BLOOD PRESSURE AND BAROREFLEX SENSITIVITY AFTER ANTHRACYCLINE CHEMOTHERAPY IN CHILDHOOD WITH RESPECT TO FATTY ACID METABOLISM

ZÁVODNÁ E.[1], HRSTKOVÁ H.[2], BALCÁRKOVÁ P.[1], NOVÁKOVÁ Z.[1], HONZÍKOVÁ N.[1], FIŠER B.[1]

[1]Department of Physiology, Faculty of Medicine, Masaryk University Brno
[2] First Department of Paediatric Internal Medicine, Brno Faculty Hospital – Children's Hospital, Brno

A b s t r a c t

Late effects of cardiotoxic therapy on childhood cancer were studied. Body and circulation parameters were compared in 206 healthy controls (C), and 97 children and adolescents after antitumour treatment (T) at the age of 11–21 years with respect to plasma lipid level. We recorded inter-beat intervals (IBI), systolic (SBP) and diastolic (DBP) blood pressures beat-to-beat for 5 min (Finapres). Baroreflex sensitivity (BRS) was determined by the spectral method. Variability of circulatory parameters was estimated as standard deviations: IBI (IBIsd), SBP (SBPsd), and DBP (DBPsd). Plasma lipids (cholesterol, HDL, LDL, and triglycerides) were examined. Subjects T were divided according to the level of cholesterol into two subgroups: 84 subjects (subgroup T_L) with cholesterol lower than 5 mmol/l and 13 subjects (subgroup T_H) with cholesterol higher than 5 mmol/l.

In groups T vs. C, the subjects had significantly higher BMI ($p<0.01$), but they were not obese, they had longer IBI ($p<0.01$), increased IBIsd ($p<0.05$), decreased SBP ($p<0.01$), DBP ($p<0.01$) and DBPsd ($p<0.05$), and lower BRS ($p<0.01$). The only difference between subjects T_H and T_L was a more prolonged IBI in T_L than in T_H ($p<0.05$).

The subjects after antitumour therapy had increased parasympathetic and decreased sympathetic tonic activity together with decreased baroreflex sensitivity. The increase of IBI variability was neither the result of a primary increase of vasomotor activity nor an increase of BRS response to changes in blood pressure. We can explain it by increasing parasympathetic control of the heart. The circulatory changes did not bear on obesity, but they were rather a specific effect of tumour disease and antitumour treatment.

K e y   w o r d s

Anthracycline, Blood pressure, Baroreflex sensitivity, Heart rate variability, Cholesterol

INTRODUCTION

Anthracycline therapy used in current treatment protocols of a wide variety of solid and haematological tumours may be associated with subclinical abnormalities of cardiac function that can result in late congestive heart failure

(*1*). The risk of cardiomyopathy is hard to predict; no echocardiographic abnormalities were found, for example, in a group of 117 subjects 7 years later after anthracycline therapy (*2*). Chronic cardiotoxicity is primarily due to the development of degenerative cardiomyopathy with congestive heart failure (*3*). The underlying pathogenesis mechanism may include free-radical-mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and the release of cardiotoxic cytokines (*4*). It has been suggested that anthracyclines cause cardiomyopathy because of interference with fatty acid metabolism that is connected with significantly increased levels of cholesterol or triglycerides (*5, 6*). The anthracycline-induced cardiotoxicity causes specific histopathological changes, breakdown of proteosynthesis in the heart and the liver (*7*). Anthracyclines also interact with the autonomic nervous system: they decrease the efficiency of the sympathetic part (*8*) and increase the activity of the parasympathetic part of the autonomic nervous system (*7, 9*). All these mechanisms can result in a lowering of the resting systolic and mean blood pressure (*10, 11, 12*).

In daily practice, oncologists make use of parameters of systolic function (left ventricular ejection fraction, or fractional shortening) to detect cardiotoxicity (*13, 14*), but these methods are unable to detect cardiotoxicity at an early stage. Based on increasing knowledge of the pathophysiology of anthracycline-induced cardiotoxicity and heart failure in general, new methods including assessment of heart rate variability and baroreflex sensitivity in relation to blood pressure have been proposed to identify subjects at risk of the development of congestive heart failure in an early stage.

The aim of the study was to compare body and circulatory parameters in healthy subjects and children and adolescents who were treated previously with anthracycline for malignant tumours. The evaluation of the relationship between plasma lipids and changes in circulatory regulation in subjects after treatment was taken into account.

MATERIALS AND METHODS

We studied 303 children and adolescents aged 11–21 years. The control group consisted of 206 healthy children and adolescents (C; 97 boys and 109 girls, mean $\pm$ SD: age 15.2 $\pm$ 2.8 years, body height 167.2$\pm$2.8 cm, weight 56.8$\pm$13.1 kg, body mass index – BMI 20.1$\pm$2.9 kg/m^2), and the group of children and adolescents after the treatment for a malignant tumour by cardiotoxic therapy consisted of 97 subjects (T; 56 boys and 41 girls, mean $\pm$ SD: age 15.8 $\pm$ 3.2 years, body height 166.6$\pm$12.1 cm, weight 60.4$\pm$12.1 kg, BMI 21.5$\pm$3.9 kg/m^2). Children and adolescents were treated by standard therapy according to their diagnosis. The treatment with possible cardiotoxic side effects included anthracyclines, cyclophosphamide, and radiotherapy of mediastinum. The anticancer therapy was terminated on average 3 years before this study, and they had no clinical signs of cardiotoxicity. The effect of this therapy on cardiovascular parameters was evaluated with respect to plasma level of cholesterol. Plasma lipids – cholesterol, high-density lipids (HDL), low-density lipids (LDL), and triglycerides – were examined. The subjects T were divided according to the level of cholesterol into two subgroups: 84 subjects with cholesterol lower than 5 mmol/l (T$_L$; mean $\pm$ SD: age 15.8 $\pm$ 3.1 years, body height 167.2$\pm$11.9 cm, weight 60.5$\pm$15.2 kg, BMI 21.4$\pm$3.9 kg/m^2), and 13 subjects with cholesterol higher

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than 5 mmol/l (T_H; mean ± SD: age 15.7±3.7 years, body height 162.6±13.2 cm, weight 60.6±19.0 kg, BMI 22.3±4.3 kg/m^2). Body mass index was higher in T than in C (p<0.01); no further difference in BMI was detected between T_L and T_H. The following differences in plasma lipid levels (in mmol/l) were found between subgroups T_L and T_H: cholesterol 3.9±0.5 vs. 5.9±0.7, p<0.001; LDL 2.2±0.4 vs. 3.6±0.6, p<0.001; HDL 1.4±0.3 vs. 1.5±0.5, n.s.; TG 0.9±0.4 vs. 2.2±1.6, p<0.001. All other differences in age and body characteristics among the groups were insignificant.

The protocol was approved by the ethics committee. All subjects and their parents, respectively, gave their informed consent.

Short-term variability in blood pressure and inter-beat intervals, and baroreflex sensitivity determination

We recorded IBI, SBP, and DBP beat-to-beat, on finger arteries by Finapres (OHMEDA, USA) in all subjects. The recordings were taken in 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. The power spectra of variability of IBI, SBP and DBP, and cross-spectra between IBI and SBP were calculated. The gain factors between variations in SBP and IBI, or instantaneous values of heart rate respectively, were calculated at a frequency of 0.1 Hz (15) and taken as a measure of baroreflex sensitivity (index BRS in ms/mmHg). Short-term variability in these variables was determined as standard deviations from 5-minute recordings (IBIsd, SBPsd, DBPsd).

Statistics

The individual data from the examinations were continuously saved in the table processors – Excel and Statgraphics. The differences between the values of all parameters in particular groups were evaluated by the Mann-Whitney test.

RESULTS

The differences between cardiovascular parameters of the two groups, C and T, are presented in *Fig. 1*. Children and adolescents in group T had prolongation of IBI, increased IBIsd, decreased SBP, DBP and DBPsd, lower BRS in comparison with group C. The only difference between subjects T_H and T_L was a more prolonged IBI in T_L than in T_H (T_L vs T_H: 802.8±142.2 vs. 721.2±127.2 ms, p<0.05). All other differences were insignificant (T_L vs T_H: mean SBP 99.8±16.4 vs. 101.5±13.9 mmHg; mean DBP 58±8.5 vs. 61.9±10.1 mmHg; IBIsd 52.6±23.8 vs. 43.8±16.8 ms; SBPsd 5.1±1.6 vs. 4.5±1.9 mmHg; DBPsd 2.9±0.7 vs. 2.8±0.8 mmHg; BRS 8.9±4.4 vs. 9.9±5.3 ms/mmHg).

DISCUSSION

The subjects after antitumour treatment had higher BMI than controls, but they were not obese. They had longer mean IBI, lower BRS, and decreased SBP and DBP in comparison with the controls. These changes are signs of increased parasympathetic and decreased sympathetic activity.

Blood pressure was lowered in our subjects after anthracycline therapy, as described earlier (*10, 11, 12*). The significant decrease of systolic and diastolic blood pressure could be explained e.g. by a direct effect of anthracycline on the

sympathetic nerves of the arteries. Anthracycline may cause persistent release of noradrenaline at rest. After electrical stimulation of sympathetic nerves noradrenaline release is suppressed (*8*). On the other hand, low heart rate has also a lowering effect on blood pressure.
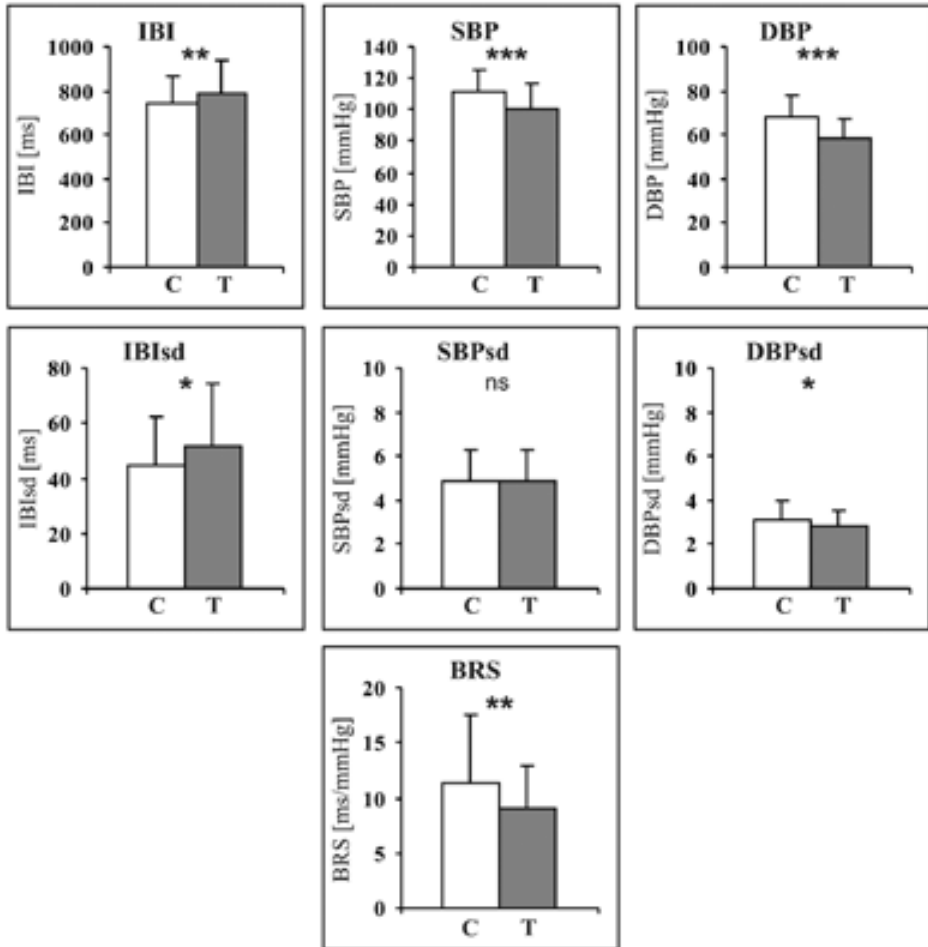

Fig. 1.
Differences between controls and subjects treated by cardiotoxic therapy

Legends: IBI – inter-beat interval, SBP and DBP – systolic and diastolic blood pressure, IBIsd – standard deviation of IBI, SBPsd and DBPsd – standard deviation of systolic and diastolic blood pressure, BRS – baroreflex sensitivity; C – group of controls, T – group of patients after antitumour therapy; statistics by Mann-Whitney test: C vs.T – * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ns insignificant.

Discussing the increased variability of IBI in the subjects treated, we have to take into account that the increase of variability in IBI can be caused by the following effects: by an increase of primary vasomotor activity and variability in blood pressure (*16*), by an increase of BRS (*16*) and therefore an increase of the response of IBI to changes in blood pressure, or by an increase of parasympathetic tonic control of the heart, because BRS is a mean IBI dependent (*17*). In our group of subjects treated by cardiotoxic therapy, the increased variability in IBI can be explained by an increase of parasympathetic tonic control of the heart, because they had longer mean IBI. We can only speculate on which of the mechanisms can take part in this change. It cannot be BRS, because this was decreased, but, for example, proteosynthesis infliction of cholinesterase in the heart can cause an increased action of acetylcholine (*7*).

As to lower BRS in the subjects treated, it is questionable whether this change is a primary one. This could be a compensating mechanism linked with a primary blood pressure decrease. The baroreflex sensitivity is an index of the autonomic control of the heart. In adult subjects, baroreflex sensitivity was shown to decrease with age and its large inter-individual variability was found (*18*). Pathologically low baroreflex sensitivity (BRS < 3 ms/mmHg) was found to be a marker of an increased risk of sudden cardiac death in patients after myocardial infarction (*19, 20*). It is very low in patients with congestive heart failure. Therefore it seems useful to follow up the further development of BRS in subjects treated with anthracyclines.

Surprisingly, the circulatory changes were more pronounced in subgroup T_L than in T_H, even though insignificantly. Therefore we suppose that circulatory changes do not bear on obesity but are rather a specific effect of tumour disease and antitumour treatment.

Závodná E., Hrstková H., Balcárková P., Nováková Z., Honzíková N., Fišer B.

KREVNÍ TLAK A CITLIVOST BAROREFLEXU U DĚTÍ A ADOLESCENTŮ PO CHEMOTERAPII ANTRACYKLINY VZHLEDEM K METABOLISMU LIPIDŮ

S o u h r n

Studovali jsme pozdní efekt kardiotoxické terapie dětských nádorových onemocnění.

Vyšetřili jsme tělesné a oběhové parametry 206 zdravých dětí (skupina C) a 97 dětí a adolescentů ve věku 11–21 let, kteří prošli protinádorovou léčbou (skupina T) ve vztahu k metabolismu lipidů.

Registrovali jsme tepové intervaly (IBI), systolický a diastolický krevní tlak (SBP, DBP) tep po tepu po dobu pěti minut (Finapres). Citlivost baroreflexu (BRS) jsme určili spektrální metodou. Variabilitu oběhových parametrů jsme stanovili jako směrodatnou odchylku IBI (IBIsd), SBP (SBPsd) a DBP (DBPsd). Laboratorně jsme určili spektrum lipidového metabolismu (cholesterol, HDL, LDL, triglyceridy). Skupinu T jsme rozdělili na 2 podskupiny podle hodnot hladiny cholesterolu v krvi (T_L : počet osob n=84, cholesterol<5 mmol/l; T_H : n=13, cholesterol>5 mmol/l).

Skupina T ve srovnání s C měla statisticky významně vyšší BMI (p<0,05), jehož hodnota však nezasahovala do rozmezí pro obezitu, prodloužený tepový interval IBI (p<0,01), zvýšenou hodnotu variability tepového intervalu IBIsd (p<0,05), snížený SBP (p<0,01), DBP (p<0,01) i DBPsd (p<0,05) a nižší BRS (p<0,01). Jediný rozdíl mezi podskupinami T_L a T_H bylo prodloužení IBI u T_L (p<0,05).

Dětští pacienti po prodělané protinádorové léčbě měli zvýšenou parasympatickou a sníženou sympatickou aktivitu spojenou se sníženou citlivostí baroreflexu. Zvýšená variabilita tepových intervalů není výsledkem ani primárně zvýšené vazomotorické aktivity, ani zvýšené baroreflexní odpovědi na tlakové změny. Lze ji vysvětlit zvýšením vlivu parasympatického autonomního nervového systému na řízení srdeční činnosti. Oběhové změny nesouvisí s obezitou, lze je přičítat specifickému efektu vlastního nádorového onemocnění a jeho léčbě.

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