Diagnostic significance of a mild decrease of baroreflex sensitivity with respect to heart rate in type 1 diabetes mellitus

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Short title: Baroreflex sensitivity with respect to heart rate in diabetes

Summary

Decreased baroreflex sensitivity is an early sign of autonomic dysfunction in patients with type-1 diabetes mellitus. We evaluated the repeatability of a mild baroreflex sensitivity decrease in diabetics with respect to their heart rate. Finger blood pressure was continuously recorded in 14 young diabetics without clinical signs of autonomic dysfunction and in 14 age-matched controls for 42 minutes. The recordings were divided into 3-minute segments, and the mean inter-beat interval (IBI), baroreflex sensitivity in ms/mmHg (BRS) and mHz/mmHg (BRSf) were determined in each segment. These values fluctuated in each subject within 42 minutes and therefore coefficients of repeatability were calculated for all subjects. Diabetics compared with controls had a decreased mean BRS ($p = 0.05$), a tendency to a shortened IBI ($p=0.08$), and a decreased BRSf ($p=0.17$). IBI correlated with BRS in diabetics ($p=0.03$); this correlation was at $p=0.12$ in the controls. BRSf was IBI independent (controls: $p=0.81$, diabetics: $p=0.29$). We conclude that BRS is partially dependent on mean IBI. Thus, BRS reflects not only an impairment of the quick baroreflex responses of IBI to blood pressure changes, but also a change of the tonic sympathetic and parasympathetic heart rate control. This is of significance during mild changes of BRS. Therefore, an examination of the BRSf index is highly recommended, because this examination improves the diagnostic value of the measurement, particularly in cases of early signs of autonomic dysfunction.

Keywords:

Baroreflex sensitivity, diabetes mellitus, inter-beat interval, repeatability

Introduction

Decreased baroreflex sensitivity (BRS) is one of the early signs of cardiovascular autonomic neuropathy in patients with type 1 diabetes mellitus. Decreased BRS as a mark of diabetic autonomic dysfunction was found in both adults (Martiniskova *et al.* 2009, Svacinova *et al.* 2005) and children (Boysen *et al.* 2007, Pozza *et al.* 2007). It was demonstrated that the decrease of BRS correlated with age, gender (Laitinen *et al.* 1998), higher HbA1c (Krause *et al.* 2009), with the duration of diabetes mellitus (Pozza *et al.* 2007), with structural changes of vessels (Stakos *et al.* 2005), and baroreflex delay (Javorka *et al.* 2011). Low BRS was linked to a decreased parasympathetic and an increased sympathetic control of the cardiovascular system. It was also shown that abnormalities in cardiac parasympathetic regulation precede impairment of blood vessel sympathetic control (Javorka *et al.* 2005).

Low BRS is a risk factor for the early stage of development of essential hypertension (Honzikova *et al.* 2006, Krontoradova *et al.* 2008a, Honzikova and Fiser 2009, Honzikova and Zavodna 2012, Novakova 2013) and its severe complications including stroke, myocardial infarction and sudden cardiac death (Honzikova *et al.* 2000, Honzik et al 2010, Celovska *et al.* 2010). An early diagnosis of baroreflex control impairment in patients with diabetes mellitus is therefore important with respect to possible prevention.

It has been known for decades that BRS decreases during different physiological loads. In spite of the fact that BRS also fluctuates under resting conditions (Honzikova *et al.* 2003), its repeatability from recordings taken within three weeks (Jira *et al.* 2006) or two weeks (Dietrich *et al.* 2010) was proved.

Baroreflex sensitivity is usually defined as the change of the inter-beat interval (IBI) associated with a change of systolic blood pressure in ms/mmHg as the BRS index. Another possibility of baroreflex sensitivity determination is based on the calculation of a change of instantaneous heart rate related to a change of systolic blood pressure expressed in bpm/mmHg (Ackermann *et al.* 1989) or in mHz/mmHg as the BRSf index (Zavodna *et al.* 2006). The index in bpm/mmHg is usually used in animal experiments (Hong *et al.* 2012). Information acquired using the BRS or BRSf indices may differ because the relationship between IBI and heart rate is non-linear. Thus, in case that a decreased BRS is linked to a shortened IBI, changes of BRS and BRSf may provide the same information (Honzikova *et al.* 2006). On the other hand, an age-dependent prolongation of IBI in children causes a difference in the age-related values of BRS and BRSf (Zavodna *et al.* 2006). The BRS index is more influenced by the mean IBI than BRSf, and therefore the actual tonic sympathetic and parasympathetic control of the mean IBI may influence information about beat-by-beat baroreflex sensitivity measured by the BRS index. This means that an intervention affecting not only baroreflex, but also IBI, may lead to partial misinterpretation of physiological processes based on BRS values without considering mean IBI (Nieminen *et al.* 2010). Furthermore, the BRSf index seems to be a better indicator of the effectivity of baroreflex sensitivity to suppress blood pressure fluctuations (Krontoradova *et al.* 2008b).

The aim of our study was to evaluate the repeatability of the mild baroreflex impairment determined in diabetics with respect to the spontaneous resting fluctuation of baroreflex sensitivity and mean IBI. Because recordings lasting 3-5 minutes are usually used during measurements of baroreflex sensitivity, we evaluated 14 segments lasting 3-minutes from recordings of duration of 42 minutes in each subject. We tested whether values of IBI, BRS, and BRSf in diabetics and healthy controls reveal individual characteristic features in spite of their spontaneous fluctuation within 42 minutes and whether BRS and BRSf correlate with IBI.

Differences of BRS and BRSf together with IBI between diabetics and controls were evaluated within partial segments and whole recordings. Thus, the reliability of detection of baroreflex impairment in diabetics with respect to the length of recording was taken into account.

Methods

Subjects

We examined 14 patients with type 1 diabetes mellitus and 14 healthy controls of the same age and gender (7 women and 7 men in each group). All subjects were examined in the laboratory of the Dept. of Physiology, Jessenius Faculty of Medicine, Comenius University in Martin, Slovakia. Only patients without any signs of neuropathy of the autonomous nervous system were included in this study. The mean age of the controls (21.9 ± 0.9 years) and diabetics (22.3 ± 1.2 years) did not differ significantly. Blood pressure was also similar in both groups: 112±12/59±9 mmHg for diabetics and 116±12/59±5 mmHg for controls. The duration of diabetes mellitus was 12.5 ± 1.4 years. Insulin was the only therapy used in the diabetics group. The fasting glycaemia of the diabetics was 6.8-13.5 mmol/l. HbA1c was 4.7% for the controls and 9.2% for the diabetics. The range for physiological values of HbA1c was 4-6% (measured by DCA 2000 + Bayer Corp., Elkhart, IN, USA). The diabetics had relatively high values of HbA1c and fasting glycaemia, probably caused by the lability of child diabetes and, moreover, sometimes by insufficient compensation.

The Ethics Committee of Comenius University in Martin approved the study, and all participants of the study gave their consent.

Pressure recording and spectral analysis

Finger arterial blood pressure (Finapres, Ohmeda) was continuously recorded in resting lying subjects in spontaneous breathing for 50-60 minutes. The volume-clamp method used in the Finapres device is a worldwide accepted method for non-invasive continuous measurement of arterial blood pressure. The differences in blood pressure values between the non-invasive volume-clamp method and invasive intra-arterial pressure were analysed in several studies. It was found that absolute values of systolic and diastolic blood pressure measured by the volume-clamp method are overestimated and underestimated, respectively, compared to brachial and invasive aortic blood pressures (Porter *et al.* 1991, Jellema *et al.* 1996). On the other hand, non-invasive finger arterial pressure measurement is able to precisely follow the blood pressure changes during various manoeuvres and spontaneous blood pressure oscillations (Jellema *et al.* 1996, Castiglioni *et al.* 1999). Since our study was focused on the analysis of relations between blood pressure and heart rate oscillations, we regard the methodology used as validated for baroreflex sensitivity analysis.

We analysed recordings lasting 42 minutes to avoid transient changes at the beginning and at the end of the recordings. Systolic blood pressure (SBP), IBI, instantaneous values of the inter-beat frequency (IBF) were determined beat-by-beat, interpolated by cubic spline, and equidistantly sampled (10 Hz).

These preprocessed signals were divided into 3-minute non-overlapping segments (14 segments for each subject). The autocorrelation functions of IBI, IBF and SBP, the cross-correlations between IBI and SBP, or IBF and SBP, and the spectra of these correlations were computed for each segment. Coherence between IBI and SBP or between IBF and SBP respectively, was computed (Honzikova *et al.* 1992, Zavodna *et al.* 2006).

We limited the frequency range used for further evaluation with the aim to minimise the effect of spontaneous respiration of the subject on blood pressure and IBI variability, because respiration usually leads to an overestimation of a calculated value of BRS (Frederiks *et al.* 2000, Bothova *et al.* 2010). The upper limit of the analysed range was set lower than the respiratory frequency of the subjects (about 0.15 Hz), and the lower limit of the analysed range was set to 0.06 Hz, because it was proved that spontaneous respiration is not stable; the depth and the rate of respiration vary mostly at frequencies below this value (Honzikova *et al.* 1995). Considering only segments with a coherence higher than 0.5, BRS was calculated in this frequency band (0.06 – 0.12 Hz) as the ratio of the cross spectra between IBI and SBP and the power spectra of SBP. BRSf was calculated in this frequency band as the ratio of the cross spectra between IBF and SBP and the power spectra of SBP (Zavodna *et al.* 2006).

Thus, we assessed all measures in 14 segments lasting for 3 minutes in each subject. Finally, we calculated the medians of IBI, BRS, and BRSf from these 14 segments in each subject.

Statistics

Many methods were developed to compare intra- and inter-individual variability. Their use depends on the number of repetitions of measurements and intervals between measurements. We chose a coefficient of repeatability based on ANOVA, which informs what percentage of the total variability was explained by differences between the subjects (inter-individual variability). A high coefficient of repeatability indicated that the given measure was a highly individual characteristic. This method was implemented as a function in Matlab. The function did not provide the p-value, but it classified the system measured into three groups: 1) the measurement

system is capable, 2) the measurement system may be acceptable, and 3) the measurement system is not capable. The coefficient of repeatability was evaluated for IBI, BRS, and BRSf separately. We evaluated whether IBI, BRS, and BRSf differed between diabetics and controls. Because of the non-normal distribution of these parameters within the 14 segments analysed in each subject, we took the median of the given parameter for each subject as a representative value for the whole recording. These medians satisfied the conditions required for counting mean values for groups and a T-test between diabetics and controls. The relationships between the medians of BRS or BRSf respectively, and IBI were evaluated by the Pearson correlation coefficient.

In the next step, a comparison of the IBI, BRS, and BRSf values between the diabetics and the controls was performed for all segments of the recordings lasting 3 minutes to test the reliability when calculated from shorter recordings. We assumed that in the case of one experimental examination we can measure a 3-minute long segment at any random time from the whole 42 minutes' recording. In this regard, a comparison of a pair of segments from the recordings of the controls and the diabetics does not depend on the order of the segments. Thus, we compared the values of IBI, BRS and BRSf from 14 segments of recordings of all diabetics with the values of these measures from 14 segments of the control recordings making 14 x 14 = 196 combinations. That means, we compared the differences in the indices analysed between the diabetics and the controls for all combinations of data segments using a Mann-Whitney test (significance of the test: $p < 0.05$). In the last step, we evaluated whether this significance of differences in BRS/BRSf depended on the significance of differences in IBI (Fisher factorial test).

Results

The values of repeatability coefficients for IBI, BRS and BRSf measured in whole recordings, their means, standard deviations and the significance of the differences between diabetics and controls are given in Table 1. IBI had high repeatability coefficients, BRS and BRSf had a lower coefficient of repeatability. IBI was classified by Matlab's function as 1 (the measurement system was capable), BRS and BRSf as 2 (the measurement system could be acceptable). However, this type of analysis was not originally made for a non-stationary biological system, and this analysis had stringent criteria. Computing the BRS and BRSf indices had a lot of restricting conditions which decreased inter-individual variability (frequency band, coherence), but not intra-individual variability. In the context of the restricting conditions of BRS and BRSf calculation we can conclude that their coefficient of repeatability was sufficient. The diabetics had lower coefficients of repeatability of BRS and BRSf than the controls. The coefficient of repeatability increases when inter-individual variability increases and/or intra-individual variability decreases. The diabetics and the controls had almost the same intra-individual variability of BRS and BRSf, but the controls had higher inter-individual variability; therefore the controls had higher repeatibility. While the diabetics had significantly lower BRS, no significant difference in the BRSf index was found.

The distribution of all values of all parameters for each subject is shown in Figure 1. This graph shows that the range of values is individually characteristic for all subjects in all parameters. The distribution of all values of all parameters for each segment lasting 3 minutes is shown in Figure 2. For IBI the dispersion of the values does not vary significantly with time. A range of the segment values of BRS and BRSf is more variable than that of IBI, but the variability between the segments is still lower than the variability between the subjects showed in Figure 1 (which is also expressed by the coefficient of repeatability in Table 1).

In Table 2, the correlation coefficients between IBI and BRS or BRSf are shown. Whereas the correlation between IBI and BRS was significant in diabetics and insignificant but still appreciable in controls, BRSf did not correlate with IBI in both groups.

In the next step we compared the values of IBI, BRS and BRSf from 14 segments of the recordings of all diabetics with the values of these measures from 14 segments of the control recordings making 14 x 14 = 196 combinations, and we calculated the proportion of significant differences from all 196 combinations. This proportion was 0.23 for IBI; this means that the diabetics had a significantly shorter IBI in 23% of all combinatorial pairs of segments than the controls. The proportion of BRS was 0.26 and the proportion of BRSf was 0.04. Thus, the diabetics had a significantly lower BRS in 26% of all combinatorial pairs and a lower BRSf in 4% of all combinatorial pairs than the controls. Consequently, the diabetics had a significantly lower IBI and BRS in a quarter of all combinatorial pairs of segments than the controls. A Fisher factorial test proved that the significance of BRS depended on the significance of IBI ($p<0.05$), but BRSf was independent of IBI. This result corresponded with the result of the correlation analysis in Table 2, and it is illustrated in Figure 3.

Discussion

We have shown that a decrease of BRS in diabetic patients ($p=0.047$) occurred together with a tendency to a shortening of IBI ($p=0.088$). This shortening of IBI could reflect a relatively mildly decreased parasympathetic and/or increased sympathetic control of the mean heart rate. A tendency to a decrease of the BRSf index in diabetics was also observed.

The reliability of a mild baroreflex sensitivity impairment detection was tested by evaluation of the repeatability of indices BRS and BRSf calculated from long-lasting blood pressure recordings

(42 min). We showed that despite fluctuations of the assessed parameters within a recording in each subject, the differences among the subjects were greater than intra-individual fluctuations. In about one quarter of the combinations of the 3-minute segments, the diabetics had significantly lower IBI and BRS. In the case of BRSf only 4% of the combinations differed significantly. This fact shows that at the beginning of a pathological baroreflex-sensitivity decrease, changes of BRS and BRSf are detectable more reliably in recordings longer than 3-5 minutes, as are usually used in many studies. We proved that these slightly different results based on the analysis of short or long recordings are caused by spontaneous fluctuation of baroreflex sensitivity. In case of a baroreflex-sensitivity variation around a critical pathological value we can underestimate or overestimate this change using a short recording. A long recording improves the signal-to-noise ratio and better estimates the real mean values. Therefore, we concluded that comparing the reliability of baroreflex sensitivity of diabetics by using recordings of blood pressure and inter-beat fluctuations lasting for 3 or 42 minutes, the reliability of detection of its mild decrease is higher when longer recordings are analysed.

Comparing this study of baroreflex sensitivity in young diabetic patients with a study of BRS and BRSf in young hypertensive patients we can see a different pattern of changes. In hypertensive patients, both indices, BRS and BRSf, were significantly decreased without any change of IBI (Honzikova *et al.* 2006). Furthermore, the decrease of BRS and BRSf correlated with the development of the disease and such a finding brought evidence that impairment of baroreflex sensitivity plays an important role in the early stage of hypertension, even though the autonomic control of the mean heart rate did not reveal any change. On the other hand, our finding of a decreased BRS linked to a shortened IBI and a non-significant decrease of BRSf in diabetic patients suggests that the early autonomic dysfunction in diabetics involves both the effects of the autonomic nerves on the heart, i.e. the tonic and short-term control of the heart rate. A mild

impairment of baroreflex sensitivity was significantly detectable only by the BRS index because this index was influenced by mean IBI, as was documented by correlation analysis.

On the basis of our study we conclude that a significant decrease of BRS occurs together with a shortening of IBI in patients with type 1 diabetes mellitus. Since BRS is partially dependent on mean IBI, the change of the BRS index reflects not only an impairment of quick baroreflex responses of IBI to blood pressure changes, but also the change of tonic sympathetic and parasympathetic control of the heart rate. This can explain why BRS is more sensitive for detection of baroreflex impairment in diabetics than the BRSf index, which is IBI independent. On the other hand, using BRS for the detection of baroreflex impairment, mean IBI should be taken into account for a pathophysiological interpretation of the results.

Limitation of the study

The study groups of 14 diabetics and 14 controls are small. However, we should consider that recordings lasting for about one hour in resting conditions are burdensome for volunteers. Therefore, we minimised the number of volunteers to obtain the answer to our question. This size of the groups might have an impact on statistical significance. It could well be supposed that a greater number of volunteers could improve the significance of the statistics.

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Table 1: Coefficients of repeatability, means (counted from individual medians), standard deviations and p-values of differences (T-test) between patients with type 1 diabetes mellitus and controls in inter-beat intervals (IBI) and baroreflex sensitivity indices (BRS and BRSf).

Parameter	**Group**	**Coefficient of repeatability**	**Mean ± standard deviation**	**T-test p-value**
IBI	diabetics	89.2 (%)	825±108 ms	0.088
	controls	89 (%)	901±115 ms	
BRS	diabetics	48.8 (%)	9.7±4.6 ms/mmHg	0.047
	controls	77.1 (%)	14.1±7.3 ms/mmHg	
BRSf	diabetics	54.9 (%)	14.6±6.3mHz/mmHg	0.171
	controls	76.8 (%)	18.7±8.8 mHz/mmHg	

Table 2: Pearson correlation coefficients between inter-beat intervals (IBI) and baroreflex sensitivity indices (BRS or BRSf) for patients with type 1 diabetes mellitus and controls.

Parameter	**Group**	**Correlation coefficient**	**p-value**
BRS	diabetics	0.58	0.031
	controls	0.43	0.127
BRSf	diabetics	0.07	0.814
	controls	-0.35	0.289

Legends to figures

Figure 1: Individual characteristics of values of inter-beat intervals (IBI) and baroreflex sensitivity indices (BRS and BRSf) measured fourteen times in each subject (14 controls and 14 diabetics). The box plots illustrate medians (white points), interquartile ranges and outliers (black points) of individual values in each subject.

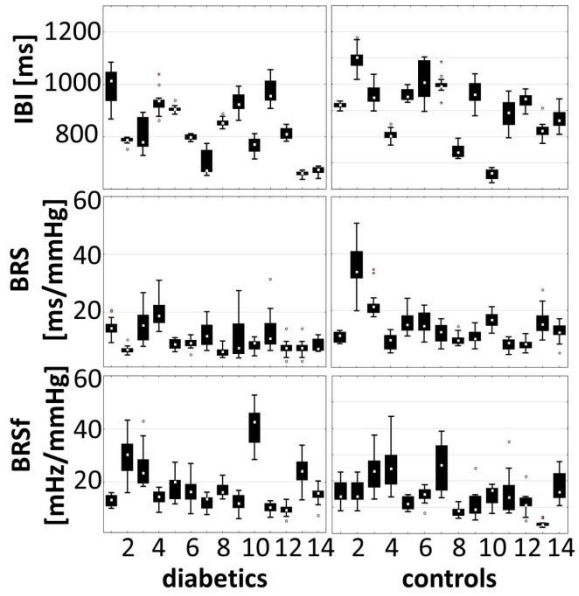

Figure 2: Fluctuation of inter-beat intervals (IBI) and baroreflex sensitivity indices (BRS and BRSf) measured in controls and diabetics in 14 segments lasting 3 minutes within forty-two minutes. The box plots illustrate medians (white points), interquartile ranges and outliers (black points) of values in both groups in each segment.

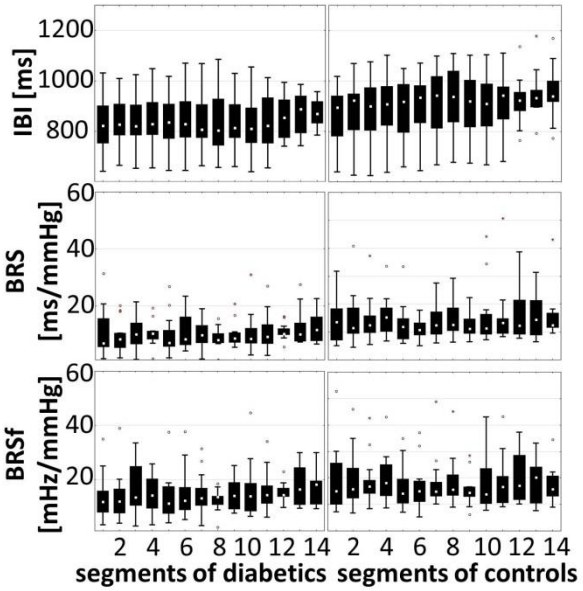

Figure 3: Dependence of BRS and BRSf on inter-beat interval (IBI) in diabetics and controls.