

Original Article

QT Dispersion Immediately after Exercise Test Improves Sensitivity and Specificity for Diagnosis of Ischemic Heart Disease

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ABSTRACT

Objectives: To evaluate the validity of QT-dispersion immediately after a treadmill exercise electrocardiography (ECG) test for diagnosis of ischemic heart disease in the presence or absence of exercise induced significant ST-segment depression.

Methods: We studied 80 patients (70 men and 10 women) without history of myocardial infarction (MI). All patients underwent treadmill exercise ECG test and coronary angiography. The patients were classified into two groups: Group I: included 30 patients with normal coronary angiography and Group II: included 50 patients with angiographically documented coronary artery disease (CAD).

Results: There was a significant increased QT dispersion ($p < 0.05$) immediately after exercise and a significant ST segment depression ($p < 0.05$) in patients with CAD than those with normal coronary artery, but no significant difference at baseline and after six minutes during recovery ($p = \text{NS}$). Predictive indices revealed that QT dispersion immediately after exercise was a valid

indicator for prediction of ischemic heart disease. Its sensitivity was 80%, specificity 83%, accuracy 81%, positive predictive value 88% and negative predictive value 71%. There was a significant correlation between coronary artery stenosis and QT dispersion immediately after exercise ($r = 0.786$ and $p < 0.01$) and QT dispersion (60 ms) corresponded to coronary artery stenosis (70%) in patients with single vessel disease. There was a good agreement between two observers and no significant difference as regards intraobserver and interobserver variability. Stepwise logistic multivariate analysis revealed a significant relation between hypertension status, left ventricular hypertrophy and increased QT dispersion immediately after exercise test in patients with CAD ($p < 0.05$).

Conclusion: QT dispersion, immediately after exercise is a clinically useful marker of exercise induced myocardial ischemia independent of the presence or absence of exercise-induced significant ST-segment depression.

KEYWORDS : exercise test , ischemic heart disease, QT dispersion

INTRODUCTION

Treadmill exercise ECG test is one of the most common non-invasive diagnostic methods used to detect ischemic heart disease^[1]. Many modifications have been proposed for improving its diagnostic accuracy^[2]. However, false positive and false negative results occur at an undesirably high rate despite all of these modifications^[3]. Many institutions overcome this problem by the combined use of other non-invasive diagnostic techniques, such as exercise thallium-201 scintigraphy or dobutamine stress echocardiography. However, these tests are expensive and far from simple, as a high degree of skill is required to interpret the results. For this reason, treadmill exercise ECG test still retains its clinical importance despite advances in non-invasive diagnostic methods for detecting ischemic heart disease and the establishment of diagnostic techniques that reduce false positive and false negative rates in

clinically important ways^[4]. QT dispersion, as measured using a standard 12-lead ECG, is a marker of an inhomogeneous ventricular repolarization phase^[5]. Several investigators have reported that heterogeneity of the ventricular repolarization phase increases during cardiac stress because of transient myocardial ischemia. This increase is reflected in an increase in the QT dispersion^[6].

The aim of the study was to evaluate the validity of QT-dispersion immediately after a treadmill exercise ECG test for diagnosis of ischemic heart disease in the presence or absence of exercise induced significant ST-segment depression.

PATIENTS AND METHODS**Study patients:**

Eighty patients were included in the study. All patients were referred by their physicians to the

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Table 1

QT dispersion (ms) and peak ST-segment depression (mm) in both groups of the study (mean \pm SD)

	Group I	Group II	p-value
QTd (Baseline) (ms)	40 \pm 9	38 \pm 8	NS
QTd (Immediately after exercise)	44 \pm 6	72 \pm 19	<0.05
QTd (6-minutes after exercise)	41 \pm 10	39 \pm 9	NS
ST-segment depression (mm)	0.42 \pm 0.11	1.75 \pm 0.23	<0.05

mm = millimeter, ms = millisecond, QTd = QT dispersion, NS = not significant

cardiology clinic at Farwania hospital for assessment of chest pain. All patients were evaluated clinically by looking at the history, physical examination, 12-leads ECG and routine laboratory investigations.

Exclusion criteria included patients with history of myocardial infarction (MI), intraventricular conduction disturbances, and strain patterns due to left ventricular hypertrophy, atrial fibrillation, treatment with antiarrhythmic drugs that affect the QT interval and treatment with digoxin. No patient had history of congenital long QT syndrome.

Exclusion was based on medical history, physical examination and 12-lead electrocardiogram to avoid confounding factors.

Treadmill exercise ECG test protocol:

All patients in the study underwent the exercise ECG test using standard or modified Bruce models at the baseline of the study. Resting blood pressure (measured manually by arm-cuff sphygmomanometer) was measured in supine and standing positions before the test. Patients with orthostatic hypotension (defined as a decrease of > 20 mmHg of systolic blood pressure after standing) were excluded. Resting ECG was done for all patients to exclude patients with significant ST-segment changes, left bundle branch block or tachyarrhythmias. Patients with typical chest pain on the test day were excluded and were asked to follow up with the physician and to come back after 6 weeks. Blood pressure was recorded midway through each stage and at peak exercise.

The stress ECG test was terminated if there was a decrease in blood pressure (>20 mmHg), significant arrhythmias (non-sustained or sustained ventricular tachycardia), typical chest pain (test limiting angina) or >2 mm ST-segment depression from the baseline was noted.

ST-segment level was measured 60 ms after the J point in all 12 leads. Exercise induced significant ST-segment depression was defined as horizontal or downsloping ST-segment depression 1 mm in any lead present within the first two minutes of the recovery period^[7].

Table 2

Stepwise logistic multivariate analysis of patients with QT dispersion versus those without QT dispersion immediately after exercise

Variables	Coefficient	p-value	95% CI
Age	0.1653	NS	0.470 - 1.439
Gender	0.1082	NS	0.591 - 1.266
Hypertension	0.6321	<0.05	1.929 - 3.095
Left ventricle hypertrophy	0.5873	<0.05	1.761 - 2.593
Diabetes status	0.1852	NS	0.774 - 1.337
Smoking	0.2184	NS	0.896 - 1.067

NS = not significant

Recovery after exercise:

After achieving peak workload, the treadmill was stopped and blood pressure, heart rate, rhythm and symptoms were recorded immediately with the patient in the standing position (no cool down period). The same data were also recorded at 1, 3, 5 and 6 minutes into recovery in the supine position. Monitoring was terminated at six minutes into the recovery unless warranted by symptoms or electrocardiographic changes.

Measurement of the QT dispersion:

The QT interval was measured manually by two observers using calipers from the onset of the QRS to the end of the T wave defined as the return to the TP baseline. When U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. Three consecutive cycles were measured in each of the standard 12 leads and from the three values a mean QT interval was calculated. When the end of the T wave could not be identified the lead was not included. A minimum of seven leads including at least three precordial leads, were required for QT dispersion to be calculated. The QT dispersion (QTd) was defined as the difference between the maximum and minimum QT interval occurring in any of the 12 ECG leads. Heart rate correction of the measured QT dispersion was done using Bazett's formula and corrected QTd was calculated by measuring the difference between maximum and minimum corrected QT intervals in each ECG tracing^[8].

Coronary angiography:

Selective coronary cine angiography was performed for all patients in the study. Fifteen patients were referred to chest hospital, 35 patients underwent angiography in Egypt, 15 patients went to Syria for their angiography and ten patients underwent cardiac catheterization at some centers in England. Coronary stenoses were quantified visually and luminal narrowing of $>70\%$ was considered a hemodynamically significant coronary artery lesion.

Table 3

Indices for prediction of ischemic heart disease by QT dispersion and ST-segment depression immediately after exercise ECG test

	TP	TN	FN	FP	Sen	Spec	Acc	PPV	NPV
QT dispersion	40	25	10	5	80%	83%	81%	88%	71%
ST depression	35	22	15	8	70%	73%	71%	81%	59%

TP= true positive, TN = true negative, FN = false negative, FP= false positive, Sen = sensitivity, Spec = specificity, Acc = accuracy, PPV = positive predictive value, NPV = negative predictive value

There were two groups:

Group I: included 30 patients with normal coronary angiography.

Group II: included 50 patients with angiographically documented coronary artery disease, (20 patients had single vessel disease, 18 patients had two vessel disease and 12 patients had three vessel disease).

Statistical analysis:

Continuous variables are summarized as a mean \pm standard deviation (SD). Comparison between two groups was performed with t-test for continuous variables and chi-square test for categorical variables. A p-value <0.05 was considered statistically significant and a p-value <0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with increased QT dispersion after exercise in the patients with coronary artery disease. The strength of the association with increased QT dispersion was presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables. The agreement between the two observers was verified by using the method of Bland and Altman^[9]. Mean of the difference between two observers and SD were calculated to obtain limits of agreements. Upper limit of agreement = mean of difference + 2SD. Lower limit of agreement = mean - 2SD. For good agreement at least 95% of values must lie within the limits of agreement.

The validity of QT dispersion immediately after exercise ECG stress test to detect ischemic heart disease was assessed by estimating the predictive indices and Kappa coefficient to determine the overall agreement with the data obtained from the coronary angiography.

Kappa coefficient value (k) = (Observed frequency of agreement - Expected frequency of agreement) / (Total observed - Expected frequency of agreement).

Predictive indices:

True positive (TP), true negative (TN), false positive (FP) and false negative (FN) were

Table 4

Intraobserver and interobserver variability in measurement of QT dispersion immediately after exercise ECG test

	Intraobserver variability (1)	Intraobserver variability (2)	Variability
Absolute difference	6 ms	5 ms	4 ms
p-value	NS	NS	NS

NS = notsignificant

calculated. Sensitivity = TP / (TP+FN), specificity = TN / (TN+FP), positive predictive value = TP/(TP+TN), negative predictive value = TN/(TN+TP) and accuracy = (TP+TN) / (TP+TN+FP+FN).

Simple linear regression (Least-square method) was used for correlation of the parameters of the study: $Y = b + aX$ where, a = slope and b = intercept.

RESULTS

Clinical characteristics:

As regards of age and gender, there was no significant difference between both groups of the study (53.31 ± 8.24 versus 48.6 ± 3.43 years, respectively, p = NS, 43 (86%) versus 27 (90%) males, p = NS and 7 (14%) versus 3 (10%) females, p = NS) respectively.

There was no significant difference between both groups regarding percentage of patients with history of smoking and hypercholesterolemia [38 (76%) versus 24 (80%) patients, p = NS and 32 (64%) versus 15 (50%) patients, p = NS] respectively. There was no significant difference regarding the resting heart rate between both groups (89.25 ± 5.93 versus 78.5 ± 8.72 beats/minute respectively, p = NS) but there was a significant increase in systolic and diastolic blood pressure in the hypertensive patients than the normotensives (179.5 ± 12.41 versus 122.35 ± 8.11 mmHg, and 104.8 ± 5.32 versus 76.84 ± 6.18 mmHg, respectively, p < 0.05).

Exercise ECG test:

There was no significant difference between both groups as regards the duration of exercise ECG test, peak heart rate, blood pressure response during and after exercise and heart rate recovery after exercise during recovery.

There was a significant increased QT dispersion immediately after exercise in patients from Group II than patients from Group I (72 ± 19 versus 44 ± 6 ms respectively, p < 0.05) and significant increased ST - segment depression in Group II than Group I (1.75 ± 0.23 versus 0.42 ± 0.11 mm respectively, p < 0.05) but no significant difference in QT dispersion at baseline and 6-minutes after exercise during recovery (38 ± 8 versus 40 ± 9 ms and 39 ± 9 versus 41 ± 10 ms respectively, p < 0.05) as shown in Table 1.

Table 5

Agreement of the results of coronary angiography and QT dispersion after exercise

	CAD +ve	CAD -ve	Total
QT dispersion +ve	40	5	45
QT dispersion -ve	10	25	35
Total	50	30	80

Kappa coefficient = 0.853

CAD = coronary artery disease

Stepwise logistic multivariate analysis revealed a significant relation between hypertension status and left ventricular hypertrophy as independent variables and QT dispersion immediately after exercise in the patients with CAD ($R = 0.6321$ & 0.5873 , $95\% \text{ CI} = 1.929 - 3.095$ & $1.761 - 2.593$ respectively, $p < 0.05$). However, there was no significant relation between age of the patients, gender, smoking, and diabetes mellitus status (Table 2).

There was a significant correlation between coronary artery stenosis (%) and QT dispersion (ms) in patients with single vessel disease ($y = 0.63x + 15.6$, $r = 786$, $p < 0.01$), and QT dispersion (60 ms) of dependent Y axis corresponded with coronary artery stenosis (70%) of independent X axis (Fig.1).

The predictive indices showed that QT dispersion is valid for prediction of patients with ischemic heart disease as sensitivity of QT dispersion was 80%, specificity 83%, accuracy 81%, positive predictive value 88% and negative predictive value 71% with decreased number of false positive and false negative cases as compared with results of ST segment depression alone (Table 3).

As regards reproducibility, there was no significant difference in interobserver variability and intraobserver variability ($p = \text{NS}$, Table 4) and there was a good agreement between QT dispersion measurements by both observers more than 95% of the measurements were between the upper and lower limits of agreement [mean +2SD & mean - 2SD], (Fig. 2).

There was a good agreement between data of coronary angiography and both QT dispersion and ST-segment depression with Kappa coefficient [0.876 for QT dispersion versus 0.765 for ST-segment depression], (Table 5,6).

DISCUSSION

Almost a century after Einthoven's invention of the string galvanometer, the surface ECG retains its central place in cardiological diagnosis. In seeking to extract yet more information from the standard 12 lead ECG, much attention has been given in recent years to the measurement of QT dispersion. The QT interval reflects the duration of

Table 6

Agreement of the results of coronary angiography and ST segment depression after exercise

	CAD +ve	CAD -ve	Total
ST-depression +ve	35	8	43
ST-depression -ve	15	22	37
Total	50	30	80

kappa coefficient = 0.758

CAD = coronary artery disease

depolarization and repolarization of the ventricular myocardium^[10]. A potential clinical application of this interlead difference was proposed in 1990 by Day and co-workers^[11], who suggested that this difference in QT duration may provide an index of the inhomogeneity of the repolarization, which they called QT dispersion.

Increased QT dispersion on the surface ECG is generally attributed to heterogeneity of ventricular repolarization under individual electrodes and has important clinical correlates in patients with a wide range of heart disorders. Attribution of QT dispersion to heterogeneity of repolarization implies that surface electrodes record temporal information that is unique to the underlying myocardium. However, increased QT dispersion also may be explained simply by increased differences in the projection of the T wave vector onto different leads, particularly when repolarization is abnormal and measurement of QT offset becomes imprecise in the presence of flat or isoelectric T waves^[12].

Although treadmill exercise ECG is one of the most common non-invasive methods for diagnosing ischemic heart disease, it is not always accurate for detecting significant coronary stenosis. Exercise-induced ST-segment depression is generally used as an indicator for predicting significant coronary stenosis and is said to have a sensitivity of 50 to 70% and a specificity of 70 to 90%^[13]. The false positive rate of this indicator is high (approximately 25 to 50%), particularly among women, although it is dependent to some extent on the demographic characteristics of the patient^[14].

Increased QT dispersion is frequently observed in patients with severe ventricular arrhythmias^[15] and in patients with myocardial infarction^[16]. The value of QT dispersion has also been reported in patients with ischemic heart disease in the absence of myocardial infarction^[17]. We have reported that QT dispersion is increased during exercise induced myocardial ischemia in patients with a sensitivity and specificity of 80 and 83%, respectively.

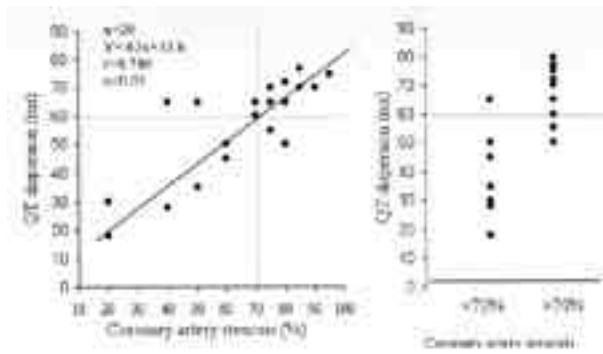


Fig. 1: Left panel, correlation between coronary artery stenosis and QT dispersion after exercise and right panel, individual data for QT dispersion in patients subclassified according to significant coronary artery stenosis (<70% or >70%)

Our results revealed that QT dispersion > 60 ms immediately after exercise is considered positive for the presence of myocardial ischemia and it can be used as indicator to predict severity of coronary artery disease and this is in agreement with the results of Koide *et al*^[18]. The present study also demonstrated significantly greater QT dispersion immediately after exercise in the group with significant coronary stenosis than in those without. These results suggest that changes in QT dispersion due to exercise are a useful indicator of significant coronary stenosis. Although the mechanisms responsible for these findings are unknown, increased QT dispersion induced by exercise most likely results from increased heterogeneity of ventricular repolarization due to transient myocardial ischemia^[19]. We classified patients with angiographically proved coronary artery disease as regards the extent of coronary atherosclerosis into single, two and three vessel disease groups. As regards the severity of stenotic lesions, we considered luminal narrowing of > 70% as the breakpoint of the hemodynamically significant coronary artery lesion. Therefore, we found a significant correlation between coronary artery stenosis and QT dispersion after exercise only in the 20 patients with single vessel disease.

The reproducibility of measurement of resting QT dispersion has been debated^[20]. The improved reproducibility of QT dispersion measurements immediately after exercise when compared with resting QT dispersion, is probably due to increased T-wave amplitude, a sharpened downstroke of the T-wave and better end of the T-wave definition. The reproducibility of QT dispersion measurements immediately after exercise makes this a useful indicator of significant coronary stenosis^[21].

QT dispersion immediately after exercise is an independent predictor and a statistically significant indicator of significant coronary stenosis. In men, QT dispersion immediately after exercise was significantly more sensitive and tended to be more

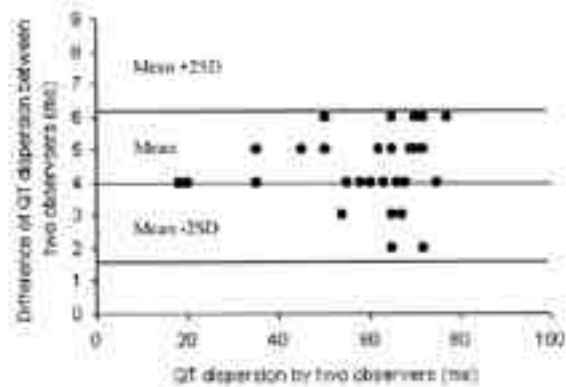


Fig. 2: Plot of the mean values obtained by two observers versus the difference of these values

specific, although the difference was not statistically significant, than exercise induced significant ST-segment depression as an indicator of significant coronary stenosis^[22]. In contrast, in women, QT dispersion immediately after exercise tended to be slightly less sensitive but was significantly more specific than significant ST-segment depression. There was no significant difference between men and women in the sensitivity and specificity of QT dispersion immediately after exercise, for detecting significant coronary stenosis^[23].

Koide *et al*^[21] reported that there was a statistically significant positive correlation between QT dispersion immediately after exercise and ST-segment depression immediately after exercise, but the correlation coefficient was relatively small. Furthermore, there was no significant difference in the sensitivity and specificity of QT dispersion immediately after exercise as an indicator of significant coronary stenosis when exercise-induced significant ST-segment depression was present and when it was absent. The reason for this finding is unclear, but it is possible that QT dispersion, which is a marker of heterogeneity of the ventricular repolarization phase, and ST segment depression, which occurs due to a subendocardial injury current, may be electrophysiologically different markers of myocardial ischemia.

Stierle *et al*^[6] reported that in patients with CAD, a greater interlead variation (QT-SD, standard deviation of the mean of all measured QT intervals in a single patient) than in patients with normal coronary arteries. This considerable inconsistency in QT behavior between leads correlated well with the extent of myocardial ischemia. The greater interlead variation in patients with myocardial ischemia indicates that an increase in QT dispersion arises from an inhomogeneous extent of QT interval changes across all electrocardiographic leads. In patients with 3-vessel CAD, myocardial

ischemia is a process affecting several areas of the left ventricular myocardium. Ischemia induced changes in repolarization will therefore be present across several leads of surface ECG. From a statistical point of view, standard deviation of QT intervals could be more appropriate than a QT range, because it incorporates values from all leads instead of two.

Limitation of the study:

1. Relatively small number of patients.
2. Patients with old myocardial infarction were not included in the study, as QT dispersion is not valid for assessment of exercise induced ischemia in this group of patients, and old MI is considered one of confounders which increase false positive results.
3. The study is not completely blind to observers.

CONCLUSION

Our study proposes that QT dispersion immediately after exercise is a clinically useful marker and valid indicator of exercise induced myocardial ischemia independent of the presence or absence of exercise-induced significant ST-segment depression.

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