Changes in QT Dispersion during Adenosine Infusion

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Summary

Background: QT dispersion (QTd) measurement during treadmill stress testing has been shown to improve the accuracy of exercise electrocardiogram (ECG) in the detection of significant coronary artery disease (CAD).

Hypothesis: The aim of this study was to determine whether adenosine-induced changes in QTd could predict significant CAD and to assess its efficacy as a diagnostic index in patients undergoing adenosine stress test.

Methods: QT interval measurements were made in 57 consecutive patients undergoing adenosine sestamibi stress test. Patients with an abnormal stress test underwent coronary angiography. Patients with significant disease by coronary angiography (> 70% stenosis) were classified as having CAD (Group 1), and those with normal stress images and/or normal coronaries by angiography were classified as having no CAD (Group 2).

Results: QT dispersion increased from 28.2 ± 4.5 to 43.8 ± 4.5 ms with a Δ QTd of 15.53 ± 3.68 in Group 1 ($p = 0.001$) and from 28.4 ± 2.6 to 34.8 ± 2.8 ms with a Δ QTd of 6.58 ± 2.21 ms in Group 2 ($p = 0.006$). Patients in Group 1 had a significantly higher increase in QTd (Δ QTd) than the patients in Group 2 ($p < 0.03$). Addition of Δ QTd (> 10 ms) to the ST depression during adenosine infusion would increase the sensitivity of the ECG from 23 to 65% and decrease the specificity from 91 to 70% for diagnosis of significant CAD.

Conclusions: Δ QTd is significantly more prolonged in patients with CAD during adenosine infusion. It increases the sensitivity of the stress ECG in diagnosis of CAD during adenosine infusion when used as an adjuvant index.

Key words: adenosine, QT dispersion, repolarization, stress testing

Introduction

QT dispersion (QTd), a marker of regional variation of ventricular repolarization, is known to be prolonged in acute and chronic myocardial ischaemia.^{1, 2} It also has been shown to decrease after angioplasty and thrombolysis.^{3, 4} Recently, there have been attempts to utilize this parameter to detect coronary artery disease (CAD) noninvasively in patients with chronic CAD. Measurement of QTd during treadmill stress test has been shown to improve the accuracy of exercise electrocardiogram (ECG) in the detection of significant CAD in both men and women.^{5–7} With the aging of the population, chemical stress, that is, adenosine, is an increasingly used modality to detect CAD. The ECG changes during adenosine infusion have a very low sensitivity (10–30%) in detecting CAD.⁸ There are few reports in the literature of increase in QTd during adenosine or dipyridamole infusion.^{8–10}

The aim of this study was to determine whether chemical stress (adenosine)-induced changes in QTd could predict significant CAD and to assess its efficacy as a diagnostic index in patients undergoing adenosine stress test.

Methods

All patients who underwent adenosine sestamibi stress test at our stress laboratory over a period of 6 months were prospectively included in this study. Patients with atrial arrhythmias, intraventricular conduction delays, paced rhythm, and patients on medications that prolong QT interval were excluded.

Study Protocol

After giving informed consent, patients received an infusion of adenosine at 140 μ g/kg/min for 6 min. Sestamibi was injected at peak stress and images were obtained immediately and 3 to 4 h post infusion (stress–rest sequence). Patients with reversible defect on these images went on to have coronary angiograms. Stress images and angiograms were reviewed by two independent investigators. Stenosis in the coronary arteries of > 70% of luminal diameter was defined as significant.

Twelve-lead ECGs were obtained at rest and 2, 4, and 6 min during adenosine infusion in patients undergoing adenosine sestamibi stress test.

Patients with significant disease by coronary angiography (> 70% stenosis) were classified as having CAD (Group 1), and those with normal stress images and/or normal coronaries by angiography were classified as having no CAD (Group 2).

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QT Analysis

QT interval was measured from the beginning of the QRS complex to the end of the T wave. QT dispersion was obtained using a semiautomated system ("QT GUARD" GE-Marquette Electronics, Milwaukee, Wisc., USA) with manual overread. Briefly, the end of the T wave was identified in each lead using the least square fit method from the digitized ECG. Leads in which the end of the T wave could not be identified were excluded from the analysis. QT dispersion was calculated as the difference between the maximum and minimum QT interval. Δ QT dispersion was obtained by subtracting QTd at rest from maximum QTd during the test. Patients with fewer than six valid leads for QT analysis were excluded from the analysis.

To assess reproducibility of the method of QT measurement, two ECGs were obtained at rest 5 to 10 min apart in 15 patients selected at random. The average variability noted between the two baseline measurements was only 5 ms for a QT interval with a correlation coefficient of 0.98 ($p < 0.0001$) and 3.5 ms for QTd with a correlation coefficient of 0.72 ($p = 0.003$).

Statistical Analysis

All intervals are presented as mean $\pm$ standard error (SE). Statistical analysis was performed using the paired Student's *t*-test for comparison of QTd before and after stress. The independent samples *t*-test was performed to compare the two groups. Probability of $< 5\%$ (0.05) was considered significant. Statistical Package for Social Sciences (SPSS) pc software (version 8.0) (SPSS, Inc., Chicago, Ill., USA) was used for statistical analysis.

Results

The study included 57 patients (23 men, 34 women). Eight patients (14%) were excluded because fewer than six valid leads were available for QTd analysis. In all, 17 patients in Group 1 and 32 patients in Group 2 were eligible for QTd analysis.

Baseline characteristics of the eligible patients in the two groups are shown in Table I. The two groups were well matched in all factors known to influence baseline QT interval and QTd (Table I).

The results of QT analysis of the patients in Group 1 are presented in Table II (mean $\pm$ SE). Baseline QT and QTc intervals at rest were comparable in the two groups. QT dispersion was noted to increase on adenosine infusion in both groups (from 28.2 ± 4.5 to 43.8 ± 4.5 ms with a Δ QTd of 15.53 ± 3.68 (confidence interval [C.I.] 7.74–23.32) in Group 1 ($p = 0.001$). QT dispersion increased from 28.4 ± 2.6 to 34.8 ± 2.8 ms with a Δ QTd of 6.58 ± 2.21 ms (CI 2.07–11.09) in Group 2 ($p = 0.006$). There was borderline statistical significance in the difference between the maximum QTd measured during stress in the two groups (43.8 ± 4.5 ms [Group 1] and 34.8 ± 2.8 ms [Group 2]) ($p = 0.08$). However, the patients with significant coronary stenosis (Group 1) had a significantly higher increase in the QTd (Δ QTd) than the patients with normal coronaries (Group 2) ($p < 0.03$) (Table II).

TABLE I Baseline clinical data on the patients

	Group 1 (n = 17)	Group 2 (n = 31)
Age (years)	69 $\pm$ 2	63 $\pm$ 2
Sex (M: F)	7:10	9:22
HTN (%)	13 (76)	20 (65)
LVH by ECG (%)	8 (47)	13 (42)
History of CAD (%)	6 (35)	12 (39)
Beta blockers (%)	7 (41)	12 (39)
CHF (%)	4 (23)	7 (22)

Abbreviations: M = male, F = female, HTN = hypertension, CAD = coronary artery disease, CHF = congestive heart failure, LVH = left ventricular hypertrophy, ECG = electrocardiogram.

TABLE II QT, QTc interval, and QT dispersion analysis data at rest and stress (mean $\pm$ standard error)

	Group 1 (n = 17)	Group 2 (n = 31)	Significance (p)
QT rest (ms)	405 $\pm$ 12	389 $\pm$ 6.6	NS
QTc rest (ms)	426 $\pm$ 6.5	419 $\pm$ 3.3	NS
QT stress (ms)	397 $\pm$ 10	381 $\pm$ 5.7	NS
QTc stress (ms)	422 $\pm$ 6	423 $\pm$ 4.2	NS
QTd rest (ms)	28.2 $\pm$ 4.5	28.4 $\pm$ 2.6	NS
QTd stress (ms)	43.8 $\pm$ 4.5	34.8 $\pm$ 2.8	NS
Δ QTd (ms)	15.5 $\pm$ 3.7	6.5 $\pm$ 2.2	0.03

Abbreviations: QTd = QT dispersion, QTc = corrected QT interval.

The ECG was positive for ischemic changes in only four patients during adenosine infusion, each of them with documented CAD by angiography (Group 1). The sensitivity and specificity of ST depression on ECG for diagnosis of CAD were 23 and 91%, respectively. Using an arbitrary value of Δ QTd > 10 ms for the diagnosis of significant CAD, the sensitivity, specificity, positive predictive value, and negative predictive value increased to 59, 66, 48, and 75%, respectively, during adenosine infusion. Addition of Δ QTd to the ST depression as an adjuvant index would increase the diagnostic yield of the ECG during adenosine infusion to 65% sensitivity and 70% specificity.

Discussion

The results of our study confirm that QTd increases in CAD during adenosine infusion-induced cardiac stress. It conforms to the earlier reports of increase in QTd noted in patients with CAD on treadmill stress testing.^{5,6} Adenosine causes relative ischemia in the myocardium by preferentially diverting blood to normal coronary vessels rather than to atherosclerotic vessels. Increase in QTd noted during such a relative ischemic state suggests that QTd is a very sensitive and early marker of myocardial ischemia. The magnitude of change in QTd between rest and stress noted in our study was much smaller

than that noted in the studies involving treadmill stress test⁵⁻⁷ but is comparable with the prior reports involving chemical stress.⁹⁻¹¹ Reproducibility has been a major drawback in using QTd as a diagnostic parameter because of inconsistencies in its measurement due to both intra- and interobserver variability.¹²⁻¹⁴ Measurements of QT interval using a computerized algorithm has been suggested to decrease the 20–30% intraobserver variation noted in manual measurements.^{14, 15} Using such a computerized algorithm, we have been able to show better reproducibility in the measurement of QT interval and QTd, making Δ QTd a more reliable and reproducible diagnostic index.

ST depression in ECG during adenosine infusion has been reported to have a low sensitivity—15% in women and about 30% in a predominantly male group—with very high specificity;⁸ hence, the sensitivity of 16% noted in our study group is no surprise. Addition of Δ QTd as an adjuvant parameter along with ST depression increases the sensitivity of the ECG up to 65% with a specificity of 70%, comparable with the exercise ECGs. Hence, the addition of a computer software to the stress ECG machines to obtain these measurements would make the ECGs more informative during chemical stress. However, as an independent diagnostic index, Δ QTd seems to be limited by its low sensitivity and specificity. Its negative predictive value seems to be of most clinical relevance. Moreover, the inability to obtain QTd in patients with atrial arrhythmias or bundle-branch blocks, patients on medications that prolong QT interval, and patients with a paced rhythm excludes a sizeable group of patients. Added to this is the need for high-quality recordings with minimal baseline variations to have more than six leads valid for QTd analysis. This could be a major issue in treadmill stress testing, hence excluding significant number of patients.

This study is limited by the relatively small size of the study population groups. Furthermore, no angiograms were performed in patients with a normal stress image. As these patients had a post-test probability for CAD of <5% after a negative scan, we do not expect this to have a significant effect on the result. In addition, validity of the concept of QTd has been questioned. In a prospective evaluation of discharge ECGs in 280 patients post myocardial infarction, 83% of whom were on beta blockers, Zabel *et al.* found no prognostic value for any of the indices of ventricular repolarization.¹⁶ In an accompanying editorial, Coumel *et al.* suggest that QTd could be related more to the projection effect than local activity, especially in the limb leads.¹⁷ They also point out the need for further technical refinement, a closer look at QT dynamicity, and caution against the use of a single value of QTd to draw conclusions. We believe that our results would still be valid, as the measurement and comparison of QTd in patients before and after an intervention leading to ischemia, using a reproducible method as in our study, addresses many of the above concerns.

Conclusion

Δ QT dispersion is significantly more prolonged in patients with CAD during adenosine infusion. It increases the sensitiv-

ity of the stress ECG in the diagnosis of CAD during adenosine infusion when used as an adjuvant index. As a diagnostic index, Δ QTd is limited by its low sensitivity and specificity. Technical difficulties in the measurement of QTd limit its use in all patients.

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