Cardiac function and cardiopulmonary performance in patients after treatment for non-Hodgkin's lymphoma*

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Authors conducted a one-year prospective study to determine whether CHOP regimen (cyclophosphamide, doxorubicin, vincristin, and prednisone), used in the treatment of aggressive non-Hodgkin's lymphoma, is associated with the presence of an early impairment of cardiac function. Forty seven patients were prospectively examined (27 male and 20 female) aged 49±14 years who were treated with CHOP regimen. Rest echocardiography was performed at baseline and one-year control. Cardiopulmonary exercise test was carried out at one-year control examination. The ejection fraction (EF), parameters of diastolic function, myocardial performance index (MPI), and pVO_2 were used as parameters of cardiopulmonary performance. The cumulative dose (CD) of doxorubicin was 277±56 (300 mg/m^2) was given. The baseline EF 64±5% (64%) decreased to 58±7% (57%) at the one-year control ($p<0.0001$). 23% of patients exhibited a drop in EF >10% during the follow-up. 43% revealed a pathologically increased value of MPI >0.55, and 47% impaired diastolic function compared to the baseline values, respectively. 21% of patients exhibited a decrease of pVO_2 <20 ml/kg/min, and 17% pVO_2 <80% of the reference value, respectively. None of the patients developed signs of heart failure. The Doppler parameters of both diastolic and global LV function were the most affected measures and significantly influenced the cardiopulmonary performance. Multivariate analysis showed that CD ≥300 mg/m^2 (OR=8.08; $p<0.05$) and the presence of risk factors (OR=9.48; $p<0.008$) are the best predictors of cardiotoxicity.

The results show that subclinical cardiac impairment was frequent in patients receiving the CHOP regimen with safe cumulative doses of doxorubicin. The value of described changes for the development of heart failure has to be assessed during the prospective follow-up.

Key words: cardiotoxicity, doxorubicin, non-Hodgkin's lymphoma

Anthracyclines play an important role in cancer therapy. The use of these agents has been limited by occurrence of cardiotoxicity. Doxorubicin is one of the most widely used antineoplastic agents in the treatment of lymphomas [1]. The incidence of congestive heart failure during doxorubicin treatment has been reported to be 3% at a dose of 400 mg/m^2 and 7% at a dose of 550 mg/m^2 [2]. High rates of mortality have been attributed to induced congestive heart failure (CHF) by doxorubicin [3].

In respect of the success of the treatment of hematological malignancies and long-term survival of patients, the development of late cardiotoxicity becomes of great importance. The definition of chronic anthracycline-induced cardiotoxicity varies in published studies. A newly used definition differentiates between an early impairment (within one year after the treatment) and late impairment (more than one year after treatment) [4]. The cumulative incidence of CHF varied from 1.6% to 2.8% [2, 5]. Using a spectrum of newly introduced diagnostic methods, many authors reported an increasing number of cardiac abnormalities in long-term survivors. However, a majority of these data are from pediatric studies [5–7]. The CHOP regimen (cyclophosphamide, doxorubicin, vincristin, predisone) or its variants is still considered as a standard in the first-line therapy of aggressive malignant lymphomas [1]. There are few data considering the toxicity of the regimen. The potential cardiotoxicity of the first-line therapy should be considered in relation to the further devel-

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opment of the disease and additive treatment. Moreover, many patients with lymphomas have other risk factors such as advanced age, concomitant heart disease etc. The present study was carried out to analyze prospectively the early doxorubicin-induced cardiac abnormalities within one year of the treatment using the CHOP regimen and its variant.

Patients and methods

The group studied consisted of 47 patients who were diagnosed and treated at the Department of Internal Medicine Hemato-oncology of Faculty Hospital Brno during the years 2001–2003 and were consecutively entered into the study. Only patients treated with CHOP regimen as a first-line therapy (cyclophosphamide 750 mg/m^2 i.v. on day 1, doxorubicin 50 mg/m^2 i.v. on day 1, vincristin 1.4 mg/m^2 i.v. on day 1 and prednisone 100 mg/m^2 p.o. on day 1–5) were enrolled in the follow-up. Doxorubicin was administered intravenously as a short-term infusion in saline.

The characteristics of patients are given in Table 1. Only two patients showed a decreased ejection fraction (EF) before the treatment as a result of previous myocardial infarction. The most frequent risk factor of cardiotoxicity was advanced age and hypertension (Tab. 2). The description of CHOP therapy and disease management is summarized in the Table 3. The data show that the majority of patients received a cumulative dose (CD) of doxorubicin in the range of 200–300 mg/m^2. Fifteen (32%) patients received an additional oncological treatment that consisted of the co-administration of immunotherapy (the administration of rituximab in r-CHOP regimen) and in two cases a high-dose chemotherapy followed with autologous peripheral stem cell transplantation.

Examinations. The examinations were carried out before starting the treatment and at one year of follow-up. Cardiac evaluation included baseline physical examination, ECG and rest echocardiographic examination (ATL HDI 3000, USA). The ejection fraction was calculated in accordance to the biplane Simpson's rule [8]. Diastolic function was measured using pulsed Doppler echocardiography and assessed in accordance to the published recommendations. Each variable measured represents a mean value from three consecutive variables. All patients showed a persistent sinus rhythm. We have used the Doppler parameters for assessing the diastolic dysfunction: isovolumic relaxation period (IRP), deceleration time (DT) and index E/A. The diastolic dysfunction was diagnosed only in the presence of pathological changes of all three variables [8]. Myocardial performance index (MPI) is a new Doppler-derived index, which is defined as the sum of isovolumic contraction and relaxation time divided by the ejection time [9]. Cardiopulmonary exercise test on an ergometer (Oxycon Delta Jaeger, Germany) was routinely performed only during one-year control. Symptom-limited continually graded protocol (ramp-test) was used until the symptoms or exhaustion occurred. To examine the cardiopulmonary exercise capacity, a simultaneous non-invasive determination of gas exchange parameters was used. The O_2 uptake and CO_2 output was measured breath-by-breath. The peak oxygen consumption (pVO_2) parameter was used as a marker of cardiopulmonary exercise capacity for the study [10]. The impaired cardiopulmonary exercise capacity was assessed either as a decrease of pVO_2 below 20 ml/kg/min or a decreased value of pVO_2 below 80% of the reference value.

Table 1. Clinical characteristics of patients

Characteristic	Value
N	47
Male/female	27/20
Age at diagnosis [years]	49 ± 14 (51) (18–76)
CD of doxorubicin [mg/m^2]	277 ± 56 (300) (50–400)
RT [n/%]	9/19%
RT [Gy]	40 ± 5 (40) (30–50)

CD – cumulative dose, RT – radiotherapy involving mediastinum

Table 2. Risk factors of cardiotoxicity

Factor	No/(%)
EF <50% at baseline	2 (4%)
Age >60 years	14 (30%)
CAD	9 (19%)
Hypertension	11 (23%)
Diabetes mellitus	3 (6%)
Radiotherapy involving mediastinum	9 (19%)

EF – ejection fraction, CAD – coronary artery disease

Table 3. Treatment characteristics

Variable	No/(%)
CD <200 mg/m^2	2 (4%)
CD 200 – 300 mg/m^2	43 (92%)
CD >300 mg/m^2	2 (4%)
CD <300 mg/m^2	14 (30%)
CD ≥300 mg/m^2	33 (70%)
CHOP + additional treatment	15 (32%)
CHOP alone	23 (49%)
CHOP + radiotherapy	9 (19%)

CD – cumulative dose of doxorubicin, CHOP – therapeutic regimen CHOP (cyclophosphamide, doxorubicin, vincristin, prednisone)

All examinations were performed during a single day in one department.

Risk factors of cardiotoxicity. The cumulative dose of doxorubicin, advanced age >60 years, decreased left ventricular function, presence of pre-existing cardiac risk factors (hypertension, coronary artery disease, diabetes, valvular heart disease) and radiotherapy involving the mediastinum were evaluated as risk factors for the cardiac impairment accompanying the oncological treatment [11, 12].

Cardiotoxicity. The cardiotoxicity of oncological treatment was assessed by means of the presence of pathological findings on echocardiography examination. The institution's lower limit of the normal EF is 50%. The cardiac event was defined primarily either as a drop of the EF >10% of an absolute value from baseline or a drop below the limit. Secondly, the presence of pathological changes of others parameters was assessed as follows: the pattern of diastolic impairment (impaired relaxation, pseudo-normalization, restrictive type), the presence of MPI >0.55 (the limit in our laboratory).

The clinical signs of cardiotoxicity were based on the presence of the symptoms of heart failure.

Statistical analysis. The results are presented as mean ± standard deviation, median and intervals. The statistical analysis was based on the paired bi-directional Student's t-test, chi-square test (for non-parametric values), univariate and multivariate regression analysis. A p-value <0.05 was considered as a significant change. We used the statistical program NCSS 6.0 (Number Cruncher Statistical Systems, Kaysvile, Utah, USA) for the purpose of statistical analysis.

All subjects gave their informed consent. The Committee for Ethics of Medical Experiments on Human Subjects of Faculty Hospital Brno approved the study. The study was designed and conducted in accordance with the Declaration of Helsinki.

Table 4. Changes of echocardiographic parameters

Variable	Before treatment	One-year control	p-value [paired t-test]
EF [%]	64±5 (64) 45–68	58±7 (57) 39–69	0.0001
MPI	0.45±0.08 (0.47) 0.20–0.55	0.54±0.15 (0.53) 0.28–1.0	0.0001
E/A	1.16±0.37 (1.05) 0.45–2.12	1.06±0.42 (1.04) 0.48–2.39	0.01
DT [ms]	167±29 (164) 120–220	190±36 (185) 124–280	0.0001
IRP [ms]	91±12 (90) 62–120	103±11 (100) 80–125	0.001

EF – ejection fraction, MPI – myocardial performance index, E/A – Doppler index of left ventricular filling, DT – deceleration time, IRP – isovolumic relaxation time

Table 5. Presence of pathological values at one-year control

Variable	Before treatment No/(%)	One-year control No/(%)	p-value [chi-square test]
Drop in EF >10%		11 (23%)	not compared
EF <50%	2 (4%)	2 (4%)	n.s.
MPI >0.55	6 (13%)	20 (43%)	0.01
Diastolic dysfunction	11 (23%)	22 (47%)	0.02
pVO_2 <20 ml/kg/min		10 (21%)	not compared
pVO_2 <80% of R.V.		8 (17%)	not compared

EF – ejection fraction, MPI – myocardial performance index, pVO_2 – peak oxygen consumption at the exercise, R.V. – reference value

Results

Significant changes in echocardiographic parameters of left ventricular (LV) function compared to the baseline were diagnosed at one-year control. Ejection fraction significantly decreased (p<0.0001) in the entire group. Doppler parameters of both global (p<0.01) and diastolic function were also significantly changed (Tab. 4). Two patients, who showed decreased EF before the treatment, were clinically stable during the follow-up. None of the other patients showed the pathological decline of EF below the physiological limit, but 23% of patients were diagnosed of having an asymptomatic decline more than 10%. A majority of patients exhibited changes in both Doppler parameters. A pathologically increased value of MPI occurred in 43% of cases (p<0.01) and impaired diastolic function in 47% (p<0.02), respectively. Impaired relaxation of left ventricle was diagnosed in all cases (Tab. 5).

Because all of the echocardiographic and exercise parameters may be influenced by age and gender a sub-analysis was carried out. The comparison between sub-groups in accordance to the gender revealed no significant difference. Using a linear regression analysis all the variables except ejection fraction and MPI correlated with age significantly. The value of EF and the change of EF did not correlate with the maximal CD of the doxorubicin given. However, the Doppler parameters and pVO_2 highly correlated with the CD; this means that the higher doses of doxorubicin given correlate with the increase of MPI, decrease of E/A index, prolongation of DT and IRP, respectively. The higher CD inversely correlates with peak oxygen uptake on exercise (Tab. 6).

The pVO_2 has also been influenced by age as well as gender. Our sub-analysis shows a significant correlation with age (Tab. 6). The comparison between males and females demonstrates higher values of pVO_2 in the male sub-group (28.9±3.84 ml/kg/min in males versus 23.2±4.8 ml/kg/min in females; p<0.0001), but the presence of pathological findings was not different. The Table 5 shows that 21% of patients responded with a pathological decreased value of pVO_2

<20 ml/kg/min and the variable pVO_2 was below the reference limit in 17%, respectively.

The pVO_2 did not correlate with the EF as well as the change of EF, but significantly correlated with the Doppler parameters of both global and diastolic function in the entire group (Tab. 7). When the linear regression analysis in the sub-group with the drop in EF was carried out, the pVO_2 showed a poor relationship to EF again. The highly significant relation to the MPI, E/A, IRP and age is apparent (Tab. 7).

The univariate and multivariate analysis were carried out to assess the relationship among cardiac events and risk factors of cardiotoxicity. We used as a cut-off for CD the value 300 mg/m^2 and for age the value 60 years, respectively. These parameters and gender were modeled separately. In the respect to the presence of a relatively small number of patients with accompanying diseases and radiotherapy involving the mediastinum, we decided to include these clinical variables into multivariate statistical analysis as one response variable designed as RF (risk factors). The first analysis was calculated only for the change of EF >10% as a "cardiac event"; in the second one the sum of "all cardiac events" (EF, MPI, diastolic dysfunction) was used as a response variable.

The univariate analysis shows a non-significant relationship between cardiac event and all parameters tested. However, a significant correlation was found between CD ≥300 mg/m^2, the presence of hypertension and all cardiac events (Table 8). With the multivariate analysis, the presence of risk factors increases the probability of EF drop nine-times ($p<0.008$), and the CD ≥300 mg/m^2 increases the occurrence of all cardiac events eight-times ($p<0.05$), respectively. Both statistical models reveled high statistical significance (Tab. 9).

Table 6. Linear regression analysis between age, cumulative dose and parameters of cardiopulmonary function

Variable	Age [yrs]		CD of doxorubicin [mg/m^2]	
	R	p-value	r	p-value
EF [%]	0.24	n.s.	–0.28	n.s.
△ EF [%]	0.55	0.02	–0.45	n.s.
MPI	–0.2	n.s.	0.53	0.04
E/A	–0.85	0.0001	–0.48	0.09
DT [ms]	0.64	0.003	0.72	0.0001
IRP [ms]	0.68	0.0006	0.76	0.0001
pVO_2 [ml/kg/min]	–0.74	0.0001	–0.68	0.0007

EF – ejection fraction, △EF – difference between baseline EF and control EF, MPI – myocardial performance index, E/A – Doppler index of left ventricular filling, DT – deceleration time, IRP – isovolumic relaxation time, pVO_2 – peak oxygen consumption at the exercise, CD – cumulative dose

Table 7. Linear regression analysis between pVO_2, cumulative dose, age and parameters of cardiopulmonary function

Variable	pVO_2 [ml/kg/min] (entire group; n=47)		pVO_2 [ml/kg/min] (patients with drop in EF>10%; n=11)	
	r	p-value	r	p-value
EF [%]	0.4	n.s.	0.5	n.s.
△ EF [%]	–0.17	n.s.	–0.5	n.s.
MPI	–0.31	n.s.	–0.79	0.03
E/A	0.72	0.0001	0.80	0.02
DT [ms]	–0.5	0.05	–0.30	n.s.
IRP [ms]	–0.69	0.0007	–0.91	0.001
CD [mg/m^2]	–0.68	0.0007	–0.1	n.s.
Age [yrs]	–0.74	0.0001	–0.74	0.05

EF – ejection fraction, △ EF – difference between baseline EF and control EF, MPI – myocardial performance index, E/A – Doppler index of left ventricular filling, DT – deceleration time, IRP – isovolumic relaxation time, pVO_2 – peak oxygen consumption at the exercise, CD – cumulative dose

Discussion

Because of the increasing incidence of the lymphomas and improvements in curing over the past two decades, long-term survivors should be observed for late toxicities. Today, the evaluation of cardiac complication is of growing importance for adults who might expect benefit from currently available

Table 8. Univariate analysis

Factors	No. of patients	No. of patients with drop in EF >10%	p-value [chi-square test]
Age >60 years	14	1 (7%)	n.s.
Age ≤60 years	33	10 (23%)	
CD ≥300 mg/m^2	33	7 (21%)	n.s.
CD <300 mg/m^2	14	4 (28%)	
HYP yes	11	2 (18%)	n.s.
HYP no	36	9 (25%)	
CAD yes	9	2 (22%)	n.s.
CAD no	38	9 (23%)	
DIAB yes	3	1 (7%)	n.s.
DIAB no	44	10 (23%)	
RT yes	9	3 (33%)	n.s.
RT no	38	8 (21%)	
		All cardiac events	
Age >60 years	14	13 (93%)	n.s.
Age ≤60 years	33	25 (75%)	
CD ≥300 mg/m^2	33	30 (90%)	0.01
CD <300 mg/m^2	14	8 (57%)	
HYP yes	11	11 (100%)	0.05
HYP no	36	27 (57%)	
CAD yes	9	9 (100%)	n.s.
CAD no	38	29 (76%)	
DIAB yes	3	3 (100%)	n.s.
DIAB no	44	35 (92%)	
RT yes	9	9 (100%)	n.s.
RT no	38	29 (76%)	

CD – cumulative dose of doxorubicin, HYP – hypertension, CAD – coronary artery disease, DIAB – diabetes, RT – radiotherapy involving mediastinum, EF – ejection fraction

Table 9. Multivariate analysis

Drop in EF>10%				
Factors	Significance	OR	CI 95%	Model significance
Age >60 years	0.224	0.308	0.046–2.06	0.027
CD ≥300mg/m^2	0.738	0.712	0.098–5.2	
RF	0.008	9.488	1.803–49.9	
Gender	0.229	2.664	0.54–13.14	
All cardiac events				
Factors	Significance	OR	CI 95%	Model significance
Age >60 years	0.239	4.78	0.354–64.8	0.025
CD ≥300mg/m^2	0.05	8.08	0.947–69.2	
RF	0.97	6.7	0.250–68.54	
Gender	0.87	0.18	0.09–7.34	

EF – ejection fraction, CD – cumulative dose of doxorubicin, RF – risk factors of cardiotoxicity

treatment. Unfortunately, the literary data on long-term consequences of the treatment in non-Hodgkin's lymphoma survivors are still limited. The CHOP regimen has been considered the standard treatment for patients with aggressive lymphoma for last twenty years [1].

Recently, the treatment has been improved when combined with the monoclonal antibody rituximab (anti-CD20). This compound may induce a cytokine-release syndrome accompanying the administration of the drug. No late cardiotoxic effect has been described [13]. Another agent that can cause cardiotoxicity is high-dose cyclophosphamide used in the setting of autologous stem cell transplantation, but the occurrence of cardiotoxicity is rare less than 2%. The doses of cyclophosphamide used in the CHOP regimen are too low to induce cardiotoxicity. Moreover, this agent causes more likely acute cardiotoxicity [14, 15]. Cyclophosphamide was not a part of a preparative regimen used before transplantation in our study. Radiation-associated cardiotoxicity represents a late effect in survivors who received mediastinal irradiation. But the late effects have been described after a long period of follow-up and have been associated predominantly with an increased incidence of coronary artery disease. There are conflicting data and there is no evidence of direct synergy between radiotherapy and cardiac involvement associated with chemotherapy [16, 17].

Of the agents used in the treatment of lymphomas the anthracyclines remain the most frequent causes of the heart injury [4, 18]. Although acute cardiotoxicity is rare and has not been described in any patient from our study, the development of chronic impairment over time represents a serious clinical problem [19].

Several factors increase the risk of anthracycline-induced cardiac toxicity in adults. These include advanced age >60 years, preexisting heart disease, concomitant treatment with other cardiotoxic compounds, and mediastinum involved by radiotherapy. Cumulative dose of doxorubicin is very serious risk factor and a total CD greater than 550 mg/m^2 increases the risk significantly [20]. Therefore lower doses have been recommended to avoid cardiotoxicity without compromising the anti-tumour effect. An empirical threshold of 500 mg/m^2 has been commonly used and doses below 300 mg/m^2 have been considered to be of low risk of cardiotoxicity [21]. In a comprehensive study by MILLER et al 33% of patients who received CD 400 mg/m^2 demonstrated left ventricular dysfunction, whereas none of the patients treated with lower CD developed left ventricular dysfunction [22]. In a study by HADDY et al 14% of patients who received CD 200–550 mg/m^2 of doxorubicin had left ventricular dysfunction. In both studies the cardiac toxicity was the predominant major late effect observed [23]. In a study by LIMAT et al the threshold for cumulative dose of 200 mg/m^2 was accompanied by the presence of 27% clinical and subclinical cardiotoxicity in patients treated with CHOP regimen [24]. Currently, the CD of doxorubicin in CHOP regimen over 400 mg/m^2 has not been used in our department. In the present study the majority of patients received CD 300 mg/m^2 of doxorubicin.

Despite the "safe" CD used in the study a relatively high number of patients with EF decrease was detected. Using univariate analysis, our data demonstrate that the presence of hypertension and CD of doxorubicin ≥300 mg/m^2 significantly correlates with the occurrence of all cardiac events. The multivariate analysis shows that both statistical models demonstrate significant relationship for cardiac impairment characterized either decreased EF or all cardiac events. Looking on individual correlations, we have found an important relationship between drop of EF and the presence of risk factors for cardiotoxicity, and higher CD remains a significant predictor for the occurrence of all cardiac events.

Introducing the echocardiography, stress tests, etc. into the diagnostic of anthracycline-induced cardiotoxicity has increased the number of patients with sub-clinical LV impairment [6, 25]. The studies in adults based on the detection of chronic myocardial impairment are of great interest and importance because the subclinical changes induced by doxorubicin may be aggravated during the course of a patient's life due to the increased occurrence of underlying cardiovascular diseases. In general, EF has been used as a gold standard for the assessment of cardiac toxicity. The progressive decline in EF or a drop below its lower limit has been used as a marker of cardiotoxicity. The drop in the normal range of EF has been used to detect suspected early cardiotoxicity and to avoid the acute onset of heart failure [26–28]. In our previous study, we have demonstrated that the decline in EF in the normal range was accompanied by preserved contractile reserve assessed by dynamic stress echocardiography [29]. Therefore, we can explain a non-significant link between EF, EF change and pVO_2 in the present study. The question is, whether the drop in the normal range reflects the actual pathological conditions. The weak relationship to CD of doxorubicine validates this problem. Only a long-term follow-up can clarify the predictive value of such

a finding for the further decrease in EF below the normal limit and the development CHF.

The diastolic dysfunction precedes the systolic failure in about 30% of clinical cases and has been responsible for the development of diastolic heart failure [30, 31]. The pattern of restrictive filling of the left ventricle is associated with higher filling pressure of LV and with a poor prognosis in patients. Its predictive value for cardiac morbidity and mortality is high [32, 33, 34]. A minority of our patients showed an impaired relaxation before treatment due the presence of previous heart disease. Significant impairment of all three variables was apparent at the end of one-year examination and led to the diagnosis of impaired relaxation in all cases. These Doppler findings reflect the impaired relaxation of the left ventricle and could be explained in terms of an increase of cytosolic calcium concentrations, which was already demonstrated, to be induced by the administration of anthracyclines [35, 36]. Our results demonstrate that significant abnormalities in diastolic function are associated with the administration CHOP regimen. All of the parameters significantly correlate with the CD given. We believe, that the strong correlation to age may also reflect a physiological relation of impaired relaxation to aging and the relation to advanced age as a risk factor of cardiotoxicity.

A myocardial performance index has been described as a non-invasive Doppler measurement of global ventricular function [9]. The MPI has been shown to correlate significantly with other invasive or non-invasive measures of LV function, to be relatively independent of age and hemodynamic parameters [37]. Studies have demonstrated MPI as a powerful predictive factor of morbidity and mortality in patients with various cardiac diseases. An increased value of MPI >0.5 has been shown as a powerful predictor of poor clinical outcomes in adults [38]. EIDEM et al demonstrated that significant increases in the MPI occurred before changes of conventional measures of left ventricular function at CD of anthracyclines as low as 200 mg/m^2 [39]. MPI significantly correlates with EF and FS and is significantly increased in doxorubicine-treated patients compared to the controls [40]. In our study, the MPI was the second most affected variable besides the diastolic dysfunction after chemotherapy. In addition to this, some patients showed a value of MPI >0.77, which has been of a highly predictive value for the development of CHF and five-years mortality [41, 42].

Reduction in exercise capacity has been previously described in patients taking anthracyclines. Exercise intolerance can result from cardiac, respiratory, or musculoskeletal dysfunction as well as from deconditioning [43]. In this study, we demonstrate a significantly reduced exercise capacity after treatment with CHOP regimen in some patients. We are not able to demonstrate the development of changes of cardiopulmonary performance in the respect to oncological treatment, because we have not baseline data. Clinically, the statistical analysis offers very important data. We found that pVO_2 significantly correlates with CD of doxorubicin given. Moreover, we demonstrate that the diastolic dysfunction significantly influences the exercise performance in our patients. This relationship was described in patients with ischemic heart disease and CHF. It is known, that parameters of LV diastolic function correlate better with symptoms, filling pressure and prognosis than parameters of systolic function [44, 45]. SATO et al demonstrated a significant inverse correlation between MPI and pVO_2 during cardiopulmonary exercise [46]. In another study, an inverse relation between MPI and exercise time in patients with various NYHA class was reported and MPI was found to be a good predictor of exercise tolerance [47].

Deconditioning can only partially explain the impaired cardiopulmonary response to the exercise in our study. The described echocardiographic abnormalities as a result of the chemotherapy influence cardiopulmonary dysfunction. Our data clearly demonstrate that in patients treated with CHOP regimen the Doppler indexes of both global and diastolic function may be a determinant of exercise intolerance.

A limiting factor of our study is a short-term follow-up period and a relatively small number of patients examined. The number of patients reflects the incidence of the disease from a region of our hospital. In accordance to used treatment modalities the patients may represent a relatively heterogeneous cohort. The influence of high-dose chemotherapy with transplantation and rituximab administration on the late changes of cardiac function has to be assessed in larger prospective studies. We have used the standard approach to diagnose cardiotoxicity. The diagnosis of neuroendocrine changes during the development of left ventricular dysfunction may play an important role in the diagnosis of anthracycline-induced cardiomyopathy. The results from studies on the measurement of natriuretic peptides or a change of sympathovagal balance may contribute to this problem [48, 49].

In conclusion, our results demonstrate that despite the treatment of aggressive lymphoma by means of CHOP regimen with safe CD of doxorubicin, significant presence of cardiac abnormalities has been diagnosed during one-year follow-up. The treatment modalities as well as the risk factors of cardiotoxicity, mainly the hypertension, have predominantly negatively influenced the Doppler parameters of left ventricular function. Both parameters diastolic dysfunction and myocardial performance index are responsible for decreased exercise tolerance in our patients. These results warrant a further follow-up to estimate their prognostic value.

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