group. All of them had complaint of "Palpitation". We also observed that "Short PR interval" was more frequent than those control group but this finding was not significant statistically.

In our study, QT dispersions of MVP cases were longer than control group's statistically. This finding is harmonious with previous studies. In addition, ventricular dysrhythmias were risky factors for QT dispersion prolongation in MVP cases in previous articles.[7,14] Prolonged QTc and QT dispersion indicate shift of sympathetic-vagal balance towards sympathetic predominance and reduced vagal modulation, this produces increased dispersion of ventricular repolarisation.[15] QT dispersion prolongation may lead to severe ventricular arrhythmia, for this reason our last finding is harmonious with previous results. In our study, only three had QT dispersion longer than 80 ms (Serious risk for life-threatening arrhythmia) among MVP cases but never had among control group. However, as a new finding, in our study we observed that QT dispersions of MVP cases with ischaemic-like ST segment depression were longer than those with normal electrocardiographic feature.

In previous articles, the correlation between severity of valve pathology and QT distance and between severity of valve pathology and QT dispersion have been pointed within MVP cases.[12] However, as a new finding we evaluated these correlations related to the age. In our study, we observed that QT distance and QTc distance were correlated with age among MVP cases. Probably, this was another side of the habitation of valve pathology. At this moment, it was interesting keeping in mind the study which pointed that most of cases with sudden death were younger women with QT prolongation.[3] Moreover, in our study QT dispersions of MVP cases and QTc dispersions were correlated with age. Probably, these results are related to the minimal changes with aging enough may effect electrocardiographic findings.

CLINICAL IMPLICATIONS

In our study, we observed that "dysrhythmia" in MVP cases were more frequent than those control group's. We believe that echocardiographic evaluation is necessary in subjects with palpitation whenever we observed dysrhtmia or ischaemic-like ST segment depression on their electrocardiographic examination.

Although MVP is commonly seen in general population, some lifetime changes such as prophylaxis of bacterial endocarditis, use of some drugs (beta-blockers) may be necessary to prevent symptoms, to follow-up the course and severity of the disease by two-dimensional echocardiography and to avoid some unnecessary interventions.

QT distance in the cases with MVP was never different statistically than those control cases in our study. For this reason, extra-ordinary procedures such as QT dispersion measurement should be routinely performed for risk-estimation. Doubtless, most interesting electrocardiographic finding in MVP cases is QT dispersion prolongation especially among cases with ischaemic-like ST segment depression. QT dispersion prolongation may lead to severe and fatal aryhtmia.

QT interval prolongation may also lead to severe aryhtmia. For this reason QT interval should be followed with repetitive measurements especially among aging subjects. Further studies might be necessary for high risk group. Some electrophysiologic studies and some initiative procedures (antiarhythmic prophylaxis, etc.) may be useful and life-saving especially in the more ample studies. 24-hour electrocardiographic records may be useful for detecting paroxysmal aryhtmia in these cases.

CONCLUSION

Electrocardiographic changes are more frequent in MVP cases than those without any valve pathology. QT dispersion prolongation of MVP especially among cases with ST segment change and increase of dispersion with age is most interesting feature of our study. This finding should be followed hardly keeping in mind the clinical results and importance of QT dispersion prolongation. We conclude that QT dispersion measurements should be routinely performed in the management of MVP cases.

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