QTc Dispersion Predicts Cardiac Mortality in the Elderly

The Rotterdam Study

M.C. de Bruyne, MD; A.W. Hoes, MD, PhD; J.A. Kors, PhD; A. Hofman, MD, PhD; J.H. van Bemmel, PhD; D.E. Grobbee, MD, PhD

Background—Increased QTc dispersion has been associated with an increased risk for ventricular arrhythmias and cardiac death in selected patient populations. We examined the association between computerized QTc-dispersion measurements and mortality in a prospective analysis of the population-based Rotterdam Study among men and women aged ≥55 years.

Methods and Results—QTc dispersion was computed with the use of the Modular ECG Analysis System as the difference between the maximum and minimum QTc intervals in 12 and 8 leads (ie, the 6 precordial leads, the shortest extremity lead, and the median of the 5 other extremity leads). After exclusion of those without a digitally stored ECG, the population consisted of 2358 men and 3454 women. During the 3 to 6.5 years (mean, 4 years) of follow-up, 568 subjects (9.8%) died. The degree of QTc dispersion was categorized into tertiles. Data were analyzed using the Cox proportional hazards model, with adjustment for age. For QTc dispersion in 8 leads, those in the highest tertile relative to the lowest tertile had a twofold risk for cardiac death (hazard ratio, 2.5; 95% confidence interval [CI], 1.6 to 4.0) and sudden cardiac death (hazard ratio, 1.9; 95% CI, 1.0 to 3.7) and a 40% increased risk for total mortality (hazard ratio, 1.4; 95% CI, 1.2 to 1.8). Additional adjustment for potential confounders, including history of myocardial infarction, hypertension, and overall QTc, did not materially change the risk estimates. Hazard ratios for QTc dispersion in 12 leads were comparable to those found for QTc dispersion in 8 leads.

Conclusions—QTc dispersion is an important predictor of cardiac mortality in older men and women. (Circulation. 1998;97:467-472.)

Key Words: electrocardiography • heart disease • age • risk factors • QT dispersion

Recent clinical studies have suggested that the interlead variability of the QT interval in the standard ECG, defined as QT dispersion, reflects regional differences in ventricular repolarization. Increased dispersion of recovery time is believed to increase the risk for serious ventricular arrhythmias. It is hypothesized that an important entity underlying QT dispersion is patchy myocardial fibrosis, resulting from myocardial ischemia, ventricular dilatation, and neurohormonal activation. This is supported by findings of increased QT dispersion in patients with acquired long-QT interval, MI, hypertrophic cardiomyopathy, and hypertension and LVH in diabetic patients with autonomic neuropathy. Moreover, QT dispersion has been associated with increased risk for ventricular arrhythmias and sudden death in patients with chronic heart failure, mitral valve prolapse, MI, and familial long-QT syndrome and with an increased risk for cardiac mortality in patients with peripheral arterial disease and MI.

In these previous studies, QT dispersion was measured retrospectively and manually in a limited number of cases and controls by one or more observers with the use of a digitizing tablet. Evidence from large, prospective studies on the diagnostic implications of QT dispersion is lacking. The use of a computer program to measure QT dispersion facilitates large studies and excludes intraobserver and interobserver variability. We assumed that the risk associated with increased QT dispersion applies not only to patient populations but also to the population at large; therefore, we examined whether increased QT dispersion, established by computer analysis, was associated with a higher risk for total mortality, cardiac death, sudden cardiac death, and nonfatal cardiac disease in a large nonhospitalized population of older adults.

Methods

Study Population and Baseline Data Collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors for chronic diseases in the elderly. Objectives and methods of the Rotterdam Study have been described in detail. Briefly, in the Rotterdam Study, all men and women aged ≥55 years who live in the Rotterdam district Ommoord were invited to participate (response rate, 78%). Of 7129 participants, the
baseline data, collected from 1990 to 1993, included an ECG and information on history of cardiovascular disease, established cardiovascular risk factors, and use of medications.

A digitally stored ECG was available for 6160 participants (86%). An ECG was missing for 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as weight/length$^2$ in kg/m$^2$. Hypertension was defined as systolic blood pressure of $>160$ mm Hg or diastolic blood pressure of $>95$ mm Hg or the use of antihypertensive medication for the indication of hypertension. Diabetes mellitus was defined as a nonfasting blood glucose level of $>11.1$ mmol/L or the use of antidiabetic medication. History of MI was defined as self-reported MI with hospital admission, or MI on the ECG. Presence of angina pectoris was established through use of the Rose Questionnaire.

After exclusion of 345 subjects without follow-up data, mainly because they moved to unknown addresses, and 3 subjects with ECGs of poor technical quality that could not be interpreted by the computer program, the study population consisted of 2358 men and 3454 women.

**Follow-up Procedures**

The follow-up period, which started at the baseline examination and in the present analysis lasted until April 1996, was 3 to 6.5 years (mean, 4 years). With respect to the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and nonfatal end points was obtained from the GPs working in the study district of Ommoord. These GPs, covering 85% of the cohort, have their practices computerized and through scrutiny of the report of death by the municipal health service or the GP through use of the Rose Questionnaire.

All events were classified independently by two research physicians. In case of discrepancies, the judgment reached by this expert was considered definite.

**ECG Interpretation and Measurements**

A 12-lead resting ECG was recorded with an ESAOTE-ACTA cardigraph with a sampling frequency of 500 Hz and stored digitally. All ECGs were processed with the use of MEANS to obtain ECG measurements and diagnostic interpretations. The MEANS program has been extensively evaluated by the developers and others. To adjust QT for heart rate, we calculated QTc according to Bazett’s formula: QTc = QT/√RR, where RR is the RR interval in seconds.

Normally, the MEANS program determines an overall end of T waves for all 12 leads together using a representative beat, which results from selective averaging of dominant beats, and thus QTc dispersion is not disclosed. The program was therefore adjusted to determine the end of the T wave per lead. Taking the location of the overall end of the T wave as a starting point, the program searches forward and backward to establish the lead-specific end of the T wave. If the T wave amplitude is $<50$ μV, the T wave is considered to be flat and the lead is excluded from further analysis. QTc dispersion is determined as the difference between the maximum and minimum QTc in all considered leads. Analogously, QT dispersion is determined as the difference between the maximum and minimum QT interval, without correction for heart rate, in all considered leads.

QTc dispersion measured by the MEANS program was validated against the results of two human observers on a set of 100 ECGs (unpublished data, 1997). Both observers independently marked the end of the T wave in each lead with the cursor on a high-resolution computer screen. We found a mean QTc dispersion difference between MEANS and pooled data from both observers of 5.1 ms (SD, 29.3 ms). These results are comparable with the interobserver variability between the two human observers (mean, 6.7 ms; SD, 28.4 ms). Therefore, we concluded that the performance of the program was comparable to that of human observers.

LVH was determined using voltage as well as repolarization criteria. A negative T wave was defined as $\geq$1.00-mm negative deflection of the T wave in lead II, aVF, or the precordial leads.

**Lead Selection for QTc Dispersion**

Traditionally, QTc dispersion is defined as the difference between the maximum and minimum QTc interval in 12 leads. However, in the standard 12-lead ECG, only 2 of the 6 extremity leads are actually recorded. The other 4 leads are derived mathematically from these 2 leads.

It can be shown that if there is a shortest T wave in one of the extremity leads, the other 5 extremity leads must have the same end of T (see “Appendix”). As a consequence, true QTc dispersion cannot exist among these leads, and QTc dispersion measured in these leads can only be the result of measurement inaccuracy.

Therefore, we defined QTc dispersion as the difference between the maximum and the minimum QTc interval in 8 leads (ie, the 6 precordial leads, the shortest extremity lead and the median of the 5 other extremity leads). In addition, we computed QTc dispersion in 12 leads. ECGs in which QTc dispersion could be measured in fewer than 9 of the 12 leads were excluded ($n=16$ of the 5812 subjects in the present study).

**Data Analysis**

Differences in baseline characteristics between those with and without follow-up data were examined with one-way ANCOVA, with adjustment for age and sex when appropriate.

The degree of QTc dispersion in both 8 and 12 leads was categorized in tertiles, with intertertile values of 39 and 60 ms (in 8
leads) and 47 and 66 ms (in 12 leads) respectively. In addition, QT dispersion in 8 and 12 leads was categorized in tertiles. All analyses were performed for both 8- and 12-lead measures of dispersion.

To evaluate the association between QTc dispersion and potentially confounding factors, differences in the distribution of selected baseline characteristics between subjects in tertiles of QTc dispersion were examined with one-way ANCOVA, with adjustment for age and sex when appropriate.

The Cox proportional hazards model was used to examine the risk for cardiac and total mortality and nonfatal cardiac events in relation to tertile of baseline QTc and QT dispersion, with adjustment for two sets of confounders: age and sex (the latter only when non–sex-specific risks were estimated), and all possible confounders, excluding other ECG abnormalities, resulting from the ANCOVA (P<.05). The lowest tertile of QTc dispersion or QT dispersion was taken as the reference category. To minimize the effect of missing data in the multivariate analysis, missing values of categorical variables were replaced by dummies. Missing values of continuous variables were replaced by the average value, and a dummy variable (to indicate that the participant’s individual value was missing) was added to the model.

To compare predictive value of QTc dispersion with that of other commonly used cardiovascular risk indicators, age- and sex-adjusted hazard ratios for cardiac mortality of important cardiovascular risk indicators were computed.

Influence of age and history of MI on the risk for cardiac death associated with increased QTc dispersion was examined through subgroup analyses for these possible effect modifiers.

### Results

Baseline characteristics of participants in different tertiles of QTc dispersion are presented in Table 1. Statistically significant differences existed among the three comparison groups with regard to age, systolic and diastolic blood pressure, hypertension, diabetes mellitus, history of MI, overall QTc interval, presence of negative T waves, and LVH on the basis of ECG.

The distribution of QTc dispersion, measured in both 8 and 12 leads, in cases of cardiac death during the follow-up period was shifted to the right compared with survivors (Fig 1). In addition, QTc dispersion in 12 leads was shifted to the right compared with the distribution in 8 leads, reflecting larger dispersion in 12 than in 8 leads.

During the 3 to 6.5 years (mean, 4 years) of follow-up, 568 subjects (9.8%) died: 166 (2.9%) died of a cardiac cause and 73 (1.3%) died suddenly. In 193 of the subjects (3.3%), at least one nonfatal cardiac event occurred. Cardiac mortality according to tertile of QTc dispersion for men and women is presented in Fig 2a and 2b. It appears that in men, increased risk for cardiac mortality starts at a lower level of QTc dispersion than in women.

![Figure 1. Distribution of QTc dispersion measured in 8 and 12 leads in those who die from a cardiac cause and in survivors among 5812 men and women aged ≥55 years.](image-url)
1.6 to 4.0) and sudden cardiac death (hazard ratio, 1.9; 95% CI, 1.0 to 3.7) and an increased risk for total mortality (hazard ratio, 1.4; 95% CI, 1.2 to 1.8) and nonfatal cardiac events (hazard ratio, 1.3; 95% CI, 0.9 to 1.8), although the latter result was not statistically significant (Table 2). Additional adjustment for hypertension, diabetes, and history of MI did not materially change hazard ratio estimates for cardiac and all-cause mortality, although the 95% CI of the adjusted hazard ratios for sudden death events included one. Inclusion of other ECG abnormalities, notably LVH, negative T waves, and maximum QTc interval, in this model did not influence the results.

QTc dispersion in both 8 and 12 leads ranks among the strongest predictors for cardiac mortality (Fig 3). The highest age- and sex-adjusted hazard ratios for cardiac mortality were found for LVH (hazard ratio, 2.6; 95% CI, 1.7 to 4.0) and QTc dispersion in 8 leads >60 ms (hazard ratio, 2.5; 95% CI, 1.6 to 4.0), whereas in the multivariate model, QTc dispersion in 8 leads >60 ms was the strongest predictor for cardiac mortality, followed by history of MI (hazard ratio, 2.0; 95% CI, 1.5 to 2.5). The corresponding multivariate hazard ratio for cardiac death for QTc >440 ms was identical to the age- and sex-adjusted hazard ratio, notably 2.3 (95% CI, 1.0 to 2.1).

Subgroup analysis showed that the risk for cardiac death associated with increased QTc dispersion for participants in the highest relative to the lowest tertile of QTc dispersion was not

TABLE 2. Hazards Ratios in Subjects in the Middle and Highest Tertiles Relative to the Lowest Tertile of QTc Dispersion Measured in Eight Leads and Adjusted for Age and Sex (Model A) and for All Possible Confounders (Model B)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Subgroup</th>
<th>Model A</th>
<th></th>
<th>Model B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T2 39 to 60 ms</td>
<td>T3 &gt;60 ms</td>
<td>T2 39 to 60 ms</td>
<td>T3 &gt;60 ms</td>
</tr>
<tr>
<td>Total mortality</td>
<td>All</td>
<td>1.3 (1.1-1.7)</td>
<td>1.4 (1.2-1.8)</td>
<td>1.3 (1.1-1.7)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>1.5 (1.0-2.0)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.5 (1.1-2.1)</td>
<td>1.3 (1.1-1.8)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.2 (0.9-1.7)</td>
<td>1.5 (1.1-2.0)</td>
<td>1.2 (0.9-1.7)</td>
<td>1.5 (1.1-2.0)</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>All</td>
<td>2.1 (1.3-3.4)</td>
<td>2.5 (1.6-4.0)</td>
<td>2.0 (1.3-3.3)</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>3.3 (1.6-6.9)</td>
<td>2.5 (1.2-5.2)</td>
<td>3.3 (1.6-6.9)</td>
<td>2.3 (1.4-4.8)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.2 (0.6-2.5)</td>
<td>2.5 (1.4-4.6)</td>
<td>1.2 (0.6-2.4)</td>
<td>2.5 (1.3-4.5)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>All</td>
<td>1.8 (0.9-3.5)</td>
<td>1.9 (1.0-3.7)</td>
<td>1.8 (0.9-3.5)</td>
<td>1.8 (0.9-3.5)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>3.0 (1.1-8.1)</td>
<td>2.4 (0.9-6.6)</td>
<td>3.0 (1.1-8.1)</td>
<td>2.3 (0.8-6.1)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.9 (0.3-2.5)</td>
<td>1.6 (0.6-3.8)</td>
<td>0.9 (0.3-2.5)</td>
<td>1.5 (0.6-3.5)</td>
</tr>
<tr>
<td>Nonfatal cardiac events</td>
<td>All</td>
<td>0.9 (0.6-1.3)</td>
<td>1.3 (0.9-1.8)</td>
<td>0.9 (0.6-1.3)</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>0.8 (0.5-1.3)</td>
<td>1.2 (0.8-1.8)</td>
<td>0.8 (0.5-1.3)</td>
<td>1.1 (0.7-1.7)</td>
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<tr>
<td></td>
<td>Women</td>
<td>1.0 (0.5-2.0)</td>
<td>1.6 (0.9-3.0)</td>
<td>1.0 (0.5-1.9)</td>
<td>1.6 (0.9-2.9)</td>
</tr>
</tbody>
</table>

Model A indicates adjusted for age; model B, adjusted for age, and presence of hypertension, diabetes mellitus, and history of myocardial infarction; T2, middle tertile of QTc dispersion; and T3, highest tertile of QTc dispersion.
modified by age but was more pronounced in those without a history of MI (hazard ratio, 3.5; 95% CI, 1.8 to 6.9) than in those with a history of MI (hazard ratio, 1.8; 95% CI, 0.8 to 3.9).

The risks associated with QTc dispersion based on 12 leads was very similar to the risk associated with QTc dispersion in 8 leads (Table 3). Hazard ratios tended to be higher in QTc dispersion in 8 leads compared with QTc dispersion in 12 leads, but 95% CIs hardly differed.

The risk estimates for the various end points associated with QT dispersion, without correction of the QT interval for heart rate, in 8 and 12 leads were similar but had wider 95% CIs compared with the risk estimates for QTc dispersion in 8 and 12 leads.

**Discussion**

The results of this study show that increased QTc dispersion is a strong and independent risk factor for cardiac mortality in older men and women.

Previous studies were performed in patient populations. Their findings that QT dispersion is larger in those with MI,13,14 hypertension, LVH,13 and diabetes mellitus14 are confirmed by ours. Increased risk for cardiac mortality associated with QTc dispersion has been reported in patients with peripheral artery disease1 and MI.18 Our findings provide support for an association between QT dispersion and to search for the most accurate measurement of this mechanism.

Further studies are warranted to study the mechanism underlying QTc dispersion and to search for the most accurate measure of this mechanism.

**Appendix: Relationship Between Extremity Leads**

In the standard 12-lead ECG, only 2 of the 6 extremity leads are actually recorded (eg, leads I and II); the other 4 leads are derived from mathematical relationships imposed by the lead system. Thus, for the amplitudes in the extremity leads at any time, it holds that III=(II−I)/2, aVL=(I−III)/2, and aVF=(II+III)/2. If all T waves end at the same moment, of course QT dispersion (QTD)=0. Suppose the T wave in 1 lead, say I, is shorter than that in the other leads, ending at some time instant t1. Then, with lead I equal to 0, III=II for t>t1. This means that II and III must end at the same time. Let us assume this moment to be t2. In the time interval t1<t2, lead I=0, and using the above basic relationships, aVR=−II/2,

| Table 3. Hazards Ratios in Subjects in the Middle and Highest Tertile Relative to the Lowest Tertile of QTc Dispersion Measured in 12 Leads and Adjusted for Age and Sex (Model A) and for All Possible Confounders (Model B) |
|-----------------|-------------|-------------|-------------|-------------|
| **End Point**   | **Subgroup** | **Model A** | **Model B** |
|                 | T2 47 to 66 ms | T3 >66 ms  | T2 47 to 66 ms | T3 >66 ms  |
| Total mortality | All          | 1.3 (1.0-1.6) | 1.3 (1.1-1.6) | 1.3 (1.0-1.6) | 1.3 (1.0-1.6) |
|                 | Men          | 1.5 (1.1-2.1) | 1.2 (0.8-1.6) | 1.6 (1.2-2.2) | 1.1 (0.8-1.6) |
|                 | Women        | 1.1 (0.8-1.5) | 1.4 (1.1-1.9) | 1.1 (0.8-1.5) | 1.4 (1.1-1.9) |
| Cardiac mortality | All        | 1.9 (1.2-3.0) | 2.2 (1.4-3.4) | 1.9 (1.2-3.0) | 2.1 (1.4-3.3) |
|                 | Men          | 2.9 (1.5-5.6) | 1.9 (1.0-3.8) | 3.1 (1.6-5.9) | 1.8 (0.9-3.5) |
|                 | Women        | 1.2 (0.6-2.3) | 2.4 (1.4-4.3) | 1.1 (0.6-2.2) | 2.4 (1.4-4.3) |
| Sudden cardiac death | All     | 1.8 (0.9-3.4) | 1.7 (0.9-3.1) | 1.8 (0.9-3.5) | 1.7 (0.9-3.1) |
|                 | Men          | 2.1 (0.8-5.8) | 1.9 (0.7-5.5) | 4.2 (1.6-11.3) | 2.2 (0.8-6.1) |
|                 | Women        | 1.8 (0.6-5.8) | 2.6 (1.0-6.6) | 0.6 (0.2-1.8) | 1.4 (0.6-3.3) |
| Nonfatal cardiac events | All     | 0.9 (0.7-1.4) | 1.3 (0.9-1.8) | 1.0 (0.7-1.5) | 1.4 (1.0-1.9) |
|                 | Men          | 0.9 (0.5-1.4) | 1.3 (0.9-2.0) | 1.0 (0.6-1.6) | 1.3 (0.9-2.0) |
|                 | Women        | 1.2 (0.6-2.4) | 1.2 (0.6-2.2) | 0.9 (0.5-1.8) | 1.5 (0.6-2.7) |

See Table 2 for abbreviations.
QTc Dispersion Predicts Cardiac Mortality

aVL=−III/2, and aVF=II−III. Thus, the T waves in all augmented leads end when the T waves in the leads II and III end (ie, at t2). The same argument can be applied to any extremity lead other than I. It is always true that if there is a shortest T wave in I of the extremity leads ending at some time t1, the T waves in the other 5 extremity leads must all end at the same time instant t2. Thus, the result of measuring inaccuracy. The only possible true dispersion is between these 5 leads and the single short lead, QT△=t2−t1.

Acknowledgments

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