The effect of thrombolytic therapy on QT dispersion in acute myocardial infarction and its role in the prediction of reperfusion arrhythmias

E Ornek, M Duran[1], D Ornek[2], BM Demirçelik[3], S Murat[4], A Kurtul[4], H Çiçekçioğlu, M Çetin, K Kahveci[2], C Doger[5], Z Çetin

Departments of Cardiology and [2]Anesthesiology and Reanimation, Ankara Numune Training and Research Hospital, [3]Cardiology, Fatih University Hospital, [4]Cardiology, Ankara Training and Research Hospital, [5]Health, The Ministry of health, Ankara, [1]Cardiology, Kayseri Training and Research Hospital, Kayseri, Turkey

Abstract

Purpose: We aimed to determine the effect of intravenous thrombolytic therapy on QT dispersion (QTd) and its role in the prediction of reperfusion arrhythmias.

Materials and Methods: Twenty patients with acute myocardial infarction (MI) were enrolled in the study. Measurements of QTd were carried out prior to thrombolytic therapy and before discharge. The patients were examined for ventricular arrhythmias with 24-h Holter electrocardiography monitoring after treatment and the relationship between ventricular arrhythmias and the QTd values in the early phase of MI was investigated.

Results: The values of QTd were significantly higher during the early phase of MI (60 ± 5.32 ms) than those in the late phase (53.35 ± 4.07 ms) (P = 0.032).

There was no correlation between isolated, bigeminal, trigeminal and total ventricular premature beats, accelerated idioventricular rhythm (AIVR) with QTd values. However, the patients with sustained ventricular tachycardia (VT), prolonged VT and sustained AIVR had higher corrected QTd (92 $ms^{1/2}$, 97.8 $ms^{1/2}$, 81.7 $ms^{1/2}$, respectively) than the patients without these arrhythmias (74 $ms^{1/2}$, 56.3 $ms^{1/2}$, 58.28 $ms^{1/2}$, respectively) (P = 0.022, 0.013, 0.018).

Conclusion: The values of QTd may be significantly reduced in the 1st week of acute MI and measurement of QTd in the early phase of MI may have a correlation with the following reperfusion arrhythmias: Sustained VT, prolonged VT and AIVR.

Key words: Arrhythmia, myocardial infarction, QT dispersion, reperfusion, thrombolytic therapy

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Introduction

The variation in QT interval between surface electrocardiography (ECG) leads has been considered to be valuable clinical data reflecting heterogeneity of ventricular recovery.[1] QT dispersion (QTd) is defined as the difference between maximum and minimum QT intervals measured by 12-lead ECG and is considered a predictor of arrhythmia risk.[1]

Early thrombolytic therapy in cases with acute myocardial infarction (MI) results in reduced early and late mortality along with preservation of myocardial function.[2-4] However, reperfusion with lytic therapy may have an effect on electrical stability and results in reperfusion arrhythmias.[5,6] Mortality associated with arrhythmias in the acute phase of MI is still high and restoration of blood flow by thrombolysis can paradoxically elevate this risk further.[7] Regarding the safe administration of thrombolytic therapy, the risk for arrhythmias should be determined more clearly.

Address for correspondence:
Dr. Ender Ornek,
Department of Cardiology, Ankara Numune Training and Research Hospital, Ankara, Turkey.
E-mail: ender_ornek@hotmail.com

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Measurement of QTd prior to reperfusion may predict the frequency and severity of the reperfusion arrhythmias.

In the present study, we aimed to determine the effect of intravenous thrombolytic therapy on QTd and its role in the prediction of reperfusion arrhythmias within the 1st 24 h among MI patients.

Materials and Methods

This study was a prospective, cross-sectional study and 20 patients diagnosed with acute MI were enrolled in the study. Acute MI diagnosis was established in the presence of typical rise and/or fall of creatine kinase levels with typical chest pain lasting for >30 min or ECG changes consistent with an acute MI (ST segment height >0.1 mV in at least two frontal leads or >0.2 mV in at least two precordial leads). Of the patients, 12 had anterior MIs and eight had inferior MIs.

Patients, who presented within the 1st 6 h (mean, 3.4 h) after the onset of chest pain, and who were eligible for thrombolytic therapy, were treated with an intravenous streptokinase infusion of 1.5 million unit/h. All of the patients had ST segment resolution of more than 50% at 90 min of treatment and had resolution of chest pain as indicators of successful reperfusion. Just after streptokinase infusion, by placing the bipolar electrodes corresponding to a modified V5 and a ventricular fibrillation (VF) position, 24-h Holter ECG monitoring was performed on 1 day post-thrombolysis. Holter records were carried out using an Oxford® Medilog FD2 two-channel recorder. The records were transferred to a computer and automatic arrhythmia analysis was performed using Medilog® Prima Analysis System, and verified by full disclosure 24-h recording. The values of isolated and total ventricular premature beats (VPBs), as well as frequency of the accelerated idioventricular rhythm (AIVR) ≥3 consecutive VPBs < 100 beats/min), ventricular tachycardia (VT) ≥3 monomorphic or polymorphic consecutive VPBs > 100 beats/min), sustained VT (VT lasting > 30 s), sustained AIVR (lasting ≥ 32 beats), and prolonged VT (lasting ≥ 15 beats) were determined.

In all the patients, the ECGs obtained prior to thrombolytic therapy (early phase) and in the late phase before discharge (at mean 6.7 days of infarction) were analyzed. QT interval analysis was performed manually by surface ECGs at 25 mm/s rate and 10 mV amplitude. Patients with a significant intraventricular conduction defect or atrial fibrillation were excluded from the study. Each ECG with at least seven leads being technically capable of measuring was included in the study. For each lead, the mean QT interval and corrected QT (QT_c) values were measured. QT measurements were carried out according to the standard criteria.[8] In the presence of a U wave, the intersection point of T and U waves was determined as the end of the QT interval. Correction of the QT interval with respect to heart rate was performed with Bazett's formula.[9] According to this formula, QT_c was measured by dividing the QT interval (in seconds) by the square root of the RR interval value (in seconds). QTd was defined as the difference between maximum and minimum QT intervals measured by 12-lead ECG (8) and QT_c dispersion (QT_cd) was defined as the difference between the maximum and minimum QT_c. The corrected QT_cd value was obtained by dividing the QT_cd by the square root of the number of leads, which is a measure that includes for between accounts the number of leads. There is no universal definition of abnormal QTd and QT_cd limits.

Informed consent was obtained from all patients. The study was approved by our local ethical committee. All demographic and clinical data were collected.

Statistical analysis

All data were analyzed with Statistical Package for the Social Sciences (SPSS) 13.0 software (SPSS Inc., Chicago, IL, USA). The Wilcoxon test was used to analyze whether the values in two samples differ in size while continuous variables were analyzed with Mann-Whitney U test. The relationship between the QTd and other parameters were determined by simple linear regression analysis. The results were presented as the mean ± standard deviation. A $P < 0.05$ was considered as statistically significant.

Results

The mean age of the patients was 51.75 ± 2.8 years (range, 30-73 years). The clinical characteristics of the patients are presented in Table 1.

For assessing the reproducibility (verification of the accuracy) of QT_cd measurements, different QT_cd measurements were performed randomly on 52 leads by two different raters. An insignificant average difference of 5 $ms^{1/2}$ was determined between the measurements of the two raters.

QTd and QT_cd values measured in the early MI phase

Table 1: Clinical characteristics of the patients

Clinical characteistics	Patients (*n*=20)
Mean age (±SD), years	51.75±2.8
Female, *n* (%)	1 (5)
Male, *n* (%)	19 (95)
MI history (+), *n* (%)	3 (15)
Hypertension, *n* (%)	5 (25)
Diabetes, *n* (%)	1 (5)
Smoking, *n* (%)	14 (70)
Anterior MI, *n* (%)	12 (60)
Inferior MI, *n* (%)	8 (40)

MI=Myocardial infarction; SD=Standard deviation

according to the location of infarction are outlined in Table 2. There was no significant difference between the QTd values of patients with inferior and anterior MI.

QTd, QT_cd, corrected QT_cd, and maximum and minimum values of QT and QT_c intervals before and after the thrombolytic therapy are shown in Table 3. The values of QTd (ms), QT_cd ($ms^{1/2}$) and corrected QT_cd (ms) of the patients were significantly higher during the early phase of MI than those in the late phase of MI. The decreases in the values of QTmax and QT_cmax after the thrombolytic therapy led to these differences.

During the hospitalization period, four patients (25%) developed clinical heart failure, one patient (5%) died, and one patient (5%) developed VF. The values of QT_cd and corrected QT_cd in patients who did and did not develop complications is presented in Table 4. Although the number of patients was not sufficient to make statistical comparisons, dispersion values of the patients who died or developed VF were considerably higher than the overall average values. There was no significant difference between the values of QT_cd and corrected QT_cd in patients with and without heart failure. Simple linear regression analysis revealed no correlation between the ejection fraction and peak creatine kinase levels, and QT_cd values in the late phase of MI in all patients.

Table 2: QT dispersion values according to the location of infarction during the early phase of myocardial infarction

QT dispersion values	Inferior MI (*n*=8)	Anterior MI (*n*=12)	*P*
QTd (ms)	64.81±6.85	57.04±4.14	0.23
QT_cd ($ms^{1/2}$)	82.56±9.9	70.33±6.11	0.18

MI=Myocardial infarction; QTd=QT dispersion; QT_cd=QT_c dispersion. *P*<0.05 was considered as statistically significant

Table 3: Values of QT and QT_c dispersion, corrected QT_c dispersion and maximum and minimum QT and QT_c intervals measured during the early and late phase of myocardial infarction in the study group

Values	Early phase	Late phase	*P*
QT max. (ms)	441.65±9.73	404.04±8.48	0.018
QT_c max. ($ms^{1/2}$)	474.35±9.69	377.37±9.27	0.011
QT min. (ms)	381.65±7.15	377.37±9.27	0.32
QT_c min. ($ms^{1/2}$)	401.95±6.74	395.37±6.35	0.15
QTd (ms)	60±5.32	53.35±4.07	0.032
QT_cd ($ms^{1/2}$)	75.75±8.21	65.35±5.07	0.013
Corrected QT_cd (ms)	23±3.4	20.9±3.2	0.044

Max=Maximum; Min=Minimum; QTd=QT dispersion; QT_cd=QT_c dispersion. *P*<0.05 was considered as statistically significant

Reperfusion arrhythmias

Ventricular arrhythmias after thrombolytic therapies were analyzed by a 24-h Holter ECG. VPBs were observed in all patients. The mean number of isolated VPBs in 24 h was 1189 ± 273. In the analysis of ventricular arrhythmias, bigeminal or trigeminal VPBs were observed in 15 patients (75%), both bigeminal and trigeminal VPBs in eight patients (40%), and AIVR episodes in 18 patients (90%). No correlation was found between QT_c and arrhythmia parameters. There was no correlation between QTd and the mean isolated and total VPBs in the linear regression analysis. Seventeen (85%) patients had non-sustained VT. There was no difference between patients with and without non-sustained VT in terms of QT_cd values. One (5%) patient had sustained VT with a QT_cd value of 92 $ms^{1/2}$. The mean QT_cd value for all patients was 74.2 ± 7.2 $ms^{1/2}$ (92 $ms^{1/2}$, 74.2 ± 7.2 $ms^{1/2}$, respectively $P = 0.032$). Six (30%) patients with prolonged VT had higher QT_cd than those without prolonged VT (97.8 ± 8.6 $ms^{1/2}$, 56.3 ± 5.4 $ms^{1/2}$, respectively $P = 0.012$). Sustained AIVR was determined in eight patients (40%), and QT_cd values were higher in those patients as well (81.7 ± 7.6 $ms^{1/2}$, 58.28 ± 6.4 $ms^{1/2}$, respectively $P = 0.029$) [Figure 1]. Linear regression analysis revealed a correlation between the QT_cd values and the number of episodes of arrhythmias exhibited by patients with the above-mentioned 3 types of arrhythmias.

Discussion

In acute MI, early fibrinolytic therapy is known to reduce mortality. Improvement in the left ventricular functions and reduction of late arrhythmias by enhancing electrical stability of the heart may decrease the rate of sudden deaths.[2-4] Thus, thrombolytic therapy is expected to have a positive effect on late arrhythmic events after infarction. Indeed, thrombolytic therapy have been reported to reduce late potential frequency and decrease VT frequency, which was induced spontaneously or by programmed simulation in various studies.[10,11]

It has been found that the QT interval dispersion in patients with MI was higher than those without heart

Table 4: QT dispersion values of the patients who did or did not develop complications during hospitalization period

QT cd values	Heart failure		Death		Ventricular fibrillation	
	(+)	(−)	(+)	(−)	(+)	(−)
QT_cd ($ms^{1/2}$)	77.8±8.1	75.4±9.4	94.6±6.5	74.7±5.5	89.2±7.4	73.9±8.4
Corrected QT_cd (ms)	24.2±3.1	23.5±4.4	36.5±6.4	23.2±3.7	34.6±3.6	23.5±4.2

QT_cd=QT_c dispersion

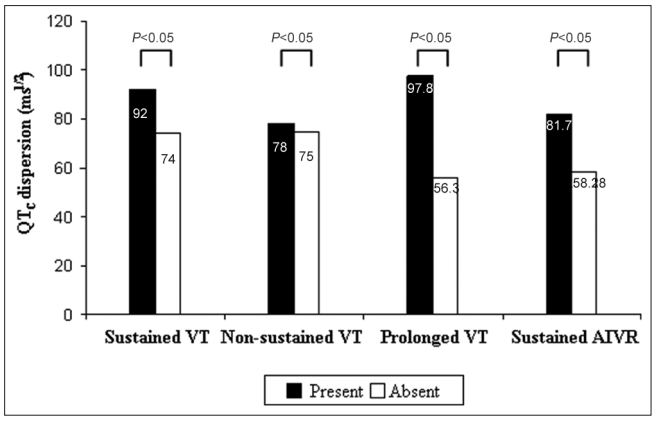

Figure 1: QT_c dispersion values in patients with ventricular arrhythmias. VT: Ventricular tachycardia; AIVR: Accelerated idioventricular rhythm

disease.[12,13] Studies focusing on the relationship of QTd and late arrhyhmias in patients with MI have contradictory results.[14-17] The current study suggested that thrombolysis could cause a significant decrease in the QTd value during the subsequent late phase of MI although any form of reperfusion including natural course and percutaneous coronary intervention could have resulted in this effect. Studies have reported contradictory results regarding the timing of QTd measurement in acute MI and the association between arrhythmias and QTd values.[18-23] Our study fell short of shedding light on those contentious issues as well.

In the present study, in order to identify the effect of infarction localization on QTd, QT_cd was measured separately in anterior and inferior MIs. Although QT_cd was higher in the anterior MI, the difference was not statistically significant. Several studies have demonstrated conflicting results on this subject.[13,17] In the study of Cowan *et al.* the mean QTd value was 70 ms in the anterior MI and 73 ms in the inferior MI while it was 48 ms in patients without MI.[13] In consistent with these findings, the mean QTd value of patients with MI was 74 ms in the present study.

While the studies have demonstrated a correlation between QTd and ejection fraction in clinical conditions other than MI, such as congestive heart failure and idiopathic dilated cardiomyopathy,[24] no evidence of such a correlation among MI patients has been reported.[25] In the present study, no difference was determined between patients with and without clinical heart failure in terms of the QTd values, and no correlation was obtained between the QTd values and ejection fraction, as well.

Reperfusion arrhythmias

In various studies, arrhythmias occurring during coronary perfusion have been analyzed. Those arrhythmias increase mortality risk. In addition to the arrhythmias observed in the acute phase of infarction, reopening of the infarct-related artery may increase the risk of arrhythmia even further and serious arrhythmias may appear.[26-30]

In large series studies focusing on thrombolytic therapy in acute MI, in particular VF arrhythmias have been investigated.[2,3] This is an uncommon arrhythmia with a frequency of 3.7-6.6%. Following MI, VF has been shown to have a frequency of 2.3-5.3% in day 1 and 2.5-15% within the first 2 weeks.[2,3,28,30] In our study, none of the patients demonstrated VF within the 1st day; only one patient (5%) demonstrated VF within the 1st week after MI. In those studies, VT and AIVR frequencies have not been taken into consideration due to the technical difficulties in their detection and their benign characteristics. In some series including the use of Holter ECG monitoring, the VT frequency was 80% and AIVR frequency was 87.5%.[29,30] In the current study, we found non-sustained VT in 17 (85%) patients and AIVR in 18 (90%) patients.

The prognostic importance of early arrhythmias in the acute phase of an acute MI is not known well. Generally, frequent and/or complex arrhythmias are regarded as independent markers of prognosis after MI.[29] In cases presenting as ischemia and left ventricular dysfunction, the risk is elevated. Studies using ECG Holter monitoring have demonstrated a relationship between high-risk ventricular arrhythmias, and sudden death and total cardiac death.[28,29] Several studies have reported controversial results regarding the likelihood of ventricular arrhythmias (such as AIVR) being an indicator of reperfusion and being a predictor of prognosis during the thrombolytic therapy.[29,30]

While there are many studies in the literature investigating the associations between QTd and arrhythmias of various clinical conditions,[1,24] the objective of this study was focusing on the relationship between the reperfusion arrhythmias and QTd particularly. In the current study, we investigated the correlation between the early period QTd and ventricular arrhythmias occurring after the thrombolytic therapy using the 24-h Holter ECG monitoring. Although there was no correlation between the isolated and the total number of VPBs and QTd, QTd values were higher in patients with serious ventricular arrhythmias, such as sustained VT, prolonged VT, and sustained AIVR. Thus, QTd may be suggested as a predictor of some reperfusion arrhythmias.

QTd is not the only predictor of arrhythmogenesis. In determining the incidence of arrhythmias, measurement of QTd in combination with the autonomic markers such as heart rate variability, T wave alternans and baroreflex sensitivity may prove to be useful in the early prediction of serious ventricular arrhythmias. By using these methods, problems and costs associated with invasive electrophysiological studies can be avoided.

In conclusion, an elevated QT_cd value can act like a marker for early prediction of reperfusion arrhythmias occurring in the acute phase of MI, such as sustained VT, prolonged VT and sustained AIVR. However, the importance of QTd in the prediction of arrhythmia risk is still unclear. By standardizing the method of QTd measurements and maintaining the availability of computerized systems that can allow practical use in many cases, the actual role of QTd in reperfusion arrhythmias may become clear.

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