Complications of mitral valve prolapse (MVP), among which serious ventricular arrhythmia and sudden death are of major importance, affect many individuals due to the high incidence of MVP itself in the community despite the actual low incidence of these complications. The present study investigated the incidence and distribution of ventricular arrhythmias according to their severity and relationship with the QT interval and dispersion of repolarization in uncomplicated isolated MVP (IMVP) cases. Fifty-eight uncomplicated IMVP patients, 33 patients with accompanying tricuspid valve prolapse (TVP), to compare its relationship with ventricular arrhythmia, and 60 age- and sex-matched control subjects were enrolled in the study. Individuals with accompanying cardiac or systemic disease, or who were on drug therapy that could potentially affect QT characteristics, were excluded. The incidence of ventricular arrhythmia was 48% in the IMVP group and 64% in the TVP group; the difference was statistically insignificant. In addition, the differences of the QT and Q peak T values were insignificant, whereas QT dispersion (QTd) and Q peak T dispersion (QpeakTd) values were significantly higher in the patient group (60±14, 54±14 ms, respectively) compared with the control group (42±10, 38±10 ms, respectively, p<0.001). Complex ventricular arrhythmias (Lown Grade ≥III) in the IMVP group had a significant relationship with QTd and QpeakTd (p<0.001), but not with QT or QpeakT. As a result of the study, it is concluded that TVP accompanying MVP does not increase the incidence of ventricular arrhythmia, that ventricular arrhythmia is related to QT dispersion rather than QT interval in IMVP, that the QT dispersion is a fairly good marker for identifying the high-risk group for serious ventricular arrhythmia and sudden death, and that QpeakT dispersion measurement is an additional indicator that could be an alternative when QT is difficult to determine in conditions such as high heart rate or the presence of U wave. (Jpn Circ J 1999; 63: 929–933)

Key Words: Mitral valve prolapse; QT dispersion

Mitrail valve prolapse (MVP) is the most commonly diagnosed valvular heart disease, especially in the young, and affects 5% of the community. Although it is reported that MVP has a good prognosis and a low incidence of complications, it is obvious that even a rare complication will affect many individuals due to the high incidence of MVP in the general population.

However, some reports point out that these complications are not as rare as was thought, the main entities being endocarditis, cerebrovascular accidents, sudden death, ventricular tachycardia and ventricular fibrillation.

Arrhythmia and sudden death are significant complications in MVP cases; a 0.5% incidence of sudden death has been reported in different MVP studies and it is suggested that the underlying mechanism of the sudden death is arrhythmogenic. It was also claimed that the prolonged QT intervals in MVP cases could be related to arrhythmia and sudden death. 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.

In the present study, we aimed to determine the relationship between intrinsic QT dispersion and ventricular arrhythmias and sudden death in young individuals suffering from uncomplicated isolated MVP (IMVP). In this respect, cases without leaflet thickening (≥5 mm), severe mitral regurgitation or left ventricular systolic dysfunction were included in the study. Although a few reports have concentrated on the clinical significance of MVP accompanying tricuspid valve prolapse (TVP), the clinical significance of TVP and its relation to the arrhythmias of MVP has not yet been clearly documented. Therefore, we excluded MVP cases with accompanying TVP after beginning the study. Our main aim was to investigate the incidence and distribution of ventricular arrhythmias, according to their severity and relation to the QT interval, and to the dispersion of repolarization in uncomplicated IMVP.

Methods

The current study was carried out in the Department of Cardiology, Faculty of Medicine, Dicle University between May 1996 and April 1998. We registered 91 individuals who underwent echocardiographic examination and were diagnosed as MVP; the group included 33 cases with accompanying TVP. Those patients who had disorders such as ischemic or rheumatic heart disease, systemic and/or pulmonary hypertension, diabetes mellitus, hyperthyroidism, stenotic valvular heart disease, congenital heart diseases, severe mitral regurgitation (>3 cm² regurgitant jet length in color flow mapping), or severe left ventricular dysfunction...
were excluded. Those patients whose clinical condition and findings evoked suspicion of a disease and who were taking QT prolonging drugs were excluded as well. In the cases of IMVP there was a history of palpitation in 66%, atypical chest pain in 72%, fatigue and dyspnea in 55%, presyncope in 9%, and syncope in 7%.

An age- and sex-matched healthy control group (n=60) was randomly formed from individuals without any cardiac disease or history of arrhythmia. Those with a QRS segment ≥120 ms and/or atrial fibrillation on the electrocardiogram were excluded from both groups in the study.

The patient group was divided into 2 subgroups: (i) IMVP group (n=58) and (ii) MVP+TVP group (n=33). All subjects underwent 24-h ambulatory ECG.

Echocardiographic Examination

In all subjects, transthoracic 2-dimensional and Doppler echocardiographic examinations were performed using a Vingmed CFM 800 echocardiographic system, using 2.5–3.5 MHz transducers. The measurements were carried out according to the standards of the American Society of Echocardiography11 using the parasternal long axis and apical 4-chamber windows.

MVP was defined as a systolic excursion of any leaflet that exceeded 3 mm from the mitral valve annulus proximally in the parasternal long axis and apical 4-chamber windows, and TVP was defined as a systolic excursion of any leaflet that exceeded 3 mm from the tricuspid valve annulus proximally in the same views. The echocardiographic examinations were recorded on a video recorder (Sony SVO-9500-MDP VHS) for further evaluation. Each echocardiogram was evaluated by 2 experienced cardiologists. Echocardiograms that were difficult to evaluate due to technical defects, and the cases in which the cardiologists could not agree, were excluded from the study.

ECG Evaluation

ECG recordings of all subjects were done with a Hewlet Packard Page Writer, which records 12 derivations simultaneously at a paper speed of 50 mm/s with a calibration of 0.5 mV/cm. In each derivation the QT intervals were measured as the time from the beginning of the QRS to the end of the T wave in milliseconds. In the presence of a U wave, QT intervals were measured to the notch between the T and U waves. The distance between the beginning of the QRS complex and the highest point of the T wave was used to measure the Q peak T interval. If the T wave was biphasic, the second peak was used. Two QT and Q peak T interval measurements from each measurable derivation were carried out by 2 observers who were uninformed about the clinical status of the patients. Derivations with an uncertain T wave end and/or peak points, or with premature complexes, were excluded. Following the measurements, the average values were calculated. QT and Q peak T intervals were corrected (QTc) according to the Bazett formula12 QTc prolongation was accepted as ≥440 ms. The differences between maximum QT and Q peak T intervals in their own category in any of the 12 derivations were calculated as QT dispersion (QTD) and Q peak T dispersion (QpeakTd), respectively.

Ambulatory ECG Recordings

The 24-h ambulatory ECG was performed by a Holter system (Del-Mar Avionics, Irvine, CA, USA) during the daily activities of all participants using CM–V1, CM–Vs, CM–DII derivations. Analysis was performed by an observer who was uninformed about the diagnosis. Premature ventricular contractions (PVC) were evaluated according to Lown and Wolf criteria (grade 0: no PVC; grade I: <30 PVC/h; grade II: >30 PVC/h; grade III: multiform PVC; grade IVa: couplets; grade IVb: ventricular tachycardia runs)13 PVC evaluated >30 PVC/h; grade III were defined as complex ventricular arrhythmias.

Statistical Analysis

The data were expressed as mean±SD. The differences between the groups were analysed by Student’s t-test, or chi-squared test. The correlation between the variances was investigated, and p<0.05 was assessed as significant.

Results

Ninety-one MVP patients and 60 control subjects were enrolled. Of 58 IMVP patients, 38 (66%) were female and 20 (34%) were male with an average age of 27±7 years; of the 33 patients suffering from both MVP and TVP, 22 (66%) were female and 11 (34%) were male with an average of 28±7 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 39 females (65%) and 21 (35%) males with an average age of 28±7 years. From the view-point of age and sex, statistically there was no significant difference between the patient and control groups. All of the subjects were in sinus rhythm on their resting ECG.
**Echocardiographic Results**

In the patient group, 58 (64%) had IMVP and 33 (36%) had MVP+TVP. The prolapse was observed in the anterior leaflet only in 29 (50%), in the posterior leaflet only in 9 (15.5%), and in both leaflets in 20 (34.5%) of the IMVP patients.

**Ambulatory Results**

Mean heart rates were 78±16 and 70±12 beats/min in the patient and control groups, respectively (p<0.01). Premature ventricular contractions were seen in 28 of the 58 IMVP cases (48%) and 21 of the 33 MVP+TVP cases (64%). When compared with the control group, the frequency of IMVP cases (48%) and 21 of the 33 MVP+TVP cases (64%) were seen less frequently in the IMVP (48%) group than in the MVP+TVP (64%) group, but it was not significant (p<0.05) (Table 1).

**QT Dispersion Results**

QT, QpeakT, QTd, and QpeakTd values were calculated in both the IMVP (n=58) and control groups (n=60). In each group, the minimum and mean numbers of measured derivations were 9 and 11.5, respectively. The mean±SD difference between the QTd measurements of the 2 independent observers (interobserver variability) was 2.74±9.35 (n=58), and the correlation coefficient was r=0.83 (p<0.001). The values of QT, QpeakT, QTd, and QpeakT in the IMVP and control groups are presented in Table 2. Mean values were higher in the IMVP group, but it was not significant (p<0.05).

In the patient group, the QTc value of 3 of 5 subjects who were defined as having at least one presyncopal attack exceeded 440 ms. Two of them had Grade II and the third had Grade III PVC. Three of 4 patients who were defined as having syncope had a QTc >440 ms, and PVC were classified as Lown Grade II in 2 and Grade IVa in the third. Ventricular arrhythmia of Grade I and II, respectively, occurred in 2 patients with prolonged QT intervals. Dispersions of QT, QpeakT, QTc, QpeakTc were calculated and the results are shown in Table 2. In IMVP cases, QTd and QpeakTd values were higher than those of the control group, which was statistically significant (p<0.001). In IMVP cases, there was no significant relationship between the grade of PVC and the QT, QpeakT, QTc or QpeakTc values. However, that kind of relation was established with QTd and QpeakTd (p<0.001) (Table 3).

**Discussion**

The incidence of PVC in MVP has been reported between 49 and 89% and it varies according to the patient study group and the MVP diagnostic criteria. The incidence is reported to increase in complicated cases such as those with an increased anterior and/or posterior leaflet thickness (≥5 mm), and those with severe mitral regurgitation or severe left ventricular systolic dysfunction; moreover, these patients are accepted as having high risk. In the current study, we found the incidence to be 48% in uncomplicated cases of MVP and 64% if MVP was accompanied by TVP (p<0.05), a lower incidence for MVP than has been reported earlier. This might reflect our relatively uncomplicated IMVP cases; in fact, there were no patients with severe mitral regurgitation and/or severe left ventricular systolic dysfunction secondary to mitral regurgitation in our study group. The presence of MVP accompanied by TVP increased the incidence; however, the difference was not significant. Previous reports have noted a 43–56% incidence of serious ventricular arrhythmia, but a lower incidence (2–17%) has been found in uncomplicated MVP. We established an incidence of 19% for complex ventricular arrhythmia Lown Grade ≥III in IMVP cases and of 21% in MVP+TVP cases. Although the mechanism of arrhythmia has not been clarified yet, different mechanisms, such as diastolic depolarization of the muscle fibers of the anterior mitral leaflet in response to stretch, initiation of ventricular ectopia and arrhythmia as a result of extreme tension on the papillary muscles, mechanical stimulation due to thickened chordae, endocardial plaque-friction lesions, increased excitability consequent to adrenergic system activation and others, can be speculated.

It is suggested that QT prolongation is related to arrhythmia sequelae in MVP cases but controversies still exist. Different studies present the incidence of QTc prolongation between 8 and 75% in MVP, whereas the Framingham Study reported no relation between these entities. Our results suggest that QTc prolongation is not a common finding. In fact, we determined neither a significant difference between the patient and control groups from the view-point of QT interval prolongation incidence nor a significant correlation between QTc and ventricular arrhythmia in MVP, which is consistent with previous studies. In spite of the contradictory information on the relation between QT prolongation and MVP, it is focused on the link between nonspecific repolarization changes and potentially malignant arrhythmia. The inter-lead variability of the QT interval measured in the 12-lead ECG is defined as QTd. Mirvis and others showed variability in QTd and established the QTd5 A close relation between disper-

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**Table 3 QT Measurements Related to Ventricular Arrhythmia According to Lown Grade of Arrhythmia in Isolated MVP Cases**

<table>
<thead>
<tr>
<th>Lown Grade</th>
<th>QT (ms)</th>
<th>QpeakT (ms)</th>
<th>QTc (ms)</th>
<th>QpeakTc (ms)</th>
<th>QTd (ms)</th>
<th>QpeakTd (ms)</th>
<th>QTc (ms)</th>
<th>QpeakTc (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>331±34</td>
<td>255±32</td>
<td>386±22</td>
<td>297±25</td>
<td>535±9</td>
<td>498±10**</td>
<td>62±11</td>
<td>57±13**</td>
</tr>
<tr>
<td>I</td>
<td>350±23</td>
<td>265±32</td>
<td>401±22</td>
<td>304±29</td>
<td>608±8**</td>
<td>498±10**</td>
<td>69±5**</td>
<td>57±13**</td>
</tr>
<tr>
<td>II</td>
<td>363±23</td>
<td>279±17</td>
<td>419±29</td>
<td>334±28</td>
<td>585±10**</td>
<td>53±7**</td>
<td>76±5**</td>
<td>65±12**</td>
</tr>
<tr>
<td>III</td>
<td>355±12</td>
<td>256±18</td>
<td>422±17</td>
<td>306±25</td>
<td>80±14</td>
<td>75±7</td>
<td>95±14</td>
<td>82±15</td>
</tr>
<tr>
<td>IVa</td>
<td>360±27</td>
<td>292±40</td>
<td>414±16</td>
<td>334±23</td>
<td>83±13</td>
<td>78±8</td>
<td>96±14</td>
<td>89±10</td>
</tr>
<tr>
<td>IVb</td>
<td>36±39</td>
<td>279±40</td>
<td>415±10</td>
<td>319±28</td>
<td>83±5</td>
<td>74±6</td>
<td>95±13</td>
<td>85±9</td>
</tr>
</tbody>
</table>

*QTc, corrected QT; QTd, QT dispersion; QpeakTc, corrected QpeakT; QpeakTd, QpeakT dispersion; QTdc, corrected QT dispersion.

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isions of QT and QTc, which are noninvasive measurements of regional variability of ventricular recovery time and serious ventricular arrhythmia, has been put forward in various reports. This kind of relation has been shown particularly in congenital long QT syndromes in drug intoxication, in hypertrophic cardiomyopathy and following acute myocardial infarction. In fact, through experimental studies, it has been concluded that the heterogeneous repolarization could contribute to ventricular arrhythmia. Therefore, increased dispersion of refractoriness may be the arrhythmic mechanism underlying MVP. Tieleman et al. and Kulan et al. determined that dispersions of QT and QTc were higher than in controls. Kulan et al. reported that MVP patients who had a higher incidence of complex ventricular arrhythmias (Lown ≥ II) had higher QTd and QTc compared with the those with a lower Lown grade of arrhythmia. However, Tieleman et al. did not determine such a relation; moreover, it is not clear in these studies whether they excluded other triggering factors of arrhythmia, such as severe left ventricular regurgitation, severe left ventricular systolic dysfunction and dilatation, and thickening of the mitral leaflets. As well, in some reports, TVP is probably present in cases of ventricular fibrillation and sudden cardiac death. We excluded the cases of MVP accompanied by TVP after the beginning of the study, and the cases of thickened fibrotic or calcified mitral leaflets, severe mitral regurgitation, severe left ventricular systolic dysfunction and/or dilated heart chambers. We determined that the QTd and QTd c values were higher in uncomplicated IMVP than in the controls (p < 0.001), and higher in patients having complex ventricular arrhythmias compared to those having Lown grade I–II arrhythmia (p = 0.001).

Recently, it has been highlighted that, especially when difficulties are encountered in measuring the QT interval, such as in cases of a high heart rate with united T and P waves, the presence of U waves or an indefinite end of the T wave, measurement of QpeakT might be of great benefit. We measured QpeakT and QpeakTd values in the MVP cases. Mean values of QpeakT and QpeakTd were not significantly different between the patient and control groups. However, the dispersion values of QpeakT and corrected QpeakT were significantly higher in the patient group and in those having complex ventricular arrhythmias in the subgroup analysis compared with those having simple PVC (p < 0.001, p < 0.001, respectively). Our results comparing QTd values to the severity of the arrhythmia are similar to those of Kulan et al. However, our study group comprised uncomplicated and IMVP cases, which we did to try and exclude other factors thought to be responsible for the pathogenesis of the arrhythmia in MVP. Nevertheless, it is not clear enough whether increased dispersion of the refractoriness is the underlying reason of the arrhythmia in MVP or not. Therefore, further studies of IMVP consisting of cases having serious ventricular arrhythmia are needed.

Previous studies have pointed out that increased QT variability reflects regional shortening as well as regional prolongation of repolarization intervals. This regional variability of the action potential interval may occur secondary to adrenergic stimulation, locally increased wall stress or ischemia. Various authors have reported high levels of and increased sensitivity to catecholamines along with their abnormal regulation in MVP patients in addition to abnormal baroreceptor modulation. An experimental animal model showed an increased dispersion of refractoriness via both prolonged and shortened regional ventricular refractoriness by the activation of the sympathetic nervous system. Another reason for an increased dispersion of refractoriness may be the regional differences in wall stresses. Increased stress on chordae due to the increased valvular surface area in MVP may create differences in wall dynamics. In this respect, a shorter action potential related to increased wall stretch was measured in an experimental model.

It is concluded that, first, the frequency of serious ventricular arrhythmia and changes in repolarization were found to be increased and a significant relationship was observed between these 2 parameters in IMVP. Second, both QpeakTd, especially if the end of the T wave was not evident, and QT were found to be favorable parameters, in addition to other risk factors, in identifying high-risk patients such as those likely to experience serious arrhythmia or sudden death. Third, cases with MVP and associated TVP have an insignificant increase in ventricular arrhythmia over the IMVP cases.

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