

EXERCISE TESTING IN CHILDREN AND ADOLESCENTS AFTER COMPLETING ANTHRACYCLINE ANTITUMOUR THERAPY

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Abstract

Analysis of cardiovascular parameters during bicycle ergometry in healthy children and adolescents and oncological patients after complete antitumour therapy was the aim of the present study. We studied 19 patients treated with anthracyclines for a malignant disease (acute lymphoblastic leukaemia), group A, and 19 healthy children and adolescents, group C. Control subjects were randomly chosen from 60 healthy volunteers at basic and secondary grammar schools in Brno, age-matched 1:1. The test was carried out on the ergometer. We used a continuous exercise test with an increment of 25 Watts/2 min until exhaustion of the subjects. The baseline values of blood pressure and heart rate and the same values immediately at the end of the test together with standard testing parameters were analysed. Baroreflex sensitivity as index autonomous regulation of blood pressure was determined by the spectral method. There were no differences between groups A and C either in baseline parameters or in mean values in the studied parameters during exercise testing. The distribution histograms of maximal tolerated load and maximal tolerated load per kg of body weight differed significantly ($p < 0.05$, F-test). In spite of significant difference in the distribution of tolerated load during exercise between treated patients and controls, the differences in mean values of all parameters were insignificant. This indicates that in the majority of subjects after anthracycline treatment the load tolerance need not be affected.

Key words

Anthracyclines, Baroreflex sensitivity, Exercise, Cardiotoxicity

INTRODUCTION

Anthracyclines are well established as highly efficacious antineoplastic agents for various leukaemias, lymphomas, and solid tumours. However, their chronic cardiotoxicity limits their aggressive use. Chronic administration of anthracyclines may be associated with subclinical abnormalities of cardiac function (1, 2). The mechanisms by which anthracyclines exert their cytotoxic activity are complex. They 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 (4, 5).

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, and the use of cardioprotective drugs (6, 7) were studied and suggested. We studied some aspects of early and late ventricular myocardial damage (8, 9) and blood pressure regulation (10, 11) after treatments with anthracyclines in childhood during the last decade.

Less attention was paid to the long-term changes in exercise capacity. The analysis of circulatory parameters at rest and during exercise, and peak oxygen consumption in children, adolescents and young adults after the treatment with anthracyclines for oncological diseases was the aim of the present study.

METHODS

STUDY POPULATION

We studied 19 patients treated with anthracyclines for a malignant disease (acute lymphoblastic leukaemia), group A, and 19 healthy children and adolescents, group C. Control subjects were chosen from 60 healthy volunteers at basic and secondary grammar schools in Brno, age-matched 1:1. All subjects (controls and patients), or their parents (if the subjects were younger than 18 years) gave their informed consent, and protocols were approved by the ethics committee.

The patients were diagnosed and treated at the First Department of Paediatric Internal Medicine, Faculty Hospital in Brno. The mean follow-up period (end of treatment to exercise testing) was 8.3 ± 3.2 (4–14) years. The mean age at the time of diagnosis and at the beginning of cancer treatment was 5.8 ± 3.0 years (1–11 years). The patients received a total cumulative dose of 178 ± 64 mg/m² of anthracyclines. Cyclophosphamide, as a part of the treatment protocol, was given to all patients in the total mean dose of $2\,305 \pm 895$ mg/m². Acute lymphoblastic leukaemia was diagnosed in all 19 patients.

The main characteristics of the study population – group A and group C, are presented in *Table 1*.

Table 1
Characteristics of groups

Groups	C (no=19)	A (no=19)
Age (years)	16.2 ± 2.2	16.2 ± 2.2
Height (cm)	171.0 ± 8.2	167.7 ± 10.0
Weight (kg)	59.6 ± 9.5	61.4 ± 12.2
BMI (kg/m ²)	20.3 ± 2.2	21.8 ± 4.2

The values are presented as means \pm standard deviations (SD). C – group of healthy controls, A – group of patients treated with anthracyclines, no – number of subjects

Dynamic stress echocardiography (DSE)

The dynamic exercise test was carried out on an ergometer. We used a continuous exercise protocol with an increment of 25 Watts/2 min until the exhaustion of the subjects. The blood pressure and heart rate were monitored at the baseline, at the end of each stage and during 6 min of the recovery. A complete two-dimensional record of four standard views of the left ventricle was completed and

stored before the exercise and immediately after finishing the test. We used the biplane Simpson rule to calculate the ejection fraction (EF, %). The exercise tolerance (ET) was measured in watts (W) and converted to maximal oxygen consumption calculated as metabolic equivalents (METs): METs = $[(13 \times \text{workload (W)} / \text{body weight (kg)} + 3.5) / 3.5]$.

Spiroergometry

We used the same continuous exercise protocol as for DSE. Spirometry examination was done on an Oxycon delta device, of Jaeger corporation. At the peak of the exercise the peak oxygen consumption was measured according to the "breath by breath" method and expressed in ml/min and ml/min/kg (pVO₂).

Baroreflex sensitivity determination

Baroreflex sensitivity was determined by the spectral method (12). We recorded continuously blood pressure and inter-beat intervals by the Peñáz method in finger arteries. The gain factor, e.g. modulus $H(f)$ of the transfer function between variations in SBP and IBI, was calculated at a frequency of 0.1 Hz according to the formula: $H(f) = G_{xy}(f) / G_{xx}(f)$, where $G_{xy}(f)$ corresponded to the cross-spectral density between SBP and IBI, and $G_{xx}(f)$ 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 BRS.

Using the same formula, the modulus at a frequency of 0.1 Hz was also calculated for the instantaneous values of the heart rate and systolic blood pressure as the second index of baroreflex sensitivity (BRSf, expressed in Hz/mmHg). BRSf is independent of pulse interval.

Statistical analysis

The results are presented as means \pm standard deviations (SD). Statistical analysis was performed by the STATISTICA, version 6.0 (StatSoft, Inc). The significance of differences between the controls and the patients was evaluated by the Mann-Whitney test and that of the distribution of values by the F-test.

RESULTS

A comparison of measurements at rest and during exercise testing is shown in *Tables 2* and *3*. The differences are not statistically significant. On the other hand, the distribution histograms of maximal tolerated load (*Fig. 1*, above) and maximal tolerated load per kg of body weight (*Fig. 1*, below) differ significantly ($p < 0.05$, F-test). The corresponding Gauss curves calculated from mean values and standard deviations indicate that some subjects in the anthracycline-treated group have significantly lower values. The fact that the difference in mean values is not significant indicates that in the majority of subjects after anthracycline treatment the load tolerance is not affected.

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 also include a concomitant mediastinum irradiation (13), an age lower than 4 years (14), or female patients (15). The decrease of the left ventricle ejection fraction (LVEF)

Table 2
Basic parameters at rest

Parameters / Groups	C	A
SBP (mmHg)	128.4 ± 8.0	127.4 ± 10.2
DBP (mmHg)	77.6 ± 5.6	79.0 ± 4.9
HR (beat/min)	73.1 ± 14.2	72.1 ± 9.8
BRS (ms/mmHg)	8.6 ± 3.3	8.1 ± 5.0
BRSf (Hz/mmHg)	0.013 ± 0.006	0.013 ± 0.006
EF (%)	63.6 ± 2.6	62.1 ± 3.3

The values are presented as means ± standard deviations (SD). C - group of healthy controls, A - group of patients treated with anthracyclines, SBP and DBP - systolic and diastolic blood pressures, HR - heart rate, BRS and BRSf - baroreflex sensitivity expressed in ms/mmHg and Hz/mmHg, EF - ejection fraction

Table 3
Parameters at the peak of work load

Parameters / Groups	C	A	P
SBP (mmHg)	186.1 ± 20.6	182.6 ± 17.0	0.54
DBP (mmHg)	91.1 ± 9.1	89.2 ± 8.2	0.66
HR (beat/min)	179.1 ± 9.9	179.7 ± 9.3	0.64
EF (%)	77.2 ± 4.0	74.8 ± 3.3	0.09
pVO ₂ (ml/min)	2 573.7 ± 685.1	2 371.1 ± 909.3	0.26
pVO ₂ (ml/min/kg)	42.9 ± 9.3	38.2 ± 13.3	0.11
Maximal work load (W)	186.8 ± 44.4	161.9 ± 58.6	0.79
Maximal work load (W/kg)	3.1 ± 0.5	2.7 ± 0.8	0.79
METs = ET	12.2 ± 2.6	10.9 ± 3.7	0.11

The values are presented as mean ± standard deviation (SD). C - group of healthy controls, A - group of patients treated with anthracyclines, SBP and DBP - systolic and diastolic blood pressures, HR - heart rate, BRS and BRSf - baroreflex sensitivity expressed in ms/mmHg and Hz/mmHg, EF - ejection fraction, pVO₂ - peak of consumption of oxygen in ml/min and ml/min/kg, METs=ET - exercise tolerance expressed in METs according to the formula: METs= [(13*workload (W))/body weight (kg) +3.5]/3.5]

of patients after therapy with anthracyclines should be recognised early to prevent severe chronic heart failure. Guidelines for following LVEF in patients undergoing anthracycline chemotherapy have been proposed (16) and LVEF in long-term survivors of anticancer therapy is evaluated in dozens of studies.

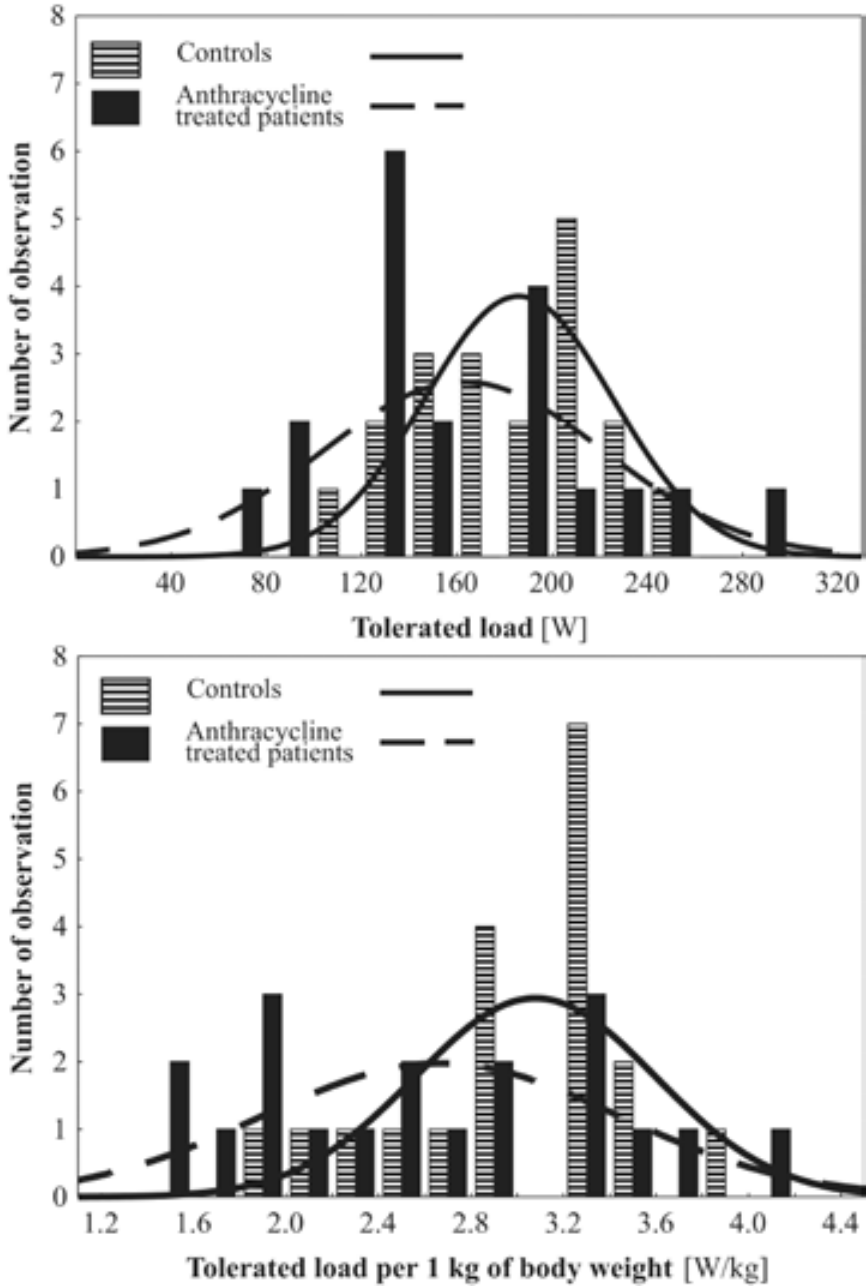


Fig. 1

A distribution histogram of maximal tolerated load (above) and maximal tolerated load per 1 kg of body weight (below).

In a group of patients treated with anthracycline in Brno we confirmed impairment of the heart by dobutamine stress echocardiography (6) and by dynamic stress echocardiography (7).

In a relatively small group in the present study we have not observed any significant decrease of the tolerated load at exercise testing. On the other hand, the significantly different distributions of tolerated load and tolerated load per kg of body weight in comparison to healthy controls indicate a lower exercise tolerance in several anthracycline-treated subjects. This is so despite of appropriate care of anthracycline-treated subjects with respect to the guidelines for prevention of heart failure. However, it is necessary to test many more anthracycline-treated subjects to estimate the proportion of affected subjects, who probably need a special treatment. A carefully dosed exercise training in those subjects is one of the possibilities.

There is no simple explanation of anthracycline therapy-induced impairments of the heart. The 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 administered at rest caused a persistent release of noradrenaline with the consequence that a subsequent electric stimulation of the sympathetic nervous system resulted only in a limited noradrenaline release (5).

We have not observed any difference in BRS between anthracycline-treated subjects and controls. We can hypothesise that cardiovascular impairment related to decreased sympathetic activity is not compensated by the concomitant decreased parasympathetic activity.

The results of our study indicate the usefulness of exercise testing in the follow-up care of subjects treated with anthracycline for malignancy many years before.

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ZÁTĚŽOVÉ VYŠETŘENÍ U DĚTÍ A ADOLESCENTŮ PO UKONČENÍ PROTINÁDOROVÉ TERAPIE ANTRACYKLINY

S o u h r n

Cílem naší studie byla analýza kardiovaskulárních parametrů během bicyklové ergometrie u zdravých dětí a adolescentů a onkologických pacientů po ukončení protinádorové terapie.

Vyšetřili jsme 19 pacientů léčených protinádorovou léčbou antracykliny (akutní lymfoblastická leukémie, skupina A) a 19 zdravých dětí a adolescentů, kontrolní skupina C. Kontroly byly náhodně vybrány ze souboru 60 zdravých dobrovolníků vyšetřených ve školách v Brně podle věku v poměru 1:1.

Při testování na ergometru jsme použili stupňovanou zátěž v krocích po 25W/2min do vyčerpání. Analyzovali jsme klidové hodnoty systolického a diastolického krevního tlaku a tepové frekvence a tytéž parametry bezprostředně po ukončení testu současně s ukazateli zátěže. Citlivost baroreflexu

jako index autonomní regulace krevního tlaku byla stanovena spektrální metodou (BRS, ms/mmHg; BRSf Hz/mmHg).

Skupiny A a C se nelišily ani v klidových hodnotách základních oběhových parametrů ani během zátěžového testu. Signifikantně se lišila distribuce hodnot maximální tolerované zátěže a maximální tolerovaná zátěž na kg tělesné hmotnosti ($p < 0,05$, F-test).

Ačkoliv jsme našli rozdíl v distribuci hodnot tolerované zátěže mezi pacienty a kontrolami, nenašli jsme rozdíly mezi průměry sledovaných hodnot. To ukazuje na skutečnost, že u většiny pacientů po prodělané léčbě antracykliny není ovlivněna fyzická výkonnost.

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