Echocardiographic evaluation of early and chronic cardiotoxicity in adult patients treated for Hodgkin's disease with ABVD regimen*

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The prospective study was conducted to determine whether standard regimen ABVD used in the treatment of Hodgkin's disease is accompanied by the presence of early and chronic myocardial impairment. The study comprised 52 patients (30 male and 22 female) aged 34±15 years (range 18–71; median 30) with Hodgkin's disease and the control group with 40 healthy volunteers (21 male and 19 female) aged 40±8 years (range 20–70; median 38). The maximal administered cumulative dose (CD) of doxorubicin was 297±50 mg/m^2 (range 150–450; median 300). Radiotherapy of the mediastinum was delivered to 27 (52%) patients with a mean dose 41±4 Gy (range 30–46; median 42). Echocardiography was performed at baseline and before each course of chemotherapy. The control examination was done at one month after the treatment and after one year. The stress echocardiography was performed at one-year control. Significant change of ejection fraction (EF) during the treatment was observed only in 10 (18%) patients (7 male/3 female) aged 29±13 years (range 18–56; median 22). The mean toxic CD of doxorubicin was 170±33 mg/m^2 (range 100–200; median 175) and the mean time of the onset EF decline was 13.3±3 weeks (range 8–16; median 14). These changes were asymptomatic, and all patients completed the treatment successfully. Four patients (8%) demonstrated significant asymptomatic decline of EF after the chemotherapy. When compared the value of EF after one-year examination, a stable significant decline of EF in the sub-group with early toxicity was found. Despite a difference in the rest EF, the exercise increment of EF did not reveal any significant difference among tested groups and the contractile reserve of the left ventricle in patients was not impaired.

The present data shows that the treatment of Hodgkin's disease with the standard ABVD regimen is accompanied with mild early and chronic asymptomatic changes of the left ventricular function. These changes were not reversible during one-year follow-up.

Key words: echocardiography, Hodgkin's lymphoma, cardiotoxicity, and doxorubicin

The anthracycline agents are among the most efficacious of antitumor drugs. However, the clinical value of these cytostatics is limited by their dose-related cardiotoxicity. Cardiotoxicity is a well-recognized clinical entity and is the most serious adverse effect limiting the use of all anthracyclines [1, 2].

Doxorubicin is the most extensively used agent. Development of congestive heart failure (CHF) is related to the cumulative dose of the drug and the presence of risk factor, such as age, female sex, previous cardiac disease and mediastinal irradiation. The incidence of doxorubicin-induced CHF is dramatically increased when the cumulative dose exceeds 550 mg/m^2 [3].

Acute or subacute injury can occur during the treatment and is usually a rare form of cardiotoxicity. It manifests as transient arrhythmias, pericarditis-myocarditis syndrome or acute failure of the left ventricle (LV). Chronic doxorubicin-induced cardiotoxicity resulting in cardiomyopathy appears within 1 year of treatment and is a most common form of damage [4].

Advances in the treatment of all stages of Hodgkin's disease have positively influenced long-term survival in many patients. The 5-year survival is approximately 90% in stages I–II, and about 60–70% in stages III–IV [5, 6]. This therapeutic success has focused attention on late adverse effect of the

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treatment protocols. The ABVD regimen containing doxorubicin was introduced in the clinical practice by BONNADONA et al and belongs to the standard protocols in the treatment of Hodgkin's disease [7].

The present study was aimed to assess by means of repeated serial echocardiography examination the early and chronic cardiotoxicity in adult patients treated with ABVD regimen for Hodgkin's disease.

Methods

Patients. Fifty-two patients (30 male and 22 female) aged 34±15 years (range 18–71; median 30) with newly diagnosed Hodgkin's disease were consecutively enrolled in the study. All patients had normal ejection fraction (EF) before the treatment (EF≥50%) and persistent sinus rhythm.

The risk factors of cardiotoxicity were presented as follows: 4 patients (8%) at the age ≥60 years, one patient with asymptomatic ischemic heart disease (2%), and 4 patients with clinically stable hypertension (8%).

The control group comprised 40 healthy volunteers (21 male, 19 female) aged 40±8 years (range 20–70; median 38).

All subjects gave mutual consent. The study was approved by the Committee for Ethics of Medical Experiments on Human Subjects of The University Hospital in Brno. The study is in accordance with the Declaration of Helsinki.

Study treatment. The ABVD treatment protocol was used. It consisted of doxorubicin (25 mg/m^2 i.v. on day 1, 15), bleomycin (10 mg/m^2 i.v. on day 1, 15), vinblastin (6 mg/m^2 i.v. on day 1, 15) and dacarbazine (375 mg/m^2 i.v. on day 1, 15). The number of given courses was 6±1 (range 3–9; median 6). The administered cumulative dose (CD) of doxorubicin was 297±50 mg/m^2 (range 150–450; median 300).

Radiotherapy of the mediastinum was delivered to 27 (52%) patients with a mean dose 41±4 Gy (range 30–46; median 42).

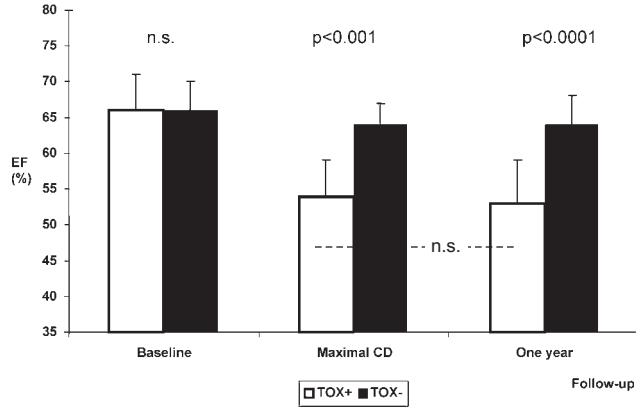

Figure 1. The comparison of rest ejection fraction (EF) at baseline, maximal cumulative dose (CD) of doxorubicin administration and one-year follow-up between subgroups of patients. TOX+: subgroup with the significant depression of ejection fraction, TOX-: subgroup without changes of ejection fraction. The data are expressed as a mean ±1 SD.

Echocardiography. Echocardiography was performed at baseline and before each course of chemotherapy. The examination was repeated one month after the treatment and after twelve months. Standard rest echocardiogram was completed in accordance to the recommendations of the American Society of Echocardiography. For the purpose of the study, we have calculated ejection fraction using two-dimensional records by means of bi-planar Simpson's rule [8]. The physiological value in our laboratory is EF ≥50%. The stress echocardiography was performed one year after the treatment. We have used a symptom limited dynamic stress test on a bicycle. The patients exercised continually with the load increment 25 W/2 min. The rest and postexercise EF was calculated from a digitized record. Exercise increment of EF >5% was considered as a physiological response [9].

The EF was calculated as a mean of three consecutive cardiac cycles. All echocardiographic examinations were done only by one examiner. Inter- and intra-observer variability for the assessment of LV EF varies in our laboratory between 5–7%.

The diagnosis of LV impairment was defined as a progressive decline of EF, which was more than 10% of an absolute value at least during two examinations and/or the drop below 50% of EF. The response of EF, which was less than 5% of the stress test, was considered as abnormal. The clinical diagnosis of cardiotoxicity was based on the signs of heart failure.

Statistics. The study was designed with a prospective of age- and sex- matched examinations. A two-tailed paired and unpaired t-test and chi-square test were used for inter- and intra-group comparisons. The values are expressed as mean ± 1SD, median and range of intervals. When the p-value was less than 0.05, the difference was considered to be statistically significant. Receiver operating characteristic curve analysis (ROC) was generated to test the predictive discrimination of patients with or without left ventricular impairment. We have used a statistical program (NCSS 6.0) for the purpose of statistical analysis.

Results

Significant change of EF during the treatment was observed only in 10 (18%) patients (7 male/ 3 female) aged 29±13 years (range 18–56; median 22). The mean toxic dose of doxorubicin was 170±33 mg/m^2 (range 100–200; median 175) and the mean time of the onset of EF decline was 13.3±3 weeks (range 8–16; median 14). All described changes were asymptomatic, and all patients completed the treatment successfully.

The changes of the EF during the treatment and after one year of follow-up are shown in Figure 1. The first significant decline in EF was observed at the CD 150 mg/m^2 and continued progressively to the maximal CD given. The final value of EF in the sub-group with cardiotoxicity was 55±3% (range

41–59; median 54) and was statistically and significantly lower compared to the others patients; EF 64±3% (range 58–70; median 64, p<0.001).

When we compared the EF after one year, we found stable significant depression of EF in the subgroup with early toxicity (55±3%; range 41–59; median 54/53±3%; range 40–58; median 53, n.s.). The difference between sub-groups remained statistically significant (p<0.0001) (Fig. 1)

During one-year follow-up, two patients (4%) died due to the progression of the malignancy. None of them had significant changes of EF during the treatment period. Recurrence of the disease was diagnosed in 13 (25%) patients and 11 (21%) subjects underwent high dose chemotherapy with the support of autologous peripheral blood stem cell transplantations.

Four patients (8%) with normal values of EF after the treatment revealed significant asymptomatic decline of EF during the follow-up, which was considered as chronic toxicity. The characteristics of patients with early and chronic toxicity (TOX+) and without toxicity (TOX-) is demonstrated in Table 1. We have found significant difference only in the age of patients. Younger patients responded to the treatment with the decline in EF.

Dynamic stress echocardiography was performed in 50 subjects (14 with early and chronic changes of EF and 36 with normal EF) and 40 controls. We have not found any inter-group difference in exercise capacity, heart rate and blood pressure, respectively (Tab. 2). The patients in TOX+ group responded to exercise with lower stress EF in the comparison to TOX- (p<0.001) and to controls (p<0.001). The exercise EF was significantly increased in all three sub-groups compared to the baseline value (p<0.0001). Despite a significant difference in the rest and stress EF between TOX+, TOX- and controls sub-groups, the exercise increment of EF did not reveal any significant difference among tested groups. We found only non significant trend to lower value of EF increment in TOX+ sub-group (TOX-: 11.7±2.5%; range 6.5–13.4; median 12.8/ TOX+: 9.7±3.8%; range 5.8–13.3; median 10, n.s.). When comparing the entire group of patients with controls, the EF increment showed no difference (Fig. 2).

Because both sub-groups differed significantly only in the age, the ROC analysis was performed to assess the predictive value of this parameter for cardiac impairment. The age 25 years demonstrates 64% sensitivity, 76% specificity, and 50% positive predictive value, and 85% negative predictive value for the decline in EF during or after the treatment (Fig. 3). Others parameters such as CD, presence of radiotherapy, or the given dose of radiotherapy have failed as predictors.

Discussion

In recent years the general health consequences of curing cancer have become of a great interest in patients. However, as the cure rate of Hodgkin's disease increases, the late complications of treatment have assumed more importance. Early and late cardiac complications of both doxorubicin and radiotherapy can limit the results of oncology treatment.

Serial echocardiography measurement of the ejection fraction is a sensitive noninvasive tool for the primary detection

Table 1. Characteristics of patients

Variables	TOX+ N=14	TOX- N=38	P value
Gender (male/female)	10/4	19/19	n.s.
Age (years)	27±12 (18–56; 22)	37±15 (19–71; 32)	0.01
CD (mg/m^2)	307±32 (200–350; 300)	296±53 (150–450; 300)	n.s.
RT (n/%)	8/57%	19/50%	n.s.
RT (Gy)	41±3 (36–44; 42)	41±5 (30–46; 42)	n.s.
CAD (n/%)	1/7%	0/0	n.s.
HYP (n/%)	1/7%	3/8%	n.s.

CD – cumulative dose of doxorubicin, RT – radiotherapy involving mediastinum, CAD – coronary artery disease, HYP – hypertension

Table 2. Results of dynamic stress echocardiography

Variables	Controls N=40	TOX+ N=14	TOX- N=36
HR rest (beat/min)	80±11 (52–90; 78)	78±10 (55–87; 80)	82±8 (60–85; 80)
HR max (beat/min)	159±12 (130–180; 159)	162±10 (135–185; 155)	165±15 (125–180; 160)
SBP rest (mmHg)	135±15 (110–150; 130)	130±10 (100–145; 125)	127±15 (115–155; 127)
SBP max (mmHg)	185±20 (140–210; 190)	190±15 (150–215; 200)	192±10 (145–200; 185)
DBP rest (mmHg)	86±9 (60–90; 90)	82±7 (70–90; 87)	80±10 (70–100; 95)
DBP max (mmHg)	98±11 (70–110; 100)	90±12 (80–110; 105)	95±11 (75–105; 100)
EF rest (%)	64±3* (60–68; 63)	53±3 (41–58; 53)	64±3❖ (57–70; 64)
EF max (%)	72±4* (64–78; 72)	67±6 (67–68; 68)	73±5❖ (60–79; 75)
EC (W/kg)	2.1±0.4 (1.1–2.6; 1.95)	2.0±0.68 (0.8–2.8; 2.2)	1.81±0.36 (1–2.8; 1.8)

*p<0.001 comparison controls versus TOX+, ❖p<0.001 comparison TOX+ versus TOX-.
HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, EF – ejection fraction, EC – exercise capacity, rest – before testing, max – peak exercise.

and follow-up of doxorubicin-induced cardiac impairment. Therefore, study of the ejection fraction should be part of the routine care of patients receiving doxorubicin treatment. The sensitivity of ejection fraction for the detection of subclinical cardiotoxicity becomes even higher when they are combined with exercise stress testing [9].

Despite dose-dependent cardiotoxic effect, doxorubicin remains in use because of its efficacy in the treatment of various types of tumors. A change in LV ejection fraction, as determined by echocardiography or radionuclide imaging, is a very good indicator of cardiac impairment. According to STEINHERZ at al, echocardiography should be performed before every additional course of doxorubicin up to a total dose of 300 mg/m^2, given with or without concurrent radiotherapy. Radionuclide angiography should also be done if the patient is receiving more than 400 mg/m^2 in one course. Echocardiography should be repeated 3, 6, 12 months after the completion of therapy and every 2 years thereafter [10]. SCHWARTZ at al proposed guidelines for monitoring doxorubicin cardiotoxicity with serial resting radionuclide ventriculography [11]. On the basis of published experiences, patients whose EF decline was more than 10% below 50% of EF are at high risk for the development of CHF, and the discontinuation of chemotherapy is recommended [11].

The pretreatment EF ≤60% in conjunction with an age 50 years marks a high risk patient for the development of heart failure. The decline in EF ≤50% during the treatment increases the development of heart failure [12].

Significant impairment of left ventricular function during doxorubicin therapy can be predicted early at low cumulative doses of doxorubicin. NOUSIANEN et al has shown that a decrease of EF with more than 4% of the cumulative dose 200 mg/m^2 had 90% sensitivity and 72% specificity. During one year after the treatment, cardiotoxicity was predicted later than expected [13].

The primary aim is to treat the cancer and some complications, and subclinical impairment of LV function should also be taken into consideration. Empirical limitation or modification of anthracycline administration can bring a risk of premature discontinuation of effective anticancer treatment. On the contrary to the published data, we have not discontinued the treatment in any patients with a significant drop of EF when they were without symptoms. The lowest value of EF in our study was 41%, and all described changes were asymptomatic. Diagnostic criteria of cardiotoxicity in this study were met early at a lower value of given dose 170 mg/m^2 of doxorubicin. These findings reflect the results from endomyocardial biopsy specimens that may show histological changes typical for doxorubicin-induced cardiotoxicity, at safe doses as low as CD 183 mg/m^2 [14]. Nonetheless, all patients completed the treatment successfully at a similar total CD of doxorubicin given in the sub-group without changes in EF.

However, described changes persisted during one-year of follow-up. The occurrence of cardiotoxicity was not influenced by radiotherapy or a total dose of irradiation. The presence of previous risk factors of cardiotoxicity was very low in our study. Surprisingly, the ROC analysis showed that younger age has an impact on the development of significant early and late decline of ejection fraction. But it should be taken into consideration, that the small number of the patients in our study might have an impact on the results of ROC-analysis. On the other hand, Hodgkin's disease manifests in younger age and only four patients in our cohort were older than 60 years, which is considered a risk factor for cardiotoxicity in adults [3].

Chronic anthracycline-induced cardiotoxicity appears within one year after the treatment [4]. In accordance to the published data, the incidence of congestive heart failure de-

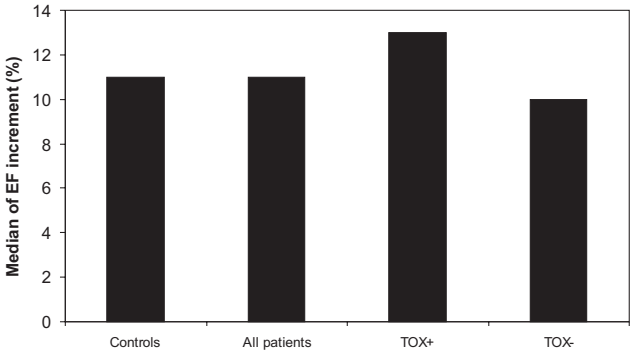

Figure 2. The comparison of exercise increment of ejection fraction (EF) during dynamic stress echocardiography between patients and control group. TOX+: subgroup with the significant depression of ejection fraction, TOX-: subgroup without changes of ejection fraction. The data are expressed as a median value.

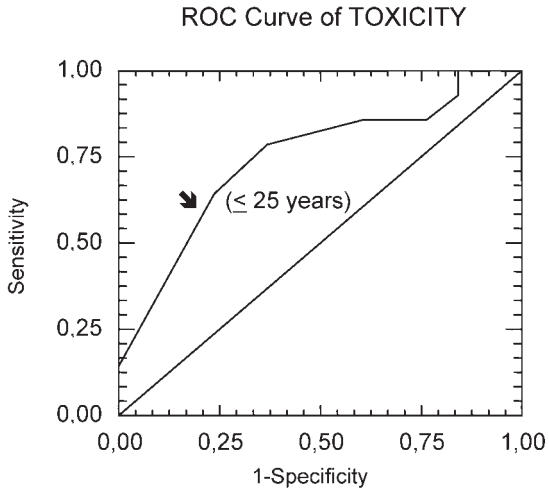

Figure 3. Receiver operating characteristic (ROC) curve analysis for separation of patients with or without toxicity. The area under the ROC curve (mean ± SEM) for the age of patients was 0.74±0.24. This was significantly different from distribution curve.

pends on the CD of the drug and is 3% at total doses of less than 400 mg/m^2, increasing to 7% at CD 550 mg/m^2 [15]. The incidence of subclinical changes seems to be higher [13, 14, 16]. In our study only 8% of studied patients revealed an asymptomatic drop of EF during a one-year follow-up.

Exercise studies may increase the chances of detecting subclinical cardiotoxicity. McKILLOP et al has suggested that the failure to increase EF by 5% over the baseline value is a marker for high risk for the development of early anthracycline-induced left ventricular dysfunction [17]. Stress echocardiography has been preferred in pediatric oncology [15, 18, 19, 20]. Using dynamic stress echocardiography, we have not found pathological response of EF in any patients. None of patients failed to increase EF >5%. Nevertheless, patients with decreased rest EF responded with lower stress EF and demonstrated the trend to the lower value of contractile reserve in the comparison to the controls and patients without changes of rest EF. However, both sub-groups of patients revealed a good exercise capacity and physiological circulatory response to dynamic stress without difference to the controls. Despite the presence of rest subclinical cardiotoxicity in asymptomatic patients the contractile reserve remains still preserved. These data are of great clinical importance for further follow-up or the disease management in the case of the recurrence of malignancy.

Conclusion

The study shows that the treatment of Hodgkin's disease with the standard ABVD regimen is accompanied with mild early, and chronic asymptomatic changes of the left ventricular function that did not affect the administration of doxorubicin. But these changes were not reversible during one-year of follow-up. The clinical value of described abnormalities for the development of late cardiotoxicity or heart failure has to be assessed in long-term prospective study.

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