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THE RELATIONSHIP BETWEEN THE CAROTID INTIMA-MEDIA THICKNESS, BAROREFLEX SENSITIVITY, VARIABILITY IN BLOOD PRESSURE AND HEART RATE, AND EJECTION FRACTION IN NORMOTENSIVES AND HYPERTENSIVES

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A b s t r a c t

A complex analysis of the relationship between the carotid intima-media thickness (IMT) and baroreflex sensitivity was performed in normotensives and hypertensives with respect to the signs of tonic and reflex autonomic control of heart rate and blood pressure (BP). We studied 25 treated hypertensives (Hy; 47.4±9.2 years) and 23 healthy controls (Norm; 43.5±8.1 years). The age difference was insignificant. IMT and ejection fraction were determined ultrasonographically. From the 5–minute beat-to-beat recordings of BP (Finapres) the following were determined: baroreflex sensitivity by spectral method as BRS (in ms/mmHg) and BRSf (in mHz/mmHg), short-term variability of inter-beat intervals (IBI), and systolic and diastolic BP (SBP and DBP) as standard deviations (IBI_{sd}, SBP_{sd}, DBP_{sd}), and by spectral method as the spectral power at a frequency of 0.1 Hz (in absolute and relative units – $SBP_{0.1}$, $DBP_{0.1}$, $IBI_{0.1}$, $SBP_{0.1r}$, $DBP_{0.1r}$, $IBI_{0.1r}$). 24–hour variability of SBP, DBP and IBI was derived from 24–hour recordings of BP and ECG as a difference in day and night values and as indices ASDNN and SDANN. Significant differences between Hy and Norm were detected in IMT (Hy: 0.624±0.182, Norm: 0.522±0.070 mm; p<0.01), BRS (Hy: 3.5±1.6, Norm: 5.7±2.3 ms/mmHg; p<0.01), BRSf (Hy: 5.34±2.15, Norm: 8.56±4.08 mHz/mmHg; p<0.01), IBI_{SD} (Hy: 26.3±9.8, Norm: 39.1±15.7 ms; p<0.001), $IBI_{0.1}$ (Hy: 3079±3823, Norm: 7599±6697 ms^2/Hz; p<0.01), $SBP_{0.1r}$ (Hy: 0.027±0.021, Norm: 0.045±0.028r.u.; p<0.01), $DBP_{0.1r}$ (Hy: 0.040±0.027, Norm: 0.068±0.036r.u.; p<0.01), SBP (Hy: 131±21, Norm: 116±17 mmHg; p<0.01), DBP (Hy: 77±16, Norm: 64±12 mmHg; p<0.01). A complete correlation analysis between all parameters was performed. The hierarchical multiple regression analysis by means of the forward selection of regressors proved an additive positive effect of age and BMI on the development of IMT in normotensives, but the influence of mean BP was insignificant . The same analysis performed in hypertensives showed that their thick IMT is not further influenced either by age or by BMI or by mean BP. Taking all subjects together, the dependence of IMT on age and mean BP from 24–h recordings was shown. A correlation of IMT with BRS and BRSf confirmed the hypothesis that the thickened carotid wall has a lower compliance and therefore baroreflex sensitivity is lower. IMT correlates with many indices but the increase of IMT in healthy subjects is dependent on age and BMI. BP plays a role besides age in the thickening of the carotid wall during the development of hypertension. It is probable that therapy in hypertonics decreases only sympathetic activation, but decreased BRS, which is a risk factor for sudden cardiac death after myocardial infarction, is not influenced by therapy.

Key words

Carotid intima-media thickness, Baroreflex sensitivity, Heart rate variability, Blood pressure variability

Abbreviations used

ASDNN, the mean of standard deviations of RR intervals determined in 5-minute periods of 24-hour ECG; BMI, body mass index; BP, blood pressure; BRS, baroreflex sensitivity in ms/mmHg; BRSf, baroreflex sensitivity in mHz/mmHg; DBP, diastolic blood pressure; DBP_{sd}, standard deviation of diastolic blood pressure determined from the 5-minute beat-to-beat recordings; $DBP_{0.1}$, variability of diastolic blood pressure determined as the spectral power at a frequency of 0.1 Hz (in $mmHg^2$/Hz) from the 5-minute beat-to-beat recordings of blood pressure; $DBP_{0.1r}$, variability of diastolic blood pressure determined as the spectral power at a frequency of 0.1 Hz (in relative units) from the 5-minute beat-to-beat recordings of blood pressure; DBP_{d-n} day-night difference of DBP determined from 24-h blood pressure monitoring; DBP_d, mean of diastolic blood pressure determined for day period of 24-h monitoring; DBP_n mean of diastolic blood pressure determined for night period of 24-h monitoring; DBP_{24h}, mean of diastolic blood pressure determined from 24-h monitoring; ECG, electrocardiogram; EF, ejection fraction in %; HR, heart rate; HR_d mean of heart rate determined for day period of 24-h monitoring; HR_n mean of heart rate determined from night period of 24-h monitoring; HR_{24h} mean of heart rate determined from 24-h monitoring; Hy, group of hypertensives; IBI, inter-beat interval (ms); IBI_{sd} standard deviation of inter-beat intervals determined from the 5-minute beat-to-beat recordings of blood pressure; $IBI_{0.1}$, variability of inter-beat intervals determined as the spectral power at a frequency of 0.1 Hz (in ms^2/Hz) from the 5-minute beat-to-beat recordings of blood pressure; $IBI_{0.1r}$, variability of inter-beat intervals determined as the spectral power at a frequency of 0.1 Hz (in the relative unit) from the 5-minute beat-to-beat recordings of blood pressure; IMT, intima-media thickness; MBP_{24h}, averaged mean values of blood pressure from 24-h monitoring; Norm, group of normotensives; RR interval, heart period from ECG; SBP, systolic blood pressure; SBP_{sd}, standard deviation of systolic blood pressure determined from the 5-minute beat-to-beat recordings; $SBP_{0.1}$, variability of systolic blood pressure determined as the spectral power at a frequency of 0.1 Hz (in $mmHg^2$/Hz) from the 5-minute beat-to-beat recordings of blood pressure; $SBP_{0.1r}$, variability of systolic blood pressure determined as the spectral power at a frequency of 0.1 Hz (in the relative unit) from the 5-minute beat-to-beat recordings of blood pressure; SBP_{d-n}, day-night difference of SBP determined from 24-h blood pressure monitoring; SBP_d, mean of systolic blood pressure determined for day period of 24-h monitoring; SBP_n, mean of systolic blood pressure determined for night period of 24-h monitoring; SBP_{24h}, mean systolic blood pressure determined from 24-hour monitoring; SD, standard deviation; SDANN, standard deviation of mean RR intervals determined in 5-minute periods in 24-h ECG.

INTRODUCTION

The baroreflex is one of the basic mechanisms regulating blood pressure. Changes in the frequency of the baroreceptor afferent discharge transmitted to the central nervous system trigger reflex adjustments that buffer or oppose changes in blood pressure. Arterial baroreceptors are mechanosensitive nerve endings that innervate the adventitia of the carotid sinus and the aortic arch and they are stimulated by mechanical deformation during vascular stretch. Therefore the sensitivity of the reflex response to the blood pressure variations depends on compliance of aortic and carotid arteries or their stiffness, respectively. Stiffening of the aortic wall and of the carotid sinus wall is likely to decrease the sensitivity of aortic and carotid barorecep-

tors. This is the reason for the actual interest in studying the relationship between the carotid intima-media thickness (IMT) and baroreflex sensitivity.

Baroreflex has not only a long-lasting effect on the mean blood pressure, but it also dampens short-term variations in blood pressure through autonomic adjustments in 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 the change of systolic blood pressure. This index, abbreviated as BRS, is expressed in ms/mmHg. Most often, dynamic changes of BRS and of the mean IBI are concomitant (*1*). Under some circumstances, as e.g. effect of aging (*2*) or a central effect of substance P (*3*), the tonic and short-term reflex heart-rate regulation can be partially independent of each other. Therefore the index BRSf in mHz/mmHg was introduced (*4*), which is less dependent on the mean IBI than BRS.

The gain of baroreflex sensitivity is suppressed during various types of the strain by central mechanisms, but its resting value reveals also long-lasting changes. It decreases with age in healthy subjects. The decline of BRS with age was first described by *Gribbin et al*. (*5*). A plausible explanation is the increase of arterial stiffness and the decrease of baroreceptor sensitivity. The measurement of 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 remodelled in response to haemodynamic changes, for instance in hypertensive patients. It was proved that ultrasound measurement at the far wall of the carotid artery is in good correlation with histology measurements. The latest studies show the association of an increase in IMT with hypertension (*6, 7*). A correlation of carotid artery stiffness with age in young adults was also reported (*8*). On the other hand it was proved that a low BRS was linked with a decreased short-term and circadian variability in heart rate (*9, 10*), with an increased blood-pressure variability (*9*), and with decreased contractility (*11*). It is not fully elucidated whether the complex manifestation of an autonomic dysfunction is a consequence of the primary stiffness of the baroreceptor area in carotid and aortic arteries.

In this study we have evaluated the complex involvement of changes of IMT in an autonomous regulation of heart rate and blood pressure. The relationship between IMT and indices of baroreflex sensitivity, e.g. BRS and BRSf, was studied in normotensives and hypertensives with respect to the signs of tonic and reflex autonomic control of heart rate and blood pressure. This included not only the mean values of BP and IBI measured for 5 minutes in finger arteries or monitored for 24 hours, but also their variabilities. The ejection fraction was also evaluated.

METHODS

Subjects

We studied 25 treated hypertensives (eleven men and fourteen women; mean±SD: age 47.4±9.2 years, body height 172.9±10.9 cm, weight 81.1±15.4 kg, body mass index 27.0±4.2 kg/m^2) and 23 normotensives (seven men and sixteen women; age 43.5±8.1 years, body height 169.9±6.5 cm, weight

74.1±13.5 kg, body mass index 25.6±3.9 kg/m^2). There were no significant differences between both 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 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 an increase in BP (≥140 mmHg systolic and ≥90 mmHg 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 of them 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.

The relationship between the thickness of carotid intima-media measured ultrasonographically was compared with baroreflex sensitivity determined by the spectral method as BRS (in ms/mmHg) and BRSf (in mHz/mmHg); with short-term variability of IBI, and systolic and diastolic blood pressures (SBP and DBP) determined from the 5-minute beat-to-beat recordings of blood pressure as standard deviations (SBP_{sd}, DBP_{sd}, $IBI_{sd)}$ and by the spectral method as the spectral power at a frequency of 0.1 Hz (in absolute and relative units – $SBP_{0.1}$, $DBP_{0.1}$, $IBI_{0.1}$, $SBP_{0.1r}$, $DBP_{0.1r}$, $IBI_{0.1r}$); with 24-hour variability of SBP, DBP and IBI derived from 24-hour recordings as a difference in day and night values and indices ASDNN and SDANN; and the ejection fraction (EF).

Carotid ultrasound, ejection fraction

The ejection fraction was determined ultrasonographically (Agilent Sonos 5500, Philips) by conventional procedure. 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 with all subjects in supine position with the neck extended in mild rotation. The scanning protocol was performed with the above-mentioned ultrasound device equipped with a 3–11 MHz high-resolution transducer. Measurements were performed on both the right and the left common carotid artery. The artery was examined on a far 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, we took this average value and determined the mean value of both (together a. carotis dextra and a. carotis sinistra) as an average IMT.

Ambulatory blood pressure and ECG monitoring

Ambulatory blood pressure monitoring 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 blood pressure measurements every 20 min (daytime) 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 analysed to obtain daytime (from 6 a.m. to 9 p.m. hours), and night-time (from 10 p.m. to 5 a.m. hours) average systolic and diastolic blood pressures and heart rate, and also the difference between day and night values of blood pressure.

A two-channel, 24-hour ECG recording was performed (SeerMC Marquette, Hellige). Two non-spectral indices of heart rate variability were computed: the SDANN index – the standard deviation

of mean RR intervals determined in 5–minute periods in 24 hours. SDANN is sensitive to frequencies below 0.0017 Hz (10–minute cycle). The ASDNN index – the mean of standard deviations of RR intervals determined in 5–minute periods in 24 hours – is sensitive mostly to frequencies above 0.003 Hz.

Short-term variability in blood pressure and inter-beat intervals, and baroreflex sensitivity determination

We recorded IBI, SBP and DBP beat-to-beat, on finger arteries by the Penaz non-invasive method (Finapres OHMEDA, USA) in all subjects. The recordings were taken in sitting position at rest during a 5–minute period. Breathing was synchronised 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 power spectra of variability of IBI, SBP and DBP, and cross-spectra between IBI and SBP were calculated.

Short-term variability in these variables was determined as SBP_{sd}, DBP_{sd}, $IBI_{sd,}$ $SBP_{0.1}$, $DBP_{0.1}$, $IBI_{0.1}$, $SBP_{0.1r}$, $DBP_{0.1r}$, and $IBI_{0.1r}$. The gain factor, e.g. modulus H(f) of the transfer function between variations in SBP and IBI, was calculated at a frequency (f) of 0.1 Hz according to the formula: H(f) = Gxy(f)/Gxx(f), where Gxy(f) corresponded to the cross-spectral density between SBP and IBI, and Gxx(f) corresponded to the spectral density of SBP. The value of the modulus at a frequency of 0.1 Hz was taken as a measure of BRS (*12*).

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 mHz/mmHg).

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 coefficients. Because an increase of IMT is multifactorially conditioned, the characteristic interrelationships were analysed by multiregression analysis. We have evaluated dependence of IMT on age, BMI, and mean BP of 24–h monitoring.

RESULTS

The differences between the cardiovascular parameters of the two groups, hypertensive and normotensive, are presented in *Table 1*. IMT was significantly increased in patients with hypertension ($p<0.01$), and baroreflex sensitivity measured by both indices (BRS and BRSf) was significantly lower in hypertensives ($p<0.01$). As to short-term variabilities, its suppression was revealed in IBI in the total variability (IBI_{sd}, $p<0.001$) and at a frequency of 0.1 Hz as well ($IBI_{0.1}$, $p<0.01$). On the other hand, only a relative power at a frequency of 0.1 Hz was lower in BP ($SBP_{0.1r}$, $p<0.01$; $DBP_{0.1r}$, $p<0.01$). No significant differences were observed either for 24 hours' variabilities expressed as differences between day and night values or indices ASDNN and SDANN, or for the ejection fraction between hypertensives and controls.

A correlation analysis of IMT, BRS, BRSf, EF and IBI_{sd} with all parameters examined in normotensives and hypertensives is in *Table 2*.

For the demonstration of the interrelationship of IMT and baroreflex sensitivity with other parameters studied, the most important correlations in all subjects were as follows: IMT correlated negatively with BRS ($p<0.05$) and BRSf ($p<0.05$), with short-term variability of IBI (IBI_{sd} $p<0.05$), and positively with daily (SBP_{d}, DBP_{d}),

Table 1
Differences between cardiovascular parameters in normotensives and hypertensives

PARAMETERS	Normotensives	Hypertensives
INTIMA-MEDIA THICKNESS		
Average of both (mm)	0.522±0.070	0.624±0.182 **
24-h BLOOD PRESSURE AND HEART RATE (mean values during 24-hour measurement)		
Systolic blood pressure (mmHg)	116±8	129±8 ***
Diastolic blood pressure (mmHg)	75±5	83±7 ***
Mean arterial pressure (mmHg)	88.9±5.9	98.4±7.0 ***
Heart rate (bpm)	79.0±5.8	80.3±6.6
BLOOD PRESSURE AND INTER-BEAT INTERVAL (Finapres, averaged values for 5 min)		
Systolic blood pressure (mmHg)	116±17	131±21 **
Diastolic blood pressure (mmHg)	64±12	77±16 **
Inter-beat interval (ms)	830±118	819±146
Heart rate (Hz)	1.23±0.18	1.26±0.24
SHORT-TERM VARIABILITY OF BLOOD PRESSURE AND INTER-BEAT INTERVALS: (SD of 5-min recordings and spectral power at a frequency of 0.1 Hz)		
SBP_{sd} (mmHg)	5.03±1.56	5.41± 1.79
$SBP_{0.1}$ ($mmHg^2$/Hz)	146±125	110 ±124
$SBP_{0.1r}$ (r.u.)	0.045±0.028	0.027± 0.021**
DBP_{sd} (mmHg)	2.61±0.54	2.67 ±0.86
$DBP_{0.1}$ ($mmHg^2$/Hz)	60.8±43.4	40.7± 40.7
$DBP_{0.1r}$ (r.u.)	0.068±0.036	0.040 ±0.027**
IBI_{sd} (ms)	39.1±15.7	26.3±9.8 ***
$IBI_{0.1}$ (ms^2/Hz)	7599±6697	3079±3823 **
$IBI_{0.1r}$ (r.u.)	0.040±0.023	0.030±0.020
24-h BLOOD PRESSURE AND HEART RATE VARIABILITY (indices derived from 24-hour monitoring)		
SBP day - night value (mmHg)	10.6±8.7	13.4±10.0
DBP day - night value (mmHg)	8.1±4.8	8.8±7.2
SDANN (ms)	145±53	128±35
ASDNN (ms)	63±21	54±14
BAROREFLEX SENSITIVITY		
BRS (ms/mmHg)	5.69±2.32	3.51±1.58 **
BRSf (mHz/mmHg)	8.56±4.08	5.34±2.15 **
EJECTION FRACTION		
EF (%)	66.0±5.0	64.4±7.0

The values are presented as mean±standard deviation. Statistical analysis by Mann-Whitney test: normotensives versus hypertensives * $p< 0.05$, ** $p< 0.01$, *** $p< 0.001$

Table 2
Correlation analysis of IMT, BRS, BRSf, EF, and IBI_{sd} with all parameters examined in normotensives and hypertensives

	Normotensives					**Hypertensives**				
	IMT	BRS	BRSf	EF	IBI_{sd}	IMT	BRS	BRSf	EF	IBI_{sd}
Age	0.53*	-0.60**	-0.56**	-0.22	-0.43*	0.17	-0.14	-0.54**	0.31	-0.06
Height	-0.05	0.23	0.28	0.06	0.01	0.44*	-0.04	0.31	-0.39	-0.002
BMI	0.45*	0.07	-0.01	-0.29*	-0.26	0.05	0.17	0.29	-0.33	0.08
IMT	1	-0.20	-0.35	-0.10	-0.52**	1	-0.11	-0.11	-0.18	0.10
EF	-0.10	0.41	0.19	1.00	0.30	-0.18	0.32	-0.09	1	0.37
SBP	0.10	-0.17	-0.08	0.13	-0.35	-0.02	-0.32	-0.06	-0.44*	-0.23
DBP	0.08	0.15	0.27	0.06	-0.15	-0.02	-0.07	0.27	-0.52**	-0.13
IBI	0.10	0.25	-0.30	0.46*	0.27	0.06	0.47*	-0.45*	0.50*	0.51**
BRS	-0.20	1	0.80***	0.42*	0.72***	-0.11	1	0.54**	0.32	0.64***
BRSf	-0.35	0.80***	1	0.19	0.59**	-0.11	0.54**	1	-0.09	0.17
SBP_{sd}	-0.16	-0.36	-0.33	0.04	0.07	0.17	-0.21	-0.12	-0.01	0.37
$SBP_{0.1}$	0.05	-0.34	-0.34	0.28	-0.10	0.10	-0.36	-0.07	-0.11	0.15
$SBP_{0.1r}$	0.21	-0.13	-0.17	0.40	-0.18	-0.05	-0.34	-0.13	-0.11	-0.15
DBP_{sd}	-0.04	0.01	0.13	-0.06	0.13	0.06	-0.04	0.002	0.20	0.46*
$DBP_{0.1}$	0.16	-0.25	-0.25	0.20	-0.17	0.03	-0.14	-0.01	-0.05	0.29
$DBP_{0.1r}$	0.33	-0.40	-0.45*	0.38	-0.44*	0.07	-0.25	-0.01	-0.27	-0.12
IBI_{sd}	-0.52*	0.72***	0.59**	0.30	1	0.10	0.64***	0.17	0.37	1
$IBI_{0.1}$	-0.27	0.68	0.52**	0.54**	0.68***	0.07	0.63	0.29	0.28	0.87***
$IBI_{0.1r}$	0.22	0.05	0.02	0.34	-0.25	-0.10	0.14	0.32	-0.04	0.00
$SBP_{d\text{-}n}$	0.06	-0.03	0.10	0.07	-0.05	-0.34	0.03	-0.14	0.32	0.38
$DBP_{d\text{-}n}$	0.26	-0.07	0.09	0.19	-0.11	-0.25	0.07	-0.04	0.07	0.43*
SDANN	-0.28	0.52*	0.23	0.22	0.65***	0.11	0.05	0.19	-0.12	0.22
ASDNN	-0.29	0.60**	0.30	0.31	0.74***	0.32	0.41*	0.08	0.07	0.54**
SBP_{d}	0.37	-0.00	-0.14	-0.02	-0.13	0.08	0.15	0.33	-0.34	0.19
DBP_{d}	0.42*	-0.23	-0.21	-0.09	-0.35	0.01	0.09	0.37	-0.46*	0.22
MBP_{d}	0.41	-0.14	-0.19	-0.10	-0.27	0.02	0.11	0.38	-0.45*	0.21
HR_{d}	0.16	-0.21	0.12	-0.26	-0.12	-0.17	-0.20	0.24	-0.13	-0.31
SBP_{n}	0.24	0.01	-0.18	-0.03	-0.08	0.26	0.20	0.34	-0.35	-0.12
DBP_{n}	0.27	-0.03	-0.12	-0.26	-0.15	0.06	0.12	0.53**	-0.51**	-0.18
MBP_{n}	0.30	-0.12	-0.25	-0.18	-0.16	0.10	0.22	0.52**	-0.44*	-0.14
HR_{n}	-0.28	-0.43*	-0.05	-0.43*	-0.17	0.04	-0.33	0.18	-0.04	-0.24
SBP_{24h}	0.29	-0.01	-0.16	0.02	-0.09	0.15	0.18	0.37	-0.37	0.17
DBP_{24h}	0.38	-0.20	-0.17	-0.07	-0.33	-0.18	0.09	0.41*	-0.50*	0.12
MBP_{24h}	0.38	-0.07	-0.18	-0.06	-0.21	0.04	0.15	0.44*	-0.49*	0.15
HR_{24h}	0.03	-0.31	0.02	-0.23	-0.16	-0.24	-0.21	0.25	-0.06	-0.35

The values are presented as Spearman's correlation coefficient and its level of statistical significance: * $p< 0.05$, ** $p< 0.01$, *** $p< 0.001$

night (SBP_n, DBP_n) and mean values of BP during 24 hours (MBP_{24h}) measured by Holter monitoring (generally for SBP_{24h} and MBP_{24h} $p<0.01$, for DBP_{24h} $p<0.05$), and with age ($p<0.01$). Baroreflex sensitivity (BRS and BRSf), which was negatively age-dependent ($p<0.05$), correlated positively with parameters of short-term IBI variability (IBI_{sd} and $IBI_{0.1}$ $p<0.05$), BRS correlated also negatively with daily, night and mean values of BP ($p<0.05$) and positively with EF ($p<0.01$).

The hierarchical multiple regression analysis by means of the forward selection of regressors proved an additive positive effect of age and BMI on the development of IMT in normotensives, but the influence of mean of MBP_{24h} was insignificant *(Table 3).* The corresponding equation is:

IMT [mm] = 0.1469 + 0.0048*age [years] + 0.0065*BMI [kg/m^2]; $p<0.01$

The same analysis performed in hypertensives has shown that their IMT is not further influenced either by age or by BMI or by MBP_{24h}. Taking all subjects together, the dependence of IMT on age and MBP_{24h} was shown. The corresponding equation is:

IMT [mm] = -0.3434 + 0.0046*age [years] + 0.0076* MBP_{24h} [mmHg]; $p<0.01$

DISCUSSION

Our study of a complex involvement of changes of the carotid intima-media thickness in changes of autonomous regulation of heart rate and blood pressure has not only confirmed that hypertensive patients have an increased IMT and a decreased BRS as was previously proved (*7, 13, 14*), but it brought a deeper insight into the changes of the dynamics of regulation which involves signs of an increased sympathetic and decreased parasympathetic activity.

A correlation of IMT with BRS and BRSf in all subjects is a measure of decreased baroreceptor response on fluctuations in blood pressure. It confirms the hypothesis that the thickened carotid wall has lower compliance and therefore variations in BP stimulate less dynamically the nerve endings of baroreceptors. The BRSf

Table 3

The hierarchical multiple regression analysis by means of the forward selection of regressors predicting IMT

Normotensives			Normotensives and hypertensives		
Step	Added variable in consecutive steps	R^2	Step	Added variable in consecutive steps	R^2
1	Age	0.273 **	1	Age **	0.175
2	BMI	0.420 **	2	MBP_{24h} **	0.255
3	MBP_{24h}	0.423 *	3	BMI **	0.269

Statistical significance of R^2 for equation: * $p< 0.05$, ** $p< 0.01$

index is less dependent on mean IBI and its relationship with IMT corresponds with this hypothesis as well.

A correlation analysis showed that some more factors also correlate with IMT. It is questionable which of these factors influence the thickening of the carotid wall. Therefore we have analysed the influence of age, BMI, and mean BP from 24–h blood pressure monitoring on the increase of IMT. A multiregression analysis showed that an influence of age on the development of IMT is essential. In hypertensives the influence of BP predominates as it is documented by comparison of IMT between hypertensives and healthy controls. It is necessary to take into account that the actual value of BP in hypertonics does not correspond to the BP, which led to the development of IMT some years ago, but IMT as an age-related parameter reflects the influence of BP on IMT in the subject's history similarly as the plasma level of glycosylated haemoglobin reflects previous levels of glycaemia. BMI in normotensives also plays an important role in increasing IMT. On the other hand, 24–h mean BP was not significantly related to carotid IMT in healthy controls when the influence of age was included. A similar finding for the influence of brachial SBP and age on IMT was described by *Tanaka et al*. (*15*). They also performed parallel analysis for the influence of carotid artery SBP and age on carotid IMT, where the significance of the additive effect of SBP to age remained.

Previous studies of the inter-relationship between BRS and the variability in SBP and IBI brought evidence that low BRS is associated with decreased variability in IBI together with increased variability in SBP. These changes are especially distinct in young nontreated hypertonic patients (*16*). Our comparison of hypertonics and normotonics confirmed a correlation between BRS decrease and low short-term variability in IBI, but no increase in short-term blood pressure variability was found. It cannot be eliminated that this effect is conditioned by therapy. BP variability was markedly suppressed especially at a frequency of 0.1 Hz, which is clearly seen in spectral power distribution.

A low variability of IBI in hypertonics was present not only at a frequency of 0.1 Hz, but also during 5 minutes' recordings quantified as SD of IBI. A low variability of IBI at a frequency of 0.1 Hz is caused by low BRS and by the corresponding low reflex variations in parasympathetic activity. It is characteristic of this frequency range that the variations in vasomotor tone are primary and the corresponding heart-rate variations are induced by baroreflex. Though heart-rate variability at this frequency is mediated predominantly by n. vagus, it is still necessary to take into account the effect of beta-blockers which were used in therapy in some patients. The effect of beta-blockers on heart rate variability is different in the respective frequency ranges and is low, if any, at a frequency of 0.1 Hz (*17*). After myocardial infarction, beta-adrenergic blockade does not alter heart rate variability, thus preserving its predictive value (*18*). The interpretation of decreased variability of IBI in hypertonics measured as SD of 5 minutes' recordings is different. It reflects the decrease in reflex responsiveness of both systems, sympathetic and parasympathetic.

On the other hand, the resting heart rate, which is conditioned by tonic activity of both systems, sympathetic and parasympathetic, was unchanged in our group of hypertonics.

Positive correlations between BRS and the SDANN and ASDNN indices of heart rate variability derived from Holter ECG recordings were observed in healthy controls, similarly as in the study of *Lucini et al.* (*10*). These correlations disappeared by using the BRSf index. Thus it can be speculated that this correlation was due to changes in mean heart rate during a day. None of these indices of 24–h heart rate variability, and the difference in day and night values of blood pressure as well, revealed any significant differences between hypertonics and controls. Previously it was shown that low values of SDANN and ASDNN indices were linked with a risk of sudden cardiac death (*19*). Our findings support the hypothesis that tonic vagal control of heart rate is not changed in hypertonics.

No patients suffered from heart failure; EF did not correlate with IMT. The correlation of EF with baroreflex sensitivity and variability in IBI, and mean IBI respectively, could be explained by a prolongation of the ejection period of cardiac cycle during longer IBI.

The main conclusion resulting from our study has a prognostic value in a situation when a hypertensive subject would be attacked by myocardial infarction. Decreased parasympathetic and increased sympathetic activity are risk factors in patients after myocardial infarction. In treated hypertonics, an unchanged tonic control of heart rate by autonomic nerves was observed, but due to greater IMT a decreased reflex parasympathetic activity manifested by low BRS was present. The hypertonics treated exhibit no marked signs of increased sympathetic activity, blood pressure is normalised by therapy, and blood pressure variability is unchanged. It is probable that therapy in hypertonics affects only one of the potential risk factors; it decreases only sympathetic activation but decreased BRS, which is also a risk factor for sudden cardiac death after myocardial infarction, is not influenced by therapy.

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Lábrová R., Honzíková N., Fišer B., Maděrová E., Vysočanová P., Nováková Z., Závodná E., Jíra M., Semrád B.

VZTAH MEZI TLOUŠŤKOU STĚNY A. CAROTIS, CITLIVOSTÍ BAROREFLEXU, VARIABILITOU V KREVNÍM TLAKU A SRDEČNÍ FREKVENCI A EJEKČNÍ FRAKCÍ U NORMOTONIKŮ A HYPERTONIKŮ

S o u h r n

Cílem práce byla komplexní analýza vztahů tloušťky stěny a. carotis (IMT) a citlivosti baroreflexu (BRS) u normotoniků a hypertoniků s ohledem na projevy tonického a reflexního autonomního řízení srdeční frekvence a krevního tlaku.

Vyšetřili jsme 25 léčených hypertoniků (Hy; 47,4±9,2 let) a 23 zdravých normotoniků (Norm; 43,5±8,1). Věkový rozdíl mezi skupinami nebyl statisticky významný. Pomocí ultrazvuku jsme stanovili tloušťku stěny a. carotis a ejekční frakci. Z pětiminutového záznamu krevního tlaku tep po tepu (Finapres) jsme určili: citlivost baroreflexu spektrální metodou jako BRS (ms/mmHg) a BRSf (mHz/mmHg); krátkodobou variabilitu systolického a diastolického krevního tlaku (SBP, DBP) a tepových intervalů (IBI) jako standardní odchylku z pětiminutového záznamu (SBP_{sd}, DBP_{sd}, IBI_{sd}); spektrální metodou jako výkon spektra při frekvenci 0,1 Hz (v absolutních a relativních jednotkách – $SBP_{0.1}$, $DBP_{0.1}$, $IBI_{0.1}$, $SBP_{0.1r}$, $DBP_{0.1r}$, $IBI_{0.1r}$). Dvacetičtyřhodinová variabilita byla stanovena z 24hod záznamů krevního tlaku (rozdíl denních a nočních hodnot: $SBP_{d\text{-}n}$, $DBP_{d\text{-}n}$) a EKG (SDANN a ASDNN).

Statisticky významné rozdíly mezi skupinami jsme našli u parametrů: IMT (Hy: 0,624±0,182; Norm: 0,522±0,070 mm; p<0,01), BRS (Hy: 3,5±1,6; Norm: 5,7±2,3 ms/mmHg; p<0,01), BRSf (Hy: 5,34±2,15; Norm: 8,56±4,08 mHz/mmHg; p<0,01), IBI_{sd} (Hy: 26,3±9,8; Norm: 39,1±15,7 ms; p<0,001), $IBI_{0.1}$ (Hy: 3079±3823, Norm: 7599±6697 ms^2/Hz; p<0,01), $SBP_{0.1r}$ (Hy: 0,027±0,021; Norm: 0,045±0,028 r.u.; p<0,01), $DBP_{0.1r}$ (Hy: 0,040±0,027; Norm: 0,068±0,036 r.u.; p<0,01), SBP (Hy: 131±21, Norm: 116±17 mmHg; p<0,01), DBP (Hy: 77±16, Norm: 64±12 mmHg; p<0,01). Provedli jsme kompletní korelační analýzu mezi všemi parametry. Stupňovitá regresní analýza ukázala aditivní pozitivní vliv věku a nadváhy (BMI) na vývoj IMT u normotoniků, nepotvrdil se vliv hodnot průměrného krevního tlaku (MBP_{24h}). Stejná analýza u hypertoniků neprokázala vliv věku, BMI a MBP_{24h} na velikost IMT. Vliv věku a MBP_{24h} byl prokázán u celého souboru sledovaných osob (Hy+Norm).

Korelace IMT s BRS a BRSf potvrzuje hypotézu, že zesílená cévní stěna a. carotis má sníženou poddajnost, a proto je snížena citlivost baroreflexu. IMT koreluje s celou řadou faktorů, ale zvětšování IMT u zdravých osob souvisí s věkem a BMI. Při rozvoji hypertenze se uplatňuje vedle věku BP. Je pravděpodobné, že léčbou můžeme u hypertoniků snížit jen velikost sympatické aktivace, ale ne citlivost baroreflexu, která je v případě infarktu myokardu rizikovým faktorem pro náhlou srdeční smrt.

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