Electrocardiography

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QT-Interval Dispersion in Acute Myocardial Infarction Is Only Shortened by Thrombolysis in Myocardial Infarction Grade 2/3 Reperfusion

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Summary

Background: Increased QT interval dispersion (QTd) has been found in patients with acute myocardial infarction (AMI). In previous studies this has been shown to decrease with thrombolysis.

Hypothesis: The aim of this study was to compare the effects of reperfusion by primary percutaneous transluminal coronary angioplasty (PTCA) and by thrombolysis on QTd and correlate these results with the degree of reperfusion.

Methods: We studied 60 patients with a first AMI. The study cohort included 40 consecutive patients who had received thrombolysis (streptokinase or rt-PA); 20 additional consecutive patients with successful primary PTCA, all with preselected Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow by predefined selection criteria (12 stents); and 20 controls. A 12-lead ECG for QTd calculation was recorded before thrombolysis or PTCA and immediately after the procedure. All values were corrected according to Bazett's formula (QTcd). QTd and QTcd values before and after each procedure in three groups and the respective percent changes of Δ QTd and Δ QTcd were compared separately.

Results: QTd and QTcd were significantly increased before thrombolysis/PTCA versus normals. An angiogram performed after thrombolysis showed adequate reperfusion (TIMI grade

2/3) in 20 patients, while in the other 20 only TIMI 0/1 reperfusion was achieved. Thrombolysis-TIMI flow 2/3 and PTCA significantly reduced QTd (from 68 ± 10 to 35 ± 8 ms, $p < 0.001$, Δ QTd = $48 \pm 11\%$, in the Thr-TIMI flow 2/3 group, and from 79 ± 11 to 38 ± 9 ms, $p < 0.001$, Δ QTd = $52 \pm 9\%$, in the PTCA group), while in the Thr-TIMI flow 0/1 group no significant changes were recorded. A percent QTd decrease $> 30\%$ had 96% sensitivity, 85% specificity, and 93% positive and 94% negative predictive value, respectively, for TIMI 2/3 flow.

Conclusions: A significant decrease in QT dispersion may provide an additional electrocardiographic index for successful (TIMI 2/3) reperfusion.

Key words: thrombolysis, primary percutaneous transluminal coronary angioplasty, acute myocardial infarction, QT dispersion

Introduction

Previous studies have shown that the QT interval in a 12-lead electrocardiogram (ECG) varies from lead to lead.^{1,2} QT interval dispersion (QTd) is defined as the difference between the minor and major QT values in a 12-lead ECG. This dispersion reflects regional variation of the ventricular repolarization,^{3–5} which may cause ventricular reentry and severe ventricular arrhythmias. An increased QTd is considered a marker of susceptibility to ventricular arrhythmias.^{6–8} QT dispersion is also increased in heart failure, ventricular hypertrophy, and myocardial infarction.^{9–14} Successful thrombolysis (Thrombolysis in Myocardial Infarction [TIMI] 2/3 or 3) in the context of the Second Thrombolytic trial of Eminase (anistreplase) in Acute Myocardial Infarction (TEAM-2) trial has been shown to lower the increased QTd in acute myocardial infarction (AMI).¹⁵

The aim of this study was to assess the influence of reperfusion by primary percutaneous transluminal coronary angiography (PTCA) and thrombolysis on QTd in AMI and to correlate it with the degree of reperfusion achieved.

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Methods

Patients

The cohort included 60 patients with a first AMI who were studied retrospectively. All patients presented with ST-segment elevation (≥ 0.1 mV in at least two contiguous leads), typical symptoms, and/or creatine phosphokinase (CPK)-MB levels elevated above normal by at least twofold.

Forty consecutive patients received thrombolytic therapy (streptokinase or recombinant tissue plasminogen activator [rt-Pa]) within the first 6 h of onset of symptoms.

Twenty patients who underwent primary PTCA during the acute phase of MI and in whom TIMI grade-3 flow was achieved, comprised a comparison group. Patients were excluded if they were not in sinus rhythm or showed any intraventricular conduction disturbance in their ECGs.

A control group of 20 healthy individuals was also included.

Coronary Angiography

Angiography to determine perfusion status was performed 2 to 4 h after the administration of thrombolytic therapy. One experienced observer (S.F.) assessed coronary reperfusion using the TIMI classification system:¹⁶ grade-0: no antegrade flow beyond the point of occlusion; grade-1: contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction; grade-2: the contrast opacifies the artery distal to the obstruction, but with a delayed rate of entry or clearance of contrast into and from the vessel; grade-3: complete perfusion—the contrast opacifies the artery with normal rate of entry and clearance. Patients were divided into two groups according to the results of thrombolytic therapy: reperfusion group ([Thr]-TIMI flow 2/3) and occlusion group (Thr-TIMI flow 0/1).

Using the same system, the coronary perfusion status in the additional 20 patients who underwent primary PTCA was assessed by two experienced operators (G.P., V.V.).

Electrocardiography

Simultaneous 12-lead ECGs were recorded at a paper speed of 25 mm/s when patients arrived at the Emergency Department and upon completion of thrombolytic therapy or PTCA. Using electronic calipers, QT interval and QTd were measured from the onset of QT to the end of the T wave (defined as return to the TP baseline) after the ECG had been scanned and digitized with custom-made software. In the case of prominent U waves, the nadir of the curve between the T and U wave was used as the end of the T wave. When the accurate calculation of the QT interval in a lead was not possible, it was not used. Measurement of a minimum of seven leads with at least three precordial leads was required for inclusion of the patient. To minimize any inaccuracy in the measurement of the QT interval, three to five measurements of the QT were taken from each lead, and from these values a mean QT was calculated.¹⁷ For the same reason, ECGs with very abnormal/low-amplitude T waves were excluded. Furthermore, the heart rate-cor-

rected QT interval (QTc) values according to Bazett's formula^{18,19} were calculated as follows: $QTc = QT / \text{square root of the RR interval in s}$. The QTd was measured by subtracting the minimal from the maximal QT value in all ECGs. QTc dispersion (QTcd) was calculated similarly to QT dispersion. Percent changes of QT and QTc dispersion ($\Delta QTd\%$, $\Delta QTcd\%$) induced by the reperfusion procedures were also calculated.

Statistical Analysis

The two groups were further subdivided according to the reperfusion procedure and degree of reperfusion: Group A1: Thr-TIMI flow 2/3; Group A2: Thr-TIMI flow 0/1; and Group B: PTCA group (TIMI flow 3 by definition). We compared QT and QTcd before and after each procedure in the three subgroups, as well as the respective percent changes (ΔQTd , $\Delta QTcd$), with data collected from 20 healthy individuals studied at the Onassis Cardiac Surgery Center. All the results were expressed as mean $\pm$ standard deviation (SD). For comparison among the four groups, Student's unpaired *t*-test was used. The paired *t*-test was used for postprocedural changes. Sensitivity, specificity, and positive and negative predictive values for the percent QTd changes pertaining to the degree of reperfusion were also calculated.

Results

Achievement of Coronary Flow

The clinical and angiographic data of our patients are shown in Table I.

Forty patients received thrombolytic therapy (streptokinase or rt-PA). Coronary angiography showed that the 20 patients in Group A1 (15 men, 5 women, mean age 57 ± 13 years) had satisfactory reperfusion (TIMI grade 2/3).

In Group A2, 20 patients (18 men, 2 women, mean age 55 ± 7 years) had no satisfactory reperfusion (TIMI grade 0/1).

In Group B (PTCA), all 20 patients (17 men, 3 women, mean age 60 ± 12 years) had adequate reperfusion at the end of the procedure (TIMI grade 3, by preselection). Stents were placed in 12 patients.

Normal controls were 23–75 (mean 57 ± 10) years of age, free of hypertension, coronary artery disease or valve disease, and had normal ECGs, specifically without left ventricular hypertrophy or conduction defects (Table II).

QT Dispersion Data (Figs. 1, 2)

The QTd and QTcd of our healthy controls were 31 ± 12 and 45 ± 15 , respectively.

During the acute phase of MI and before any intervention, the QTd and QTcd were greater than the normal values. The average QTd was 68 ± 10 , 78 ± 13 , 79 ± 11 (ms) and the average QTcd was 81 ± 19 , 92 ± 25 , 92 ± 18 (ms) in the Thr-TIMI grade 2/3, Thr-TIMI grade 0/1, and PTCA groups, respectively (not significant between groups).

TABLE I Clinical and angiographic data of patients studied

	PTCA (n = 20)	Thr-TIMI 2/3 (n = 20)	Thr-TIMI 0/1 (n = 20)	Controls (n = 20)
Sex	17M, 3F	15M, 5F	18M, 2F	12M, 8F
Age	60 (12)	57 (13)	55 (7)	57 (10)
MI	11 An, 8 In, 1La	5 An, 12 In, 2 AL, 1L	9 An, 8 In, 3 La	
Art	11 LAD, 8 RCA, 1 Cx	7 LAD, 13 RCA	9 LAD, 8 RCA, 3 Cx	
Thr		13 Sk, 7 rtPA	11 Sk, 9 rtPA	
TIMI flow	20 (3)	9 (3), 11 (2)	11 (0), 9 (1)	

Abbreviations: PTCA = percutaneous transluminal coronary angioplasty, Thr = thrombolysis, M = male, F = female, MI = myocardial infarction, An = anterior, In = inferior, La = lateral, Art = artery, LAD = left anterior descending artery, RCA = right coronary artery, Cx = circumflex, SK = streptokinase, rtPA = recombinant tissue plasminogen activator.

TABLE II QTd and QTc changes after PTCA and after thrombolysis in the Thr-TIMI 2/3 and 0/1 groups, compared with controls

	PTCA	Thr-TIMI 2/3	Thr-TIMI 0/1	Controls
Pre QTd	79 (11)	68 (10)	78 (13)	31 (12)
Pre QTcd	92 (18)	81 (19)	92 (25)	45 (15)
Post QTd	38 (9) ^a	35 (8) ^a	67 (16)	
Post QTcd	46 (11) ^a	45 (12) ^a	77 (22)	
PreQT	380 (53)	380 (37)	369 (39)	
PreQTc	434 (38)	422 (31)	418 (30)	
PostQT	388 (41)	379 (39)	382 (36)	
PostQTc	448 (53)	421 (19)	416 (42)	
%ΔQTd	52 (9)	48 (11)	15 (10) ^a	
%ΔQTcd	48 (14)	44 (15)	16 (10) ^a	

^a $p < 0.001$. *Abbreviations:* QTd = QT dispersion, QTcd = QT dispersion corrected for heart rate. Other abbreviations as in Table I.

FIG. 1 In the reperfusion group, %ΔQTd and %ΔQTcd were similar but remarkably greater than the corresponding values for the occlusion group. ■ = Pre-procedure, □ = post procedure. PTCA = percutaneous transluminal coronary angioplasty, Thr = thrombolysis, TIMI = Thrombolysis in Myocardial Infarction trial. * $p < 0.001$.

FIG. 2 Increased QT dispersion (QTd) in acute myocardial infarction decreased significantly (* $p < 0.001$) in the PTCA and Thr-TIMI grade 2/3 groups, while it remained almost the same in the Thr-TIMI grade 0/1 group. Abbreviations as in Figure 1. * $p < 0.001$.

After reperfusion therapy, average QTd and QTcd were reduced significantly in Thr-TIMI grade 2/3 (35 ± 8 , 45 ± 12 ms, $p < 0.001$) and PTCA (38 ± 9 , 46 ± 11 ms, $p < 0.001$) groups.

No remarkable changes were seen in the Thr-TIMI grade 0/1 group (67 ± 16 , 77 ± 22 ms, $p > 0.05$).

We emphasize that the T-wave morphology/amplitude and QT/QTc duration were not significantly changed in Groups A1, A2, and B ($380 \pm 37/422 \pm 31$, $369 \pm 39/418 \pm 30$, $380 \pm 53/434 \pm 38$ vs. $379 \pm 39/421 \pm 19$, $382 \pm 36/416 \pm 42$, $388 \pm 41/448 \pm 53$), respectively.

There were no significant differences between the %ΔQTd and %ΔQTcd changes in the Thr-TIMI grade 2/3 and PTCA groups (48 ± 11 , 44 ± 15 vs. 52 ± 9 , 48 ± 14 , $p > 0.05$). These changes were significantly greater than the %ΔQTd and %ΔQTcd in the Thr-TIMI grade 0/1 group (15 ± 10 , 16 ± 10 , $p < 0.001$) (Table III).

Changes were similar in the Thr-TIMI grade 2 (11 patients, ΔQTd = 47%, ΔQTcd = 45%) and the Thr-TIMI grade 3 (9 patients, ΔQTd = 51%, ΔQTcd = 45%) groups.

Our results showed that a %QTd and %QTcd reduction > 30 had a 96 and 80% sensitivity, an 85 and 95% specificity, and 93 and 97% positive and 94 and 70% negative predictive values, respectively, for predicting achievement of TIMI grade 2/3 perfusion (Table III).

TABLE III Diagnostic accuracy of QTd changes for predicting TIMI 2/3 flow

	Sensitivity	Specificity	(+) Predictive value	(-) Predictive value
% Δ QTd > 30 (%)	96	85	93	94
% Δ QTcd > 30 (%)	80	95	97	70

Abbreviations as in Table II.

Discussion

Overall left ventricular function and prognosis of patients with MI are related to successful reperfusion and an open infarct-related coronary artery.²⁰ The early establishment of adequate coronary blood flow is equally important.

During the acute phase of MI, the ventricular susceptibility to severe ventricular arrhythmias and arrhythmic death is a major risk. Our findings, which showed increased QTd during the first hours of MI, are in accordance with previous studies.^{14, 15}

Karagounis *et al.* showed that successful thrombolysis reduces increased QTd in AMI.²¹ Paventi *et al.* found that thrombolysis did not cause significant changes of QTd on Day 3 but on Day 10 of AMI.²² However, there is no general agreement on the significance of this finding. Thus, Fiol *et al.*²³ found no difference in mean QTc, the percentage of leads with a QTc > 440 ms, and the QTd itself in 272 patients who did or did not develop ventricular fibrillation in AMI.

The present study demonstrated that both pharmaceutical (thrombolysis) and mechanical (PTCA) reperfusion in AMI had beneficial effects from the arrhythmic point of view by promptly decreasing the QTd close to the values of healthy individuals. This is the first report on the acute influence of both reperfusion therapies on QTd, as well as on the comparison between them, which showed similar favorable results when adequate reperfusion was achieved.

From our findings we also determined the %QTd reduction (% Δ QTd > 30) above which TIMI 2/3 reperfusion can be predicted with a strong sensitivity, specificity, and predictive value. For this cut-off point we prefer to use QT interval values uncorrected for heart rate because of the known suboptimal correction that is given by Bazett's formula, especially for rapid heart rates.¹⁹ In the Rotterdam study, risk estimates for the various endpoints associated with QTd without correction of the QT interval for heart rate were similar but had wider 95% confidence intervals compared with the risk estimates for QTcd.²⁴ In a recent study from our institution, we found that the QTd is not affected by heart rate over a wide range of cardiac frequencies.²⁵ Zabel *et al.*²⁶ and Zareba and Moss²⁷ also showed that the QTd was independent of heart rate. We thus believe that QTd measurement may be a useful clinical tool that can correctly guide our approach to patients with AMI.

In the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) study,²⁸ TIMI 3 reperfusion was considered the most advantageous with regard to the hemodynamic picture and hospital mortality. However, as for hospital mortality, there was no significant difference between TIMI grades 2 (7.4%) and 3 (4.4%, $p < 0.08$), while there was

significant difference in mortality between TIMI grade 0 or 1 (8.9%) compared with overall TIMI grades 2 or 3 (5.7%, $p < 0.04$). Similarly, while TIMI 3 flow had significantly better ejection fraction and wall motion than TIMI 2 flow, this latter group also had better function than TIMI 0 and 1. According to our results, no differentiation could be established between patients with TIMI grades 2 and 3 flow, probably because of the small numbers, while the former group differed significantly from Groups 0–1. Buszman *et al.*²⁹ and more recently Braga *et al.*,³⁰ also grouped together TIMI grades 2 and 3 as signifying satisfactory reperfusion. Murakami *et al.*,³¹ using an aspiration thrombectomy catheter in AMI, considered TIMI grades 3 and 2 as signifying a successful procedure. Furthermore, Kornowski *et al.*³² separated TIMI 0–1 flow in stenting of perimyocardial infarction syndromes.

Study Limitations

The small number of patients is a limitation of our study. We tried to enroll patients with a technically acceptable ECG to avoid possibly misleading results. This is not always easy in the context of an AMI. With greater numbers, differences in QTd between TIMI 2 and 3 might have emerged. The difficulties in the definition of the end of the T wave are known, and therefore we excluded patients if reliable measurement of QT interval was not possible in at least seven leads in their ECGs. There were also no significant T(U)-wave morphology/amplitude differences among the three groups, which could affect our results. The value of QTd is still under discussion. According to Malik and Batchvarov,⁴² QTd is a crude and approximate measure of abnormality of the complete course of repolarization. It is probable that only grossly abnormal values (e.g., ≥ 100 ms), outside the range of measurement error have practical value. Moreover, according to Franz and Zabel³³ there are two main hypotheses to explain the electrophysiologic basis of QTd. The local hypothesis explaining QTd with spatial differences in action potential duration mirrored in the various QT intervals competes with the global hypothesis explaining the variation in surface ECG measurements with different projections of a common T-wave vector.

Another limitation is the lack of follow-up for ventricular arrhythmia development in these patients. It would be useful to compare the acute changes of QTd with other arrhythmogenic markers (late potentials, heart rate variability)^{34–38} and other electrocardiographic markers of successful reperfusion, such as a prompt decrease of ST elevation.³⁹ Kostis and Belina found that QTd offers valuable information in combination with heart rate variability.⁴⁰ Lee *et al.* consider that QTd in ad-

dition to ejection fraction and late potentials gives independent information concerning ventricular arrhythmia induction during electrophysiologic studies.⁴¹

Conclusions

Our findings are in accordance with preexisting limited evidence¹⁵ that a significant decrease in QT dispersion is a marker of TIMI grade 2/3 reperfusion, achieved either with thrombolysis or PTCA. Whether this sign can have incremental value in addition to previously proposed markers, together with its possible beneficial effect on ventricular arrhythmias at follow-up, remains to be evaluated.

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