Prevalence of Q-T Interval Dispersion in Type 1 Diabetes and Its Relation With Cardiac Ischemia

The EURODIAB IDDM Complications Study Group

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OBJECTIVE — The interlead variation in duration of the Q-T interval on the surface electrocardiogram (Q-T interval dispersion [QTd]) has been shown to predict mortality in type 2 diabetic patients. We evaluated the prevalence of QTd prolongation in the EURODIAB population and its relation to corrected Q-T interval (QTc), sex, age, duration of diabetes, blood glucose control, and complications.

RESEARCH DESIGN AND METHODS — A total of 3,042 type 1 diabetic patients were studied. QTc was calculated according to the Bazett's formula; QTc > 0.44 s was considered abnormally prolonged. QTd was calculated using the difference between the maximum and the minimum QTc in any thoracic lead. QTd > 0.080 s was considered abnormally prolonged.

RESULTS — The prevalence of an increased QTd was 7%. A significant relation was observed between QTd prolongation and diastolic blood pressure (P < 0.05). A higher prevalence of QTd prolongation was observed in patients with ischemic heart disease (P = 0.004), whereas no relationship was observed with retinopathy, albumin excretion rate, or measures of somatic and autonomic neuropathy. QTc and QTd were significantly related (P = 0.001); however, a proportion of patients with normal QTd showed a prolonged QTc (> 0.44 s).

CONCLUSIONS — In patients with type 1 diabetes, QTd is associated with ischemic heart disease and diastolic blood pressure but not neuropathy. Although QTd is statistically related to duration of QTc, increased QTd and increased QTc identify different patients, and their predictive value deserves prospective evaluation.

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The Q-T interval in the electrocardiogram (ECG) reflects the total duration of ventricular myocardial depolarization and repolarization. It has been shown that a prolonged Q-T interval is associated with sudden death and poor survival in healthy subjects (1) and in a variety of clinical conditions, including newly diagnosed type 2 diabetes (2), nephropathy (3), and type 1 diabetes (4,5).

The observation that the Q-T interval exhibits a certain degree of spatial variability on the epicardial surface (6) has led to the hypothesis that differences in the duration of the Q-T interval between ECG leads may reflect heterogeneity in recovery of excitability (7). Based on the evidence that nonuniform repolarization provides a substrate for the development of malignant ventricular arrhythmias (8), prolongation in the duration of the Q-T interval has been advocated as a more predictive marker of arrhythmias and mortality than the maximum duration of the Q-T interval (9).

The interlead variation in duration of the Q-T interval on the surface ECG has been referred to as Q-T interval length dispersion or Q-T dispersion (QTd). It has been shown that the QTd is predictive of mortality in normal subjects and different groups of patients. Increased QTd has been described in patients with recent myocardial infarction (10), long Q-T syndrome (9,11), heart failure (12), and hypertrophic cardiomyopathy (13). Furthermore, QTd has been related to arrhythmia and mortality in these patients and in healthy subjects (14). QTd has also been studied in selected groups of diabetic patients (15,16) and has been shown to predict mortality in type 2 diabetic patients (2,17). However, only one recent study has reported on the prevalence of increased QTd in diabetic populations and its relation to diabetic complications (5).

The EURODIAB Type 1 Diabetes Complications Study is a cross-sectional clinic-based study of complications in type 1 diabetic patients. The prevalence of acute metabolic and chronic complications (nephropathy, retinopathy, and neuropathy) and QTc prolongation in this study have been previously reported (18,19).

The aims of the present study were to evaluate the prevalence of increased QTd in the EURODIAB population and its relationship to QTc, demographic and clinical parameters, and complications.

RESEARCH DESIGN AND METHODS — Details on the subjects and the procedures of the EURODIAB
study have been published elsewhere (18). In brief, 3,250 type 1 diabetic patients (1,668 men and 1,582 women) were randomly selected from 31 centers in 16 countries across Europe. The mean (SD) age was 32.7 years (10.7) and duration of diabetes 14.7 years (9.3). HbA1c was centrally assessed with an enzyme immunoassay and the mean (SD) was 6.7% (1.9; normal range 2.9–4.2%).

Retinopathy was assessed by retinal photographs centrally graded by a single observer. Each patient’s level of retinopathy (absent, background, or proliferative) was determined in the worse eye (20).

Nephropathy was assessed using albumin excretion rate (AER) calculated centrally from a single timed 24-h urine collection. AER was defined as \( \leq 20 \) µg/min. Microalbuminuria was defined as AER >20 and <200 µg/min, and macraalbuminuria was defined as AER ≥200 µg/min (21).

For the assessment of sensory neuropathy, vibration perception threshold was measured using centrally calibrated biothesiometers and age-related reference values (22). Autonomic neuropathy was assessed by measuring the change in heart rate (heart rate variability) and blood pressure (postural hypotension) on standing upright after resting supine for at least 5 min. The cardiovascular tests were performed and evaluated according to the Ewing method (23). A single observer calculated centrally the postural change in ECG-recorded heart rate as the ratio of the longest R-R interval between the 28th and 32nd beats after standing to the shortest interval between the 13th and 17th beats (R-R ratio). Blood pressure was measured once in the horizontal position and once 60 s after standing using a Hawksley random-zero sphygmomanometer. Diabetic autonomic neuropathy was diagnosed in the presence of postural hypotension with a decrease in systolic blood pressure of >30 mmHg and/or loss of heart rate variability (R-R ratio <1). Patients were asked about the presence of symptoms suggestive of neurological damage, and ankle and knee reflexes were assessed. The presence of peripheral neuropathy was defined as two of four abnormalities among vibration perception threshold, cardiovascular tests, symptoms, and ankle/knee reflexes.

The presence of ischemic heart disease (IHD) was determined on the basis of a structured standardized questionnaire concerning history of angina or myocardial infarction and a resting ECG, which was centrally classified according to the Minnesota Code (24).

**Q-T interval duration**

R-R and Q-T intervals were measured with a ruler on the resting ECG tracing; five consecutive beats were considered on lead V5. The Q-T interval was measured from the beginning of the QRS complex to the end of the downslope of the T wave (crossing of the isoelectric line); when a U wave was present, the Q-T interval was measured to the nadir of the curve between the T and U waves. The Q-T interval corrected for the previous cardiac cycle length (QTc) was calculated according to Bazett’s formula (25): QTc = QT / (RR)\(^{1/2}\). Two observers who were unaware of the grouping of any subject measured all of the intervals. The QTc for each subject was considered the mean value of the five calculated intervals and the mean of the reading of the two observers to minimize interobserver variability. QTc >0.44 s was considered abnormally prolonged.

**Q-T interval dispersion**

R-R and Q-T intervals were also measured for the same three consecutive cardiac cycles on the six thoracic leads. These leads were all available for 3,042 patients. The measurement on the thoracic leads was performed by a single investigator, who was blinded with respect to the patient characteristics. The dispersion of QTc was calculated using the difference between the maximum and minimum QTc in any thoracic lead (6,11). A QTd >0.080 s was considered abnormally increased.

**Statistical analysis**

Student’s t test was used to test for differences in means for those with QTd ≤0.080 s and those with QTd >0.080 s, and \( \chi^2 \) test was used to test for differences in proportions for those with QTd ≤0.080 s and those with QTd >0.080 s. Mantel Haenszel \( \chi^2 \) test was used to test for a trend in percentages of those with QTd >0.080 s across groups, and linear regression was used to test for differences and trend in mean QTd levels across groups when there were more than two groups. Logistic regression was used to assess the association between QTd >0.080 s and IHD adjusting for blood pressure. Standardized odds ratios, i.e., the relative odds associated with an increase in 1 SD, were calculated for continuous variables. Because the distribution for QTd was slightly skewed, the square root of QTd was used for analysis involving QTd as a continuous variable.

**RESULTS** — The prevalence of increased QTd in the whole population was 7% (8.4% in men and 5.1% in women; \( P = 0.001 \)). The mean (SD) QTd was 0.044 s (0.021) in the whole population, 0.045 s (0.006) in men, and 0.044 s (0.005) in women (\( P = 0.04 \)).

A significant relation was observed between increased QTd and diastolic blood pressure (\( P < 0.05 \)), whereas no relation was found with age, duration of diabetes, HbA1c, BMI, waist-to-hip ratio, systolic blood pressure, insulin dose, or level of physical activity (Table 1).

The relationship between QTd and microvascular and macrovascular complications of diabetes was also evaluated. A higher prevalence of increased QTd was observed in patients with IHD (\( P = 0.004 \)), whereas no relationship was found with retinopathy, increased AER, and peripheral or autonomic neuropathy (Table 2).

Table 3 shows that in a model considering patients not receiving antihypertensive drugs, the relationship between QTd and QTd is independent of sex and systolic blood pressure (model 1) or diastolic blood pressure, whereas the relation between QTd and diastolic blood pressure is lost when considered together with IHD (model 2).

A significant relation was observed between QTc and QTd (\( P = 0.001 \)) in both men and women. However, 10.1% of men and 16.7% of women with normal QTd showed a prolonged QTc.

**CONCLUSIONS** — Several studies have described a poor survival prognosis in type 1 diabetic patients compared with nondiabetic populations. Sudden death has been reported as a common cause of death in type 1 diabetic patients affected by autonomic neuropathy (23). Based on the observations of long QT syndrome (26) and sudden infant death (27), it has been postulated that QT prolongation predisposes cardiac arrhythmias and sudden death.

It has been suggested that the interlead variability of QTc is a better predictor...
Q-T interval dispersion in type 1 diabetes

Table 1—Demographic details by the presence and absence of increased QTd

<table>
<thead>
<tr>
<th></th>
<th>QTd ≤ 0.080 s</th>
<th>QTd &gt; 0.080 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>2,831 (93)</td>
<td>211 (7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.7 ± 10.1</td>
<td>33.7 ± 11.1</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>14.7 ± 9.1</td>
<td>15.7 ± 10.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.73 ± 1.86</td>
<td>6.66 ± 1.96</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 2.9</td>
<td>23.4 ± 3.0</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.86 ± 0.12</td>
<td>0.86 ± 0.13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.4 ± 11.4</td>
<td>77.6 ± 11.8*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.3 ± 17.8</td>
<td>123.7 ± 19.3</td>
</tr>
<tr>
<td>Insulin dose (units)</td>
<td>44.9 ± 15.4</td>
<td>45.2 ± 16.2</td>
</tr>
<tr>
<td>Maximum exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, more than once per week</td>
<td>3.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Mild, weekly</td>
<td>33.0</td>
<td>26.2</td>
</tr>
<tr>
<td>Moderate, weekly</td>
<td>32.4</td>
<td>35.2</td>
</tr>
<tr>
<td>Vigorous, weekly</td>
<td>31.4</td>
<td>32.7</td>
</tr>
</tbody>
</table>

Data are means ± SD, n (%), or %. Significant difference between QTd ≤0.080 s and QTd >0.080 s, with P < 0.05.

of arrhythmias and death than QTc duration (9). This has been confirmed in the general population (1) and groups of outpatients with newly diagnosed diabetes (2), nephropathy (3), or type 2 diabetes (17). However, in recent prospective studies of type 2 diabetic patients (28) and type 1 diabetic patients (5), QTc but not QTd was the predictor of mortality. The present study is the first large study aimed at assessing the prevalence of increased Q-T interval dispersion in patients with type 1 diabetes and offers the opportunity to evaluate the prevalence of increased QTd and the exposure-complication relationships in a large sample of European patients.

The lack of serum electrolytes and left ventricular hypertrophy measures in the EURODIAB study may limit the interpretation of results. However, because the sample of patients is relatively young, the prevalence of left ventricular hypertrophy and the percentage of patients with electrolyte disturbances or those taking drugs potentially interfering with Q-T interval duration should be very small and have little impact on the findings.

An upper limit of normal QTd has never been defined. A large study, designed to estimate the normal range of QTd, evaluated 1,000 digitized ECG recordings from normal subjects: the 97.5th percentile for QTd was 0.076 s (29). On the basis of this observation and for the purpose of this study, an upper limit of normal of 0.080 s was chosen. This threshold was predictive of death in the general population studied by Elming et al. (1). In the EURODIAB cohort, the prevalence of increased QTd was 7%, with a significant difference between men and women (8.4 and 5.1%, respectively). Rosming et al. (5) reported a prevalence of 23.1% in a cohort of type 1 diabetic patients with a higher mean age (41 years) and duration of disease (22 years). QTc prolongation and increased QTd were significantly related. However, the

Table 2—QTd by nephropathy, retinopathy, IHD, and neuropathy

<table>
<thead>
<tr>
<th></th>
<th>Mean QTd (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin excretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 µg/min</td>
<td>0.041 (0.040–0.042)</td>
<td>125</td>
<td>6.4 (5.4–7.5)</td>
</tr>
<tr>
<td>20–200 µg/min</td>
<td>0.042 (0.040–0.044)</td>
<td>41</td>
<td>6.5 (4.6–8.5)</td>
</tr>
<tr>
<td>&gt;200 µg/min</td>
<td>0.043 (0.040–0.045)</td>
<td>22</td>
<td>8.7 (5.2–12.2)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.041 (0.040–0.042)</td>
<td>70</td>
<td>5.8 (4.5–7.1)</td>
</tr>
<tr>
<td>Nonproliferative</td>
<td>0.041 (0.040–0.043)</td>
<td>56</td>
<td>6.9 (5.2–8.6)</td>
</tr>
<tr>
<td>Proliferative</td>
<td>0.039 (0.036–0.042)</td>
<td>14</td>
<td>5.6 (2.8–8.5)</td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0.041 (0.040–0.042)</td>
<td>176</td>
<td>6.4 (5.5–7.3)</td>
</tr>
<tr>
<td>Present</td>
<td>0.044 (0.041–0.047)</td>
<td>25</td>
<td>11.5 (7.3–15.7)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0.041 (0.040–0.042)</td>
<td>135</td>
<td>6.9 (5.8–8.0)</td>
</tr>
<tr>
<td>Present</td>
<td>0.043 (0.041–0.044)</td>
<td>56</td>
<td>6.7 (5.0–8.4)</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0.042 (0.041–0.043)</td>
<td>118</td>
<td>6.8 (5.7–8.0)</td>
</tr>
<tr>
<td>Present</td>
<td>0.042 (0.040–0.043)</td>
<td>78</td>
<td>6.9 (5.4–8.4)</td>
</tr>
</tbody>
</table>

0.070
hypothesis that the two parameters provide different information is supported by the observation that a significant proportion of men and women with normal QTd (<0.08 s) have a prolonged QTc (>0.44 s). Furthermore, in patients with long QT syndrome, QTd is more predictive of the efficacy of antiarrhythmic drugs than QTc (11). A longitudinal study is needed to assess which of the two is more predictive for arrhythmias and/or death in type 1 diabetic patients.

A role of cardiac ischemia in Q-T interval dispersion is suggested by the observation that QTd is prolonged in patients immediately after an acute myocardial infarction and tends to reduce thereafter (10). Moreover, Moreno et al. (30) have shown that thrombolysis reduces QTd proportionally to the Thrombolysis in Myocardial Infarction (TIMI) degree of reperfusion. Some studies have shown that early and late QTd after acute myocardial infarction predict malignant arrhythmias and death (10,30). However, this conclusion has been challenged by other studies (31).

In the EURODIAB study, the prevalence of IHD was 9% in men and 10% in women, whereas the prevalence of silent ischemia (defined as ECG changes without prior positive history) was 6% (22). We found that increased QTd was associated with the presence of IHD. This relation suggests a possible role of IHD, even silent, in the pathogenesis of increased QTd in type 1 diabetic patients. In the EURODIAB study, the prevalence of IHD was assessed by means of a resting ECG, and it is known that an exercise ECG can reveal IHD more often in type 1 diabetic patients (32). Therefore, in a proportion of the patients with abnormal QTd and absence of IHD on resting ECGs (6%), increased QTd could be attributed to undiagnosed cardiac ischemia. However, the low sensitivity (11.5%) and positive predictive value (12.4%) does not confer to QTd the role of a screening tool for IHD in type 1 diabetic patients.

Drugs like B-blockers or ACE inhibitors are known to reduce QTd (33,34) and, being more likely to be prescribed to patients with IHD, could have weakened the relation between QTd and IHD. This hypothesis, however, is not confirmed by the analysis performed excluding all the patients treated with antihypertensive drugs (Table 3).

Patients with hypertrophic cardiomyopathy show an increased QTd, which is predictive of arrhythmias and sudden death (35). It is therefore possible that the relation between QTd and diastolic blood pressure observed in the present study is mediated through left ventricular hypertrophy. Unfortunately, data on left ventricular hypertrophy in the EURODIAB cohort are lacking to test this hypothesis. Moreover, the relation between QTd and diastolic blood pressure is weak and probably mediated through IHD (Table 3).

A role of autonomic neuropathy in duration of Q-T interval in diabetic patients has been proposed, because diabetic patients with autonomic neuropathy show longer QTc compared with those without autonomic neuropathy (36). In the EURODIAB cohort, we have reported that men with neuropathy and/or impaired heart rate variability (an index of autonomic dysfunction) showed a significantly higher mean QTc compared with men without this complication, after adjustment for confounders. A similar difference was observed for the prevalence of QTc prolongation, suggesting a role for autonomic dysfunction in QTc prolongation in men. The relation between QTc prolongation and autonomic neuropathy was not observed in women (19). The hypothesis of a relation between QT dispersion and autonomic neuropathy has been addressed in few small studies, which showed higher QTd values in groups of patients with abnormal cardiovascular tests (37). However, studies using cardiac meta-iodo-benzylguanidin (MIBG) imaging for the diagnosis of autonomic neuropathy of the heart did not confirm this relation (16).

No relation between QTd and autonomic neuropathy was found in the present study. It is possible that, although the autonomic nervous system influences the total duration of repolarization, other factors play a major role in the variability of depolarization and repolarization through myocardial mass.

An independent association of high plasma glucose concentration and QTc prolongation has been reported in nondiabetic subjects (38). Because instantaneous blood glucose values were not measured during the ECG recording, the relationship between blood glucose levels and QTc or QTd cannot be evaluated in the EURODIAB population. In the present study, no significant association was found between increased QTd and HbA1c levels, suggesting no evident influence of mean blood glucose values on QTd. However, a possible influence of blood glucose on QTd cannot be excluded and is worthy of further investigation in view of the complexity of the relation of diabetes with cardiovascular morbidity and mortality.

The EURODIAB IDDM Complications Study is a clinic-based and not a population-based study. However, most type 1 diabetic patients in Europe attend centers such as those taking part in the study. Nevertheless, some degrees of selection bias may have occurred, but as we have previously argued (18), this should result in an underestimation of the risk factor/complication relationships we observed.

In conclusion, we have shown that 7% of type 1 diabetic patients in the EURODIAB cohort have an increased QTd (>0.080 s). QTd is associated with IHD and diastolic blood pressure, and although it is statistically related to duration of QTc, increased QTd and increased QTc identify different patients. A prospective study to assess the predictive value of in-

<table>
<thead>
<tr>
<th>Model 1:</th>
<th>Standardized odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>1.009</td>
<td>0.863–1.176</td>
<td>0.9094</td>
</tr>
<tr>
<td>Sex</td>
<td>0.554</td>
<td>0.402–0.765</td>
<td>0.0003</td>
</tr>
<tr>
<td>IHD</td>
<td>1.941</td>
<td>1.168–3.226</td>
<td>0.0105</td>
</tr>
<tr>
<td>Model 2:</td>
<td>Standardized odds ratio</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.126</td>
<td>0.965–1.314</td>
<td>0.1308</td>
</tr>
<tr>
<td>Sex</td>
<td>0.564</td>
<td>0.410–0.777</td>
<td>0.0004</td>
</tr>
<tr>
<td>IHD</td>
<td>1.967</td>
<td>1.184–3.266</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Table 3—Logistic regression model testing the association between QTd and IHD, blood pressure, and sex (excluding patients on antihypertensive therapy)
increased QTd and its impact on mortality in type 1 diabetic patients is in progress.

APPENDIX

The EURODIAB Type 1 Diabetes Complications Study Group


Coordinating Center


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References


2. Naas AA0, Davidson NC, Thompson C, Cummings F, Ogston SA, Jung RT, Newton RW, Struthers AD: QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin-dep


16. Wei K, Dorian P, Newmann D: Association between QTd and autonomic dysfunction in patients with diabetes


