Clin Auton Res (2004) 14 : 369–375
DOI 10.1007/s10286-004-0185-z

RESEARCH ARTICLE

Jerica Maver
Martin Štrucl
Rok Accetto

Autonomic nervous system activity in normotensive subjects with a family history of hypertension

Abstract This study was designed to address alterations in autonomic nervous system activity in normotensive subjects with a family history of hypertension. We compared the autonomic nervous system activity in 59 normotensives with a family history of hypertension and 46 normotensives with no family history of hypertension. Skin blood flow was measured using laser-Doppler method on the nailfold skin in the resting condition, during systemic cooling and during upright tilting. Finger blood pressure, pulse and ECG were monitored by a finapres device. Heart rate, systolic pressure and microvascular flow power spectral analyses were performed using fast Fourier transformation. Baroreflex sensitivity was estimated with the sequence method. Compared to the control group, normotensives with a family history of hypertension showed significantly higher systolic pressure, decreased proportion and area of the high-frequency band of the heart rate variability power spectrum and reduced baroreflex sensitivity in the resting condition as well as a decreased proportion and area of the high-frequency band of the heart rate variability power spectrum during systemic cooling. We also proved a different time course of baroreflex sensitivity during upright tilting in the two groups. In contrast, we did not find any significant differences in the parameters of systolic pressure and microvascular variability power spectra between the two groups. Our results indicate that even normotensives with a family history of hypertension exhibit an increased ratio of sympathetic to parasympathetic activity at the cardiac level; however, they do not show any alteration of the vascular sympathetic reactivity.

Key words baroreflex · autonomic nervous system · hypertension · tilt-table test

Received: 17 October 2003
Accepted: 5 April 2004

J. Maver, MD, PhD · Prof. M. Štrucl, MD, PhD
Institute of Physiology, Medical Faculty
University of Ljubljana
Ljubljana, Slovenia

J. Maver, MD, PhD
Franc Derganc General Hospital
Dept. of Cardiology
Šempeter pri Gorici, Slovenia

J. Maver, MD, PhD (✉)
Ivana Regenta 14
5000 Nova Gorica, Slovenia
Tel.: +386-5/330-1401
Fax: +386-5/393-9146
E-Mail: jerica.maver@bass.si

R. Accetto, MD, PhD
University Medical Centre Ljubljana
Division of Hypertension
Ljubljana, Slovenia

Introduction

Strong evidence exists that essential hypertension and the autonomic nervous system (ANS) are closely interrelated. A number of studies have revealed that cardiovascular homeostasis is altered at an early stage of essential hypertension development [1, 19, 36]. Furthermore, according to Julius' hypothesis essential hypertension is caused by disturbance in reflex control of the cardiovascular system [19]. Developed hypertension is characterized by predominance of sympathetic over parasympathetic activity [1, 20, 44]. Basic and human studies showed that predominance of sympathetic over parasympathetic activity could be caused by alterations in vasomotor and other centers of the central nervous system [1, 6, 20]. Such changes in the ANS activity could be conducive to high blood pressure, which may impair baroreceptor reflex [1]. According to the results of a study on hypertensive rats, baroreflex sensitivity could be decreased even before hypertension development [1], which speaks in favor of a causative role of decreased

baroreflex sensitivity in hypertension development [24]. Human studies are based mainly on non-invasive methods of the ANS assessment. Heart rate, blood pressure and microvascular flow variability as well as baroreflex sensitivity are believed to be good measures of assessing the ANS activity [2, 3, 5, 23].

In *developed hypertension* decreased baroreflex sensitivity [32, 39] and other findings proving increased sympathetic over vagal activity at the cardiac level [12, 14, 24] were repeatedly reported. In contrast, results of studies on blood pressure variability power spectrum alterations in developed hypertension are more conflicting [25, 39, 45]. Using infrared photoplethysmography Radaelli found no difference in the arteriolar skin blood flow variability power spectrum between hypertensives and controls [39].

A family history of hypertension is recognized as a risk factor of hypertension development [9, 11, 18]. However, only about 30 % of young subjects with a family history of hypertension developed significantly higher blood pressure at a later age of 22 as compared to those without a family history of hypertension [16]. In *normotensives with a family history of hypertension* increased low-frequency bands of the heart rate and blood pressure variability power spectra were shown [28, 35]. Heart rate variability changes found in normotensive subjects are considered to be a good indicator of later hypertension development [8, 21, 29, 43]. Similarly as in *borderline hypertensives*, the results of baroreflex studies on normotensive subjects with a family history of hypertension [22, 35, 46, 49] are also in disagreement with each other. It was shown on monozygotic and dizygotic twins that baroreflex sensitivity was strongly genetically determined [47].

We designed our study to address alterations of the ANS activity, in particular baroreflex sensitivity, in normotensive subjects with a family history of hypertension. Considering higher expectancy of hypertension and statistical continuum of normotensives with a family history of hypertension, we hypothesized that they already exhibit altered activity of the ANS.

Materials and methods

Two groups of normotensive subjects not taking any medication participated in the study. The first group comprised 59 normotensive subjects with a family history of hypertension. The second group comprised 46 normotensives without a family history of hypertension. The recruitment of subjects began by introducing the study design to medical students and trainees, after which they decided whether they wanted to participate or not. Those having hypertension, diabetes, hyperlipidemia, or any other chronic or acute disease, and pregnant women were excluded from the study. Family history of hypertension was considered to be present if at least one of the subject's parents started taking antihypertensive medication at the age of 55 years or earlier. Informed consent was obtained from each subject. The investigation conformed to the principles outlined in the Declaration of Helsinki.

The study was performed at a room temperature of 22 °C following a 30-minute rest. The subjects were not allowed to drink coffee, tea, alcohol or to smoke at least eight hours before experiments. All experiments took place in the afternoon. First, blood pressure of the upper arm was measured using mercury sphygmomanometer. The guidelines of the World Health Organization and International Society of Hypertension were observed [10].

For beat-to-beat measurement of systolic, diastolic and mean arterial pressure on digital arteries as well as the heart rate, a finapres device (The Ohmeda 2300 Finapres Blood Pressure Monitor, Stockholm, Sweden) was used [15, 30, 50]. Simultaneously, ECG was monitored. Microvascular blood flow was determined on the right-hand index finger nailfold skin using laser-Doppler flowmeter (Periflux PF4, Stockholm, Sweden) with the original laser probe [4]. Measurements were performed in the resting condition, during left arm cooling with water at about 15 °C and during ten-minute upright tilting (65°). After each measurement flow was allowed to return to the resting level. By means of Neurocard software Fast Fourier transformation was performed from 6-minute recordings enabling us to draw a heart rate variability power spectrum, which the finapres device measures through the pulse rate of digital arteries. A systolic pressure and microvascular flow variability power spectra were also drawn by the same software. Areas in the very low- (0.003 to 0.04 Hz), low- (0.04 to 0.15 Hz) and high-frequency band (0.15 to 0.4 Hz) were determined [48]. The proportions of low- and high-frequency band of the heart rate variability power spectrum were also determined as a percentage of the total power.

Baroreflex sensitivity was estimated in the resting condition, during cooling and during upright tilting using the sequence method [13, 37] and based on the same recordings. Computer software developed at our institution was utilized. Baroreflex sensitivity was also determined at consecutive half-minute intervals during ten-minute upright tilting. A simultaneous increase or decrease of RR interval in ECG of at least 4 ms and that of systolic blood pressure of at least 1 mmHg was regarded as an indicator of baroreflex activation [33, 41].

Statistical analysis

The SPSS 6.0 statistical package was used. Mean values for baroreflex sensitivity and proportions of low- and high-frequency bands in the heart rate variability power spectrum were calculated for each group of subjects. Since the surface areas in very low-, low- and high-frequency bands of the heart rate, systolic pressure and microvascular flow variability power spectra showed a skewed distribution, data were evaluated for statistical analysis following a natural logarithmic transformation. Results are represented as mean values ± standard error. By means of a simple factorial ANCOVA procedure we studied the total variation in the aforementioned parameters divided into two components: a family history of hypertension as a factor (0 – yes, 1 – no) and brachial systolic blood pressure as a covariate. Since multiple comparisons were performed, the significance level was adjusted. The Bonferroni test was considered too rigorous; therefore, the significance level for each individual comparison was set at less than 0.01.

Multiple regression model was built with baroreflex sensitivity in the resting condition as a dependent variable. The following independent variables were included: heart rate, brachial systolic and diastolic pressure, age and presence (1) or absence (0) of a family history of hypertension. A stepwise procedure was used.

Results

Although still in the normotensive range, brachial systolic blood pressure was significantly higher in normotensives with a family history of hypertension as compared to normotensives without a family history of

hypertension. Brachial diastolic blood pressure, finger diastolic and systolic blood pressures and the heart rate did not differ significantly between the two groups (Table 1). During systemic cooling heart rate decreased and blood pressure increased significantly in both groups of subjects; the opposite happened during upright tilting. There were no significant differences in heart rate and blood pressure during cooling and tilting between the two groups.

After adjustment for the difference in brachial systolic pressure, the proportion and area of the high-frequency band of the heart rate variability power spectrum in the resting condition and during systemic cooling were significantly decreased in normotensive subjects with a family history of hypertension compared to normotensives without a family history of hypertension. On the contrary, we did not find any significant differences between the two groups with regard to other parameters of the heart rate variability power spectra in the resting condition, during contralateral hand cooling and during upright tilting (Table 2).

There were also no significant differences between the two groups with regard to the parameters of the systolic pressure variability power spectra in the resting condition, during contralateral hand cooling and during upright tilting after adjustment for the difference in systolic pressure had been performed.

Concerning the parameters of the microvascular variability power spectra in the resting condition, during contralateral hand cooling and during upright tilting after adjustment for the difference in systolic pressure, there were no significant differences between the two groups.

Baroreflex sensitivity in the resting condition was significantly reduced in normotensives with a family history of hypertension as compared to the control group. There was no significant difference between the two groups in baroreflex sensitivity during contralateral hand cooling (Fig. 1). During the first and the second half-minute intervals of upright tilting, baroreflex sensitivity was significantly decreased in normotensives with a family history of hypertension as compared to the subjects without a family history of hypertension. During

Table 1 General data on subjects

	Predisposed	Non-predisposed	p
Age (years)	28.6±0.5	25.7±0.7	ns
Gender (F/M)	31/28	32/14	ns
BMI (kg m^{-2})	22.6±0.3	22.5±0.4	ns
Smoking (yes/no)	13/46	6/40	ns
Heart rate (min^{-1})	68.1±1.3	64.5±1.2	ns
SBP (mmHg)	122.4±2.0	114.7±1.6	0.011
DBP (mmHg)	81.2±1.2	77.0±1.3	ns
SFP (mmHg)	107.5±1.6	103.9±1.8	ns
DFP (mmHg)	72.0±0.9	70.2±1.0	ns

BMI body mass index; *SBP* brachial systolic blood pressure; *DBP* brachial diastolic blood pressure; *SFP* finger systolic blood pressure; *DFP* finger diastolic blood pressure; *ns* statistically non-significant; *Predisposed* with a family history of hypertension; *Non-predisposed* without a family history of hypertension

Table 2 Heart rate variability power spectrum

	Predisposed	Non-predisposed	p (predisposition to hypertension)	p (BSP)
VLF-rest (ln ms^2)	13.4±0.1	13.4±0.1	ns	ns
LF-rest (ln ms^2)	13.5±0.1	13.7±0.2	ns	ns
LF-rest (%)	33.7±1.5	29.6±2.1	ns	0.02
HF-rest (ln ms^2)	13.6±0.1	14.2±0.2	< 0.001	ns
HF-rest (%)	34.5±2.1	46.6±2.9	0.004	ns
VLF-cool (ln ms^2)	13.5±0.1	13.5±0.1	ns	0.017
LF-cool (ln ms^2)	13.5±0.1	13.7±0.2	ns	0.014
LF-cool (%)	31.2±1.9	29.39±2.2	ns	ns
HF-cool (ln ms^2)	13.6±0.1	14.3±0.2	0.001	ns
HF-cool (%)	36.6±2.2	47.2±3.0	0.008	ns
VLF-tilt (ln ms^2)	13.4±0.1	13.4±0.1	ns	ns
LF-tilt (ln ms^2)	13.8±0.1	13.7±0.1	ns	0.013
LF-tilt (%)	45.6±2.3	46.7±3.0	ns	ns
HF-tilt (ln ms^2)	12.3±0.1	12.6±0.1	ns	ns
HF-tilt (%)	14.4±1.6	16.4±1.5	ns	ns

VLF, LF, HF very low-, low- and high-frequency band of the spectrum in the resting condition (rest), during systemic cooling (cool) and during upright tilting (tilt); *ns* statistically non-significant; *Predisposed* with a family history of hypertension; *Non-predisposed* without a family history of hypertension. Values are represented as mean value ± standard error. The last two columns indicate the significance of influence of a family history of hypertension and brachial systolic blood pressure (BSP) on the variation of the variables in the first column (ANCOVA)

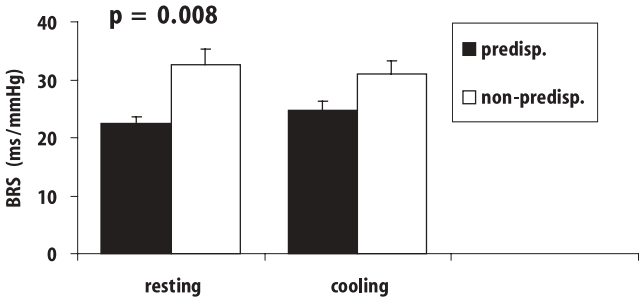

Fig. 1 Baroreflex sensitivity (BRS) in normotensives with a family history of hypertension (predisp.) as compared to normotensives without a family history of hypertension (non-predisp.) in the resting condition (resting) and during contralateral hand cooling (cooling)

the remaining half-minute intervals of the ten-minute tilting, baroreflex sensitivity was not significantly different between the two groups (Fig. 2). Multiple regression model showed that baroreflex sensitivity in the resting condition was significantly influenced by the heart rate, age and family history of hypertension. On the contrary, it was not significantly influenced either by brachial systolic or diastolic blood pressure (Table 3).

Discussion

The principle finding of our study is that normotensives with a family history of hypertension showed the alteration of some indices of the ANS activity compared to the control group. After adjustment for difference in brachial systolic pressure we found a decreased proportion and area of the high-frequency band of the heart rate variability power spectrum in the resting condition and during systemic cooling, as well as a reduced baroreflex sensitivity in the resting condition and during the first minute of upright tilting. In the parameters of the systolic pressure and microvascular flux variability power spectra, there were no significant differences between the two groups.

Both groups included normotensive subjects; however, normotensives with a family history of hypertension exhibited higher systolic pressure as compared to normotensives without a family history of hypertension. Diastolic pressure was not significantly different between the two groups. These results are in agreement with the results of Pitzalis [38]. Other studies investigating normotensives with a family history of hypertension showed higher systolic and diastolic pressure [22] or only higher diastolic pressure [35] in comparison with the control group. The observation that even normotensives with a family history of hypertension demonstrate higher blood pressure is in accordance with Pickering's principle of continuum, where normotensives with a family history of hypertension occupy the intermediate

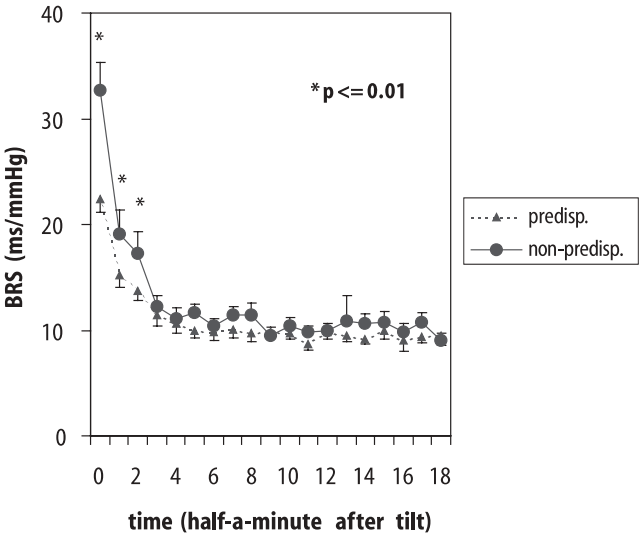

Fig. 2 Baroreflex sensitivity (BRS) during upright tilting in normotensive subjects with a family history of hypertension (predisp.) and in normotensives without a family history of hypertension (non-predisp.)

Table 3 Multiple regression model with baroreflex sensitivity in supine position (BRS) as a dependent variable

	B	SE B	p
Heart rate	−0.8	0.1	< 0.0001
Predisposition	−5.0	0.3	0.0367
Age	−0.8	2.4	0.0016
Constant	107.0	10.6	< 0.0001

Predisposition predisposition to hypertension
BRS = 107.0 − 0.8*heart rate − 5.0*predisposition − 0.8*age

place between normotensives without a family history of hypertension and hypertensive subjects [36].

Predominance of sympathetic over parasympathetic nervous system activity is one of the basic characteristics of developed hypertension [7, 20, 39, 44]. It was proven even in borderline hypertensives [26, 40] and in normotensives with a family history of hypertension [31, 44]. Our results showed a decreased proportion and area of the high-frequency band of the heart rate variability power spectrum in normotensives with a family history of hypertension, which speaks in favor of increased sympathetic over vagal activity at the level of the sinus node. We found reduced baroreflex sensitivity in the resting condition in the group with a family history of hypertension, which is in accordance with the results of Lopes et al. [22] and also indicates decreased ability of vagus activation at the sinus node. In contrast, such a result is in disagreement with other studies which failed to show any differences in baroreflex sensitivity in normotensives with a family history of hypertension as compared to the control group [35, 38]. Reduced barore-

flex sensitivity at an early stage of hypertension could be a possible pathogenetic mechanism of exaggerated sympathetic activity resulting in higher blood pressure. An alternative explanation could also be that increased sympathetic activity (induced by some alteration in the central nervous system, for example) could damage baroreflex regulation. This dilemma can not be solved by the results of our study. Nevertheless, our multiple regression model does indicate an influence of a family history of hypertension on baroreflex sensitivity. It is reasonable to assume that a family history of hypertension is associated with reduced baroreflex sensitivity. According to the results of our multivariate analysis increasing age also reduces baroreflex sensitivity, which is in agreement with the results of other studies [17, 34]. The animal basic studies revealed that baroreflex sensitivity is a dynamic phenomenon with a substantial variation in time [1, 2], which could be of great importance in evaluating the ANS activity in hypertension. The novelty in our study is the assessment of time course of baroreflex sensitivity during provocation test (upright tilting). We found that during the first minute of such a position baroreflex sensitivity rapidly (almost exponentially) decreased. We showed that during the first two half-minute intervals of upright tilting baroreflex sensitivity was lower in normotensives with a family history of hypertension as compared to the controls. During the remaining nine minutes of ten-minute upright tilting there was no significant difference between the two groups. Our study was the first to demonstrate such results. This means that the time constant of baroreflex sensitivity changes during tilting may be different between the two groups of subjects. It is known that stretch-activated calcium channels in membranes of vascular smooth muscles take part in the reception of pressure changes taking place on baroreceptors [6]. It could be that these channels are altered as early as in the pre-hypertensive stage of hypertension. Such an explanation can not be proved by the results of our study. To solve this question baroreceptors should be studied using specific calcium-channel blockers.

ANS activity in normotensives with a family history of hypertension was further explored by systolic pressure and microvascular variability power spectral analysis. Systemic cooling and upright tilting are standard methods for peripheral sympathetic activity evaluation [42]. Similar to some other studies, systemic cooling was performed by immersion of the whole left arm into water, while skin blood flow was measured on the other hand. Water at 15 °C was used, which activates cutaneous thermoreceptors without causing pain [27]. After adjustment for the difference in brachial systolic pressure we did not find any significant differences in parameters of systolic pressure or microvascular flux variability power spectra between the two groups, which speaks against any alteration in peripheral sympathetic activity in normotensive subjects with a family history of hypertension and is in agreement with the results of Radaelli, who found no difference in the arteriolar skin blood flow variability power spectrum between hypertensives and controls [39].

Our results indicate that although still in the normotensive range in both groups of subjects, systolic blood pressure was significantly higher in normotensives with a family history of hypertension as compared to normotensives without a family history of hypertension. As compared to the control group, normotensives with a family history of hypertension exhibit a decreased proportion and area of the high-frequency band of the heart rate variability power spectrum in the resting condition and during cooling, reduced baroreflex sensitivity in the resting condition as well as an altered time course of baroreflex sensitivity during tilting. These findings could lead to the conclusion that even in normotensives with a family history of hypertension the ratio of sympathetic to parasympathetic activity at the level of the heart is shifted in favor of the former.

In our study the time course of baroreflex sensitivity during tilting was introduced together with an assessment of other indicators of the ANS activity in normotensives with a family history of hypertension in the resting condition, during systemic cooling and during upright tilting. The results of our study demonstrate that normotensives with a family history of hypertension manifest no alteration in peripheral sympathetic reactivity at the vascular level; however, they display an increased ratio of sympathetic to parasympathetic activity at the cardiac level, which could be conducive to higher systolic blood pressure.

Acknowledgements This study was supported by the Research Council of Slovenia Grant No. L3–7874–0381/96.

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