Influence of Cardiac Autonomic Neuropathy on Heart Rate Dependence of Ventricular Repolarization in Diabetic Patients

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OBJECTIVE — Prolongation of the QT interval and increased QT dispersion are associated with a poor cardiac prognosis. The goal of this study was to assess the long-term influence of the autonomic nervous system on the heart rate dependence of ventricular repolarization in patients with diabetic autonomic neuropathy (DAN).

RESEARCH DESIGN AND METHODS — We studied 27 subjects (mean age 51.8 years) divided into three age- and sex-matched groups: nine control subjects, nine diabetic subjects with DAN (mostly at a mild stage; DAN+), and nine diabetic subjects without DAN (DAN−). DAN was assessed on heart rate variations during standard maneuvers (Valsalva, deep-breathing, and lying-to-standing maneuvers). No subject had coronary artery disease or left ventricular dysfunction or hypertrophy, and no subject was taking any drugs known to prolong the QT interval. All subjects underwent electrocardiogram and 24-h Holter recordings for heart rate variations (time and frequency domain) and QT analysis (selective beat averaging QT/RR relation, nocturnal QT lengthening).

RESULTS — Rate-corrected QT intervals (Bazett formula) did not differ significantly between the three groups. The diurnal and nocturnal levels of low frequency/high frequency, an index of sympathovagal balance, were significantly reduced in DAN+ subjects. Using the selective beat–averaging technique, a day-night modulation of the QT/RR relation was evidenced in control and DAN− subjects. This long-term modulation was significantly different in DAN+ subjects, with a reversed day-night pattern and an increased nocturnal QT rate dependence.

CONCLUSIONS — In diabetic patients with mild parasympathetic denervation, QT heart rate dependence was found to be impaired, as determined by noninvasive assessment using Holter data. Analysis of ventricular repolarization could represent a sensitive index of the progression of neuropathy. The potential prognostic impact of a reversed day-night pattern with steep nocturnal QT/RR relation still remains to be defined.

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F acets of ventricular repolarization, including the length of the QT interval on surface-resting electrocardiogram (ECG), are a matter of growing interest because of their potential prognostic significance (1–4). There are a large number of physiological factors influencing the duration of the QT interval, including age, sex (5), and, most importantly, heart rate and autonomic nervous system (ANS) activity. Experimental and clinical studies evaluating the effects of ANS activity on ventricular repolarization have yielded conflicting results (6–8). However, these studies were based on different protocols and were applied to different populations. In addition, the methods used for measuring and adjusting the QT interval in accordance with heart rate were not uniform, and the ECG leads used were not always the same.

Cardiac autonomic neuropathy is associated with a poor cardiac prognosis, in particular with an increased risk of sudden death in diabetic patients (9). A lengthening of the QT interval and alteration of the QT dispersion have been reported in patients with diabetic autonomic neuropathy (DAN) (1,10,11) and appear also to have prognostic significance (10,12).

The goal of this study was to assess the long-term influence of the ANS (and mainly the parasympathetic limb) on the heart rate dependence of ventricular repolarization from long-term Holter ECG data in diabetic patients with or without dysautonomia and without cardiac disease.

RESEARCH DESIGN AND METHODS

Population

The population enrolled in this retrospective study comprised 27 subjects (12 women, 15 men; mean age 51.8 years, range 39–66 years), divided into three groups of subjects (age and sex-matched):

Table 1—*Clinical characteristics of subjects*

	Control	DAN+	DAN−
n	9	9	9
Age (years)	51.3 ± 8.6	52.3 ± 8.4	51.9 ± 7.4
Women	4	4	4
BMI (kg/m^2)	23.0 ± 2.3*	28.1 ± 6.4	26.4 ± 2.8
Sport practice	0	0	1
Smokers	0	4	4
Alcohol	0	0	0
Duration of diabetes (years)	—	15.7 ± 8.8	11.0 ± 4.7
Hypertension	0*	6	6‡
Insulin therapy	0	3	3
Peripheral neuropathy	0	7†	2
HbA$_{1c}$ (%)	—	8.1 ± 2.5	7.6 ± 2.2
Plasma creatinine (μmol/l)	—	90 ± 20	92 ± 16
ACE inhibitors	0	4†	0
Calcium antagonists	0	1	1
Diuretics	0	1	0
Central antagonists	0	1	1
β-blockers	0	0	0
LV-end diastolic diameter (mm)	46 ± 3	49 ± 5	47 ± 4
LV shortening fraction (%)	35 ± 7*	42 ± 7	41 ± 8
LV mass index (g/m^2)	88 ± 20	103 ± 27	103 ± 33

Data are *n* or means ± SD, unless otherwise noted. LV mass index was evaluated by echocardiography according to Devereux and Reichek (27). LV = left ventricle. *$P \leq 0.05$, control vs. DAN+; †$P \leq 0.05$, DAN+ vs. DAN−; ‡$P \leq 0.05$, DAN− vs. control.

nine control subjects, nine type 2 diabetic patients with DAN (DAN+), and nine type 2 diabetic patients without DAN (DAN−).

The diabetic subjects were patients who were referred to Jean Verdier University Hospital as being beyond the scope of a protocol designed to assess silent myocardial ischemia (13,14). They were selected according to strict inclusion criteria: absence of coronary artery disease (no history of angina or myocardial infarction, a negative exercise ECG stress test, a negative thallium-201 myocardial scintigraphy with intravenous infusion of dipyridamole, and no significant alteration of ST segment on a 48-h ambulatory ECG recording) and normal left ventricular function (as assessed by echocardiographic indexes). None of the patients were taking drugs known to prolong the QT interval (in particular, β-blockers were withdrawn at least 48 h before entry into the study).

Control subjects were asymptomatic volunteers recruited at Lariboisière University Hospital who showed a complete negative cardiovascular evaluation, including blood pressure, resting 12-lead ECG, echocardiogram, exercise stress test, and Holter monitoring. All were free of any cardiovascular medication.

Cardiac autonomic function tests

DAN was defined as an alteration in at least one of the three bedside clinical tests evaluating parasympathetic innervation to the heart, as proposed by Ewing et al. (10) and as previously described (14). Briefly, the RR interval variations were measured during the tests, using a computerized device (Q-med). The Valsalva test, conducted with the patient seated, consisted of forced exhalation and maintaining a pressure of 40 mmHg for 15 s. The result was expressed as the ratio RR maximum/RR minimum. The test was done three times consecutively, and the mean value for this ratio was taken. The deep breathing test was performed in a previously trained subject and consisted of the subject taking six deep breaths in 1 min in a supine position. The results were expressed as the mean value for the ratio of maximal heart rate/minimal heart rate. During the lying-to-standing test, the maximal heart rate (about the 15th beat)/minimal heart rate (about the 30th beat) ratio was calculated. The results of the three tests were compared with those

from a control series, with age taken into account (15). The reproducibility of these methods has been demonstrated in diabetic patients: the coefficients of variations are 9.2, 12.6, and 6.4% for the Valsalva, deep-breathing, and lying-to-standing tests, respectively (16).

ECG data

The QT intervals were manually measured by two cardiologists blind to the protocol on a 12-lead resting ECG printed at a paper speed of 25 mm/s, according to the method of Lepeschkin and Surawicz (17). In each lead, the QT interval was the mean of three successive individual intervals. The RR interval used for QT rate correction was the mean of all the sinus available RR intervals, and the rate correction was made by the Bazett formula (square root of the mean RR interval). QT dispersion was calculated as the difference between the longest and shortest QT interval from all available leads.

Holter data

A 24-h ambulatory Holter was recorded and further digitized at 128 samples per second. Tapes were then manually validated and transferred onto a personal system, dedicated to heart rate variability (HRV) and QT analysis. In addition, a diurnal period corresponding to the 8 consecutive awake hours with the highest heart rate, and a nocturnal period corresponding to the 4 consecutive sleeping hours with the lowest heart rate were separately analyzed.

Heart rate and heart rate variability. The mean sinus RR interval was calculated together with three time-domain HRV parameters: SDNN (standard deviation of consecutive RR intervals), a global index of sinus variability, and two vagal activity indexes—PNN-50 (percentage of normal consecutive RR intervals differing by >50 ms) and RMSSD (root mean of squared successive differences) (18). The difference between the mean nocturnal and diurnal RR intervals was also computed. HRV was also studied in the frequency domain. The power spectra obtained were integrated over low-frequency (LF) and high-frequency (HF) bands, as recommended by the International Task Force on HRV (18). The LF/HF ratio was calculated and log transformed to normalize the distribution.

QT analysis. QT analysis from long-term ECG was mainly based on the assess-

Table 2—RR interval and time-domain heart rate variability, RTa/RR and QTa/RR correlations, and nocturnal QT lengthening (Holter data)

	Control	DAN+	DAN−
n	9	9	9
RR and heart rate variability			
RR (ms)			
24-h period	858 ± 98	793 ± 86	798 ± 43
Diurnal period	762 ± 116	736 ± 79	737 ± 42
Nocturnal period	1025 ± 121	895 ± 104	901 ± 74‡
Nocturnal minus diurnal period	263 ± 97	159 ± 68	164 ± 61‡
SDNN			
24-h period	154 ± 32*	94 ± 23	118 ± 25‡
Diurnal period	107 ± 35*	61 ± 14†	99 ± 25
Nocturnal period	92 ± 23*	59 ± 17	78 ± 21
PNN 50			
24-h period	7.6 ± 7.4	3.1 ± 3.5	6.0 ± 3.7
Diurnal period	4.8 ± 6.4	2.0 ± 2.5	4.4 ± 3.4
Nocturnal period	14.8 ± 15.6	6.3 ± 8.0	9.1 ± 6.4
RMSSD			
24-h period	31.1 ± 10.8	24.9 ± 6.4	30.6 ± 5.9
Diurnal period	25.5 ± 10.6	22.6 ± 5.1	28.4 ± 5.3
Nocturnal period	42.1 ± 19.7	28.4 ± 10.1	33.5 ± 8.5
Log LF/HF			
24-h period	0.388 ± 0.217*	0.013 ± 0.146†	0.446 ± 0.296
Diurnal period	0.610 ± 0.168*	0.071 ± 0.193†	0.652 ± 0.184
Nocturnal period	0.158 ± 0.273*	−0.143 ± 0.112†	0.224 ± 0.369
QT selective beat averaging analysis			
QTa/RR slope			
Diurnal period	0.149 ± 0.043 (0.95)	0.119 ± 0.056 (0.81)	0.147 ± 0.034 (0.94)
Nocturnal period	0.109 ± 0.048 (0.86)*	0.161 ± 0.058 (0.92)	0.108 ± 0.055 (0.80)
Diurnal minus nocturnal period	0.040 ± 0.056*	−0.042 ± 0.074†	0.038 ± 0.064
Nocturnal QT lengthening			
QT RR-1	23.6 ± 11.0	14.7 ± 8.7	16.8 ± 3.7
QT RR 60	11.2 ± 7.7	6.2 ± 6.2	10 ± 5.3
RR min overlap	810 ± 110	718 ± 86	716 ± 51
RR max overlap	984 ± 131	878 ± 87	923 ± 57

Data are means ± SD. For QT selective beat-averaging analysis, coefficients of correlation between QTa and RR are given between parentheses. QT RR-1, nocturnal QT lengthening according to the preceding RR interval. QT RR 60, nocturnal QT lengthening according to the preceding RR interval, with a stable RR interval over the preceding minute; overlap, range of comparable heart rates between both periods, from maximal RR overlap (RR max overlap) to minimal RR overlap (RR min overlap). *$P \leq 0.05$ control vs. DAN+; †$P \leq 0.05$ DAN+ vs. DAN−; ‡$P \leq 0.05$ DAN− vs. control.

ment of the heart rate dependence of the QT interval. This was evaluated by calculating the QT/RR relation on ECG templates obtained with a selective beat averaging technique, as previously reported (19). Briefly, the QT apex interval (from beginning of QRS to apex of the T wave; QTa interval) was measured over the preceding RR intervals, but in relative stable rate conditions (RR-2 = RR-1 ± 50 ms and RR min-1 = RR-1 ± 15 ms), and each individual QRS-T was incorporated into the closest RR template. In our experience, with the selective beat−averaging technique, the slopes of the QT/RR relation are steeper and the correlation coefficients are higher than with the beat-to-beat approach (all individual sinus beats),

and the within-subject reproducibility is good, as has been previously shown (20).

For QT/RR relation, repolarization duration was analyzed by a fully automated technique. The beginning of the QRS was identified on the vector magnitude of the ECG signal using the first derivative of the initial deflection of the QRS. The apex of the T wave was defined as the peak of the parabola interpolated through the samples of the T wave.

In addition to the QT heart rate dependence, the amplitude of the nocturnal QT lengthening, defined as the mean difference between nocturnal and diurnal QT intervals over the range of common RR intervals (rate independent analysis), was analyzed (21).

Statistical analysis
All data are given as means ± SD. Between-group comparisons were computed by nonparametric tests (Wilcoxon and χ^2 for unpaired series). Correlations between continuous parameters were calculated according to a linear regression model.

RESULTS

Clinical characteristics
There were no significant differences in the major clinical characteristics between the three groups (Table 1). However in the DAN+ and DAN− subjects, BMI was higher and hypertension more frequent than in control subjects. Peripheral
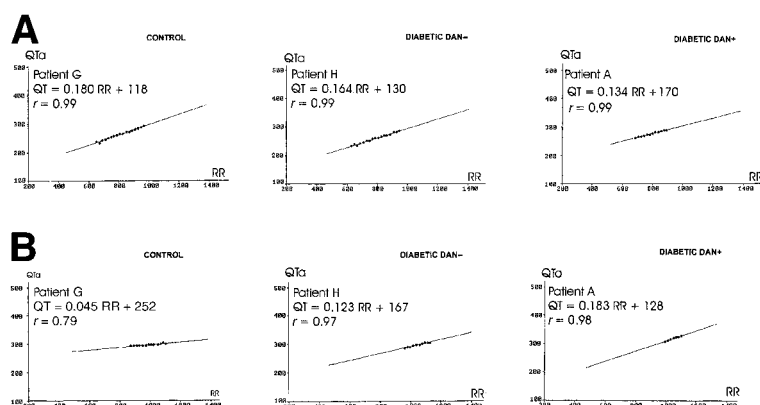
Figure 1—*Diurnal (A) and nocturnal (B) QTa/RR slopes. Individual examples are age- and sex-matched from each group. Data are in ms.*

neuropathy and use of ACE inhibitors were both more frequent in DAN+ than in DAN− patients. Based on the results of the cardiac autonomic function tests in the DAN+ group, five subjects had mild DAN (one abnormal test), one had confirmed DAN (two abnormal tests), and three had severe DAN (three abnormal tests).

Resting ECG Data
The RR interval was significantly shorter ($P < 0.05$) in the DAN+ and DAN− than in control subjects (735 ± 94, 735 ± 77, and 899 ± 161 ms, respectively). However, no significant differences were observed for the QT or QTc interval (402 ± 56, 404 ± 23, and 390 ± 24 ms, respectively). The magnitude of QT dispersion was also similar in the three groups (38 ± 10, 39 ± 6, and 34 ± 9 ms, respectively).

Heart rate variability
Mean RR intervals were consistently shorter in the diabetic subjects when compared with the control subjects (Table 2). The SDNN was significantly reduced in DAN+ and DAN− subjects compared with in control subjects. The diurnal SDNN was significantly shorter in the DAN+ than in the DAN− subjects, and the nocturnal SDNN was significantly shorter in DAN+ than in control subjects. For parasympathetic indexes, only the RMSSD on the 24-h period tended to be lower in the DAN+ than in the DAN− group ($P = 0.051$). In DAN+ patients, the LF/HF in the 24-h period analysis and during the diurnal and nocturnal period was significantly lower than in control and DAN− subjects and was reversed during the night.

Selective beat averaging
Correlation coefficients of the QTa/RR slopes based on selective beat averaging were much higher than for beat-to-beat analysis ($0.80-0.95$) (Table 2; Fig. 1). An autonomic modulation of the QTa/RR relation was evidenced in control subjects using this technique, and this trend (steeper diurnal than nocturnal slopes) was preserved in DAN− subjects. Most importantly, this long-term modulation was significantly different in DAN+ subjects, with a reversed day/night pattern: the nocturnal QT rate dependence was increased and the difference between diurnal and nocturnal QTa/RR slopes was negative.

Nocturnal QT lengthening
There was a nonsignificant trend toward a decreased nocturnal QT lengthening in DAN+ subjects when compared with control and DAN− subjects (Table 2).

CONCLUSIONS — The goal of this study was to assess the long-term influences of the ANS on the QT heart rate dependence in a model of diabetic patients with parasympathetic denervation. The major findings can be summarized as follows: *1*) QT heart rate dependence evaluation discriminated better between control subjects and DAN+ subjects than the time-domain HRV parameters; *2*) the nocturnal QT heart rate dependence evaluation was increased in DAN+ subjects when compared with DAN− and control subjects; and *3*) the physiological long-term autonomic modulation of the QT heart rate dependence was impaired in DAN+ subjects, with a reversed day/night pattern.

Characteristics of the QT interval are recognized as powerful discriminators between two populations, in the long QT syndrome and after myocardial infarction (3,4). In the present study, the QTc did not differ significantly among DAN+, DAN−, and control subjects, a finding in accordance with a recently published meta-analysis (11). The fundamental reason is that applying any formula supposes QT dynamicity to be a physiological constant. This study demonstrates that this is not so. Dynamicity is a characteristic of individuals, modulated by the ANS. Bellavere et al. (1) found a steeper heart rate dependence in DAN+ subjects than in DAN− and control subjects (calculated by measuring resting QT interval and QT interval during different autonomic tests). Ewing et al. (10) also reported a significantly steeper QT/RR relation in DAN+ diabetic subjects. Our study differs from the latter in that the data were taken separately in the daytime and nighttime.

HRV analysis and cardiac autonomic neuropathy
In our population, the time-domain HRV parameters did not correctly discriminate DAN+ and DAN− subjects, except for diminished global HRV indexes. However, in DAN+ patients, the LF/HF ratio, an index of sympathovagal balance, was significantly reduced during the diurnal and nocturnal periods and was reversed during the night.

Significance of an altered QT/RR relationship
Differences in the circadian behavior of QT/RR slopes observed between DAN+ subjects versus DAN− and control subjects may be related to an altered autonomic modulation rather than to an intrinsic myocardial abnormality. Indeed, our diabetic patients were not affected by coronary heart disease, left ventricular dysfunction or hypertrophy, or significant thyroid disease, and were not taking antiarrhythmic drugs (including β-blockers), all factors known to affect QT interval duration, dispersion, or variability. Both DAN+ and DAN− groups included the same proportion of hypertensive patients and had similar left ventricle mass indexes (Table 1). To our knowledge, neither hypertension nor antihypertensive drugs (except for β-blockers) have been reported as playing a role in the cardiac autonomic function tests or in QT interval

heart rate−dependence evaluation (22). Therefore, if one accepts that the ventricular substrate was not impaired in our patients, then the reversed day-night pattern appears to be associated with the cardiac neuropathy itself.

Long-term circadian influences on ventricular repolarization in healthy subjects have been described by Browne et al. (21), who showed that QT duration was increased by 25 ms at night in a heart rate−independent manner. This was confirmed in diabetic neuropathy and coronary artery disease (6,7). Our group was the first to demonstrate that ANS activity exerts a long-term modulation on QT heart rate dependence (5,23,24). Our DAN+ subjects were recruited on the basis of clinical parasympathetic denervation. One could assume that the observed differences in autonomic modulation of QT heart rate dependence are attributable to parasympathetic denervation. In keeping with this finding are results from in vitro and in vivo studies. Studies on canine myocardium have reported an increase of action potential duration and ventricular refractory periods with vagal stimulation (acetylcholine), suggesting the inverse effect of parasympathetic blockade (25). In humans, parasympathetic blockade with atropine (with or without atrial pacing) has been shown to result in a higher QT heart rate dependence (i.e., QT interval decreases more at high heart rates) at baseline and during exercise (26).

Clinical implications

The duration of the QT interval and QT dispersion have emerged as prognostic factors in many clinical settings, such as in postmyocardial infarction, congenital long-QT syndrome, and chronic heart failure and in large subsets of the general population (2−4). In DAN+ patients, an abnormally high incidence of sudden death (9,10) and an abnormal QT interval duration and/or variability have been noted, suggesting a link between the two (1,10). Ewing et al. (10) also found a longer QT interval in diabetic patients who died during follow-up (mostly sudden deaths) as compared with patients who survived. Recent studies have assessed the prognostic significance of an increased QT dispersion in type 2 diabetes (12). A long-term follow-up on a large cohort of diabetic patients should help in assessing the prognostic significance of

QT heart rate−dependence evaluation, in particular in patients with DAN.

In conclusion, in diabetic patients affected by mostly mild parasympathetic denervation, QT heart rate dependence assessed from Holter data was found to be clearly impaired; furthermore, a reversed day-night pattern was observed, associated with an impaired sympathovagal balance. The analysis of ventricular repolarization could represent a sensitive index of the progression of neuropathy; this possibility should be tested in a larger series of patients. The evolution and potential prognostic impact of a reversed day-night pattern with steep nocturnal QT/RR relation still remains to be defined.

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