QT dispersion as a predictor of long-term mortality in patients with acute myocardial infarction and clinical evidence of heart failure

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Background QT interval dispersion is a marker of inhomogeneous ventricular repolarization, and therefore has the potential to predict re-entry arrhythmias. Following acute myocardial infarction, increased QT dispersion has been associated with a higher risk of ventricular arrhythmias. However, whether or not QT dispersion predicts prognosis post-acute myocardial infarction is not clear. We addressed this issue by analysing the AIREX study registry.

Methods AIREX was a follow-up study of 603 post-acute myocardial infarction patients who exhibited clinical signs of heart failure and were randomly allocated to ramipril or placebo. An interpretable 12-lead ECG obtained between day 0 and day 9 after the index infarction (median time 2 days) was available in 501 patients. We examined whether QT dispersion was a predictor of all-cause mortality in the AIREX study registry (mean follow-up 6 years).

Results QT dispersion measurements were significantly increased in patients who subsequently died (QT dispersion: 92.0 ± 38.5 ms vs 82.7 ± 34.3 ms, P = 0.005; rate corrected QT dispersion: 105.7 ± 42.7 ms vs 93.1 ± 35.9 ms, P<0.001). Univariate analysis showed that QT dispersion was a predictor of all-cause mortality risk (QT dispersion: hazard ratio per 10 ms 1.05, [95% CI 1.02 to 1.09], P = 0.004; rate corrected QT dispersion: 1.07 [1.03 to 1.10], P<0.001); an increase of 10 ms added a 5–7% relative risk of death. QT dispersion remained an independent predictor of all-cause mortality risk on multivariate analysis (QT dispersion: 1.05 [1.01 to 1.09], P = 0.027; rate corrected QT dispersion: 1.05 [1.01 to 1.09], P = 0.022).

Conclusion QT dispersion, measured from a routine 12-lead ECG following acute myocardial infarction complicated by heart failure provides independent information regarding the probability of long-term survival. However, the low sensitivity of this electrocardiographic marker limits its usefulness for risk stratification if used in isolation.

Key Words: QT dispersion, myocardial infarction, heart failure.

Introduction

The inter-lead variability of QT intervals on a surface electrocardiogram (ECG) correlates significantly with the dispersion of repolarization and with the dispersion of recovery of ventricular excitability[1,2]. Since inhomogeneity of ventricular repolarization represents an arrhythmogenic electrophysiological substrate[3,4], QT dispersion may provide clinically valuable information.

Increased QT dispersion is a marker of susceptibility to ventricular arrhythmias in hereditary long QT syndromes[5,6]. It has been associated with ventricular arrhythmias in hypertrophic cardiomyopathy[7] and mitral valve prolapse[8] and with sudden death in both hypertrophic cardiomyopathy[7] and chronic heart failure[9]. Increased QT dispersion has been reported in patients with idiopathic ventricular fibrillation[10] and has been shown to be an independent predictor of sudden death and arrhythmic events in dilated cardiomyopathy[11]. In addition, risk of drug arrhythmogenesis may be predicted by increased QT dispersion[12].

It has been suggested that increased QT dispersion predicts the risk of ventricular arrhythmias early in the
course of acute myocardial infarction and that it is increased in patients who are susceptible to ventricular arrhythmias at a later stage. Increased dispersion of ventricular repolarization on the 12-lead ECG has been shown to predict arrhythmic death in patients with previous myocardial infarction. Data on the prognostic value of QT dispersion recorded in the late post acute infarction period are conflicting. It remains uncertain whether QT dispersion measured in the early post-infarction phase is predictive of long-term mortality.

Therefore, we set out to examine whether QT dispersion was a predictor of long-term, all-cause mortality risk in patients with clinical heart failure after acute myocardial infarction, by using data from the Acute Infarction Ramipril Efficacy EXtension (AIREX) study registry.

Methods

The design, outcome definitions and results of the AIRE and AIREX studies have been published. Briefly, the AIRE study was an international, randomized, double blind, placebo-controlled study, which assessed the effect of the angiotensin-converting enzyme (ACE) inhibitor ramipril on the survival of patients with clinical heart failure after acute myocardial infarction. Patients were eligible for inclusion if they had a definite acute myocardial infarction and clinical evidence of transient or persistent heart failure at any time from hospital admission to randomization (between day 2 and day 9 after the index acute myocardial infarction, mean randomization day 5).

The AIREX study investigated the mortality status of all 603 U.K. patients recruited in the AIRE study, 3 years after its close (mean follow-up 59 months). In the current study, the mortality status of patients in the AIREX study registry was updated to August 1997; that is 5 years after recruitment of the last patient (mean follow-up 72 months).

Analysis of QT dispersion

A standard 12-lead ECG recorded at 25 mm . s$^{-1}$ speed and 10 mm . mV$^{-1}$ gain using a variety of ECG recorders, and obtained before randomization was available in 598 of the 603 AIREX study patients. The recordings available for analysis represented a heterogeneous group, most were simultaneous 12 lead ECGs but some were simultaneous three-lead recordings.

A minimum of seven leads, of which at least four were precordial, was required for QT dispersion to be calculated. QT and RR intervals were measured in at least two consecutive cycles, and the mean value for each lead was considered for further calculations. Fifty-seven ECGs did not fulfil these criteria and were excluded from the analysis. Thirty-three ECGs were excluded due to atrial fibrillation and seven due to complete heart block.

The remaining 501 ECGs were included in our study. Complete bundle branch block was noted in 34 of them. The mean time from admission to analysed ECG was 1-5 days (median 2 days), and more than 90% of the ECGs were obtained before day 5 after the index infarction.

ECGs were selected at random and analysed for QT dispersion by two observers blind to outcome using a high resolution SummaSketch III (Summagraphics®) digitizing tablet and customized software. Standard criteria were applied for the QT measurements. QT interval was measured from the onset of the QRS complex to the end of the T wave, defined visually as the point of return of the T wave to baseline. Where the T wave was interrupted by a U wave, the QT interval was measured to the nadir between the T and U waves. Results are given as QT dispersion (the difference between the maximum and minimum QT across the 12-lead ECG) and rate corrected QT dispersion (using Bazett’s formula). Intra and inter-observer variabilities were examined in a 5% random sample of study ECGs. The mean difference was 1-5 ms and the relative error 16-9% (intra-observer), and 4-5 ms and 24-5% (inter-observer).

The associations between measurements of QT dispersion and all-cause mortality during the 6-year follow-up period were examined. Mode of death was defined only in the main AIRE study. Therefore, the associations between QT dispersion measurements and mode of death was confined to the shorter follow-up defined by the AIRE study.

Detailed definitions and classification of mode of death in the AIRE study have been described elsewhere. Two modes of death were examined in the current analysis: sudden cardiac and circulatory failure death.

Statistical analysis

Baseline characteristics of different patient groups were compared by use of a two-sample t-test for continuous variables and chi-square tests for categorical variables.

Cox proportional hazards models were used to analyze the associations between QT dispersion measurements and subsequent end points. Hazard ratios, 95% confidence intervals and P values were derived from univariate and multivariate analyses.

First, a univariate analysis was performed with the QT dispersion measurement as the only variable entered in the Cox model. Then, to adjust for any confounding, the QT dispersion measurement and all available important baseline patients characteristics (age; gender; thrombolytic therapy for the index acute myocardial infarction, beta-blocker, diuretic, digoxin and aspirin therapies at randomization; allocation to ramipril or placebo; left ventricular ejection fraction; multiple clinical signs of heart failure; previous medical history of heart failure, myocardial infarction, angina and diabetes mellitus; ECG classification of the index infarction as to its...
Table 1 QT interval and QT dispersion measurements according to mortality status and the electrocardiographic presence of bundle branch block

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=320)</th>
<th>Deceased (n=181)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean QT (ms)</td>
<td>382·0 ± 44·7</td>
<td>385·3 ± 44·9</td>
<td>0·42</td>
</tr>
<tr>
<td>Mean QTc (ms)</td>
<td>431·8 ± 33·4</td>
<td>447·2 ± 40·2</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>QT dispersion (ms)</td>
<td>82·7 ± 34·3</td>
<td>92·0 ± 38·5</td>
<td>0·005</td>
</tr>
<tr>
<td>QTc dispersion (ms)</td>
<td>93·1 ± 35·9</td>
<td>105·7 ± 42·7</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients without bundle branch block n=467</th>
<th>Patients with bundle branch block n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean QT (ms)</td>
<td>381·8 ± 43·6</td>
<td>402·1 ± 55·8</td>
</tr>
<tr>
<td>Mean QTc (ms)</td>
<td>435·1 ± 35·5</td>
<td>469·1 ± 39·3</td>
</tr>
<tr>
<td>QT dispersion (ms)</td>
<td>85·6 ± 35·7</td>
<td>91·6 ± 40·8</td>
</tr>
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</table>

Mean ± SD.

location and Q-wave development; heart rate in the analysed ECG were simultaneously entered into a Cox proportional hazards model. QT dispersion measurements were included in this model as a continuous variable. Measurements of the left ventricular ejection fraction using multiple methods, were available in 136 (27·2%) patients and were entered into the analysis as a categorical variable using the mean (39%) as a cut-off point. The inclusion of left ventricular function surrogate variables such as the presence of multiple clinical signs of heart failure and the use of diuretic therapy in the multivariate model aimed to offer further correction for the degree of left ventricular dysfunction and compensate for the incomplete left ventricular ejection fraction dataset.

All P values are two-tailed, and a significance level of 0·05 was used. Statistical analyses were performed using SPSS, version 6·1.

Results

At a mean follow-up of 6 years, death from all causes had occurred in 181 (36·1%) of the 501 patients included in our analysis. Measurements of QT dispersion were significantly increased among those who died (Table 1).

QT dispersion measurements were found to be predictive of long-term, all-cause mortality risk on univariate analysis (QT dispersion: hazard ratio per 10 ms 1·05, [95% CI 1·02 to 1·09], P=0·004; rate corrected QT dispersion: 1·07 [1·03 to 1·10], P=0·001). To put this result in perspective the corresponding hazard ratio for left ventricular ejection fraction on univariate analysis was 1·12 per 5% (1·00 to 1·19, P=0·04). Importantly, when QT dispersion measurements were considered along with 17 major variables in a multivariate Cox regression model, they remained significant independent predictors of mortality risk with essentially unaltered hazard ratios (QT dispersion: 1·05 [1·01 to 1·09], P=0·027; rate corrected QT dispersion: 1·05 [1·01 to 1·09], P=0·022). Based on the hazard ratios, it is apparent that there is an additional 5% mortality risk for every 10 ms increase in QT dispersion.

To explore the relation between dispersion of ventricular repolarization, as assessed in the 12-lead ECG and mortality in more detail, we divided the study population into three equally sized groups according to their rate corrected QT dispersion level (<78·2 ms, 78·2–107·9 ms, ≥108 ms). Absolute mortalities in the low, medium and high rate corrected QT dispersion groups were 29·1, 36·1 and 42%, respectively (P for trend=0·019) (Fig. 1(a)). When the mortality in the three groups was studied in the multivariate model, it appeared that the increased rate corrected QT dispersion group was at a particularly high risk (Fig. 1(b)). This finding suggests that the risk associated with rate corrected QT dispersion is not linear, but that there is a threshold effect.

The sensitivity, specificity and positive predictive value of the increased rate corrected QT dispersion (≥108 ms) as a predictor of death were 39·3%, 71·4% and 42%, respectively.

To investigate the clinical characteristics that may be associated with increased rate corrected QT dispersion, we compared the high risk, raised rate corrected QT dispersion group of patients with the medium and low rate corrected QT dispersion groups together (Table 2). Heart rate was higher and Q wave acute myocardial infarction more frequent in the increased rate corrected QT dispersion group. These patients were also less likely to have been on beta-blocker therapy at randomization.

QT dispersion measurements in the ECGs showing bundle branch block were not significantly different from ECGs with normal intraventricular conduction (Table 1). When multivariate analysis was performed after excluding patients with bundle branch block, QT dispersion remained an independent predictor of mortality (1·04 [1·00 to 1·09], P=0·04).

The associations between QT dispersion measurements and mode of death were examined only with
Figure 1 (a and b) Cox-regression non-adjusted (a) and adjusted (b) survival plots for the three rate corrected QT dispersion groups. — high (≥108 ms); – – – = medium; ····· = low (<78.2 ms).
univariate analysis, since the smaller number of events precluded a meaningful multivariate analysis (sudden death n=52, circulatory failure death n=37). Increased rate corrected QT dispersion was a predictor of sudden death risk in the entire study population ($1.07 [1.01$ to $1.13]$, $P=0.03$). The association between increased rate corrected QT dispersion and circulatory failure death was not statistically significant, but the hazard ratio was similar to that of sudden death ($1.05 [0.97$ to $1.13]$, $P=0.19$).

Table 2  Patients characteristics and treatments at baseline in the high versus the low and medium rate corrected QT (QTc) dispersion groups

<table>
<thead>
<tr>
<th>Low–Medium QTc dispersion (&lt;108 ms)</th>
<th>High QTc dispersion (≥108 ms)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q wave AMI n=333</td>
<td>219 (65.8)</td>
<td>132 (78.6)</td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>79.3 ± 16.8</td>
<td>82.6 ± 15.5</td>
</tr>
<tr>
<td>Beta-blocker n=333</td>
<td>47 (14.1)</td>
<td>13 (7.7)</td>
</tr>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>64.3 ± 9.9</td>
<td>65.1 ± 9.6</td>
</tr>
<tr>
<td>Gender (male) n=333</td>
<td>252 (75.8)</td>
<td>127 (75.6)</td>
</tr>
<tr>
<td>Location of AMI n=333</td>
<td>193 (58)</td>
<td>109 (64.9)</td>
</tr>
<tr>
<td>Multiple clinical signs of HF</td>
<td>177 (53.2)</td>
<td>79 (47.0)</td>
</tr>
<tr>
<td>Mean LVEF (%) (n=136) (mean ± SD)</td>
<td>45.1 ± 17.4</td>
<td>43.3 ± 11.9</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>249 (74.8)</td>
<td>120 (71.4)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>167 (50.2)</td>
<td>93 (55.4)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>277 (83.2)</td>
<td>139 (82.7)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>217 (65.2)</td>
<td>111 (66.1)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>16 (4.8)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous AMI</td>
<td>78 (23.4)</td>
<td>41 (24.4)</td>
</tr>
<tr>
<td>Previous HF</td>
<td>28 (8.4)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>108 (32.4)</td>
<td>58 (34.5)</td>
</tr>
<tr>
<td>DM</td>
<td>35 (10.5)</td>
<td>12 (7.1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>7 (2.1)</td>
<td>8 (4.8)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages. AMI=myocardial infarction; HF=heart failure; LVEF=left ventricular ejection fraction; DM=diabetes mellitus.

Discussion

The major finding of this study is that QT dispersion is an independent predictor of long-term, all-cause mortality risk in patients with acute myocardial infarction and clinical evidence of heart failure. Of particular interest is our finding that the predictive value of QT dispersion is not only independent of all the major clinical variables but also of all the well-known electrocardiographic predictors of mortality after acute myocardial infarction, namely location and type of the infarction and heart rate.

The low sensitivity (39.3%) and positive predictive value (42%) of a high rate corrected QT dispersion (≥108 ms) in predicting mortality indicates that this index suffers from a high false-positive rate. The higher specificity (71.4%) indicates a better prognosis for patients with a low or medium rate corrected QT dispersion. These numbers are, nevertheless, comparable to the prognostic value of a left ventricular ejection fraction <30% in predicting long-term mortality risk post-acute myocardial infarction (sensitivity 41%, positive predictive value 29% and specificity 88%)[25].

Whilst this electrocardiographic marker conveys an independent mortality risk and can identify additional patients at high risk of death, its clinical usefulness, when viewed in isolation, to select patients for more intense secondary prevention in this population is limited by its low sensitivity. As all patients in this study would be regarded as high risk, the value of QT dispersion as a prognostic predictor in a general post-acute myocardial infarction population might be different and certainly requires further assessment.

Another finding of this study was that rate corrected QT dispersion appeared to be predictive of sudden death. This finding is in keeping with the concept that increased QT dispersion, reflecting increased disparity of regional ventricular repolarization times, predisposes to sustained ventricular arrhythmias.

The population studied was large and at increased risk of death from the outset, and this, combined with the long follow-up, led to a large number of end-points. This not only gave our study a considerable statistical power to examine the predictive value of QT dispersion measurements with univariate analysis but also permitted performance of a meaningful multivariate analysis, in which QT dispersion measurements were tested adjusting for all the major clinical parameters simultaneously[26]. In addition, the large number of events
means that suggested criteria for overfitting data were not violated\cite{27}. All the associations between QT dispersion measurements and clinical outcomes were evaluated for adherence to the assumption of proportional hazards and in all cases the criteria of proportionality were fulfilled.

**Biological mechanisms**

A link between QT dispersion and cardiac mortality is biologically plausible. The role of local disparity of recovery time on ventricular vulnerability to reentry arrhythmias including fibrillation has been emphasized by many investigators\cite{4,28}. This kind of inhomogeneity has been experimentally shown to reduce the threshold for ventricular fibrillation in dogs\cite{3} and has been associated with the inducibility of ventricular arrhythmias during programmed electrophysiological studies in humans\cite{29}.

In the setting of acute myocardial infarction and particularly when left ventricular dysfunction ensues, QT dispersion may be influenced by many potential mechanisms operating at the time. Acute ischaemia has been shown to dynamically increase QT dispersion\cite{30} while reperfusion reduces QT dispersion\cite{31}. Cardiomyocyte necrosis and slippage, disturbed intercellular connections, altered ventricular geometry and dilatation, and reactive hypertrophy, are all part of the ventricular remodelling process after acute myocardial infarction. All these factors are liable to have an effect on the heterogeneity of ventricular repolarization\cite{32} and unfavourably influence QT dispersion.

A differential contraction–excitation feedback in the presence of regional wall-motion abnormalities can generate further local electrophysiological inhomogeneity\cite{33,34}. Our finding of increased QT dispersion in patients with Q wave acute myocardial infarction may be explained by the more marked remodeling and dilatation in this group. Finally, the activation of the neurohormonal systems after acute myocardial infarction is universal, being more pronounced and persistent in patients who develop left ventricular dysfunction\cite{35,36}. Acting on myocytes with different viability and electrophysiological properties it may further increase the disparity in ventricular repolarization. In addition, this may be achieved through the patchy myocardial fibrosis high levels of angiotensin II can provoke\cite{37}.

**QT dispersion and mortality prediction in other post-acute myocardial infarction studies**

A retrospective, case-control study\cite{17} suggested that QT and rate corrected QT dispersion on ‘late’ ECGs recorded at least 4 weeks, but not on ‘early’ ECGs recorded 2 or 3 days after infarction may be associated with subsequent all-cause mortality risk. However, matching in this study was only for age and gender and other imbalances in baseline patients characteristics were not taken into account. In addition, ‘late’ ECGs were available for less than half of the study population and the baseline characteristics between survivors and patients who died were further imbalanced. In a more recent prospective, long-term follow-up study of unselected acute myocardial infarction survivors\cite{18}, QT dispersion failed to predict subsequent risk. However, the small number of end-points (21 deaths, nine arrhythmic events) and the late ECG recordings (before hospital discharge) make this study’s results far from conclusive for the prognostic value of QT dispersion in the early post-infarction period. In addition, the suggested criteria for overfitting data in the multivariate model used in this study were violated (10 variables fitted, instead of a maximum of three advised)\cite{27}.

It must be emphasized that our study population was distinct from those examined in other studies in that all patients exhibited clinical signs of heart failure post-acute myocardial infarction. Therefore, it is unknown whether our findings are also applicable in a general post-acute myocardial infarction population. The average values for QT dispersion in our study population appear to be higher than those reported by other investigators for unselected post-acute myocardial infarction patients\cite{17–19}. This may be explained by the fact that congestive heart failure itself has been associated with increased QT dispersion\cite{11,38} and a significant positive correlation between left ventricular ejection fraction and QT dispersion in post-acute myocardial infarction patients has been demonstrated\cite{39}.

The changes occurring in QT dispersion following acute myocardial infarction are dynamic and therefore the timing of the QT dispersion measurement may be crucial when examining its prognostic value. In view of the effects of acute ischaemia on QT dispersion, early recordings may contain additional information on residual ischaemia. QT dispersion increases from the very first hours\cite{13,23}, possibly is greatest around day 3\cite{40} and then falls with time in most cases\cite{41}. In our study the analysed ECGs were recorded between day 0 and day 9 after the index infarction (mean day 1.5, median day 2, 90% of the recordings before day 5). Although the exact timing of the dynamic QT dispersion changes post-acute myocardial infarction have not been fully elucidated, almost all our recordings were obtained within a time window during which QT dispersion is thought to be increased. In addition, the distributions of the times of ECG recording among survivors and patients who died were identical. Therefore, we believe that the findings of this study cannot have been influenced by different ECG recording times.

**Conclusion**

In conclusion, our data indicate that in patients with clinical heart failure after acute myocardial infarction,
increased QT dispersion measured on an ECG obtained typically during the first week of hospitalization, is an independent predictor of long-term, all-cause mortality and a univariate predictor of sudden death. As a result, additional patients at high risk of death could be identified and more aggressive and appropriate therapy can be instituted. However, the low sensitivity of this electrocardiographic marker to identify patients at risk for death during long-term follow-up, limits its usefulness for risk stratification if used in isolation.

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References