Baroreflex sensitivity in patients with type I diabetes mellitus

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Abstract

OBJECTIVES: To date, the clinical usefulness of measuring baroreflex sensitivity (BRS) to detect impairment of the autonomic nervous system in patients with diabetes mellitus (DM) type I has not been evaluated sufficiently (Mlčáková *et al.* 2008). The aim of the current study was the determination and statistical comparison of the mean values of BRS in our DM type I patients cohort and in a control group of healthy volunteers as well as the determination of BRS value dependency on the duration of diabetes and the level of glycemic control in DM I patients. We also aimed to determine the inter-individual and intra-individual variability of BRS in our patients.

MATERIAL AND METHODS: We examined 100 patients with type I diabetes mellitus (37 women and 63 men, mean age 30 years, duration of the disease ≥ 10 years) and 40 healthy, age- and sex-matched, subjects. Data from the patient cohort were subsequently analysed for duration of the diabetes and the level of glycemic control as assessed by glycated haemoglobin (HbA1c). We used a simple proportional test to compare the occurrence of impaired BRS in the patient cohort and the control group, and a simple linear regression to assess associations between BRS and duration of the diabetes and the levels of glycemic control.

RESULTS: The mean BRS value in our group of diabetic patients and the control group were 10.15 ms/mmHg and 13.35 ms/mmHg, respectively. II. Statistically significant association between BRS impairment and the duration of the disease or level of glycemic control was not confirmed in our patient cohort. III. We observed an increased inter-individual variability and a relatively low intra-individual variability of BRS in patients with DM type I.

CONCLUSIONS: We found a statistically highly significant difference between the proportions of impaired BRS in the group of diabetics vs. control. However, BRS did not correlate with the duration of the disease or with the level of glycemic control significantly. Albeit not reaching statistical significance, trends could be observed, which we consider clinically interesting.

ORIGINAL ARTICLE

INTRODUCTION

End-organ damage is a typical feature of diabetes mellitus. The most frequent complication affecting both the peripheral and autonomic nervous system is diabetic neuropathy.

The issue of diabetic autonomic neuropathy remains still relevant as it affects negatively the quality of life, even in the early stages of diabetes. Efforts for its detection in the pre-clinical stages have mainly informative and prognostic value for the clinical practise as beside the absolute glycemic control with insulin in DM type I. patients, there is practically no pathogenetic treatment.

The cardiovascular baroreflexes participate in a control of the heart rate and short-term blood pressure variations. The arterial baroreceptors are mechanosensitive nerve fibre endings consisting of loops and ramifications of the axon terminals in the adventitia or in the interface between the media and adventitia of the arteries. They are localized predominantly in two regions – carotic sinus and aortal arch. Activity in the afferent A and C fibres is generated by alterations of the expansion and tension in the vessel wall. Afferentation from the carotic sinus and aortal arch goes via glossopharyngeal and vagal nerves to the bodies of neurons in the petrosal ganglion. The neuronal bodies of aortal baroreceptors are located in the ganglion nodosum. The central integration takes place at the level of nucleus tractus solitarii, in the caudal and rostral ventrolateral medulla oblongata, in the nucleus ambiguus and dorsal part of vagal nucleus (Spyer *et al.* 1997). The insular cortex, amygdale, hypothalamus, thalamus, cingular cortex and prefrontal cortex take part in the integration of information from the baroreceptors (Henderson *et al.* 2004; Kimmerly *et al.* 2007; Sykora *et al.* 2007; Sykora *et al.* 2009; Weisz *et al.* 2001).

The baroreflex sensitivity (BRS) is calculated using various measurement techniques of heart rate (HR) alterations (in ms) compared to alterations of the blood pressure (BP) (in mmHg). Concomitant continual recording of HR and BP alterations has been the most frequently used method in the clinical practice. Currently, the priority has been given to the non-invasive measurement techniques, such as Finapres (FINger Arterial PRESure) that continuously records BP and HR values in the finger artery. The autonomic reactivity is evaluated by spontaneous blood pressure fluctuations, using various model situations as deep breathing, Valsalva manoeuvre, orthostatic stress, applying suction on the carotid arteries (neck suction test) or pharmacologically (La Rovere *et al.* 2008; Westerhof *et al.* 2004). Aside from the magnitude of HR and BP responses, also the latency of the response and phase relation are evaluated (Eckberg, 1980; Eckberg *et al.* 1984; Ferrer *et al.* 1991). BRS reflect the activation capacity of the baroreceptors on the increase of vagal efferent activity, i.e. vagal reactivity (Eckberg 1980; Eckberg *et al.* 1984). The BRS value in normal subjects is approximately around 15 ms/mmHg (Sykora *et al.* 2007; Kamińska *et al.* 2008).To date, the clinical utility of BRS as a relatively novel method to detect the autonomic nervous system impairment in the patients with DM type I has not been evaluated sufficiently and therefore, it does not belong to the standards of the ANS evaluation.

The aim of this study was the determination and statistical comparison of the mean values of BRS in our DM type I patients cohort and a control group of healthy volunteers as well as the determination of BRS value dependency on the duration of diabetes and the level of glycemic control in DM I patients. We also attempted to determine the inter-individual, as well as intra-individual, variability of BRS in our patients.

Table 1. Characteristic of patients with DM I and controls.

DM type I	DM type I (n = 100)	Control (n = 40)
Mean age	29.95	29.92
Men/women ratio	63/37	26/14
Mean BMI value	23.5	23.3

Mean disease duration was 16 years (range 8–38; SD 6.54) and mean Hb1Ac value was 8.7% (range 6–12.7; 1.43)

MATERIAL AND METHODS

We examined 100 patients with type I diabetes mellitus. The patients were examined at standardized conditions, in the morning hours, in a quiet room with a constant air temperature; the patients took light breakfast and applied their usual morning insulin dose. Other medication was discontinued for at least 24 hours prior the examination and intake of alcohol and coffee as well as smoking were banned day and eve prior examination. The control group consisted of 40 healthy, age- and sex-matched, individuals.

Data from our cohort of diabetes type I patients were subsequently processed in terms of duration of the diabetes and the level of glycemic control. Duration of the disease ranged from 10 to 38 years. We assessed the level of glycemic control on the basis of the level of glycated haemoglobin (HbA1c) in the blood (in %) according to the DCCT guidelines (Lachin *et al.* 2007); we considered the value of less than 7% as normal. In our patient cohort the range was 6.0–12.7%. The data was obtained using questionnaires filled-in by patients. (Table 1) (Sykora *et al.* 2008).

The blood pressure for BRS calculation was measured non-invasively using the Finometer (FMS, Finapres Medical Systems BV, Amsterdam, Netherlands). This device uses the volume clamp method for a continuous recording of blood pressure and heart rate from the artery in the finger (beat-to-beat). We placed a right-fit cuff on the third finger of the person's non-dominant

upper extremity. During the measurement patients and control subject laid supine with the hand with the cuff at the level of the heart. The continuous BP was recorded for 10 minutes. The baroreflex sensitivity was assessed using the cross-correlation sequential method (Westernhof *et al.* 2004). The BRS is expressed in ms/mmHg. The analysis has been performed using the software of the FMS Company (Finapres Medical Systems BV, Amsterdam, Netherlands).

Statistical methods

The results are expressed as median ± IQR. Between-group comparisons were made using single proportion test and linear regression. The analysis of variability for two factors (subjects and repetitions) and variability coefficient (ANOVA tests) were used for the evaluation of reproducibility. A p value of less than 0.05 was regarded as statistically significant.

RESULTS

The study group consisted of 100 patients with DMI, the control group of 40 volunteers. Basic characteristics are given in Table 1.

For reproducibility reasons the BRS results were obtained from 5 consecutive examinations over 5 consecutive days in three DM type I patients at standardized conditions (Table 2).

BRS mean values obtained from our diabetic patients and the control group are given in Table 3.

The simple proportional test used for the comparison of the numbers of BRS deteriorations in the diabetic group vs. controls – we found a highly significant difference between the proportions (p=0.0002)

2. Results of the statistical analysis of our patient cohort in terms of disease duration and glycated haemoglobin values

We used a simple linear regression for the statistical analysis (Table 4, 5, and Figure 1, 2)

Table 2. Baroreflex sensitivity values in the repeated examination in individual patients.

	BRS
Patient No. 1	15.7
	10.5
	14.2
	24
	14.9
Patient No. 2	3.3
	5.6
	3.9
	6.9
	4.1
Patient No. 3	18.8
	13.6
	11.8
	12.6
	13.4

Table 3. BRS mean values in DM type I patients and in the control group.

	DM type I patients		Controls	
	median	*IQR*	*median*	*IQR*
BRS (ms/mmHg)	**10.15**	15.9–6.7	**13.35**	20.3–8.5

Table 4. Dependency of BRS on the disease duration in our group of patients.

Parameter	Simple linear regression results	
BRS	p= 0.1032, (r = –0.164748)	**NS**

Table 5. Dependency on the glycated haemoglobin values in our patient cohort.

Parameter	Simple linear regression results	
BRS	p= 0.1183 (r = –0.157986)	**NS**

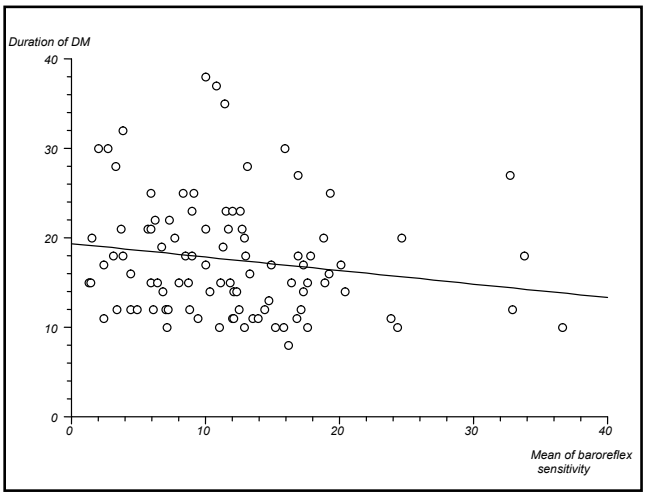

Figure 1. Scatter plot with BRS and duration of the disease.

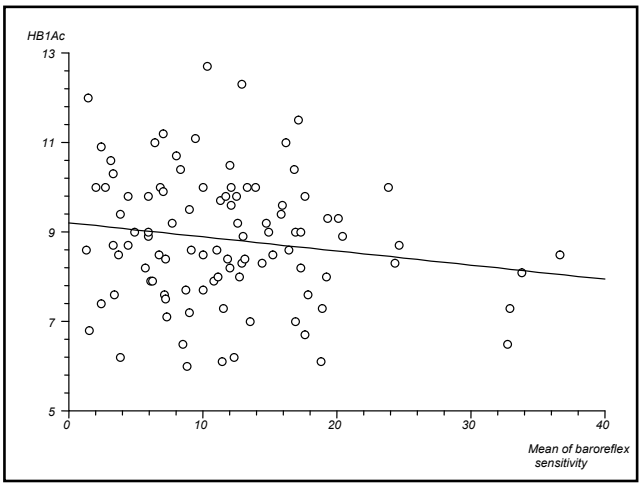

Figure 2. Scatter plot with BRS and glycated haemoglobin values.

3. Reproducibility test results

Table 6 and Table 7.

Table 6. Analysis of variability.

Parameter	*p*-values between the repetitions	*p*-values between the subjects
BRS	*p*=0.45; NS	*p*=0.001; S

Table 7. The mean coefficient of variability (CV).

Parameter	CV	%	SD%
BRS	**0.2724**	27.2	6.6071

DISCUSSION AND CONCLUSION

1. The mean BRS values in our cohort of diabetic patients were 10.15 ms/mmHg, while in the control group it was 13.35 ms/mmHg.
2. We did not confirm statistically significant dependency of BRS values on the disease duration or level of glycemic control. Although the *p*-values were low, there is a trend towards statistical significance when comparing the diabetics vs. the control group. We consider them clinically interesting, albeit not significant**.**

Vinik *et al*. (2004) stated in his paper, that the highest deterioration rate of the nerve fibres function appears shortly after the onset of type I diabetes mellitus; between the 2nd and 3rd years there is a slowing of progression that continues gradually at the level of ANS dysfunction. The onset of the disease in type I diabetic patients is usually known, however the autonomic nervous system dysfunction stays subclinical and asymptomatic for years and often the first clinical symptoms occur in the advanced and irreversible stages of the diabetic autonomic neuropathy (DAN) (Vinik *et al.* 1999).

According to Solders *et al.* (1977) the autonomic nervous system dysfunction is present in 25% of children with diabetes already at time of diagnosis. The deterioration of autonomic functions was directly proportional to the metabolic control of diabetes. At time of diagnosis of diabetes, a moderate grade of impairment of the ANS was present in 30–50% of patients; there was no association with age, duration of diabetes or glycaemia.

Due to the above mentioned inconsistent information the relationship between impairment of the autonomic nervous system and duration of the diabetes remains unclear (Vinik *et al.* 1999).

In our cohort of 100 patients with type I diabetes mellitus we investigated the relationship of the BRS to the disease duration and the values of glycated haemoglobin as the marker of long-term glycemic control. The inclusion criterion in our study was disease duration ≥ 10 years. The disease durarion ranged from 10 to 38 years with the mean 17.6 years. Assessing the metabolic control of diabetes, we looked at the last value of glycated haemoglobin; the blood samples were taken shortly before the examination of the BRS. Statistical analysis of the data from our cohort did not show any statistically significant association between the BRS and the duration of the disease. Similarly, we could not find any statistical significance when comparing the BRS results with the level of glycemic control based on the values of glycated haemoglobin in the patients with type I DM.

On the basis of our results we incline to the opinion that duration of the disease as a risk factor for the development of cardiovascular autonomic nervous system dysfunction is less significant when considering the duration of type I diabetes mellitus ≥ 10 years. The glycated haemoglobin has been regarded as a marker of long-term diabetic control, however a single value shows a picture of diabetic control only over the last 3 months prior to blood sampling and is not an image of a real long-term diabetic compensation (several months to years).
3. The reproducibility test in BRS showed only a nonsignificant difference between the repetitions in the single patient, however, there was a significant difference in BRS values between the subjects which shows a higher inter-individual variability.

We found a relatively low intra-individual variability of this technique when adding the variability coefficient to obtain data on similarity of dispersion of the BRS values.

Summarised, estimation of BRS seem to be an suitable method to detects impairment of autonomic nervous system in type I diabetic patiens. However, it does not reflect the duration of the disease nor the actual glycemic compensation levels. Most probably, the degree of autonomic impairment correlates only to long-term compensation levels of the diabetes.

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