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The value of QT interval dispersion for identification of total mortality risk in non-insulin-dependent diabetes mellitus

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Abstract. Sawicki PT, Kiwitt S, Bender R, Berger M (Heinrich-Heine University of Düsseldorf, Düsseldorf; Germany). The value of QT interval dispersion for identification of total mortality risk in non-insulin-dependent diabetes mellitus. *J Intern Med* 1998; **243:** 49–56.

Objectives. To delineate different risk markers including the difference between the maximum and the minimum length of the QT interval in ECG corrected for heart rate (QTc dispersion) as predictors of total, cardiac and cerebrovascular mortality in NIDDM patients.
Design. Case-control, follow-up study until death or for a period of 15 to 16 years.
Setting. Tertiary care centre, University Hospital of Düsseldorf, Germany.
Subjects. 216 unselected consecutive NIDDM patients.
Main outcome measures. Total, cardiac, and cerebrovascular mortality.

Results. During the follow-up 158 (73%) patients died. In the Cox proportional hazards model QTc dispersion was the most important independent predictor of total mortality (risk ratio (RR) 3.3; difference for RR: 0.05 $s^{1/2}$; $P = 0.001$). Additional independent risk markers were age, male sex, systolic blood pressure, diabetic retinopathy, micro- or macroproteinuria, total serum cholesterol and HDL cholesterol. The QTc dispersion was also an independent predictor of cardiac and cerebrovascular mortality.
Conclusions. The results of this long-term follow-up study indicate that QT dispersion in a routine ECG is a useful marker to identify NIDDM patients with a high mortality risk.

Keywords: cardiac mortality, cerebrovascular mortality, non-insulin-dependent diabetes mellitus, QT interval, risk factors, total mortality.

Introduction

Patients with non-insulin-dependent diabetes (NIDDM) exhibit a major decrease in life expectancy when compared to non-diabetic population [1]. Most of these patients die due to myocardial infarction, heart failure or stroke [2, 3]. In epidemiological studies several independent mortality predicting markers have been identified such as age, sex [4], microalbuminuria [5], hypertension [6], smoking [7], poor glycemic control [8, 9], hyperlipidaemia [10] and preexisting cardiac and cerebrovascular morbidity [11].

An association between a prolonged QT interval in ECG and cardiac deaths has been found in various diseases including coronary artery disease [12] after myocardial infarction [13], in chronic heart failure [14], hypertrophic cardiomyopathy [15], peripheral vascular disease [16], alcoholic liver disease [17], in patients with autonomic neuropathy [18–20] and in diabetic nephropathy [21]. However, to our knowledge, in non-insulin-dependent diabetic patients the length of the QT interval, as compared to the other known predictors of mortality, has not been investigated in a long-term study.

Patients and methods

All consecutive NIDDM patients who were referred during the years 1980 and 1981 to our department for improvement of metabolic control were enrolled into a follow-up study. NIDDM was defined as non-keto-acidotic manifestation of diabetes mellitus after the age of 40 and a subsequent treatment with diet alone or oral hypoglycaemic agents for more than

one year. The patients were followed until death or for a period of 15–16 years. After the initial hospitalisation the patients were under medical care of their family physicians. Antihypertensive drug treatment was initiated when blood pressure values exceeded 160/95 mmHg. None of the patients were undergoing anti-arrhythmic therapy. All baseline measurements were performed at the entry into the study during hospitalisation: medical history, ECG, x-ray of the chest, pulses of the lower limbs, ankle reflexes and fibration sense using a scaled tuning fork. For diagnosis of retinopathy direct fundoscopy in mydriasis was performed by an ophthalmologist. Autonomic neuropathy was assessed according to Ewing [22] by the measurement of RR interval variation in the electrocardiogram (ECG) between the supine and standing position; values below 1.03 were regarded as a sign of autonomic neuropathy. Kidney function was assessed by measurements of serum creatinine and creatinine clearance. Proteinuria was measured by a laser turbidimeter method in a timed 24 hour urine sample with normal values $\leq$ 60 mg per 24 h [23]. Microproteinuria was defined as previously described as protein excretion of 60-500 mg per 24 h [23]. Glycated haemoglobin (HbAlc) was measured by a thiobarbiturate method (reference range 4.3–5.8% of total haemoglobin). Daily glycemic profiles with five blood glucose estimations during 24 hours were obtained during the five days of inpatient treatment. Serum lipid concentrations were assessed in the fasting state. QT interval analysis was done on a single 12-leads conventional non-computerised registration ECG at the time the patient was included into the study. A single observer, unaware of the diagnoses and the outcome of the respective patient, measured retrospectively one QT interval in every lead on a surface ECG (50 mms-speed). QT interval was taken from the onset of the QRS to the end of the T wave (i.e. return to the T/P baseline). If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. QT intervals were corrected with Bazett's formula $QT_c = QT/^2\sqrt{RR}$. QT dispersion was defined as the difference between maximum and minimum QT. Atrial fibrillation and ventricular ectopy were assessed in the same ECG recording.

For the assessment of the precision of the actual observer (S.K.) ECGs of 66 diabetic patients were evaluated in a blind and independent manner. The patients were extensively evaluated for the presence of factors influencing the length of the QT interval. 44 patients had no signs of autonomic diabetic neuropathy and received no treatment except insulin. In 22 patients diabetic autonomic neuropathy was present as assessed by a test battery for cardiovascular reflexes including spectral analysis of the heart rate variability. The actual observer (S.K.) measured the QT intervals twice on two different days without knowing the diagnosis or the identification of the actual patient. In addition, the same ECGs were evaluated by an independent observer specially trained in QT measurements. The mean difference between the two measurements of the study observer (S.K.) was 0.0085 $s^{1/2}$ (SD 0.00276 $s^{1/2}$). Both measurements were quite similar, indicating a good measurement precision as shown also by the intra-class-correlation coefficient of $r = 0.935$. The mean difference in the QTc dispersion measurements between the two independent observers was 0.001 $s^{1/2}$ (SD 0.00385 $s^{1/2}$). The within-subject standard deviation [24] was 0.002101 $s^{1/2}$ yielding a repeatability of 0.00557 $s^{1/2}$; this means that the expected difference of the study observer S.K. for the same subject is expected to be less than 0.00557 $s^{1/2}$ for 95% of pairs. In a variance components model [25] containing subject and observer as random effects between-observer standard deviation was 0.000565 $s^{1/2}$, and the within-observer standard deviation was 0.00252 $s^{1/2}$, showing that the observer effect is lower than the general within-observer measurement error.

Time and cause of death were extracted from death certificates and from records of hospitals and general practitioners. The underlying causes of death were classified according to the International Classification of Diseases (ICD-9) [26]. The cause of death was categorised as unidentified when the patient died at home without a previous diagnosis of a fatal disease and when no other cause of death was identified. No patients were lost to follow-up and data regarding the exact time of death were available for all 158 patients. Approval has been obtained from the local Ethics Committee.

Statistical analysis

The results are presented as frequencies, means with 95% confidence intervals or standard deviations, and medians with interquartile ranges. Associations between continuous variables were investigated by

means of Spearman rank correlation coefficients. For comparison of groups the Kruskal-Wallis test and the Wilcoxon rank sum test were used. Incidence rates of mortality were evaluated by life table analysis and the log rank test. *P*-values below 5% were regarded as significant. To adjust for confounding factors the proportional hazards model of Cox [27] was used. For computations the procedures MEANS [28], UNIVARIATE [28], FREQ [28], CORR [28], NPARIWAY [28], GLM [28], VARCOMP [28], LIFETEST [29] and PHREG [30] of SAS were used.

Results

At baseline there was a significant relevant association (Spearman correlation coefficient $r \geq 0.3$) between QTc dispersion and age ($r = +0.42$, $P = 0.0001$), creatinine clearance ($r = -0.31$, $P = 0.0001$) and the maximal QTc interval ($r = +0.57$, $P = 0.0001$). QTc dispersion was significantly longer in female patients ($n = 148$; 0.074 vs. 0.064 $s^{1/2}$, $P = 0.0421$), patients with diabetic retinopathy ($n = 56$; 0.080 vs. 0.068 $s^{1/2}$, $P = 0.0126$), non-smokers ($r = 166$, 0.074 vs. 0.058 $s^{1/2}$, $P = 0.0031$), patients with a history of myocardial infarction ($r = 21$; 0.087 vs. 0.069 $s^{1/2}$, $P = 0.0194$), patients with occlusive artery disease of lower limbs ($n = 34$; 0.091 vs. 0.067 $s^{1/2}$, $P = 0.0013$), patients with signs of coronary artery disease ($n = 61$; 0.079 vs. 0.068 $s^{1/2}$, $P = 0.0195$) and patients with signs or history of congestive heart failure ($n = 78$; 0.081 vs. 0.066 $s^{1/2}$, $P = 0.0019$).

At baseline, 32 patients were treated with diet only, 10 received in addition oral hypoglycaemic agents and 174 received insulin. Mean QTc dispersion was comparable between these three groups (0.064; 0.067 and 0.073 $s^{1/2}$, $P = 0.2875$). Antihypertensive agents were prescribed in 118 patients. Diuretic agents were given to 48 patients, betablockers to nine and calcium channel blockers to seven patients, while 54 patients received combination of two or more antihypertensive agents. Patients receiving diuretics had a significantly longer QTc dispersion when compared to patients without such therapy (0.065 vs. 0.093 $s^{1/2}$, $P < 0.0001$). Also patients on multiple antihypertensive therapy had a prolonged QTc dispersion (0.068 vs. 0.082 $s^{1/2}$, $P = 0.0045$). Treatment with betablockers or calcium channel blockers was not associated with a significant difference in the QTc dispersion. In a multifactorial ANOVA model treatment with diuretics and antihypertensive treatment with several antihypertensive agents were both independently associated with a longer QTc dispersion.

Table 1 Baseline characteristics of all patients, patients who survived and patients who died during the follow-up period of 15 to 16 years

Variable	All patients n = 216	Patients who survived n = 58	Patients who died n = 158
Female/male	148/68	36/22	112/46
Age (years)	63 (54–71)	54 (48–61)	69 (57–74)
Body mass index (kg m^{-2})	25 (22–28)	26 (23–30)	25 (21–28)
Known diabetes duration (years)	10 (5–15)	6 (4–11)	11 (5–16)
Proteinuria (g per 24 hr)	0.0 (0.0–0.1)	0.0 (0.0–0.03)	0.0 (0.0–0.1)
Serum creatinine (μM)	92 (80–104)	89 (80–104)	92 (79–106)
Creatinine clearance (ml s^{-1})	0.98 (0.73–1.3)	1.17 (0.90–1.43)	0.92 (0.69–1.22
Peripheral neuropathy (%)	44	47	42
Autonomic neuropathy (%)	39	45	37
Diabetic retinopathy (%)	27	7	34
HbAlc (%)	8.9 (8.1–10.5)	8.8 (8.2–10.2)	9.1 (8.0–10.5)
Systolic blood pressure (mmHg)	140 (130–150)	130 (120–140)	140 (130–150)
Diastolic blood pressure (mmHg)	80 (80–90)	80 (80–90)	80 (75–90)
Smokers (%)	21	36	16
Total cholesterol ($mmolL^{-1}$)	6.1 (5.2–6.9)	6.0 (5.3–6.9)	6.1 (5.2–6.9)
HDL cholesterol ($mmolL^{-1}$)	1.1 (0.8–1.3)	1.1 (0.8–1.3)	1.0 (0.8–1.3)
Triglycerides ($mmolL^{-1}$)	2.0 (1.4–3.0)	1.9 (1.3–3.0)	2.0 (1.4–3.0)
Maximal QTc-period ($s^{1/2}$)	0.442 (0.422–0.474)	0.429 (0.412–0.447)	0.452 (0.426–0.479)
Mean QTc-periods ($s^{1/2}$)	0.413 (0.394–0.432)	0.406 (0.392–0.432)	0.415 (0.395–0.433)
QTc dispersion ($s^{1/2}$)	0.069 (0.045–0.094)	0.044 (0.024–0.050)	0.078 (0.053–0.099)
RR interval in the ECG (s)	0.752 (0.685–0.860)	0.80 (0.73–0.90)	0.74 (0.68–0.83)

Data are frequencies or medians with interquartile ranges in parenthesis.

Table 2 Independent predictors of total mortality in 216 non-insulin-dependent diabetic patients followed until death or for a period of 15 to 16 years. Results of the Cox proportional hazards model

Variable	Parameter estimate	Standard error	*P*-value	Difference for risk ratio	Risk ratio	95% CI for risk ratio
QTc dispersion	1.204	0.135	0.0001	0.05 $s^{1/2}$	3.33	2.56–4.34
Age	0.371	0.100	0.0002	10 years	1.45	1.20–1.76
Male sex	0.711	0.211	0.0008	yes/no	2.04	1.35–3.08
Diabetic retinopathy	0.571	0.187	0.0022	yes/no	1.77	1.23–2.55
Micro- or macro-proteinuria	0.519	0.176	0.0032	yes/no	1.68	1.19–2.37
Systolic blood pressure	0.149	0.056	0.0079	10 mmHg	1.16	1.04–1.30
Total cholesterol	0.239	0.104	0.022	2 mM	1.27	1.04–1.56
HDL cholesterol	−0.210	0.100	0.0352	0.5 mM	0.81	0.67–0.99

During the follow-up period 158 patients (73%) died. The baseline characteristics of all patients and those who survived or died are shown in Table 1. The following factors were included in a stepwise regression analysis (backward selection): age, gender, known diabetes duration, body mass index, history or signs of coronary artery disease, congestive heart failure, occlusive artery disease of lower limbs, presence of diabetic retinopathy, systolic and diastolic blood pressure, treatment with diuretic agents, antihypertensive treatment with two or more agents, insulin treatment, heart rate, total serum cholesterol, HDL cholesterol, log triglycerides, HbAlc, serum creatinine, proteinuria ≥ 60 mg per 24 hr, smoking, QTc dispersion, atrial fibrillation and presence of ventricular ectopy in a resting ECG. In the final model independent predictors of total mortality were the length of QTc dispersion, age, male sex, systolic blood pressure, total cholesterol, HDL cholesterol, presence of diabetic retinopathy and micro- or macro-proteinuria (Table 2). When QTc dispersion was replaced in the Cox model by the length of the maximum QTc interval the risk ratio was 1.5 ($P = 0.0001$). Goodness-of-fit was evaluated by tests of trend in the hazard ratio [28], which yielded nonsignificant results, and by residual plots, which showed no clear violations of the proportional hazards assumption. Of the 108 patients with QTc dispersion above the median of 0.0686 $s^{1/2}$, 101 died during the follow-up as compared to 57 of those with a lower/equal length of QTc dispersion figure. There was a continuous increase in the mortality risk with prolongation of the QTc dispersion. The main causes of death were cardiac (46%) (Table 3). Significant predictors of cardiac mortality were the length of QTc dispersion, age, male sex, presence of diabetic retinopathy, total cholesterol and proteinuria ≥ 60 mg per 24 hr (Table 4). The length of QTc dispersion was the only significant independent predictor of cerebrovascular mortality (RR 3.9; 95% CI 2.0–7.6; $P = 0.0001$) (Table 5)

Discussion

This is to our knowledge the first long-term follow-up study to show that an increased QT dispersion in a routine ECG is a major determinant of total mortality risk in NIDDM patients (Table 2, Fig. 1). In fact, in no other disease or condition the predictive power of

Table 3 Causes of death for patients with a QTc dispersion below and above the median of 0.0686 $s^{1/2}$

Cause of death (ICD-9 code)	QTc dispersion ≤ 0.0686 $s^{1/2}$ n = 108	QTc dispersion > 0.0686 $s^{1/2}$ n = 108
Total Mortality	57	101
Cardiac (410; 427; 411; 428; 789)	23	49
Cerebrovascular (431; 433)	9	14
Septicaemia (038)	7	10
Malignoma (154; 162)	7	5
Gastrointestinal (571; 578)	3	1
Accident, suicide, violence (959; 968)	2	3
Unidentified (798)	6	19

Table 4 Results of the Cox proportional hazards model for cardiac mortality using the same covariates as in Table 2

Variable	Parameter estimate	Standard error	*P*-value	Difference for risk ratio	Risk ratio	95% CI for risk ratio
QTc dispersion	1.228	0.207	0.0001	0.05 $s^{1/2}$	3.41	2.27–5.12
Age	0.328	0.147	0.0256	10 years	1.39	1.04–1.85
Male sex	0.924	0.324	0.0044	yes/no	2.52	1.33–4.75
Diabetic retinopathy	0.849	0.273	0.0019	yes/no	2.34	1.37–3.99
Micro- or macro-proteinuria	0.582	0.256	0.0230	yes/no	1.79	1.08–3.00
Systolic blood pressure	0.157	0.084	0.0623	10mmHg	1.17	0.99–1.38
Total cholesterol	0.331	0.146	0.0232	2 mM	1.39	1.05–1.85
HDL cholesterol	−0.154	0.137	0.2607	0.5 mM	0.86	0.66–1.12

QTc dispersion for the mortality risk is as great as it seems to be in NIDDM. Despite the fact that the risk associated with a prolongation of QTc dispersion was independent of other known risk factors and markers which were assessed in this study, we think that a prolonged QTc interval indicates a cluster or a focus of several detrimental conditions frequently present in NIDDM patients and may perhaps therefore be used as a sum indicator of the total mortality risk.

Recently, in non-diabetic patients a prolonged QTc interval and/or QTc dispersion were described as mortality risk markers in chronic heart failure [14], hypertrophic cardiomyopathy [15], coronary heart disease [12, 31], peripheral artery disease [16] and after myocardial infarction [13]. Such co-morbidity is particularly frequent in NIDDM patients and may remain undiagnosed. Since in the baseline examination coronary angiography and echocardiography were not included, some cardiac morbidity was probably missed. Also, in some patients diabetic autonomic neuropathy and volume overload, which are both associated with prolongation of the QT interval and with an increased risk of mortality, might have been overlooked with the methods used in this investigation. In addition, disturbed glucose metabolism of the heart may have directly contributed to an impaired myocardial electrical stability. Interestingly, in a recent report of the Zutphen Elderly Study QTc duration was associated with levels of insulin and glucose tolerance [32]. The authors speculated that reduced myocardial glucose uptake may be involved in impaired cardiac repolarisation as indicated by a prolongation of the QT interval. QT prolongation may also result from cardiac adrenergic dysinervation with altered balance of sympathetic and parasympathetic cardiac nerve activity [18, 33, 34] and/or myocardial cell defects [35] and lead to a reduced electrical stability. Hypothetically, prolonged QTc dispersion indicates the presence of electrical myocardial inhomogenity, which may be expected to create a potential difference during repolarisation and generate an excitatory current of a sufficient magnitude to re-excite the fibres with the shorter action potential duration and consecutively lead to re-entry arrhythmias [36]. On the other hand, generally prolonged QTc duration, without a prolonged QTc dispersion, may also be present in diabetic patients [21]. Sympathetic imbalance or blockade of potassium channels may be responsible for a general QT interval prolongation and can produce early after-depolarisations that lengthen repolarisation and cause triggered activity and ventricular tachyarrhytmias

Table 5 Independent predictors of cerebrovascular mortality in 216 non-insulin-dependent diabetic patients followed until death or for a period of 15 to 16 years. Results of the Cox proportional hazards model

Variable	Parameter estimate	Standard error	*P*-value	Difference for risk ratio	Risk ratio	95% CI for risk ratio
QTc dispersion	1.316	0.358	0.0002	0.05 $s^{1/2}$	3.73	1.85–7.52
Age	0.542	0.287	0.0592	10 years	1.72	0.98–3.02
Systolic blood pressure	0.291	0.156	0.0628	10 mmHg	1.34	0.99–1.82
Total cholesterol	0.423	0.238	0.0747	2 mM	1.53	0.96–2.43

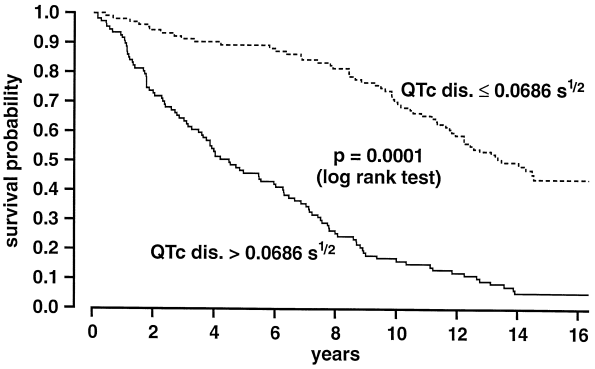

Fig. 1 Kaplan–Meier curves of survival over the study period of 15–16 years of 216 patients with non-insulin-dependent diabetes mellitus and a QTc dispersion at baseline below and above the median of 0.0686 $s^{1/2}$; $P = 0.0001$ (log rank test).

[37]. Both prolonged QTc dispersion and increased mean or maximum QTc duration are generally acknowledged to predispose to serious ventricular arrhythmias [33, 36]. We have previously shown that the length of the mean and maximum QTc duration predisposes to death in IDDM patients with nephropathy [21]. Since the major prognostic factor in the present study was not the mean QTc duration but rather the QTc dispersion, it might be speculated that in NIDDM patients the increased mortality risk is better described by the prolongation of the QT dispersion, as caused for example by patchy myocardial fibrosis, ventricular dilatation and focal myocardial ischemia [12, 30, 38]. In IDDM diabetic patients with nephropathy the increased mortality risk [21] is probably better described by general QT prolongation, which is often caused in these patients by autonomic neuropathy with consecutive sympathetic imbalance [18, 33, 34, 37].

Abnormalities in myocardial repolarisation could contribute to the increased mortality in NIDDM patients either directly through sudden or unexpected death [14, 15, 39] or indirectly by impairing the survival during intercurrent diseases or complications frequently present in NIDDM patients. It is of note that in this study patients with a QTc dispersion > 0.0686 $s^{1/2}$ had a three times higher mortality risk due to unidentified causes including unexpected death (Table 3).

In some [12, 31] but not in all studies [40] in unselected non-diabetic populations prolongation of QT interval predicted cardiac mortality and morbidity. In this investigation, NIDDM patients with a history of coronary heart disease, diuretic treatment or antihypertensive treatment with two or more agents already had a longer QTc dispersion at baseline. However, in the Cox proportional hazards model QTc dispersion predicted mortality independently of the pre-existing morbidity and the kind of antihypertensive or hypoglycaemic treatment at baseline, Surprisingly, QTc dispersion was not only a statistically significant independent predictor of total and cardiac mortality but also of cerebrovascular mortality. This may perhaps be explained by a higher overall morbidity and/or an increased risk for cerebrovascular embolism of cardiac origin in patients with prolonged QT interval, or a higher frequency of cardiac complications after a cerebrovascular event in such patients.

The proportion of smokers among survivors was significantly greater as compared to patients who died (Table 1). This surprising result is most probably caused by the 10 years lower mean age of the smoking patients. At baseline, smoking was associated with a significantly shorter QTc duration, which might have been caused by a higher mortality rate in smoking patients with prolonged QT intervals before the beginning of the study. Even if QTc dispersion is removed from the stepwise regression analysis smoking is still not associated with a survival benefit indicating that the presence of strong confounding factors, such as age, is responsible for the difference in smoking between survivors and patients who died as described in Table 1.

In accordance with previous reports, we found that age, male sex, presence of diabetic retinopathy, systolic blood pressure, total and HDL cholesterol, and elevated urinary protein excretion were significant independent predictors of total mortality in the NIDDM patients [1–6]. The quality of metabolic control, as assessed only once at baseline by measurement of glycated haemoglobin, was not an independent predictor of mortality in this study. This is in contrast to the results in IDDM patients [41] and in accordance with some large [2, 42] but not all studies [8, 9] in NIDDM populations. Intervention studies soon to be completed [43] may bring more clarity to the importance of glycemic control in NIDDM. Since the development of diabetic microangiopathic complications depends not only on the quality of glycemic control but also upon the remaining life expectancy it may be speculated that in NIDDM patients the prognostic importance of glycemic control could decrease with prolongation of the QTc interval and QTc dispersion.

In conclusion, dispersion of the QTc interval is an important independent marker for total, cardio- and cerebrovascular mortality in non-insulin-dependent diabetes mellitus. Since this parameter is easy to assess it may help identifying high risk patients in daily clinical practice. Intervention studies aiming at reducing this severely increased risk should be undertaken.

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