The Significance of Baroreflex Sensitivity in Hypertensive Subjects with Stroke.

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Short title: Baroreflex Sensitivity and Stroke.

Summary

The relationship between baroreflex sensitivity expressed in ms/mmHg (BRS) and in Hz/mmHg (BRSf) in hypertensives with stroke in comparison with a group of stroke-free control ones was evaluated. A total of 26 patients (66±10 years of age, 11 female/15 male) with a history of the first ever ischemic stroke (6 month and more after stroke onset), which was neuroradiologically confirmed, were studied. These were compared to 30 hypertensive patients without history of any cardiovascular event, being of similar age and sex. BRS and BRSf were determined by the sequence and spectral methods (five-minute non-invasive beat-to-beat recording of blood pressure and inter-beat interval, controlled breathing at a frequency of 0.1 Hz). A significant negative correlation between spontaneous BRS and blood pressure (BP) represented by grade of hypertension was present ($r = –0.52$, $p<0.001$). Differences between hypertensives with stroke and stroke-free control ones were detected in BRS obtained by the spectral method (BRS spect $p=0.0237$, BRSf spect $p=0.0285$) or BRS obtained by sequence method (BRS seq $p=0.0532$, BRSf seq $p=0.0273$). The greatest decline in BRS values was in hypertensive stroke patients with metabolic syndrome, who had BRS values <3 ms/mmHg. We found out that BRS and BRSf were more impaired in stroke patients with essential hypertension even 6 months and more after stroke onset than in stroke free hypertensive patients. This finding was independent of age-dependent decrease of BRS. Examination of baroreflex sensitivity as a marker of autonomic dysfunction along with global cardiovascular risk stratification of individuals seems to be a method for identifying patients at high residual cardiovascular risk.

Key Words: Baroreflex sensitivity, Autonomic nervous system, Hypertension, Stroke, Age.

Introduction

Arterial baroreflex is one of the most important physiological mechanisms controlling homeostasis of blood pressure (BP) (Schachter 1997). Impaired baroreflex sensitivity (BRS) is a marker of autonomic dysfunction; it plays a major role in the long-term development of arterial hypertension and related complications (Schachter 1997, Izzo *et al.* 1999). BP is one of the most powerful determinants of stroke, however not a single one. The function of arterial baroreflex seems to be another important determinant in the process (Liu *et al.* 2007). Stroke is the third leading cause of death worldwide after heart disease and cancer (Baker 2008). Approximately 15 million people are affected by stroke annually, of whom one third die and another third is permanently disabled (Baker 2008). Currently, much interest has been focussed on the interaction between autonomic dysfunction and global cardiovascular risk. Baroreflex system exhibits a degree of tonic negative feedback by aortic-carotid and cardiopulmonary baroreceptors, so that it can alter sympathetic and parasympathetic nervous system output immediately, providing counter-regulatory increases and decreases in pressure or volume to maintain homeostasis (Izzo *et al.* 1999). The baroreceptors regulate BP by means of vagal component that reduces the heart rate or alternatively, by adrenergic component increasing peripheral resistance and heart rate (Schrezenmaier *et al.* 2007). BRS is quantified in ms of R-R interval duration to each mmHg of arterial pressure. Normal BRS value is approximately 15 ms/mmHg (La Rovere *et al.* 2001), shows large interindividual differences (Jíra *et al.* 2006). Index BRSf expressed in Hz/mmHg is less dependent on pulse interval changes than BRS (Al-Kubati *et al.* 1997). Reduced BRS is associated with a shift in autonomic balance towards sympathetic dominance, which leads to coronary vasoconstriction, platelet aggregability, arrhythmogenesis, impaired ventricular remodelling and higher cardiovascular risk (Mancia *et al.* 1999, Robinson *et al.* 2003). Increased activity of sympathetic nervous system together with the renin-angiotensin-aldosteron system result in

vascular changes, arterial stiffness, and increased BP eventually causing myocardial hypertrophy (Mancia *et al.* 1999). These effects contribute to a vicious cycle of hypertension and related complications.

Furthermore, the baroreceptor reflex is considered to be blood pressure buffer system for damping short-term variations of arterial pressure (Schachter 1997). It has always been thought that baroreceptors have minor importance in "chronic" hypertension because of complete resetting to any new mean arterial pressure level (Persson 2005). The ability of baroreceptors to normalize increases in BP is achieved by a process termed as resetting. BP has to remain elevated for 48 hours in order for complete resetting to occur (Krieger 1988). The current role of arterial baroreceptors in hypertension is being reviewed. Baroreflex is the most important nervous regulatory mechanism involved not only in short-term but also in long-term BP control (Persson 2005). Decreased BRS with additional risk factors (obesity, lack of exercise, smoking) in children and adolescents predisposes to the development of an early stage of essential hypertension (Krontorádová *et al.* 2008).

Mechanisms and effects of blood pressure dysregulation in stroke are not fully elucidated. Central control mechanisms of baroreflex arch that are vital for its integrity may be damaged after stroke (Robinson *et al.* 2003). Impaired cardiac BRS may be due to impaired central processing of baroreceptor information following stroke or reduced baroreceptor activity due to increased large artery stiffness (Eveson *et al.* 2005). Previous experimental studies suggested that BRS is damaged after acute ischemic stroke (within 72 hours of acute stroke onset) and that it predicts the long-term disability and mortality associated with stroke (Robinson et al. 2003). Decreased BRS was found in patients with acute intracerebral hemorrhage and correlated with increased beat-to-beat BP variability (Sykora *et al.* 2008). The value of baroreflex sensitivity in hypertensive subjects with stroke in chronic phase has not been extensively studied. The aim of the present study was to evaluate significance of

spontaneous BRS and BRSf in hypertensive patients 6 month and more after stroke onset (chronic phase). The relationship between cardiac BRS or BRSf in hypertensives with stroke in comparison with a group of stroke-free control ones was evaluated.

Methods

We studied 56 treated hypertensives (thirty-two male/ twenty-four female). A total of 26 patients (fifteen male/ eleven female, mean±SD: age 66±10 years, range 45-85 years, body mass index 32.0±3.5 kg/m^2) with a history of the first ever ischemic stroke (6 – 24 months after stroke onset), which was neuroradiologically confirmed (CT, NMR), were studied. These were compared to 30 hypertensive patients (seventeen male/ thirteen female, mean±SD: age 65±6 years, range 43-82 years, body mass index 28.5±3.2 kg/m^2) without history of any cardiovascular event. Patients with stroke commonly suffered from type 2 diabetes mellitus (34.6% vs. 13.3%), arrhythmias in the history (23.0% vs. 3.3%) in comparison to patients without stroke. Stroke patients had higher body mass index (32.0±3.5 kg/m^2 vs. 28.5±3.2 kg/m^2) and surprisingly lower total serum cholesterol level (4.43±1.36 vs. 4.94±1.20 mmol/l).

The study was performed in the department of non-invasive cardiology at the Faculty of Medicine at UPJS in Kosice. All subjects were examined according to standardized protocol. The diagnosis of hypertension was established by Hypertension guidelines from the European Society of Hypertension/European Society of cardiology 2007, secondary forms of hypertension were excluded. Patients were on standard antihypertensive and hypolipidemic - statins therapy. These included: calcium channel blockers (n=26), beta-blockers (n=32), angiotenzin-converting enzyme inhibitors (n=41), diuretics (n=14), central antihypertensive agents (n=7), statins (n=38) and acetylsalicylic acid (n=28). In both groups of subjects there were no significant differences in the standard antihypertensive therapy. Exclusion criteria

included the following: atrial fibrilation, recordings of more than five ectopics per minute and other cardiac arrhythmias, present-day mean systolic BP > 160 mmHg or diastolic BP > 100 mmHg, acute myocardial infarction, history and evidence of left ventricular dysfunction, unstable angina, renal function impairment (creatinine more than 200 μmol/l), age under 18 years old, non-cooperative patient, and end-stage diseases. All subjects had a history of arterial hypertension, and were in sinus rhythm. They were hemodynamically stable, independent in their daily living activities, subjects with diabetes mellitus had $HbA_{1c} \leq 6.5\%$. Patients were from the Department of Geriatric Medicine and 4th Department of Internal Medicine of the UPJS Faculty Hospital in Košice. All subjects gave their informed written consent, and the local Ethics committee approved of the study.

BP was measured continuously by the non-invasive BP monitor (COLLIN CBM 7000, Japan), with the appropriately sized cuff applied to the wrist of the hemiparetic arm in stroke subjects and non-dominant arm in control subjects. The cuff was maintained at heart level. The non-invasive BP monitor uses vascular unloading technique to measure systolic BP, diastolic BP on a beat-to-beat basis. Control BP was measured in the brachial artery on the other arm by the ausculatory technique. Three surface electrocardiographic chest leads were attached for continuous ECG monitoring.

Patients were asked to avoid alcohol, caffeine and nicotine 24 hours prior to procedure. The examination was performed in a quiet room at a constant temperature with subdued light. After 15 minutes of rest, after achievement satisfactory BP and ECG signal and the stabilization of BP at the same level, a phase of first recording followed. Subjects lay supine on a coach with their heads propped up.

Special sensor (COLLIN CBM 7000, Japan) was placed around wrist where radial artery is maximally pulsatile for beat- to-beat indirect continuous 5-min blood pressure recordings and inter-beat interval (IBI) measurements. Subjects were asked to maintain a respiratory rate 17-

20 breaths per minute. They were allowed to adjust the tidal volume according to their own comfort. Breathing was synchronized by a metronome at 0.33 Hz. Three consecutive 5-minute recordings of BP and IBI were obtained. In each subject the arithmetic average of three recording was calculated. Signals were low-pass filtered. A non-invasive monitor of BP and IBI (COLLIN CBM 7000, Japan) was used. IBI and BP were recorded simultaneously to a computer with an analogue digital converter. The data were analysed using specially designed software.

The spontaneous fluctuations in systolic BP and IBI were analysed with the two methods: spectral technique using a protocol of controlled breathing (BRS spect) and sequence technique (BRS seq). We performed cross-spectral analysis to assess the IBI changes associated with systolic BP oscillations. BRS or BRSf was estimated from the modulus of the cross spectrum of R-R interval and systolic BP at a frequency of 0.1 Hz. BRSf index was calculated on the basis of the instantaneous value of IBI measured beat-by-beat. The BRS seq was assessed by analysing the slopes of spontaneously occurring sequences of three or more consecutive beats in which systolic BP and IBI of the following beat increased or decreased in the same direction in a linear fashion.

Statistics

The data were analysed using Scope Win 95 software. Statistical data were expressed as mean±SD, category variables in percentage. For each BRS measurement, a single regression analysis was performed. The Pearson coefficients of correlation were calculated for each variable. Comparisons between data obtained in different groups were made by analysis of variance (ANOVA). Antihypertensive medications and statins were not excluded, therefore they were considered to be another variable. A P value of <0.05 was considered to be significant. Statistical analysis was performed using Microsoft Office Excel and GNU Octave 2.1.73

Results

56 subjects were divided into 3 groups based on grades of hypertension according to new consensus Hypertension guidelines from the European Society of Hypertension/European Society of cardiology 2007 (table 1). The majority of patients belonged to the category of arterial hypertension grade 2 and 3. Significant negative correlation between spontaneous BRS and BP represented by grade of hypertension was present ($r = –0.52$, $p<0.001$). Essential hypertension is associated with decreased BRS/BRSf and that the higher the grade of hypertension present the lower BRS/BRSf values found ($p=0.0012/p=0.0015$). The most evident decline in BRS/BRSf was in grade 3 of arterial hypertension ($p<0.05/p<0.05$), especially in patients with target organ damage as stroke. The value of spontaneous BRS was lower in stroke hypertensive patients than in stroke-free hypertensive controls: BRS obtained by the spectral method (BRS spect) was 4.0±2.2 vs. 6.4±3.5 ms/mmHg, $p=0.0237$ or BRS obtained by the sequence method (BRS seq) was 5.9±3.0 vs. 8.4±6.4 ms/mmHg, $p=0.0532$. We also revealed significant BRSf decrease in hypertensives with stroke (BRSf spect $p=0.0285$, BRSf seq $p=0.0273$). The differences between baroreflex sensitivity parameters (BRS and BRSf) in hypertensives and hypertensives with stroke are presented in table 2. The coincidence of arterial hypertension, diabetes mellitus, metabolic syndrome (presence of essential hypertension, insulin resistance, glucose intolerance, abnormal lipoprotein metabolism and central obesity) and stroke is associated with extremely high cardiovascular risk. All 5 patients with these criteria had BRS values <3 ms/mmHg, higher grade of disability and 2 of them died during one year. A clinically noticeable difference in gender was not shown in BRS values. The mean BRS seq was 5.5±3.4 ms/mmHg in women vs. 5.8±5.7 ms/mmHg in men, the mean BRS spect was 6.0±3.9 ms/mmHg in women vs. 6.1±3.8 ms/mmHg in men.

An inverse relationship between age and BRS has been demonstrated ($r = –0.34$, $p<0.05$). BRS determined by the spectral and sequence method was correlated with biological parameters. There was only a slight positive correlation between BRS and serum cholesterol ($r = 0.51$, $p<0.05$).

Discussion

It was previously shown that BRS was impaired after acute stroke (72 hours within of acute stroke onset in Robinson *et al.* study 2003, Sykora *et al.* 2008). There is also established evidence of abnormal BRS in animal models after stroke and other cerebrovascular diseases (Liu *et al.* 2007, Robinson *et al.* 2003). One study on rats demonstrated that BRS is a new predictor for stroke incidence in hypertension and that pharmacological restoration of arterial baroreflex function by a small dose of ketanserin can delay the occurrence of stroke in rat (Liu *et al.* 2007). In our study we have demonstrated that the value of BRS and BRSf was significantly lower in hypertensive subjects even 6 months and more after ischemic stroke onset (chronic phase) in comparison to stroke-free hypertensive controls. BRS values reflect sensitivity of baroreceptors and balance of the autonomic nervous system in the body, but BRSf index corresponds only to the baroreceptor activity. Using the two indices BRS and IBI-independent BRSf we could evaluate complex BRS and better reflect the development of the BRS (Zavodna *et al.* 2006), especially in patients with target organ damage. Several studies have confirmed that essential hypertension is connected with decreased BRS (Head 1994, Ormezzano *et al.* 2008). In support of these studies we have confirmed noticeable negative correlation between BRS and BP. Essential hypertension was associated with decreased BRS, and grade of hypertension was inversely correlated with BRS values. The most evident decline in BRS values was found in those with grade 3 arterial hypertension, especially in patients with target organ damage such as stroke. Patients with stroke suffered more from type

2 diabetes mellitus and arrhythmias in the history (atrial fibrillation), had higher body mass index (BMI) and lower total serum cholesterol level in comparison to patients without stroke. Hypertensive stroke patients with metabolic syndrome had BRS values <3 ms/mmHg. The finding that impaired BRS is not a benign phenomenon was confirmed by Robinson study and multicenter ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study in patients after myocardial infarction. Stroke patients with BRS ≤5 ms/mmHg in Robinson study had a poorer prognosis (28% vs. 8% mortality rate during follow up period), there were no significant differences in age, stroke severity, stroke type, or casual BP (Robinson *et al.* 2003). BRS is an independent risk factor for morbidity and major adverse cardiovascular events in hypertensive patients (Ormezzano *et al.* 2008). Except for classic risk factors such as elevated blood pressure, abnormal serum lipids or glucose, BRS seems to be an integral predictor for future cardiovascular events in patients with arterial hypertension (Lantelme *et al.* 2002). Furthermore, it is convenient in clinical practice for being non-invasively measured. Cerebral infarction can significantly affect cardiovascular regulation that is associated with adverse prognosis. Cardiac complications of stroke patients are common, including ventricular arrhythmias, sudden death and symptoms related to ischemic heart disease. Impaired cardiac BRS after acute stroke may also be associated with central autonomic cardiovascular dysautoregulation (Robinson *et al.* 2003, Sykora *et al.* 2008). A diminished BRS and also heart rate variability is an independent risk factor for sudden death (La Rovere *et al.* 2000). According to ATRAMI and Robinson studies, impaired BRS seems to provide a long-term prognostic value for cardiovascular morbidity and mortality (Robinson *et al.* 2003, La Rovere *et al.* 2000).

The influence of population characteristics on the values of BRS was examined. An inverse relationship between BRS and age was demonstrated. A combination of high BP and old age was associated with a significant reduction in BRS. Hypertension and ageing may

have a synergistic effect on cardiac parasympathetic function, which ultimately cause prolongation in baroreflex response (Peckerman *et al.* 2001). A defect in central mediation of arterial baroreflex especially in stroke patients may be the major cause of impaired baroreflex with aging rather than decreased vascular distensibility or a defect in the generation of baroreceptor activity (Chapleau *et al.* 2005). A total of 26 hypertensive subjects with stroke were compared to 30 hypertensive patients, being of similar age, to eliminate age-dependent decrease of BRS. Age-dependent decrease of BRS corresponds to the age-related structural changes of the carotid wall (Láborová *et al.* 2005). Measurement of intima-media thickness of the carotid wall along with BRS measurement seems to be additive method for identification cardiovascular risk in hypertensives and subclinical atherosclerosis in subjects with high normal BP. BRS could identify hypertensives with major cardiovascular events on statin therapy who have very high cardiovascular risk, but different residual risk to become a victim of another cardiovascular event. A clinically significant difference with gender was not shown in BRS values.

Antihypertensive and statin therapy, which was not excluded, could have influenced BRS values. Long-term BP control with modern antihypertensive drugs such as Angiotenzin converting enzyme inhibitors (ACEI), Angiotenzin II receptor blockers, Calcium channel and Beta-blockers improves baroreflex functions (Munakata *et al.* 2003, Gonsorčík *et al.* 2002, Chen *et al.* 1999). Despite the fact that potential increases in BRS values may have resulted from these medications in hypertensive and stroke patients, they had BRS values still impaired in comparison with healthy subjects. It is evident that the influence of medication on BRS values and interpretation of results needs more investigation in the future. The study needs to have a prospective focus in order to establish BRS as a novel risk stratifier in hypertensive patients.

We conclude that autonomous nervous dysfunction and the inappropriately active sympathetic nervous system in patients with arterial hypertension is an important etiopathogenetic factor that contributes also to progression of disease, and the resultant cardiovascular risk. In this study, BRS and BRSf values were more impaired in ischemic stroke patients (chronic phase) with essential hypertension than in stroke free hypertensive patients. Hypertensive stroke patients with metabolic syndrome features had BRS values <3 ms/mmHg. Examination of baroreflex sensitivity as a marker of autonomic dysfunction along with global cardiovascular risk stratification of individuals seems to be a method for identifying patients at high cardiovascular risk. Using the two indices BRS and IBI-independent BRSf we could evaluate complex BRS and better reflect the development of the BRS in patients with target organ damage.

Acknowledgement

There is no form of financial support or grant associated with this study.

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List of Tables:

Table 1. Baroreflex sensitivity values obtained by both sequence and spectral methods based on grade of arterial hypertension.

Arterial hypertension category	SBP (mmHg)	DBP (mmHg)	BRS seq vs. BRS spect ms/ mmHg	BRSf seq vs. BRSf spect Hz/mmHg
grade1 N = 5 (8.92%)	140 -159	90 - 99	8.4±3.0 vs. 9.5± 4.0	0.0082±0.0040 vs. 0.0090±0.0035
grade2 N=22 (39.28%)	160 -179	100 -109	7.2±6.9 vs. 8.4±6.4	0.0075±0.0035 vs. 0.0079±0.0030
grade3 N=29 (51.78%)	≥ 180	≥ 110	4.5±2.5 vs. 6.4±5.4	0.0052±0.0020 vs. 0.0055±0.0035

The values are presented as mean ± standard deviation (SD), category variables in percentage, BRS – baroreflex sensitivity in ms/mmHg, BRSf – baroreflex sensitivity in Hz/mmHg, BRS seq – BRS values obtained by sequence method, BRS spect – BRS values obtained by spectral method, SBP – systolic blood pressure, DBP – diastolic blood pressure, N– total of subjects (percentage)

Table 2. Differences between baroreflex sensitivity parameters in hypertensives and hypertensives with stroke

Parameter	Hypertensives n= 30	Hypertensives with stroke n=26	P-value
Systolic/diastolic blood pressure (mmHg)	127/81 ± 13/9	139/85 ± 10/7	0.0417/ 0.0911NS
Inter-beat-interval (ms)	834 ± 126	816 ± 157	0.0451
BRS seq (ms/mmHg)	8.4 ± 6.4	5.9 ± 3.0	0.0532 NS
BRSf seq (Hz/mmHg)	0.0083 ± 0.0045	0.0055 ± 0.0030	0.0273
BRS spect (ms/mmHg)	6.4 ± 3.5	4.0 ± 2.2	0.0237
BRSf spect (Hz/mmHg)	0.0090 ± 0.0047	0.0064 ± 0.0022	0.0285

The values are presented as mean ± standard deviation, BRS seq – baroreflex sensitivity values obtained by sequence method in ms/mmHg, BRS spect – baroreflex sensitivity values obtained by spectral method in ms/mmHg, BRSf seq – baroreflex sensitivity obtained by sequence method in Hz/mmHg, BRSf spect – baroreflex sensitivity obtained by spectral method in Hz/mmHg, statistical analysis by ANOVA, NS–not significant