Physiol. Res. 54: 593-600, 2005

Age-dependent Relationship between the Carotid Intima-Media Thickness, Baroreflex Sensitivity, and the Inter-Beat Interval in Normotensive and Hypertensive Subjects

R. LÁBROVÁ, N. HONZÍKOVÁ[1], E. MADĚROVÁ, P. VYSOČANOVÁ, Z. NOVÁKOVÁ[1], E. ZÁVODNÁ[1], B. FIŠER[1], B. SEMRÁD

Department of Internal Cardiology, Faculty Hospital, and [1]Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Received February 15, 2005
Accepted May 4, 2005

Summary

The interrelationship between baroreflex sensitivity expressed in ms/mm Hg (BRS) or in Hz/mm Hg (BRSf), carotid wall thickness (IMT), and age was investigated in hypertensive and normotensive subjects with respect to the mean inter-beat interval (IBI) and blood pressure (BP). BP monitoring was performed in 25 treated hypertensives (Hy; 47.4±9.2 years of age) and 23 normotensives (Norm; 44.5±8.1 years). IMT was measured by ultrasonography. BRS and BRSf were determined by the spectral method (five-minute non-invasive beat-to-beat recording of BP and IBI, Finapres, controlled breathing at a frequency of 0.33 Hz). Significant differences between Hy and Norm were detected in IMT (Hy: 0.624±0.183, Norm: 0.522±0.070 mm; p<0.01), BRS (Hy: 3.5±1.6, Norm: 5.7±2.3 ms/mm Hg; p<0.01), BRSf (Hy: 0.005±0.002, Norm: 0.009±0.004 Hz/mm Hg; p<0.01), systolic BP (Hy: 131±21, Norm: 116±17 mm Hg; p<0.01) and diastolic BP (Hy: 77±16, Norm: 64±12 mm Hg; p<0.01). A significant correlation was found between age and IMT (Norm: 0.523, p<0.05; Hy+Norm: 0.419, p<0.01), age and BRS (Norm: -0.596, p<0.01; Hy+Norm: -0.496, p<0.01), age and BRSf (Norm: -0.555, p<0.01; Hy: -0.540, p<0.01; Hy+Norm: -0.627, p<0.01), age and IBI (Hy: 0.478, p<0.05), age and diastolic BP (Hy: -0.454, p<0.05), BRS and IMT (Hy+Norm: -0.327, p<0.05) and BRSf and IMT (Hy+Norm: -0.358, p<0.05). Hypertensive patients have increased IMT and decreased BRS and BRSf. The positive correlation between age and IMT and the negative correlation between age and BRS and BRSf are in agreement with the hypothesis that the age-dependent decrease of baroreflex sensitivity corresponds to the age-related structural changes of the carotid wall. Using two indices of baroreflex sensitivity, BRS and BRSf, we could show that baroreflex sensitivity in hypertensives is lower not only due to thickening of the carotid wall, but also due to aging.

Key words
Intima-media thickness • Baroreflex sensitivity • Hypertension • Age • Heart rate

Introduction

Changes in arterial blood pressure are sensed indirectly through baroreceptor responsiveness to mechanical deformation during vascular stretch. Arterial baroreceptors are mechanosensitive nerve endings that innervate the adventitia of the carotid sinus and aortic arch. Changes in the frequency of baroreceptor afferent

Fax +420 241 062 164
E-mail: physres@biomed.cas.cz http://www.biomed.cas.cz/physiolres

discharges transmitted to the central nervous system trigger reflex adjustments that buffer or oppose changes in pressure, i.e. the baroreceptor reflex provides a powerful negative feedback mechanism of blood pressure regulation.

The baroreflex regulates short-term variations in blood pressure through autonomic adjustments of heart rate, cardiac output, and peripheral resistance. Usually, baroreflex sensitivity is studied, which is defined as the change of the inter-beat interval (IBI) due to a change of systolic blood pressure. This index abbreviated as BRS is expressed in ms/mm Hg. Most often, dynamic changes of the BRS and mean IBI are concomitant (Honzíková *et al.* 1997). Under certain circumstances, such as aging (Závodná *et al.* 2001) or a central effect of substance P (Brattstrom and Seidenbecher 1992), the tonic and short-term reflex heart-rate regulation can be partially independent of each other. Therefore the index BRSf in Hz/mm Hg was introduced (Al-Kubati *et al.* 1997), which is less dependent on the mean IBI than BRS.

Baroreflex sensitivity decreases with age in healthy subjects. This decline of BRS with age was first described by Gribbin *et al.* (1971) and confirmed not only in healthy (Madden *et al.* 2003) but also in post-myocardial infarction patients (Al-Kubati *et al.* 1999). A plausible explanation of these results may be due to an increase of arterial stiffness and a decrease of baroreceptor sensitivity.

Impairment of baroreflex sensitivity may have an important effect on long-term regulation of blood pressure. It is low in hypertensive patients as was described in a large number of studies. It is not fully elucidated whether this decrease is primary and which mechanisms lead to the dampening of baroreflex sensitivity. Stiffening of the aortic wall and of the carotid sinus wall is likely to decrease the sensitivity of aortic and carotid baroreceptors. The measurement of the intima-media thickness (IMT) evaluates the changes of the intima, which may correspond to hyperplasia or atherosclerosis together, and also adaptive changes in the region of the media, which may be adaptively remodeled in response to hemodynamic changes, for instance in hypertensive patients. It was proved that ultrasound measurement at the far wall of the carotid artery is in good agreement with histological measurements. The latest studies have shown the association of an increase in IMT with hypertension (Zanchetti *et al.* 1998, de Vries *et al.* 2000, Tanaka *et al.* 2001). A correlation of carotid artery stiffness with age in young adults has also been reported (Urbina *et al.* 2004).

The hypothesis that an age-dependent decrease of baroreflex sensitivity in healthy subjects is related to an age-dependent increase of IMT and additively augmented in hypertensive patients was the aim of the present study. Therefore, the association of IMT with baroreflex sensitivity was analyzed in their complex involvement in an autonomous regulation of heart rate and blood pressure (BP) in healthy and hypertensive subjects. The relationship between IMT and baroreflex sensitivity was studied in normotensives and hypertensives with respect to their age and to the signs of tonic autonomic control of heart rate and blood pressure as mean IBI for 5 min and blood pressure measured in finger arteries or monitored for 24 h. Two indices of baroreflex sensitivity, BRS and BRSf, were evaluated to disclose, and suppress respectively, the effect of mean heart rate on the index of baroreflex sensitivity.

Methods

Subjects

We studied 25 treated hypertensives (eleven men and fourteen women; mean±SD: age 47.4±9.2 years, range 24-58 years, body height 171.4±10.3 cm, weight 79.9±15.4 kg, body mass index 27.1±4.2 kg/m^2) and 23 normotensives (seven men and sixteen women; age 44.5±8.1 years, range 25-58 years, body height 169.9±6.3 cm, weight 74.1±13.2 kg, body mass index 25.6±3.8 kg/m^2). There were no significant differences between the two groups in these baseline characteristics. Patients with hypertension were recruited randomly from the outpatient Departments of Internal Cardiology of the Faculty Hospital in Brno. All patients had mild-to-moderate essential hypertension and they had no history or evidence of left ventricular dysfunction, previous myocardial infarction, stroke, or diabetes mellitus. The diagnosis of hypertension was established by the presence of increased BP (≥140 mm Hg systolic and ≥90 mm Hg diastolic BP) and the absence of clinical or laboratory evidence suggestive of secondary forms of hypertension. Hypertension was diagnosed as sustained on the basis of several BP measurements made successively by the general practitioner referring the patient to the Faculty Hospital in Brno.

Predictably, all patients were receiving blood-pressure lowering medications and some also lipid-lowering medications with cardiovascular effects. These included: diuretics (n=10), calcium channel blockers (n=9), angiotensin-converting enzyme inhibitors (n=11), beta-blockers (n=18), and statins (n=2). Discontinuation of medications for the purpose of this study was not justified.

Control subjects were recruited from volunteers at the Department of Internal Cardiology and the Department of Physiology. All subjects gave their informed consent, and protocols were approved by the ethics committee.

Carotid ultrasound

Ultrasound measurement of carotid intima-media thickness represents the measurement of a double contour of the vessel wall of the carotid artery, which results from an ultrasound echo from two differently echogenic tissues. The first contour on the far wall of the common carotid corresponds to the transition between non-echogenic blood and the hyperechogenic intima; the second contour corresponds to the transition between the hypoechogenic media and the hyperechogenic adventitia.

B-mode ultrasonography was performed in all subjects in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (Agilent Sonos 5500, Philips) equipped with a 3-11 MHz high-resolution transducer. Measurements were performed on both the right and left common carotid artery. The artery was examined on the farther wall from the transducer at a distance of 1 cm proximally from the transition of the *a. carotis communis* into the bulbus. Five measurements in this position were performed (sections of 2 mm) twice by the same physician and an average of these measurements was calculated. Subsequently, using these average values we determined the mean value of both (*a. carotis dextra* and *sinistra*) as an average IMT.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was carried out by the Tonoport IV device (Marquette Hellige). The cuff was placed on the non-dominant arm. The device was programmed to take a blood pressure measurement every 20 min (day-time) or every 40 min (night-time). The time at which the device was applied was the same (±1 h) in all patients. The patients were instructed to attend their usual day-to-day activities but to keep still at the times of measurements. The recording was then analyzed to obtain day-time (from 06:00 to 18:00 h) and night-time (from 22:00 to 05:00 h) average systolic and diastolic blood pressures and heart rate.

Baroreflex sensitivity

We recorded inter-beat intervals, systolic and diastolic blood pressures beat-to-beat, on finger arteries by the Penaz non-invasive method (Finapres OHMEDA, USA) in all subjects. The recordings were taken in the sitting position at rest during a 5-min period. Breathing was synchronized by a metronome at 20 breaths per minute (0.33 Hz) and the subjects were allowed to adjust the tidal volume according to their own comfort. The gain factor, e.g. modulus H(f) of the transfer function among variations in systolic blood pressure and inter-beat intervals, was calculated at a frequency of 0.1 Hz according to the formula: $H(f) = Gxy(f)/Gxx(f)$, where Gxy(f) corresponds to the cross-spectral density between systolic blood pressure and inter-beat intervals and Gxx(f) corresponds to the spectral density of systolic blood pressure. The value of the modulus at a frequency of 0.1 Hz was taken as a measure of baroreflex sensitivity, BRS (ms/mm Hg).

Using the same formula, the modulus at a frequency of 0.1 Hz was also calculated for the instantaneous values of the heart rate and systolic blood pressure as the second index of baroreflex sensitivity (BRSf, expressed in Hz/mm Hg).

Statistics

The individual data from the examinations were continuously saved in the table processors – Excel and Statgraphics. The significance of differences and correlations was evaluated by the Mann-Whitney test and Spearman's correlation coefficient.

Results

The differences between cardiovascular parameters of the two groups, hypertensive and normotensive are presented in Table 1.

In patients with hypertension IMT was significantly increased in both carotids ($p<0.01$). No significant differences were observed either for the averaged inter-beat interval measured by continuous recording at rest for 5 min, or for heart rate during day or night derived from 24-h monitoring. On the other hand, both BP measurements (5 min continuously by Finapres or 24-h ABPM) showed a significantly higher systolic and diastolic BP in hypertensives than in normotensives (in spite of their treatment). Baroreflex sensitivity (BRS and BRSf) was significantly higher in normotensive subjects.

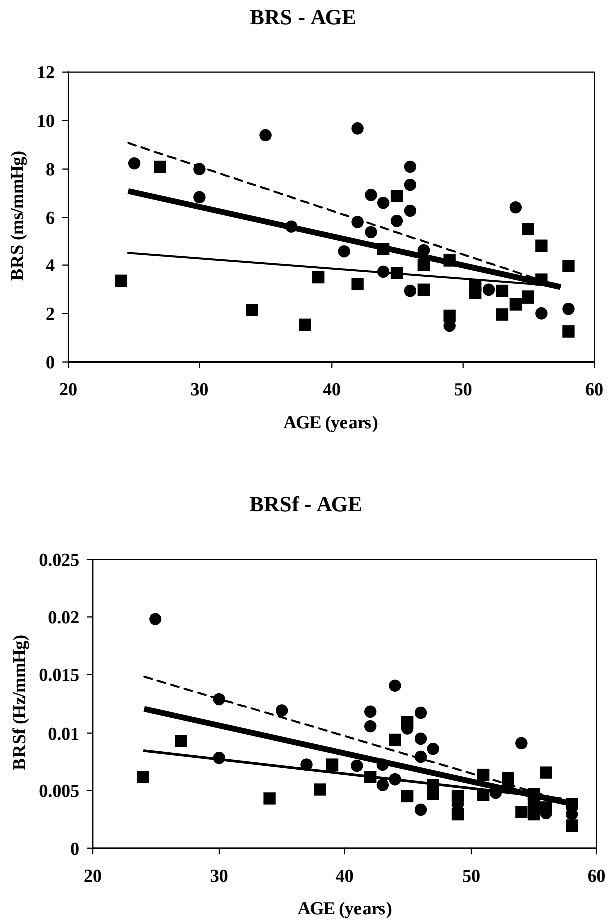

Fig. 1. Negative correlation between age and baroreflex sensitivity. BRS, baroreflex sensitivity in ms/mm Hg; BRSf, baroreflex sensitivity in Hz/mm Hg; dots and dashed line – normotensives; squares and thin line – hypertensives; full line – all subjects; significant Spearman´s correlation coefficient ($p<0.01$) for age and BRS in normotensives and all subjects, and for age and BRSf in normotensives, hypertensives and all subjects

Age-dependence of IMT, blood pressure, inter-beat intervals and baroreflex sensitivity was analyzed in both groups (Table 2). The regression coefficients of the dependence of IMT on age were positive in both groups (hypertensives b = 0.0033, normotensives b = 0.0046 mm/year). Therefore we merged both groups into one. As to the age-dependence of blood pressure and inter-beat interval, the diastolic blood pressure decreased and the mean inter-beat interval prolonged with age in hypertensives under therapy. We have found negative regression coefficients of BRS and BRSf on age (Fig. 1) in both groups (BRS: hypertensives b = –0.046, normotensives b = –0.181 ms/mm Hg/year; BRSf: hypertensives b = –0.0001, normotensives b = –0.0003 Hz/mm Hg/year). We also correlated BRS or BRSf with IMT in all subjects and in both subgroups of hypertensives and normotensives (Fig. 2). A significant correlation between IMT and both indices of baroreflex sensitivity – BRS and BRSf ($p<0.05$) was found in the whole group.

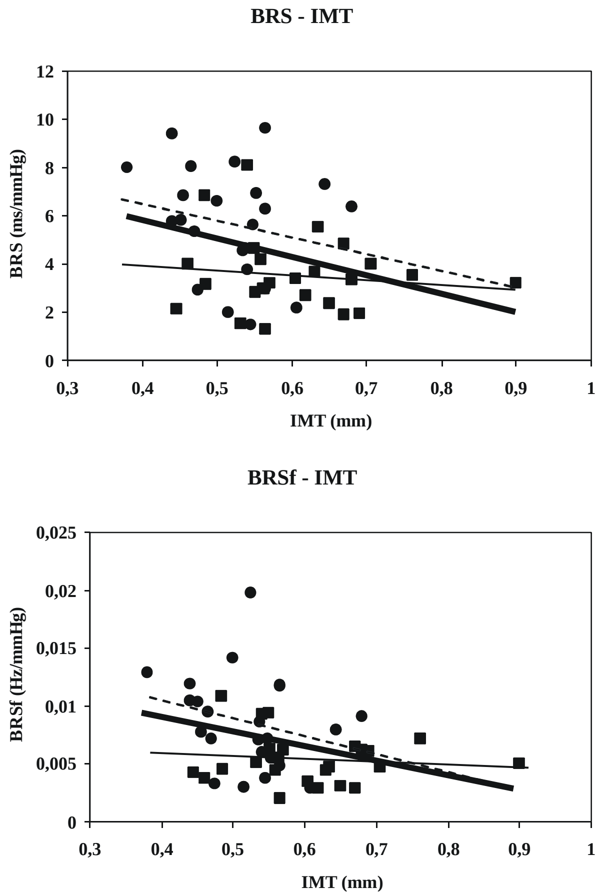

Fig. 2. Correlation between intima-media thickness and baroreflex sensitivity. IMT, intima-media thickness; BRS, baroreflex sensitivity in ms/mm Hg; BRSf, baroreflex sensitivity in Hz/mm Hg; dots and dashed line – normotensives; squares and thin line – hypertensives; full line – all subjects; significant Spearman´s correlation coefficient ($p<0.05$) for BRS and IMT, BRSf and IMT in all subjects

Discussion

It was previously shown that the thickness of the carotid wall increases with age and is augmented in hypertensive subjects. This process is associated with a decrease of BRS (de Vries *et al.* 2000, Gianaros *et al.* 2002, Semrád *et al.* 2004). In our study, we have not only confirmed that hypertensive patients have increased IMT and decreased BRS, but we have newly introduced the BRSf index in the analysis of the relationship between changes of IMT and baroreflex sensitivity. We also revealed BRSf decrease in hypertensives.

Table 1. Differences between cardiovascular parameters in normotensives and hypertensives

PARAMETERS	Normotensives	Hypertensives
INTIMA-MEDIA THICKNESS		
a. carotis sinistra (mm)	0.530±0.075	0.660±0.340 *
a. carotis dextra (mm)	0.513±0.069	0.587±0.082 **
Average of both (mm)	0.522±0.070	0.624±0.183 **
BLOOD PRESSURE AND INTER-BEAT INTERVAL (Finapres, averaged values for 5 min)		
Systolic blood pressure (mm Hg)	116±17	131±21 **
Diastolic blood pressure (mm Hg)	64±12	77±16 **
Inter-beat interval (ms)	831±118	819±145
24-h BLOOD PRESSURE AND HEART RATE (values during day/night)		
Systolic blood pressure (mm Hg)	118±9/107±11	132±8/118±12 **/**
Diastolic blood pressure (mm Hg)	77±7/69±6	85±8/76±8 **/**
Heart rate (bpm)	80±7/75±5	82±8/73±5
BAROREFLEX SENSITIVITY		
BRS (ms/mm Hg)	5.7±2.3	3.5±1.6 **
BRSf (Hz/mm Hg)	0.009±0.004	0.005±0.002 **

The values are presented as mean±SD; Statistical analysis by Mann-Whitney test: normotensives vs. hypertensives * p<0.05, ** p<0.01

Table 2. Correlation between age and cardiovascular parameters

PARAMETERS	All subjects	Normotensives	Hypertensives
INTIMA-MEDIA THICKNESS			
a. carotis sinistra	0.464 **	0.523 *	0.298 ns
a. carotis dextra	0.322 *	0.514 *	–0.017 ns
Average of both	0.419 **	0.523 *	0.171 ns
BLOOD PRESSURE AND INTER-BEAT INTERVAL (Finapres, averaged values for 5 min)			
Systolic blood pressure	0.085 ns	0.199 ns	–0.237 ns
Diastolic blood pressure	–0.038 ns	0.089 ns	–0.454 *
Inter-beat interval	0.255 ns	–0.042 ns	0.478 *
BAROREFLEX SENSITIVITY			
BRS (ms/mm Hg)	–0.497 **	–0.596 **	–0.139 ns
BRSf (Hz/mm Hg)	–0.627 **	–0.555 **	–0.540 **

The values are presented as Spearman´s correlation coefficient with statistical evaluation: * p<0.05, ** p<0.01, ns – not significant

The reason for the introduction of the BRSf index should be discussed. Changes in baroreflex sensitivity are usually coincidental with changes of the mean heart rate. Typically, during a work load, increased influence of sympathetic and decreased influence of parasympathetic activity on both the mean heart rate and BRS was found (Honzíková *et al.* 1997). The correlation between BRS and heart rate or the mean inter-beat interval, respectively, was described by several investigators (Bristow *et al.* 1971, Abrahamson *et al.* 2003). During different periods of life we can see a partially independent development of the mean inter-beat interval and BRS: the age-related heart-rate decrease in children is BRS-independent (Závodná *et al.* 2001); the age-dependent BRS decrease in adults need not be accompanied by heart rate changes as it is documented by our analysis presented in this study. In resting healthy subjects of the same age, we can record very different values of BRS at a very similar heart rate (Honzíková *et al.* 2003). Different approaches were tested to eliminate the influence of the mean inter-beat interval on the actual value of BRS. Abrahamson *et al.* (2003) propose to standardize a patient´s BRS to a fixed heart rate of 60 bpm by regression of the logarithm of BRS on the heart rate and reading BRS at 60 bpm from the regression line. The data for this regression were obtained in response to bicycle ergometry. This method does not seem to be ideal, because it was also shown that the linearity between log-BRS and heart rate is guaranteed only between heart rates of 80 and 120 bpm (Wesseling *et al.* 2003). A different non-linear approach was introduced by Al-Kubati *et al.* (1999). Baroreflex sensitivity was calculated on the basis of the instantaneous value of heart rate measured beat-by-beat, and the index was signed as BRSf. We applied this method in our study.

Measurement of intima-media thickness of the carotid wall is a valid marker of early, subclinical atherosclerosis (Bonithon-Kopp *et al.* 1996), and there may be several explanations for the relationship between IMT and BRS. First, atherogenesis may reduce BRS by structural changes in vessel wall composition. Second, the so-called functional mechanisms related to the progression of atherosclerosis (e.g. paracrine factors) have also been shown to affect BRS (Chapleau *et al.* 1995). On the other hand, it is necessary to take into account the age-related BRS decrease in healthy subjects (Gribbin *et al.* 1971, Madden *et al.* 2003). We have shown a positive correlation between age and IMT and a negative correlation between age and BRS and BRSf in the whole group of subjects. This is in agreement with the hypothesis that the age-dependent decrease of baroreflex sensitivity corresponds to the age-related structural changes of the carotid wall. A comparison of IMT and BRS, and BRSf respectively, in healthy subjects and hypertensives showed that the age-related increase of IMT and the decrease of BRS and BRSf were significantly weakened in hypertensives. The correlation between IMT and age, or BRS and age, was not significant in hypertensives. It is necessary to take into account that an actual value of blood pressure in hypertonics does not correspond to the blood pressure, which led to the development of IMT some years ago. Probably the influence of high blood pressure on IMT and on BRS predominates during the time of hypertension development, before the antihypertensive therapy is used, as is documented by the comparison of IMT and BRS between hypertensives and healthy controls. Thus the relationship between IMT and age, and BRS and age could be masked in hypertensives. Although a correlation between IMT and BRS was present, it was relatively low in our study (r^2=0.08). Nevertheless, this value is similar to that in the study of Gianaros *et al.* (2002), in which r^2=0.06 was significant for the number of tested subjects (n=82). Also the correlation between IMT and BRSf was significant (r^2=0.08) in our study.

Going into further details, it was interesting to compare the correlation of IMT and indicators of the tonic and reflex regulation of heart rate with age in normotensive and hypertensive subjects. In normotensives, the increase of IMT was accompanied only by a BRS and BRSf decrease, the mean IBI was unchanged. This was an opposite development of the partial independence of tonic and reflex regulation of heart rate, as we could see in children in whom the mean IBI prolonged with age and BRS was unchanged (Závodná *et al.* 2001). A different situation appeared in hypertensives. We did not see any additive thickening of their IMT with age, but their mean IBI, which could be taken as a measure of the tonic autonomic regulation of heart rate, was prolonged with age. The additive influence of age on baroreflex sensitivity could be detected by the BRSf index only.

In our patients, prolongation of the inter-beat interval can be present due to the therapy, similarly as a decrease of the diastolic blood pressure. This could be an explanation why we have found an age-dependent prolongation of the mean IBI, although there was no difference in the mean IBI for both total groups of normotensives and hypertensives. Furthermore, this can be the clue for understanding the inconsistency between normotensives and hypertensives in the relationship between age and the mean IBI and BRS, and why the significance for an age-dependent development of baroreflex sensitivity in hypertensives was well pronounced for the BRSf index only. In healthy subjects, in whom the mean IBI was age-independent, the development of BRS and BRSf with age was proved. However, in hypertensives, in whom IBI was significantly prolonged with age, this change of IBI masked the BRS decrease so that an additive baroreflex sensitivity decrease corresponding to age was demonstrated by the BRSf index.

We conclude that hypertensive patients have an increased IMT and a decreased BRS and BRSf. The positive correlation between age as well as IMT and the negative correlation between age and BRS and BRSf in the whole group of subjects are in agreement with the hypothesis that the age-dependent decrease of baroreflex sensitivity corresponds to the age-related structural changes of the carotid wall. A comparison of the relationship between IMT and BRS or BRSf in healthy and hypertensive subjects showed that the age-related increase of IMT and the decrease of BRS and BRSf are significantly attenuated in hypertensives. Using the two indices of baroreflex sensitivity, BRS and BRSf, we could evaluate the effect of the mean heart rate on the index of baroreflex sensitivity and disclose that the development of the mean heart rate can mask a BRS decrease. We could thus show that baroreflex sensitivity in hypertensives is lower not only due to thickening of the carotid wall, but also due to aging.

Acknowledgements

Supported by grants IGA (NA/7362-3) and MSM (0021622402). Preliminary results of this study were presented at the 79th Meeting of the Czech and Slovak Physiological Societies in Plzeň, February 5-7, 2003 (Lokaj *et al.* 2003, Závodná *et al.* 2003) and at the 80th Meeting of the Czech and Slovak Physiological Societies in Prague, February 3-6, 2004 (Honzíková *et al.* 2004, Závodná *et al.* 2004).

References

ABRAHAMSON C, AHLUD C, NORDLANDER M, LIND L: A method for heart rate-corrected estimation of baroreflex sensitivity. *J Hypertens* **21**: 2133-2140, 2003.

AL KUBATI MAA, FIŠER B, SIEGELOVÁ J: Baroreflex sensitiviy during psychological stress. *Physiol Res* **46**: 31-37, 1997.

AL KUBATI MAA, HONZÍKOVÁ N, FIŠER B: Baroreflex sensitivity in patients after acute myocardial infarction. *Scripta Medica* **72**: 337-244, 1999.

BONITHON-KOPP C, TOUBOUL PJ, BERR C, LEROUX C, MAINARD F, COURBON D, DUCIMETERE P: Relation of intima-media thickness to atherosclerotic plaques in carotid arteries: the vascular aging (EVE) study. *Arterioscler Thromb Vasc Biol* **16**: 310-316, 1996.

BRATTSTROM A, SEIDENBECHER T: Central substance-P increased blood-pressure, heart-rate and splanchnic nerve activity in anesthezed rats without impairment of the baroreflex regulation. *Neuropeptides* **23**: 81-86, 1992.

BRISTOW JD, BROWN EB, CUNNINGHAM DJC, HOWSON MG, STRANGE PETERSON E, PICKERING TG, SLEIGHT P: Effect of bicycling on the baroreflex regulation of pulse interval. *Circ Res* **28**: 582-592, 1971.

CHAPLEAU MW, CUNNINGHAM JT, SULLIVAN MJ, WACHTEL RE, ABBOUD FM: Structural versus functional modulation of the arterial baroreflex. *Hypertension* **26**: 341-347, 1995.

DE VRIES R, LEFRANDT J, TERPSTRA W, SMIT A, MAY J: Baroreflex function is related to intima media thickness of the carotid artery in mild to moderate hypertensive subjects. *J Hypertens* **18**: S204, 2000.

GIANAROS PJ, JENNINGS JR, OLFASSON GB, STEPTOE A, SUTTON-TYRRELL K, MULDOON MF, MANUCK SB: Greate intima-media thickness in the carotid bulb is associated with reduced baroreflex sensitivity. *Am J Hypertens* **15**: 486-491, 2002.

GRIBBIN B, PICKERING TG, SLEIGHT P, PETO R: Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* **24**: 424-431, 1971.

HONZÍKOVÁ N, SEMRÁD B, FIŠER B, LÁBROVÁ R: Heart rate variability and baroreflex sensitivity in healthy subjects and in postinfarction patients treated by thrombolysis. *Exp Clin Cardiol* **2**: 69-72, 1997.

HONZÍKOVÁ N, KRTIČKA A, NOVÁKOVÁ Z, ZÁVODNÁ E: A dampening effect of pulse interval variability on blood pressure variations with respect to primary variability in blood pressure during exercise. *Physiol Res* **52**: 299-309, 2003.

HONZÍKOVÁ N, FIŠER B, NOVÁKOVÁ Z, ZNOJIL V, ZÁVODNÁ E: Reproducibility of baroreflex sensitivity in young adults. *Physiol Res* **53**: 12P, 2004.

LOKAJ P, ZÁVODNÁ E, NOVÁKOVÁ Z, PADĚROVÁ J, VÁCLAVKOVÁ P, HRSTKOVÁ H, FIŠER B, HONZÍKOVÁ N: Differences in circulatory parameters between healthy and hypertensive adolescents, and adolescents with white coat effect. *Physiol Res* **52**: 32P, 2003.

MADDEN KM, LEVY WC, JACOBSON A, STRARRON JR: The effect of aging on phenylephrine response in normal subjects. *J Am Aging Association* **26**: 3-9, 2003.

SEMRÁD B, LÁBROVÁ R, DUFKOVÁ E, VYSOČANOVÁ P, FIŠER B, HONZÍKOVÁ N, NOVÁKOVÁ Z, ZÁVODNÁ E: Relation between carotid wall thickness, age and baroreflex sensitivity in normotensive and hypertensive subjects. *Physiol Res* **53**: 55P, 2004.

TANAKA H, DINENNO FA, MONAHAN KD, DESOUZA CHA, SEALS DR: Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. *Arterioscler Thromb Vasc Biol* **21**: 82-87, 2001.

URBINA EM, SRINIVASAN SR, KIELTYKA RL, TANG R, BOND MG, CHEN W, BERENSON GS: Correlates of carotid artery stiffness in young adults: the Bogalusa heart study. *Atherosclerosis* **176**: 157-164, 2004.

WESSELING KH: Should baroreflex sensitivity be corrected for heart rate? *J Hypertens* **21**: 2015-2018, 2003.

ZANCHETI A, BOND MG, HENNING M, NEISS A, MANCIA G, PALU CD, HANSSON L, MAGNANI B, RAHN KH, REID J, RODICIO J, SAFAR M, ECKES L, RAVINETTO R: Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from European Lacidipine Study on Atherosclerosis. *J Hypertens* **16**: 949-961, 1998.

ZÁVODNÁ E, HRSTKOVÁ H, NOVÁKOVÁ Z, HONZÍKOVÁ N: Age-related development of baroreflex sensitivity and mean pulse interval in children. *Physiol Res* **50**: P33, 2001.

ZÁVODNÁ E, HONZÍKOVÁ N, NOVÁKOVÁ Z, KRTIČKA A: Comparison of baroreflex sensitivity determined by cross-spectral and continuous alpha index methods. *Physiol Res* **52**: 46P, 2003.

ZÁVODNÁ E, HONZÍKOVÁ N, NOVÁKOVÁ Z, HRSTKOVÁ H: The relationship between variability in blood pressure and pulse intervals in hypertensive adolescents. *Physiol Res* **53**: 45P, 2004.

Reprint requests

N. Honzíková, Department of Physiology, Faculty of Medicine, Masaryk University in Brno, Komenského nám. 2, 662 43 Brno, Czech Republic. FAX: +420-549 493 748. E-mail: nhonziko@med.muni.cz