SCRIPTA MEDICA (BRNO) – 73 (3): 201–208, *September 2000*

BAROREFLEX SENSITIVITY AND A 24-HOUR BLOOD PRESSURE PROFILES IN CHILDREN AND ADOLESCENTS WITH ESSENTIAL HYPERTENSION

NOVÁKOVÁ Z.[1], HONZÍKOVÁ N.[1], HRSTKOVÁ H.[2], FIŠER B.[1], VÁCLAVKOVÁ P.[2]

[1]Department of Physiology and [2]1[st] Department of Pediatrics, Faculty of Medicine, Masaryk University, Brno

A b s t r a c t

The aim of the present study was to investigate baroreflex sensitivity expressed in ms/mmHg (BRS) and Hz/mmHg (BRSf) in children and adolescents with essential hypertension.

Thirty-three children and adolescents (age 15.3±2.6 years) with systolic casual blood pressure (CBP) >140 mmHg (three measurements at least one week apart) were examined. Ambulatory blood pressure (ABP) monitoring, BRS and BRSf measurements (spectral method; blood pressure and pulse interval recording by Finapres for 5 minutes; metronome controlled breathing at 0.33 Hz frequency) were performed in each subject. Two groups were established on the basis of 24-hour systolic ABP: A (n=17), systolic ABP>125 mmHg; B (n=16), physiological ABP (systolic ABP≤125 mmHg) but increased CBP.

Statistically significant differences ($P<0.05$) in BRSf (0.0145±0.005 *vs.* 0.0232±0.011 Hz/mmHg), weight (77.7±13.5 *vs.* 59.1±19.0 kg), height (176±7 *vs.* 163±15 cm) and age (16.8±1.0 *vs.* 13.7±2.9 years) were found between groups A and B. Systolic ABP correlated with age, height, weight and BRSf. BRSf correlated with height. The mean pulse interval correlated with BRS but not with BRSf.

We conclude that BRSf, which is pulse-interval independent, is significantly decreased in children and adolescents with high systolic ABP. Since BRSf correlated with both systolic blood pressure and height, it may be considered a connecting link between height and blood pressure in our group.

K e y w o r d s

baroreflex sensitivity, spectral analysis, ambulatory blood pressure monitoring, essential hypertension, adolescents

INTRODUCTION

Baroreceptor control of the circulation has generally been thought to be associated with short-term buffering of changes in arterial pressure rather than with long-term setting of pressure levels. Recently, evidence has been accumulated which suggests that impairment of the baroreflex, either by local changes in the carotid sinus or by environmental or genetical influences working through cortical modulation of the reflex gain, may have an important effect on long-term arterial pressure. Further interest in the baroreflex has been stimulated when several studies have demonstrated that autonomic control, measured by either baroreflex sensitivity or heart rate variability, is a powerful independent prognostic factor which adds to other clinical measures of risk stratification in patients with left ventricular damage or in those who have survived myocardial infarction. Inter-relationships of these mechanisms are complex, poorly understood and subject to many confounding factors *(1).* Many studies have been conducted in order to explain the role of decreased baroreflex sensitivity in the development of hypertension in adults but very little is known about the relationship between blood pressure and baroreflex sensitivity in hypertensive children and adolescents. This is understandable because the phenylephrine method, which is usually used, cannot be employed in children for ethical reasons.

The method of baroreflex sensitivity determination used in our laboratory is based on spectral analysis of the spontaneous variability of blood pressure and pulse intervals *(2)*. Baroreflex sensitivity can be expressed in ms/mmHg as BRS *(3)* or in Hz/mmHg as BRSf *(4).* Both BRS and BRSf determinations were carried out in healthy children and adolescents. In 180 subjects studied (age, 10-22 years) no correlation has been found between BRS and age *(5, 6).* This finding may have been caused by large inter-individual differences in BRS values because 16% of the subjects had BRS < 5ms/mmHg. A similar, low value of BRS has been found in hypertensive patients in several studies. Other studies have shown that BRS is dependent on the mean pulse interval *(7, 8).* On the contrary, BRSf, which is a mean pulse interval independent index, decreases with age in children and adolescents *(9)* as does the compliance of arteries. BRSf in young healthy adults is a long-term characteristic because the values measured at one-year intervals correlate with each other *(10).*

The aim of the present study was to investigate baroreflex sensitivity expressed by two units, i.e., ms/mmHg (BRS) and Hz/mmHg (BRSf) in children and adolescents with essential hypertension.

MATERIALS AND METHODS

Subject population

Thirty-three children and adolescents (mean age SD, 15.3±2.6 years; 8 girls and 25 boys) participated in the study. They were included if their systolic casual blood pressure (CBP) was higher than 140 mmHg on three different examinations made at least one week apart by their physicians extablishing their primary diagnosis. Any form of secondary hypertension was ruled out by routine clinical, x-ray and laboratory examination. Body height and weight were recorded and information on their medical histories and the use of medication were obtained using a questionnaire. The study was approved by the Ethical Committee.

Ambulatory blood pressure monitoring

Twenty four-hour blood pressure monitoring was carried out with an oscillometric device (Space Lab International). In each subject, an appropriate cuff was chosen from three different cuff sizes available and attached to the non-dominant arm. The subjects were instructed to relax their arms during blood pressure measurements which were made every 10 or 15 min during the day and every 30 min during the night. A minimum of 40 recordings had to be obtained during the study period.

Baroreflex sensitivity determination

Blood pressure was recorded by an indirect continuous measurement in finger arteries (Finapres, Ohmeda) during an interval of 5 min between 9 a.m. and noon. The subjects were in a sitting and resting position. Recordings were taken during both spontaneous and synchronised breathing. During the latter, the rhythm of breathing was controlled at 20 breaths per min (0.33 Hz) by a metronome; the subjects were allowed to adjust the tidal volume according to their own comfort.

Beat-to-beat values of systolic pressure and those of pulse intervals were measured for further analysis. For spectral analysis, these parameters were linearly interpolated and equidistantly sampled at 2 Hz. The linear trend was removed. Auto-correlation and cross-correlation functions, relative power spectra (relative division of the power into frequency ranges in arbitrary units), absolute power and cross-spectra, coherence and modulus between pulse intervals and systolic pressure, were calculated *(2)*. The gain factor, i.e., H[f] modulus of the transfer function between variations in systolic blood pressure and pulse intervals, was calculated in the frequency range [f] according to the formula:

$$Gxy[f]=H[f].Gx[f],$$

where Gxy[f] is cross-spectral density between systolic pressure and pulse intervals; Gx[f] is the spectral density of systolic pressure. The value of modulus at a frequency of 0.1 Hz was taken as a measure of baroreflex sensitivity. This was expressed by two units: ms/mmHg-BRS *(3)* and Hz/ mmHg-BRSf *(4)*.

Statistical analysis

The subjects were divided into two groups according to the mean values of their systolic ambulatory blood pressure (ABP) derived from 24-hour measurement by a Holter monitor as follows: group A (n=17), mean systolic ABP > 125 mmHg; group B (n=16), mean systolic ABP≤125 mmHg. These values were chosen in accordance with the 1999 World Health Organisation - International Society of Hypertension Guidelines for the Management of Hypertension *(11)*. The mean values and standard deviations of all parameters (BRS, BRSf, 24-hour systolic and diastolic ABP, pulse intervals, weight, height, and age) were calculated for both groups. The correlation between the parameters was examined by means of Pearson's correlation coefficient. The p value<0.05 was considered significant. The differences between the groups were compared by means of the Wilcoxon test. For each group, 24-hour profiles of systolic and diastolic BP were evaluated.

RESULTS

A comparison of 24-hour BP profiles between groups A (ABP > 125 mmHg) and B (ABP≤125 mmHg) showed a minimal difference in diastolic blood pressure in the morning hours (*Fig. 1*). In group A, systolic BP values were elavated both during the day and at night.

Differences between the mean value of circulatory parameters and the indices of body development of groups A and B were determined; the mean values, SD and statistical significance of differences are shown in *Table 1*. Differences between BRSf, weight and height values and age of group A and those of group B were statistically significant.

The inter-relationships of BRS, BRSf, 24-hour mean systolic and diastolic blood pressures, pulse intervals, weight, height, and age calculated for all subjects are shown in *Table 2*. The mean systolic BP correlated significantly with age, height, weight, and BRSf. BRSf correlated with height, but not with age or

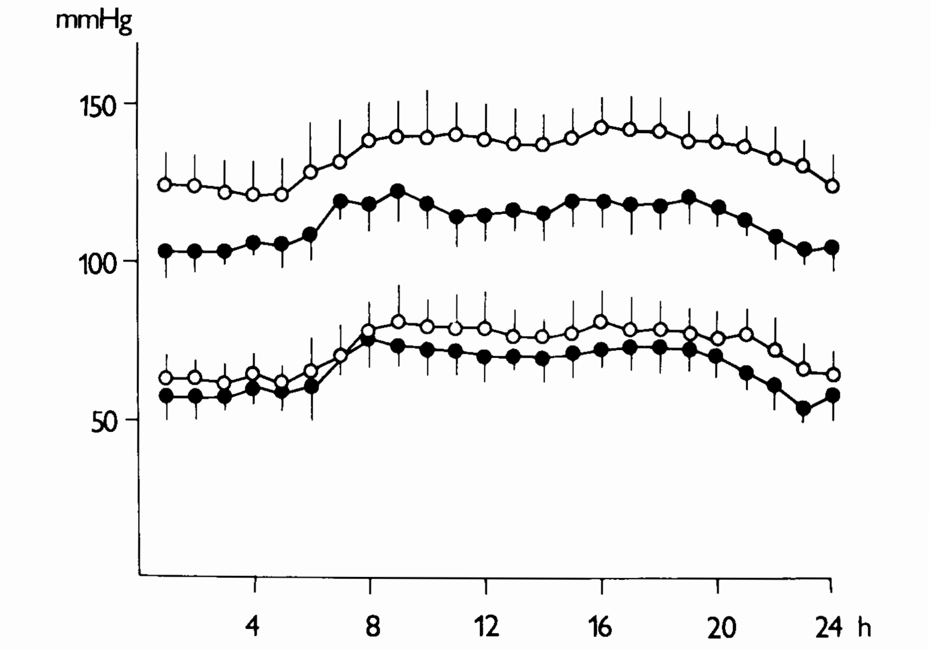

Fig. 1
Twenty-four-hour profiles of systolic and diastolic blood pressure in the subjects with mean systolic ambulatory blood pressure >125mmHg (circles) and mean systolic ambulatory blood pressure ≤ 125mmHg (dots).

weight. Although there was a correlation between BRS and BRSf, BRS correlated, in addition to BRSf, only with the pulse interval. The pulse interval correlated with BRS but not with BRSf.

DISCUSSION

A relationship between age and BP values measured by ambulatory BP monitoring has been investigated in several studies *(12).* The blood pressure values obtained by 24-hour ambulatory monitoring in young hypertensive subjects were by several mmHg lower than those obtained by casual office measurements. *Mancia et al. 1995 (13)* found that the average values of ambulatory 24-hour monitoring or measurement at home were about 125/80 mmHg in contrast to an average of 140/90 mmHg from casual measurements. In order to verify this relationship in a sample of the young Czech population, we used a simple classification based on the mean 24-hour BP values *(11, 12)*, in which 125 mmHg was considered the upper limit of normal systolic BP which corresponds to 140 mmHg of casual BP pressure.

Table 1
Comparison of the subjects with mean systolic ABP >125 mmHg (group A, n=17) and those with mean systolic ABP≤125 mmHg (group B, n=16).

Parameter Systolic ABP Diastolic ABP	Group A 133.1 ± 6.9 72.0 ± 5.4	Group B 115.4 ± 5.3** 66.8 ± 4.4**
Age (years)	16.8 ± 1.0	13.7 ± 2.9 *
Weight (kg)	77.7 ± 13.5	59.1 ± 19.0 *
Height (m)	1.76 ± 0.07	1.63 ± 0.15 *
BRS (ms/mmHg)	8.1 ± 3.5	13.2 ± 7.8
BRSf (Hz/mmHg)	0.01454 ± 0.00571	0.02322 ± 0.01138 *
PI (ms)	745.7 ± 109.4	742.4 ± 138.6

ABP – ambulatory blood pressure (mmHg), BRS - baroreflex sensitivity (ms/mmHg), BRSf – baroreflex sensitivity (Hz/mmHg), PI - pulse interval (ms), * A versus B, $P < 0.05$, Wilcoxon test, ** A versus B, $P < 0.01$, Wilcoxon test

Table 2
Correlation coefficients between variables in 33 subjects

	Height	Weight	sABP	dABP	PI	BRS	BRSf
Age	0.8179**	0.6766**	0.5491**	0.3391	0.0959	- 0.2826	- 0.3223
Height		0.7624**	0.5223**	0.1346	0.2002	- 0.3011	- 0.3809*
Weight			0.4974**	0.1369	0.0921	- 0.2937	- 0.3299
sABP				0.4733**	0.2292	- 0.3437	- 0.4653**
dABP					- 0.1430	- 0.2029	- 0.1934
PI						0.3526*	- 0.1166
BRS							0.8602**

sABP – mean systolic ambulatory blood pressure, dABP – mean diastolic ambulatory blood pressure, PI - pulse interval, BRS - baroreflex sensitivity (ms/mmHg), BRSf - baroreflex sensitivity (Hz/mmHg), * $P < 0.05$, ** $P < 0.01$

Although ”white coat hypertension” seems to occur in 20% of the adult hypertensive population, this phenomenon has rarely been described in adolescents *(14).* In our study, white coat hypertension was experienced by about half of the subjects. This finding indicates that white coat hypertension is more frequent in children and adolescents than in adults and, therefore, to make a reliable diagnosis of hypertension may require its confirmation by ambulatory blood pressure monitoring.

A comparison of the 24-hour profiles of BP between the subjects with the mean systolic ABP >125 mmHg and those with ABP≤125 mmHg showed an increase in BP in the morning hours in both groups. However, in the subjects with high mean values of systolic ABP, systolic BP revealed increased levels both during the day and at night. The morning increase in BP corresponds to increased sympathetic activity *(15).* The finding of this difference between the two groups is in agreement with the hypothesis that increased sympathetic activity is present only during the morning hours in children with low 24-hour blood pressure while sympathetic activity is increased during the whole 24-hours of ambulatory monitoring in hypertensive adolescents.

The increased systolic BP in our subjects can be attributed to their higher body weight. The impact of obesity on ambulatory blood pressure in children and adolescents is known *(16).* This fact may be explained by secretion of leptin by adipose tissue, which increases sympathetic activity in obese patients with essential hypertension *(17).*

The next body parameter, height, was also found to correlate with systolic BP. The height of children, as a factor determining the value of systolic blood pressure, was found to be important in many studies *(18, 19, 20).*

An interesting finding concerning the baroreflex is the difference found between BRS (expressed in ms/mmHg) and BRSf (expressed in Hz/mmHg). As described previously, BRS is dependent on the pulse interval (7, 8), whereas BRSf is pulse-interval independent (4). We observed a significant decrease in BRSf with age *(10, 21).* Since BRSf correlates with both systolic BP and height, it might be a connecting link between height and blood pressure.

Nováková Z., Honzíková N., Hrstková H.[1], Fišer B., Václavková P.[1]

CITLIVOST BAROREFLEXU A 24-HODINOVÝ PROFIL KREVNÍHO TLAKU U DĚTÍ A DOSPÍVAJÍCÍCH S ESENCIÁLNÍ HYPERTENZÍ.

S o u h r n

Cílem předkládané práce bylo zjistit baroreflexní sensitivitu srdce vyjádřenou dvěma způsoby - v ms/mmHg a v Hz/mmHg u dětí a dospívajících s esenciální hypertenzí.

Bylo vyšetřeno 33 dětí a dospívajících průměrného věku 15.3±2.6 roku, kterým byl opakovaně (v intervalu jednoho týdne a více) v ordinaci praktického lékaře naměřen systolický krevní tlak >140 mmHg. U všech dětí bylo provedeno 24-hodinové ambulatorní monitorování krevního tlaku.

BRS a BRSf byly určeny pomocí spektrální analýzy pětiminutového kontinuálního záznamu krevního tlaku a tepových intervalů (Finapres, Ohmeda) při řízeném dýchání 20/min. Podle průměrných hodnot systolického krevního tlaku získaných při ambulatorním monitorování (sABP) byly děti rozděleny do dvou skupin: skupina A (sABP >125 mmHg, počet osob n=17); skupina B (sABP≤125 mmHg, n=16).

Statisticky významné rozdíly ($p<0.05$, Wilcoxon) mezi oběma skupinami byly nalezeny pro BRSf (A vs. B: 0.0145±0.005 vs. 0.0232±0.011 Hz/mmHg), hmotnost (77.7±13.5 vs. 59.1±19.0 kg), výšku (176±7 vs. 163±15 cm) a věk (16.8±1.0 vs. 13.7±2.9 rok). Systolický krevní tlak (sABP) koreloval s věkem, výškou, hmotností a BRSf sledovaných osob. BRSf dále korelovala s výškou. Hodnota BRS korelovala s průměrným tepovým intervalem, BRSf je na tepovém intervalu nezávislá.

Uzavíráme, že citlivost baroreflexu vyjádřená jako BRSf, která je nezávislá na průměrném tepovém intervalu, je signifikantně nižší u dětí a dospívajících s vysokým systolickým krevním tlakem. BRSf koreluje se systolickým tlakem krve a tělesnou výškou a může být spojovacím článkem mezi těmito dvěma parametry.

ACKNOWLEDGEMENT

This study was supported in part by grant no. 3900-3 from IGA of the Czech Ministry of Health and grant CEZ:J07/98:141100004 from the Grant Agency of the Czech Ministry of Education.

REFERENCES

1. *Sleight P*. The importance of the autonomic nervous system in health and disease. Aust NZ J Med 1997; 27: 467-473.
2. *Honzíková N.* Spectral Analysis of Circulatory Rhythms. Masaryk University, Brno, 1992, 125 pp.
3. *Honzíková N, Fišer B, Honzík J*. Noninvasive determination of baroreflex sensitivity in man by means of spectral analysis. Physiol Res 1992; 41: 31-37.
4. *Al-Kubati MAA, Fišer B, Siegelová J.* Baroreflex sensitivity during psychological stress. Physiol Res 1997; 46: 31-37.
5. *Honzíková N, Fišer B, Nováková Z*. Heart rate and baroreflex sensitivity in children and adults. In: 3rd Czech-French-Slovak Symposium. Obernai, France: New Frontiers in Basic Cardiovascular Research, 1998:17.
6. *Semrád B, Fišer B, Honzíková N.* Ageing and cardiac autonomic status. In: Malik M, ed. Clinical Guide to Cardiac Autonomic Tests. Dordrecht, Boston, London: Kluwer Academic Publishers, 1998; 285-300.
7. *Honzíková N, Semrád B, Fišer B*. Baroreflex sensitivity and heart rate variability in patients after myocardial infarction: effect of thrombolytic therapy. In: Man inīt Veld AJ, van Montfrans GA, Langewouters GJ, Lie KI, Mancia G, eds. Proceedings of the two Satellite Symposia to the Seventh Meeting of the European Society of Hypertension, Amsterdam: Measurement of heart rate and blood pressure variability in man.1995: 113-117.
8. *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 1997; 2: 69-72.
9. *Fišer B, Honzíková N, Semrád B, Nováková Z.* Aging and baroreflex sensitivity. Fundamental and Clinical Pharmacology 1998; 12(Suppl 1): 74.
10. *Fišer B, Honzíková N, Nováková Z, Hrstková H*. Baroreflex sensitivity in children and young adults. J Physiol (London) 1998; 511:113P.
11. Guidelines Subcommittee: 1999 World Health Organization - International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens 1999; 17: 151-183.
12. *Reichert H, Lindinger A, Frey O, et al.* Ambulatory blood pressure monitoring in healthy children. Pediatr Nephrol 1995; 9: 282-286.
13. *Mancia G, Sega R, Bravi D, et al.* Ambulatory blood pressure normality: results from the PAMELA study. J Hypertens 1995; 13: 1377-1390.
14. *Koch VH, Furusawa EA, Saito MI, et al.* White coat hypertension in adolescents. Clin Nephrol 1999; 52(5):297-303.
15. *Halberg F, Drayer JIM, Cornťlissen G, Weber MA*. Cardiovascular reference data base for recognizing circadian mesor- and amplitude-hypertension in apparently healthy men. Chronobiologia 1984; 11: 275-298.

16. *Lurbe E, Alvarez V, Liao Y, et al*. The impact of obesity and body fat distribution on ambulatory blood pressure in children and adolescents. Am J Hypertens 1998; 11(4Pt1):418-424.
17. *Narkewicz K, Somers VK, Mos L, Kato M, Accurso V, Palatini P*. An independent relationship between plasma leptin and heart rate in untreated patients with essential hypertension. J Hypertens 1999; 17: 245-249.
18. *Soergel M, Kirschstein M, Busch CH, et al.* Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents. A multicenter trial including 1141 subjects. J Pediatr 1997; 130: 178-184.
19. *De Man SA, Andrť JL, Bachmann H, et al.* Blood pressure in childhood: pooled findings of six European studies. J Hypertens 1991; 9: 109-114.
20. Task Force on Blood Pressure Control in Children: Report of Second Task Force on Blood Pressure Control in Children - 1987. Pediatrics 1987; 79: 1-25.
21. *Hrstková H, Závodná E, Fišer B, Honzíková N*. Relationship between anamnestic determined physical activity and baroreflex sensitivity after anthracycline treatment. Čs Pediatrie 2000; 55(5): 281-287