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Comparison of Baroreflex Sensitivity Determined by Cross-Spectral Analysis at Respiratory and 0.1 Hz Frequencies in Man

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Summary

Non-invasive methods of determination of baroreflex sensitivity (BRS, ms/mmHg) are based on beat-to-beat systolic blood pressure and inter-beat interval recording. Sequential methods and spectral methods at spontaneous breathing include transient superposition of breathing and 0.1 Hz rhythms. Previously, a cross-spectral method of analysis was used, at constant breathing rate using a metronome set at 0.33 Hz, enabling separate determination of BRS at 0.1 Hz ($BRS_{0.1Hz}$) and respiratory rhythms ($BRS_{0.33Hz}$). The aim of the present study was to evaluate the role of breathing in the spectral method of BRS determination with respect to age and hypertension. Such information would be important in evaluation of BRS at pathological conditions associated with extremely low BRS levels. Blood pressure was recorded by Finapres (5 minutes, controlled breathing at 0.33 Hz) in 118 healthy young subjects (YS: mean age 21.0±1.3 years), 26 hypertensive patients (HT: mean age 48.6±10.3 years) with 26 age-matched controls (CHT: mean age 46.3±8.6 years). A comparison of $BRS_{0.1Hz}$ and $BRS_{0.33Hz}$ was made. Statistically significant correlations were found between $BRS_{0.1Hz}$ and $BRS_{0.33Hz}$ in all groups: YS: $r=0.52$, $p<0.01$, HT: $r=0.47$, $p<0.05$, and CHT: $r=0.70$, $p<0.01$. The regression equations indicated the existence of a breathing-dependent component unrelated to BRS (YS: $BRS_{0.33Hz}=2.63+1.14*BRS_{0.1Hz}$; HT: $BRS_{0.33Hz}=3.19+0.91*BRS_{0.1Hz}$; and CHT: $BRS_{0.33Hz}=1.88+1.01*BRS_{0.1Hz}$; differences between the slopes and the slope of identity line were insignificant). The ratios of $BRS_{0.1Hz}$ to $BRS_{0.33Hz}$ were significantly lower than 1 ($p<0.01$) in all groups (YS: 0.876±0.419, HT: 0.628±0.278, and CHT: 0.782±0.260). Thus, BRS evaluated at the breathing rate overestimates the real baroreflex sensitivity. This is more pronounced at low values of BRS, which is more important in patients with pathologic low BRS. For diagnostic purposes we recommend the evaluation of BRS at the frequency of 0.1 Hz using metronome-controlled breathing at a frequency that is substantially higher than 0.1 Hz and is not a multiple of 0.1 Hz to eliminate respiratory baroreflex-non-related influence and resonance effect on heart rate fluctuations.

Key words

Baroreflex sensitivity • Controlled breathing • Spectral analysis • Hypertension • Respiration

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Introduction

Recently, much attention has been paid to baroreflex sensitivity (BRS) of the heart in pathophysiological, psychological, and clinical studies. BRS is the determination of the change of inter-beat interval duration produced by changing the arterial blood pressure by 1 mmHg. These data are of clinical relevance, namely in prediction of the risk of sudden cardiac death (La Rovere *et al.* 1998, Honzíková *et al.* 2000), in

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evaluating the risk of development of essential hypertension (Honzíková *et al.* 2006, Krontorádová *et al.* 2008, Honzíková and Fišer 2009), and in the assessment of the condition of patients with essential hypertension (Lábrová *et al.* 2005). Low BRS is also associated with obesity (Lazarova *et al.* 2009). All studies provide essentially comparable results, despite of different absolute values, complicating the standardisation of clinical evaluation. The approaches used differ both in the stimuli producing primary blood pressure changes and in the mathematical procedures of BRS calculation from recordings of spontaneous variations in blood pressure. The methods used to stimulate baroreceptors include administration of vasoconstrictive or vasodilative substances and stimulation of baroreceptors by neck suction. Mathematical procedures that enable the calculation of BRS from recordings of blood pressure and inter-beat fluctuations that last several minutes include the sequential method (evaluation of upward- and downward-sloping groups of pulses in spontaneous recordings), various indices based on cross-spectral analysis, alpha index, wavelet approach, and LP analysis. A number of studies have compared BRS results as obtained by different methods (Persson *et al.* 2001, Krticka *et al.* 2000, Krticka and Honzikova 2001, Lipman *et al.* 2003, Laude *et al.* 2004).

A special factor influencing BRS is breathing. The influence of breathing on the BRS value with respect to the methodology of BRS determination is still a matter of debate. The effects of paced breathing on low-frequency (LF) and high frequency (HF) bands in power spectra of systolic blood pressure, inter-beat intervals, and BRS by cross-spectral method have been examined in our lab for nearly 20 years. In our early study, voluntarily controlled breathing was used on 12 subjects in 7 experimental sessions with breathing intervals ranging from 3 to 17 s (Honzíková *et al.* 1992). The phenomenon of resonance at breathing frequency of 0.1 Hz, as described earlier (Hirsch and Bishop 1981), manifested as a great increase in peak amplitude at 0.1 Hz in cardiac intervals spectrum. On the other hand, BRS calculated at various breathing rates in both frequency ranges, 0.1 Hz and HF, remained relatively constant for each subject, but they differ from each other inconsistently in individual recordings. There was not any systemic relationship between BRS values calculated at 0.1 Hz and at HF range (Honzíková *et al.* 1992). It has also been shown (Honzíková *et al.* 1995) that spontaneous irregularity in the rate and depth of spontaneous breathing produced spectral components in the low frequency circulatory spectra and therefore breathing may influence the 0.1 Hz rhythm as well. Since that time, determination of BRS by cross-spectral method at the frequency of 0.1 Hz using controlled breathing at 0.33 Hz has been used in our studies. Breathing frequency 0.33 Hz was chosen because of two reasons: this frequency is not a multiple of 0.1 Hz (prevention of resonance effect) and it is somewhat higher than spontaneous breathing rate in majority of people. Spontaneous rate of breathing is very different in different people and for standardisation of measurement a unified frequency should be determined. It is easier to control breathing at a little bit higher than lower rate compared to spontaneous breathing. Our decision to calculate BRS at 0.1 Hz is also due to the report non-baroreflex factors influencing respiratory sinus arrhythmia in both human and animal studies (Akselrod *et al.* 1981, Eckberg 2003, Eckberg and Karemaker 2009, Tzeng *et al.* 2009).

The influence of breathing on BRS calculated by a sequence method is variable due to superposition of respiratory and 0.1 Hz rhythms; and is of great importance in examination using breathing at the resonance frequency of 0.1 Hz (Halamek *et al.* 2003).

There is no reliable information on whether a systematic difference between the indices of BRS calculated at breathing and at 0.1 Hz rhythms could influence the application of BRS measurements in clinics. Such information would be important in evaluation of BRS at pathological conditions associated with extremely low BRS levels. In these cases a small overestimation or underestimation might be of clinical relevance. We therefore decided to compare the difference between the BRS index calculated at a breathing frequency range and at 0.1 Hz rhythm in healthy subjects and hypertensive patients using cross-spectral analysis of variations of blood pressure and cardiac intervals during controlled breathing.

Methods

Subjects

One hundred eighteen young healthy subjects (mean age 21.0±1.3 years), 26 treated hypertensive patients (mean age 48.6±10.3 years), and 26 age-matched controls to hypertensive patients (mean age 46.3±8.6 years) were included in the present study. Blood pressure was significantly lower in young healthy subjects compared

Table 1. Differences in age, blood pressure and inter-beat intervals in studied groups.

	Young subjects	Controls to hypertensives	Hypertensive patients
No	118	26	26
Age [years]	20.98 ± 1.26 ** °°	46.27 ± 8.56	48.58 ± 10.29
SBP [mmHg]	117.31 ± 12.8 °°	117.19 ± 16.62 ++	129.35 ± 16.85
DBP [mmHg]	62.88 ± 9.02 °°	64.38 ± 11.77 +	74.08 ± 16.07
IBI [ms]	824.53 ± 138.96	827.31 ± 96.98	864.00 ± 163.55

Young subjects vs. controls to hypertensives: ** p<0.01; young subjects vs. hypertensive patients: °° p<0.01; controls to hypertensives vs. hypertensive patients: + p<0.05, ++ p<0.01; SBP – systolic blood pressure, DBP – diastolic blood pressure, IBI – inter-beat intervals.

with the other two groups and also in controls compared hypertensive patients (Table 1). Patients with hypertension were recruited randomly from the outpatient of the Department of Internal Cardiology of the Faculty Hospital in Brno. All patients had mild-to-moderate essential hypertension with no history or evidence of left ventricular dysfunction, previous myocardial infarction, stroke, or diabetes mellitus. The diagnosis of hypertension was established by elevation of blood pressure (≥140 mmHg systolic and ≥90mmHg diastolic blood pressures) in absence of clinical or laboratory evidence of a secondary form of HT. The diagnosis of sustained HT was based on repeated blood pressure measurements. All patients were individually treated through the study by angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, calcium channel blockers, and statins.

Both groups of healthy subjects were volunteers recruited at the Department of Internal Cardiology and Department of Physiology, and university students. All subjects gave their informed consent, and protocols were approved by the ethics committee of the Faculty of Medicine.

Continuous blood pressure measurement and BRS determination

Indirect, continuous 5-minute blood pressure recordings from finger arteries (Finapres, Ohmeda, Madison, USA) were performed in sitting, resting subjects between 9 a.m. and noon. The recordings were taken during synchronised breathing. Breathing was set on constant rate according to the LED-bar metronome at 20 breaths/min (0.33 Hz). The subjects were allowed to adjust the tidal volume to their own comfort.

The beat-to-beat values of systolic blood pressure and of inter-beat intervals were measured for further analysis. For spectral analysis, the parameters were linearly interpolated and equidistantly sampled at 2 Hz. The linear trend was removed. The autocorrelation and cross-correlation functions, power spectra and cross-spectra, coherence and the modulus (gain) between variations of systolic blood pressure and inter-beat intervals were calculated. The modulus H[f] representing BRS was calculated as the quotient between the cross-spectral density of variation of inter-beat intervals and systolic blood pressure (ms*mmHg) and the power spectral density of variations in systolic blood pressure (mmHg*mmHg).

$$H[f] = Gxy[f] / Gx[f]$$

where Gxy[f] corresponds to the cross-spectral density between systolic blood pressure and inter-beat intervals; Gx[f] corresponds to the spectral density of systolic blood pressure. The mathematical procedures have been previously described in detail (Zavodna *et al.* 2006).

BRS was determined at two frequency bands, at 0.1 Hz ($BRS_{0.1Hz}$), and at a frequency of controlled breathing of 0.33 Hz ($BRS_{0.33Hz}$).

Statistical analysis

The relationship between $BRS_{0.1Hz}$ and $BRS_{0.33Hz}$ was analyzed in each group. Association between pairs of variables was assessed by means of Pearson´s coefficient. Relationship $BRS_{0.1Hz}/BRS_{0.33Hz}$ was calculated and 95 % confidence interval (CI) of this relationship was determined in each group as mean value ± SEM * 1.96. The significance of differences was evaluated by the Mann-Whitney test.

Results

The comparison of BRS and coherence between variations in blood pressure and inter-beat intervals in

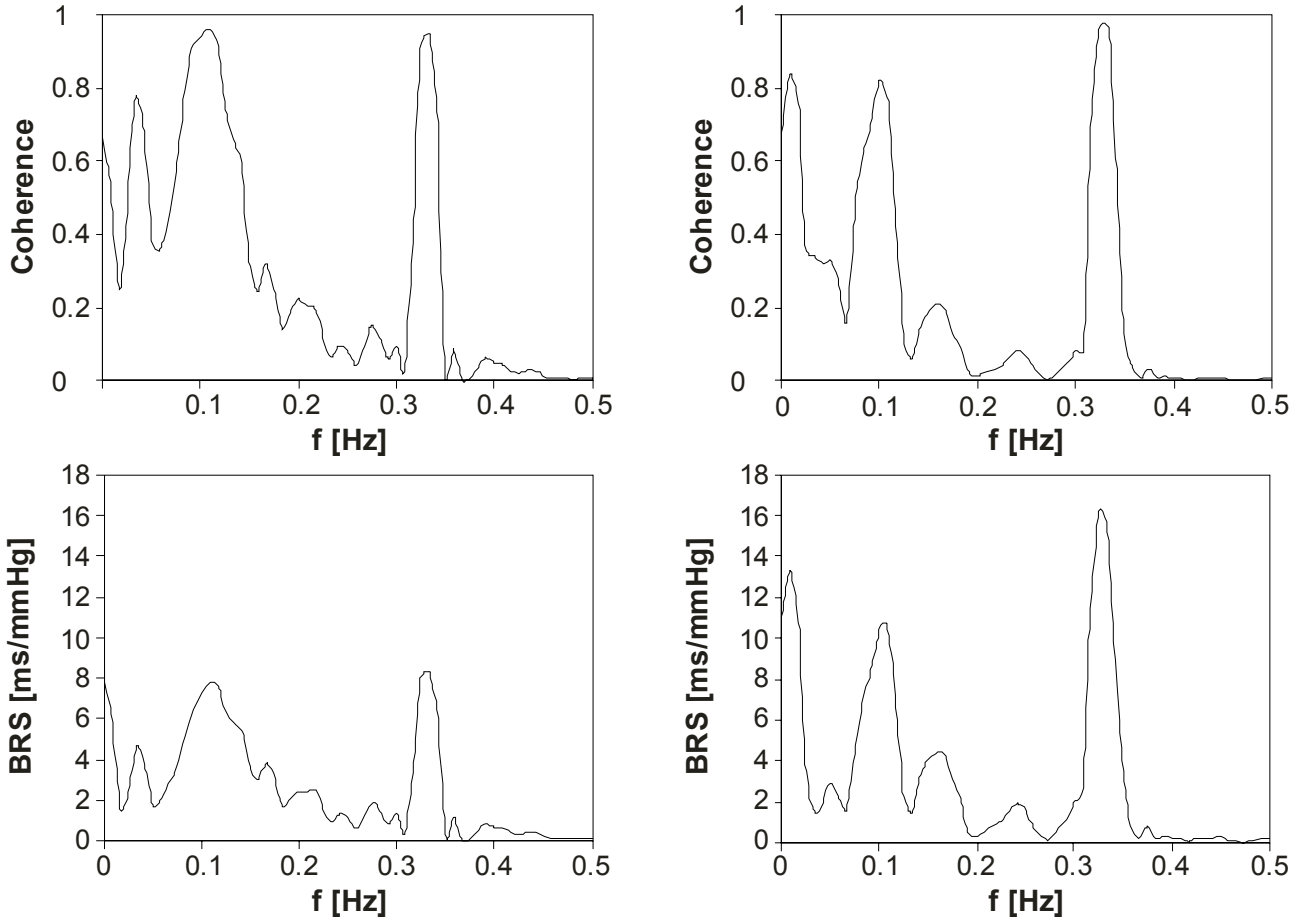

Fig. 1. Example of baroreflex sensitivity (BRS) and coherence calculated in two subjects (left and right) in total frequency range between 0 and 0.5 Hz.

individual recordings revealed inconsistent differences in the relationship between the values at the frequencies 0.1 Hz and of 0.33 Hz. Examples of coherence and BRS calculated in two subjects (Fig. 1 left and right) in whole frequency range between 0 and 0.5 Hz show that BRS calculated at the respiratory frequency can be both higher or lower than that calculated at a frequency of 0.1 Hz.

Nevertheless, statistically significant correlations were found between $BRS_{0.1Hz}$ and $BRS_{0.33Hz}$ in all groups: in young subjects $r=0.52$, $p<0.01$; in hypertensive patients $r=0.47$, $p<0.05$; and in controls to hypertensive patients $r=0.70$, $p<0.01$ (Fig. 2).

The regression equations were:

For young subjects, $BRS_{0.33Hz}=2.63+1.14*BRS_{0.1Hz}$;
For hypertensive patients, $BRS_{0.33Hz}=3.19+0.91*BRS_{0.1Hz;}$; and
For controls to hypertensive patients, $BRS_{0.33Hz}=1.88+1.01*BRS_{0.1Hz.}$

These regression equations indicated the existence of a breathing-dependent component not related to BRS.

The ratios of $BRS_{0.1Hz}$ to $BRS_{0.33Hz}$ were significantly lower than 1 ($p<0.01$) in all groups:

Young subjects: $BRS_{0.1Hz}/BRS_{0.33Hz}=0.876\pm0.419$; $p<0.01$;
Hypertensive patients: $BRS_{0.1Hz}/BRS_{0.33Hz}=0.628\pm0.278$; $p<0.01$; and
Controls to hypertensive patients: $BRS_{0.1Hz}/BRS_{0.33Hz}=0.782\pm0.260$; $p<0.01$.

Thus, BRS evaluated at the breathing frequency overestimates the real BRS. This was more pronounced at low values of BRS (Fig. 3). Significant correlation between the relationship of $BRS_{0.1Hz}/BRS_{0.33Hz}$ and $BRS_{0.1Hz}$ was found in hypertensive patients only ($p<0.05$).

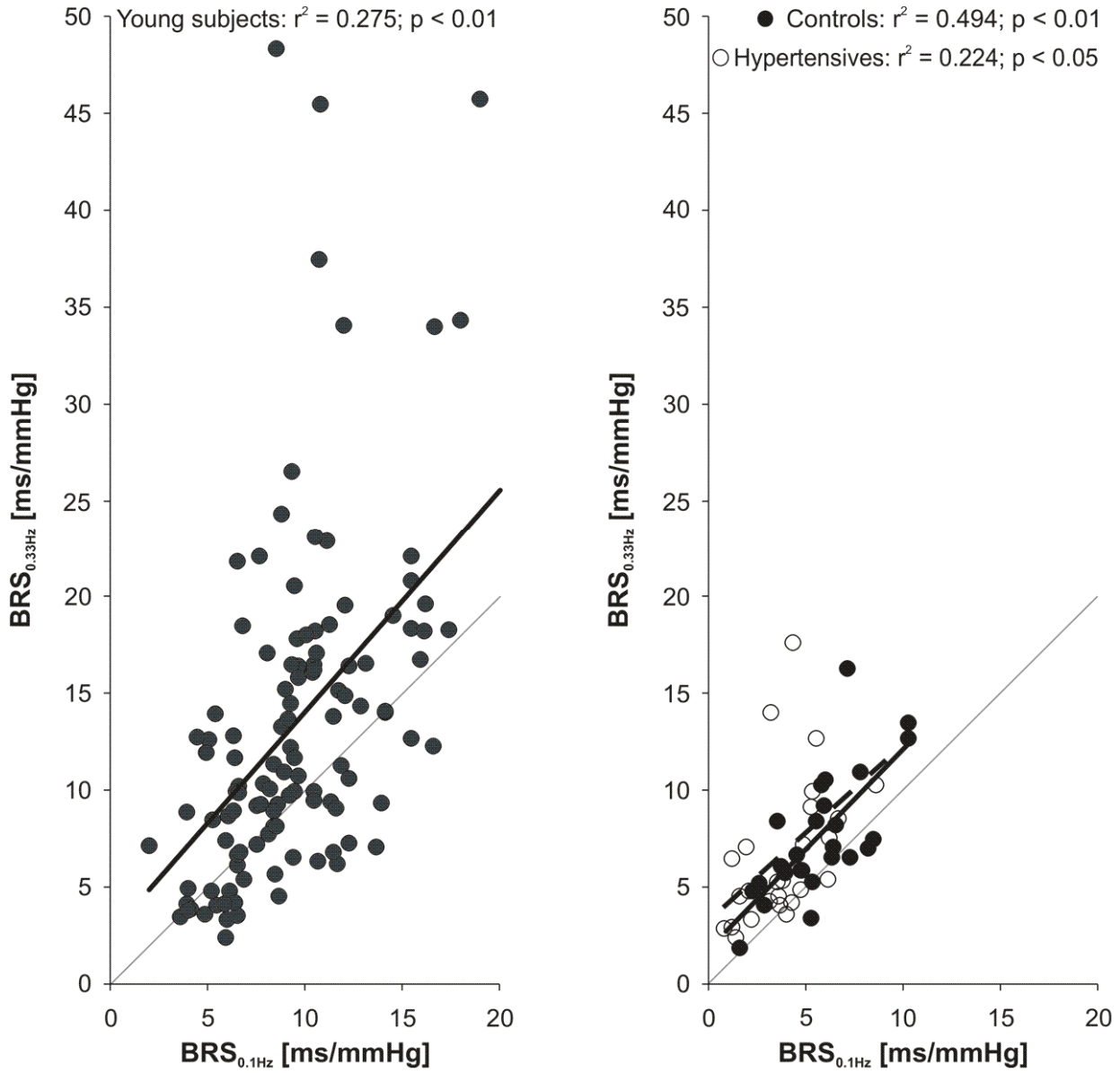

Fig. 2. Correlation between $BRS_{0.1Hz}$ and $BRS_{0.33Hz}$ in young healthy subjects (left), and in controls to hypertensive patients and hypertensive patients (right). $BRS_{0.1Hz}$ – baroreflex sensitivity at 0.1 Hz; $BRS_{0.33Hz}$ – baroreflex sensitivity at 0.33 Hz. Left – dots and thick full line – young subjects, thin line – identity line. Right – dots and thick full line – controls to hypertensive patients, circles and dashed line – hypertensive patients, thin line – identity line.

Discussion

The difference between BRS values determined at 0.33 Hz and 0.1 Hz frequencies was explained using a combination of the BRS index with mechanisms of blood pressure and inter-beat interval variations in these two frequency bands. BRS is defined as the change of the inter-beat interval per unit of blood pressure change. From this point of view, the regulatory link between blood pressure and inter-beat interval changes is mediated only by vagal nerve input at breathing frequency. However, it has been previously shown using pharmacological blockade that although vagal control of heart rate is also dominant at 0.1 Hz, sympathetic control is involved as well (Akselrod *et al.* 1981). When comparing the calculated value of BRS at the breathing and 0.1 Hz frequency ranges, it is necessary to keep in mind that the respiratory sinus arrhythmia is mediated not only by baroreflex but also by a central component (Eckberg 2003, Gilad *et al.* 2005, Eckberg and Karemaker 2009, Tzeng *et al.* 2009), by afferent stimuli from stretch receptors in the lungs and thoracic wall (Taha *et al.* 1995), and by resonance (van de Vooren *et al.* 2007).

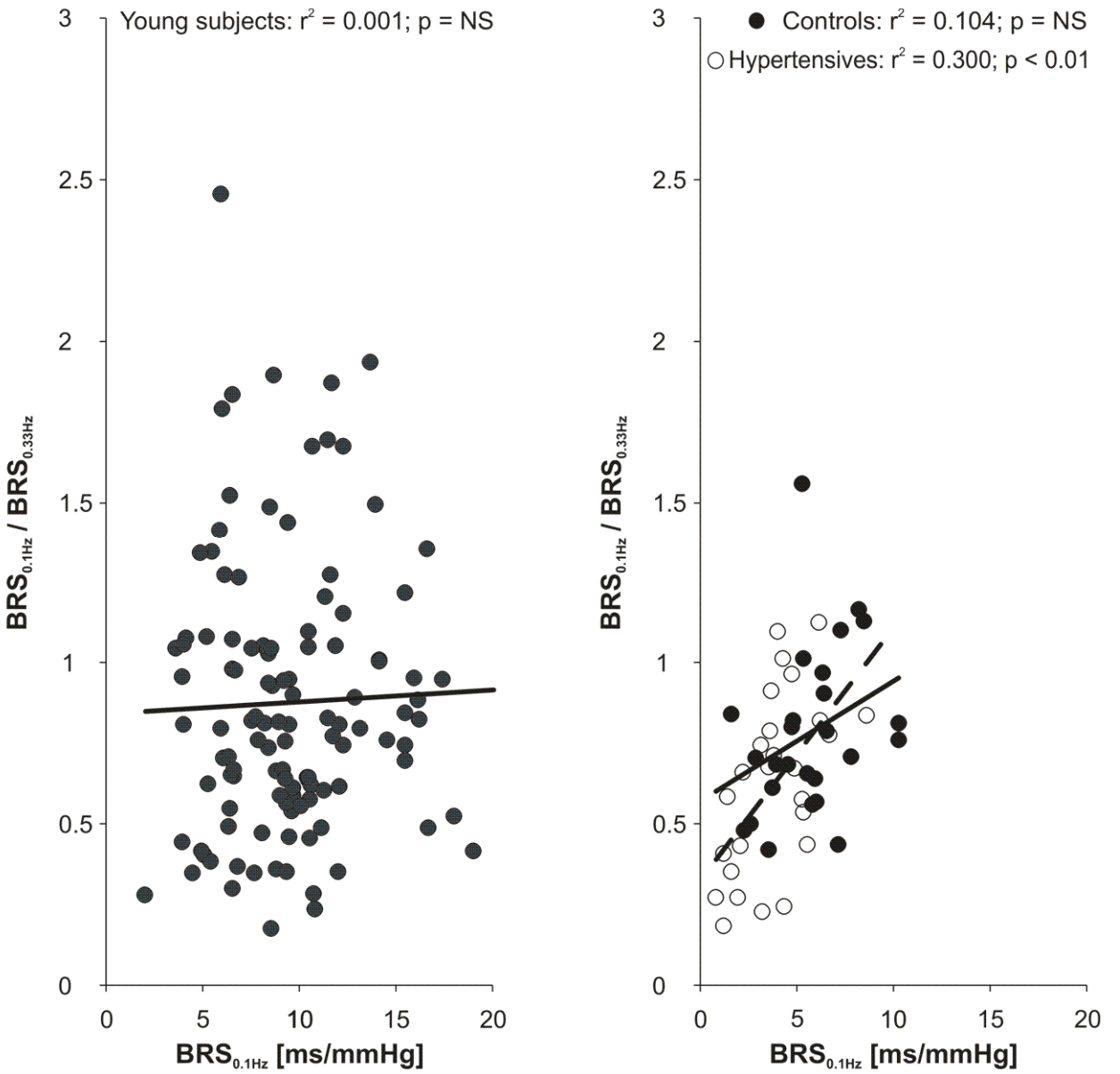

Fig. 3. Correlation between the ratios of $BRS_{0.1Hz}/BRS_{0.33Hz}$ and $BRS_{0.1Hz}$ in young healthy subjects (left), and in controls to hypertensive patients and hypertensive patients (right). Left – dots and thick full line – young subjects; right – dots and thick full line – controls to hypertensive patients, circles and dashed line – hypertensive patients.

In the present study, our previous observation of individual differences in BRS determined in one recording at different rhythms, respiratory and 0.1Hz, obtained in a small group of subjects (Honzíková *et al.* 1992) was confirmed. This indicates the existence of a breathing-dependent non-BRS-related component that differs among individuals. Furthermore it is known that during spontaneous breathing individual differences in the frequency and regularity of respiration are present. These variations in the depth and frequency of respiration cause variations in blood pressure and heart rate in low frequency band (at 0.1 Hz and slower rhythms) interfering with different mechanisms of origin (Honzíková 1996) and enhancing BRS calculated at 0.1 Hz (Fredericks *et al.* 2000). Therefore, it is necessary to decide whether to establish the BRS on several-minute-lasting recordings of resting blood pressure and inter-beat intervals fluctuations during spontaneous or controlled breathing. Evidently, controlled breathing is preferred. As to possible mental load associated with controlled breathing, Pinna *et al.* (2006) supported the idea that paced breathing near a spontaneous respiratory frequency does not alter cardiovascular autonomic regulation in comparison with spontaneous breathing.

Our study clearly documents that the values of BRS at 0.1 Hz calculated under conditions separating

circulatory LF fluctuations from respiratory influences are lower compared with BRS values at respiratory rate, but this phenomenon is present only statistically; an opposite relationship can occur in some subjects. Fredericks *et al.* (2000) have also shown that respiration at the frequency of 0.1 Hz enhanced the value of BRS determined at 0.1 Hz compared with BRS if respiration was controlled at the frequency of 0.25 Hz. However, many clinical studies use a sequence method (Pozza *et al.* 2007, Ormezzano *et al.* 2008, Madden and Lockhart 2009) or spectral analysis of spontaneous variations in blood pressure and heart rate (Johansson *et al.* 2005, Nasr *et al.* 2005, Frasch *et al.* 2009), or at paced breathing at resonance frequency of 0.1 Hz (Halamek *et al.* 2003). On the other hand, this special approach of paced breathing at 0.1 Hz as applied in patients with heart failure seems to be of clinical relevance using evaluation of phase shift (Halamek *et al.* 2003).

In conclusion, determination of BRS by spectral method at spontaneous breathing frequency overestimates real BRS. For diagnostic purposes we recommend the evaluation of BRS at the frequency of 0.1 Hz using metronome-controlled breathing at a frequency that is substantially higher than 0.1 Hz and is not a multiple of 0.1 Hz to eliminate respiratory baroreflex-non-related influence and resonance effect on heart rate fluctuations.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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