

Usefulness of automatic QT dispersion measurement for detecting exercise-induced myocardial ischemia

Egzersizle oluşan miyokard iskeminin değerlendirilmesinde otomatik QT dispersiyonun kullanımı

Bonpei Takase, Nobuyuki Masaki, Hidemi Hattori*, Masayuki Ishihara*, Akira Kurita*

Department of Intensive Care Medicine, National Defense Medical College, and Division of Biomedical Engineering*
National Defense Medical College Research Institute, Saitama, Japan

ABSTRACT

Objective: The electrocardiographic index of QT dispersion (QTd) is related to the occurrence of arrhythmia. In patients with suspected or known coronary artery disease, QTd may be affected by exercise. We investigated whether QTd that is automatically calculated by a newly developed computer system could be used as a marker of exercise-induced myocardial ischemia.

Methods: The design of this study was prospective and observational. Eighty-three consecutive patients were enrolled in this study. Their QTd was measured at rest and after 3 min of exercise during exercise-stress Thallium-201 scintigraphy and compared with conventional ST-segment changes. The patients were classified into 4 groups (normal group, redistribution group, fixed defect group, redistribution with fixed defect group) based on the result of single photon emission computed tomography. As statistical analysis, one-way ANOVA with post-hoc Scheffe's method, receiver-operating characteristics (ROC) and multiple logistic regression analysis were performed.

Results: At rest, QTd was significantly greater ($p<0.05$) in the fixed defect group (52 ± 21 ms) and the redistribution with fixed defect group (53 ± 20 ms) than in the normal group (32 ± 14 ms) and the redistribution group (31 ± 16 ms). However, QTd tended to increase after exercise in the redistribution group, while QTd tended to decrease in the normal group, the fixed defect group, and the redistribution with fixed defect group (QTd after exercise, normal group, 28 ± 17 ms, redistribution group, 35 ± 19 ms, fixed defect group, 43 ± 25 ms, redistribution with fixed defect group, 49 ± 27 ms). Exercise significantly increased QTcd (RR interval-corrected QT dispersion) in the redistribution group. The best cut-off values of QTd and QTcd obtained from ROC curves for exercise-induced myocardial ischemia were 41.6 ms and 40.4 ms, respectively (QTd - AUC 0.68, 95%CI 0.53-0.83 and QTcd - AUC 0.67, 95%CI 0.55-0.80). Using these values as cut-off ones, QTd, QTcd, and conventional ST-segment change had comparable sensitivities and specificities for detecting exercise-induced myocardial ischemia (sensitivity - 60%, 58% and 49%, respectively; specificity - 78%, 80% and 83%, respectively). In addition, multiple logistic regression analysis showed that QTd (OR=2.01, 95%CI 1.15-4.10, $p<0.05$), QTcd (OR=2.12, 95% CI 1.02-4.30, $p<0.05$) and ST-segment change (OR=1.89, 95%CI 1.03-3.40, $p<0.05$), were the significantly associated with exercise-induced myocardial ischemia.

Conclusion: QT dispersion and/or QTcd after exercise could be a useful marker for exercise-induced myocardial ischemia in routine clinical practice. (*Anadolu Kardiyol Derg 2009; 9: 189-95*)

Key words: QT interval, coronary artery disease, myocardial ischemia, Thallium-201 scintigraphy, logistic regression analysis, predictive values of tests

ÖZET

Amaç: QT dağılımının (QTd) elektrokardiyografik indeksi aritminin sıklığı ile ilgilidir. Koroner hastalığından şüphelenilen veya bilinen hastalarda da QTd egzersiz sırasında değişiklik gösterir.

Yeni gelişmiş bir bilgisayar sistemi ile otomatik olarak hesaplanan QT dağılımının, egzersizle oluşan miyokard iskeminin bir belirleyicisi olarak kullanıp kullanamayacağını araştırdık.

Yöntemler: Bu çalışmanın tasarımı prospektif ve gözlemseldir. Seksen üç ardışık hasta bu çalışmaya dahil edildi. QTd istirahatta ve stres-egzersiz Talyum-201 sintigrafi taraması sırasında, egzersizin üçüncü dakikasından sonra ölçüldü ve konvansiyonel ST-segment değişiklikleriyle kıyaslandı. Hastalar, tek foton emisyon bilgisayarlı tomografi sonucuna dayanan dört grupta sınıflandırıldı (normal grup, redistribüsyon grubu, sabit defekt grubu, sabit defektli grubun redistribüsyonu). İstatistiksel analiz olarak, tek yönlü ANOVA, ROC ve çoklu lojistik regresyon analizleri yapıldı.

Bulgular: İstirahatta, QT sabit defekt (52 ± 21 ms) ve sabit defekt redistribüsyon (53 ± 20 ms) gruplarında normal ve redistribüsyon grubundan (32 ± 14 ms) (31 ± 16 ms) önemli şekilde daha büyüktü ($p<0.05$). Bununla beraber, egzersiz sonrasında QTd redistribüsyon grubunda yükseliş gösterirken, aynı zamanda QTd normal, sabit defekt ve sabit defekt redistribüsyon gruplarında azalmaya yöneldi (egzersizden sonra QTd: normal grup - 28 ± 17 ms,

Address for Correspondence/Yazışma Adresi: Bonpei Takase, M.D., F.A.C.C., F.A.H.A. National Defense Medical College, Department of Intensive Care Medicine, 3-2 Namiki, Tokorozawa, Saitama, Japan, 359-8513. Phone: +11 81 42 995 1597 Fax: +11 81 42 925 0967 E-mail: bonpeit@ndmc.ac.jp and dui1577@db3.so-net.ne.jp

©Telif Hakkı 2009 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2009 by AVES Yayıncılık Ltd. - Available on-line at www.anakarder.com

redistribüsyon grubu - 35 ± 19 ms, sabit defekt grubu - 43 ± 25 ms, sabit defekt redistribüsyon grubu - 49 ± 27 ms). Egzersiz, QTcd dağılımını (RR- düzeltilmiş QT dağılımı) redistribüsyon grubunda önemli bir şekilde yükseltti. Egzersizle oluşan miyokard iskemisi için ROC eğrilerinden elde edilen QTd (EAA 0.68, %95GA 0.53- 0.83) ve QTcd'nin (EAA- 0.67, %95GA 0.55- 0.80) en iyi tanımlayıcı değerleri 41.6 ms ve 40.4 ms idi, sırasıyla. (Bu tanımlayıcı değerleri olarak kullanıldığında, QTd, QTcd ve konvansiyonel ST-segment değişikliği egzersizle oluşan miyokard iskemiyi göstermek için karşılaştırılabilir duyarlılık ve özgüllüğe sahipti (duyarlılıkları, 60%, 58% ve 49%, sırasıyla; özgüllükleri, 78%, 80% ve 83%, sırasıyla). Ayrıca, çoklu lojistik regresyon analizinde QTd (OR=2.01, %95GA 1.15-4.10, $p < 0.05$), QTcd (OR=2.12, %95 GA 1.02-4.30, $p < 0.05$), ve ST-segment değişikliği (OR=1.89, %95GA 1.03-3.40, $p < 0.05$), egzersizle oluşan miyokard iskemisi ile anlamlı ilişkide oldukları bulundu.

Sonuç: Egzersizden sonra, QTd ve /veya QTcd, egzersizle oluşan miyokard iskemisi için rutin klinik pratikte faydalı bir belirleyici olabilir. (*Anadolu Kardiyol Derg 2009; 9: 189-95*)

Anahtar kelimeler: QT interval, koroner arter hastalığı, miyokard iskemisi, Talyum-201 sintigrafisi, lojistik regresyon analizi, testlerin tahmini değerleri

Introduction

Exercise testing has been widely used for diagnosing coronary artery disease (CAD) in routine clinical practice. ST-segment changes are the standard electrocardiographic parameters examined during exercise testing. However, there are several confounding factors, and the overall accuracy of ST-segment changes during exercise testing ranges around 70%-80% (1, 2). Thus, in order to improve the diagnostic accuracy of the electrocardiogram (ECG) during exercise testing, the use of QT interval changes in response to exercise-induced myocardial ischemia has been previously proposed (3, 4). In addition, automatic measurement of QT interval changes during exercise testing has been developed (5, 6).

QT dispersion is the most widely used QT interval index (7, 8). However, few studies have examined in detail whether automatically measured QT dispersion can accurately diagnose exercise-induced myocardial ischemia.

Therefore, we analyzed automatically measured QT dispersion during exercise-stress Thallium-201 scintigraphy, and we studied whether QT dispersion could be a marker for exercise-induced myocardial ischemia.

Methods

Study populations

We prospectively studied 83 consecutive patients who were suspected or known to have CAD and who required exercise-stress Thallium-201 scintigraphy to evaluate their myocardial ischemia. These patients were recommended and selected from 1248 patients who underwent regular exercise treadmill testing to perform exercise-stress Thallium-201 scintigraphy because of either suitable for exercise-stress Thallium-201 scintigraphy or higher likelihood of suspected coronary artery disease. Exercise-stress Thallium-201 scintigraphy was undertaken within one month of regular treadmill testing. Some patients despite having a positive exercise-induced ischemic ECG changes refused to enter into the direct cardiac catheterization procedure. The study population consisted of 62 men and 21 women who were 18 to 82 years of age (mean age, 62 ± 11 years old). The male patient of 18-year old was included because of exercise-induced angina symptom and suspected familial hypercholesterolemia. In addition, a 82-year old patient was included because of typical exertional angina symptom and he could perform exercise-stress Thallium-201 scintigraphy. None of these patients

had any ECG abnormalities on resting ECG that would have precluded the measurement of ischemic ST or T wave changes (such as bundle branch block), Wolf-Parkinson-White syndrome, the findings of left ventricular hypertrophy, the presence of a Q wave > 0.04 sec duration in a lead that could be used for measuring QT parameters and ST segment depression, and the presence of baseline ST segment morphology defined as a depression or an elevation of 1 mm or more as compared to the isoelectric line in a lead that could be used to measure QT parameters and ST segment depression. Patients, who were taking medications that influence the QT interval, such as Class I and III anti-arrhythmic agents, were excluded. In addition, all medication including nitrate and β -blockers were discontinued at least for five times longer periods than drug's half time at the time of exercise-stress Thallium-201 scintigraphy except nitroglycerin sublingual administration at the time of angina attack. The informed consents were obtained in each patients and the study protocol was approved by the Ethics Committee.

Exercise-stress Thallium-201 scintigraphy

Treadmill exercise testing was performed using the Bruce or modified Bruce protocol. Exercise was continued until the heart rate reached 85% of the maximum heart rate (age-predicted target heart rate) estimated from the age of each patient. When patients could not exercise to the target heart rate, they continued exercising until exhaustion or the occurrence of cardiac symptoms, such as precordial discomfort, dyspnea, or palpitations. Throughout the study, 12-lead ECGs were monitored continuously and recorded at 1 min intervals with a Marquette CASE 12 (Marquette Electronics, Inc., Milwaukee, WI, USA). ST segment depression was measured 80 ms after the J point. A horizontal or downsloping ST-segment depression of at least 1.0 mm was considered significant for exercise-induced ischemia. At 1 min before peak exercise, 740 MBq of Thallium-201 was intravenously injected. Stress and delayed Thallium-201 single photon emission computed tomography (SPECT; Millennium MG, Marquette GE Med. Milwaukee, WI, USA) images were obtained 10 min and 4 h after the administration of Thallium-201, respectively. The SPECT images were interpreted visually. Reversible and/or fixed defects that reflect ischemia and/or necrosis were identified by experienced investigators with expertise in nuclear cardiology who were blinded to the clinical information and any ECG parameters, including QT and ST-T wave measurements. A reversible defect was considered to be redistribution. Based on the experts' interpretations, the patients were divided into four groups: a normal group, a redistribution group, a fixed defect group, and a redistribution with fixed defect group.

Measurement of QT dispersion (QTd)

During exercise testing, 12-lead ambulatory ECG monitoring was done using a MARS recorder (GENIE, Marquette GE Med.). QTd was automatically calculated from the monitoring record using a commercially available software package (QT-Guard, GE Med.). In addition, the corrected QTd (QTcd) was simultaneously obtained using the same software. QTcd was calculated using Bazze't's formula; $QTcd = QTd / \sqrt{RR\text{-interval}}$. These parameters were continuously measured during exercise-stress Thallium-201 scintigraphy and were analyzed before exercise with the patient in the sitting position and then 3 min after exercise.

The QTd is defined as the longest minus the shortest QT interval recorded by the 12-lead ECG. The algorithm used for the QTd is a least-squares fit line method (9). In this method, a least-squares fitted line around the neighborhood of the maximum down-slope tangent of the T wave is calculated. Then, the point of intersection of this line with the isoelectric T-P segment line is used as the endpoint of the T wave. For the QTd to be calculated, there must be more than 8 valid leads.

Statistical analyses

All of the statistical analyses were performed using SPSS version 11.0 (SPSS Japan Inc., Tokyo, Japan). To examine whether the distribution of each parameter showed normal curve or not, we calculated their skewness. As a result, tests showed that each parameter suggested to be normally distributed so that we used parametric statistics even if data numbers were small. All data are presented as mean±SD and 95% confidence interval (CI). We used one-way ANOVA for comparing means of the measurements among the four groups. Scheffe's method was used as the post hoc test. The test accuracy was defined

based on the same methodology and criteria that are used in conventional exercise testing (10). A true-positive (TP) was defined as an abnormal test result in an individual with disease (either a reversible defect or a fixed defect in this study); a false-positive (FP) was defined as an abnormal test result in an individual without disease; a true-negative (TN) was defined as a normal test result in an individual without disease; and a false-negative (FN) was defined as a normal test result in an individual with disease. Based on these definitions, a positive predictive value (PPV) for disease was calculated according to the formula, $PPV = TP / (TP + FP)$, and a negative predictive value (NPV) for disease was calculated according to the formula, $NPV = TN / (TN + FN)$. Multiple logistic regression analysis was done to identify the independent variables for detecting for reversible defect (indicating exercise-induced myocardial ischemia). Receiver operating characteristics (ROC) curve was used to acquire appropriate sensitivity and specificity of QTd and QTcd after exercise for diagnosing exercise-induced myocardial ischemia (reversible defect). The best cut off values of QTd and QTcd were obtained from ROC curve. The differences were considered to be significant if $p < 0.05$.

Results

Clinical characteristics of the study population (Table 1)

Valid QTd data was obtained for all 83 patients studied. There were no significant differences in the prevalence of cardiac risk factors among the four groups. There were no differences in treatments among the four groups, except for the use of nitrates and β -blockers, which was more prevalent in the fixed defect group and in the redistribution with fixed defect group than in the other two groups.

Table 1. Clinical characteristics of the study population

| Parameters | Normal group (n=47) | Redistribution group (n=11) | Fixed defect group (n=12) | Redistribution with fixed defect group (n=13) |
|------------------------|---------------------|-----------------------------|---------------------------|---|
| Age, years | 61±11 | 67±5 | 62±17 | 59±19 |
| Men, n | 12 | 3 | 5 | 1 |
| CABG, n (%) | 2 (4%) | 1 (9%) | 0 | 3 (23%) |
| PTCA, n (%) | 1 (6%) | 1 (9%) | 4 (33%) | 1 (8%) |
| Smoking, n (%) | 13 (27%) | 4 (33%) | 6 (50%) | 6 (46%) |
| Hypertension, n (%) | 17 (36%) | 7 (67%) | 8 (67%) | 6 (46%) |
| Diabetes, n (%) | 1 (2%) | 4 (33%) | 2 (17%) | 5 (38%) |
| Hyperlipidemia, n (%) | 4 (9%) | 1 (9%) | 6 (50%) | 6 (46%) |
| Nitrates, n (%) | 8 (18%) | 1 (9%) | 6 (50%) | 11 (88%)* |
| Calcium blocker, n (%) | 4 (9%) | 1 (9%) | 4 (34%) | 6 (46%) |
| β blocker, n (%) | 4 (9%) | 4 (33%) | 6 (50%) | 11 (88%)* |
| ACE-I / ARB, n (%) | 13 (27%) | 4 (33%) | 1 (8%) | 8 (63%) |
| No medication, n (%) | 17 (36%) | 4 (33%) | 1 (8%) | 1 (8%) |

Data are presented as Mean±SD, One-way ANOVA showed that F values were > 26.3 in each parameters and * $p < 0.05$ vs. normal group, redistribution group, and fixed defect group (by post-hoc Scheffe's tests) Hypertension (>160/95 mmHg); Diabetics (fasting blood glucose >110 mg/dl); Hyperlipidemia (total cholesterol >230 mg/dl); ACE-I/ARB, angiotensin converting-enzyme inhibitor/ angiotensin receptor blocker, CABG - coronary artery bypass surgery, PTCA - percutaneous coronary intervention

QT interval and QTd

We could not evaluate QTd at peak exercise in the present study, since the increased heart rate at peak exercise precluded QT interval measurement in many of the leads of most patients. Therefore, QTd was evaluated at rest and 3 min after exercise.

QTd and QTcd at rest in the fixed defect group and in the redistribution with fixed defect group were greater than in the normal group and the redistribution group (Fig. 1, p<0.05). The maximum and minimum QT intervals at rest and 3 min after exercise were not statistically different among the four groups (Table 2).

When the effects of exercise on QTd and QTcd were measured, the QTd and QTcd after exercise were greater in the redistribution with fixed defect group than in the normal group (p<0.05); compared to the normal group, QTd and QTcd tended to be greater in the other three groups (Fig. 2, p<0.1 or p<0.05). QTcd was significantly greater in the fixed defect group and the redistribution with fixed defect group than in the normal group (p<0.05).

We also compared ΔQTd/QTd at rest and ΔQTcd/QTcd at rest among the four groups; these were defined as: ΔQTd = [QTd after exercise - QTd at rest]; ΔQTcd = [QTcd after exercise - QTcd

at rest]. Using these definitions, ΔQTd/QTd at rest and ΔQTcd/QTcd at rest were then obtained. Compared to the normal group, ΔQTcd/QTcd was significantly greater in the redistribution group (p<0.05). In addition, ΔQTd/QTd tended to be greater in the redistribution group than in the normal group (Fig. 3).

The sensitivities and specificities of QTd, QTcd, and the conventional treadmill test index (ST-segment changes) for detecting exercise-induced myocardial ischemia, as reflected by a reversible defect on Thallium 201 scanning (including both the redistribution group and the redistribution with fixed defect group), were similar; the sensitivities were 60% for QTd, 58% for QTcd, and 49% for ST-segment changes, while the specificities were 78% for QTd, 80% for QTcd, and 83% for ST-segment changes. The cut-off value for QTd was 42 ms, and for QTcd it was 40 ms; in both cases, these were the median values. These values were coincidentally identical to the best cut-off values obtained from ROC curves; QTd - 41.6 ms and QTcd - 40.4 ms, respectively, as shown in Figure 4 (for QTd - AUC 0.68, 95% CI 0.53 to 0.83 and QTcd - AUC - 0.67, 95%CI 0.55 to 0.80).

In overall study populations, 32% of the patients who showed positive QTd (cut off value of 42 ms) had ST-segment depression

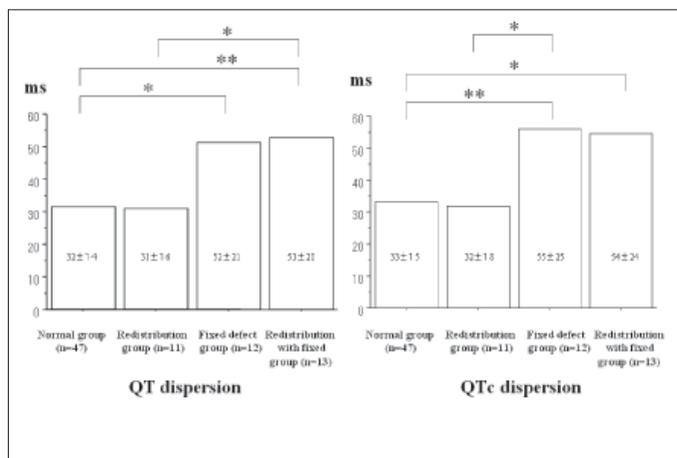


Figure 1. QT and QTc dispersion at rest
All measurements are expressed as mean±SD, ms; Column indicates mean values; * p<0.05; ** p<0.01. QTd - QT dispersion, QTcd - corrected QT dispersion

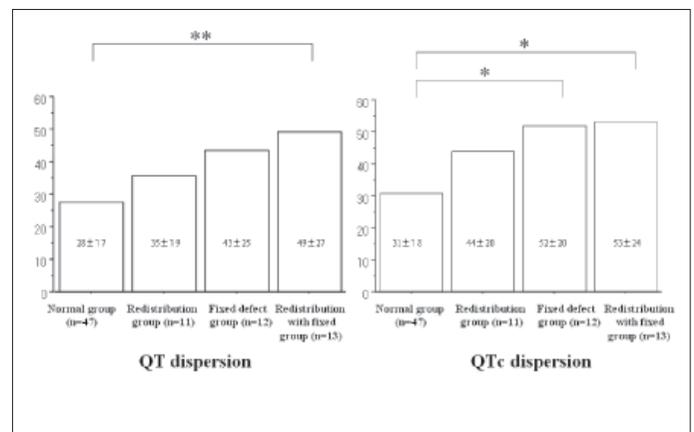


Figure 2. QT and QTc dispersion after exercise
All measurements are expressed as mean±SD, ms; Column indicates mean values; * p<0.05; ** p<0.01
QTd - QT dispersion, QTcd - corrected QT dispersion

Table 2. Changes in the QT interval with exercise

| Variables | Normal group (n=47) | Redistribution group (n=11) | Fixed defects group (n=12) | Redistribution with fixed defect group (n=13) |
|----------------|---------------------|-----------------------------|----------------------------|---|
| At rest | | | | |
| Maximum QT, ms | 394±40 | 397±41 | 394±34 | 388±26 |
| Minimum QT, ms | 361±49 | 350±37 | 356±33 | 340±57 |
| QTd*, ms | 31±15 | 30±16 | 51±22 | 53±25 |
| After exercise | | | | |
| Maximum QT, ms | 359±40 | 365±40 | 372±36 | 360±23 |
| Minimum QT, ms | 330±37 | 337±34 | 325±60 | 312±26 |
| QTd*, ms | 27±15 | 35±12 | 42±20 | 49±20 |

Data are presented as Mean±SD, One-way ANOVA showed that F values were > 26.3 in each parameters resulting in *p<0.01 among the 4 groups
QTd - QT interval dispersion

but not reaching positive criteria while 28% of the patients who met positive criteria for a ST-segment changes did not meet a QTd positive criteria. In addition, when the sensitivity and specificity of a combined index of QTd and ST-segment changes (a positive test defined as either positive for QTd index [QTd and/or QTcd] or ST-segment) were evaluated, the combined index showed tendency to increase sensitivity and specificity of 71% and 85%, respectively. Independent predictors for detecting exercise-induced myocardial ischemia are shown in Table 3, indicating that odds ratio of QTd, QTcd and ST-segment change for detecting exercise-induced myocardial ischemia were 2.01 (95%CI 1.15 to 4.10, $p < 0.05$), 2.12 (95% CI 1.02 to 4.30, $p < 0.05$) and 1.89 (95% CI 1.03 to 3.40, $p < 0.05$), respectively. Concerning with exercise-induced arrhythmias, 5% of overall study patients showed exercise-induced isolated ventricular premature contractions. However, there were no relation between QTd(QTcd) and the arrhythmia occurrence.

Discussion

In this study, we demonstrated that QT dispersion is a good marker for exercise-induced myocardial ischemia as assessed by Thallium-201 scintigraphy, which reflects exercise-induced myocardial ischemia. The QT dispersion and RR-corrected QTcd have similar sensitivities and specificities to conventional ST-segment changes. As shown in Figure 3, QTd and QTcd increased significantly during exercise in patients with redistribution on exercise-stress Thallium-201 scintigraphy. This increment was most profound in patients who had only a reversible defect (the redistribution group).

Table 3. Independent predictors for detecting exercise-induced myocardial ischemia in multiple logistic regression analysis

| Independent variables | Odds ratio | Confidence Intervals | p |
|-----------------------|------------|----------------------|-------|
| Qtd | 2.01 | 1.15-4.10 | <0.05 |
| QTcd | 2.12 | 1.02-4.30 | <0.05 |
| ST-segment change | 1.89 | 1.03-3.40 | <0.05 |

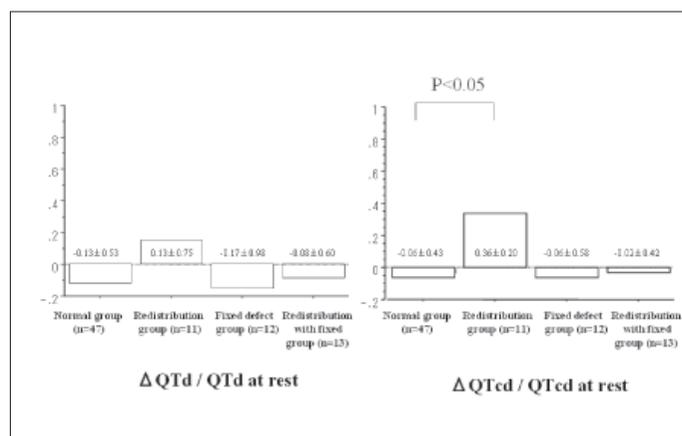


Figure 3. Comparison of $\Delta QTd/QTd$ at rest and $\Delta QTcd/QTcd$ at rest
All measurements are expressed as mean \pm SD, ms; Column indicates mean values; * $p < 0.05$; ** $p < 0.01$

QTd - QT dispersion, QTcd - corrected QT dispersion $\Delta QTd = QTd$ after exercise - QTd at rest

Especially, around 30% of patients in QTd (QTcd) positive patients and the patients who had a positive ST-segment change showed borderline values of ST-segment and QTd(QTcd), respectively. In addition, a combined index of QTd and ST-segment changes showed tendency to improve diagnostic accuracy for detecting exercise-induced myocardial ischemia. Thus, measuring QTd by our automatic measuring system could possibly become a good index adding diagnostic power on conventional ST-segment changes.

The results described in the previous paragraph suggest that QTd and QTcd are sensitive not only for myocardial repolarization disorder but also for myocardial ischemia. This can be explained by the discrepancy of the regional QT interval that is caused by gaps in the action potential durations in individual myocardial or transmural myocardial cells, sometimes extending to include cells from the endocardium to the epicardium. This can reflect local myocardial injury (11, 12). On the other hand, QTd has been considered to be a projection of the T-wave vector to each lead (13-15). A new index, the principal component analysis ratio (PCAr), is one of the major components calculated from the whole vector during myocardial repolarization. PCAr represents T-wave morphology as a number and eliminates lead-to-lead differences in QT information (5). Given this, PCAr is a more ideal parameter than QTd. Thus, a study comparing QTd and PCAr would be interesting and should be conducted in the near future.

Our results show that automatic computer-measured QTd is useful for diagnosing exercise-induced myocardial ischemia. Recently, QT parameters such as QTd, QT peak dispersion (another new QT parameter (12)), and PCAr have been automatically computer calculated (9, 16). However, the determination of the end of the T-wave is still a problem even when using excellent computer algorithms based on advanced technology. Further data from studies similar to our study are needed to determine whether automatically calculated indices are useful in clinical practice. Earlier studies have shown that QTd, QTcd, and PCAr measurements are useful for predicting the occurrence of fatal arrhythmia (7, 8, 17-19). These QT parameters increase in CAD patients (20-25). The most recent reports dealing with QT parameters have suggested that manual measurement might lack accuracy and objectivity (26). Therefore, automatically calculated QT parameters from clean ECG tracings, using methods described in this study, can be more valuable and beneficial than the conventional, manually measured indices. In addition, recent report of Schmidt et al (27) showed QTd measured in exercise-stress Thallium-201 scintigraphy did not correlate with myocardial ischemia detected by exercise-stress Thallium-201 scintigraphy. However, they measured QTd at peak exercise so that faster heart rate possibly confounded the measurement of QTd. We measured QTd and QTcd at the recovery phase of exercise. These methodological differences could explain the discrepancy between their report and our study results. We recently confirmed these results in the previous report (28).

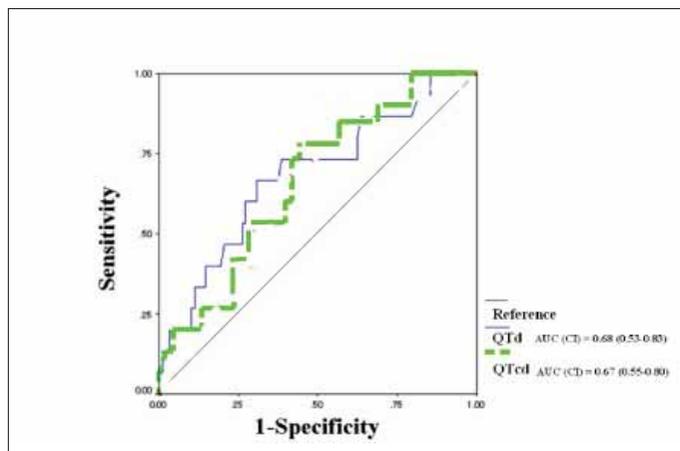


Figure 4. ROC curves of QT and QTc dispersion after exercise-induced myocardial ischemia

Study limitations

In the present study, as many as 88% of the patients in some groups were taking β -blockers or HMG-CoA inhibitors (statins). Our study included patients who were at greater than intermediate CAD risk, so that the predictive accuracy of QTd for exercise-induced myocardial ischemia in relatively low risk patients is unknown. Second, even though we excluded the patients who were taking medications that largely preclude QT interval measurement, such as class I and III anti-arrhythmic agents, some patients were taking anti-anginal agents, such as calcium channel blockers, that can affect QT parameters. The effects of anti-anginal agents on the diagnostic accuracy of QTd cannot be completely excluded. However, in the clinical setting, exercise-stress Thallium-201 scintigraphy is mostly performed on patients taking anti-anginal medications. Thus, our observation is still very relevant for routine clinical practice. Moreover, as described in the method section, particularly in this study, these medications were discontinued at the exercise-stress Thallium-201 scintigraphy. Third, QTd(QTcd) was not measured at the end of recovery phase during exercise test. The reason why we measured QTd(QTcd) at 3 min after exercise was the concept that the influence of exercise would be more precisely detected measured close to peak exercise, but not being influenced by the faster heart rate. However, like ST-segment changes, QTd(QTcd) measured at the end of recovery phase during exercise test should be interesting enough to be investigated. This is another limitation of this study. Fourth, the other limitation of this study is that there is no data on coronary angiogram because several patients did not undergo coronary angiography. However, according to previous reports (29, 30), exercise-stress Thallium-201 scintigraphy could detect coronary angiography proved coronary artery disease more than 90% accuracy. In this aspect, exercise-stress Thallium-201 scintigraphy could be used as standard even if it is not completely accurate. Lastly, the number of each subgroup was less than 30 patients so that a large-scale study is necessary in order to draw final conclusion about the use of QT data.

The reason why the significant difference was observed between normal and fixed defect groups is not clear and could not be explained from the results of this study. However, fixed

defect sometimes include small amount of peri-infarction ischemia. We suggest that this small amount of exercise-induced myocardial ischemia could possibly reflect the significant difference of QTd (QTcd) between two groups.

Conclusion

The computer measured QTd and/or QTcd is a good marker for exercise-induced myocardial ischemia. QTd and/or QTcd determined after exercise can improve the accuracy of diagnosing myocardial ischemia in routine clinical practice. Especially, QTd add a possible compensatory diagnostic power to conventional ST-segment change so that QTd could be useful as a new diagnostic tool during exercise stress testing. Considering medical care costs, and given that regular treadmill exercise stress testing is much less expensive than exercise-stress Thallium-201 scintigraphy, use of computer measured QTd and/or QTcd could have a great impact on the medical treatment of patients with suspected or known CAD.

References

1. Miranda CP, Liu J, Kadar A, Janosi A, Froning J, Lehmann KG, et al. Usefulness of exercise-induced ST-segment depression in the inferior leads during exercise testing as a marker for coronary artery disease. *Am J Cardiol* 1992; 69: 303-7.
2. Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* 1976; 85: 277-86.
3. Wu SC, Secchi MB, Radice M, Giagnoni G, Sachero A, Oltrona L, et al. Sex differences in the prevalence of ischemic heart disease and in the response to a stress test in a working population. *Eur Heart J* 1981; 2: 461-5.
4. Ellestad MH, Savitz S, Bergdall D, Teske J. The false positive stress test. Multivariate analysis of 215 subjects with hemodynamic, angiographic and clinical data. *Am J Cardiol* 1977; 40: 681-5.
5. Zabel M, Malik M, Hnatkova K, Papademetriou V, Pittaras A, Fletcher RD, Franz MR. Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. *Circulation* 2002; 105: 1066-70.
6. Stolestiy LN, Pai RG. Value of QT dispersion in the interpretation of exercise stress test in women. *Circulation* 1997; 96: 904-10.
7. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994; 343: 327-9.
8. Lee KW, Kligfield P, Dower GE, Okin PM. QT dispersion, T wave projection and heterogeneity of repolarization in patients with coronary artery disease. *Am J Cardiol* 2000; 87: 148-51.
9. Xue Q, Reddy S. Algorithms for computerized QT analysis. *J Electrocardiol*. 1998;30 (Suppl): 181-6.
10. Chaitman BR. Exercise stress testing. In: Braunwald E, editor. *Heart disease - 5th ed.* Philadelphia; W.B. Saunders Company 1997: 161-3.
11. Cheng J, Kamiya K, Liu W, Tsuji Y, Toyama J, Kodama I. Heterogeneous distribution of the two components of delayed rectifier K⁺ current: a potential mechanism of the proarrhythmic effects of methanesulfonanilide class III agents. *Cardiovascular Res* 1999; 43: 135-47.
12. Inoue M, Shimizu M, Ino H, Yamaguchi M, Terai H, Hayashi K, et al. Q-T peak dispersion in congenital long QT syndrome - possible marker of mutation of HERG-. *Circ J* 2003; 67: 495-8.

13. Lee KW, Kligfield P, Dower GE, Okin PM. QT dispersion, T-wave projection, and heterogeneity of repolarization in patients with coronary artery disease. *Am J Cardiol* 2001; 87: 148-51.
14. Macfarlane PW, McLaughlin SC, Rodger JC. Influence of lead selection and population on automated measurement of QT dispersion. *Circulation* 1998; 98: 2160-7.
15. Kligfield P, Okin PM, Lee KW, Dower GE. Significance of QT dispersion: replay (letter). *Am J Cardiol* 2003; 91: 1291.
16. Savelieva I, Yap YG, Yi G, Guo X, Camm AJ, Malik M. Comparative reproducibility of QT, QT peak, and T peak-T end intervals and dispersion in normal subjects, patients with myocardial infarction, and patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 1998; 21 (11 Pt 2): 2376-81.
17. Glancy JM, Garratt CJ, Woods KL, Bono DP. QT dispersion and mortality after myocardial infarction. *Lancet* 1995; 345: 945-8.
18. Zabel M, Acar B, Klingenheden T, Franz MR, Hohnloser SH, Malik M. Analysis of 12-lead morphology for risk stratification after myocardial infarction. *Circulation* 2000; 102: 1252-7.
19. Okin PM, Devereux RB, Fabsitz RR, Lee ET, Galloway JM, Howard BV. Principal component analysis of T wave and prediction of cardiovascular mortality in American Indians. *Circulation* 2002; 105: 714-9.
20. Schneider CA, Voth E, Baer FM, Horst M, Wagner R, Sechtem U. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. *Circulation* 1997; 96: 3913-20.
21. Kelly RF, Parillo JE, Hollenberg SM. Effect of coronary angioplasty on QT dispersion. *Am Heart J* 1997; 134: 399-405.
22. Moreno FL, Vilanueva MT, Karagounis LA, Anderson JL. Reduction in QT interval dispersion by successful thrombolytic therapy in acute myocardial infarction. *Circulation* 1994; 90: 94-100.
23. Sporton, SC, Taggart P, Sutton PM, Walker JM, Hrdman SM. Acute ischemia: a dynamic influence on QT dispersion. *Lancet* 1997; 349: 306-9.
24. Takase B, Tujimoto T, Kitamura K, Hamabe A, Uehata A, Isojima K, et al. Angioplasty decreases QT dispersion in patients with angina pectoris but not in patients with prior myocardial infarction. *Clin Cardiol* 2001; 24: 127-31.
25. Carluccio E, Biagioli P, Bentivoglio M, Mariotti M, Politano M, Savino K, et al. Effects of acute myocardial ischemia on QT dispersion by dipyridamole stress echocardiography. *Am J Cardiol* 2003; 91: 385-90.
26. Kautzner J, Yi G, Camm AJ, Malik M. Short- and long-term reproducibility of QT, QTc, and QT dispersion measurement in healthy subjects. *Pacing Clin Electrophysiol* 1994; 17 (5 Pt 1): 928-37.
27. Schmidt M, Schneider C, Theissen P, Erdmann E, Schicha H. QT dispersion in comparison to TI-201-SPECT for detection of myocardial ischaemia. *Int J Cardiol* 2006; 113: 327-31.
28. Masaki N, Takase B, Matsui T, Kosuda S, Ohsuzu F, Ishihara M. QT peak dispersion, not QT dispersion, is a more useful diagnostic marker for detecting exercise-induced myocardial ischemia. *Heart Rhythm* 2006; 3: 424-32.
29. Sharir T, Bacher-Stier C, Dhar S, Lewin HC, Miranda R, Friedman JD, et al. Identification of severe and extensive coronary artery disease by postexercise regional wall motion abnormalities in Tc-99m sestamibi gated single-photon emission computed tomography. *Am J Cardiol* 2000; 86: 1171-5.
30. Lima RS, Watson DD, Goode AR, Siadat MS, Ragosta M, Beller GA, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. *J Am Coll Cardiol* 2003; 42: 64-70.