Increased QTc Dispersion Is Related to Blunted Circadian Blood Pressure Variation in Normoalbuminuric Type 1 Diabetic Patients

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A reduced nocturnal fall in blood pressure (BP) and increased QT dispersion both predict an increased risk of cardiovascular events in diabetic as well as nondiabetic subjects. The relationship between these two parameters remains unclear. The role of diabetic autonomic neuropathy in both QT dispersion and circadian BP variation has been proposed, but data have been conflicting. The aim of the present study was to describe associations between QT dispersion and circadian BP variation as well as autonomic function in type 1 diabetic patients. In 106 normoalbuminuric (urinary albumin excretion <20 μg/min) normotensive patients, we performed 24-h ambulatory BP (Spacelabs 90207) and short-term (three times in 5 min) power spectral analysis of RR interval oscillations, as well as cardiovascular reflex tests (deep breathing test, postural heart rate, and BP response). No patient had received (or had earlier received) antihypertensive or other medical treatment apart from insulin. In a resting 12-lead electrocardiogram, the QT interval was measured by the tangent method in all leads with well-defined T-waves. The measurement was made by one observer blinded to other data. The QT interval was corrected for heart rate using Bazett's formula. The QTc dispersion was defined as the difference between the maximum and the minimum QTc interval in any of the 12 leads. When comparing patients with QTc dispersion below and above the median (43 ms), the latter had significantly higher night BP (114/67 vs. 109/62 mmHg, $P < 0.003$/$P < 0.001$), whereas day BP was comparable (129/81 vs. 127/79 mmHg). Diurnal BP variation was blunted in the group with QTc dispersion >43 ms with significantly higher night/day ratio, both for systolic (88.8 vs. 86.2%, $P < 0.01$) and diastolic (83.1 vs. 79.5%, $P < 0.01$) BP. The association between QTc dispersion and diastolic night BP persisted after controlling for potential confounders such as sex, age, duration of diabetes, urinary albumin excretion, and HbA_{1c}. Power spectral analysis suggested an altered sympathovagal balance in patients with QTc dispersion above the median (ratio of low-frequency/high-frequency power: 1.0 vs. 0.85, $P < 0.01$). In normoalbuminuric type 1 diabetic patients, increased QTc dispersion is associated with reduced nocturnal fall in BP and an altered sympathovagal balance. This coexistence may be operative in the ability of these parameters to predict cardiovascular events. *Diabetes* 50:837–842, 2001

Recently, the role of night blood pressure (BP) in relation to cardiovascular morbidity and mortality has raised a great deal of interest (1). Several cross-sectional studies find associations between blunted circadian BP variation and cardiovascular complications (2–4). Longitudinal studies suggest an association between the reduction of the usual nocturnal fall in BP and future cardiovascular events in essential hypertension (5,6) and diabetes (7,8). The excess in mortality observed in diabetes is mainly due to cardiovascular causes and is almost confined to patients with abnormal urinary albumin excretion (UAE) (9,10). Increasing levels of albuminuria are accompanied by reductions in nocturnal BP fall in diabetic patients (11), even in the normoalbuminuric range (12).

On the surface electrocardiogram (ECG), the QT interval and QT dispersion (the difference between the maximum and minimum QT interval in a 12-lead ECG) have been reported to reflect abnormalities in ventricular repolarization (13–15). QT interval prolongation is associated with cardiac death in apparently healthy subjects (16,17) as well as in subjects with type 1 or type 2 diabetes (18–21), although it still remains to be demonstrated in population-based studies. The background for this association remains largely unknown.

Thus, disturbed night/day BP variation and QT interval prolongation both seem to be associated with increased risk of cardiovascular events in diabetic as well as nondiabetic subjects. However, to date, no study has investigated the relationship between these two parameters in diabetic patients.

In diabetic patients with autonomic neuropathy, the prognosis is particularly poor (22). Several studies have proposed a role for diabetic autonomic neuropathy in the QT prolongation (23–29). In addition, diabetic autonomic neuropathy is associated with a lack of nocturnal BP fall (30–33). Power spectral analysis appears more sensitive than ordinary bedside tests in the detection of early autonomic neuropathy (34–36).

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AMBP, ambulatory blood pressure; BP, blood pressure; ECG, electrocardiogram; HF, high-frequency; LF, low-frequency; UAE, urinary albumin excretion.

TABLE 1
Clinical parameters for patients (n = 106) divided according to QTc dispersion and QTc interval medians

	QTc dispersion		Maximum QTc interval	
	<43 ms	>43 ms	<409 ms	>409 ms
n	53	53	53	53
Age (years)	40.6 ± 9.2	38.4 ± 9.1	37.8 ± 9.1	41.3 ± 8.9
Gender (M/F)	49%/51%	57%/43%	60%/40%	45%/55%
Duration of diabetes (years)	21.4 ± 10.4	18.7 ± 9.5	18.8 ± 9.9	21.6 ± 10.1
Insulin (U/kg)	0.64 ± 0.16	0.65 ± 0.19	0.64 ± 0.18	0.65 ± 0.17
BMI (kg/m^2)	24.0 ± 2.4	24.0 ± 3.0	24.0 ± 2.8	23.9 ± 2.6
HbA_{1c} (%)	8.4 ± 0.8	8.5 ± 1.3	8.3 ± 1.0	8.5 ± 1.1
Blood glucose (mmol/l)	12.1 ± 5.1	10.4 ± 4.8	11.2 ± 5.1	11.3 ± 5.0
UAE (μg/min)	5.2 ×/÷ 1.9	5.1 ×/÷ 1.7	5.1 ×/÷ 1.8	5.2 ×/÷ 1.7
AMBP measurement (type of day)				
Working/day off/half of each	47%/42%/11%	34%/53%/13%	42%/47%/11%	40%/47%/13%
Number of sleeping hours	7.2 ± 1.1	7.4 ± 1.2	7.4 ± 1.1	7.3 ± 1.2
Smoking status				
Nonsmoking/moderate/heavy	62%/30%/8%	72%/20%/8%	72%/22%/6%	62%/28%/10%
Physical activity				
Not active/moderate/active	57%/34%/9%	59%/22%/19%	60%/27%/13%	56%/28%/16%

Unless otherwise stated, data are means ± SD, except UAE, which are geometric means ×/÷ tolerance factor. There are no significant differences between patients with QTc dispersion or QTc interval below and above median values.

Therefore, the aim of this study was to describe associations between QT measurements and circadian BP variation as well as autonomic function (described by power spectral analysis) in a group of normoalbuminuric type 1 diabetic patients well characterized with regard to factors known to influence these parameters (UAE, glycemic control, physical activity, smoking, and medical treatment).

RESEARCH DESIGN AND METHODS

Patients participated in a prospective study addressing identification of risk factors for the development of complications in type 1 diabetes. All patients were considered for the present study, and all data are from examinations made at year 2. All had normal UAE (<20 μg/min in at least two of three overnight collections) and no chronic diseases, and none received antihypertensive or other continuos medical treatment apart from insulin. Other aspects regarding baseline examinations in these patients have previously been published (12).

After at least 10 min rest in the supine position, a 12-lead ECG was recorded at a paper speed of 25 mm/s on a six-channel recorder. The ECG was scanned into a personal computer, and specially designed software was used for QT interval measurement. On the screen, the ECG was magnified 800%, and the PR baseline, the beginning of the QRS complex, and the T-wave were manually depicted. A tangent to the steepest portion of the down-sloping T-wave was calculated by the program, and the QT interval was automatically measured from the onset of the QRS complex to the intersection between the tangent and the PR baseline. The tangent was verified by manual inspection and modified by the operator if necessary. Only leads with well-defined T-waves were accepted for measurement, and visible U-waves were excluded. The QT and RR interval were measured in three consecutive cycles, and a mean value for each lead was determined. The QT interval was corrected for heart rate using Bazett's formula ($QTc = QT\sqrt{RR}$) (37,38). The QTc dispersion was defined as the difference between the maximum and minimum QTc interval in any of the 12 leads. Of 114 patients, 5 had diphasic or flat T-waves or had less than four measurable leads in either the frontal or precordial leads. All measurements were made by one observer blinded to clinical data. To estimate the intra-observer variability, 25 ECGs were scanned twice and the QT interval measured again. The mean absolute difference and relative error (mean absolute difference in percentage of mean measured value) was 5.7 ms and 1.4%, respectively, for the QTc interval and 5.4 ms and 14%, respectively, for the QTc dispersion.

Ambulatory BP (AMBP) was measured by an oscillometric technique (Spacelabs 90207 [39]), with readings at 20-min intervals throughout 24 h. Three patients with >2 missing hours in the record were excluded. Measurements were performed during a day with normal activities at home or at work. Individually reported sleeping times were implemented in the calculation of day and night BP. UAE was measured by radioimmunoassay and expressed as the geometric mean of three overnight collections made within 1 week. HbA_{1c} was determined by high-performance liquid chromatography (nondiabetic range 4.4–6.4%), and blood glucose was determined by Reflolux II (Boehringer Mannheim, Mannheim, Germany). Leisure time physical activity was graded as follows: passive (not participants), moderate (physical exercise once or twice a week), and active (physical exercise more than twice a week). Tobacco consumption was graded as nonsmokers (no daily use of tobacco for at least the last year), moderate smokers (<15 cigarettes per day), and heavy smokers (>15 cigarettes per day). Three patients smoking one packet of pipe tobacco a week were classified as moderate smokers.

The autonomic tests were performed at ~10:00 A.M. in a quiet room with subdued light, with only the patient and the laboratory technician who made the examination present. Patients had to refrain from smoking, eating, and drinking 2 h before the examination. After resting in the supine position for 15 min, RR intervals were measured using an online telemetrical transmitter (VariaPulse TF3; Sima Media Olomouc, Olomouc, Czech Republic [40]). Short-term power spectral analysis was obtained in three positions (supine-standing-supine), each of at least a 5-min duration, resulting in 3 × 256 artifact-free heartbeats. In addition to automatic filtering (using a recognition algorithm), each record was visually scrutinized for ventricular ectopic beats. In the calculations, a modified fast Fourier transformation was used (41). Low-frequency (LF) (0.05–0.15 Hz, mediated by interaction of sympathetic and vagal activity) and high-frequency (HF) (0.15–0.50 Hz, representing pure vagal activity) components were determined and expressed as natural log milliseconds squared. The intra-individual coefficient of variation of two measurements performed within 1 week in our laboratory was 15.9% (LF power) and 11.3% (HF power) (12). Coefficient of component variance (square root of power/mean RR) was calculated for the two components. This parameter accounts for a possible impact of the mean RR level on the amplitude of the HF and LF component (42). In addition, the mean square of successive RR differences was calculated. Three cardiovascular reflex tests were also performed: HR variation to deep breathing (inspiration-expiration difference, average of two determinations), HR response to standing up (30:15 ratio), and BP response to standing up. The tests were performed and evaluated in accordance with the procedure described by Ewing et al. (43). The study was approved by the local ethics committee, and patients gave their written informed consent.

Statistical analysis. To approximate normal distribution, UAE values were log-transformed before analysis. Differences between the two groups were tested by the Student's t test (unpaired). For noncontinuous variables, the χ^2 test with Yates correction was used. Correlations were analyzed using Pearson's test. To control for possible confounders, a multiple regression analysis was performed. All statistical tests were two-sided and were carried out at the 5% level of statistical significance. Results are expressed as mean ± SD, except for UAE, which is presented as geometric mean ×/÷ tolerance factor.

RESULTS

Clinical characteristics of the patients are given in Table 1. Patients (n = 106) were divided both according to median

TABLE 2
BP values and autonomic indexes for patients (n = 106) divided according to QTc dispersion and QTc interval medians

	QTc dispersion			Maximum QTc interval		
	<43 ms	>43 ms	P	<409 ms	>409 ms	P
Systolic AMBP (mmHg)						
24-h	121 ± 8.7	124 ± 9.5	NS	122 ± 7.6	123 ± 10.0	NS
Day	127 ± 8.1	129 ± 9.7	NS	127 ± 8.2	128 ± 10.4	NS
Night	109 ± 8.4	114 ± 10.3	<0.01	110 ± 8.3	113 ± 10.9	NS
Night/day ratio (%)	86.2 ± 5.3	88.8 ± 4.7	<0.01	87.1 ± 5.3	87.7 ± 5.3	NS
Diastolic AMBP (mmHg)						
24-h	74 ± 5.1	76 ± 6.3	<0.03	74 ± 5.2	76 ± 6.3	NS
Day	79 ± 5.6	81 ± 6.5	NS	79 ± 5.6	81 ± 6.7	NS
Night	62 ± 5.5	67 ± 6.9	<0.01	64 ± 6.1	65 ± 7.0	NS
Night/day ratio (%)	79.5 ± 6.4	83.1 ± 6.0	<0.01	81.1 ± 6.7	81.4 ± 6.3	NS
LF power (ln ms^2)	5.2 ± 1.4	5.7 ± 1.1	0.06	5.7 ± 1.3	5.2 ± 1.2	<0.02
HF power (ln ms^2)	6.2 ± 1.4	5.8 ± 1.4	NS	6.3 ± 1.4	5.7 ± 1.4	<0.04
LF/HF ratio	0.85 ± 0.22	1.0 ± 0.2	0.01	0.93 ± 0.24	0.92 ± 0.20	NS
LF centerfreq. (mHz)	98.2 ± 33.5	93.0 ± 22.9	NS	101.0 ± 26.3	90.3 ± 29.8	NS
HF centerfreq. (mHz)	232.2 ± 50.0	246.5 ± 59.9	NS	235.7 ± 54.2	243.1 ± 56.3	NS
Mean RR interval (ms)	969 ± 132	926 ± 147	NS	946 ± 135	911 ± 138	0.01
LF CCV (%)	1.7 ± 1.3	2.2 ± 1.2	NS	2.2 ± 1.4	1.7 ± 1.1	0.06
HF CCV (%)	2.8 ± 1.7	2.4 ± 1.8	NS	2.8 ± 1.9	2.3 ± 1.6	NS
MSSD (ln ms^2)	7.2 ± 1.3	6.9 ± 1.3	NS	7.3 ± 1.3	6.7 ± 1.3	<0.02

Data are means ± SD. LF power: power in the LF band (0.05–0.15 Hz). HF power: power in the HF band (0.15–0.50 Hz). Centerfreq, mean center frequency; CCV, coefficient of component variance (square root of power/mean RR); MSSD, mean square of successive RR differences.

QTc dispersion (43 ms) and to median QTc interval (409 ms). Clinical characteristics for groups were similar. BP values and autonomic indexes are presented in Table 2. Patients with QTc dispersion >43 ms had significantly higher night BP compared with patients with QTc dispersion <43 ms (Δ systolic night BP: 5.1 mmHg, 95% CI 1.4–8.6; Δ diastolic night BP: 4.4 mmHg, 2.0–6.8), whereas day BP was comparable in the two groups. Consequently, diurnal BP variation was blunted in the group with QTc dispersion above the median with significantly higher night/day ratio for both systolic (88.8 ± 4.7 vs. 86.2 ± 5.3%, $P < 0.01$) and diastolic (83.1 ± 6.0 vs. 79.5 ± 6.4%, $P < 0.01$) BP. Diurnal BP profiles for the two groups are depicted in Fig. 1. As indicated in Table 3 (individual values illustrated in Fig. 2), both systolic and diastolic night BP and the night/day ratio correlated with QTc dispersion, which was in contrast to the daytime BP. To rule out a possible confounding effect of the heart rate correction, we also analyzed the data using QT dispersion without correction for heart rate; the results and associations were similar (e.g., QT dispersion vs. night diastolic BP: $r = 0.27$, $P < 0.01$).

Power spectral analysis demonstrated a relative increase in the LF component (significantly increased ratio LF/HF power) in patients with QTc dispersion above the median, and QTc dispersion and ratio LF/HF power were positively correlated ($r = 0.37$, $P < 0.001$). The classic cardiovascular reflex tests did not reveal any differences between the two groups.

In a multiple regression analysis, diastolic night BP in combination with ratio LF/HF power were significant predictors of QTc dispersion (adjusted $R^2 = 0.16$, $P < 0.001$), whereas inclusion of sex, age, physical activity, duration of diabetes, UAE, type of day for AMBP, and HbA_{1c} did not add explanatory information.

Nondippers (defined as patients with a systolic and diastolic night BP fall <10%) had significantly increased QTc dispersion compared with patients with preserved nocturnal BP fall (63.7 ± 11.1 vs. 45.5 ± 20.3 ms, $P < 0.02$) and also had a relatively increased LF component (ratio LF/HF power: 1.2 ± 0.22 vs. 0.93 ± 0.21, $P < 0.01$).

When comparing patients with maximum QTc interval above and below the median value (409 ms), BP values

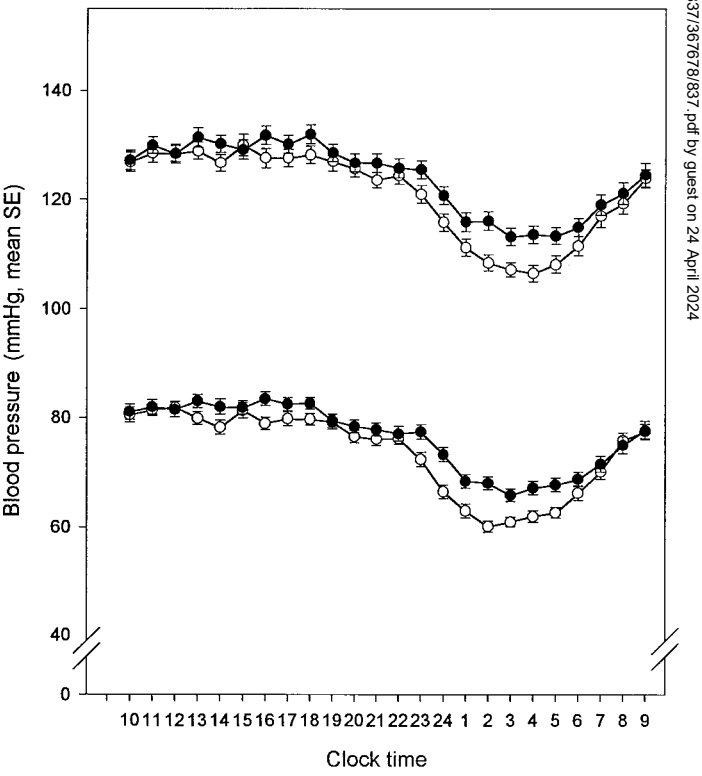

FIG. 1. Diurnal BP profiles in patients divided according to median QTc dispersion (43 ms) ○, Lowest QTc dispersion (<43 ms), n = 53; ●, highest QTc dispersion (>43 ms), n = 53.

TABLE 3
Correlations between day and night AMBP versus QTc dispersion (n = 106)

	QTc dispersion	
	r	P
Daytime		
Systolic AMBP	0.13	0.205
Diastolic AMBP	0.10	0.295
Nighttime		
Systolic AMBP	0.27	0.006
Diastolic AMBP	0.32	0.001
Night/day ratio		
Systolic AMBP	0.24	0.015
Diastolic AMBP	0.30	0.002

were similar, and night/day ratios were almost identical in the two groups (Table 2), with no significant associations between QTc interval and BP (Table 3). Autonomic indexes showed significant attenuations in both LH and HF components in patients with a maximum QTc interval >409 ms (Table 2). The classic autonomic tests suggested a higher degree of autonomic dysfunction in patients with maximum QTc interval above the median, but results for the two groups were not statistically different (data not shown).

DISCUSSION

Our data describe for the first time an association between nocturnal BP and QTc dispersion in diabetic patients: blunted circadian BP variation is associated with increased QTc dispersion. Notably, this association is present independently of potential confounding factors (sex, glycemic control, physical activity, smoking, medical treatment, etc.) and observed in strictly normoalbuminuric patients. In patients with essential hypertension, Kohno et al. (44) found that nondippers had significantly increased QTc dispersion compared with dippers. The percentage of nondippers would seem high in their study (39%), and they did not find a significant correlation between nocturnal BP and QTc dispersion; otherwise, the data are in agreement with our study. Recently, Gryglewska et al. (45) described QTc dispersion and 24-h AMBP in elderly hypertensive individuals. Data on circadian BP variation were not reported, but night BP was higher, although not significantly, in subjects with QTc dispersion above the median. Because arbitrary night and day periods were used (in contrast to individually reported sleeping times), circadian BP variation may be erroneously underestimated (46).

As for the background for this association, we found that patients with increased QTc dispersion had significantly higher relative LF power. LF power is considered as a marker of sympathetic modulation, but it should be stressed that, at present, isolation of a parameter that solely estimates sympathetic activity has not been accomplished. In several studies, diabetic autonomic neuropathy has been found to be associated both with defects in I^{123} m-iodobenzylguanedine uptake, which is considered a marker of sympathetic innervation of the heart, and with increased QT dispersion but without correlation between these two measurements, underlining that the electrophysiological mechanisms behind QT dispersion remain to be fully elucidated (47,48). QT dispersion is presumed to reflect regional repolarization differences in the heart (47,49). In essential hypertension, increased QT dispersion has been connected with left ventricular hypertrophy (50), and furthermore, in other studies, left ventricular hypertrophy has been associated with nondipping (2). Thus, left ventricular hypertrophy could be a cofactor in the association between increased nocturnal BP and QT dispersion (44,45). We did not determine left ventricular mass in our study, and only longitudinal studies can reveal the temporal relationship and possible causal connections between development of abnormalities in QTc dispersion, circadian BP variation, and autonomic function.

An association between QT dispersion and ischemic heart disease has been proposed in both diabetic (51) and nondiabetic (52) patients. The majority of our patients had normal QT parameters, and none had symptoms or ECG signs of ischemic heart disease and were, as mentioned, normoalbuminuric and thus presumably constitute low-risk patients. The association between QT measurements and BP profile should also be tested in a general diabetic population. Because invasive tests were not performed, early subclinical myocardial ischemic disease cannot be excluded. Coronary microangiopathy (possibly related to diabetes) leading to interstitial fibrosis may also play a role; however, our data do not permit an evaluation of this hypothesis. UAE was similar in the two groups, but this similarity may be ascribed to the inclusion of strictly normoalbuminuric subjects.

The associations with nocturnal BP and autonomic function seemed different for QTc dispersion and maximum QTc interval. The former is associated with nocturnal BP and possibly relatively increased sympathetic modulation, whereas QTc interval prolongation is associated attenuated autonomic indexes. Only a minority of the patients (31 patients or 29%) had both QTc dispersion >43 ms and QTc interval >409 ms. This may point to differences in pathophysiological mechanisms for the two parameters: QTc interval prolongation seems to be an indicator of autonomic failure (25,27,53,54), whereas increased QTc dispersion may be related to unbalanced sympathetic activity, left ventricular hypertrophy (44), or ischemic heart disease (51).

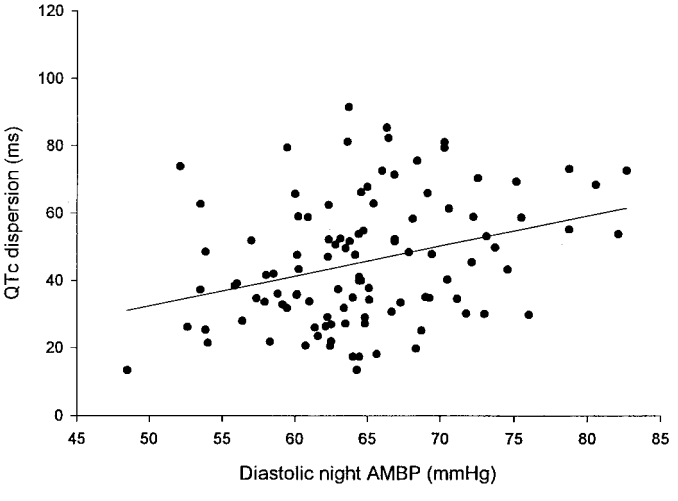

FIG. 2. QTc dispersion versus diastolic night AMBP in normoalbuminuric type 1 diabetic patients (r = 0.32, P < 0.01, n = 106).

In conclusion, increased QTc dispersion and reduced nocturnal fall in BP, both factors related to increased cardiovascular risk, coexist with altered sympathovagal balance in normoalbuminuric type 1 diabetic patients.

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