QT Dispersion Has No Prognostic Information for Patients With Advanced Congestive Heart Failure and Reduced Left Ventricular Systolic Function

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Background—QT dispersion is a potential prognostic marker of tachyarrhythmic events and death, but it is unclear whether this applies to patients with congestive heart failure (CHF).

Methods and Results—Of the 1518 patients with advanced CHF and left ventricular dysfunction enrolled in the Danish Investigations of Arrhythmia and Mortality on Dofetilide-CHF (Diamond-CHF) study, a baseline ECG was available in 1319 patients. Of these, QT dispersion could be measured in 703 patients. During a median follow-up of 18 months (minimum 1 year), 285 patients (41%) died. The median QT dispersion was 70 ms (34/155 ms [5%/95% percentiles]), with no difference between survivors and nonsurvivors. Survival analysis revealed no prognostic information derived from QT dispersion regarding all-cause mortality (risk ratio 1.00, 95% CI 1.00 to 1.00; \( P = 0.74 \)), cardiac mortality (risk ratio 1.00, 95% CI 1.00 to 1.01; \( P = 0.55 \)), or cardiac arrhythmic mortality (risk ratio 1.00, 95% CI 0.99 to 1.01; \( P = 0.38 \)).

Conclusions—QT dispersion has no prognostic value regarding all-cause mortality, cardiac mortality, or cardiac arrhythmic mortality for patients with advanced CHF and reduced left ventricular systolic function. (Circulation. 2001;103:831-835.)

Key Words: electrophysiology ■ heart failure ■ prognosis ■ arrhythmia

Roughly half of the very high mortality in patients with congestive heart failure (CHF) is described as sudden death and is assumed to be associated with arrhythmias, in particular, ventricular tachycardia and fibrillation. In spite of much effort, there is to date no specific method for identifying CHF patients prone to arrhythmic death.

Within the last decade, QT dispersion has been proposed as a descriptor of ventricular repolarization inhomogeneity and, as such, a potential prognostic tool in the detection of future ventricular tachyarrhythmic events and death. The prognostic value of QT dispersion has been explored in several cardiac disorders, especially for patients with inborn long-QT syndromes and for patients with acute myocardial infarction (MI).

Ever since Barr et al in 1994 found a significantly greater QT dispersion in patients with ischemic cardiomyopathy suffering a sudden death, QT dispersion has gained increasing interest as a prognostic tool in patients with CHF. To date, it remains unsettled whether QT dispersion bears any prognostic value for patients with CHF, because the results of various prognostic studies have been conflicting. Part of the explanation for the conflicting results may lie in the measuring technique of the QT dispersion, as much as both interobserver and intraobserver reproducibility of this parameter is often found to be low. Another uncertainty lies in the size of the reported investigations. Multivariate survival analysis requires both a large number of patients included and, not least, a large number of end points to provide a trustworthy result.

The aim of the present study was to describe the QT dispersion for patients with advanced CHF and reduced left ventricular systolic function and to evaluate the prognostic value of this parameter. Being the largest study so far to evaluate QT dispersion for patients with CHF prospectively, this investigation has the advantage of having both a sufficient number of patients included and a sufficient number of end points.

Methods

Patients
The present study was a predefined substudy to the Danish Investigations of Arrhythmia and Mortality on Dofetilide-CHF (Diamond-
CHF) study, which has been described in detail previously.\(^7\)\(^8\) In brief, it was a double-blind placebo-controlled study with the aim of prospectively evaluating the effect of dofetilide on mortality for patients with CHF. The study was conducted in 34 hospitals in Denmark from 1993 to 1996. Patients ≥18 years of age were consecutively enrolled if they were hospitalized with CHF of all causes with New York Heart Association (NYHA) functional class III or IV within the last month before hospitalization. In addition, the patients were required to have a left ventricular systolic dysfunction with a wall motion index ≤1.2, corresponding to an ejection fraction ≤35. In agreement with the main study protocol, a predose baseline 12-lead ECG was available locally in all of the 1518 patients enrolled. According to our substudy protocol, an additional predose baseline ECG was to be sent to us for central evaluation. This was achieved in 1319 patients.

Patients with an acute MI within 7 days, locally measured significant QT prolongation (corrected QT interval >460 ms, 500 ms with bundle branch block [BBB]), severe noncardiac disease, severe electrolyte abnormality, or severe renal dysfunction or patients receiving a class I or class III antiarrhythmic drug were excluded. Also excluded were patients unwilling to participate or incapable of participation.\(^2\)

Written informed consent was obtained. The Danish Board of Health and the involved ethical committees approved the study.

### QT Dispersion

Of the 1319 ECGs recorded, QT dispersion could be determined in 630 ECGs (48%). In the rest, QT dispersion could not be measured because of atrial fibrillation (n=371), <9 readable leads (n=259), poor recording quality (n=11), pacemaker rhythm (n=45), and bigemini (n=3). In addition to the 630 ECGs, another 73 ECGs from placebo-treated patients without ECG before randomization but with a measurable ECG taken within 6 days after randomization were included in the study, leaving 703 patients with a measurable ECG for further study.

QT intervals were measured in all 12 leads of a standard ECG by 1 of 2 experienced observers with use of a computerized digitizer tablet (Cherry, Mk III Graphic tablet, resolution 0.1 mm). The QT interval for each lead was calculated as the mean of 2 consecutive QT intervals, measuring from the beginning of the QRS complex to the nadir between the T and the U waves. Whenever such a distinction was not possible, the lead was discarded from analysis. QT dispersion was defined as minimum minus QT interval.

### Follow-Up

All patients were followed for a minimum of 1 year (median follow-up 18 months). Information on end points was gathered from the participating hospitals and from the Danish Central Person Registry, in which all deaths in Denmark are registered within 2 weeks of occurrence. No patient was lost to follow-up.

### End Points

The primary end point was all-cause mortality; secondary end points included death from cardiac causes, arrhythmic cardiac death, and nonarrhythmic cardiac death. Members of an event committee and of an arrhythmia committee reviewed all available data in connection with an end point, and they classified on a blinded basis these end points according to the Cardiac Arrhythmia Pilot Study (CAPS) criteria\(^a\) (with the exception that successful resuscitation of cardiac arrest was not considered as death).

### Statistical Analysis

All statistical analysis was made by use of the Statistical Analysis System (SAS Institute). Continuous data are described as median and 5%/95% percentiles. Comparison between groups was made by χ\(^2\) test for discrete data and by nonparametric ANOVA (Kruskal-Wallis test) for continuous data.

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<tr>
<th>Characteristics</th>
<th>Baseline demographics</th>
<th>Male sex</th>
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<th>Duration of heart failure, mo</th>
<th>Current smoker</th>
<th>Medical history</th>
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<th>Wall motion index, U</th>
<th>NYHA functional class 3 or 4</th>
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Values are percentage (number); all continuous variables are median and percentiles (5%/95%).

Survival analysis was performed by use of Kaplan-Meier estimates and curves (with QT dispersion dichotomized by the upper quartile) as well as univariate and multivariate proportional hazards (Cox) models. Variables in the final Cox models were chosen from univariate results, by backward selection, and from biological considerations. Assumptions of the models (β estimates for linearity of continuous variables, proportional hazards, and interactions) were tested, including the appropriateness of using QT dispersion as a continuous variable. Results are expressed as relative risk (RR) with a 95% CI.\(^6\)\(^10\)

A test was considered statistical significant at P≤0.05. Serum creatinine displayed significant interaction with several variables and did not influence the importance of QT dispersion and was therefore not included in the final models.

### Results

**Baseline Characteristics and QT Dispersion**

Table 1 shows the baseline characteristics of the 703 patients for whom QT dispersion was obtained. The median QT dispersion was 70 (34/151 [5%/95% percentiles]) ms with a range of 17 to 252 ms. Patients with ischemic heart disease had a greater QT dispersion (74 [34/155] ms) than did patients without ischemic heart disease (66 [33/126] ms, P<0.0004). There was no difference in QT dispersion for
patients with or without BBB (QRS ≥120 ms): 68 (36/141) ms versus 74 (32/156) ms, P > 0.4. Also, there was no difference in QT dispersion between groups treated with or without β-blockers, digoxin, diuretics, or ACE inhibitors.

**End Points and QT Dispersion**
During follow-up, 285 (41%) patients died. Table 2 shows QT dispersion in subgroups of patients with primary and secondary end points.

**Reproducibility of QT Dispersion**
Interobserver and intraobserver reproducibility was tested in a random sample of 90 patients. The interobserver difference was 14 (−39/78) ms (corresponding relative error 28%). Intraobserver differences were 4 (−36/52) ms and 14 (−39/78) ms, with corresponding relative errors of 14% and 29%, respectively.

**Univariate Survival Analysis**
QT dispersion was dichotomized from the upper quartile (>102 ms) to make mortality curves for the various end points. Only the curve for all-cause mortality is shown in the Figure; the curves for the other end points showed similar trends and the same lack of statistical significance (log-rank test: cardiac death, P > 0.2; arrhythmic cardiac death, P > 0.3; and nonarrhythmic cardiac death, P > 0.4).

Univariate Cox analyses for QT dispersion (continuous variable) for end points are shown in Table 3.

![Cumulative mortality as estimated by Kaplan-Meier method. Patients with QT dispersion >102 ms (upper QT dispersion quartile, n = 175) seem to be at increased risk of dying. However, log-rank test shows this to be without statistical significance.](image)

| TABLE 2. QT Dispersion in Subgroups of Patients With or Without End Points |
|-----------------------------|-----------------|-----------------|-----------------|
| End Point                   | Events, n       | With Event      | Without Event   | P    |
| All-cause mortality         | 285             | 70 (34/151)     | 70 (33/152)     | 0.87 |
| Cardiac death               | 219             | 70 (33/155)     | 70 (34/148)     | 0.63 |
| Cardiac arrhythmic death    | 131             | 72 (34/155)     | 70 (34/149)     | 0.28 |
| Cardiac nonarrhythmic death | 88              | 69 (33/155)     | 70 (34/151)     | 0.55 |

Values for QT dispersion are median and 5%/95% percentiles.

Of the baseline variables listed in Table 1, only the following reached a value of P ≤ 0.05 in the univariate Cox model for all-cause mortality: age per 10 years (1.55, 1.35 to 1.77; P < 0.0002), heart rate per 10 beats (1.10, 1.02 to 1.18; P < 0.02), serum creatinine >130 mmol per liter (1.99, 1.51 to 2.62; P < 0.0002), history of diabetes (1.38, 1.05 to 1.83; P < 0.03), wall motion index (1.21, 1.05 to 1.41; P < 0.02), NYHA III or IV (1.35, 1.06 to 1.72; P < 0.02), use of digoxin (1.36, 1.08 to 1.73; P < 0.01), and use of diuretics (2.76, 1.23 to 6.19; P < 0.02).

The presence of BBB tended to increase the risk of mortality, although the likelihood ratio test did not reach a value of P ≤ 0.05 (1.25, 0.99 to 1.58; P > 0.05).

**Multivariate Survival Analysis**
Results from the multivariate Cox analysis are shown in Table 4. Analysis was first made for all-cause mortality, and the variables included in the final model for all-cause mortality were then also tested in a separate analysis for the secondary end points. No multivariate prognostic value of BBB was found for all-cause mortality (1.06, 0.83 to 1.35; P > 0.6), cardiac death (1.23, 0.93 to 1.62; P > 0.1), or arrhythmic cardiac death (1.19, 0.83 to 1.70; P > 0.3).

Finally, the prognostic value of QT dispersion for all-cause mortality was evaluated in subgroups stratified by sex, age (<60 years, ≥60 years), wall motion index (<0.8, 0.8 to 1.2), smoking status, BBB, serum creatinine (≥130 mmol/L, >130 mmol/L), NYHA class (I and II, III and IV), diabetes, ischemic heart disease, arterial hypertension, β-blocker, digoxin, and dofetilide. In all subgroups without exception, risk ratios for QT dispersion were found to be 1.0, with a very narrow 95% CI. The corresponding probability values were in the range of 0.1 to 1.0.

**Discussion**
The present study has 2 major findings. First, it convincingly shows that for patients with advanced CHF and reduced left ventricular function, QT dispersion has no prognostic value in
Brooksby et al has a number of endpoints (n = 34 patients). Galinier et al found QT dispersion 8.4 ms, 95% CI 1.1 to 14.9) for patients dying before transplantation from sudden death or ventricular tachyarrhythmia (RR for ischemic or idiopathic dilated cardiomyopathy suffering heart disease (number of events 12 and 16, respectively). In contrast, the opposite was observed in post-MI patients presenting with signs of CHF within 2 to 9 days after infarction (number of deaths 181, RR 1.05, 95% CI 1.02 to 1.09; P = 0.004). However, they found a large overlap in QT dispersion between survivors and nonsurvivors (92.0 ± 38.5 versus 82.7 ± 34.3 ms, P = 0.005), limiting the use of QT dispersion as a prognostic marker. Other studies using multivariate analysis have shown no prognostic information from QT dispersion regarding mortality in patients with CHF, but of these studies, only the study presented by Brooksby et al has a number of end points (n = 71) that comes close to justifying the use of multivariate survival analysis.

The reason for the discrepancy in the results of the above-mentioned studies is not obvious, but several factors may influence the results. First, recent research has indicated that QT dispersion is not a direct marker of ventricular repolarization status but merely a crude marker of T-wave morphology. T-wave morphology can be assessed by T loops, which may in turn be a more precise descriptor of ventricular action potential heterogeneity. Also, only a few studies have reported a satisfying reproducibility of QT dispersion, whereas other studies mostly have both an intraobserver and interobserver relative error >20%. This low reproducibility can be caused by (false or true) extreme QT interval values; therefore, various expressions for QT dispersion have been proposed describing the variation of all QT intervals measured: variation coefficients and standard deviations. However, these methods have the weakness of not giving the "true" extreme QT-interval value sufficient power. QT dispersion is highly dependent on how QT intervals are measured. Unfortunately, there is no consensus on how to measure the QT interval, and because of the difficulty mainly in defining the end of the T wave, this has led to several definitions of the QT interval and hence to QT dispersion. In addition, there is also a lack in consensus regarding whether QT dispersion should be heart rate–corrected or not. In spite of little evidence for doing so, it is often reported as heart rate–corrected.

Another point of uncertainty is the number of events considered in multivariate survival analysis. Discrepancy in results regarding the prognostic value of QT dispersion in multivariate survival analysis could very easily be caused by the fact that analysis is often made without a sufficient number of end points. Most investigators note a high number of patients included in their studies without taking into consideration that an appropriate number of end points are also necessary.

The investigation made by Spargias et al fulfilled the criteria for multivariate survival analysis. Although they found a small but statistically significant prognostic value of QT dispersion for patients with clinical CHF, we did not find this in our patients with CHF. However, the 2 patient populations were very different. The population in the study of Spargias et al consisted of early post-MI patients (in whom...
QT dispersion is known to be heterogeneously increased27) with clinical evidence of heart failure, and there were estimates of left ventricular function in only 136 of the 501 patients included. Besides, their patients had a much better prognosis than did the patients included in the present study: during a follow-up of 6 years, 181 patients (36.1%) died. Our study population had both advanced CHF (NYHA III or IV within the last month before randomization) and severely affected left ventricular systolic function. Survival in this population was markedly lower; during a median follow-up of 18 months, 41% had died. Although the cause of CHF was not specified in the present study population, 71% had a history of ischemic heart disease, and 55% had had an MI.

The presence of BBB affects the QT interval, but it is not clear whether this should also have an effect on QT dispersion. Although some investigators17 have reported an influence on QT dispersion by BBB, QT dispersion in patients with BBB did not differ from QT dispersion in patients without BBB, both in our study and in other studies.18,21 Therefore, QT dispersion was not influenced by the presence or absence of BBB in our study, we found it appropriate to include ECGs with BBB and also to evaluate the prognostic importance of this factor by including it as a variable in survival analysis. Although there was a tendency toward prognostic importance in univariate analysis, this was not found when multivariate analysis was performed.

Study Limitations
The present study is a substudy based on a large randomized trial. This contains certain advantages, such as a well-defined population, close monitoring of the patients, and exclusion of patients receiving class I or IV antiarrhythmic drugs (which are known to affect QT dispersion). However, it also has some disadvantages. Usual markers of poor prognosis may be blurred by inclusion/exclusion criteria: in our case, prognosis in patients evaluated by NYHA classification and left ventricular systolic function was by definition poor at entry; therefore, the prognostic value of these variables may not be the same as in a mixed population. Most important, a baseline QTc interval >460 ms (>500 ms if BBB) found by the local investigators was considered to be an exclusion criterion. This may very well have excluded some patients with repolarization abnormalities, although for the ECGs available, we found no correlation between QTc interval and QT dispersion.

Conclusions
In a large population of patients with advanced CHF and left ventricular systolic dysfunction, QT dispersion is greater than in normal subjects. However, there is no prognostic information regarding all-cause mortality, cardiac mortality, or cardiac arrhythmic mortality from QT dispersion in these patients.

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References
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