Original Research

QT Dispersion: Comparison Between Diabetic and Non-Diabetic Individuals and Correlation with Cardiac Autonomic Neuropathy

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Introduction: The QT interval on the resting electrocardiogram (ECG) expresses the myocardial depolarisation and repolarisation time. Elevated values of QT dispersion (QTd) are associated with cardiovascular mortality in diabetics. Cardiac autonomic neuropathy (CAN) is a common complication of diabetes that is also associated with increased morbidity and mortality. However, there are no data in the literature concerning the relation between CAN and QTd in diabetics. The aim of this study was to investigate: 1) the differences in QTd between diabetics and non-diabetics; 2) the differences in QTd between those with type 1 and type 2 diabetes; 3) the relation between QTd and CAN.

Methods: The study population included 184 diabetics (63 type 1, group D1; 121 type 2, group D2) and 100 healthy controls who had similar age and sex distribution to D1 (n=44) and D2 (n=56) subjects. CAN assessment was made using the standard Ewing and Clarke tests. The QT interval was measured on the 12-lead resting ECG. QTd was calculated automatically using special software.

Results: QTd values did not differ significantly between controls and D1 (p=0.15) or D2 (p=0.27). QTd was significantly greater in D2 than in D1 (p=0.02). There was no significant difference in QTd between those with and without CAN in either group of diabetics.

Conclusions: QTd values do not differ between individuals with and without diabetes. Type 2 diabetes is associated with higher QTd values than is type 1 diabetes. CAN does not affect QTd in diabetics.

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The QT interval on the electrocardiogram (ECG) reflects the depolarisation and repolarisation time of the left ventricular myocardium.[1] Previous studies have shown that patients with prolongation of the QT interval, either congenital or acquired, often experience episodes of sudden death due to malignant ventricular arrhythmias.[2,3] QT dispersion (QTd), the difference between the greatest and smallest values of the QT interval on any of the twelve leads of the resting ECG, is an index of myocardial electrical activity.[4,5] An increase in QTd reflects heterogeneity in the electrical stimulation of the myocardium that can lead to ventricular arrhythmias.[6,7] Some studies in recent years have shown that QTd values are a prognostic factor for cardiac mortality in diabetics.[8-10]

Cardiac autonomic neuropathy (CAN) is a common complication of diabetes[11,12] and leads to increased mortality,[13,14] due to the occurrence of malignant ventricular arrhythmias associated with an increase in QTd.[15,16] A previous study in our centre showed that the duration of the QT interval corrected for heart rate (QTc) is significantly and independently related with the existence and severity of CAN in diabetics.[17] Studies to date have produced con-

flicting results as regards the relation between CAN and QTd.[18-21] Furthermore, there are no data in the literature concerning the existence of differences in QTd values between individuals with type 1 and type 2 diabetes.

The purpose of this study was to investigate: 1) the differences in QTd between diabetics and non-diabetics; 2) the differences in QTd between those with type 1 and type 2 diabetes; 3) a possible correlation between CAN and QTd.

Material and methods

We studied 184 patients with diabetes (63 type 1, group D1; 121 type 2, group D2), who were selected at random from all the diabetics followed in the Diabetic Centre of our hospital, and 100 healthy controls who had similar age and sex distribution to D1 (n=44) and D2 (n=56) subjects. Inclusion criteria for the controls were the absence of any history of diabetes and normal levels of fasting serum glucose, according to the recommendations of the American Diabetes Association.[22] All subjects of the study underwent a full clinical examination and history, from which any concurrent diseases and medication were recorded. Patients with atrial flutter or fibrillation, a cardiac pacemaker, atrioventricular block or bundle branch block and frequent extrasystoles were excluded from the study, since in such cases the ECG quality is not appropriate for the measurement of QT intervals.[1] None of the diabetics had hypoglycaemia or acute disease during the preceding 24 hours (conditions that could affect the results of the tests of the cardiac autonomic nervous system).[11] Any individuals who were taking drugs known to affect autonomic nervous system activity were also excluded from the study.

The tests took place between 7-9 a.m. in an environment with stable temperature (22-24^{o} C). The subjects were instructed not to smoke, eat, or drink coffee prior to examination. In the case of the diabetics, antidiabetic medication was given at the end of the examination.

The study was carried out in accordance with the Helsinki Declaration. All subjects participated voluntarily after being given a detailed explanation of the purpose of the study. Demographic and clinical data from the diabetics and controls are shown in Table 1.

Diagnosis of diabetes

The diagnosis of diabetes type was based on the history and on data from the patients' personal records. The criterion for a diagnosis of type 1 diabetes was the appearance of the disease at an age below 35 years, with initiation of insulin therapy within the first year from diagnosis, and/or a history of diabetic ketoacidosis.[22] None of the patients had a special type of diabetes; thus the remaining patients were considered to have type 2.[22]

Diagnosis of CAN

For the diagnosis of CAN we used the four standard tests proposed by Ewing and Clarke[11] and the Consensus Statement of the members of the American Diabetes Association and the American Neurological Academy.[12] Heart rate variability during the tests of deep breathing, rising from the supine position and the Valsalva manoeuvre was evaluated automatically from changes in the RR interval on the ECG by special software (VariaCardio, TF4 Medical Research Limited, Leeds, UK).[23] The change in blood pressure was calculated as the difference between the mean value of the last two of three measurements made while the subject was in a supine position and the value recorded 60 seconds after the adoption and maintenance of an upright position.[11,12] Orthostatic hypotension was defined as a drop in systolic blood pressure $\geq$20 mmHg and/or a drop in diastolic pressure $\geq$10 mmHg.[11,12]

Evaluation of the three first tests, which depend on changes in heart rate, was performed using published tables based on age.[11,24] The diagnosis of CAN was made when at least two tests were pathological.[11]

Measurement of the QT interval on the ECG

A 12-lead resting ECG was recorded from all subjects. A scanner was used to transfer the ECG to a computer as a digitised image for analysis. The QT interval was measured from the start of the QRS complex to the point where the T-wave intersected the isoelectric line. The accuracy of the test for QT variability was evaluated in 20 subjects (10 diabetics and 10 controls) in our laboratory and the coefficient of variance was 2.1 $\pm$ 0.9%. The QT interval corrected for heart rate (QTc) was calculated using Bazett's formula: $QTc = QT/\sqrt{RR}$.[25] The dispersions of QT and QTc were calculated by the same program, using the greatest and smallest values of QT and QTc from any of the twelve leads.

Other measurements

The subjects were classified as smokers or non-smok-

Table 1. Clinical and demographic characteristics of the study population (mean ± standard deviation unless otherwise noted).

	Controls for type 1 diabetes	Type 1 diabetics	p (type 1 vs. controls)	Controls for type 2 diabetes	Type 2 diabetics	p (type 2 vs. controls)	p (type 1 vs. type 2)
n	44	63		56	121		
Age (years)	32.7 ± 5.8	32.0 ±10.7	0.66	60.8 ± 8.6	61.8 ± 9.1	0.53	0.75
Men/women (%)	65.9/34.1	61.9/38.1	0.67	57.1/42.8	59.5/40.5	0.76	0.01
Systolic blood pressure (mmHg)	117.1 ± 11.3	122.1 ± 12.6	0.04	130.8 ± 18.5	138.1 ± 18.4	0.02	<0.001
Diastolic blood pressure (mmHg)	75.5 ± 7.6	75.5 ± 6.7	0.98	78.2 ± 9.5	80.1 ± 9.9	0.28	0.007
Body mass index (Kg/m^2)	24.67 ± 3.24	24.02 ± 3.16	0.43	26.72 ± 3.74	27.50 ± 3.92	0.26	<0.001
Waist-to-hip ratio	0.87 ± 0.06	0.88 ± 0.05	0.95	0.89 ± 0.06	0.92 ± 0.06	0.004	0.01
Duration (years): median (range)	–	11.0 (7.0-20.0)		–	9.0 (3.0-16.5)		0.01
HbA1c (%)	5.4 ± 0.39	8.35 ± 1.9	<0.001	5.6 ± 0.6	7.7 ± 1.6	<0.001	0.01
Glucose (mg/dl)	93.2 ± 13.6	193.4 ± 100.9	<0.001	97.2 ± 15.4	165.3 ± 45.9	<0.001	0.01
Cholesterol (mg/dl)	216.3 ± 46.6	205.1 ± 51.0	0.27	224.5 ± 44.5	220.2 ± 43.0	0.24	0.05
LDL cholesterol (mg/dl)	142.3 ± 51.9	127.2 ± 51.6	0.15	146.9 ± 46.4	143.9 ± 42.0	0.28	0.01
HDL cholesterol (mg/dl)	50.4 ± 19.3	53.8 ± 17.2	0.35	49.6 ± 12.9	44.2 ± 11.3	0.01	<0.001
Triglycerides (mg/dl)	118.3 ± 66.7	120.3 ± 69.6	0.88	139.5 ± 81.5	160.3 ± 79.5	0.14	0.002
Smokers n (%)	20 (45.5)	24 (38.1)	0.44	12 (21.4)	24(19.8)	0.80	0.01
Total CAN score: median (range)	0	2.0 (1.0-5.0)		0	3.0 (1.0-5.0)		0.01

CAN – cardiac autonomic neuropathy; LDL – low density lipoprotein; HbA1c - glycosylated haemoglobin; HDL – high density lipoprotein.

ers. In all cases we measured the weight, height, waist and hip circumference, and calculated the body mass index (BMI, Kg/m^2) and waist-to-hip ratio (WHR). Arterial hypertension was diagnosed when the systolic blood pressure was ≥140 mmHg or the diastolic pressure ≥90 mmHg,[26] or when the patient was taking antihypertensive drugs.

Blood samples were taken from all subjects in the early morning, after 12-14 hours' fasting. All samples were analysed automatically in the hospital's biochemical laboratory. Creatinine, total cholesterol, high density lipoprotein cholesterol (HDL) and triglycerides were measured enzymatically by a Technicon RA-XT analyser. Low density lipoprotein cholesterol (LDL) was calculated using the equation of Friedewald et al.[27] Glucose was measured by the oxidase-hyperoxidase method (Zafeiropoulos, Greece). Glycosylated haemoglobin (HbA_{1c}) was measured by high liquid chromatography (Roche Diagnostics, Manheim, Germany – intra-assay coefficient of variation: 1.2%, inter-assay coefficient of variation: 1.1%) with normal range 4.1-6.2%.

Statistical analysis

The data collected were codified and entered into a computer for analysis by statistical software (SPSS 10.0, Chicago, IL, USA). All variables analysed were checked for normal distribution. For the comparison of quantitative variables that were normally distributed in diabetics and in controls, as well as in the groups with and without CAN, the t-test for independently paired observations was used. For quantitative variables without normal distribution the Mann-Whitney U test was used. Comparison of qualitative variables in the study groups was made using the χ^2 test. P values <0.05 were considered statistically significant.

Results

Comparisons between D1 and controls

As expected, levels of fasting blood glucose and HbA_{1c} were significantly higher in the D1 group than in controls ($p<0.0001$). Systolic blood pressure was also greater in group D1 ($p=0.04$, Table 1).

With regard to the QT interval, QTc was greater in group D1 than in controls ($p=0.05$). Neither QT duration nor QTd differed significantly between D1 and controls ($p=0.42$ and $p=0.15$, respectively, Table 2).

Comparisons between D2 and controls

Fasting blood glucose and HbA_{1c} levels were significantly higher in the D2 group than in controls ($p<0.001$). Systolic blood pressure was also greater in group D2 ($p=0.02$). In addition, D2 had greater WHR ($p=0.004$) and lower levels of HDL cholesterol ($p=0.01$) (Table 1).

The values of the minimum QT interval ($p=0.05$) and QTc dispersion ($p=0.04$) were significantly greater in the D2 group than in controls. However, the values of QT interval ($p=0.18$), QTd ($p=0.27$) and QTc ($p=0.14$) did not differ significantly between the two groups (Table 2).

Comparisons between D1 and D2

As expected, D2 subjects were older ($p<0.001$), had greater BMI ($p<0.001$), WHR ($p=0.007$), higher levels of total cholesterol ($p=0.05$), LDL cholesterol ($p=0.01$) and triglycerides ($p<0.001$), lower levels of HDL cholesterol ($p=0.0002$) and higher systolic ($p<0.0001$) and diastolic ($p=0.01$) blood pressure than those in the D1 group. D1 subjects had higher levels of fasting glucose ($p<0.001$) and HbA_{1c} ($p=0.01$) and longer known duration of diabetes ($p=0.01$). In addition, group D1 included more smokers than group D2 ($p=0.01$) (Table 1).

Subjects in D2 had greater values of minimum, maximum and mean QT duration ($p<0.02$ in all three cases), as well as greater values of QT and QTc dispersion ($p<0.04$ for both) than D1 subjects. However, the two groups did not differ as regards QTc ($p=0.13$) (Table 2).

Comparisons between diabetics with and without CAN

D1 subjects with CAN had greater age ($p=0.01$) and longer known duration of diabetes ($p=0.02$) compared to those without CAN. They also had higher systolic blood pressure ($p=0.004$), as well as higher levels of fasting glucose ($p=0.01$), HbA_{1c} ($p=0.04$), total cholesterol ($p=0.006$) and LDL cholesterol ($p=0.03$) (Table 3). D1 subjects with CAN had significantly greater values of QTc than those without ($p<0.0001$). However, there were no significant differences in QT interval ($p=0.70$) or the dispersion of QT and QTc ($p=0.29$ and $p=0.22$, respectively) between those with and without CAN (Table 4).

D2 subjects with CAN had greater known duration of diabetes than those without CAN ($p=0.001$, Table 3) and greater values of maximum QT ($p=0.004$), QT ($p=0.03$), QTc ($p<0.0001$) and QTc dispersion

Table 2. Values of QT interval, corrected QT (QTc), their dispersions, and RR intervals in diabetics and controls (mean ± standard deviation).

	Controls for type 1 diabetes	Type 1 diabetics	p (type 1 vs. controls)	Controls for type 2 diabetes	Type 2 diabetics	p (type 2 vs. controls)	p (type 1 vs. type 2)
QT min (ms)	299.7 ± 33.5	304.5 ± 26.3	0.42	315.8 ± 34.7	327.2 ± 26.2	0.05	0.02
QT max (ms)	344.3 ± 28.3	342.6 ± 26.5	0.72	357.1 ± 55.6	369.9 ± 32.9	0.15	0.02
QT mean (ms)	321.8 ± 34.8	324.1 ± 24.8	0.68	339.9 ± 35.9	348.0 ± 28.9	0.18	0.02
QT dispersion (ms)	39.8 ± 11.3	42.6 ± 13.2	0.15	42.7 ± 15.4	46.3 ± 19.8	0.27	0.04
QTc mean (ms)	355.5 ± 23.7	367.2 ± 31.2	0.05	366.3 ± 20.9	376.4 ± 42.6	0.14	0.13
QTc dispersion (ms)	46.4 ± 18.4	44.3 ± 11.9	0.34	44.3 ± 14.9	51.2 ± 20.6	0.04	0.04
RR min (ms)	783.4 ± 138.2	764.7 ± 116.2	0.44	789.0 ± 143.2	788.8 ± 142.7	0.002	0.24
RR max (ms)	861.8 ± 161.2	846.3 ± 15.1	0.63	851.6 ± 145.4	851.2 ± 144.9	0.001	0.83
RR mean (ms)	801.6 ± 200.1	808.0 ± 137.6	0.86	817.8 ± 144.3	817.5 ± 143.8	0.02	0.66

Table 3. Clinical and demographic characteristics of the diabetic patients in relation to the existence or not of cardiac autonomic neuropathy (mean ± standard deviation unless otherwise noted).

	Type 1 diabetes No CAN	Type 1 diabetes CAN	p	Type 2 diabetes no CAN	Type 2 diabetes CAN	p
n	33	30		68	53	
Age (years)	28.9 ± 7.4	35.6 ±12.5	0.01	62.0 ± 8.7	61.6 ± 9.7	0.81
Men/women (%)	85/15	37/63	<0.001	56/44	64/36	0.35
Systolic blood pressure (mmHg)	118.0 ± 8.6	127.0 ±14.7	0.004	135.9 ±18.0	140.7 ± 18.5	0.16
Diastolic blood pressure (mmHg)	75.5 ± 5.8	75.3 ±7.5	0.90	79.8 ±7.5	80.2 ±12.4	0.80
Body mass index (Kg/m^2)	23.83 ± 2.62	24.15 ± 3.68	0.69	27.12 ± 3.66	27.89 ± 4.23	0.29
Waist-to-hip ratio	0.88 ± 0.04	0.87 ± 0.05	0.62	0.92 ± 0.07	0.93 ± 0.05	0.46
Duration (years): median (range)	10.0 (6.5-14.5)	18.0 (7.75-22.0)	0.02	7.0 (2.0-10.0)	11.0 (5.0-20.0)	0.001
HbA_{1c} (%)	7.9 ± 1.5	8.9 ± 2.3	0.04	7.6 ±1.6	7.7 ± 1.4	0.77
Glucose (mg/dl)	166.8 ± 66.9	221.1 ± 122.3	0.03	160.8 ± 49.3	172.4 ± 41.6	0.17
Cholesterol (mg/dl)	188.5 ± 49.6	223.1 ± 45.9	0.006	222.6 ± 43.6	218.4 ± 43.1	0.60
LDL cholesterol (mg/dl)	113.8 ± 55.3	141.7 ± 42.2	0.03	145.6 ± 41.9	142.8 ± 42.9	0.70
HDL cholesterol (mg/dl)	50.8 ±14.1	56.8 ±19.6	0.16	44.7 ±11.3	43.4 ±11.4	0.54
Triglycerides (mg/dl)	119.7 ± 75.5	123.0 ± 63.6	0.85	160.9 ± 75.5	161.0 ± 85.1	0.98
Smokers (%)	36	40	0.76	20.6	18.9	0.48

Abbreviations as in Table 1.

Table 4. Values of QT interval, corrected QT (QTc), their dispersions, and RR intervals (mean ± standard deviation) in diabetics in relation to the existence or not of cardiac autonomic neuropathy (CAN).

	Type 1 diabetes No CAN	Type 1 diabetes CAN	p	Type 2 diabetes no CAN	Type 2 diabetes CAN	p
QT min (ms)	302.6 ±26.4	307.7 ± 26.1	0.44	311.5 ± 32.6	321.7 ± 36.5	0.11
QT max (ms)	342.3 ± 26.8	343.8 ± 26.5	0.82	353.9 ± 31.3	373.4 ± 42.5	0.004
QT mean (ms)	323.3 ± 24.9	325.7 ± 24.9	0.70	333.8 ± 30.3	347.9 ± 40.7	0.03
QT dispersion (ms)	38.7 ± 11.2	36.1 ± 10.3	0.29	43.6 ±15.4	50.0 ± 23.9	0.07
QTc mean (ms)	347.8 ± 20.7	389.2 ±25.7	<0.001	361.5 ± 44.8	395.9 ± 30.0	<0.001
QTc dispersion (ms)	46.1 ± 11.3	42.4 ±12.5	0.22	47.9 ± 16.7	55.3 ±24.0	0.04
RR min (ms)	818.9 ± 114.1	704.9 ± 86.3	<0.001	803.5 ± 138.5	770.0 ± 147.1	0.20
RR max (ms)	927.3 ± 160.3	757.3 ± 93.6	<0.001	870.7 ± 140.9	826.1 ± 147.4	0.09
RR mean (ms)	877.1 ± 139.1	731.9 ± 87.9	<0.001	833.7 ± 138.6	796.8 ± 149.1	0.16

(p=0.04). QTd was greater in those with CAN, but the difference did not reach statistical significance (p=0.07) (Table 4).

Discussion

The duration and dispersion of the QT interval reflect various subclinical disturbances, such as left ventricular hypertrophy, ischaemia and myocardial fibrosis. Indeed, it seems that the severity of these lesions is positively correlated with an increase in QTd.[19,28] This also explains the findings of studies that showed QTd to be the best independent prognostic index for cardiac death in patients with D2.[8-10]

The findings presented here are in accordance with those of earlier studies that found no relation between QTd and CAN in either D1[18,29] or D2[19] subjects. In contrast, they disagree with the findings of one study that found significant differences between D1 subjects with CAN and those who did not have that complication.[30] The subjects of the latter study had a shorter duration of diabetes and worse glycaemic control. In addition, our findings disagree with those of smaller studies of D2 patients that found CAN to be associated with higher QTd values.[19,20]

Takebayashi et al[21] showed that D2 patients had greater QTd than healthy controls when sex and age were taken into account. In contrast, our study found no significant differences in QTd between D1 or D2 subjects and healthy controls. Our findings are in agreement with those of another study that found no significant differences in QTd between diabetics and controls.[31] In addition, the findings of this study agree with those of previous studies showing that QTc duration is greater in diabetics with CAN.[17,18]

This study demonstrates for the first time that D2 patients have a greater prolongation of the QT interval and greater QTd than do those with D1. D2 patients are older than D1 patients, whereas hypertension, left ventricular hypertrophy and ischaemic heart disease are more common in D2[32] and affect QTd.[1] Their greater age is associated with myocardial fibrosis and with biochemical changes in the myocardium, resulting in disturbances of repolarisation and prolongation of the QT interval and QTd.[32]

In conclusion, this study shows that: 1) values of QTd do not differ significantly between diabetics and healthy controls; 2) patients with D2 have greater prolongation of the QT interval and greater QTd than do those with D1; 3) CAN does not affect QTd in either type of diabetes.

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