New Parameters in the Interpretation of Exercise Testing in Women: QTc Dispersion and QT Dispersion Ratio Difference

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Summary

Background: It has been reported that the increase of QT dispersion (QTD) that occurs due to increased inhomogeneity of the ventricular repolarization because of transient ischemia obtained by standard 12-lead electrocardiogram (ECG), the changes during exercise, and the differences between exercise and rest increase the accuracy of exercise test in the diagnosis of coronary artery disease (CAD).

Hypothesis: This study was designed to investigate the value of QTD parameters, which are reported to increase the diagnostic accuracy of exercise test in women.

Methods: Ninety-seven women who had undergone coronary angiography and exercise test were evaluated for diagnosis of chest pain. QT dispersion was calculated using the measurements of the highest and lowest values of QT interval obtained by ECG during peak exercise. The QTc using Bazett's equation, and the QTD ratio (QTDR) using QT/RR were calculated, and QTcD and QTD ratios were obtained. The difference between QTcD and QTDR was determined by extracting the rest values from the exercise values.

Results: The groups with normal coronaries (n = 48), single-vessel CAD (n = 24), and multivessel CAD (n = 25) were compared. The obtained QTD parameters at peak exercise and their differences between exercise and rest were found to be significantly increased in patients with CAD ($p < 0.001$).

Furthermore, these parameters were found to be higher in the patients with multivessel CAD than in those with single-vessel disease ($p < 0.05$). With the parameters QTcD > 60 ms and QTDR $> 10\%$, greater sensitivity and specificity were obtained compared with ST-segment depression. The highest diagnostic accuracy was obtained with the QTD parameters calculated from the differences between rest and exercise values. The diagnostic accuracy of the difference of QTcD > 15 ms and the difference of QTDR $> 5\%$ was relatively higher than the other parameters (sensitivity, specificity, and negative and positive predictor values are 84, 88, 84, 87% and 84, 96, 85, 95%, respectively).

Conclusion: The use of QTD parameters as variables of ECG, which is easily obtainable in the evaluation of exercise ECG in women, increases the diagnostic accuracy of the exercise test. In addition, the evaluation of QTD variables may provide information about the incidence of CAD.

Key words: electrocardiography, exercise, QT dispersion, women

Introduction

Prevalence, clinical presentation, and performance obtained by methods of diagnosing coronary artery disease (CAD) are different for men and women.¹ It is accepted that the data from studies regarding diagnosis and management of CAD, mainly performed on male patients, cannot be totally adapted to women.^{2,3} Standard exercise electrocardiography (ECG), the least expensive and most widely used method of diagnosing ischemic heart diseases, gives less reliable results in women.^{3–5}

QT and QTc dispersion (QTD, QTcD) obtained by using standard 12-lead ECG is a marker of nonhomogeneous ventricular repolarization⁶ and is known to be related to severe ventricular arrhythmias.⁷ It is reported that QTD increases because of an increase in heterogeneity of ventricular repolarization caused by transient myocardial ischemia occurring as a result of stress.^{8,9} On the other hand, it has been shown that

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QTD decreases subsequent to successful thrombolysis in acute myocardial infarction.¹⁰ Recently, it has been reported that QTD obtained by exercise ECG increases the diagnostic reliability of ST-segment changes.^{11, 12} We planned this study to test whether, in addition to QTD and QTcD, the QT dispersion ratio (QTDR), which is shown to be more specific than QTcD for ventricular arrhythmias,¹³ and differences between exercise and rest QTcD and QTDR, which are first evaluated, increase the diagnostic accuracy of ECG in women.

Methods

In all, 97 consecutive women (mean age 55 ± 9 years) admitted to our hospital because of chest pain and who were undergoing coronary angiography but had no previous myocardial infarction, either clinically or electrocardiographically, were included in the study. Patients were excluded from the analysis if they had atrial fibrillation, bundle-branch blocks, pacemakers, or were treated with any drugs known to affect the QT interval. Before coronary angiography, all patients underwent a symptom-limited exercise test, using the Bruce protocol.¹⁴ Twelve-lead ECG recordings were taken before exercise, every 3 min during exercise, during peak exercise, and during the recovery period. Two independent observers determined the ST-segment level, and inconsistencies were resolved by consensus. The ST-segment level was measured relative to the PR segment since the U-P segment usually is unclear during exercise. Horizontal or downsloping ST-segment depression of ≥ 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 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.¹⁵ Considering all derivations, ST-segment depressions of ≥ 1 mm were summed. The interval from the beginning of the QRS complex to the point at which the T wave returned to the isoelectric line was manually measured as the QT interval using a $2 \times$ magnifying glass on rest and peak exercise ECG, including as many derivations as possible. When the U or P wave was confused, the point at which the descending arm of the T wave crossed the P or U wave was considered 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 T-wave amplitude < 0.05 mV and baseline wandering or artifact, that lead was excluded from the analysis. The QT interval was corrected using Bazett's equation¹⁶ ($QTc = QT/\text{square root of } RR \text{ in s}$). Differences between the highest and lowest QT and QTc intervals on rest and exercise ECG were found as QTD and QTcD. The QTDR was obtained by the formula of $(QTD/RR\text{-ms}) \times 100$.¹³ An observer blinded to the clinical and angiographic findings for the patients measured the QT intervals. By taking the differences between QTD, QTcD, and QTDR at rest and at peak exercise, the QTD difference (QTDD), QTcD difference (QTcDD), and QTDR difference (QTDRD) were obtained.

Coronary Angiography

All patients underwent coronary angiography on multiple projections by the Judkins technique 2 weeks following the exercise test. Two observers evaluated coronary angiograms, and the presence of $\geq 50\%$ narrowing in the major epicardial coronary arteries indicated CAD.

Statistical Analysis

All data were expressed as mean $\pm$ standard deviation (SD), with a 95% confidence interval (CI). The Bonferroni test was used to detect significant differences between groups, and analysis of variance was used together with post hoc comparisons. A significant difference was thought to be present if $p < 0.05$. According to the cut-off values determined, considering the lower limit of 95% (CI) in the patients with single-vessel disease, the exercise QTcD, QTDR, QTcDD, and QTDRD values were compared with angiographic data. Their sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) to determine CAD were calculated. In 26 randomized patients, QTD measurements were repeated by another observer blinded to the clinical and angiographic findings, and interobserver agreement was assessed by linear regression by Bland-Altman analysis¹⁷ and then the repeatability coefficient was calculated. The SPSS package (Statistical Package for Social Sciences, SPSS, Inc., Chicago, Ill., USA) (version 8.0) was used to perform all statistical calculations.

Results

Patients were evaluated by dividing them into three groups according to the results of coronary angiography: Patients with no determined CAD ($n = 48$, mean age 54 ± 8 years); those with single-vessel disease ($n = 24$, mean age 54 ± 7 years); and those with multivessel disease ($n = 25$, mean age 58 ± 6 years). Of the patients with single-vessel disease, 18 had left anterior descending CAD, 2 had circumflex CAD, and 4 had right CAD. Of the patients with multivessel disease, 21 had left anterior descending CAD, 19 had circumflex CAD, and 14 had right CAD. Ages, body mass indices, rest and peak exercise systolic and diastolic blood pressures, and peak exercise double product were similar in the three groups (Table I). The QTD measurements were obtained from 10.97 ± 0.76 (9–12) and 10.52 ± 0.91 (9–12) derivations on rest and exercise, respectively. The difference of the QTD measurements between observers as $\pm$ SD was 3.1 ± 9.2 ms ($p = 0.1$) and the repeatability coefficient was 0.78 ($p = 0.001$) at rest; they were 2.3 ± 9.7 ms ($p = 0.24$) and 0.83 ($p < 0.001$), respectively, at peak exercise. The average of absolute differences between measurements by the two observers was 7.7 ms at rest and 8.8 ms on exercise.

The totals of the obtained ST-segment depressions during exercise, and the exercise QTD, QTcD, and QTDR, and

TABLE I Characteristics of groups

	Normal (n = 48)	SVD (n = 24)	MVD (n = 25)
Age (years)	54 ± 8	54 ± 7	58 ± 6
BMI (kg/m ²)	27.3 ± 2.3	27.3 ± 3	27.5 ± 2.8
HR (beats/min)	85 ± 20	83 ± 20	85 ± 18
SBP (mmHg)	132 ± 19	141 ± 11	135 ± 17
DBP (mmHg)	83 ± 10	87 ± 9	84 ± 9
Exercise time (min)	6.9 ± 2.4	6.1 ± 2.3	6.2 ± 2.6
Peak exercise HR (beats/min)	157 ± 15	158 ± 15	152 ± 14
Peak exercise SBP (mmHg)	176 ± 11	180 ± 24	177 ± 22
Peak exercise DBP (mmHg)	93 ± 7	97 ± 7	96 ± 12
Double product ^a	276 ± 32	283 ± 50	271 ± 42

For whole parameters $p > 0.05$.

^a mmHg × (beats/min) × 10⁻².

Abbreviations: HR = heart rate, BMI = body-mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, SVD = single vessel disease, MVD = multivessel disease.

QTDD, QTcDD, and QTDRD values were different for each group (Table II). While the measurements for QTD and QTcD at rest in the patients with multivessel disease were found to be higher than those of the patients with no CAD, there was no difference between the other groups (Table II).

Diagnostic Value of ST-Segment Depression

There was ST-segment depression of ≥ 1 mm in 30 of 49 patients with CAD, but the exercise ECG was evaluated as

TABLE II Comparison of electrocardiographic findings in the groups

	Normal (I) (n = 48)	SVD (II) (n = 24)	MVD (III) (n = 25)	p Values
ST (mm)	-4.4 ± 4	-6.8 ± 4.8	-7.9 ± 5.3	NS ^{a, c} /0.015 ^b
QTDr (ms)	31 ± 12	35 ± 18	40 ± 14	NS ^{a, c} /0.039 ^b
QTDe (ms)	23 ± 9	44 ± 17	60 ± 15	<0.001 ^{a, b, c}
QTcDr (ms)	38 ± 17	42 ± 20	49 ± 16	NS ^{a, c} /0.042 ^b
QTcDe (ms)	38 ± 15	72 ± 28	95 ± 21	<0.001 ^{a, b, c}
QTDRr (%)	4.9 ± 2.3	5.1 ± 2.4	6.2 ± 2.1	NS ^{a, b, c}
QTDRc (%)	6.1 ± 2.5	11.6 ± 4.5	15 ± 3.2	<0.001 ^{a, b, c}
QTDD (ms)	-7.2 ± 11	9.6 ± 17.6	20.2 ± 8.8	NS ^{a, c} /0.012 ^b
QTcDD (ms)	-0.6 ± 16	29.6 ± 28	45.6 ± 13.9	NS ^{a, c} /0.014 ^b
QTDRD (%)	1.3 ± 2.6	6.4 ± 4.7	8.8 ± 2.2	NS ^{a, c} /0.034 ^b

^a Comparing groups I–II.

^b Comparing groups I–III.

^c Comparing groups II–III.

Abbreviations: QTDr = rest QT dispersion, QTDe = exercise QT dispersion, QTcDr = rest QTc dispersion, QTcDe = exercise QTc dispersion, QTDRr = rest QT dispersion ratio, QTDRc = exercise QT dispersion ratio, QTDD = rest-exercise QT dispersion difference, QTcDD = rest-exercise QTc dispersion difference, QTDRD = rest-exercise QT dispersion ratio difference, NS = not significant.

normal in just 28 of 48 patients without CAD (sensitivity 61%, specificity 58%, NPV 60%, and PPV 60%).

Diagnostic Value of Exercise QTD Parameters

It was determined that exercise QTD and QTcD were predominantly high in the patients with CAD and even higher in the patients with multivessel disease (Table II). In single-vessel disease, exercise QTD was 44 ± 18 ms (95% CI, 37–52 ms), QTcD was 72 ± 28 ms (95% CI, 60–83 ms), and QTDR was $11.6 \pm 4.5\%$ (95% CI, 9.6–13.4%) (Fig. 1). According to this, the lower limit of the 95% CI for exercise QTD and QTcD was taken as the cut-off value. Although the specificity of QTD > 40 ms to determine CAD is high, its sensitivity was low (sensitivity 67%, specificity 94%, NPV 74%, PPV 92%). When we investigated the diagnostic value of QTcD > 60 ms for CAD, we found that it diagnosed 38 of 49 patients with CAD, whereas QTcD was found as ≤ 60 ms in 43 of 48 patients without CAD (sensitivity 78%, specificity 90%, NPV 80%, and PPV 88%). Sensitivity and specificity rates of QTcD > 60 ms did not change when it was accompanied by ST-segment depression (75 and 89%, respectively). Parallel to the exercise QTDR of 11.6 ± 4.5 (95% CI, 9.6 ± 13.4%) in

FIG. 1 The values in 95% confidence interval (CI) of QTc dispersion (QTcD) (A) and QTc dispersion ratio (QTDR) (B) with exercise electrocardiography in the three groups (QTcD: normal: 34–43 ms; single-vessel disease [SVD]: 60–83 ms; multivessel disease [MVD]: 86–104 ms; QTDR: normal: 5.4–6.9%; SVD: 9.6–13.4%; MVD: 13.6–16.3%).

TABLE III Sensitivity, specificity and predictive values of different parameters on exercise test

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
ST $\geq$ 1 mm	61	58	60	60
QTcDe > 60 ms	78	90	80	88
QTDR $>$ % 10	78	92	80	91
QTcDD > 15 ms	84	88	84	87
QTDRD > 5%	84	96	85	95

Abbreviations: NPV = negative predictive value, PPV = positive predictive value. Other abbreviations as in Table II.

patients with single-vessel disease, QTDR > 10% was taken as the positive criterion, and sensitivity, specificity, NPV, and PPV were found to be 78, 92, 80, and 91%, respectively (Table III). Diagnostic value did not increase when evaluated together with ST-segment depression (sensitivity 77%, specificity 93%).

Diagnostic Value of QTcDD and QTDRD

A prominent increase in QTcDD and QTDRD was observed in the patients with CAD and was found to be even higher in patients with multivessel disease than in those with single-vessel disease (Table II). QTcDD was found to be 29.6 ± 28 ms (95% CI, 18–41 ms, Fig. 2) in patients with single-vessel disease. When 15 ms was taken as the cut-off value, QTcDD > 15 ms diagnosed 41 of 49 patients with CAD and QTcDD $\leq$ 15 ms diagnosed in 42 of 48 patients with normal coronary arteries (sensitivity 84%, specificity 88%, NPV 84%, PPV 87%). In addition to QTDRD being higher in patients with CAD than in those with normal coronary arteries, it was prominently higher in patients with multivessel disease than in those with single-vessel disease (Table II). When the cut-off value for QTDRD, which was found to be $6.4 \pm 4.7\%$ (95% CI, 4.4–8.4, Fig. 2) in single-vessel disease was taken as 5%, QTDRD > 5% diagnosed 41 of 49 patients with CAD and was $\leq$ 5% in 46 of 48 normal patients (sensitivity 84%, specificity 96%, NPV 85%, PPV 95%) (Table III).

Discussion

It is difficult to diagnose CAD in women suffering from chest pain. In recent meta-analyses, it was found that ST-segment depression in women had significantly lower specificity rates than those in men.¹⁸ The false-positive rate in women depends on disease prevalence and ranges from 25% in patients with typical angina to 50% in patients with atypical chest pain.¹⁹ Several mechanisms have been suggested to explain the high false-positive rate of ST-segment depression in women, including the fact that estrogen has a chemical structure similar to digitalis. It has been suggested that this may be partially responsible for the high prevalence of false-positive test results in women.¹¹ Some new criteria lessening this limitation of the

Fig. 2 The values in 95% confidence interval (CI) of QTc dispersion difference (QTcDD) (A) and QT dispersion ratio difference (QTDRD) (B) between exercise and rest electrocardiography in the three groups (QTcDD: normal: -5–4 ms; SVD: 18–41 ms; MVD: 40–51 ms; QTDRD: normal: 0.5–2%; SVD: 4.4–8.4%; MVD: 8–9.7%). Abbreviations as in Figure 1.

exercise test have been reported.^{1, 12, 20, 21} Among these, the Duke treadmill score, based on the scoring of classical ST-segment deviation, exercise duration, and exercise-induced chest pain, has been reported to increase the diagnostic value of the exercise test in women.¹ In studies evaluating the relationship between QTD and transient myocardial ischemia in patients without previous myocardial infarction, it was shown that QTD increased in response to the transient ischemia.^{8, 9, 11, 12} Likewise, whether QTD measurements indicating increased inhomogeneity of the ventricular repolarization phase due to myocardial ischemia have increased the diagnostic value of the exercise test in women in whom the criteria of ST-segment changes are not enough for a diagnosis has not been well investigated. In a unique study¹¹ evaluating in detail the QTD and QTcD values measured at peak exercise in women, higher diagnostic values than those for ST-segment depression have been reported. While sensitivity of QTcD > 70 ms to diagnose CAD was 75%, when QTD parameters were considered together with ST-segment depression and reversible defects on scintigraphy, it was observed that the specificity rate increased but the sensitivity rate decreased.¹¹ The extent of CAD was not evaluated in this study.

In our study, in addition to QTD parameters, we also investigated the value of QTDR, which was found superior to QTcD in the diagnosis of ventricular fibrillation, and QTcD and QTDR differences at rest and on exercise to diagnose CAD and predict its extent in women.¹³ Since up to now no absolute cut-off value has been obtained from the studies, we determined the cut-off value according to the lowest values in 95% CI from the group of patients with the least extensive CAD. Thus, exercise QTD, QTcD, QTDR, QTcDD, and QTDRD cut-off values were calculated as 40 ms, 60 ms, 10%, 15 ms, and 5%, respectively. Although specificity of exercise QTD > 40 ms was high, its sensitivity was found to be low (94–67%). On the other hand, we obtained higher sensitivity, specificity, and predictive values from other parameters. According to the cut-off value of 70 ms in the study performed by Stoletniy and Pai,¹¹ sensitivity was slightly lower (85 vs. 78%) but specificity was higher (74 vs. 90%) than the results obtained by the cut-off value we determined for QTD and QTcD. When we took the cut-off value as 70 ms, sensitivity and specificity were found to be 68 and 92%, respectively. In addition, we obtained similar diagnostic values with QTDR, which was first evaluated as a sign of transient ischemia and obtained by the ratio of QT/RR cycle length rather than from the standard QT correction. Evaluation of all the parameters together with ST-segment depression provided no additional gain.

The QTDRD and QTcDD, calculated by determining the difference between rest and exercise QTD values, were found predominantly high in patients with CAD.^{9, 12} Also, the difference between rest and stress QTD due to pacing has been reported to correlate with lactate production of the heart;⁹ however, its significance in the diagnosis of CAD has not been evaluated. When the criteria of QTcDD > 15 ms was taken into account, the specificity rate obtained by QTcD did not change significantly but the sensitivity rate increased (from 78 to 84%). Predictive values also were found to be higher (NPV 84%, PPV 87%). The diagnostic value of QTDRD > 5% was investigated, and sensitivity, specificity, and predictive values were found to be higher (sensitivity 84%, specificity 96%, NPV 85%, PPV 95%).

Relationship of QTD Parameters and the Extent of Coronary Artery Disease

Our results show that QTD parameters may be an indicator of extensive CAD in addition to their use in the diagnosis of CAD in women. We know, however, that the relation of QTD to the extent of CAD has not been investigated in detail. This study shows that stress-induced QTD and exercise–rest differences in women are significantly higher in the patients with multivessel disease. Moreover, in patients with single-vessel disease, both total ST-segment depression and QTD values measured at rest were similar to those seen in the normal group, but were higher in the patients with multivessel disease than in the normal group.

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 observed increase in QTD. The increase in QTD due to the effect of CAD is thought to be parallel to the degree of ischemia.^{11, 12} The increase in QTD caused by ischemia is thought to result partially from an impaired response of the ischemic myocardium to catecholamines or to an abnormal flux of calcium ion.²⁰ As is known, the end of the T wave electrocardiographically 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 in turn QTD. This hypothesis explains why the diagnostic value of QTD is higher than that of the ST-segment depression that appears in later phases after ischemia formation. Therefore, the return to normal of resting regional wall motion abnormalities following coronary angioplasty in single-vessel CAD²² may account for the increase in resting QTD and QTcD due to diastolic dysfunction because of ischemia, and even for the correlation of QTD increase with diastolic dysfunction in the patients with multivessel CAD. Also, determination of a prominent increase even in QTD measurements after exercise in the patients with CAD shows that QTD parameters can also be used in the patients who are not able to reach the predicted target heart rate during exercise.¹² All these data explain how QTD measurements give more reliable results compared with the criteria of ST-segment depression frequently seen with exercise in women and leading to false-positive results. High diagnostic values obtained using differences between rest and exercise QTD parameters reveal the relationship of ischemia on rest and exercise. Additional studies are needed to explain this relationship.

Limitations of the Study

Although all the evaluators were blinded to clinical and angiography data, ST-segment changes followed by the observers form potential source of errors in QT measurements. 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 QTD. Moreover, inability to determine T wave more precisely and thus failure to measure it correctly affects the calculations of QTD, especially at very fast heart rates.²³ Therefore, if the end of the T wave could not be reliably determined, QT interval measurements were not obtained and these leads were excluded from analysis. In our study, we obtained interobserver correlations similar to those previously reported,^{11, 24, 25} which showed repeatability of QTD parameters with a high accuracy rate. Although the statistical power of these observations was clearly significant, the number of patients studied was limited. New studies performed in a larger number of patients will shed further light upon the use of QTD parameters to determine double- or triple-vessel diseases, and hence the extent of CAD. Apart from this, evaluation of QT parameters in early phases of the exercise test will provide better understanding of the cause–result relationship leading to increase in QTD due to ischemia.

Conclusion

Evaluation of QTD parameters, especially exercise and rest QTcD and QTDR differences, increases sensitivity and specificity of the exercise test, which shows a significant number of false-negative results in women. In addition, the increase in QTD parameters with exercise shows a correlation with the extent of coronary artery disease.

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