Predictive Power of Increased QT Dispersion in Ventricular Extrasystoles and in Sinus Beats for Risk Stratification After Myocardial Infarction

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Background—QT dispersion, commonly measured in sinus beats (QTd-S), can also be calculated in premature ventricular beats (QTd-V). To date, no studies have addressed the relation between these 2 variables.

Methods and Results—In 148 patients with remote myocardial infarction and premature ventricular beats on a routine ECG, QT dispersion, defined as the difference between the maximum and the minimum QT interval across the 12-lead ECG, was calculated separately for the ventricular extrasystole and the preceding sinus beat. In the total group of patients, QTd-V was greater than QTd-S (83 ± 33 versus 74 ± 34 ms, respectively; P = 0.001). During a follow-up period of 35 ± 17 months, arrhythmic events (sustained ventricular tachycardia, ventricular fibrillation, or sudden death) were noted in 30 patients. A QTd-V of ≥100 ms was a stronger univariate marker of arrhythmic events than was a QTd-S of ≥100 ms, and multivariate analysis selected only prolonged QTd-V (hazard ratio 3.81, 95% CI 2.2 to 11.2) and low ejection fraction (hazard ratio 3.05, 95% CI 1.6 to 7.6) as independent predictors of arrhythmic events.

Conclusions—The magnitude of QTd-V was greater than that of QTd-S in the total group of patients. Prolonged QTd-V is associated with a significantly increased risk for arrhythmic events in postinfarction patients, and the prognostic significance of QTd-V exceeds that of QTd-S. (Circulation. 2000;101:1693-1697.)

Key Words: electrocardiography ■ intervals ■ myocardial infarction ■ risk factors

A n interload difference between the maximum and the minimum QT interval in the 12-lead ECG, defined as QT dispersion, may provide a measure of myocardial repolarization inhomogeneity. Increased QT dispersion has been shown to be a predictor of spontaneous malignant ventricular arrhythmias and mortality in patients with remote myocardial infarction. However, a recent publication of Zabel et al showed that QT dispersion analyzed by computer algorithm from digitized data was not a predictive value for arrhythmic events and all-cause mortality in patients after myocardial infarction. A variety of methodological difficulties inherent in the method of assessment of QT dispersion may be responsible for reported contradictory findings. A major difficulty in measuring QT dispersion is the absence of objective criteria for determination of the QT-interval offset in ECG leads with low-amplitude T waves or with T waves merged with U waves. Because of the markedly higher amplitude of T waves in premature ventricular beats, compared with sinus beats, the difficulty in determining the T wave should be encountered less frequently when calculating QT dispersion in premature ventricular beats (QTd-V) than when calculating QT dispersion in sinus beats (QTd-S).

To date, no information comparing QTd-V with QTd-S is available. Therefore, the present study was designed to assess the relation between these 2 variables and to compare the prognostic significance of QTd-V and QTd-S in postinfarction patients with premature ventricular beats on a routine ECG.

Methods

Study Population
The study population consisted of 148 patients after myocardial infarction who exhibited premature ventricular beats on a standard 12-lead ECG and who had been referred to our institution for 24-hour ECG monitoring. The diagnosis of acute myocardial infarction during initial hospitalization required at least 2 of the following criteria: (1) characteristic chest pain lasting ≥20 minutes, (2) elevation in serum creatine kinase to at least twice the upper limit of normal, and (3) typical ECG changes in a postadmission series of ECGs.

Thrombolytic therapy was received by 81 patients (55%) during the acute phase of myocardial infarction. Seventeen patients (11%) underwent delayed PTCA or CABG during their initial hospitalization. β-Blocker treatment was administered to 108 (73%) patients, and angiotensin-converting enzyme inhibitors were administered to 31 (21%) patients at hospital discharge.

Patients treated with class I or III antiarrhythmic drugs at presentation, patients with atrial fibrillation or flutter, complete bundle branch block, or pacemaker rhythm, and patients with unmeasurable QT intervals of sinus beats or ventricular premature beats in >4 ECG leads were not included in the study group. The
clinical characteristics of 148 patients formed the study group of this report are summarized in Table 1.

The indications for 24-hour ECG were to evaluate complaints (syncope, dizziness, palpitation, and angina) or the risk after myocardial infarction. Standard ECGs were recorded 1 to 12 months (5±2 months) after myocardial infarction as a routine examination before 24-hour ECG monitoring.

ECG Analysis
Simultaneous 12-lead ECGs were recorded at a paper speed of 25 mm/s and were assessed at 4-fold enlargement for accurate measurement of QT intervals by the same experienced observer who was blinded to the clinical status of patients and follow-up results. The QT intervals were measured manually as premature ventricular beats and as the last preceding sinus beat; if the QRS complex of ventricular extrasystole merged with the T wave of the preceding sinus beat, the calculation was made on the earlier sinus beat. The end of the T wave was defined as a return to the isoelectric line. When a U wave interrupted the T wave, a tangent was drawn to the steepest descent of the T wave to the isoelectric line. Intersection of this tangent with the isoelectric line was considered as the end of the T wave. If the end of the T wave could not be reliably determined, measurements of the QT interval were not made, and these leads were excluded from the analysis. QT dispersion, defined as the difference between the maximum and the minimum QT intervals, was calculated separately for the ventricular extrasystole and preceding sinus beat. A minimum of 8 leads was required for QTd-V and QTd-S to be calculated. Intraobserver variability (between 2 measurements) and interobserver variability (between 2 observers) in the measurements of QT dispersion were calculated by using 30 randomly selected and duplicated ECGs; the average absolute difference between the 2 measurements was determined.

Follow-Up
Patients included in the study group were followed up after inclusion and were contacted at 6-month intervals throughout the study to determine their clinical status. Occurrence of documented sustained ventricular tachycardia, ventricular fibrillation, or sudden death was considered to be an arrhythmic event. Sustained ventricular tachycardia was defined as tachycardia of >100 bpm, lasting for ≥30 s or associated with hemodynamic compromise. Patients were considered to have died suddenly if death occurred within 1 hour after new or more serious symptoms. Also, patients who died unexpectedly during sleep were considered to have died suddenly. Adverse outcome represented by the arrhythmic event was considered to be a complete observation. Surviving patients were censored on the last day of known follow-up status. Patients were also censored at the date of nonsudden death.

Statistical Analysis
Continuous variables were expressed as mean±SD. Student t test, χ² test, and linear regression analyses were used where appropriate. Differences were taken to be significant at P<0.05.

TABLE 1. Characteristics of Study Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), n (%)</td>
<td>127 (86)</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>61±9</td>
</tr>
<tr>
<td>Anterior myocardial infarction, n (%)</td>
<td>62 (42)</td>
</tr>
<tr>
<td>Inferior myocardial infarction, n (%)</td>
<td>55 (37)</td>
</tr>
<tr>
<td>Multiple myocardial infarctions, n (%)</td>
<td>31 (21)</td>
</tr>
<tr>
<td>&gt;10 PVBs/h on 24-h ECG monitoring, n (%)</td>
<td>139 (94)</td>
</tr>
<tr>
<td>Repetitive PVBs on 24-h ECG monitoring, n (%)</td>
<td>105 (71)</td>
</tr>
<tr>
<td>NSVT on 24-h ECG monitoring, n (%)</td>
<td>61 (41)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%, n (%)</td>
<td>41 (28)</td>
</tr>
</tbody>
</table>

NSVT indicates nonsustained ventricular tachycardia.

The univariate relation of arrhythmic events to variables collected at the baseline examination was assessed by log-rank test. In this analysis, dichotomized descriptors (male; aged ≥60 years; time between myocardial infarction and start of the follow-up <5 months; left ventricular ejection fraction <40%; QTd-S ≥80, ≥90, and ≥100 ms; QTd-V ≥80, ≥90, and ≥100 ms; repetitive ventricular premature beats on ambulatory ECG monitoring; prematurity index of ventricular premature beats ≤1; and right bundle branch block configuration of ventricular premature beats) were represented as a value of 1 if present. In addition, the prognostic value of QTd-V, which was divided into 3 categories (<80 ms, ≥80 and <100 ms, and ≥100 ms), was assessed. Kaplan-Meier curves were used to illustrate the difference in event-free survival between groups.

Cox proportional hazards analysis was applied to extract the independent covariates and to estimate their hazard ratios. Three models were examined by this procedure. In the first model, all variables with at least a trend toward prognostic significance (P<0.1) were entered. In the second model, QTd-S was excluded from the analysis, and in the third model, QTd-V was excluded from the analysis.

Results

QTd-V and QTd-S
The mean number of available ECG leads was 10±1 for the calculation of QTd-S and 11±1 for the calculation of QTd-V (P=0.000). All 12 leads were used in 82 patients (55%) for the measurement of QTd-V and in 51 patients (34%) for the measurement of QTd-S. The average absolute values of intraobserver and interobserver variability of QT dispersion measurements were 11 and 14 ms, respectively, for QTd-S and 9 and 12 ms, respectively, for QTd-V.

In the total group of 148 patients, the mean QTd-V was 83±33 ms, and the mean QTd-S was 74±34 ms (P=0.001). Compared with the values of QTd-S, the values of QTd-V were higher in 92 (62%) of the 148 patients, lower in 46 (31%) of the patients, and identical in 10 (7%) of the patients. There was a weak but significant correlation between measurements of QTd-V and QTd-S (Figure 1). Similarly, in a subgroup of 43 patients for whom all 12 ECG leads were available for analysis of QTd-V and QTd-S, the mean value of QTd-V was greater than mean value of QTd-S (82±27 and 67±31 ms, respectively; P=0.018). Correlation between the values of QTd-V and QTd-S was stronger in this subgroup compared with the total group (r=0.37, P=0.000).

Clinical Outcome
During a mean follow-up period of 35±17 months, 30 patients (20%) met end-point events. Of these patients, 16 died suddenly, 13 had documented sustained ventricular
tachycardia, and 1 patient with ventricular fibrillation was successfully resuscitated at the time of hospital stay. Because of symptomatic complex premature ventricular beats, treatment with antiarrhythmic drugs was used during follow-up (before sudden death or the occurrence of malignant ventricular tachycardia) in 7 patients (23%) in the group with subsequent arrhythmic events and in 21 patients (18%) in the group without subsequent arrhythmic events. Sotalol was administered in 16 patients; amiodarone, in 7 patients; and other antiarrhythmic agents, in 5 patients. The treatment with antiarrhythmic drugs during follow-up was guided by the results of programmed ventricular stimulation in 6 patients and by the results of ambulatory ECG monitoring in 22 patients.

Prognostic Value of QT Dispersion

QTd-V was significantly greater in the group of patients with arrhythmic events than in the group without arrhythmic events (99\(\pm\)28 versus 79\(\pm\)34 ms, respectively; \(P=0.003\)). Similarly, QTd-S was greater in patients with than in patients without arrhythmic events during follow-up (94\(\pm\)37 versus 69\(\pm\)31 ms, respectively; \(P=0.000\)).

The results of univariate analysis performed on 15 evaluated descriptors by use of the log-rank test are shown in Table 2. Values of sensitivity, specificity, and positive and negative predictive accuracy calculated according to a dichotomy point of 100 ms were as follows: 50\%, 80\%, 39\%, and 86\%, respectively, for QTd-S and 67\%, 75\%, 41\%, and 90\%, respectively, for QTd-V. Among patients with QTd-V \(\geq\)100 ms, 41% developed arrhythmic events compared with 10% of those with QTd-V <100 ms; Figure 2 shows the Kaplan-Meier event-free survival curves with QTd-V \(<\)80 ms, QTd-V \(\geq\)80 and <100 ms, and QTd-V \(\geq\)100 ms.

The results of the Cox proportional hazards analyses of 3 models for predicting arrhythmic events are listed in Table 3. Among variables analyzed in the first model and in the second model, only 2 (increased QTd-V and low left ventricular ejection fraction) were independent predictors of arrhythmic events. When QTd-V \(\geq\)100 ms versus QTd-V <80 ms was used instead of QTd-V \(\geq\)100 ms versus QTd-V <100 ms in the first model of the Cox procedure, the value of \(\chi^2\) increased from 31.84 to 33.28. Dispersion of QTd-S reached the significant predictive value only in model 3, in which QTd-V was not analyzed. Model 2 was better than model 3 in predicting arrhythmic events (\(\chi^2=31.44\) [\(P=0.000\)] versus \(\chi^2=20.43\) [\(P=0.000\)], respectively).

Discussion

Relation Between QTd-V and QTd-S

This is the first study to evaluate the relation between QT dispersion measured in sinus beats and in spontaneous premature ventricular beats. The results of the present study indicate that QTd-V is significantly greater than QTd-S. This finding is in accord with the clinical study of Day et al., who have observed significantly greater QT dispersion in ventricular extrasystoles introduced by right ventricular stimulation than in the preceding sinus complexes, regardless of the

Figure 2. Cumulative probability of survival free of arrhythmic events in relation to 3 categories of QTd-V.
coupling interval tested. Our results are also in agreement with animal studies in which dispersion of ventricular recovery time during programmed ventricular stimulation exceeded dispersion during atrial pacing because of the greater contribution of activation time difference during ventricular than atrial stimulation. Thus, shifting activation from simultaneous biventricular activation during sinus rhythm to sequential activation during ventricular premature beats may cause augmentation of QT dispersion measured in spontaneous premature ventricular beats. Also, a plausible explanation for the difference in values of QTd-V and QTd-S could be that the number of leads available for analysis of QTd-V was greater than that for analysis of QTd-S. However, this difference had a limited importance, because values of QTd-V were also greater than values of QTd-S in the subgroup of patients in whom all 12 ECG leads were used for analysis of QTd-V and QTd-S.

**Predictive Value of QT Dispersion**

As in the total population of patients who survived a myocardial infarction, the group of postinfarction patients with premature ventricular beats on a standard ECG is not uniform, and categories of patients with a higher and a lower risk also exist. The identification of patients at increased risk of malignant ventricular arrhythmias is problematic and remains a major management goal. The data of the present study show that measurement of QTd-V may be used for risk stratification in postinfarction patients with premature ventricular beats on a routine ECG. The results of the multivariate analysis indicate that the prognostic significance of QTd-V exceeds that of QTd-S. In predicting arrhythmic events, the sensitivity and positive and negative predictive accuracy were higher for QTd-V ≥100 ms than for QTd-S. However, a high overlapping of the values for QTd-V and QTd-S was observed between patients with and without susceptibility to arrhythmic events, and the positive predictive accuracy of both these measures in predicting arrhythmic events was relatively low at all evaluated dichotomy points. Nevertheless, the value of positive predictive accuracy of QTd-V and QTd-S exceeds that obtained with the use of conventional noninvasive procedures. In the study group of Farrell et al, low left ventricular fraction, reduced heart rate variability, and abnormal signal-averaged ECG had lower values of positive predictive accuracy (10%, 17%, and 17%, respectively) in predicting arrhythmic events after myocardial infarction. Higher values of positive predictive accuracy of QTd-V and QTd-S in the present study may be related to overrepresentation of patients with an increased risk of arrhythmic events. Our study group consisted of patients with premature ventricular beats assessed by a routine ECG. This might lead to the selection of patients with an anatomic substrate for malignant ventricular arrhythmias. This suggestion is probable because the analysis of 24-hour ECG monitoring revealed at least 1 episode of nonsustained ventricular tachycardia in 41% of our patients, and the incidence of arrhythmic events during follow-up was higher in the present study than in other comparable studies.

In contrast to the results of the present study, Zabel et al did not find an association between the occurrence of arrhythmic events in postinfarction patients and increased QTd-S. Zabel et al calculated QTd-S on ECGs that were recorded at hospital discharge, whereas in the present study, QTd-S was measured on ECGs obtained at least 1 month after myocardial infarction. Ventricular remodeling starts soon after myocardial infarction, but any infarct expansion may progress beyond the hospital stay. Remodeling of the infarcted left ventricle and the extent of the final myocardial damage determine the changes in QTd-S. This relation might explain why increased QTd-S measured earlier, at hospital discharge, was not a predictor of arrhythmic events in the study of Zabel et al.

**Study Limitations**

A limitation of the present study is that the sample size was relatively small. This was partly due to the exclusion of patients treated with antiarrhythmic drugs at presentation and of patients who were not eligible for calculation of QTd-S. Standard ECGs were recorded at 25 mm/s, but it was reported that recording at 50 mm/s did not improve the accuracy of the QT measurement because it resulted in obscuring the end of the T wave.

The duration of QT intervals was measured manually. At present, it has not been established that computerized measurements of QT dispersion are more accurate than manual measurements. Recently, Tran et al recommended a man-
ual method for QT-interval measurements as a preferred procedure for QT dispersion studies.

In summary, our data demonstrate that in the total group of patients, QTd-V was greater than QTd-S. Prolonged QTd-V is associated with a significantly increased risk for arrhythmic events, and the prognostic significance of QTd-V exceeds that of QTd-S. Further studies comparing the prognostic implications of QTd-V and QTd-S are warranted to establish the real value of these variables in stratifying risk in patients after myocardial infarction.

References
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