Time dependent variability of QT dispersion after acute myocardial infarction and its relation to ventricular fibrillation: a prospective study

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Abstract

Objective—To show whether increased QT dispersion on admission predicts ventricular fibrillation after acute myocardial infarction, and to determine the nature of time related changes in QT dispersion.

Design—Prospective cohort study.

Setting—Coronary care units of three teaching hospitals in Newcastle-upon-Tyne over an eight month period.

Patients—All had acute myocardial infarction according to World Health Organization criteria.

Interventions—For all patients, QT dispersion (QTd) and Bazett rate corrected QTc dispersion (QTcd) were measured from a high quality 12 lead ECG recorded on admission at a paper speed of 50 mm/s. In a subset, serial ECGs were recorded regularly to show time related changes in QTcd following acute myocardial infarction.

Main outcome measures—Occurrence of ventricular fibrillation within the first 24 hours after myocardial infarction.

Results—Data collected from 201 patients, 12 of whom (6%) developed ventricular fibrillation within 24 hours. Neither QTd nor QTcd differed between those developing ventricular fibrillation and those who did not: QTd mean (SD), 74 (24) ms (95% confidence interval (CI) 59 to 89) *v* 66 (24) ms (95% CI 62 to 70), respectively; QTcd, 86 (26) ms^{0.5} (95% CI 70 to 102) *v* 77 (29) ms^{0.5} (95% CI 72 to 82), respectively. Significant QTcd changes occurred early after myocardial infarction.

Conclusions—Admission QTd and QTcd do not predict ventricular fibrillation after acute myocardial infarction. There are significant changes in QTcd with time, which may account for this measured lack of correlation.

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Keywords: acute myocardial infarction; arrhythmia; ventricular fibrillation; QT dispersion

Many techniques have been studied in an effort to identify those patients most at risk of ventricular fibrillation. One such technique is the QT dispersion measurement, defined by Cowan and colleagues in 1988 as the difference between the maximum and minimum QT interval measurements on the standard 12 lead ECG.¹ We have previously shown this simple and non-invasive measurement to be a marker for inhomogeneity of ventricular recovery.² In that study we showed a strong ($r = 0.84$) and highly significant ($p < 0.001$) correlation between QT dispersion and the dispersion of ventricular recovery time from simultaneous epicardial mapping during cardiac surgery. Similar work by Hardman and associates has confirmed the association between QT dispersion and dispersion of endocardial monophasic action potentials by catheter mapping.³

Increased QT dispersion has been shown to be associated with increased risk of cardiac death in patients with non-insulin dependent diabetes mellitus⁴ and those awaiting heart transplantation,⁵ and with risk of arrhythmia in patients with congenital long QT syndromes.⁶ However, there is debate over whether increased QT dispersion predicts the occurrence of primary ventricular fibrillation early after myocardial infarction. Our pilot study showed

a significant difference between admission QT dispersion in patients developing ventricular fibrillation or not developing it following acute myocardial infarction (mean (SD), 105 (17) ms, 95% confidence interval (CI) 74 to 136 ms, *v* 87 (15) ms, 95% CI 81 to 93 ms, respectively).⁷ This has been repeated by other researchers without agreement (fig 1). In this paper we present a prospective cohort study specifically designed to test this association and we show new data to account for the lack of consensus.

The aims of the study were to show whether QT dispersion is increased in patients who develop early ventricular fibrillation following acute myocardial infarction, and to determine the nature of time related changes in QT dispersion measurements.

Methods

POWER CALCULATION

From published preliminary data we have estimated that mean (SD) admission QT dispersion is 80 (20) ms after acute myocardial infarction, which increases to 100 (20) ms in those developing ventricular fibrillation.⁷ Using an anticipated incidence of ventricular fibrillation of 7.5% in power estimates, a sample of 15 patients developing ventricular fibrillation in a population of 200 shows a 90% likelihood of

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Figure 1 QT dispersion measurements in various studies. Numbers along the top show group sizes, figures in parentheses indicate number with ventricular fibrillation. Error bars show 95% confidence intervals for the means, except for Tomassoni and colleagues¹⁹ which shows the 25th and 75th centile measurements. VF, ventricular fibrillation.

detecting a difference of this size at a 5% probability level.

PATIENTS

This prospective study included patients with acute myocardial infarction admitted to the three coronary care units of hospitals serving the city of Newcastle-upon-Tyne during a nine month period.

INCLUSION CRITERIA

Inclusion criteria follow the World Health Organization definition of acute myocardial infarction: typical history of severe central chest pain radiating to neck or arm of duration greater than half an hour, confirmatory ECG changes of ST elevation > 2 mm in chest leads or > 1 mm in limb leads, and a rise in serum cardiac enzyme concentrations to more than twice the upper limit of normal.

DATA COLLECTION

Data collected included demographic information, detailed drug history and previous cardiovascular history, a high quality 12 lead ECG on admission (paper speed of 50 mm/s where possible), serum potassium concentration on admission, and serial creatine kinase MB isoenzyme concentrations. In 12 patients, serial ECGs were recorded automatically at approximately 40 minute intervals by a Mortara ELI-100 instrument with sufficient memory for at least eight hours, and further ECGs were recorded daily for five days. Ventricular fibrillation requiring DC cardioversion was identified on the clinical monitoring equipment. Left ventricular failure was defined as typical clinical and chest x ray findings of pulmonary oedema requiring treatment.

QT DISPERSION MEASUREMENT

All ECGs were analysed by a single observer blinded to patient identity, timing, and clinical information. Heart rate was measured from three consecutive RR intervals, and infarct site

was defined as the area with maximum ST segment elevation. QT intervals were measured as previously documented.¹ The relation between QT interval and heart rate has been extensively explored. Bazett's rate correction is the one most widely used and has been validated during the early period of acute myocardial infarction.⁸⁻⁹ QT dispersion was defined as the difference between the maximum and minimum QT intervals; corrected QTc dispersion was defined as the difference between the maximum and minimum Bazett rate corrected QT intervals; and adjusted QTc dispersion was defined as the QTc dispersion divided by the square root of the number of leads in which QT intervals were measurable. The QTc standard deviation, defined as the standard deviation of the Bazett rate corrected QT intervals, represents a measure of spread which is statistically more reliable than the range, as described by Hnatkova and colleagues.¹⁰

DRUG TREATMENT

The effects of antiarrhythmic agents, anticonvulsants,¹¹ phenothiazines,¹² digoxin,¹³ and benzodiazepines¹⁴⁻¹⁵ on the ventricular myocardium are well documented. These effects may be either proarrhythmogenic or antiarrhythmogenic, depending on the circumstances, and have been shown to affect the QT interval. To avoid confounding of results because of the pharmacological effects of these drugs, electrophysiological results from patients prescribed these agents were excluded from the analysis.

INFARCT SIZE

A measure of early infarct size was made using the formula described by Clemmenson and colleagues, based on ST elevation.¹⁶ This gives a figure approximately equal to the percentage of left ventricular myocardium that is jeopardised, and has been shown to correlate well with final QRS derived infarct sizing using the Selvester technique.

QT DISPERSION PROFILES

To follow changes in QT dispersion with time, serial ECGs were analysed in 12 patients. Profiles of corrected QTc dispersion against time were plotted.

STATISTICAL ANALYSIS

For categorical data, the χ^2 test was used. For continuous data, the two sample *t* test was used where distributions did not differ significantly from normal. For measures of infarct size, the distributions were significantly skewed and the non-parametric Mann-Whitney U test was used. Spearman's rank correlation method was used to test for linear association. Classical analysis of variance (ANOVA) was used to test for differences between multiple groups. All tests were performed using statistics package Unistat IV on a PC compatible computer. Results are expressed as a ratio of the relevant population with percentages in parentheses or as a mean and standard deviation with 95% confidence intervals (CI) where appropriate.

Table 1 Clinical information

	No ventricular fibrillation		Ventricular fibrillation	
	ECG analysis included	ECG analysis excluded	ECG analysis included	ECG analysis excluded
Female	49/149 (33%)	11/40 (28%)	3/8	1/4
β Blocker	39/149 (26%)	8/40 (20%)	0/8	1/4
Previous myocardial infarction	56/149 (38%)	20/40 (50%)	5/8	2/4
Previous coronary bypass	5/149 (3%)	5/40 (8%)	0/8	1/4
Left ventricular failure	38/138 (28%)	18/38 (47%)	4/8	2/4
Mortality	10/149 (7%)	3/40 (8%)	2/8	0/4
Age (years)	65 (12), 63 to 66	68 (7), 65 to 70	62 (12), 49 to 74	68 (6), 52 to 84
Infarct score (%)	10.4 (9.3), 8.9 to 12.0	9.9 (9.0), 7.0 to 12.8	9.7 (9.5), 1.7 to 17.6	19.3 (17.2), 0 to 62
Peak CK-MB (units/l)	83 (79), 69 to 97	88 (83), 61 to 116	82 (21), 48 to 115	208 (80), 9 to 406
Serum potassium (mmol/l)	4.19 (0.52), 4.09 to 4.28	4.28 (0.54), 4.13 to 4.42	4.22 (0.20), 4.00 to 4.43	3.73 (0.25), 3.11 to 4.36
Mean arterial pressure on admission (mm Hg)	96 (22), 92 to 100	97 (17), 92 to 103	100 (18), 79 to 124	81 (17), 40 to 122

Categorical variables are given as n (%), continuous variables as mean (SD), 95% confidence interval.

Results

PATIENTS

Data were collected from 201 patients, of whom 12 (6%) subsequently developed ventricular fibrillation within 24 hours of the onset of symptoms (range 0.25–23 hours after ECG, median 1.75 hours). Clinical information is shown in table 1. Only the peak creatine kinase MB isoenzyme (CK-MB) differed significantly ($p < 0.05$) between patients with and without ventricular fibrillation.

ECG INFORMATION

ECG information was excluded from 44 patients: eight with atrial fibrillation and 43 because of the current prescription of anti-arrhythmic agents, benzodiazepines, phenothiazines, anticonvulsants, or digoxin (seven patients had both reasons for exclusion). For comparison, the results of excluded patients are also shown in table 1. ECG data are shown in table 2.

The rate corrected QTc dispersion was the originally proposed measure of QT interval variability and correlated highly with all other measures of QT interval variability: corrected QTc dispersion versus uncorrected QT dispersion, Spearman's $\rho = 0.86$, $p < 0.00005$; versus adjusted QTc dispersion, $\rho = 0.99$, $p < 0.00005$; versus QTc standard deviation, $\rho = 0.95$, $p < 0.00005$.

FACTORS AFFECTING QT DISPERSION

Neither QT dispersion nor QTc dispersion differed significantly between patients who had episodes of ventricular fibrillation and those who did not (fig 2). QTc dispersion (mean (SD) $\text{ms}^{0.5}$) was not affected by any of the following: *previous myocardial infarction* (no myocardial infarction, 76 (29), 95% CI 69 to 83, *v* myocardial infarction, 78 (28), 95% CI 71 to

Figure 2 QTc dispersion scatterplots. Horizontal lines represent mean values for each group and a circle represents each result. VF, ventricular fibrillation.

85); *infarct score* (Spearman's $\rho = 0.055$, NS); *infarct site* (anterior, 79 (30), 95% CI 72 to 86, *v* inferior, 77 (25), 95% CI 71 to 83, *v* lateral/posterior, 92 (41), 95% CI 61 to 123, NS by ANOVA); and *β blockade* (no β blocker, 77 (29), 95% CI 72 to 82, *v* β blocker, 78 (29), 95% CI 68 to 88).

QT DISPERSION PROFILES

Of the 12 patients studied with serial ECGs, seven had resolution of clinical symptoms and more than a 25% reduction in maximum ST segment elevation within one hour of thrombolytic treatment. This was suggestive of reperfusion, although angiographic confirmation was unavailable. Profiles of corrected QTc dispersion for all patients studied with serial ECGs are shown in fig 3, grouped by resolution or persistence of symptoms and ST segment elevation.

Table 2 Electrocardiographic information

	No ventricular fibrillation (n=149)		Ventricular fibrillation (n=8)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Heart rate (beats/min)	81 (22)	77 to 85	91 (20)	78 to 104
Maximum QTc interval ($\text{ms}^{0.5}$)	476 (45)	468 to 484	482 (46)	453 to 511
Minimum QTc interval ($\text{ms}^{0.5}$)	399 (37)	393 to 405	396 (29)	378 to 414
Mean QTc interval ($\text{ms}^{0.5}$)	442 (37)	436 to 448	438 (30)	419 to 457
QT dispersion (ms)	66 (24)	62 to 70	74 (24)	59 to 89
Corrected QTc dispersion ($\text{ms}^{0.5}$)	77 (29)	72 to 82	86 (26)	70 to 102
Adjusted QTc dispersion ($\text{ms}^{0.5}$)	23 (9)	21 to 25	26 (7)	22 to 30
QTc standard deviation ($\text{ms}^{0.5}$)	24 (10)	22 to 26	26 (10)	20 to 32

Figure 3 Examples of profiles of QTc dispersion. Each frame shows the corrected QTc dispersion profile for a single patient over the first eight hours after admission. Patients' data are grouped by resolution or persistence of symptoms and ST segment elevation following thrombolysis. The first group (group A) had resolution of symptoms and ST elevation, whereas the second (group B) did not.

Discussion

Neither QT dispersion nor QTc dispersion differed significantly between patients who had episodes of ventricular fibrillation and those who did not (table 2). Correlations between all proposed measures of QT interval variability were high and of very high significance. The very close correlation between corrected QTc dispersion and the three other measures of QT interval variability provides more rigorous statistical evidence of a spread rather than a chance finding due to outlying values. This provides further, albeit indirect, evidence that the QT dispersion measurement is an indicator of real differences in surface QT intervals, rather than a measurement artefact.

Profiles show that QTc dispersion changes from hour to hour, and this evidence of variability may well account for the lack of measured difference between patients with and without episodes of ventricular fibrillation. QTc dispersion fell in patients with resolution of symptoms and a reduction in ST elevation following thrombolysis, whereas it increased in those who did not show these features. These differences persisted, and late differences in profiles are consistent with published work showing significantly lower QT dispersion in patients with angiographically proven reperfusion at nine days after the onset of symptoms.¹⁷

Strengths of this study include its prospective nature and its specific aim to explore QT dispersion and the relation to ventricular fibrillation following acute myocardial infarction. Using a cohort study, problems with matching, as in case-control studies, are reduced. In addition, the methodology of QT dispersion used has been well described and published.

A significant limitation of the study is the small number of patients with episodes of ventricular fibrillation. The study was powered to detect a mean difference in corrected QTc dispersion of 20 ms^{0.5} between patients developing or not developing ventricular fibrillation. However, the observed mean difference was much smaller (9 ms^{0.5}) and the study is underpowered to show a difference of this size. Nevertheless, a real but small difference of this magnitude would be unlikely to be of clinical benefit in view of the range of measured QTc dispersion measurements.

Results of the previously reported studies based on multicentre trials for other purposes are shown in fig 1. The three largest of these¹⁸⁻²⁰ were also negative. The two positive studies both have methodological differences from the others. Yunus and colleagues measured QT dispersion from only the six anterior chest leads.²¹ Previous work shows that this technique is likely to affect the QT dispersion measurements significantly.^{10 22 23} Further, their ECGs were recorded at 25 mm/s, which has

been shown to increase the inaccuracy of measurement.¹ Zaputovic and colleagues included 32 patients with sustained ventricular tachycardia after myocardial infarction among their 39 cases.²⁴ Their positive result may reflect the predominant arrhythmia of ventricular tachycardia. The substrate for ventricular tachycardia is more likely to be established scar tissue and these cases may therefore be expected to differ from those with ventricular fibrillation.²⁵ Oikarinen and associates found significant differences in QT dispersion between well matched patient groups presenting with ventricular tachycardia or ventricular fibrillation after myocardial infarction.²⁶

CONCLUSIONS

This study provides further evidence that admission QT dispersion does not differ between patients who do or do not subsequently develop ventricular fibrillation after acute myocardial infarction. Evidence of real time changes in QT dispersion is shown during the early phase of recovery after infarction. This variability may explain the lack of correlation between increased QT dispersion at admission and ventricular fibrillation following an infarct, despite the attractive theoretical links between dispersion of ventricular recovery and ventricular fibrillation.

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