Arterial blood pressure and baroreflex sensitivity 1 – 18 years after completing anthracycline therapy

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The analysis of short-term blood pressure regulation in children, adolescents and young adults 1 to 18 years after the treatment with anthracyclines known to have cardiotoxic side effects for oncological diseases was the aim of the present study.

Thirty-one subjects treated with anthracyclines (P_A) and 11 subjects treated with different antitumour drugs (P_0) were investigated twice (the interval between two investigations 1 – 9 years). Three hundred and thirty-nine healthy subjects served as controls (C).

Systolic (SBP), diastolic blood pressures (DBP) in the finger arteries and inter-beat interval (IBI) were recorded beat-to-beat (FINAPRES, Ohmeda, metronome controlled breathing, 5 minute recording); the values were corrected by auscultatory blood pressure measurements. Baroreflex sensitivity (BRS, ms/mmHg) was determined by a spectral method. As the investigated subjects were of different ages, the measured values were standardised on the age of 16 years by linear regression, and only standardised values (IBI_{16}, SBP_{16}, DBP_{16} and BRS_{16}) were further analysed.

No differences were found between P_A, P_0 and C in BRS_{16} and IBI_{16}. SBP_{16} and DBP_{16} were significantly lower in P_A (102.1±8.3/59.7±7.1 versus C: 114.1±12.4/69.0±9.5 mmHg; $p<0.001/p<0.001$; mean from two investigations). SBP_{16} but not DBP_{16} was also lower in P_0 (102.7±12.6/64.5±9.7 mmHg; $p<0.01$/no significant) than in C. The correlation coefficient between SBP_{16} and period after treatment in P_A was -0.11 (no significant) and -0.06 in DBP_{16} (no significant). Thus, there is not seen a trend to normalisation.

Conclusion: The anthracycline antitumour therapy in children decreases blood pressure and within 18 years after the treatment there is not observed a trend toward normal values. BRS was not influenced by the anthracycline therapy.

Key words: Anthracyclines – Baroreflex sensitivity – Blood pressure – Cardiotoxicity

Cardiac events associated with chemotherapy vary in incidence and may occur not only acutely, or subacutely, but also many years after the treatment termination. They consist of ECG changes and arrhythmias, myocarditis, cardiomyopathy and congestive chronic heart failure (CHF) together with mild blood pressure changes. As to blood pressure changes, both hypertension and hypotension as a complication of therapy by alkylating agents (cisplatin, camustine), antimetabolites (fluorouracil) and antimicrotubule agents (etoposide, teniposide) were reported [1].

Anthracyclines are well established as highly efficacious antineoplastic agents for various leukaemias, lymphomas and solid tumours. However, chronic cardiotoxicity limits their aggressive use. The chronic administration of anthracyclines may be associated with subclinical abnormalities of cardiac function [2]. The mechanisms by which anthracyclines exert their cytotoxic activity are complex. It may include free-radical-mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and the release of cardiotoxic cytokines [3]. Anthracyclines also interact with the autonomous nervous system: The complex of 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 [4]. The interaction between anthracyclines and the sympathetic nervous system was also reported [5].

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Baroreflex plays the important role in regulation of blood pressure. Baroreflex sensitivity (BRS) is an index of autonomic control of the heart, it was also reported, that BRS is an individual characteristics and reproducible feature [6]. In adults, it has been shown that BRS decreases with age [7]. Pathologically low BRS (<3ms/mmHg) has been found to be a marker of increased risk of sudden cardiac death in patients after myocardial infarction [8, 9]. Low baroreflex sensitivity is pathological sign even in some other diseases such as essential hypertension [10] or diabetes mellitus [11]. For a long time, baroreflex sensitivity has been estimated mainly by the phenylephrine method [12], i.e., invasive application of a vasoactive drug. The developed method of assessing variability in blood pressure and pulse intervals by spectral analysis (non-invasive) has facilitated investigation of BRS also in children.

Screening for and identifying risk factors before patients start anthracycline therapy, strategy of rate and cumulative dose of drug administration with respect to other risk factors, using cardioprotective drugs and long-term monitoring of patients are studied and suggested. Lesser attention is paid to the long-term changes of blood pressure in these patients, nearly no information about BRS can be found.

The analysis of circulatory parameters and short-term blood pressure regulation in children, adolescents and young adults 1 to 18 years after the treatment with cardiotoxic anthracyclines for oncological diseases was the aim of the present study.

Patients and methods

Study population. Forty two patients (group P; 24 male, 18 female) were studied after the treatment for a malignant tumor; a mean age of 14.4±3.4 years at the first examination. The most frequent diagnosis had been acute lymphoblastic leukaemia. All patients were recruited randomly from the First Department of Paediatric Medicine of Faculty Hospital in Brno, and they had no history or evidence of diastolic dysfunction, mitral insufficiency, previous myocardial infarction, stroke, or diabetes mellitus.

The group of patients was divided into two subgroups. Subgroup P_A included 31 patients treated with anthracyclines (either doxorubicin or daunorubicin). The cumulative anthracycline dose ranged from 150 to 615 mg/m^2. Seven patients had been treated with additional mediastinal radiation (mean dose 20 Gy). The second subgroup P_0 included 11 patients treated by other antitumor therapy. All patients were examined twice.

A group of 339 healthy children and adolescents (C; 179 boys and 160 girls) at a mean age of 14.8±2.9 years was used as control. Healthy subjects were recruited from volunteers at the basic and secondary grammar schools in Brno.

All subjects (controls and patients), or their parents – (if a patient was below 18 years), gave their informed consent. The protocols of our study were approved by the ethics committee.

The main clinical characteristics of the study population are shown in Table 1.

Blood pressure measurement and baroreflex sensitivity determination. We recorded continuously beat-to-beat inter-beat intervals, systolic and diastolic blood pressure in finger arteries (Finapres; OHMEDA, USA). The finger cuff was placed on the second phalanx of the middle or ring finger of the subject's dominant hand. The hand was fixed at the level of the participant's heart.

The recordings were taken in all subjects in sitting position at rest during a 5-minute period. Breathing was synchronised by a metronome at 20 breathes per minute (0.33 Hz), and the subjects were allowed to adjust the tidal volume according to their own comfort. The mean values of inter-beat intervals (IBI), systolic (SBP) and diastolic blood pressure (DBP) from these 5 minute records were calculated. The measured values were corrected by auscultatory blood pressure measurement on the non-dominant arm performed immediately before the recorded period.

The gain factor, e.g. modulus H(f) of the transfer function between variations in SBP and IBI, was calculated at

Table 1. The main clinical characteristics of the studied population

Groups		P_A n=31	P_0 n=11	C n=339
Parameters		(16boys)	(8boys)	(179boys)
Age (years)	1st examination	14.4±3.4	14.3±2.8	14.8±2.9
	2nd examination	18.0±4.2	19.3±3.2	
Period after treatment (years)	1st examination	4.2±3.3	5.9±3.9	
	2nd examination	7.8±3.1	10.9±4.9	
Height (cm)	1st examination	160.5±15.2	155.6±15.2	166.8±12.0
	2nd examination	169.9±10.7	168.0±12.7	
Weight (kg)	1st examination	54.7±15.9	48.8±16.5	56.1±13.1
	2nd examination	64.5±14.1	62.1±17.0	
Body mass index (kg/m^2)	1st examination	20.8±3.6	19.5±4.0	19.9±2.9
	2nd examination	22.1±3.4	21.6±4.1	
Diagnosis	ALL	16	4	
	NHL	4	0	
	MH	9	0	
	Histiocytosis X	0	5	
	Other	2	2	
Treatment	Anthracyclines (mg/m^2)	244.2 ±106.6	0	
	Vinca alcaloids (mg/m^2)	13.7 ± 5.4	1547.8 ± 2976.3	
	Cyclophosphamide (mg/m^2)	4357 ± 2016.2	5400 ± 2400	
	RT (n)	7	0	
	Dexrazoxane (n)	19	0	

P_A – subgroup of patients with anthracyclines therapy, P_0 – subgroup of patient treated by other antitumor drugs, C – healthy controls.
Values are presented as mean ± SD (standard deviation), n – number of subjects, RT – radiotherapy of mediastinum, ALL – acute lymphoblastic leukaemia, MH – Hodgkin's disease, NHL – non-Hodgkin's lymphoma, Other – teratoma, neuroblastoma, acute myeloid leukaemia.

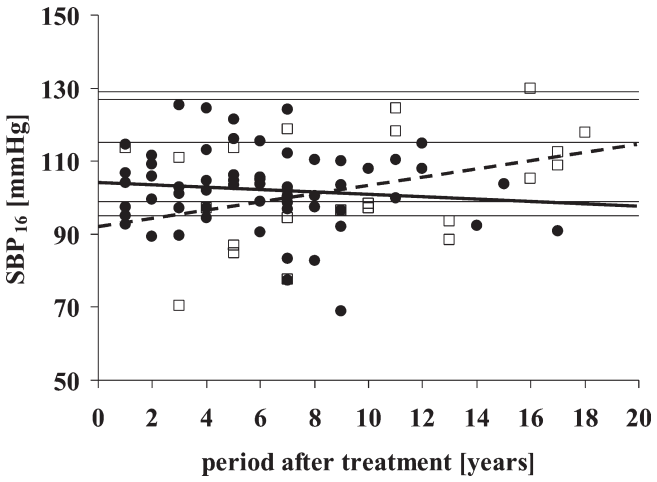

Figure 1. Relationship between the period after treatment and SBP_{16} Horizontal slight lines correspond to the 5th, 10th, 50th, 90th, 95th percentiles of SBP_{16} in a control group; dots and full line – patients with anthracyclines therapy (subgroup P_A); squares and dashed line – patients treated by other antitumor drugs (subgroup P_0); SBP_{16} – standardised value of systolic blood pressure.

a frequency 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 baroreflex sensitivity (BRS) expressed in ms/mmHg.

Standardisation of measured values according to age. As the patients were of different ages in the time of examination, all the cardiovascular parameters were standardised according to the age. There were used the measured values of our control group for standardisation. Linear regression coefficients (b) were calculated for controls, and the equal coefficients were used for the standardisation of measured values of group P. The age range of the healthy subjects was 11–21 years, the mean age being 16 years. Thus, we standardised all the measured values on the age of 16 years according to the formula:

standardised value = b * (16 – actual age in years) + measured value.

Only standardised values (IBI_{16}, SBP_{16}, DBP_{16} and BRS_{16}) were further analysed.

Statistics. Statistics were performed using the StatSoft – STATISTICA software. All the data are expressed as the mean±SD. When appropriate, Mann-Whitney test, student t-test and Pearson correlation coefficient were used for the statistical evaluation. The level of $p<0.05$ was considered statistically significant.

Table 2. Measured and standardised values of parameters in both examinations of patients

Groups	P_A		P_0	
Number of measurement	1st	2nd	1st	2nd
IBI (ms)	766±142	778±115	714±107	770±133
IBI_{16} (ms)	754±110	745±128	734±134	718±151
SBP (mmHg)	100.8±10.6	104.2±14.7	104.1±19.2	104.4±18.2
SBP_{16} (mmHg)	103.2±8.4	100.9±12.9	106.0±16.8	99.4±14.2
DBP (mmHg)	59.1±10.2	60.5±9.4	67.3±13.7	62.6±11.8
DBP_{16} (mmHg)	59.8±9.5	59.6±8.7	67.8±13.3	61.2±10.5
BRS (ms/mmHg)	10.0±5.6	8.3±3.7	12.0±6.8	8.1±4.3
BRS_{16} (ms/mmHg)	10.0±5.6	8.4±3.7	12.0±6.8	8.2±4.2

P_A – subgroup of patients with anthracyclines therapy, P_0 – subgroup of patient treated by other antitumour drugs, IBI – inter-beat intervals, measured value and IBI_{16} – standardised value of inter-beat intervals; SBP- systolic blood pressure, measured value and SBP_{16} – standardised value of systolic blood pressure; DBP – diastolic blood pressure, measured value and DBP_{16} – standardised value of diastolic blood pressure; BRS – baroreflex sensitivity, measured value and BRS_{16} – standardised value of baroreflex sensitivity.

Results

Standardised values were calculated for the resting blood pressure, inter-beat intervals and BRS. The linear regression coefficients found in controls which were used for further standardisation were: b_{IBI}=15.916ms/year; b_{SBP}=1.5308mmHg/year; b_{DBP}=0.4415mmHg/year; b_{BRS}=-0.0167 ms/mmHg/year. The results of measured values IBI, SBP, DBP, BRS and standardised values IBI_{16}, SBP_{16}, DBP_{16} and BRS_{16} in both examinations of patients are shown in Table 2.

The standardised values for a group of patients (P_A and P_0) were further calculated as a mean from both measurements, and these mean values were used for the statistical analysis. The mean values IBI_{16}, SBP_{16}, DBP_{16} and BRS_{16} of controls and both group of patients with statistical significant differences are presented in Table 3. There were found no differences between C, P_A and P_0 in BRS_{16} and IBI_{16}. SBP_{16} and DBP_{16} were significantly lower in P_A versus C. SBP_{16} but not DBP_{16} was also lower in P_0 than in C.

The relationship between the period after treatment and SBP_{16} in both subgroups of patients is shown in Fig. 1. Horizontal lines correspond to the 5th, 10th, 50th, 90th, and 95th percentiles of SBP_{16} in a control group. The regression line of group P_A is approximately 10 mmHg under the line corresponding to 50th percentile of the control group and the correlation coefficient between the period after treatment and SBP_{16} is not significant (r=-0.11); thus there is no tendency to normalisation. The difference between the slopes in P_A and P_0 was significant ($p<0.05$), but the correlation coefficient in P_0 (r=0.37) is under the value of statistical significance; whether there is a trend to normalisation in the P_0 group cannot be decided on the basis of our data.

Fig. 2 demonstrates the same relationship for DBP_{16} as in Fig.1 for SBP_{16}. There is no trend to normalisation in group P_A (r=-0.06). Similarly, the existence of a trend to normalisation in group P_0 cannot be decided on the basis of our data; the value of the correlation coefficient (P_0, r=0.34) was under the

value of statistical significance, but the difference between the slopes in P_A and P_0 was significant ($p<0.05$) as in SBP_{16}.

Discussion

Cardiotoxicity as a side-effect of the anthracycline treatment may occur in patients with underlying risk factors even at low anthracycline doses. Risk factors are also a concomitant mediastinum irradiation [13], age lower than 4 years [14], or female patients [15]. The decrease of the left ventricle ejection fraction (LVEF) of patients after therapy with anthracyclines should be recognised early to prevent severe chronic heart failure. Guidelines for following LVEF in patients undergoing the anthracycline chemotherapy have been proposed [16] and LVEF in long-term survivors of anticancer therapy is evaluated in dozens of studies.

Though the blood pressure decrease after the antitumour therapy is a well-known early complication [17, 18], it was rarely reported as a late effect [19, 20]. In some studies no blood pressure changes were observed [21]. But, on the other hand, it was recently reported that in these normotensive subjects the brachial artery reactivity to cuff deflation after its occlusion was decreased, and a damage to the endothelium was supposed to be the cause of an impairment of the vasodilative response of arteries.

The heart function in children and young adults after chemotherapy in Brno has been examined for many years (22–30). In recent years, we have extended our studies by testing the efficacy of autonomic control of the heart rate and blood pressure regulation. In a preliminary study there was found correlation between LVEF, or fractional shortening (FS) respectively, and BP decrease [31]. Therefore our present study deals with long-term changes of the blood pressure regulation. This study has shown that blood pressure is lower in both groups of the cancer survivors, in those treated with anthracyclines or some other therapy comparing with healthy population. But it seems that in children treated without anthracyclines there is a tendency for blood pressure normalisation.

There is not unique explanation of the low blood pressure values found in cancer survivors treated with anthracyclines. They may be associated with the decreased left ventricular ejection fraction [31], but possible toxic effects of anthracyclines on the sympathetic nervous system should be also taken into account. The direct effects of anthracyclines on the sympathetic nerves of rat arteries have been described. Anthracycline administrated at rest caused a persistent release of noradrenaline with the consequence that a subsequent electric stimulation of the sympathetic nervous system resulted only in limited noradrenaline release [5].

We have used continuous finger arterial blood pressure measurement by Finapres. This method has been used for decades in healthy population, but it is not often used in paediatrics. It was repeatedly proved that the blood pressure values measured at rest by Finapres corresponded to the intra-arterial records not only in adults, but also in children [32], even though not exactly. The comparison of measurements of blood pressure by Finapres and by auscultatory method in 217 children by Tanaka et al. 1994 [33] and in 316 children by Závodná et al. 2005 [34] have clearly shown that this measurement has similar accuracy as in adults, and that this method is useful for clinical application in children. The advantage of finger arterial blood pressure measurement in this study was not only the possibility to calculate BRS, but also to get real resting values, because children were sitting for 15 minutes at rest before each measurement.

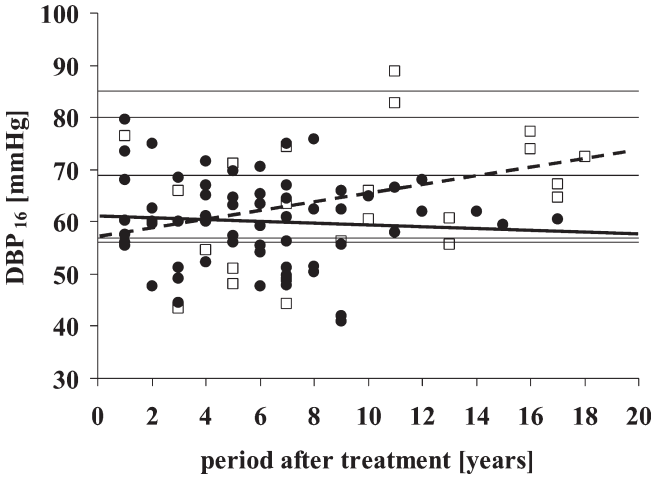

Figure 2. Relationship between the period after treatment and DBP_{16} Horizontal slight lines correspond to the 5th, 10th, 50th, 90th, 95th percentiles of DBP_{16} in a control group; dots and full line – patients with anthracyclines therapy (subgroup P_A); squares and dashed line – patients treated by other antitumour drugs (subgroup P_0); DBP_{16} – standardised value of diastolic blood pressure.

Table 3. Standardised values in groups of control and patients with statistical analysis

PARAMETERS	GROUPS		
	C (n=339)	**P_A** (n=31)	**P_0** (n=11)
IBI_{16} (ms)	754±110	768±119	726±116
SBP_{16} (mmHg)	114.1±12.4	102.1±8.3***	102.7±12.6++
DBP_{16} (mmHg)	69.0±9.5	59.7±7.1***	64.5±9.7
BRS_{16} (ms/mmHg)	10.5±5.5	9.2±3.5	10.1±3.8

C – control group, P_A – subgroup of patients with anthracyclines therapy, P_0 – subgroup of patients treated by other antitumour drugs. The values were calculated as a mean from both measurement.

IBI_{16} – standardised value of inter-beat intervals; SBP_{16} – standardised value of systolic blood pressure; DBP_{16} – standardised value of diastolic blood pressure; BRS_{16} – standardised value of baroreflex sensitivity; n – number of subjects.

Statistics by Mann-Whitney test: C vs P_A: *** $p< 0.001$; C vs P_0:++ $p< 0.01$; P_A vs P_0: insignificant

Our study has shown that the decreased blood pressure is not accompanied with changes in BRS. We can hypothesize that cardiovascular impairment related to the decreased sympathetic activity is not compensated by the concomitant decreased parasympathetic activity.

The results of our study indicate a usefulness of long-term monitoring not only of signs of cardiomyopathy, but also of subtle deviations from physiological cardiovascular functions in children who underwent a combined anticancer therapy.

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