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# Spontaneous baroreflex sensitivity in subjects with type 1 diabetes with and without cardiovascular autonomic neuropathy

## Wrażliwość odruchów baroreceptorów tętniczych u chorych na cukrzycę typu 1 w zależności od obecności neuropatii autonomicznej sercowo-naczyniowej

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## Abstract

**Introduction:** The clinical usefulness of baroreflex sensitivity (BRS) in the early detection of autonomic dysfunction in patients with diabetes is not well established. The aim of the study was the evaluation of BRS in subjects with type 1 diabetes with and without cardiovascular autonomic neuropathy (CAN).

**Material and methods:** The group examined consisted of 39 patients with type 1 diabetes (mean age 30.5 ± 8.8 years; diabetes duration 12.1 ± 6.9 years; BMI 23.7 ± 2.8 kg/m$^2$; $HbA_{1c}$ 7.6 ± 1.9%). The control group consisted of 18 sex and age–matched healthy adults. Blood pressure, heart rate and chest respiratory movements were monitored continuously by non-invasive means (Portapres). In order to recognise CAN standard Ewing tests were performed. BRS was assessed in the lying (L-BRS) and standing (S-BRS) positions by the frequency domain technique.

**Results:** Ten patients (25.6%) had CAN (the CAN(+) group). In the CAN(+) group BRS was significantly lower than in the CAN(–) group in the lying and standing positions (respectively L-BRS 4.4 ± 2.1 *vs.* 10.0 ± 4.9 ms/mm Hg; $p < 0.05$; S-BRS 3.3 ± 1.6 *vs.* 7.0 ± 2.2 ms/mm Hg $p < 0.001$). BRS did not differ significantly between the CAN(–) and control group (respectively L-BRS 10.0 ± 4.9 *vs.* 13.1 ± 5.5 ms/mm Hg p=NS; S-BRS 7.0 ± 2.2 *vs.* 7.9 ± 4.0 ms/mm Hg p = NS).

**Conclusions:** BRS differentiated well the subjects with CAN from the group without CAN. However, the study did not enable us to confirm the value of BRS in the early detection of autonomic dysfunction among patients with type 1 diabetes who showed no abnormalities in standard cardiovascular tests. **(Pol J Endocrinol 2008; 59 (5): 398–402)**

***Key words:*** *baroreflex sensitivity, diabetes type 1, cardiovascular autonomic neuropathy*

## Streszczenie

**Wstęp:** Przydatność kliniczna oceny wrażliwości odruchu z baroreceptorów tętniczych (BRS, *baroreflex sensitivity*) we wczesnym rozpoznawaniu dysfunkcji układu autonomicznego u chorych z cukrzycą nie jest do końca ustalona. Celem pracy była ocena BRS w grupie chorych z cukrzycą typu 1 w zależności od obecności neuropatii autonomicznej sercowo-naczyniowej (CAN) rozpoznanej na podstawie klasycznych testów sercowo-naczyniowych.

**Materiał i metody:** Grupę badaną stanowiło 39 chorych z cukrzycą typu 1 (śr. wiek 30,5 ± 8,8 lat; czas trwania cukrzycy 12,1 ± 6,9 lat; BMI 23,7 ± 2,8 kg/m$^2$; $HbA_{1c}$ 7,6 ± 1,9%). Grupę kontrolną stanowiło 18 zdrowych osób dobranych pod względem płci i wieku. W badaniu wykorzystano nieinwazyjny ciągły pomiar ciśnienia tętniczego (Portapress) z równoczesną rejestracją EKG i ruchów oddechowych klatki piersiowej. W celu rozpoznania neuropatii sercowo-naczyniowej przeprowadzono testy Ewinga. Wrażliwość odruchu baroreceptorów obliczono metodą analizy widmowej, w pozycji leżącej (L-BRS) i stojącej (S-BRS).

**Wyniki:** Neuropatię autonomiczną sercowo-naczyniową rozpoznano u 25,6% chorych z cukrzycą typu 1 (grupa CAN(+)). Osoby te charakteryzowały się istotnie niższymi wartościami L-BRS i S-BRS w porównaniu z chorymi bez CAN (grupa CAN(–) (odpowiednio: L-BRS 4,4 ± 2,1 *vs.* 10,0 ± 4,9 ms/mm Hg, $p < 0,05$; S-BRS 3,3 ± 1,6 *vs.* 7,0 ± 2,2 ms/mm Hg, $p < 0,001$). Nie stwierdzono istotnych statystycznie różnic w BRS w grupie CAN(–) i w grupie kontrolnej (odpowiednio: L-BRS 10,0 ± 4,9 *vs.*13,1 ± 5,5 ms/mm Hg, p=NS; S-BRS 7,0 ± 2,2 *vs.* 7,9 ± 4,0 ms/mm Hg, p = NS).

**Wnioski:** Wrażliwość odruchu baroreceptorów różnicowała dobrze chorych z cukrzycą i CAN od chorych bez tego powikłania. W badaniu nie potwierdzono jednak znaczenia oceny BRS we wczesnym wykrywaniu zaburzeń w funkcjonowaniu układu autonomicznego serca u chorych z cukrzycą typu 1 i prawidłowymi wynikami klasycznych testów sercowo-naczyniowych. **(Endokrynol Pol 2008; 59 (5): 398–402)**

***Słowa kluczowe:*** *wrażliwość odruchu z baroreceptorów tętniczych, cukrzyca typu 1, neuropatia autonomiczna sercowo-naczyniowa*

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## Introduction

Cardiovascular autonomic neuropathy (CAN) is a common but probably very often overlooked complication of diabetes [1]. The reported prevalence of CAN varies depending on the patient cohort studied, the testing modalities selected and the criteria used to define CAN. On the basis of the EURODIAB IDDM Complications Study CAN was clinically identified in 36% of patients with type 1 diabetes [2]. Prospective studies have documented an increased risk of mortality among subjects with CAN, compared to individuals without CAN [3–5]. This increased mortality has been attributed to an increased incidence of silent myocardial infarction, risk of sudden cardiac death and cardiovascular disease [5]. Since autonomic neuropathy is associated with increased mortality, early detection of this complication is essential.

Symptoms of CAN are often non-specific and should not be considered markers of its presence [6, 7]. Cardiovascular autonomic neuropathy is usually examined indirectly using cardiovascular reflex tests. It is generally accepted that the diagnosis of CAN should be based on the results of a battery of autonomic tests. The consensus statement of the San Antonio Conference held in 1988 recommended the battery of five cardiovascular reflex tests proposed by Ewing and Clarke for diagnosing CAN [8, 9]. These tests are still recommended for the routine screening and monitoring of the progression of CAN [10].

Cardiovascular autonomic function tests, although useful in clinical practice, have some limitations. These tests must be rigorously standardised, require the cooperation of the patients examined and are time-consuming. More simple and reliable methods of detecting and quantifying cardiovascular dysfunction are of clinical interest. Power spectral analysis of heart rate variability has been reported to provide useful information on autonomic function in diabetic patients [11–13]. With improved technology spontaneous baroreceptor cardiac reflex sensitivity, otherwise known as baroreflex sensitivity (BRS), is used to assess autonomic function in diabetic patients. Traditionally BRS has been assessed by measuring the changes in the RR interval produced in reflex to pharmacologically-induced changes in blood pressure [14]. Non-invasive beat-to-beat blood pressure measurement allows assessment to be made of the relationship between spontaneous changes in blood pressure and pulse interval in the time and frequency domain. Baroreflex-mediated bradycardia seems to be impaired in diabetic subjects relatively early, before apparent abnormalities in standard cardiovascular tests can be detected [15–17]. On the other hand, it was found that the BRS in diabetics with pathological Ewing scores did not differ from the BRS in healthy subjects [18].

The aim of this study was to evaluate BRS by power spectral analysis in diabetic subjects with and without CAN as recognised by standard cardiovascular reflex tests.

## Material and methods

We studied 39 patients with type 1 diabetes, 27 women (69.2%) and 12 men (30.8%) aged between 19 and 52 (mean ± SD 30.5 ± 8.8) years. Patients were recruited from the Department of Endocrinology and Diabetology of the Nicolaus Copernicus University. Patients with arterial hypertension or a history or clinical manifestation of cardiovascular disease, renal failure or alcohol abuse were excluded from the study. Diabetic complications were found in 22 patients. In 16 patients (41%) we found sensorimotor distal symmetric polyneuropathy, in 10 (25.5%) retinopathy and in 7 subjects (17.9%) microalbuminuria. All patients were on intensive insulin therapy. The control group consisted of 18 healthy non-diabetic volunteers who were matched by age and sex. The characteristics of both groups are shown in Table I.

The study protocol was approved by the local Ethics Committee and written informed consent was obtained from each subject. The study was performed in the morning, in a quiet room with the temperature controlled between 22 and 24°C. Subjects attended the laboratory at least two hours after a light breakfast, before which the usual morning insulin dose had been injected. They were asked to avoid physical exercise, stress, alcohol, coffee and smoking for 12 hours before

**Table I.** *The characteristics of the diabetic and control subjects*

**Tabela I.** *Charakterystyka grupy chorych na cukrzycę i grupy kontrolnej*

| | Diabetic patients n=39 | Control subjects n=18 | p |
|---|---|---|---|
| Male/female | 27/12 | 12/6 | – |
| Age (years) | 30.5±8.8 | 31.4± 9.3 | NS |
| Height [cm] | 170.3±8.7 | 170.9± 9.2 | NS |
| Weight [kg] | 69.3±12.9 | 64.7± 13.7 | NS |
| BMI [kg/m$^2$] | 23.7±2.8 | 22.0± 3.32 | < 0.05 |
| Diabetes duration [years] | 12.1±6.9 | – | – |
| $HbA_{1c}$ (%) | 7.6±1.9 | – | – |
| SBP [mm Hg] | 111.4±18.5 | 112.7±8.4 | NS |
| DBP [mm Hg] | 61.9±11.4 | 61.0±10.0 | NS |

Data are shown as mean values ± SD; n — the number of subjects in a given condition; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure (average values of the 1 min recording by Portapres in the sitting position)

the study. Diabetic patients with hypoglycaemia during the previous 24 hours were excluded from the study.

### *The assessment of baroreflex sensitivity*

After resting for 20 minutes subjects underwent continuous recording of beat-to-beat blood pressure, ECG and chest respiratory movements. 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 [19]. The Portapres cuff was applied to the middle finger of the non-dominant arm. The height correction transducer was taped to the subject at the chosen reference level, namely the 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 to keep the finger at heart level to prevent the occurrence of hydrostatic height differences between the finger cuff and the heart [20]. 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 familiarisation the data were collected.

Data collection consisted of 15 minutes of continuous recordings with the subject in the sitting, supine and standing position. Two stationary 5-minute fragments (in the supine and standing positions) were taken for BRS analysis. Mean systolic and diastolic blood pressure were evaluated on the basis of a one-minute recording in the sitting position. Arterial pressure, ECG and respiratory activity were visually monitored, digitised at 300 samples per second and stored onto the hard disk of a personal computer for offline analysis. Baroreflex sensitivity was assessed by a frequency-domain approach. This methodology has been described in detail by others [21, 22]. Briefly, the analysis in the frequency domain was performed by splitting systolic blood pressure (SBP) and RR interval signals into consecutive segments of 512 beats and by removing the segments containing non-stationarities. In the segments in which around 0.1 Hz SBP and RR interval powers had a coherence > 0.5 the squared ratio between the powers of corresponding spectral components of the RR interval and the SBP variabilities was computed. This provided the á-coefficient used as an index of baroreflex sensitivity.

### *Traditional evaluation of autonomic neuropathy (CAN)*

The presence of autonomic neuropathy was assessed by conventional tests as described by Ewing: deep breathing, Valsalva manoeuvre, handgrip and standing. These were adapted to the use of the Portapres device. For each test we used the normative values provided by Ewing. The results were classified as normal, borderline or abnormal [8]. After Bellavere, a normal response was graded as 0, a borderline as 1 and an abnormal response as 2 points. Subjects with a total score equal to or greater than 2 points were regarded as having CAN [11].

### *Statistical analysis*

The results are expressed as mean ± SD. Between-group comparisons were made using Student's unpaired *t*-test (after testing for normality using the Shapiro-Wilk test). For multiple comparisons variance analysis was applied. A $p$ value of less than 0.05 was regarded as statistically significant.

## Results

The mean values of all Ewing's tests were within the normal ranges in the examined and control groups, although the 30:15 ratio while standing up was significantly lower in the diabetic patients (Table II). In diabetic patients pathological and borderline responses were observed in the handgrip test in 23.1% and 10.3 % subjects respectively. Two subjects (5.1%) had pathological and one (2.6%) had borderline results in the deep breathing test. The Valsalva ratio was abnormal in two patients (5.1%).

Ten diabetic patients (25.6%) had a total score between 2 and 4 points and these were classified as ha-

**Table II.** *Mean values of Ewing's tests in the examined and control groups*

**Tabela II.** *Średnie wartości parametrów mierzonych w testach Ewinga w grupie badanej i kontrolnej*

| Test | Diabetic patients | Control subjects | p |
|---|---|---|---|
| Deep breathing ($HR_{max}$–$HR_{min}$) [beats/min] | 26.5 ± 10.0 | 26.5 ± 6.3 | NS |
| Valsalva ratio ($V_{max/min}$) | 1.65 ± 0.26 | 1.54 ± 0.32 | NS |
| Standing (30:15 ratio) | 1.44 ± 0.3 | 1.61 ± 0.2 | < 0.05 |
| Standing (ΔSBP) [mm Hg] | 15.9 ± 9.7 | 16.4 ± 11.8 | NS |
| Handgrip (ΔDBP) [mm Hg] | 19.6 ± 10.9 | 24.8 ± 15.7 | NS |

Data are shown as mean values ± SD; $HR_{max}$–$HR_{min}$ — the increase of heart rate during the deep breathing test; $V_{max/min}$ — the ratio between the longest RR interval after the Valsalva manoeuvre and the shortest during the procedure; 30:15 — the ratio between the longest RR interval around the 30th heart beat and the shortest around the 15th heart beat after standing; ΔSBP — the difference between systolic blood pressure 1–2 min. after standing up and systolic blood pressure in the supine position; ΔDBP — the increase in diastolic blood pressure during the handgrip test

**Table III.** *The characteristics of the diabetic subjects with (CAN(+)) and without (CAN(–)) cardiovascular autonomic neuropathy in comparison with control subjects*

**Tabela III.** *Charakterystyka grupy chorych na cukrzycę w zależności odobecności neuropatii autonomicznej sercowo-naczyniowej (CAN(+) i CAN(–)) w porównaniu z grupą kontrolną*

| | CAN(+) n = 10 | CAN(–) n = 29 | Control subjects n = 18 |
|---|---|---|---|
| Male/female | 3/7 | 9/20 | 6/12 |
| Age [years] | 28.8 ± 7.0 | 30.5 ± 7.0 | 31.4 ± 9.3 |
| Diabetes duration [years] | 14.6 ± 8.6 | 11.2 ± 6.2 | – |
| Height [cm] | 172.1 ± 9.6 | 169.7 ± 8.5 | 170.9 ± 9.2 |
| Weight [kg] | 68.9 ± 16.6 | 69.4 ± 11.8 | 64.7 ± 13.7 |
| BMI [kg/m$^2$] | 22.9 ± 3.2 | 24.0$^a$ ± 2.6 | 22.0$^a$ ± 3.3 |
| $HbA_{1c}$ [%] | 7.8 ± 2.3 | 7.5 ± 1.8 | – |
| SBP [mm Hg] | 112.1 ± 17.2 | 111.1 ± 19.2 | 112.7 ± 8.7 |
| DBP [mm Hg] | 63.0 ± 10.4 | 61.5 ± 11.9 | 61.0 ± 10.0 |

Data are shown as mean values ± SD; n — the number of subjects in a given condition; BMI — body mass index; P — systolic blood pressure; P — diastolic blood pressure (average values of the 1 min recording by Portapres in the sitting position), $^a$ < 0.05

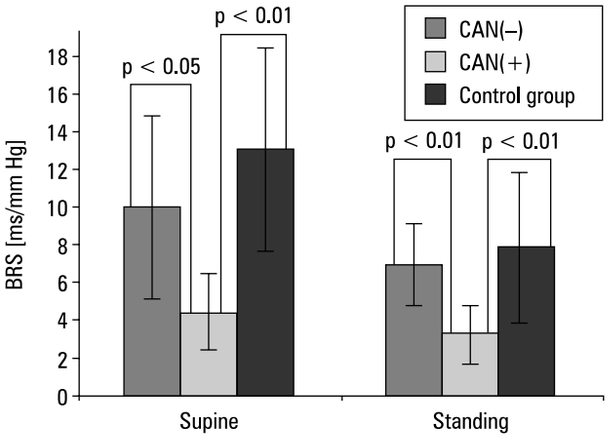


**Figure 1.** *BRS in the supine and standing positions in the CAN(+) and CAN(–) groups in comparison with the control subjects*

**Rycina 1.** *BRS w pozycji leżącej i po pionizacji u chorych na cukrzycę CAN(+) i CAN(–) w porównaniu z osobami z grupy kontrolnej*

ving CAN (the CAN(+) group). In the control group borderline responses in the handgrip test were observed in 38.1% subjects. None of the healthy subjects exhibited a pathological score. The characteristics of the CAN(+) and CAN(–) groups in comparison with the control group are shown in Table III. In the CAN(+) group BRS was significantly lower in the supine and standing positions than in the CAN(–) group and control subjects. There were no significant differences in BRS in either position between the CAN(–) group and healthy controls (Fig. 1).

## Discussion

Arterial baroreceptors play an important role in the short-term regulation of arterial pressure. They are stretch receptors that respond to arterial distension determined by intravascular pressure. Baroreceptors convey impulses to the nucleus tractus solitarius in the brain stem. Afferent stimuli from baroreceptors are transmitted via the vagus nerve (to form the carotid sinus receptors) and via nerve fibres that join the glossopharyngeal nerve (to form the aortic arch baroreceptors) and finally reach the vagal nucleus. Vagal stimuli decrease the heart rate. Nucleus tractus solitarius also inhibits sympathetic centres, resulting in vasodilatation and a reduction in the sympathetic stimulation of the heart [23]. Impaired baroreceptor function in diabetes is probably due to both structural and functional changes in the neural pathways of the baroreflex arch [16, 24].

Our study was an attempt to determine the value of BRS in the early detection of CAN in patients with type 1 diabetes. In our study all three groups of subjects, namely CAN(+), CAN(–) and controls, were comparable in age and blood pressure. The CAN(+) and CAN(–) groups were also comparable in diabetes duration, glycaemic control ($HbA_{1c}$) and BMI. BRS differentiated well the CAN(+) group from the CAN(–) group. We did not, however, find any differences in BRS between diabetic patients without CAN and the control group.

There are discrepancies between our results and those of the study by Frattola et al. [15]. In this study BRS was significantly lower in the group of diabetic patients with no abnormalities in standard cardiovascular tests than in healthy subjects. In Frattola's study the group of diabetics consisted of insulin-dependent and non-insulin-dependent subjects. We wanted to assess cardiac autonomic function in a homogenous group of diabetics and so recruited only patients with type 1 diabetes. The differences in characteristics of the groups studied make the results obtained in the two studies difficult to compare. However, a group of type 1 diabetic patients without microvascular complications similar to ours was studied by Weston et al. [16]. In this group, who did not give evidence of CAN in standard cardiovascular tests, BRS was significantly reduced in the supine and standing positions in comparison with controls.

The results obtained by Frattola and Weston [15, 16], which contrast with our own, indicate that estimation of baroreflex cardiac modulation by joint analysis of blood pressure and RR interval fluctuations is more sensi-

tive in detecting cardiac autonomic dysfunction than traditional autonomic tests. In the study by Frattola et al. BRS was also more sensitive in detecting autonomic neuropathy than quantification of RR interval variability [15]. On the other hand, Ducher et al. showed in a small study of 13 diabetic patients that BRS did not differ in 5 diabetic patients with pathological Ewing scores compared to the remaining diabetic patients and to healthy subjects. In Ducher's study pathological or borderline responses were also observed in healthy subjects. None of these subjects, however, exhibited a pathological score [18]. Similarly, in our study borderline results of the handgrip test were found in the control group, and the total score did not enable CAN to be diagnosed either.

Variations in the results of cardiovascular autonomic tests conducted on healthy subjects confirm that these results depend on the co-operation of the subjects. The presence of peripheral sensory neuropathy may also influence the results, particularly those of the handgrip test. Ducher's study indicates that in asymptomatic patients the results of cardiovascular autonomic tests may not reflect alterations in cardiac autonomic function. The author suggests that the results obtained by both Ewing's tests and the assessment of BRS be compared before a diagnosis of CAN is established [18].

Cardiovascular autonomic function tests are still recommended in the diagnosis of CAN [10]. These tests have a prognostic value. It has been demonstrated that abnormalities in cardiovascular tests are strongly associated with an increased risk of silent myocardial ischaemia and mortality [1, 5]. Reduced BRS is a strong risk factor for cardiac death in patients after myocardial infarction and with heart failure [25]. We have some evidence that a blunted BRS is associated with an adverse prognosis in diabetes [26]. In diabetic patients the prognostic value of BRS should, however, be confirmed in follow-up studies in larger cohorts. Normal values and standards of assessment of BRS should also be provided. Thus we do not have adequate evidence to base a diagnosis of CAN on the assessment of BRS alone.

## Conclusions

BRS differentiated well subjects with CAN from those without. In this study we did not confirm, however, the value of BRS in the early detection of autonomic dysfunction among patients with type 1 diabetes who showed no abnormalities in standard cardiovascular tests.

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