Is the Corrected QT Interval a Reliable Indicator of the Severity of Diabetic Autonomic Neuropathy?

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OBJECTIVE— We investigated whether the corrected QT interval correlated with two other tests for diagnosing autonomic dysfunction in 60 type I diabetic patients with proven peripheral neuropathy. The mean age ± SD was 48.3 ± 11.2 yr, the mean duration of diabetes was 24.9 ± 11.4 yr, and the mean HbA_1 was 9.3 ± 2.4%.

RESEARCH DESIGN AND METHODS— All patients underwent three autonomic function tests: *1*) the standard five cardiovascular Ewing tests, each scored 0 (normal), 0.5 (borderline), or 1.0 (abnormal). We used the sum of the abnormal findings for the analysis, the cardiovascular autonomic score; 2) measurement of the corrected QT interval taken from a routine electrocardiogram recording; and 3) static and dynamic pupillometry: measurement of dark adapted pupil diameter as percentage of total iris diameter and of pupil constriction latency using an infrared light reflex technique.

RESULTS— No significant correlation was found between age, duration of diabetes, or HbA_1 and any of the autonomic function tests, except for one between age and cardiovascular autonomic score ($r = 0.3202$, $P = 0.0126$). Corrected QT interval did not correlate with cardiovascular autonomic score, pupil diameter, or constriction latency. A significant inverse correlation was found between cardiovascular autonomic score and pupil diameter ($r = -0.4861$, $P < 0.001$) and constriction latency ($r = 0.3783$, $P < 0.001$). Pupil diameter and constriction latency correlated well ($r = -0.4276$, $P < 0.001$).

CONCLUSIONS— The corrected QT interval did not correlate with cardiovascular autonomic tests nor pupillometry results. The corrected QT interval therefore should not be used for the diagnosis of the severity of diabetic autonomic neuropathy.

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Type I diabetes, insulin-dependent diabetes mellitus; AN, autonomic neuropathy; HR, heart rate; BP, blood pressure; QTc, corrected QT; AER, albumin excretion rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; CAS, cardiovascular autonomic score; PD, pupil diameter; CL, constriction latency; IRIS, infrared light reflex technique: type II diabetes, non-insulin-dependent diabetes mellitus.

Researchers have reported that 50% of all patients who have had diabetes for >25 yr have AN (1). Ewing et al. (2) demonstrated that AN has a poor prognosis, with increased incidence of sudden death, silent myocardial infarction, and renal failure shown in a 5-yr prospective study of 73 asymptomatic diabetic patients with AN. Five cardiovascular tests usually are applied, as originally described by Ewing et al. (3,4). Three of these tests assess cardiac parasympathetic pathways: changes in HR during Valsalva's maneuver, deep breathing, and active position change from supine to upright. The two other tests, measurements of BP changes after standing up and during sustained hand grip, evaluate sympathetic pathways (3,4).

Hreidarsson and Gundersen (5) demonstrated a smaller initial pupil size and reduced maximal velocity of constriction and redilatation in diabetic patients compared with normal control subjects, using infrared television-video pupillography. A number of authors have observed a lengthening of the QTc interval in patients with AN (6–9). Ewing et al. (10) suggested an association between lengthening of the QT interval and the risk of unexpected death.

No conclusive evidence exists about the correlation between the various methods of assessment of the severity of autonomic dysfunction. We therefore investigated the correlation between indicators of AN and their dependence on age, duration of the disease, and metabolic control in 60 type I diabetic patients with proven peripheral neuropathy.

RESEARCH DESIGN AND METHODS

— We studied 60 type I diabetic patients with a mean age of 48.3 ± 11.2 yr, mean duration of diabetes 24.9 ± 11.5 yr, and mean HbA_1 9.3 ± 2.4%. These patients had been selected for a large clinical intervention trial on the treatment of diabetic neuropathy with a neuropeptide. They had ei-

Table 1—*Clinical characteristics of diabetic patients and autonomic test results*

n	60
Sex	37 M/23 F
Age (yr)	48.3 ± 11.2
Duration of diabetes (yr)	24.9 ± 11.4
Nephropathy (%)	
absent/incipient/overt*	61.1/25.9/13.0
Retinopathy (%)	
absent/background/ proliferative	32.8/28.8/38.4
HbA_1 (%)	9.3 ± 2.4
QTc (ms)	409 ± 24.3
CAS *n* (%)	
Normal (0–0.5)	13 (22)
Borderline (1–2)	26 (43)
Definite (2.5–3.5)	17 (28)
Severe (4–5)	4 (7)
CL (ms)	246 ± 36.1
PD (%)	44.1 ± 8.9

Data are means ± SD
*Absent, <30 mg/24 h; incipient, >30 and <300 mg/24 h; overt, >300 mg/24 h.

ther an abnormal vibratory perception threshold and/or an abnormal temperature threshold measured at the hand as signs of peripheral neuropathy. Vibratory threshold was measured with a Vibrameter III (Somedic AB, Sweden) over the middle of the second metacarpal on the dorsal aspect of the right hand, as described by Gerritsen van der Hoop et al. (11). We measured temperature threshold for warmth and cold in the right hand using the Temperature Threshold Tester (Medelec, UK). We reported this method in detail concerning normal values and reproducibility (12).

All patients were tested at the beginning of the study: 61.1% of the patients had a normal AER (<30 mg/24 h), 25.9% had incipient nephropathy (AER >30 and <300 mg/24 h), and 13% had overt nephropathy (AER >300 mg/24 h). Four urine samples collected over a period of 12 mo before the study showed increased microalbuminuria, c.q. nephropathy. Retinopathy was present in 67.2% of the patients studied; 28.8% had background retinopathy, and 38.4% had proliferative retinopathy. The patients had taken no drugs that affect the autonomic nervous system. Patients gave their informed consent in accordance with the principles of the Declaration of Helsinki.

RESEARCH DESIGN AND METHODS— The five standard cardiovascular tests were performed as described by Ewing (3): *1*) BP in response to standing: measurement of the change in sBP after the patient stands from a supine position. A drop in BP <10 mmHg is considered normal, 10–20 mmHg borderline, and >30 mmHg abnormal; 2) HR in response to standing: calculation of the ratio between the HR that occurs at the 15th and 30th beat after standing up from a supine position. A value >1.03 is considered normal, 1.01–1.03 borderline, and <1.0 abnormal; 3) Beat-to-beat rate variation: measurement of the change in HR during deep breathing. A difference >14 beats/min is considered normal, 11–14 borderline, and ≤10 abnormal; 4) Valsalva's maneuver: calculation of the quotient of HR during and after Valsalva's maneuver. The patient blows into a mouthpiece, maintaining a pressure of ~40 mmHg for 15 s. The ratio is calculated between the highest heart frequency during Valsalva's maneuver and the lowest afterward. A ratio >1.2 is considered normal, 1.11–1.2 borderline, and <1.11 abnormal; 5) BP response to sustained hand grip: measurement of the change in dBP after sustained hand grip. A rise in BP >16 mmHg is considered normal, 11–15 mmHg borderline, and ≤10 abnormal.

Each outcome was based on the mean of three consecutive measurements. All tests were scored as normal (0 points), borderline (0.5 points), or abnormal (1.0 points). The sum of abnormal findings of the five tests varying between 0 and 5 points was used for further analysis, the CAS. HR and BP were measured with a Finapress[R] tonometer (13,14). The Finapress[R], which is based on servoplethysmo-manometry, uses the volume clamp technique. It

Table 2—*Correlation matrix between the different autonomic function tests*

	Age	Diabetes duration	HbA_1	CAS	QTc interval	CL
Age	1.0					
Diabetes duration	0.0037	1.0				
HbA_1	−0.2163	0.0037	1.0			
CAS	0.3202*	0.0423	0.0370	1.0		
QTc interval	−0.0277	0.0573	0.1022	0.0242	1.0	
CL	0.1466	0.1553	−0.1131	0.3783†	−0.1183	1.0
PD	−0.1831	−0.1720	−0.0465	−0.4861†	−0.0251	−0.4276†

Coefficients of correlation between age, duration of diabetes, HbA_1, and autonomic function tests.
*$P < 0.05$.
†$P < 0.001$.

Table 3—*Mean QT, mean QTc interval, and HR grouped for CAS results*

	QT (ms)	QTc (ms)	HR (min)
CAS			
Normal	380.0 ± 42.5	409.1 ± 31.6	75.0 ± 13.0
Borderline	364.5 ± 28.3	409.3 ± 20.9	84.7 ± 17.5
Definite	362.4 ± 27.7	409.2 ± 18.8	86.8 ± 16.0
Severe	359.5 ± 57.7	405.2 ± 36.1	86.1 ± 25.9

Data are means ± SD grouped according to the outcome of the sum of the CAS.

measures beat-to-beat HR noninvasively from the right index finger.

The QT interval was measured with the automated Siemens[R] ECG Mingograf 400/700 System (P.W. Macfarlane, Glasgow, March 1987). This system takes a routine 12-lead ECG recording and calculates the QT interval from the mean of 15 beats from all 12 leads. The QTc is calculated automatically, correcting for HR, with the formula: $QTc = QT + 1.75 \times (HR - 60)$ in milliseconds.

Both static and dynamic pupillometries were performed in darkness. Static pupillometry consisted of measuring the PD after 2 min, then after 4 min of dark adaptation with infrared photography. From the photographs the PD was determined in relation to the horizontal iris diameter and expressed as PD% (15). IRIS was used for dynamic pupillometry (16,17). With infrared light-emitting diodes and sensors mounted on a frame fixed in front of both eyes, variations in pupil size can be recorded after a light stimulus is placed in front of the right eye. The block-shaped stimulus had an intensity of 3.7 Log Troland (Troland = retinal illuminance) and a duration of 1.2 s every 5 s. The latency between onset of the stimulus and beginning of the constriction was quantified by using the first deflection in the differentiated signal as the starting point of the constriction (17). The latency of pupillary constriction was measured from at least 10 artifact-free responses for both eyes. Age-related data ± SD in control subjects, as published by Smith and Dewhurst (15) and Lanting et al. (18), were used.

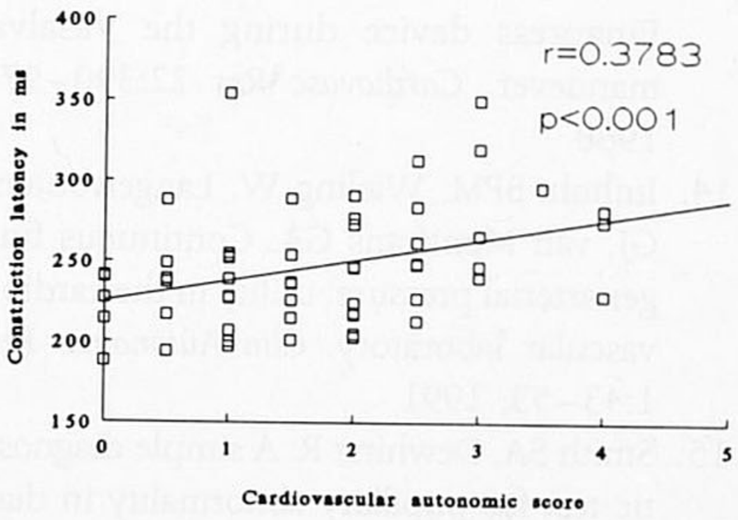

Figure 1—*Linear regression analysis of CL in ms plotted against the total CAS (0–5 points) of 60 type I diabetic patients with peripheral neuropathy.*

Statistical analysis

Data are presented as means ± SD. We performed the statistical analysis with the STATA[R] software program. Correlation coefficients between HbA_1, age, duration of diabetes, and the three methods of measuring autonomic function were calculated with standard linear regression according to the least-squares method.

RESULTS— Table 1 shows patient data and the outcomes of the three autonomic tests. The 60 type I diabetic patients selected for this study had a long duration of illness (24.9 ± 11.4 yr), and, as expected, a high percentage of the patients had increased microalbuminuria (38.9%) and retinopathy (67.2%). The mean HbA_1 level at the time of the investigations was 9.3 ± 2.4%. CAS was

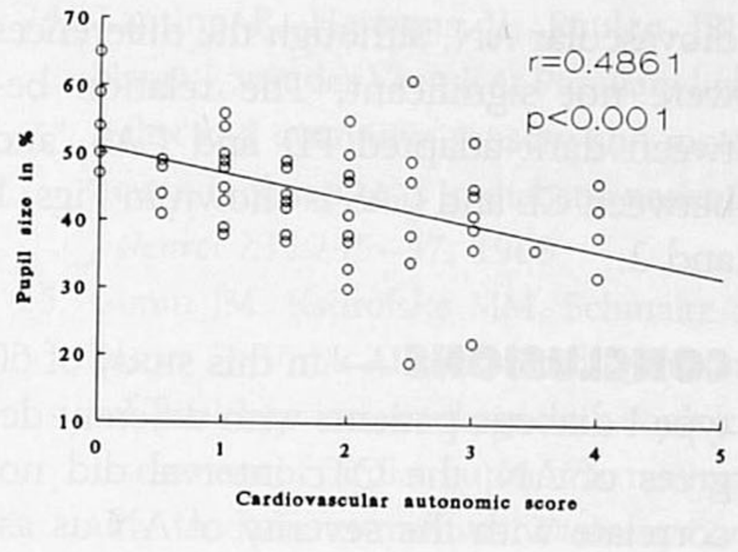

Figure 2—*Linear regression analysis of dark-adapted pupil size as percentage of total iris area (PD%) plotted against the total CAS (0–5 points) of 60 type I diabetic patients with peripheral neuropathy.*

distributed as follows: 13 (22%) patients were normal (0–0.5 points), 26 (43%) were borderline (1–2 points), 17 (28%) were abnormal (2.5–3.5 points), and 4 (7%) were severely abnormal (4–5 points).

The results of the correlation studies are given in Table 2. No significant correlation was found between age, duration of diabetes, or HbA_1 and any of the tests for dysfunction of the autonomic nervous system, apart from a correlation between age and CAS ($r = 0.3202$, $P = 0.0126$). No difference was evident by sex in either the prevalence of abnormal findings or the outcome of the different autonomic tests. QTc interval did not correlate significantly with either CAS or pupillary light reflex data. A significant inverse correlation was found between CAS and dark-adapted PD ($r = 0.4861$, $P < 0.001$) and CL ($r = 0.3783$, $P < 0.001$). Dark-adapted PD and CL correlated well ($r = -0.4276$, $P < 0.001$).

The results of the mean QT and QTc interval, and HR ± SD also were grouped with reference to the results of the CAS (normal, borderline, definite, and severe), as shown in Table 3. The QTc interval did not differ significantly among these four groups. As expected, the mean HR showed a trend of being higher in the more severe forms of car-

diovascular AN, although the differences were not significant. The relation between dark-adapted PD and CAS, and between CL and CAS is shown in Figs. 1 and 2.

CONCLUSIONS — In this study of 60 type I diabetic patients with different degrees of AN, the QTc interval did not correlate with the severity of AN as assessed by CAS or the results of static and dynamic pupillometry. That CAS correlates with age but not with duration of diabetes may be because cardiovascular AN per se is not caused by the cumulative toxic effect of chronic hyperglycemia but by other factors, apart from age. Antibody formation against autonomic nervous tissue based on genetic susceptibility, as is demonstrated by Rabinowe et al. (19), could be a factor making the pathogenesis of AN an on/off mechanism.

The measurement of dark-adapted pupil size and CL time is a relatively new method for the diagnosis of AN in diabetic patients. This study demonstrated that the results of these tests correlated well with those of the standard cardiovascular tests.

It has been reported that dark-adapted pupil size and pupillary light reflex latency decrease with age in normal patients (5,15,20). Hreidarsson (15) showed that diabetic patients have a smaller initial pupil size and a smaller response amplitude than control subjects, and that results are inversely correlated to the duration of diabetes. Hreidarsson (21) also showed an inverse correlation between pupil size and vibratory perception threshold. We did not find that age affected the results of the pupillometry tests in our diabetic patients, but this could be because we did not include normal patients in our study, whereas other investigators did (5,15).

Asymptomatic QT interval lengthening has been reported in young diabetic patients (22) and has been mentioned as a causal factor in sudden cardiac death (10,23). Lengthening of the QT interval could be caused by increased sympathetic drive and myocardial damage (22).

A limited number of studies have reported a correlation among pupillometry, cardiovascular tests, and QTc interval measurements. Lanting et al. (24) showed a positive correlation between the latency of the constriction reaction of the pupil and the thermal discrimination threshold, depicting small fiber dysfunction. Gonin et al. (25) reported a positive correlation between CAS and lengthening of the QTc interval, which we could not confirm in our study. This difference could again be attributed to patient selection: We included type I diabetic patients with known peripheral neuropathy, whereas Gonin et al. (25) included type I and II patients who had not been evaluated previously for the existence or absence of peripheral neuropathy. Cho et al. (26) reported a positive correlation between cardiovascular autonomic function tests and abnormal pupillary responses, as we did.

We conclude that the QTc interval cannot be used as a simple and reliable test to assess the severity of AN and certainly not as a substitute for the standard cardiovascular autonomic function tests.

References

1. Thomas PK, Eliasson SG: Diabetic neuropathy. In *Peripheral Neuropathy*. Dyck PJ, Thomas PK, Lambert EH, Bunge R, Eds. Philadelphia, PA, Saunders, 1987, p. 66–68
2. Ewing DJ, Campell IW, Clarke BF: Mortality in diabetic autonomic neuropathy. *Lancet* 1:601–603, 1976
3. Ewing DJ: Cardiovascular reflexes in autonomic neuropathy. *Clin Mol Med* 55: 321–27, 1978
4. Ewing DJ, Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–18, 1982
5. Hreidarsson AB, Gundersen HJG: The pupillary response to light in type I (insulin-dependent) diabetes. *Diabetologia* 28:815–21, 1985
6. Kahn JK, Sisson JC, Vinik AI: QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 64:751–54, 1987
7. Ewing DJ, Neilson JMM: QT interval length and diabetic autonomic neuropathy. *Diabetic Med* 7:23–26, 1990
8. Chambers JB, Sampson MJ, Sprigings DC, Jackson G: QT prolongation on the electrocardiogram in diabetic autonomic neuropathy. *Diabetic Med* 7:105–10, 1990
9. Jermendy G, Toth L, Voros P, Koltai MZ, Pogatsa G: QT interval in diabetic autonomic neuropathy. *Diabetic Med* 7:750, 1990
10. Ewing DJ, Bolland O, Neilson JMM, Cho CG, Clarke BF: Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 34:182–85, 1991
11. Gerritsen van der Hoop, Vecht ChJ, Van den Burg MEL, Haanstra W, Boogred W, ten Bokkel Huinink W, Heijmans JJ, Vermorken J, Jennekens FGI, Van Houwelingen JC, Gispen WH, Neijt JP: Prevention of cisplatinin neurotoxicity with an ACTH(4–9) analogue in patients with ovarian cancer. *N Engl J Med* 322:89–94, 1990
12. Bravenboer B, van Dam PS, Hop J, van Steenhoven J, Erkelens DW: Thermal threshold testing for assessment of small fibre dysfunction; normal values and reproducibility. *Diabetic Med* 9:546–49, 1992
13. Imholz BPM, van Montfrans GA, Settels JJ, van der Hoeven GMA, Karemaker JM, Wieling W: Continuous non-invasive blood pressure monitoring: reliability of Finapress device during the Vasalva manuever. *Cardiovasc Res* 22:390–97, 1988
14. Imholz BPM, Wieling W, Langewouters GJ, van Montfrans GA: Continuous finger arterial pressure: utility in the cardiovascular laboratory. *Clin Autonomic Res* 1:43–53, 1991
15. Smith SA, Dewhirst R: A simple diagnostic test for pupillary abnormality in diabetic autonomic neuropathy. *Diabetic Med* 3:38–41, 1985
16. Reulen JPH, Marcus JT, van Gilst MJ: Stimulation and recording of dynamic pupillary reflex: the IRIS technique. Part

2. *Med Biol Eng Comput* 26:27–32, 1988
17. De Vos A, Marcus JT, Reulen JPH, Peters HFM, Heimans JJ: The pupillary light reflex in diabetes mellitus: evaluation of a newly developed infrared light reflection method. *Diabetes Res* 10:191–95, 1989
18. Lanting P, Bos JE, Aartsen J, Schuman L, Reichert-Thoen JWM, Heimans JJ: Assessment of pupillary light reflex latency and darkness adapted pupil size in control subjects and in diabetic patients with and without cardiovascular autonomic neuropathy. *J Neurol Neurosurg Psychiatry* 53:912–14, 1990
19. Rabinowe SL: Immunology of diabetic and polyglandular neuropathy. *Diabete Metab Rev* 6:169–88, 1990
20. Smith SA, Smith SE: Reduced pupillary light reflexes in diabetic autonomic neuropathy. *Diabetologia* 24:330–32, 1983
21. Hreidarsson AB: Pupil size in insulin-dependent diabetes: relationship to duration, metabolic control, and long-term manifestations. *Diabetes* 31:442–48, 1982
22. Airaksinen KEJ: Electrocardigram of young diabetic subjects. *Ann Clin Res* 17: 135–38, 1985
23. Bellavere F, Ferri M, Guarini L, Bax G, Piccoli A, Cardone C, Fedele D: Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? *Br Heart J* 59:379–83, 1988
24. Lanting P, Heimans JJ, Reulen JPH, Nauta J, van der Veen EA: Pupillary light reflex and quantitive sensory and motor neural function tests in diabetic patients. *J Neurol* 235:245–47, 1988
25. Gonin JM, Kadrofske MM, Schmaltz S, Bastyr EJ, Vinik AI: Corrected QT interval prolongation as diagnostic tool for assessment of cardiac autonomic neuropathy in diabetes mellitus. *Diabetes Care* 13:68–71, 1990
26. Cho CG, Choi SC, Hong SW, Kim CI, Jang G: Pupillary responses and its correlation with other tests of neurological function in diabetic subjects (Abstract). *Diabetes* 40 (Suppl. 1):A1541, 1991