

## AUTONOMOUS REGULATION OF CIRCULATION IN CHILDREN AFTER ANTHRACYCLINE THERAPY

ZÁVODNÁ E.<sup>1</sup>, HRSTKOVÁ H.<sup>2</sup>, HONZÍKOVÁ N.<sup>1</sup>, NOVÁKOVÁ Z.<sup>1</sup>

<sup>1</sup>Department of Physiology and <sup>2</sup>First Department of Paediatrics, Paediatric Teaching Hospital, Faculty of Medicine, Masaryk University, Brno, Czech Republic

### Abstract

In this study, we evaluated the development of autonomous regulation of circulation in children who had previously been treated for malignant diseases, particularly leukaemia. We examined 105 children and adolescents aged 10 to 21 years. A control group (C) of 84 healthy children was age-matched with 21 cancer survivors after anti-cancer therapy (group M) in a ratio of four healthy children to one cancer survivor. In group M, eight children had a non-cardiotoxic therapy (subgroup A<sup>0</sup>), and 13 children were treated with cardiotoxic anthracyclines (subgroup A<sup>+</sup>). In all children, we recorded, beat-to-beat, pulse intervals (PI) and systolic (BPs) and diastolic (BPd) blood pressure by the non-invasive Peňáz method, calculated the baroreflex sensitivity of the heart and expressed it in ms/mmHg (BRS) and Hz/mmHg (BRSf).

The values of BPs and BPd, body weight and height and the body mass index (BMI) significantly correlated with age in groups C and M; BRS correlated significantly with BPs and BPd in group C, and with PI in groups C and subgroup A<sup>+</sup>. BPs correlated significantly with weight in groups C, M and subgroup A<sup>+</sup>. Using the Mann-Whitney test, we found significant differences in BPs between C and A<sup>+</sup>, ( $p < 0.01$ ) and A<sup>+</sup> and A<sup>0</sup> ( $p < 0.05$ ), in BPd between C and M, ( $p < 0.05$ ), C and A<sup>+</sup>, ( $p < 0.01$ ) and A<sup>+</sup> and A<sup>0</sup>, ( $p < 0.01$ ), and in height between C and M, ( $p < 0.01$ ) and C and A<sup>+</sup>, ( $p < 0.05$ ). The relationship between BRS and PI and that between BRS and BP were suppressed, thus demonstrating the association of anthracycline treatment with changes in cardiovascular functions. Body growth was decreased in all children after anti-cancer therapy, and blood pressure was lower only in the children who had anti-cancer anthracycline therapy.

### Key words

Baroreflex sensitivity, Anthracycline, Leukaemia, Blood pressure

### INTRODUCTION

Anthracycline antibiotics have been the most commonly used compounds in the treatment of a wide spectrum of malignant diseases, particularly leukaemia. The therapeutic use of anthracycline derivatives is limited by their side effects, especially by their cardiotoxicity. Risk factors for anthracycline cardiotoxicity involve a high cumulative dose of anthracycline, young age at the first diagnosis and additional cardiotoxic treatment and/or mediastinal irradiation. The clinical symptoms of acute cardiotoxicity include arrhythmias and ECG abnormalities. Chronic cardiotoxicity is primarily due to the development of degenerative cardiomyopathy with congestive

heart failure (1). The anthracycline-induced cardiotoxicity causes specific histopathological changes (degenerative changes in membrane and mitochondria of muscle cells), impaired proteosynthesis in heart and liver tissues, etc. (2).

Baroreflex sensitivity is an index of autonomic control of the heart. For a long time, baroreflex sensitivity has been estimated mainly by the phenylephrin method (3), i.e., invasive application of a vasoactive drug. This is the reason why only limited information has been published on the development of baroreflex sensitivity in children and adolescents. However, the recently developed method of assessing variability in blood pressure and pulse intervals by spectral analysis has facilitated investigation of BRS also in children. It is based on the recording of blood pressure and pulse intervals on finger arteries by the Peñáz non-invasive method (4). Early non-invasive studies have provided very interesting information. Although, during growth, blood pressure rises and pulse intervals prolong, between 11 and 15 years, baroreflex sensitivity correlates with neither age (5) nor the development of resting blood pressure and the mean pulse interval (6).

In adults, it has been shown that baroreflex sensitivity decreases with age and has a large inter-individual variability (7). Pathologically low baroreflex sensitivity ( $< 3\text{ms/mmHg}$ ) has been found to be a marker of increased risk of sudden cardiac death in patients after myocardial infarction (8, 9, 10). Low baroreflex sensitivity is a pathological sign in some other diseases such as heart failure, essential hypertension or diabetes mellitus.

The aim of this study was to evaluate the development of autonomous regulation of the circulation in children who had previously been treated for malignant diseases.

## MATERIALS AND METHODS

### SUBJECTS

We examined 105 children aged 10–21 years. The control group (C) of 84 healthy children was age-matched, in a ratio of four healthy children to one diseased child, with 21 cancer survivors (group M) who had been treated for malignant diseases. Group C included 58 boys and 26 girls (mean age  $\pm$  SD,  $15.5 \pm 3.2$  years) and group M consisted of 14 boys and 7 girls ( $15.5 \pm 3.2$  years).

In group M, eight children (subgroup A<sup>o</sup>) had been treated by a wide range of non-cardiotoxic therapies and 13 children (subgroup A<sup>\*</sup>) had been given cardiotoxic anthracyclines in combination with additional treatment (Table 1). The anti-cancer therapy was terminated  $117.9 \pm 57.4$  and  $34.6 \pm 32.0$  months, respectively, before this study.

The Ethics Committee approved of the study and the subjects gave their informed consent.

### PROTOCOL

We recorded pulse intervals (PI), systolic (BPs) and diastolic (BPd) blood pressure, beat-to-beat, on finger arteries by the Peñáz non-invasive method (Finapres OHMEDA) in all children. The recordings were taken in a 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.

Baroreflex sensitivity of the heart, assessed on the basis of spectral analysis, was expressed in  $\text{ms/mm Hg}$  (BRS) and in  $\text{Hz/mm Hg}$  (BRSf).

*Table 1*  
Diagnoses in group M children and the anti-cancer therapy used

	No. of subgroup A <sup>+</sup> children	No. of subgroup A <sup>0</sup> children
<b>Diagnoses</b>		
Acute lymphoblastic leukaemia	5	4
Lymphoma	6	1
Other (histiocytosis X, brain tumour, osteosarcoma, astrocytosis, soft tissue sarcoma)	2	3
<b>Treatment</b>		
Anthracycline therapy at a cumulative dose of 250.4±111.4 g/m <sup>2</sup>	13	0
Cyclophosphamide	7	0
Radiotherapy of the mediastinum	5	0
Other anti-cancer regimens	13	8

Subgroups A<sup>+</sup> and A<sup>0</sup> of group M comprised 13 and 8 children, respectively.

The gain factor, e.g. modulus  $H(f)$  of the transfer function among variations in systolic blood pressure and pulse intervals, was calculated at a frequency of 0.1Hz according to the formula:

$$H(f) = \frac{G_{xy}(f)}{G_x(f)}$$

where  $G_{xy}(f)$  corresponds to the cross-spectral density between systolic pressure and pulse intervals and  $G_x(f)$  corresponds to 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, 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 heart rate and systolic blood pressure as the second index of baroreflex sensitivity (BRSf, expressed in Hz/mmHg).

#### STATISTICS

The mean values and standard deviations of age, pulse intervals (PI), systolic blood pressure (BPs), diastolic blood pressure (BPd), baroreflex sensitivity (BRS and BRSf), body weight and height and the body mass index (BMI) were determined. Differences among the mean values were tested by the Mann-Whitney test, correlations among the parameters were evaluated by Spearman's correlation coefficients and the differences among slopes of correlations by the F test.

*Table 2*  
Body and cardiovascular characteristics (mean  $\pm$  SD) of groups and subgroups

	C	M	A <sup>+</sup>	A <sup>0</sup>
Age (years)	15.5 $\pm$ 3.2	15.5 $\pm$ 3.2	14.9 $\pm$ 2.9	16.4 $\pm$ 3.6
PI (ms)	751.7 $\pm$ 116.6	771.1 $\pm$ 147.4	760.0 $\pm$ 170.7	789.0 $\pm$ 107.3
BPs (mmHg)	112.0 $\pm$ 12.8 °°	109.8 $\pm$ 18.8	101.5 $\pm$ 11.3 $\times$	123.3 $\pm$ 21.4
BPd (mmHg)	69.2 $\pm$ 8.7 °°	65.9 $\pm$ 14.1*	59.1 $\pm$ 6.9 $\times\times$	77.0 $\pm$ 15.9
BRS (ms/mmHg)	11.5 $\pm$ 5.6	12.4 $\pm$ 7.2	13.2 $\pm$ 8.1	11.2 $\pm$ 5.8
BRSf (Hz/mmHg)	0.0199 $\pm$ 0.0091	0.0199 $\pm$ 0.0082	0.0208 $\pm$ 0.0075	0.0186 $\pm$ 0.0098
Weight (kg)	60.1 $\pm$ 14.2	54.0 $\pm$ 13.6	52.5 $\pm$ 12.9	56.4 $\pm$ 15.4
Height (cm)	169.7 $\pm$ 13.9 °	161.8 $\pm$ 11.8**	159.9 $\pm$ 12.9	164.9 $\pm$ 9.9
BMI (kg/m <sup>2</sup> )	20.6 $\pm$ 2.7	20.4 $\pm$ 3.2	20.3 $\pm$ 2.8	20.5 $\pm$ 3.9

PI, pulse intervals; BPs, systolic blood pressure; BPd, diastolic blood pressure; BRS and BRSf, baroreflex sensitivity in ms/mm Hg and Hz/mm Hg, respectively; BMI, body mass index; N.s., not significant. Significant differences were found between the following groups: C and A<sup>+</sup>, (° $P$ <0.05, °° $P$ <0.01); M and C, (\* $P$ <0.05, \*\* $P$ <0.01); A<sup>+</sup> and A<sup>0</sup>, ( $\times$  $P$ <0.05,  $\times\times$  $P$ <0.01).

*Table 3*  
Slopes of correlation between age and the cardiovascular and body parameters, and the differences in these slopes among groups and subgroups

	C vs. M			A <sup>+</sup> vs. A <sup>0</sup>		
	b (C)	b (M)	Level of significance	b (A <sup>+</sup> )	b (A <sup>0</sup> )	Level of significance
PI (ms)	9.84	12.39	$P$ <0.01	17.7	5.18	$P$ <0.01
BPs (mmHg)	2.45	3.39	$P$ <0.01	2.34	3.29	N.s.
BPd (mmHg)	0.82	2.3	$P$ <0.01	1.53	2.06	N.s.
BRS (ms/mmHg)	-0.39	-0.40	N.s.	0.14	-0.95	$P$ <0.01
BRSf (Hz/mmHg)	-0.001	-0.001	N.s.	-0.0007	-0.001	N.s.
Weight (kg)	3.14	3.00	N.s.	2.22	3.97	$P$ <0.01
Height (cm)	3.14	2.25	$P$ <0.01	2.31	2.05	N.s.
BMI (kg/m <sup>2</sup> )	0.35	0.55	N.s.	0.26	0.96	$P$ <0.01

b, slope defined by the formula  $y = a + b x$ , where  $x$  is age and  $y$  is either a cardiovascular or a body parameter.

## RESULTS

The only significant differences between healthy children (group C) and children treated for malignant diseases (group M) were in BPd and height values (group C of children had higher BPd and were taller). We did not find any significant differences between group C and subgroup A<sup>0</sup>. Subgroup A<sup>+</sup>, on the other hand, had significantly lower values of blood pressure (BPs and BPd) than group C and subgroup A<sup>0</sup>. Apart from these two parameters, there were no other differences between subgroup A<sup>+</sup> and A<sup>0</sup> children (*Table 2*).

Systolic and diastolic blood pressure, weight, height and BMI significantly correlated with age in groups C and M. BRS correlated with PI in group C and subgroup A<sup>+</sup>; in group C, BRS correlated with BPs and BPd, and BRSf correlated with height and weight.

When groups C and M were compared in terms of age-related development of the test parameters, the following findings were made in the cancer survivors: faster prolongation of pulse intervals (decrease in heart rate), faster increase in systolic and diastolic blood pressure, and slower development of height. The development of BRS, BRSf, weight and BMI was similar in both group C and group M (*Table 3*).

We made an unexpected finding in relation to BRS. This decreased with age in group C and subgroup A<sup>0</sup> but increased significantly with age in subgroup A<sup>+</sup>. We also found significant differences in PI development between group C and subgroup A<sup>+</sup> and between subgroups A<sup>+</sup> and A<sup>0</sup>. Subgroup A<sup>+</sup> had a significantly faster prolongation of PI than group C and subgroup A<sup>0</sup>. We found a deceleration in BPs development in group A<sup>+</sup> (*Table 3 and 4*).

## DISCUSSION

Baroreflex sensitivity in adults is usually measured by the index BRS. Its value, expressed in ms/mmHg, decreases with advancing age. It has been reported that the index is dependent on the mean pulse interval. The less frequently used index BRSf (expressed in Hz/mmHg), on the other hand, is independent of the mean pulse interval and, therefore, shows any decrease in baroreflex sensitivity even if the tonic effect of the vagus nerve on the heart rate is increasing. In children, the mean pulse interval prolongs with increasing age, BRS remains constant but BRSf decreases.

A rise in the index BRS, found in this study on cancer survivors previously treated with anthracycline, should not be related only to an increase in sensitivity of the baroreflex but also to a marked prolongation of pulse intervals that occurred in these survivors. A concomitant, age-related decrease in the index BRSf, which was identical to that in the healthy children, was also a very important finding. It implies that BRSf was not primarily altered in the cancer survivors treated with anthracycline and that this index, which is independent of the mean pulse interval, is a better indicator of baroreflex sensitivity development. The complex of

*Table 4*  
Slopes of correlation between age and the cardiovascular and body parameters, and the differences in these slopes among groups and subgroups

	C vs. A <sup>+</sup>			C vs. A <sup>0</sup>		
	b (C)	b (A <sup>+</sup> )	Level of significance	b (C)	b (A <sup>0</sup> )	Level of significance
PI (ms)	9.84	17.7	<i>P</i> <0.01	9.84	5.18	<i>P</i> <0.01
BPs (mmHg)	2.45	2.34	N.s.	2.45	3.29	<i>P</i> <0.05
BPd (mmHg)	0.82	1.53	<i>P</i> <0.05	0.82	2.06	<i>P</i> <0.01
BRS (ms/mmHg)	-0.39	0.14	<i>P</i> <0.05	-0.39	-0.95	<i>P</i> <0.05
BRSf (Hz/mmHg)	-0.001	-0.0007	N.s.	-0.001	-0.001	N.s.
Weight (kg)	3.14	2.22	<i>P</i> <0.01	3.14	3.97	<i>P</i> <0.05
Height (cm)	3.14	2.31	<i>P</i> <0.05	3.14	2.05	<i>P</i> <0.01
BMI (kg/m <sup>2</sup> )	0.350	0.26	N.s.	0.35	0.96	<i>P</i> <0.01

b, slope defined by the formula  $y = a + b x$ , where  $x$  is age and  $y$  is either a cardiovascular or a body parameter.

changes in tonic and reflex heart rate regulation can be explained by the anthracycline-induced suppression of cholinesterase proteosynthesis in the heart muscle with a subsequent increase in acetylcholine action (2).

The low BPs values found in the cancer survivors treated with anthracyclines are more difficult to explain. They may be due to a decrease in cardiac output during anthracycline treatment of the acute phase of their disease, because this treatment has repeatedly been reported to cause significant abnormalities of both systolic and diastolic left ventricular functions. A direct effect of anthracycline on the sympathetic nerves of rat arteries has also been described. Anthracycline administered at rest caused a persistent release of noradrenaline with the consequence that a subsequent electric stimulation of the sympathetic nervous system resulted in only limited noradrenaline release (11).

The toxic effect of anthracyclines on the sympathetic and parasympathetic nervous system may also influence the type and degree of alterations in cardiovascular functions. The low blood pressure in our children after anthracycline therapy indicated the presence of a prolonged decrease in sympathetic vasomotor activity. These children also had a tendency to bradycardia and this fact should be taken into consideration when the explanation of causes of a decrease in blood pressure due to anthracycline therapy is sought.

Long-term survivors of childhood cancer are predisposed to obesity because of the lack of physical activity, which is usually explained by psychological problems. However, the fact that these children avoid exercise may also have a physical cause, such as a long-term effect of anti-cancer therapy on the nervous and cardiovascular systems, as shown by the results of our study involving anthracycline-treated children. This is in agreement with the results reported previously (2, 11, 12, 13). However, any conclusions as to the relation of anthracycline treatment to changes in autonomic regulation of the cardiovascular system could only be drawn from the results of a long-term monitoring of the patients treated with this drug.

#### A c k n o w l e d g e m e n t s

This study was supported by grant CEZ: J07/98:141100004 from the Ministry of Education, Youth and Sports of the Czech Republic.

*Závodná E., Hrstková H., Honzíkova N., Nováková Z.*

### AUTONOMNÍ REGULACE CIRKULACE U DĚTÍ PO ANTRACYKLINOVÉ TERAPII

#### S o u h r n

V této studii jsme zhodnotili vývoj autonomní regulace krevního oběhu u dětí, které byly léčeny pro zhoubný nádor, převážně pro leukémii. Vyšetřili jsme celkem 105 dětí (skupina G) ve věku 10–21 let. Kontrolní skupina (C) 84 zdravých dětí byla vybrána s ohledem na stejný věk v poměru 4 zdravé děti na 1 dítě nemocné. Ve skupině léčené pro maligní tumor (M) bylo celkem 21 dětí. Osm dětí ze skupiny M mělo nekardiotoxickou terapii (skupina A<sup>0</sup>) a dalších 13 dětí ze skupiny M bylo léčeno kardiotoxickými antracykliny (skupina A<sup>+</sup>). U všech dětí jsme zaznamenávali tepové intervaly (PI), systolický (BPs) a diastolický (BPd) krevní tlak tep po tepu pomocí neinvazivní metody. Počítali jsme baroreflexní citlivost srdce (BRS v ms/mmHg, BRSf v Hz/mmHg). Stanovili jsme průměrné hodnoty a směrodatné odchylky věku, PI, BPs, BPd, BRS, BRSf, hmotnosti výšky a body mass indexu (BMI). Spearmanovým testem jsme stanovili korelace mezi všemi parametry. BPs a BPd, hmotnost, výška a BMI signifikantně korelovaly s věkem v C a M; BRS signifikantně korelovala s BPs a BPd ve skupině C a s PI v C a A<sup>+</sup>. BPs signifikantně koreloval s hmotností ve skupinách C, M a A<sup>+</sup>. Pomocí Mann-Whitney U testu jsme testovali rozdíly mezi všemi skupinami. Našli jsme signifikantní rozdíly mezi velikostí následujících parametrů v těchto skupinách: (C vs. A<sup>+</sup>, p<0.01; A<sup>+</sup> vs. A<sup>0</sup> p<0.05), BPd (C vs. M, p<0.05; C vs. A<sup>+</sup>, p<0.01; A<sup>+</sup> vs. A<sup>0</sup>, p<0.01), a výška (C vs. M, p<0.01 a C vs. A<sup>+</sup>, p<0.05). Antracyklinová terapie je spojena se změnami ve vývoji kardiovaskulárních funkcí. Vztah mezi BRS a PI, mezi BRS a BP byl tlumen. Tělesný růst byl opožděn u všech dětí po léčbě pro maligní tumor, krevní tlak byl snížen hlavně u dětí po terapii antracykliny.

#### REFERENCES

1. Butera G, Piciacchia D, Chesa M, Condoluci C et al. Evaluation of late cardiotoxicity of anthracycline in childhood. *Minerva Pediat* 1998; 50: 111–119.
2. Geršl V, Bajgar J, Krs O, Hrdina R, Palička V, Mazurová Y. Changes in cholinesterase activities after daunorubicin administration to rabbits. *Human and Experimental Toxicology* 1996; 15: 834–838.
3. Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: A quantitative method of assessing baroreflex sensitivity. *Circ Res* 1969; 3: 476–485.

4. *Honzíková N, Fišer B, Honzík J.* Noninvasive determination of baroreflex sensitivity in man by means of spectral analysis. *Physiol Res* 1992; 41: 31–37.
5. *Závodná E, Hrstková H, Nováková Z, Honzíková N.* Age-related development of baroreflex sensitivity and mean pulse interval in children. *Physiol Res* 2001; 50: 33.
6. *Semrád B, Fišer B, Honzíková N.* Ageing and cardiac autonomic status. In: *Clinical Guide to Cardiac Autonomic Tests*. Ed. M. Malík. Kluwer Academic Publishers, Dordrecht, Boston, London 1998: 285–300.
7. *Gribbin B, Pickering EC, Sleight P, Peto R.* Effect of age and high pressure on baroreflex sensitivity in man. *Circ Res* 1971; 29: 424–431.
8. *La Rovere MT, Specchia G, Mortara A et al.* Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. *Circulation* 1987; 59:256–262.
9. *Honzíková N, Fiser B, Semrad B.* Critical value of baroreflex sensitivity determined by spectral analysis in risk stratification after myocardial infarction. *PACE* 2000; 23 (Pt. II):1965–1967.
10. *Honzíková N, Semrád B, Fišer B, Lábrová R.* Baroreflex sensitivity determined by spectral method and heart rate variability, and two-years mortality in patients after myocardial infarction. *Physiol Res* 2000; 49: 643–650.
11. *Sakai T, Inagki R, Taniguchi T et al.* Persistent release of noradrenaline caused by anticancer drug 4-epidoxorubicin in rat tail artery in vitro. *Eur J Pharmacol* 1998; 356: 25–30.
12. *Hrstková H, Honzíková N, Fišer B, Nováková Z.* Baroreflex sensitivity, blood pressure and heart rate variability after anthracycline treatment for malignant tumour. *Script Med* 2001; 74: 187–194.
13. *Hrstková H, Honzíková N, Fišer B, Závodná E, Novotný J.* Vztah mezi anamnesticky zjištěnou tělesnou aktivitou a baroreflexní senzitivitou po léčbě antracykliny [Relationship between physical activity and baroreflex sensitivity in cancer survivors after anthracycline treatment]. *Česko-Slovenská pediatrie* 2000; 55: 281–287.