Value of the Corrected QT Interval Dispersion Obtained Exercise Electrocardiography in Determining Remote Vessel Disease in Patients with Healed Q-Wave Myocardial Infarction

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Background: QT and corrected QT dispersion (QTD, QTcD) obtained by using the standard 12-lead ECG is a marker of nonhomogenous ventricular repolarization. QTD obtained from exercise ECG increases the diagnostic reliability of ST-segment changes. The aim of this study was to investigate the diagnostic accuracy of the QTD and QTcD obtained by a 12-lead ECG during the peak exercise in determining remote vessel disease in patients with healed Q-wave MI.

Methods: Eighty patients with healed Q-wave MI (mean age 54 ± 8 years; 71 men, 9 women; 29 anterior; 51 inferior MI) who underwent exercise stress testing and coronary angiography were included in this study. Patients were divided into two groups, with (group I) and without (group II) remote vessel coronary artery disease. During peak exercise, sensitivity, specificity, negative and positive predictive value of the ST-segment depression, and QTcD were compared between both groups. Moreover, the resting and peak exercise ECG parameters were compared between group I and group II.

Results: In coronary angiography, remote vessel disease was detected in 48 patients (group I). In determining remote vessel disease, the sensitivity, specificity, and the negative and positive predictive values of the peak exercise QTcD ≥ 70 ms were significantly higher than those of the peak exercise ST-segment depression (81%, 63%, 69%, and 76% vs 71%, 53%, 55%, and 69%, respectively; $P < 0.01$ for all comparisons). In group I, QTD and QTcD were significantly higher in patients with anterior wall MI than those with inferior wall MI both during the resting and peak exercise ECG. In group II, the resting QTD and QTcD were significantly higher in patients with anterior wall MI than those with inferior wall MI. In patients with anterior wall MI and inferior wall MI, QTD and QTcD significantly increased with exercise in group I.

Conclusion: In patients with healed Q-wave MI, the value of QTcD ≥ 70 ms increases the diagnostic accuracy of the exercise stress testing in determining remote vessel disease.

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QT dispersion; exercise stress testing; remote vessel disease; Q-wave myocardial infarction

QT dispersion (QTD) and corrected QT dispersion (QTcD) obtained by using standard 12-derivation electrocardiography (ECG) is a marker of non-homogenous ventricular repolarization,¹ and known to be related to severe ventricular arrhythmias.² It is reported that QTD increases due to an increase in heterogeneity of ventricular repolariza-

tion caused by transient myocardial ischemia occurring as a result of stress.^{3,4} However, it has been shown that QTD decreases subsequent to successful thrombolysis in acute myocardial infarction (MI).⁵ Recently, it has been reported that QTD obtained from exercise ECG increases the diagnostic reliability of ST-segment changes.^{6,7} QTD is in-

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creased in the chronic phase of MI and in other chronic forms of ischemic artery disease, and there seems to be a trend towards lower values compared with the acute phase of MI, possibly due to the spontaneous dynamics or to revascularization procedures.⁸ Some studies have shown greater QTD in anterior compared to inferior MI,⁹⁻¹¹ and a correlation between QTD in MI and indirect measures of infarct size, like ejection fraction;¹² or the amount of viable myocardium in the infarct region.¹³ In these studies, it has not been reported if the other coronary arteries (noninfarct-related arteries) are responsible for increased QTD in patients with healed Q-wave MI. The authors hypothesized that during the peak exercise, increased QTD and QTcD may result from the ischemia due to remote vessel (noninfarct-related artery) disease in patients with healed Q-wave MI.

METHODS

Patients were excluded from the analysis if they had atrial fibrillation ($n = 4$), bundle branch blocks ($n = 6$), a pacemaker ($n = 1$), and valvar disease ($n = 3$). Ninety-seven patients with healed Q-wave MI were included in the study. Of these patients, 17 had developed postinfarct angina, and coronary angiography was performed without exercise stress testing. Therefore, they were excluded from the study. The remaining 80 patients (mean age 54 ± 8 years; 71 men, 9 women; 29 anterior, 51 inferior) who underwent exercise stress testing and coronary angiography 1 month after MI were included in this study. Q-wave inferior or anterior wall MI was diagnosed by the history of typical chest pain lasting > 30 minutes, and evolving characteristic ECG abnormalities, including a Q wave wider than 40 ms, and greater than 1/4 of the QRS amplitude or QS pattern in inferior wall leads (II, III, aVF) (for inferior wall MI) or the same changes in at least two anterior wall leads (V_{1-6}) (for anterior wall MI). All patients were given beta-blocker, angiotensin converting enzyme inhibitor, aspirin, and cholesterol lowering therapies. Sixty-four patients were also given nitrate therapy along with these therapies. All patients had symptom-limited exercise test using the Bruce protocol.¹⁴ Twelve-lead ECG recordings were taken before exercise, during exercise with 3-minute intervals, peak exercise, and recovery period. Two independent observers determined the ST-segment level, and inconsistencies were removed by consensus. The ST-

segment level was measured relative to the PR segment since the U-P segment usually is unclear during exercise. The horizontal or downsloping ST-segment depression ≥ 1 mm of the J point measured from the PR junction, with a relatively flat ST-segment slope depressed ≥ 1 mm, 60 ms after the J point in the three consecutive beats on two or more derivations with a stable baseline was considered to be an abnormal response and the test was accepted as positive. The interval from the beginning of QRS complex to the point where the T wave returns to the isoelectric line was measured as the QT interval manually by X2 magnifying glass on rest and peak exercise ECG, including as many derivations as possible (at least nine derivations). When the U or P wave was confused, the point where the descending arm of the T wave crossed the P or U wave was considered as the end of the T wave. Each measurement was obtained by taking the average of three consecutive beats. When the end of the T wave could not be identified with certainty, because of a T-wave amplitude < 0.05 mV and baseline wandering or artefact, that lead was excluded from the analysis. The QT interval was corrected using Bazett's equation¹⁵ ($QTc = QT/\text{square root of RR in seconds}$). Differences between the highest and lowest QT and QTc intervals on rest and exercise ECG were found as QTD and QTcD. Two observers who were unaware of the clinical and angiographic findings of the patients did measurements of QT intervals.

Coronary Angiography

All patients underwent coronary angiography on multiple projections using the Judkins technique, and left ventriculography on the left and right oblique positions within 3 days following the exercise test. Two observers evaluated the coronary angiograms and left ventriculograms. Total or subtotal occlusion of the coronary artery supplying to the asynergic field in the left ventriculography, and arteriographic features presenting thrombosis or dissected plaque were accepted as the defining features for the infarct-related artery. The presence of $\geq 50\%$ narrowing in major epicardial coronary arteries excluding infarct-related arteries indicated remote vessel coronary artery disease. Patients were divided into two groups, with (group I) and without (group II) remote vessel coronary artery disease.

Table 1. Baseline Electrocardiographic and Clinical Characteristics of the Patients in Groups I and II

	Group I (n = 48)	Group II (n = 32)
Age (year)	55 ± 8	52 ± 8
Female/Male (n)	5/34	4/37
BMI (kg/m ²)	26 ± 4	26 ± 3
Heart Rate (beats/min)	85 ± 12	87 ± 12
BP (Systolic/Diastolic mm Hg)	132 ± 21/84 ± 11	133 ± 17/84 ± 10
LVEF (%)	48 ± 8	48 ± 7
QT max (ms)	363 ± 26	359 ± 29
QT min (ms)	322 ± 26	316 ± 28
QTD (ms)	42 ± 11	43 ± 15
QTc max (ms)	431 ± 28	429 ± 25
QTc min (ms)	382 ± 29	378 ± 29
QTcD (ms)	50 ± 14	51 ± 17

BMI = body mass index; BP = blood pressure; LVEF = left ventricular ejection fraction; QT max = maximum QT interval; QT min = minimum QT interval; QTD = QT dispersion; QTc max = maximum corrected QT interval; QTc min = minimum corrected QT interval; QTcD = corrected QT dispersion.

Statistical Analysis

All data were expressed as mean ± SD. Independent Samples *t*-test was used to detect the significant differences between groups. A *P* value < 0.05 was considered as a significant difference. According to the cut-off values determined considering the lower limit of 95% confidence intervals, exercise QTcD values were compared with the level of exercise ST-segment depression based on angiographic data, and its sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) to determine the remote vessel coronary artery disease were calculated. In the whole study population, QTcD measurements were repeated by the same and another observer unaware of the clinical and angiographic findings, and intra- and interobserver agreement were assessed by linear regression with Bland-Altman analysis¹⁶ and then relative errors were calculated. The Statistical Package for the Social Sciences software package (version 8.0) (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical calculations.

RESULTS

Patients were divided into two groups as the patients with (group I) and without (group II) remote vessel disease. In coronary angiography, remote vessel disease was detected in 48 patients (group I). Of these, 13 had anterior wall MI, while 35 patients had inferior wall MI. The remaining 32 patients had Q-wave MI without remote vessel disease (group II). In patients with anterior wall MI

(n = 29), all infarct-related arteries were the left anterior descending coronary artery, and in patients with inferior wall MI (n = 51), 40 and 11 of the infarct-related arteries were the right coronary artery or circumflex coronary artery, respectively.

The baseline ECG and clinical characteristics of the patients between group I and group II are listed in Table 1. Age, female to male ratio, body mass index, heart rate, systolic and diastolic blood pressure, left ventricular ejection fraction, QT maximum, QT minimum, QTD, QTc maximum, QTc minimum, and QTcD were similar in both groups. During peak exercise systolic and diastolic blood pressure, exercise duration, metabolic equivalent (MET) value, QT maximum, QT minimum, and QTc maximum were similar, whereas heart rate and QTc minimum were significantly lower in group I than group II (Table 2).

In determining remote vessel disease, the sensitivity, specificity, and the negative and positive predictive values of the peak exercise QTcD ≥ 70 ms were 81% (39/48), 63% (20/32), 69% (20/29), and 76% (39/51), whereas the sensitivity, specificity, and the negative and positive predictive values of the peak exercise ST-segment depression were 71% (34/48), 53% (17/32), 55% (17/31), and 69% (34/49), respectively. The values of QTcD ≥ 70 ms were significantly higher than those of the peak exercise ST-segment depression (*P* < 0.01 for all comparisons) (Table 3). In group I, QTD and QTcD were significantly higher in patients with anterior wall MI than those with inferior wall MI during resting and peak exercise ECG (Table 4). When

Table 2. Comparison of Exercise Electrocardiographic and Clinical Characteristics of the Patients Between Groups I and II

	Group I (n = 48)	Group II (n = 32)
Heart rate (beats/min)	147 ± 17*	155 ± 17
BP (systolic/diastolic mmHg)	170 ± 24/89 ± 10	168 ± 23/87 ± 11
Exercise time (min)	7 ± 2.4	8 ± 3.1
Exercise METs	8.3 ± 2.5	9.1 ± 3.1
QT max (ms)	287 ± 22	278 ± 22
QT min (ms)	232 ± 22	235 ± 24
QTD (ms)	56 ± 13#	43 ± 17
QTc max (ms)	448 ± 20	445 ± 22
QTc min (ms)	361 ± 25*	376 ± 27
QTcD (ms)	87 ± 20#	69 ± 28

BP = blood pressure; QT max = maximum QT interval; QT min = minimum QT interval; QTD = QT dispersion; QTc max = maximum corrected QT interval; QTc min = minimum corrected QT interval; QTcD = corrected QT dispersion; * P < 0.05 versus group II; # P < 0.001 versus group II.

group II patients were evaluated according to the localization of MI, the resting QTD and QTcD were significantly higher in patients with anterior wall MI than those with inferior wall MI, while they were similar during peak exercise (Table 5). In group I, both in patients with anterior wall MI and

inferior wall MI, QTD and QTcD significantly increased with exercise (66 ± 12 vs 50 ± 14 ms, $P < 0.001$; 102 ± 19 vs 58 ± 18 ms, $P < 0.001$; 52 ± 11 vs 39 ± 9 ms, $P < 0.001$; 80 ± 17 vs 47 ± 10 ms, $P < 0.001$, respectively). Furthermore, QTcD significantly increased with exercise in patients with anterior and inferior wall MI in group II (76 ± 30 vs 58 ± 14 ms, $P < 0.001$; 63 ± 25 vs 44 ± 18 ms, $P < 0.001$, respectively), but QTD did not change.

The number of measurable leads were 10.5 ± 0.7 (9-12) and 10.2 ± 0.8 (9-12) in group I and II, respectively ($P > 0.05$). The relative errors for intra- and interobserver variabilities were 3.5% and 4.7% in QTcD measurements during peak exercise ECG (Figs. 1 and 2), and the mean SD of the absolute values of measurements errors in milliseconds for intra- and interobserver were 3.3 and 4.9, respectively.

Table 3. Comparison of Diagnostic Accuracy Between Exercise QTcD ≥ 70 ms and ST-Segment Depression

	QTcD ≥ 70 ms	ST-Segment Depression
Sensitivity (%)	81*	71
Specificity (%)	63*	53
Negative predictive value (%)	69*	55
Positive predictive value (%)	76*	69

QTcD = corrected QT dispersion, * P < 0.01 versus ST-segment depression.

Table 4. Comparison of the QTD and QTcD Parameters Between Patients with Anterior and Inferior wall MI in Group I

	Anterior Wall MI (n = 13)	Inferior Wall MI (n = 35)
Resting QTD (ms)	50 ± 14*	39 ± 9
Resting QTcD (ms)	58 ± 18*	47 ± 10
Exercise QTD (ms)	66 ± 12#	52 ± 11
Exercise QTcD (ms)	102 ± 19#	80 ± 17

MI = myocardial infarction; QTD = QT dispersion; QTcD = corrected QT dispersion; * P < 0.05 versus patients with inferior wall MI; # P < 0.001 versus patients with inferior wall MI.

Table 5. Comparison of the QTD and QTcD Parameters Between Patients with Anterior and Inferior Wall MI in Group II

	Anterior Wall MI (n = 16)	Inferior Wall MI (n = 16)
Resting QTD (ms)	49 ± 12*	38 ± 15
Resting QTcD (ms)	58 ± 14*	44 ± 18
Exercise QTD (ms)	47 ± 17	40 ± 17
Exercise QTcD (ms)	76 ± 30	63 ± 25

MI = myocardial infarction; QTD = QT dispersion; QTcD = corrected QT dispersion; * P < 0.05 versus patients with inferior wall MI.

Figure 1. Bland-Altman plot of intraobserver reproducibility of the corrected QT dispersion measured during peak exercise between two separate measurements.

DISCUSSION

It has recently been reported that increased QTcD seen on standard 12-lead ECGs reflects transient myocardial ischemia. QTcD immediately after exercise is useful for detecting significant coronary artery disease in patients who do not have exercise-induced chest pain or significant ST-segment depression.⁷ Also, it is a clinically useful indicator of significant coronary stenosis independent of the patient's sex or the presence or absence of exercise-induced significant ST-segment depression.¹⁷ Its

Figure 2. Bland-Altman plot of interobserver reproducibility of the corrected QT dispersion measured during peak exercise between two separate measurements.

sensitivity and specificity are similar in men and women (sensitivity 75%, 77% and specificity 85%, 88%, respectively), but more sensitive in men and more specific in women compared to exercise-induced significant ST-segment depression as an indicator of significant coronary stenosis during peak exercise.¹⁷ Similarly, it has been shown that the measurement of QTcD immediately after exercise (abnormal ≥ 70 ms; normal < 70 ms) improved the sensitivity, specificity, and accuracy of conventional ST-segment depression criteria for detecting viable myocardium in the infarct area in patients with healed Q-wave anterior wall MI from 48%, 64%, and 56% to 78%, 82%, and 80%, respectively.¹⁸ It has been reported that an increase in QTcD $> 30\%$ predicted myocardial viability with a high sensitivity and specificity during a low dose dobutamine stress echocardiography in patients with old MI, and a greater increase in QTcD% was seen in patients with viable myocardium than patients without.¹⁹ Parallel to the above data, in patients with healed anterior wall MI without residual ischemia QTcD and QTcD did not change but these parameters increased in those with residual ischemia immediately after exercise; therefore, the idea that residual ischemia plays a key role in the increase in QTcD after exercise was expressed.²⁰

In the present study, the authors observed that QTcD increased with exercise in all patients (groups I and II). In addition, they observed that QTcD and QTcD are similar between the two groups during resting ECG, although these parameters are higher in group I than group II during peak exercise. These results suggest that the increase of QTcD and QTcD are strongly related to ischemia and its degree. Apart from these, in group I and group II during resting ECG and in group I during peak exercise, QTcD and QTcD were higher in patients with anterior wall MI than those with inferior wall MI, although in group II these parameters were similar during peak exercise between patients with anterior wall and inferior wall MI. In both these, QTcD was different, but the difference was not reached statistically significance. Moreover, the differences between the ST-segment changes and QTcD were evaluated in patients with and without remote vessel disease. In determining remote vessel disease, the sensitivity, specificity, and the negative and positive predictive values of the peak exercise QTcD ≥ 70 ms were significantly higher than those of the peak exercise ST-segment depression. Based on the results, the value of

QTcD ≥ 70 increases the diagnostic accuracy of the exercise testing in the patients with remote vessel disease with healed Q-wave MI.

The mechanism for such changes in QTD could not be explained completely, but it appears likely that localized wall-motion abnormalities and increased inhomogeneity of the ventricular repolarization due to myocardial ischemia are responsible for the increased QTD. The increase in QTD caused by ischemia is thought to be, in part, a result from impaired response of ischemic myocardium to catecholamines or to an abnormal flux of the calcium ion.²¹ As known, the end of T-wave ECG indicates the beginning of mechanical diastole. Diastolic functions of the heart are impaired depending on the relaxation abnormalities occurring first after myocardial ischemia. One of the indicators of diastolic dysfunction may also be the increase in QT and QTD in turn. This hypothesis explains why the diagnostic value of QTD is higher than that of ST-segment depression appearing in later phases after ischemia formation.

Limitations

The analysis of QTD is sometimes difficult because in some cases the end of the T wave cannot be reliably determined and may lead to spurious calculations of the QTD.

Moreover, inability to determine the T wave more precisely and thus failure to measure correctly, affects the calculations of QTD, especially at fast heart rates.²² However, the authors used the Bland-Altman plot to reduce this limitation as much as possible.

CONCLUSION

In patients with healed Q-wave MI, the value of QTcD ≥ 70 ms increases the diagnostic accuracy of exercise stress testing in determining remote vessel disease.

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