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BAROREFLEX SENSITIVITY, BLOOD PRESSURE AND HEART RATE IN CHILDREN AND ADOLESCENTS AFTER ANTHRACYCLINE TREATMENT FOR MALIGNANT TUMOUR

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A b s t r a c t

The effect of anticancer therapy on cardiovascular regulation was studied in long-term survivors of childhood cancer.

Age related changes in systolic (SBP) and diastolic (DBP) blood pressure, mean cardiac interval (CI) and baroreflex sensitivity, expressed in ms/mmHg (BRS) and in Hz/mmHg (BRSf), were monitored after anthracycline treatment. The values found in 20 children treated by anthracycline therapy were compared with those recorded in 16 patients treated with non-anthracycline medication and in 177 healthy subjects.

An age-dependent increase in SBP, DBP, CI and a decrease in BRSf were observed in all groups. The age-dependent increase in SBP was decelerated in the children treated with anthracycline.

K e y w o r d s

Leukaemia, Anthracycline, Baroreflex sensitivity, Blood pressure, Age

INTRODUCTION

Since the late 1960s, a major achievement in the management of variability in a variety of neoplastic disorders has been the usage of combination chemotherapy. Anthracycline antibiotics have been the most commonly used compounds in the treatment of leukaemia. Their most important side effect is cardiotoxicity.

It has been estimated that the prevalence of childhood cancer survivors among adults (15 to 45 years of age) in the United States will increase from 1 in 1000 people in 1990 to 1 in 900 people in the year 2000 *(5)*.

With an increasing number of long-term surviving children with malignancies, there is a need to assess the quality of their lives. Different factors of the disease and the treatment modalities have various detrimental effects on the health status of surviving children. Anthracyclines are indispensable cytostatic components of chemotherapy. The long-term surviving children after treatment with anthracyclines may develop typical or subclinical signs of a cardiac dysfunction. The risk factors for anthracycline cardiomyopathy are: a high cumulative dose of anthracycline,

diagnosis followed by anthracycline treatment at young age, gender, other cardiotoxic treatment, previous mediastinal irradiation and a long-term survival after anthracycline treatment *(4).* The anthracycline-induced cardiotoxicity causes specific histopathological changes, such as degenerative changes in the muscle cells, primarily in the membrane and mitochondria, etc. The degree of these changes is dose-related. The clinical symptoms of acute (early) cardiotoxicity include arrhythmias and ECG abnormalities. Changes in cardiac function may also be due to impairment of autonomic control of the heart, which can be assessed by the spectral analysis of heart rate *(17).* Chronic cardiotoxicity is primarily due to the development of a dose-dependent degenerative cardiomyopathy with congestive heart failure (*12).*

Long-term survivors of childhood cancer are more predisposed to the metabolic syndrome, characterised by obesity, hyperlipidemia, hyperinsulinemia, hypertension and enhanced risk of Type 2 diabetes and cardiovascular disease (*3,8*). There is a known increased risk of obesity in adults after a childhood acute lymphoblastic leukaemia (*7).*

In the South Moravian region of the Czech Republic, we have monitored an average of 16 children with a new diagnosis of acute lymphoblastic leukaemia (ALL) and 55 to 60 with other malignant tumours every year. All the children suffering from ALL have been treated at the 1st Department of Paediatrics and Oncology at the Children's Hospital in Brno.

It is known that when, in a healthy subject, some parameter occasionally shows a value beyond physiological limits, it may not mean a disease. Abnormal high blood pressure or low baroreflex sensitivity (BRS) have often been found in both healthy adolescents and children on preventive examination (*21),* but the information on whether essential hypertension will develop in them has so far been sparse.

BRS is an index of the autonomic control of the heart. There is a relative relationship between BRS and blood pressure; when BRS decreases, blood pressure increases. Pathologically low BRS has been found to be the marker of an increased risk of sudden cardiac death in patients after myocardial infarction *(15, 16, 18)*. It was shown that BRS decreased with age in adults and that it decreased with an increase in blood pressure, but it is also necessary to take into account large inter-individual variability (*13*). Much of the information on BRS was obtained by the phenylephrine method (beat-to-beat measurement of blood pressure increase and pulse interval prolongation following administration of the drug). Recently, a non-invasive method of BRS determination based on spectral analysis of the variability of blood pressure and pulse interval has been developed (*14, 15).*

Because the children included in this study had completed anthracycline treatment and therefore were at risk of developing cardiovascular disease, we examined them for BRS and blood pressure.

MATERIALS AND METHODS

Method

We used a non-invasive method of BRS determination by spectral analysis of the variability of blood pressure and pulse intervals (*14*). Blood pressure was recorded non-invasively, beat-to-beat from finger arteries by Finapres (Ohmeda, USA). From the recordings taken in sitting subjects (metronome-controlled respiration at 0.33 Hz) during 5 min, beat-to-beat values of blood pressure and pulse intervals were measured and spectral and cross-spectral analyses of the variability of blood pressure and pulse intervals were performed. BRS was determined as a gain between the spectral density of blood pressure variations and the cross-spectral density of variations of blood pressure and pulse intervals at a frequency of 0.1Hz (e.g., period of 10 sec). It was expressed in ms/mmHg (BRS) or in Hz/mmHg (BRSf) (*2*). Because of its non-invasiveness, this method is suitable for BRS examination in paediatrics.

Subjects

A control group (C) of 177 healthy subjects was compared with 36 children and young adults treated for acute lymphoblastic leukaemia (ALL) or other malignant tumours at the 1st Department of Paediatrics and Oncology, Children's Hospital, Faculty of Medicine, Masaryk University in Brno (*Table 1*). All patients were in their first remission of leukaemia and had no anticancer treatment. The interval between anticancer treatment and BRS examination was 2 to 15 years. Physical examination, echocardiography and biochemical blood analysis were carried out in all them and were found to be within physiological limits.

Table 1
Cancer diagnoses of the patients

Diagnosis	Number of patients
Acute lymphoblastic leukaemia	25
Histiocytosis	3
Malignant lymphoma	5
Solid tumors	3

Systemic therapy

The children with ALL were treated with anthracycline according to the BMF 83 and BMF 87 protocols. The children with histiocytosis, malignant lymphoma, or solid tumours were treated with cytostatic drugs without anthracycline. The patients were distributed into two groups according to the anticancer therapy used, i.e., group A was treated with anthracycline and group nA without it. The patient and control groups were matched by age (*Table 2*).

Statistical analysis

The mean values and standard deviation of all parameters were compared by the Wilcoxon test, age-related changes by regression analysis and by the F-test.

Table 2
Characteristics of the groups of subjects

Group	Treatment	No. of subjects	Age (years)
C	None	177	14.8±3.3
A	Anthracycline	20	14.1±3.7
	(cumulative doses of 100–500 mg/m^2)		
nA	Without anthracycline	16	14.9±4.6

C, healthy subjects; A, patients treated with anthracyclines; nA, patients treated by non-anthracycline therapy

RESULTS

The mean values and standard deviations of systolic blood pressure, diastolic blood pressure, cardiac interval and baroreflex sensitivity in all three tested groups are presented in *Table 3*. Statistically significant differences were found between the patients treated with anthracyclines (A) and the other two groups, e.g. healthy subject (C) and patients treated by non-anthracycline therapy (nA).

An age-dependent increase in mean cardiac interval, systolic and diastolic blood pressure, and a decrease in BRSf were observed in all groups. The slope of systolic blood pressure expressed in mmHg per year was significantly lower in group A than in groups C and nA (A, 1.48; nA, 2.21; C:2.05; $p<0.05$; *Fig.1*).

Table 3
Circulatory variables in three groups of subjects

Variable	Group C	Group A	Group nA
SBP (mmHg)	113.7 ± 14.3*	102.6 ± 11.4	108.6 ± 16.4**
DBP (mmHg)	69.4 ± 9.3*	60.1 ± 10.8	69.2 ± 14.2**
CI (ms)	746 ± 146	742 ± 124	788 ± 107
BRS (ms/mmHg)	10.9 ± 6.4	11.6 ± 5.6	11.4 ± 4.7
BRSf (Hz/mmHg)	0.0200 ± 0.0084	0.0208 ± 0.0099	0.0189 ± 0.0073

C, healthy subjects; A, patients treated with anthracyclines; nA, patients treated by non-anthracycline therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cardiac interval; BRS, baroreflex sensitivity in ms/mmHg, BRSf, baroreflex sensitivity in Hz/mmHg.
*, significant differences ($P<0.01$) of A vs. C; **, significant differences ($P<0.01$) of A vs. nA

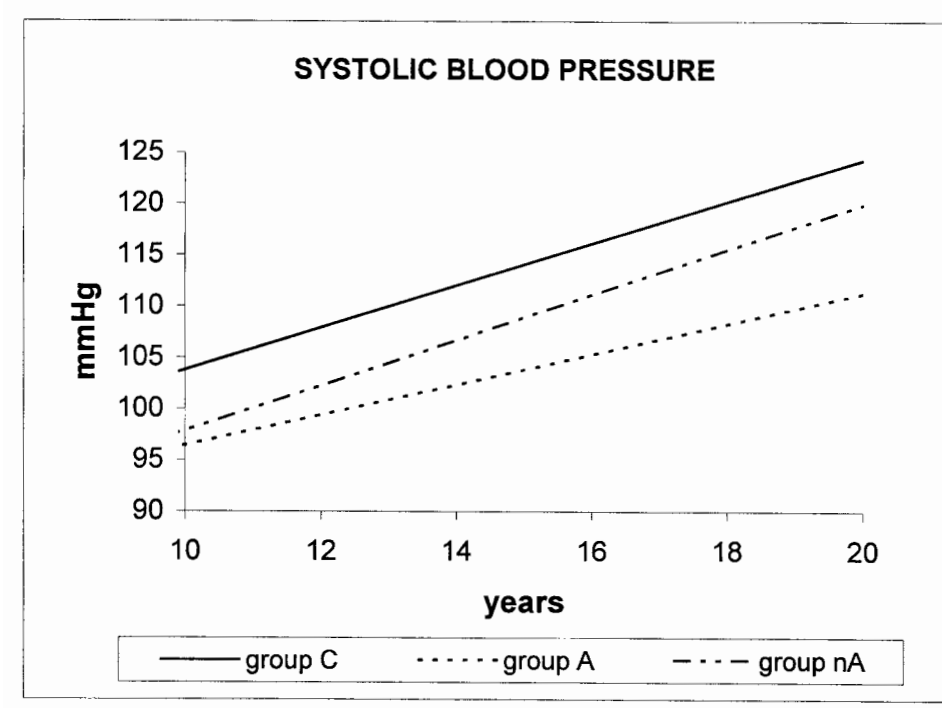

Fig.1
Age-dependent increase in mean systolic blood pressure. The slope is lower in patients treated with anthracycline (A) than in patients treated without anthracycline (nA) and healthy controls (C).

DISCUSSION

An age-related increase in blood pressure and a decrease in heart rate in children and adolescents are well-known phenomena. On the other hand, little information about the development of BRS has been available, because standard methods for determination of BRS *(23)* have not been used in children for ethical reasons. The introduction of a non-invasive method for BRS determination (*14*) provided an opportunity to study BRS in children. In our previous study we determined baroreflex sensitivity in a group of 180 children and young adults between 10 and 22 years of age. The mean values and SD for BRS and BRSf were 9.62±5.77 ms/mmHg and 0.021±0.008 Hz/mmHg, respectively (*9*).

Our study showed that, in healthy children, an increase in blood pressure and heart rate was not accompanied by changes in BRS.

However, we observed an age dependent decrease in BRSf. This decrease can most likely be explained by an age-related stiffening of the carotid sinus wall. Our heart rate data indicated that the development of autonomic nervous system regulation of the heart was not affected by anthracycline therapy. It is in agreement with a study showing diastolic cardiac myocyte dysfunction as a result of impaired calcium handling in isolated cardiac myocytes after treatment with doxorubicin (*19)*. The unchanged development of BRSf indicated that the age-related development of the vascular wall was unaffected by anthracycline therapy. An explanation of the deceleration of the SBP development is more complicated. The question is whether it could be caused by a decreased cardiac output during an acute phase of the disease and the anthracycline therapy. Significant abnormalities of the systolic and diastolic left ventricular function after anthracycline therapy were repeatedly shown to exist (*6).* Impaired sequestration of intracellular free calcium ions in myocytes is one of the factors leading to diastolic dysfunction (*19*). A low cardiac output during the anthracycline treatment can slow down autoregulatory structural changes in the wall of resistance vessels that, according to *Folkow (10),* are the most important factors for blood pressure development. A rabbit model of cardiomyopathy induced by anthracycline contributes to the understanding of this problem (*1, 11, 20).* On the other hand, a direct effect of anthracycline on the sympathetic nerves of rat arteries has been reported *(22*); it caused a persistent release of noradrenalin. Consequently, further noradrenalin release in response to electric stimulation of sympathetic nerves was suppressed.

Our study shows that anthracyclines are not only potent cytotoxic agents for healthy muscle, but also have toxic effects on sympathetic pressure regulation and thus can influence the type and degree of alteration in the development of cardiovascular function.

The results of the study have implications for clinical practise because they show the usefulness of long-term monitoring of subtle deviations from physiological cardiovascular functions in children who have undergone combined anticancer treatment.

With the development of the new anticaner drugs and the increasing success of anticancer therapy in recent years, the need for objective assessment of the overall physical condition of the treated children is increasing.

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

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CITLIVOST BAROREFLEXU, KREVNÍ TLAK A TEPOVÁ FREKVENCE U DĚTÍ A ADOLESCENTŮ S MALIGNÍMI TUMORY PO ANTRACYKLINOVÉ LÉČBĚ

S o u h r n

Sledovali jsme účinek kombinované chemoterapie na kardiovaskulární funkce u dětí, dlouhodobě přežívajících po léčbě zhoubného nádoru.

Monitorovali jsme změny ve vztahu k věku a systolickému tlaku krve (STK), diastolickému tlaku krve (DTK), tepovému intervalu (TI) a citlivosti baroreflexu v ms/mmHg (BRS) a v Hz/mmHg (BRSf) po léčbě atracykliny. Hodnoty naměřené u 20 dětí, léčených antracykliny jsme porovnávali s hodnotami u dětí, léčených pro zhoubný nádor bez antracyklinů (16 pacientů) a se 177 zdravými dětmi. S věkem související vzrůst STK , DTK, TI, a pokles BRSf jsme pozorovali u všech skupin. S věkem související vzestup STK byl u dětí, léčených antracykliny zpomalený.

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