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RESEARCH ARTICLE

Prospective investigation of autonomic cardiac neuropathy in diabetes mellitus

D. Claus
O. Meudt
C.Rozeik
K. Engelmann-Kempe
P. E. Huppert
H. Wietholtz

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D. Claus (✉) · O. Meudt
Dept. of Neurology
Hospital Darmstadt
Teaching Hospital of the Universities
of Frankfurt and Heidelberg
Heidelberger Landstraße 379
64297 Darmstadt, Germany
Tel.: +49-61 51/1 07-45 01
Fax: +49-61 51/1 07-45 99

C.Rozeik · P. E. Huppert
Dept. of Radiology I
Hospital Darmstadt
Darmstadt, Germany

K. Engelmann-Kempe · H. Wietholtz
Dept. of Internal Medicine
Hospital Darmstadt
Darmstadt, Germany

Abstract Forty-five patients with clinically manifest diabetes mellitus were investigated (25 male, 20 female, 48 ± 10 yrs, 14 diabetes type 1, 31 type 2). Duration of manifestation was 12.2 ± 9.7 yrs.

Vibration thresholds and thermal thresholds were assessed. Respiratory sinus arrhythmia (RSA) was measured during deep respiration at 6/min. The QTc-interval was assessed according to Bazett's formula. MIBG-SPECT was carried out in all 45 cases. Patients with abnormal MIBI perfusion scintigraphy had previously been excluded from the study. RSA was abnormal in 12/45 patients. The MIBG-SPECT was abnormal in 28/45 cases with dorso-septal lack of activity. No difference was seen between type 1 and 2 diabetics with regard to either vibration and thermal thresholds or RSA and MIBG-SPECT. Abnormal MIBG-SPECT was correlated with vibration threshold and abnormal heart RSA tests but not with abnormality in QTc. The mean QTc-interval was 419 ± 24 ms (QTc normal in 36, abnormal ≥ 440 ms in 9). It was longer in female than in male patients. There exists no significant correlation of QTc-interval results with either heart rate variability or MIBG-SPECT. The QTc-interval is not a sensitive parameter of autonomic cardiac denervation.

Key words respiratory sinus arrhythmia · diabetic cardiac neuropathy · QTc-interval · MIBG-SPECT

Introduction

Autonomic cardiac denervation can be assessed by both investigation of respiratory sinus arrhythmia (RSA) [1–3] and by ^{123}iodine-metaiodobenzylguanidine-single photon emission computed tomography (MIBG-SPECT) [4–7]. Impaired RSA reflects mainly parasympathetic denervation. Abnormal MIBG-SPECT indicates sympathetic cardiac innervation failure.

Overall mortality of diabetic patients with cardiac autonomic neuropathy (CAN) varies between 44 % within 2.5 years [8] and 30 % within 10 years [9, 10]. In prospective studies a 3- to 10-fold increased mortality was shown in diabetic patients with CAN compared with no CAN [11–18]. The diagnosis of CAN in diabetics indicates a five year mortality rate of 16–53 % [10, 12, 17, 19, 20].

The corrected QT-interval is known to be prolonged in patients with an autonomic diabetic neuropathy [21, 22]. QTc-prolongation was identified as an indicator of life-threatening cardiac arrhythmia [22]. A correlation was seen between QTc-prolongation and cardiac mortality [23, 24]. However, other investigators did not see a correlation between QTc and either RSA or cardiac mortality [6, 25–28]. Also, no increased incidence of ventricular late potentials was seen in the ECG of diabetic patients with prolonged QTc [21].

The aim of this prospective study was to determine the significance of abnormal cardiac autonomic inner-

vation with regard to clinical prognosis. Were cardiac events, including ischemia or arrhythmia, seen more often in patients with cardiac autonomic neuropathy?

Methods

A total 255 patients were contacted. All patients underwent a neurological examination; 45 patients were included in the study. All had normal bicycle ergometry-ECG and MIBI-SPECT (no silent myocardiac ischemia).

Exclusion criteria were history of coronary heart disease, abnormal bicycle ergometry-ECG, renal insufficiency, pregnancy, alcoholism (≥ 40 g per day), potentially toxic or interfering medication (tricyclic antidepressants, alpha blockers, beta blockers, guanethidine derivatives).

Respiratory heart rate variation was investigated in accordance with normal results from 101 subjects published elsewhere [1]. Recording was carried out after 15 minutes of rest with the QMED device (Q-Med Inc., Clark, NJ, USA). The patient was asked to breathe at a rate of 6 per minute and 25 breathing cycles were recorded for further analysis. The expiration/inspiration index (E/I), standard deviation (SD), and mean circular resultant (MCR) were assessed as described elsewhere [1]. The Valsalva index (Vals) was calculated as the mean of three investigations. The posture index (PI) was recorded as the maximum/minimum heart rate after standing up [1].

Patients with cardiac perfusion deficits had previously been excluded by ^{99m}Tc-MIBI-SPECT which was performed in all patients. After bicycle ergometry 583 MBq of ^{99m}Tc-MIBI were injected and SPECT was carried out after one hour in order to exclude hypoperfusion of the heart muscle. Sympathetic cardiac innervation was assessed by MIBG-SPECT [4]. The MIBG-SPECT was carried out 7–14 days after a normal MIBI-SPECT. 278 MBq ^{123}I-MIBG was injected and the SPECT was recorded after 4–5 hours. The SPECT recordings were interpreted as normal or abnormal by the radiologist, who was not informed about neurophysiology and clinical investigation results.

The QTc-interval was recorded as a mean of three consecutive RR intervals from a 30 s ECG recording (paper speed 50mm/s). Three consecutive QT-intervals and their corresponding RR intervals were measured manually. The investigators were unaware of the results of the other tests. The QTc-interval reflects the ventricular electrical systole. QTc-prolongation is a result of disturbed ventricular excitation recovery which is believed to be a cause of ventricular arrhythmia [24, 26, 29]. The QTc-interval was corrected in accordance with Bazett's formula (QTc = QT-time/square root of heart beat interval) [30]. The measurement was carried out by two investigators with 100 % coincidence.

The thermal perception threshold was assessed by the two alternative temporal forced choice method for warm and cold stimuli (Phywe Systeme GmbH, Göttingen, Germany) [1]. Measurement was done at the medial ankle.

The vibration perception threshold (Vib) for 100 Hz stimuli was measured by the method of limits at the big toe (Vibratester, Phywe Systeme GmbH, Göttingen, Germany) [1].

The patients were seen prospectively at 2-month intervals for a period of 2 years with questioning about cardiac events and heart rate analysis. Neurological investigation was carried out every 6 months. HbA1, blood results and liver enzymes (no alcohol) were done every 12 months. The ECG was recorded at the beginning and the end of the study.

Of the included 45 patients with CAN, 15 were contacted in September 2000 (after 4 years, 52.7 months) and questioned about cardiac events.

For statistical analysis, independent samples were compared using the non-parametric Mann-Whitney U-test (significance $p < 0.05$). Nominal differences were analyzed by Fisher's Exact test because of the small number of values. The parameter free Spearman rank correlation test was used for assessment of correlations.

This study was approved by the local ethics committee and in accordance with the Declaration of Helsinki. All patients gave their informed consent.

Patients

A total of 45 patients (25 male and 20 female) were included in the study (14 type 1 diabetes (7 female, 7 male), 31 type 2 diabetes (13 female, 18 male)). At the beginning of the study age was 48 ± 9.8 yrs and 18–58 yrs, respectively. Duration of clinically manifest diabetes mellitus was 12.2 ± 9.7 yrs.

Treatment One patient was on a diet, 6 were receiving oral antidiabetic drugs, 28 patients were on insulin treatment, and 10 cases had insulin plus oral antidiabetic drugs.

Creatinine was normal in all cases (0.88 ± 0.89) with no difference between the groups.

Results

Of the 45 patients, 30 (67 %) had a clinically manifest somatic polyneuropathy with one sign and one symptom including abnormal thermal – or vibration perception [1]. MIBG-SPECT was abnormal in 28/45 cases (62 %) with dorso-septal lack of activity (CAN+) (Figs. 1 and 2). In this group 22/28 (79 %) had a clinically manifest somatic polyneuropathy (17 symmetrical, 5 asymmetrical). MIBG-SPECT was normal in 17 cases (38 % CAN–), 8/17 (47 %) had a polyneuropathy (7 symmetrical, 1 asymmetrical). Symptoms of autonomic dysfunction

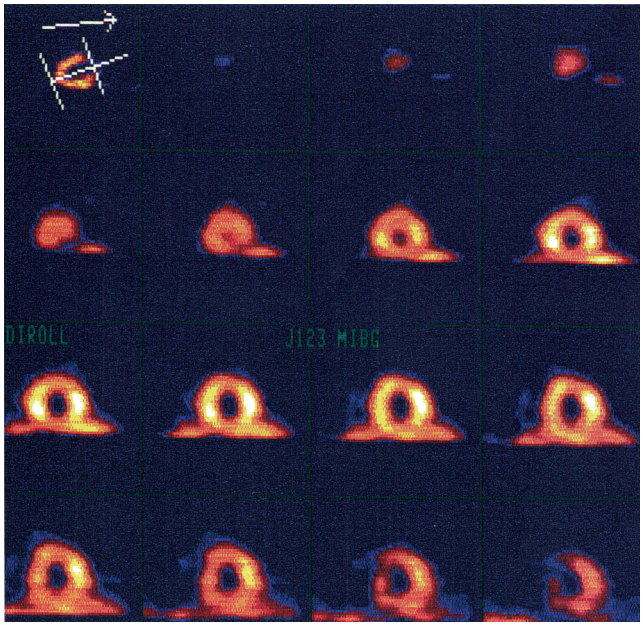

Fig. 1 Example of a normal MIBG-SPECT. Slices taken at right angles to and along the heart axis from the apex towards the heart base – showing homogeneous tracer uptake, circular structure: left ventricle.

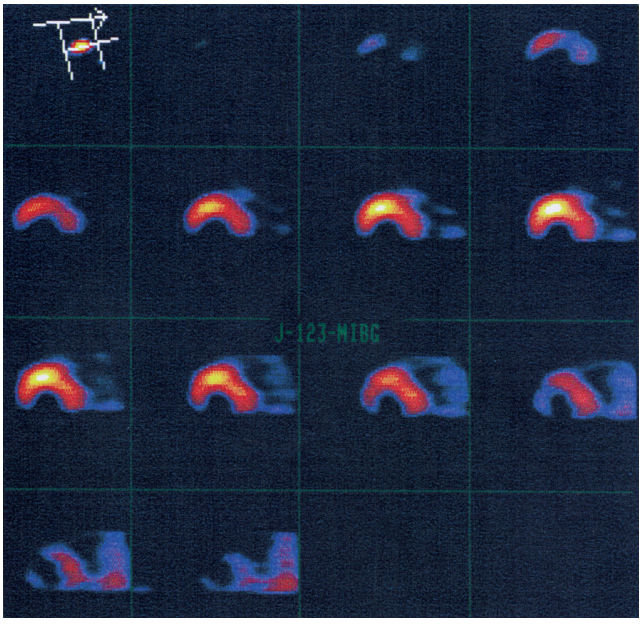

Fig. 2 Abnormal MIBG-SPECT with lack of activity in the dorso-septal heart muscle.

were mentioned by 9/45 patients (9 gustatory sweating, 8 constipation, and 8 men (32 %) erectile dysfunction). A significant correlation was seen between CAN and polyneuropathy as well as autonomic symptoms.

At least 2/5 RSA parameters were abnormal in 12 cases (6 female, 6 male, 4 type 1 diabetes, 8 type 2 diabetes). With regard to MIBG-SPECT, sensitivity of RSA was 29 % and specificity 94 % (Table 1).

RSA results showed a clear-cut correlation with CAN in accordance with MIBG-SPECT (Table 2). However, no significant difference was seen between CAN+ and CAN– patients for creatinin ($p = 0.1$), HbA1 ($p = 0.3$), or QTc length ($p = 0.2$).

Average QTc length was 419 ± 24 ms. In 9 cases QTc was abnormally prolonged (≥ 440 ms) with a mean of 447 ± 7 ms (4 female, 5 male, 1 type 1 diabetes, 8 type 2 diabetes). Of this group only 3 had abnormal RSA, and 4 had abnormal MIBG-SPECT. No correlation was seen between QTc length and abnormality in RSA or MIBG-SPECT. Furthermore, no correlation was seen between QTc and age, duration of diabetes, HbA1, clinically manifest polyneuropathy, or CAN ($p = 0.2$). However, a significant difference was found between men (408 ± 25 ms) and women (433 ± 14ms, $p = 0.003$).

Follow-up

All 45 patients were followed for 2 years. In this period no life-threatening cardiac arrhythmia, cardiac death, or death due to other reasons was registered. During the trial, HbA1 values improved as an indicator for good blood glucose control (overall HbA1 at entry 10.0 ± 3.1 %, after 12 months 9.0 ± 2.3 %, after 24 months 8.5 ± 2.1 %, $p < 0.01$).

Fifteen patients of the CAN + group (n = 28) were contactable after 4 years. No relevant cardiac arrhythmia or cardiac death had occurred.

Table 1 Fisher's Exact Test ($p = 0.017$)

	MIBG normal	MIBG abnormal	Σ
RSA normal	16	17	33
RSA abnormal	1	11	12
Total	**17**	**28**	**45**

Table 2 MIBG-SPECT versus heart rate abnormality and other parameters

	17 CAN– (MIBG normal)	28 CAN+ (MIBG abnormal)	U test P value
Age (yrs)	42 ± 11	51 ± 7	0.003
Duration of diabetes (yrs)	9 ± 9	14 ± 10	0.04
Duration of insulin (months)	69 ± 98	128 ± 145	0.6
HbA1 (%)	10.7 ± 3.8	9.6 ± 2.6	0.3
Blood glucose (mg/dl)	179 ± 73	200 ± 75	0.3
RSA E/I	1.25 ± 0.14	1.16 ± 0.18	0.01
MCR	47 ± 26	24 ± 21	0.006
SD	83 ± 43	54 ± 57	0.005
Vals	1.27 ± 0.13	1.17 ± 0.15	0.01
PI	1.28 ± 0.23	1.15 ± 0.17	0.008
QTc (ms)	426 ± 19	415 ± 26	0.21
Warm threshold (oC) right ankle	6.2 ± 2.0	8.0 ± 3.1	0.03
Cold threshold (oC) right ankle	6.2 ± 3.5	8.3 ± 4.4	0.06
Vibration perception right toe	3.2 ± 5.7	9.0 ± 8.9	< 0.001

Discussion

MIBG-SPECT is a sensitive indicator of sympathetic cardiac denervation. RSA tests are specific tests with regard to abnormal MIBG-SPECT.

QTc prolongation is a specific, albeit insensitive, indicator of diabetic autonomic failure [31]. Ward wrote that the corrected QTc value embodies complex influences [32]. In our study no prognostic significance of QTc prolongation was seen. However, the 2-year follow-up is too short and the number of patients with prolonged QTc too small to allow any valid conclusion on the effect of QTc prolongation on mortality. If cardiac ischemic disease is excluded, QTc length is not sensitive to sympathetic cardiac autonomic neuropathy defined by abnormal MIBG-SPECT. This is in accordance with other investigations. Schnell did not see a correlation between

QT length and MIBG uptake [6]. The lack of correlation between QT and MIBG was interpreted as meaning that these abnormalities are mediated by different mechanisms [28]. Thus, the increased mortality risk with QT prolongation was independent of the presence of autonomic diabetic neuropathy [24]. The discrepancy with regard to a correlation between RSA and QTc could well be a result of the definition of sympathetic cardiac autonomic neuropathy by MIBG-SPECT, which is a very sensitive technique even compared with RSA.

A gender difference – as in our study – was seen by others, with lower QTc sensitivity in women [31].

In the prospective study of O'Brien, 10 out of 84 diabetics with autonomic neuropathy had died after 2 years [17]. In another study, half of the patients with abnormal RSA and autonomic symptoms had died within two and a half years [8]. Therefore, it was likely that some patients of the CAN + group suffered relevant cardiac events during the 2–4 years' follow-up period. Cardiorespiratory death can be a result of dysrhythmia or breathing disturbances. Furthermore, sudden cardiac death in diabetic patients might be due to hypoglycemia [33]. In addition, a number of sudden and unexpected deaths occur for which no cause can be found [34]. The favorable course in our study is likely to be a result of both strict exclusion criteria, and good glycemic control, which is indicated by the reduction of HbA1 in all patients.

The positive outcome after 4 years could also be due to the fact that microvascular and other acute complications were partially prevented by good glycemic control [35, 36]. Cardiac autonomic innervation failure and left ventricular adrenergic denervation may be prevented by near-normoglycemic metabolic control [37, 38]. Schnell et al. showed in a prospective study that cardiac autonomic denervation with abnormal MIBG-SPECT can be partially reversible under intensified insulin treatment [39]. In addition, in another prospective observation with positron emission tomography, it was concluded from the results that sympathetic denervation can regress or progress in diabetic patients achieving good or poor glycemic control [40].

Furthermore, it has to be taken into consideration that other mortality risks are associated with autonomic neuropathy, such as nephropathy, cardiac myopathy, ischemic heart disease and stroke [17, 34, 41]. About half the deaths were attributable to renal failure [8, 17, 20]. Rossing and co-workers investigated 697 type 1 diabetics [42]. In the subgroup with macroalbuminuria, but not in all patients, QTc prolongation was an independent risk factor for cardiovascular mortality. However, patients with cardiac events in their history and those with abnormal ECG or renal insufficiency had been excluded from our own study. Thus, nephropathy or cardiac ischemia were unlikely causes of death in this group. This could well explain the difference to other publications, such as the cohort-based study of Veglio et al. [43]. There, QTc prolongation was a predictor of higher mortality. The authors concluded that the mechanisms linking QTc prolongation and excess mortality were probably complex and remain to be elucidated. In a metaanalysis of 17 studies [31], autonomic dysinnervation was found by reflex tests in 26 % of predominantly diabetes type 1 patients. Autonomic failure was 2.26 times more likely in patients with QTc prolongation. However, MIBG-SPECT had not been carried out and ischemic heart disease and cardiovascular medication had not been excluded in all studies included in this metaanalysis. In contrast, the patients in our own study were selected by normal ergometry, MIGB and MIBI-SPECT for exclusion of ischemic heart disease (only 45 of 255 patients were included).

Finally, one has to bear in mind the age of patients. The sensitivity of QTc is 3.9 times greater in patients aged 25 yrs. versus 55 yrs. [31]. Different age can partially explain differences of results between our study and other investigations. Thus, QTc might be a good test for autonomic failure in young men with diabetes.

Mortality is higher in CAN + patients than in diabetics with no cardiac autonomic neuropathy. It is, however, not clear whether cardiac autonomic neuropathy is the cause of death itself or whether it is an indicator of the progression of diabetes-associated complications. CAN + patients seem to have a better prognosis when diabetes mellitus is treated properly.

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