Analysis of the QT interval from repeated recordings was made in 56 patients with documented idiopathic mitral valve prolapse (IMVP). The results were compared with a control of 62 healthy volunteers in whom mitral valve prolapse was excluded by both phonocardiography and echocardiography and with two other standard populations, those of Simonson and co-workers and of Ashman. After correction for age, the maximum QT interval of the patients with IMVP exceeded the 97.5 percentile of Simonson population in 51 of 56 patients compared with only three of 62 subjects of the control group. The difference between the QT interval of patients from the upper limits of the predicted mean values of Simonson was significant (P < 0.002). The mean QTc interval in patients with IMVP was 0.48 ± 0.035 second compared with 0.038 ± 0.025 second in the control subjects. The difference between the mean QTc interval in patients with IMVP and the control subjects was significant (P < 0.005). Spontaneous prolongation in the mean QT interval was noted in 43 of 56 patients with IMVP (76.6 percent) compared with only two of 62 control subjects (3 percent). The incidence of episodic arrhythmias was 72 percent in patients with marked QTc prolongation (mean, 0.58 second) compared with 22.6 percent in patients with lesser degree of QTc prolongation (mean, 0.46 second). The results suggest that QT abnormality is common in patients with IMVP and may play an important role in the genesis of cardiac arrhythmia.

Cardiac arrhythmias are common in patients with mitral valve prolapse.1-3 Dangerous rhythm disturbances leading on occasion to sudden death have been reported in patients with this abnormality.4-7 The mechanism of these arrhythmias remains uncertain. An association between mitral valve prolapse and ST, T wave abnormalities with or without QT prolongation has also been reported.1,3,8 The incidence of QT abnormalities in these studies varied widely from 0.6 percent to as high as 64 percent.1,3 The discrepancies in the incidence of QT prolongation may reflect the variety of methods used to measure the QT interval, differences among the studied populations (due to drug therapy or presence of other cardiac abnormalities), or spontaneous variability of the QT interval in some patients. It is known that inhomogeneity in repolarization manifested as QT abnormalities is related to the genesis of arrhythmias.9,10-12 No study specifically designed to evaluate the QT interval and its relationship to arrhythmias in patients with idiopathic mitral valve prolapse (IMVP) has been previously reported. The purpose of the current investigation was to examine the QT interval in a group of patients with IMVP to determine the relation between its abnormality and the occurrence of arrhythmias.

Material and Methods

Patient Selection

Two groups of subjects were included in this study. Group 1 was composed of 56 patients (44 women and 12 men) with mitral valve prolapse, ranging in age from 18 to 73 years (mean, 46 ± 17 years). To limit this group to patients with IMVP, we excluded patients with Marfan’s syndrome, a history of rheumatic fever, and clinical or laboratory evidence of other valvular abnormalities, congenital cardiac defects, or cardiomyopathy. Referral to a cardiologist was primarily due to systolic clicks or murmurs in 21 asymptomatic patients (37.5 percent) or due to symptoms in the remaining 35 patients (62.5 percent). These symptoms included atypical chest pain in all 35, palpitation in 25 (45.5 percent), dyspnea in eight (14 percent), dizziness in seven (10.5 percent), and syncope in two (5 percent).

Phonocardiography demonstrated mid or late systolic clicks in 50 patients, and 29 had, in addition, systolic murmurs. Mitral valve prolapse was visualized by M mode echocardiography in all patients (mid to late systolic type in 51 and holosystolic in five patients). The echocardiographic diagnosis of mitral valve prolapse was accepted only when echoes from both the anterior and posterior leaflets were inscribed throughout the cardiac cycle and came together at the onset and end of systole.13 Diagnostic cardiac catheterization, including left ventriculography and selective coronary angiography, was done in 43 of the 56 patients—for investigation of chest pain in 35, systolic murmurs in five.
and syncope in three. None of the patients had significant coronary artery narrowing. In 31 patients prolapse of the mitral valve was demonstrated in the right anterior oblique view of the left ventricular angiogram as bulging of one or both leaflets of the mitral valve inferiorly and posteriorly beyond the fulcrum of the mitral valve during systole. Serum calcium and monovalent electrolyte concentrations were normal in all patients. Except for three patients receiving digoxin and two receiving propranolol, none of the 56 patients took any drugs during the study that are known to affect the QT interval.

Group 2 was a control group, composed of 62 normal volunteers (34 males and 28 females) ranging in age from 17 to 76 (mean, 34 ± 16) years. Results of auscultation, phonocardiographic recordings done in both the supine and standing positions, and echocardiograms were all normal in group 2.

Recording and Analyzing of ECGs

On three separate days in each patient and normal subjects, a 12-lead ECG followed by a two-minute rhythm strip were recorded (speed, 25 mm/sec) in the supine position after resting for 30 minutes. Sixteen patients had in addition a 24-hour Holter monitor. The QT interval was measured from the onset of the QRS complex to the end of the T wave according to the criteria of Lepeshkin and Surawicz. When the T and U waves were partially fused, the sudden change of slope between them was taken as the end of the T wave. The QT interval was not measured in extrasystolic or postextrasystolic beats. On each ECG, the QT interval and the corresponding RR interval were measured in six to ten consecutive beats in lead 2 or V6 to Vn, whichever showed the most clearly defined ending of the T wave. Their averages in each recording were termed the mean QT interval and RR interval, respectively, and the longest QT interval in these beats was termed the maximal QT interval. Without knowing previous values, two observers independently measured the same QT and RR. These duplicate measurements never differed by more than 0.02 second, and this difference never determined whether the QT interval was considered normal or abnormal. The QTC interval (K of Bazetti) was calculated by dividing the measured QT interval by the square root of the corresponding RR interval. The average for the QTC interval of the three recordings was termed mean QTC and the longest calculated as the maximum QTC. Since the standards for normal QT intervals vary from one report to another, the measured values for the maximum and mean QT interval in groups 1 and 2 were compared with two different normal populations previously reported by Simonson et al and Ashman (linear equation from Simonson et al for QT = 0.2433 - 0.14 RR + 0.003 age SEE ± 0.0164; and from Ashman, QT = k log 10 (RR) + 0.07 k + (0.373, 0.385, 0.380, and 0.390 in young men, young women, old men, and old women, respectively).

Statistical analysis was done with Student’s t test for unpaired data. The standard ECGs with two-minute rhythm strips in all patients and 24-hour or more Holter monitors in 16 patients were also examined for other abnormalities including arrhythmias.

RESULTS

The heart rate ranged from 39 to 105 per minute (mean, 74 ± 12) in group 1 and from 38 to 93 per minute (mean, 68 ± 12.5) in group 2.

After correction for age, the maximal QT interval of patients in group 1 exceeded the 97.5 percentile of Simonson and associates normal population in 51 patients (91 percent) and was at the upper limits of normal values in the remaining five patients. In the control subjects (group 2) the maximal QT interval exceeded the 97.5 percentile of the normal population of Simonson et al in three subjects and was at the upper limits of normal in four after correction for age. Figure 1 shows the maximal QT interval for all the subjects in groups 1 and 2 compared with the normal stand-
ards of Simonson et al. The mean difference between the maximal QT interval in patients with IMVP and the maximal values calculated from the linear equation of Simonson after the correction for age was highly significant (P<0.002).

The mean QTC interval ranged from 0.42 to 0.57 second in group 1 (mean, 0.48 ± 0.032 second) and from 0.33 to 0.47 second in group 2 (mean, 0.38 ± 0.025 second). The difference between mean QTC interval in the two groups was significant (P<0.005). The mean QTC interval exceeded 0.46 second in 36 patients in group 1 (range, 0.47 to 0.57; mean, 0.49 ± 0.024 second) in contrast to only one patient in group 2, in whom it was 0.47 second.

**Constancy of QT Abnormalities**

Prolongation of the mean QT interval (mean QT interval exceeding the 97th percentile of Ashman's standard) was demonstrated in all three ECG recordings in only seven patients with IMVP.
in only two of three recordings in 21 patients (37.5 percent), and in only one of three recordings in another 22 patients (39.2 percent). In six patients (9.5 percent), the mean QT interval did not exceed the 97th percentile of Ashman standards in any of the recordings. Figures 2, 3, and 4 illustrate the variation in the QT interval in lead 2 in two of the patients who were monitored for 24 hours or more. After correction for the changes in heart rate, the QTC still showed variation during monitoring.

In the control group only two subjects showed prolongation of the mean QT interval that was present in two of the recordings.

Analysis of the recordings for other ECG abnormalities showed that in addition to the prolongation of the QT interval there were ST-T-U wave abnormalities in 35 patients with IMVP (62.5 percent). These abnormalities included ST depression in inferior or lateral leads in 28 patients (50 percent), prominence of the U waves (≥1 mm in leads V₅ and V₆) in 23 patients (42 percent), and notching of the T wave in five patients (9 percent). Various dysrhythmias were noted in two-minute rhythm strips or Holter monitor in 25 patients (44.6 percent). Table 1 demonstrates the distribution and types of arrhythmias in patients with IMVP.

In the control group prominent U waves alone were detected in two subjects. Premature ventricular contractions (>6/min) occurred in three subjects, and premature atrial contractions (bigeminy) in one subject.

Relation of QT Prolongation to Incidence of Arrhythmias

Twenty-five patients with IMVP showed a marked degree of QT prolongation in at least three measurements of one of the recordings with the maximum value ranging from 0.51 to 0.62 second (mean, 0.58 ± 0.042 second). Eighteen of these patients (72 percent) had arrhythmias in the form of frequent premature ventricular contractions (eight patients), frequent premature atrial and ventricular contractions in two patients, paroxysmal atrial tachycardia with frequent premature atrial and ventricular contractions in four patients, paroxysmal atrial fibrillation with premature atrial or ventricular contractions in two patients, and recurrent ventricular tachycardia in two patients (Fig 5).

In the remaining 31 patients with IMVP, the maximum QTC interval ranged from 0.42 to 0.5 second (mean, 0.46 ± 0.028). Only seven of these patients (22.6 percent) had arrhythmias in the
form of frequent premature ventricular contractions in two, frequent premature atrial and ventricular contractions in one, paroxysmal atrial tachycardia in two, and atrial fibrillation with premature atrial or ventricular contractions in two patients. The distribution of arrhythmias in relation to QTC interval is also shown in Table 1.

**Table 1—Distribution of Arrhythmias in Relation to QTC Interval in Patients with Idiopathic Mitral Prolapse**

<table>
<thead>
<tr>
<th>Maximum QTC, sec</th>
<th>Total No. of Patients (N=56)</th>
<th>No. of Patients with Arrhythmias (N=25)</th>
<th>Type of Arrhythmia (No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.46</td>
<td>13</td>
<td>3</td>
<td>PVC (2); PAT and PAC (1)</td>
</tr>
<tr>
<td>0.47-0.5</td>
<td>18</td>
<td>4</td>
<td>PVC and PAC (1); PAT, PAC, and PVC (1); AF, PVC, and PAC (2)</td>
</tr>
<tr>
<td>0.51-0.62</td>
<td>25</td>
<td>18</td>
<td>PVC (8); PAC and PVC (2); PAT, PAC, and PVC (4); AF, PAC, and PVC (2); Recurrent VT, PAC, and PVC (2)</td>
</tr>
</tbody>
</table>

*Abbreviations: AF = atrial fibrillation; PVC = premature ventricular contractions; PAC = premature atrial contractions; PAT = paroxysmal atrial tachycardia; and VT = ventricular tachycardia.

**DISCUSSION**

Most postulated mechanisms for the arrhythmias associated with IMVP have been related to the mitral valve or left ventricular abnormalities. Abnormal mitral leaflet motion acting as a mechanical stimulus for generation of ectopic beats as suggested by some workers does not explain the intermittent nature of the arrhythmias. Wit and associates demonstrated muscle fibers in the mitral leaflet of dogs, which, when exposed to stretching or epinephrine, can initiate atrial arrhythmias. This mechanism would be difficult to prove in vivo, however, because circulating catecholamines can induce arrhythmias in many other ways. Left ventricular asynergy, frequently noted on cineangiography in patients with IMVP, does not explain the mechanism of sudden death in some patients. Preexcitation syndromes and bradycardia have also been reported as possible mechanisms for arrhythmias in patients with IMVP. None of our patients has shown ECG evidence of preexcitation or bradyarrhythmias.

This study has revealed a significant degree of QT prolongation in patients with IMVP on repeated ECG recordings. Furthermore, the high incidence of ST-T-U changes in these patients suggest the prevalence of other repolarization abnormalities. It is recognized that measurements of the QT interval are subject to errors resulting from the difficulty in defining the onset of QRS complex and the termination of the T wave. Care was taken in this study to obtain the measurements where the onset of QRS and end of T waves were best defined. The QT interval in the control group in this study was similar to the predicted mean of Simonson et al in Figure 1. This indicates that the QT prolongation noted in our patient with IMVP is not simply due to differences between the measurement techniques. Also, a generalized prolonged measurement of QT interval relative to other workers would displace all measurements upward relative to the predicted mean.

Previous reported incidence of QT prolongation in patients with IMVP varied from as low as 0.6 percent to as high as 64 percent. The QT abnormalities were subject to variations from time to time in our patients. Spontaneous changes in QT duration in patients with IMVP may be one of the explanations for the varying reports on the incidence of QT prolongation.

This study also showed significantly higher incidence of arrhythmias in patients in whom the maximum QTC was greatly prolonged compared with those with lesser degree of prolongation. These findings suggest that QT prolongation may be related to the mechanism of arrhythmias in patients with IMVP similar to that recognized in other delayed repolarization abnormalities. Spontaneous variations in QT duration in this study reflect changes in sympathetic discharge from time.
to time, thus resulting in heterogeneity of ventricular refractoriness and abnormal repolarization. Furthermore, the finding of varying QT duration in our patients and the appearance of numerous multifocal extrasystoles after exercise in patients with IMVP in other studies, in addition to reflecting changes in sympathetic discharge, suggests that such patients may respond abnormally to sympathetic stimuli. Indeed, the role of QT prolongation in producing dangerous arrhythmias and sudden death in patients with IMVP may be comparable to that reported in hereditary QT prolongation syndromes, and sudden infant death syndromes, in which arrhythmias generally occur during periods of prolonged repolarization.

It is concluded, therefore, that abnormalities of the QT interval are more common in patients with IMVP than in normal subjects. It may be necessary to review multiple ECGs to detect this abnormality. We also suggest that repolarization abnormalities may play a role in the genesis of cardiac arrhythmias in patients with IMVP, since patients with the most pronounced QT prolongation have the highest incidence of arrhythmias.

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