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Cardiac autonomic function in type 1 diabetic subjects with and without distal symmetric polyneuropathy

Abstract

Introduction. The aim of the study was evaluation of cardiovascular autonomic function, with standard cardiovascular Ewing's tests and baroreflex sensitivity (BRS) in type 1 diabetic subjects with and without sensorimotor distal symmetric polyneuropathy (DPN).

Material and methods. The examined group consisted of 39 patients with type 1 diabetes mellitus (mean age 30.5 ± 8.8 years; diabetes duration 12.1 ± 6.9 years; BMI 23.7 ± 2.8 kg/m²; HbA_{1c} $7.6 \pm 1.9\%$). The control group consisted of 18 healthy adults (mean age 31.4 ± 9.3 years; BMI 22.0 ± 3.3 kg/m²). Diagnosis of DPN was made, after neurological examination, in 16 diabetic subjects (41%). Noninvasive continuous monitoring of blood pressure (BP), heart rate and chest respiratory movements were applied (Portapres). Standard cardiovascular Ewing's tests were performed. BRS was assessed in lying (L-BRS) and

standing position (S-BRS) by frequency domain technique.

Results. Patients with DPN, in comparison to subjects without DPN, had significantly lower Valsalva ratio (1.5 ± 0.2 vs. 1.7 ± 0.3 , $P < 0.01$), lower increase of heart rate during handgrip exercise (7.0 ± 5.6 vs. 13.9 ± 8.5 bpm, $P < 0.01$), lower 30:15 ratio during tilt test (1.3 ± 0.2 vs. 1.5 ± 0.27 , $P < 0.05$) and lower S-BRS (4.9 ± 2.3 vs. 7.0 ± 2.5 ms/mm Hg, $P < 0.05$).

Conclusions. Relationship between DPN and cardiac autonomic dysfunction, diagnosed by standard cardiovascular tests and analysis of baroreflex sensitivity, indicates parallel development of both forms of diabetic neuropathy in the examined group of subjects with type 1 diabetes.

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key words: diabetic neuropathy, cardiovascular autonomic neuropathy, type 1 diabetes mellitus

Introduction

Diabetic neuropathy is the most frequent complication of diabetes [1]. Simple definition of diabetic peripheral neuropathy, useful in clinical practice describes it as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after

the exclusion of other causes" [2]. According to the classification proposed by American Diabetes Association, diabetic neuropathies are divided into two groups: generalized symmetric polyneuropathies and focal and multifocal neuropathies. Most common among generalized symmetric polyneuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and autonomic neuropathy [3]. The clinical features of distal sensory polyneuropathy are sensory deficits, like loss of feeling, or "positive symptoms", like paraesthesias, contact sensitivity or pain. Sensory deficits can lead to trauma and are thus the risk factors for diabetic foot and amputations [4]. Motor neuropathy presents with muscle weakness and atrophy [3, 4]. Autonomic neuropathy can involve the entire autonomic nervous sys-

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tem, and may be manifested by dysfunction of one or more organ systems — cardiovascular, gastrointestinal, genitourinary, sudomotor or ocular. Cardiovascular autonomic neuropathy (CAN) is the most clinically important form of autonomic neuropathy, because of its lifethreatening consequences and the availability of direct tests of cardiovascular autonomic function [5]. Clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, resting tachycardia, silent myocardial ischemia [4, 5]. Longitudinal studies have provided evidence for an increased mortality risk among diabetic individuals with CAN compared with individuals without CAN [6].

Clinical symptoms of CAN generally do not occur until long after the onset of diabetes [5]. Up to 50% cases of DPN may be also asymptomatic [3]. The absence of clinical symptoms does not exclude the existing dysfunction of peripheral nervous system, thus early diagnosis of both forms of neuropathy is necessary to prevent serious consequences of these complications [5, 7]. The diagnosis of DPN may be made by simple neurological examination. Physical or neurological examinations are ineffective for early detection of CAN, and therefore noninvasive cardiovascular test are required [3]. These tests must be rigorously standardized, require cooperation of examined subjects and are time-consuming. Spontaneous baroreflex sensitivity testing used to assess early stages of autonomic dysfunction is not available in most of diabetes centers [8, 9]. DPN, but not CAN, may be diagnosed in every physician's office. The question of relationship between both forms of neuropathy has not been still resolved [10–13].

The aim of our study was the evaluation of cardiac autonomic function by means of standard cardiovascular tests and baroreflex sensitivity, in patients with type 1 diabetes with and without distal symmetric sensorimotor polyneuropathy, diagnosed by neurological examination.

Materials and methods

We examined 39 patients with type 1 diabetes, 27 females (69.2%) and 12 males (30.8%), aged between 19 and 52 (mean 30.5 ± 8.8 years), diabetes duration 12.1 ± 6.9 years, mean HbA_{1c} $7.6 \pm 1.9\%$. Subjects were recruited from Diabetes Outpatient Clinic or from the Department of Endocrinology and Diabetology (University Hospital in Bydgoszcz). The control group consisted of 18 healthy subjects, 12 females (66.7%) and 6 males (33.3%), with fasting plasma glucose concentration below 100 mg/dL.

Subjects with arterial hypertension, symptoms of ischaemic heart disease, heart failure, renal failure and alcohol abuse were excluded from the study.

The characteristics of examined and control groups are shown in the Table 1.

The study protocol was approved by the local Ethics Committee and written informed consent was obtained from each subject.

Subjects with arterial hypertension, history or clinical symptoms of ischemic heart disease, heart failure, renal failure, supraventricular arrhythmia or alcohol abuse were excluded from the study.

Neurological examination was performed. Subjects were tested for distal symmetric sensorimotor polyneuropathy by examining pinprick, temperature, vibration perception (using 128-Hz tuning fork), 10-g monofilament pressure sensation in feet, and tendon reflexes (knee and ankle). DPN was diagnosed when at least two abnormalities were found.

The evaluation of cardiovascular autonomic function was performed in the morning, in a quiet room with the temperature controlled between 22 and 24°C. Subjects attended the laboratory at least 2 hours after a light breakfast, before which the usual morning insulin dose was injected. They were asked to avoid physical exercise, stress, alcohol, coffee and smoking for 12 hours before the study. Patients with hypoglycemia during last 24 hours were excluded from the study.

Table 1. Characteristics of examined and control group

Parameter	Examined group				Control group				P
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age (years)	30.5	8.8	19.0	52.0	31.4	9.3	20.0	55.0	NS
Height [cm]	170.3	8.7	155	191	170.9	9.2	158	188	NS
BMI [kg/m ²]	23.7	2.8	17.8	29.4	22.0	3.3	17.4	31.1	< 0.05
Diabetes duration (years)	12.1	6.9	1.0	27.0	–	–	–	–	–
HbA _{1c} (%)	7.6	1.9	5.1	13.3	–	–	–	–	–

After resting for 20 minutes subjects underwent continuous, beat-to-beat blood pressure, electrocardiogram (ECG) and chest respiratory movements recording. Blood pressure was non-invasively assessed by a volume-clamp technique (Portapres TNO-TPD Biomedical Instrumentation, Amsterdam, Netherlands). The accuracy of this technique was assessed in comparison with intra-arterial measurements [14]. The Portapres cuff was applied to the middle finger of nondominant arm. The height correction transducer was taped to the subject at the chosen reference level (anterior axillar line at the height of the lower end of the sternum) and the tube ending was fixed to the finger cuff. This height correction system eliminated the need of keeping the finger at the heart level to prevent the occurrence of hydrostatic height differences between the finger cuff and the heart [15]. Before each recording the Portapres was calibrated to obtain less than 5 mm Hg difference in comparison with sphygmomanometer measurement. Three surface electrodes were fitted to the chest to record ECG and respiratory activity. After ten minutes of familiarization data were collected.

Arterial pressure, ECG and respiratory activity were visually monitored, digitized at 300 samples/sec and stored onto the hard disk of a personal computer for off-line analysis.

Conventional cardiovascular tests, as described by Ewing [16], adapted to the use of Portapres device, were performed.

Deep breathing test — the patient breathed deeply, at rate of six breaths per minute.

The average heart rate difference (maximal minus minimal during the respiratory cycle) was calculated ($HR_{\max} - HR_{\min}$).

Valsalva maneuver — the patient blew into the empty barrel of a 20-ml syringe attached to a mercury sphygmomanometer to maintain a pressure of 40 mm Hg for 10 sec. The ratio between the longest R-R interval after Valsalva maneuver (compensatory bradycardia) and the shortest during blowing was calculated (Valsalva ratio – $V_{\max/\min}$).

Postural reflexes — the patient was lying down for 10 minutes and then stood to a full upright position. The ratio of the longest ECG R-R interval (found about the 30th beat after standing) to the shortest R-R interval (found about 15th beat after standing) was calculated (30:15 ratio). The difference between systolic blood pressure in lying position and two minutes after standing (Δ SBP) was calculated.

Handgrip test — the patient squeezed hand dynamometer to isometric maximum and then held at 30% of maximum for 5 minutes. The difference between diastolic blood pressure at the end and before the test (Δ DBP) was calculated. Additionally we measured the difference between heart rate at the end and before the test (Δ HR).

Baroreflex sensitivity was assessed by a frequency-domain approach. This methodology have been described by others in detail [17, 18]. Briefly, the analysis in frequency domain was performed by splitting systolic blood pressure (SBP) and R-R interval signals into consecutive segments of 512 beats and by removing the segments containing nonstationarities. In the segments in which around 0.1 Hz SBP and R-R interval powers had a coherence > 0.5, the squared ratio between the powers of corresponding spectral components of R-R interval and SBP variabilities was computed. This provided the α -coefficient used as index of baroreflex sensitivity. Two stationary 5-minute fragments, in lying and standing position (since 5th minute after standing up), were taken for BRS analysis (L-BRS and S-BRS, respectively).

Statistical analysis

Results are expressed as mean \pm SD. Between-group comparisons were made using Student's unpaired *t*-test (after testing for normality using the Shapiro-Wilk test). For variables which did not meet the normality criteria, the Mann-Whitney U-test was used. A *P* value of less than 0.05 was regarded as statistically significant.

Results

The results of all cardiovascular tests in examined and control groups were in normal ranges. In diabetic patients, however, 30:15 ratio was significantly lower (Table 2). Baroreflex sensitivity in supine position was also lower in the examined group of diabetics in comparison with control group (Figure 1).

In 16 diabetic patients (41%) distal symmetric sensorimotor polyneuropathy was diagnosed. In the control group there were no cases of DPN.

There were no significant differences between diabetic patients with and without DPN in age, height, BMI and HbA_{1c} level. Only diabetes duration was significantly longer in the group of subjects with DPN (Table 3).

Patients with DPN, in comparison with those without DPN, had significantly lower Valsalva ratio, lower heart rate increase during sustained handgrip and lower 30:15 ratio (Table 4).

In this group we found also significantly decreased S-BRS (Figure 2).

Discussion

The relationship between distal symmetric sensorimotor polyneuropathy and cardiovascular autonomic

Table 2. Mean values of results of cardiovascular tests in examined and control group ($HR_{max} - HR_{min}$ — the average heart rate difference during deep breathing test; $V_{max/min}$ — the ratio between the longest ECG R-R interval after Valsalva maneuver and the shortest during the procedure; ΔdBP — the difference between diastolic blood pressure at the end and before handgrip; $HR_n - HR_s$ — the increase of heart rate during handgrip; 30:15 — the ratio of the longest ECG R-R interval (found about the 30th beat after standing) to the shortest R-R interval (found about 15th beat after standing) ΔsBP — the difference between systolic blood pressure in lying position and two minutes after standing)

Parameter	Examined group		Control group		P
	Mean	SD	Mean	SD	
($HR_{max} - HR_{min}$) [beats/min]	26.5	10.0	26.5	6.3	NS
$V_{max/min}$	1.65	0.26	1.54	0.32	NS
ΔdBP [mm Hg]	19.6	10.9	24.8	15.7	NS
$HR_n - HR_s$ [beats/min]	11.1	8.2	13.2	8.7	NS
30:15 ratio	1.44	0.3	1.61	0.2	< 0.05
ΔsBP [mm Hg]	15.9	9.7	16.4	11.8	NS

Table 3. Characteristics of examined group in relation to the presence of distal symmetric polyneuropathy

Parameter	Distal symmetric polyneuropathy						P
	Absent			Present			
	n	Mean	SD	n	Mean	SD	
Age (years)	23	29.2	8.4	16	32.4	9.4	NS
Height [cm]	23	171.2	9.8	16	169.6	7.84	NS
BMI [kg/m^2]	23	23.6	2.5	16	23.9	3.3	NS
Diabetes duration (years)	23	9.5	6.0	16	15.7	6.6	< 0.01
HbA _{1c} (%)	23	7.7	1.9	16	7.3	1.9	NS

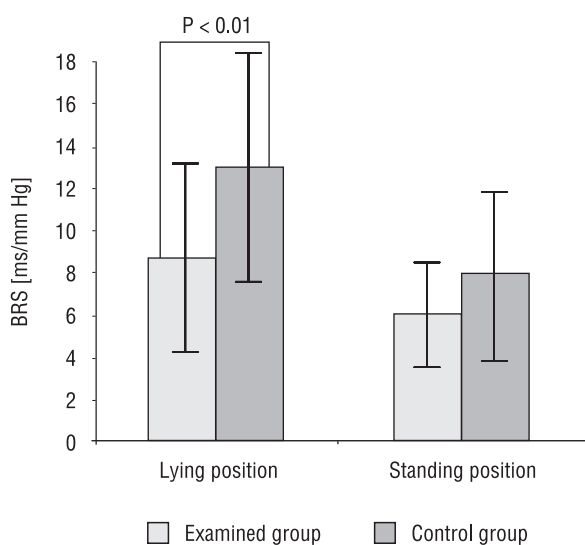


Figure 1. Mean values of baroreflex sensitivity (BRS) in supine and standing position in examined and control group

neuropathy is not well established. Some authors confirm the coexistence of both forms of polyneuropathy

[11, 19, 20], but results of others' investigations indicate independent development of CAN and DPN [10, 13]. These differences depend on the cohort studied, different methods of assessment and diagnostic criteria used. For example DPN was diagnosed by means of neurological examination [10, 20] and by electrophysiological study, as well [11, 13].

In our study neurological examination was used to diagnose DPN. We choose this simple, available for all practitioners method, intentionally. According to ADA recommendations all patients with diabetes should be screened annually for DPN by examining pinprick, temperature, vibration perception and 10-g monofilament pressure sensation at the distal halluces and ankle reflexes. Combinations of more than one test have > 87% sensitivity in detecting DPN [3].

In our study, results of standard cardiovascular tests and BRS assessment, suggest the impaired cardiac autonomic function in examined patients with type 1 diabetes and distal symmetric sensorimotor polyneuropathy in comparison with diabetic subjects without this complication.

Significantly lower Valsalva and 30:15 ratio, lower heart rate increase during handgrip confirm parasym-

Table 4. Results of cardiovascular tests in diabetic patients with and without distal symmetric polyneuropathy ($HR_{max} - HR_{min}$ — the average heart rate difference during deep breathing test; $V_{max/min}$ — the ratio between the longest ECG R-R interval after Valsalva maneuver and the shortest during the procedure; Δ dBp — the difference between diastolic blood pressure at the end and before handgrip; $HR_n - HR_s$ — the increase of heart rate during handgrip; 30:15 — the ratio of the longest ECG R-R interval (found about the 30th beat after standing) to the shortest R-R interval (found about 15th beat after standing); Δ sBP — the difference between systolic blood pressure in lying position and two minutes after standing)

Parameter	Distal symmetric polyneuropathy						P
	Absent			Present			
	n	Mean	SD	n	Mean	SD	
$HR_{max} - HR_{min}$ [beats/min]	23	27.9	8.1	16	24.6	12.3	NS
$V_{max/min}$	23	1.7	0.3	15	1.5	0.2	< 0.01
Δ dBp [mm Hg]	23	21.7	11.2	16	16.4	10.1	NS
$HR_n - HR_s$ [beats/min]	23	13.9	8.5	16	7.0	5.6	< 0.01
30:15 ratio	23	1.5	0.27	16	1.3	0.2	< 0.05
Δ sBP [mm Hg]	23	16.1	9.1	16	15.7	10.8	NS

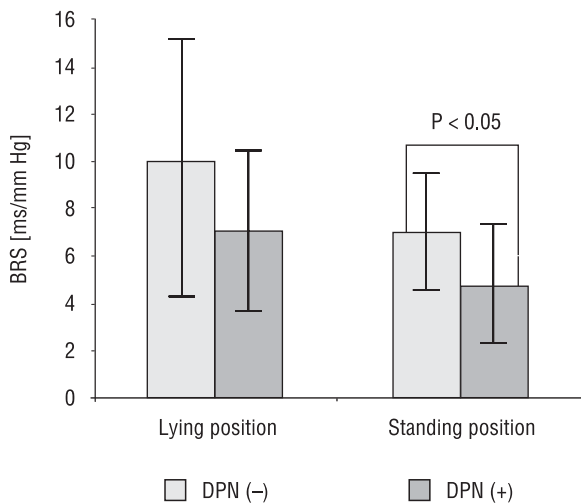


Figure 2. Mean values of baroreflex sensitivity (BRS) in supine and standing position in diabetic subjects with and without distal symmetric polyneuropathy (DPN)

pathetic and sympathetic dysfunction, and worse cardiovascular system adaptation to imposed conditions in patients with DPN.

In most studies cardiovascular autonomic function was assessed by standard tests. Our results are similar to those obtained by Luch et al. [11]. They found lower Valsalva and 30:15 ratio in patients with type 1 diabetes and peripheral neuropathy in comparison with patients without peripheral neuropathy. In this work also heart rate variation in deep breathing test was diminished in subjects with peripheral neuropathy.

This complication was diagnosed not only by clinical examination, but also by electromyography and quantifying nerve conduction velocity.

In another study, patients with DPN, diagnosed by means of electrophysiology testing, had lower $HR_{15} - HR_{30}$ difference (the difference between heart rate about 30th and 15th second after standing) and lower heart rate variability during deep breathing test, in comparison with subjects without DPN. In this study patients with both types of diabetes (type 1 and type 2) were included and authors did not provide the separate characteristics of subjects with type 1 diabetes. Besides, examined patients were older (mean age 44.3 years) and had worse glycemic control (mean HbA_{1c} 9.29%) than our subjects [19].

The results of EURODIAB Prospective Complications Study also confirm the relationship between CAN and DPN in subjects with type 1 diabetes. During this study 17% of subjects developed cardiovascular autonomic neuropathy, diagnosed by orthostatic measurements (blood pressure and heart rate variability during standing). In this study, in multivariate analysis, distal symmetric sensorimotor polyneuropathy was an independent factor for development of autonomic neuropathy [20].

In the study conducted in the group of 506 insulin treated diabetics, CAN was confirmed in 16.6%, and DPN in 23% of subjects. The frequency of DPN, but not CAN, increased with age. In subjects with diabetes duration under 10 years the frequency of both forms of neuropathy was the same. In subjects with diabetes duration above 20 years DPN was more frequent than autonomic neuropathy (42 vs. 31%). This can be explained by difficulties in cooperation, proper performance and interpretation of cardiovascular tests in older patients. Authors suggest that it can not be excluded, that lower frequency of CAN in older patients is due to lower survival rate of patients with CAN diagnosed in young age [10].

The results of Töyry et al. study indicate entirely independent development of both forms of neuropathy in patients with type 2 diabetes. The frequency of CAN was not different in two groups of subjects, with and without DPN, diagnosed by means of neurological examination and electrophysiology testing [13]. To explain these results authors suggest different pathogenesis of both forms of neuropathy. Probably hyperglycemia is not the only factor involved in the pathogenesis of autonomic neuropathy. The contribution of other — immunologic, inflammatory and growth factors is considered. The coincidence of severe cardiovascular autonomic neuropathy and iritis, autoimmune condition, described by Guy was the first report taking into account the possible influence of immunological factors on CAN development [21]. In subjects with type 1 diabetes and symptomatic CAN, autoantibodies directed against structures of the autonomic nervous system (vagus nerve, sympathetic ganglion and adrenal medulla) are more frequent than in the group of diabetics without CAN [22, 23]. In the prospective study Granberg et al. showed, that the presence of these autoantibodies can predict the development of cardiovascular autonomic neuropathy in the future [24]. In addition, the relationship between autoantibodies and DPN was not confirmed in patients with type 1 diabetes [25]. This evidence indicates, that besides hyperglycemia, other factors are responsible for development of autonomic neuropathy. It also explains, why DPN and CAN may develop independently.

In this work, in the evaluation of cardiovascular autonomic function we also used baroreflex sensitivity assessment. Traditionally BRS is assessed by measuring the changes in R-R interval produced in reflex to pharmacologically induced changes in blood pressure [26]. Non-invasive beat-to-beat blood pressure measurement, applied in our study, allows to assess the relationship between spontaneous changes in blood pressure and pulse interval. Baroreflex — mediated bradycardia seems to be impaired in diabetic subjects relatively early, before apparent abnormalities in standard cardiovascular tests can be detected [9, 27, 28]. Our results indicate, that it is impaired also in patients with diabetes and DPN.

Meijer et al. evaluated the coexistence of autonomic neuropathy, assessed by baroreflex sensitivity in supine position, and distal symmetric polyneuropathy, diagnosed by the use of scales based on symptoms and neurological examination. This study was conducted in the group of patients with DPN and foot ulcers. In this study BRS below 3 ms/mm Hg was regarded as abnormal [12]. It was the same value that was proved to be a marker of sudden death in patients with heart failure and after myocardial infarction [29, 30]. In diabetic pa-

tients the prognostic value of BRS has not been established and normal ranges of BRS has not been determined. In Meijer study 52% of patients with DPN had BRS below 3 ms/mm Hg. On the other hand, the rest of examined patients (48%) with evident, complicated by foot ulcer, polyneuropathy had BRS regarded as normal. These results confirm the hypothesis about independent development of sensorimotor and autonomic neuropathy.

Our patients had less advanced distal sensorimotor polyneuropathy and none of them had neuropathic ulcer. We did not find BRS below 3 ms/mm Hg (in the group with DPN all values were above 4 ms/mmHg and mean BRS in supine position was 7.1 ms/mm Hg — Figure 1). However, in standing position, BRS was significantly lower in the group with distal sensorimotor polyneuropathy. This reflects impaired baroreflex-mediated bradycardia and confirms the defect in the activation of central parasympathetic pathways in patients with DPN.

Conclusions

The relationship between DPN and cardiac autonomic dysfunction, diagnosed by cardiovascular tests and analysis of baroreflex sensitivity, confirms parallel development of both forms of diabetic neuropathy in the examined group of type 1 diabetic subjects. The possibility of autonomic neuropathy should be considered in each subject with diabetic sensorimotor polyneuropathy.

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