The evaluation of left ventricular function in childhood cancer survivors by pharmacological stress echocardiography*

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Late cardiotoxicity after anthracycline chemotherapy for childhood cancer is well recognized sequelae. Many long-term survivors may have subclinical cardiac dysfunction undetectable at a baseline evaluation. Various tests have been utilized for the diagnosis of left ventricular impairment. Recently, low-dose dobutamine stress echocardiography has been proposed as a more sensitive screening test.

We have applied low-dose dobutamine stress echocardiography (5–10 μg/kg/min) in 36 asymptomatic survivors (20 male/16 female aged 14.6 ± 4.7 years) treated with a cumulative dose of 226 ± 106 mg/m^2 of doxorubicin. The median follow-up was 5 years. Control group consisted of 20 sex and age matched volunteers (12 male/8 female aged 12.6 ± 4.9 years).

We found significant differences in mean velocity of circumferential fibre shortening, myocardial performance index (Tei index), left ventricular posterior wall thickening and endsystolic wall stress at a baseline. The stress response was significantly blunted only in a patient group in the following parameters: endsystolic wall stress, isovolumic relaxation time and myocardial performance index. The threshold response was abnormal (0–5% improvement of a variable only) in 45% of subjects from a control group in one or two parameters. On the contrary, 63% of subjects from a patient group responded pathologically (the worsening of a variable) in one or more parameters. We have not found a good correlation between risk factors of late cardiotoxicity and stress changes of left ventricular function parameters.

Low-dose dobutamine stress echocardiography is safe and feasible diagnostic tool in children and adolescents. Dobutamine significantly increases the differences in cardiac variables between healthy population and asymptomatic survivors for childhood cancer. In comparison to the controls, most asymptomatic patients revealed subclinical myocardial damage at test. The predictive value for the development of clinical symptoms and cardiac complications need to be assessed in a large prospective study.

Key words: Dobutamine stress echocardiography, cardiotoxicity, doxorubicin, children.

Cardiotoxicity is a well recognized sequelae of anthracycline therapy for childhood cancer. Although anthracycline chemotherapy for the treatment of childhood cancer is known to be highly efficacious, its use has been limited by the risk of treatment related cardiac toxicity [7]. In both adults and children, the risk of the development of cardiotoxicity increases with the cumulative dose of anthracycline [28]. Anthracycline cardiotoxicity can be divided arbitrarily into early and late, depending on when it presents [7]. Late clinically apparent cardiotoxicity occurring more than 5 years after anthracycline therapy is rare in comparison to subclinical cardiotoxicity which is very frequent. Subclinical cardiotoxicity can progress to clinical manifestations which are potentially severe and fatal [23, 24, 25]. The subclinical cardiotoxicity has been mostly characterized by the presence of morphological and functional abnormalities of the left ventricle (LV) on echocardiographic examination. The prevalence of these abnormalities varies widely be-

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tween presented studies from 65% to 85% in children who received cumulative doses of doxorubicin between 240 and 360 mg/m^2 [9]. However, the frequency of subclinical cardiac abnormalities does not seem to be closely related to the cumulative dose of anthracycline.

Numerous noninvasive cardiac tests have been used to diagnose cardiac impairment. Echocardiography may be used for determining structural (wall thickness, internal diameter) and functional (systolic and diastolic) impairment of the LV. Moreover, other indexes such as parameter of left ventricular afterload (endsystolic wall stress), load independent measure of contractility (stress-velocity index) and index of global LV function (Tei index) can be assessed. The introduction of stress tests may increase the sensitivity of cardiac abnormality detection [7, 27].

In the present study we used the low-dose dobutamine stress test in asymptomatic survivors of childhood cancer to determine if inotropic challenge with dobutamine could unmask echocardiographic abnormalities in the diagnosis of late subclinical cardiotoxicity.

Patients and methods

Study subjects. The study group consisted of children and young adults previously treated for cancer with doxorubicin at the Department of Pediatrics, Masaryk University, Brno, Czech Republic. Thirty six patients (20 male/16 female) aged 14.6 $\pm$ 4.7 years (median 14.5 years) were enrolled in the study. The diagnosis of malignancy was established at the age of 9.1 $\pm$ 4.6 years (median 9 years). Mean time of the follow-up was 5.5 $\pm$ 2.4 years (median 5 years). All subjects were asymptomatic, without medication and with a good quality of life comparable with the controls. All children and adolescents (further referred as a patient group) were in a complete long-term remission of their malignancy. No cardiac complications were detected during the anticancer treatment, all subjects had normal findings on ECG and the heart appeared to have a normal size on a chest roentgenogram. Most of them were examined echocardiographically with the findings of normal ejection fraction at the completion of the chemotherapy.

The mean administered cumulative dose of doxorubicin was 226 $\pm$ 106 mg/m^2 (median 240 mg/m^2). Eight (27%) patients received mediastinal irradiation with a cumulative dose of 24 $\pm$ 7.1 Gy (median 20.5 Gy).

Twenty healthy age-matched volunteers (12 male/8 female) aged 12.6 $\pm$ 4.9 years (median 14.5 years) served as control subjects (further referred as a control group). There were no statistically significant differences between patients and controls in age, BSA and sex.

All subjects or their parents gave informed consent. If the subject was a minor, the parents were present during the examination. The study was approved by the Committee for Ethics of Medical Experiments on Human Subjects of The University Hospital Brno. The study complies with the Declaration of Helsinki.

Echocardiography. The echocardiographic equipment consisted of ATL Ultramark 7 with 3.75 and 2.5 MHz transducer and the program for stress test. All subjects were examined in the left decubitus position and the measurements were recorded in accordance to standard recommendations [11, 14]. Doppler examinations of mitral and aortic flow were performed with the range-gated pulsed Doppler technique. The ultrasound beam was aligned as parallel to flow as possible with the sample volume positioned at the tips of mitral leaflets or LV outflow tract.

Echocardiographic measurement. Left ventricular cavity and posterior free dimensions at end-diastole (LVED, LVPWD) and end-systole (LVES, LVPWS) were measured with an average of 3 cycles reported. The LV volumes were calculated according to the M-mode formula of Teicholz and the ejection fraction (EF) was calculated as follows:

$EF = 100 \times (LVEDV - LVESV)/LVEDV\ (\%)$ [11].

LV fractional shortening (FS) was computed as:

$FS = 100 \times (LVED - LVES)/LVED\ (\%)$ [11].

Left ventricular posterior wall thickening (LVPWTh) was calculated using the formula:

$LVPWTh = 100 \times (LVPWS - LVPWD)/LVPWD\ (\%)$ [11].

Left ventricular end-systolic meridional wall stress (ESS) was calculated according to the method of Grossmann et al [10]:

$ESS = 1.35 \times (MBP \times LVES)/4 \times LVPWS \times (1 + LVPWS/LVES)\ (g/cm^2)$,

where MBP is mean blood pressure. MBP was estimated by the formula:

$MBP = (2DBP + SBP)/3$,

where DBP is diastolic blood pressure and SBP is systolic blood pressure. The mean velocity of circumferential fiber shortening (mVcf) was calculated as follows:

$mVcf_c = (LVED - LVES)/(LVED \times LVET)\ (c/s)$ [11]

and corrected for heart rate ($mVcf_c$), where LVET is the ejection time of LV measured from Doppler record of aortic flow. Doppler-derived myocardial performance index (Tei index) has been calculated using the formula [27]:

$MPI = (ICT + IRT)/LVET$,

where ICT is isovolumic contraction time and IRT isovolumic relaxation time. ICT and IRT were obtained by subtracting LVET from the interval between mitral flow closure and opening.

Doppler measurements of mitral flow evaluated the diastolic function. The peak velocity of early rapid filling (E) and the peak velocity of atrial contribution (A) were recorded and an E/A ratio was calculated. The deceleration time (DT) and the LV isovolumic relaxation time (IRT) were also determined [3].

Dobutamine stress test. Dobutamine (Dobutrex, Eli Lilly) was administered by continuous infusion in a large vein of the arm. Once the baseline recordings were obtained, continuous dobutamine infusion was initiated in two four-minute periods with the rate of 5 and 10 μg/kg/min. Electrocardiogram (ECG) and blood pressure (BP) were continuously monitored during the entire procedure. BP was measured noninvasively by means of sphygmomanometry. The echocardiographic examination was performed during the last minute of dobutamine infusion.

Dobutamine infusion is usually terminated prematurely if any of the following complications occurs : 1) arrhythmias; 2) an increase of systolic or diastolic BP >30% above the baseline level; 3) a decrease of systolic or diastolic BP to >20% below the baseline level; 4) an increase of heart rate (HR) >40% above the baseline level; 5) significant discomfort or anxiety.

The same investigator, who was blinded to clinical data of the patient, performed all echocardiographic measurements and studies.

Statistical analysis. The data were expressed as a mean $\pm$1 standard deviation (SD) and a median. Statistical analysis was performed by the paired t-test, unpaired t-test and chi-square test. Statistical significance was considered acceptable for $p<0.05$. Simple or multiple linear regression analysis was utilized to assess the relation between variables measured.

The threshold for the response in any parameter measured in individual subject was defined as a 5% change from the baseline value. More than 5% improvement was considered as a physiological response, the 0–5% change as an abnormal response, and the worsening below the baseline was considered as a pathological response to the stress test. The statistical programs Microsoft Excel Win 98 a NCSS 6.0 (Number Cruncher Statistical Systems of Dr. Jerry L. Hintze, USA) were used for the statistical analysis.

Results

All subjects completed dobutamine stress test safely without any adverse effects. Hemodynamic parameters at the baseline and during the test were measured and compared. Small doses of dobutamine led to a small and significant increase of systolic BP (SBP) in both patient and control groups and did not influence the HR and diastolic BP (DBP) without differences between subgroups.

Parameters of systolic function. All subjects had values of all rest parameters of systolic function within the normal range. However, significant differences in $mVcf_c$ ($p>0.05$) as well as in MPI_c ($p<0.02$) were apparent. The LV posterior wall thickness did not differ in the groups. On the contrary, the relative thickening of LV posterior wall was significantly

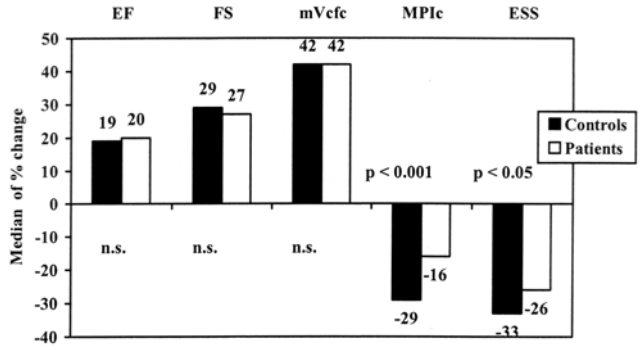

Figure 1. The comparison of the median of the percentual changes after the dobutamine stimulation in parameters of LV function in controls and patients. EF – ejection fraction, FS – fractional shortening, $mVcf_c$ – mean velocity of circumferential fiber shortening, MPI_c – myocardial performance index, ESS – endsystolic stress of left ventricle.

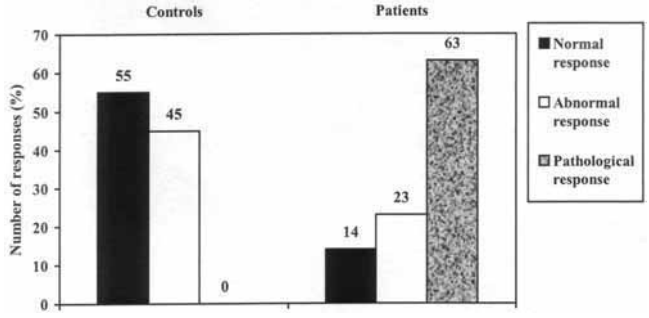

Figure 2. The response to the dobutamine stress echocardiography in patients and controls.

greater in controls ($p<0.05$). Endsystolic wall stress was increased in patients ($p<0.03$).

The administration of 10 μg/kg/min of dobutamine improved significantly all parameters of the systolic function in both groups, however, significant differences between stress values in $mVcf_c$, MPI_c and ESS were evident (Tab. 1). The response of MPI_c and ESS to positive inotropic stimulation was strikingly blunted in patients (Fig. 1).

Parameters of diastolic function. We did not find any pathological changes in Doppler values of rest mitral flow as well as IRT. At the rate of 10 μg/kg/min of dobutamine the E/A ratio increased significantly due to the enhanced early filling in both groups. The velocity of atrial contraction remained unchanged. The deceleration time revealed no significant difference at rest as well as at stress in both patients and controls. Only IRT was significantly prolonged in patients at rest. The physiological shortening of IRT after dobutamine was much more pronounced in controls than in patients (Tab. 2).

Individual response to the test (threshold response). The threshold for the physiological response to 10 μg/kg/min of dobutamine was established as more than 5% improvement

Table 1. Changes of parameters of left ventricular systolic function during the low-dose (10 μg/kg/min) dobutamine stress test

Parameter	Patients	Controls	p-value**
EF – rest (%)	64 ± 4 (64)	66 ± 4 (66)	n.s.
EF – stress (%)	76 ± 5 (76)*	78 ± 4 (80)*	n.s.
FS – rest (%)	35 ± 5 (35)	36 ± 3 (36)	n.s.
FS – stress (%)	45 ± 4 (45)*	47 ± 4 (48)*	n.s.
$mVcf_c$ – rest (c/s)	1.41 ± 0.29 (1.39)	1.51 ± 0.21 (1.49)	0.05.
$mVcf_c$ – stress (c/s)	2.01 ± 0.51 (1.95)*	2.16 ± 0.33 (2.16)*	0.05
MPI_c – rest	0.4 ± 0.11 (0.4)	0.34 ± 0.009 (0.37)	0.02
MPI_c – stress	0.36 ± 0.12 (0.35)*	0.25 ± 0.1 (0.25)*	0.0001
LVPWD (mm)	6.9 ± 1.2 (7)	6.6 ± 1.2 (7)	n.s.
LVPWTh – rest (%)	44 ± 10 (45)	48 ± 6 (46)	0.05
LVPWTh – stress (%)	53 ± 10 (54)*	58 ± 8 (58)*	0.05
ESS – rest (g/cm^2)	62 ± 12 (61)	55 ± 14 (54)	0.03
ESS – stress (g/cm^2)	42 ± 10 (44)*	36 ± 11 (34)*	0.04

Data are expressed as a mean ±1 SD and median (in parenthesis).
* – p<0.001 statistical significance for the changes of the variable in the individual subgroup, ** – statistical significance between subgroups, EF – ejection fraction, FS – fractional shortening, mVcfc – mean velocity of circumferential fiber shortening, MPIc – myocardial performance index, LVPWD – left ventricular posterior wall enddiastolic diameter, LVPWTh – percentual systolic thickness of left ventricular posterior wall, ESS – endsystolic stress of left ventricle.

Table 2. Changes of parameters of left ventricular diastolic function during the low-dose (10 μg/kg/min) dobutamine stress test

Parameter	Patients	Controls	p-value**
E – rest (cm/s)	88 ± 12 (86)	88 ± 13 (88)	n.s.
E – stress (cm/s)	102 ± 15 (102)*	102 ± 16 (102)*	n.s.
A – rest (cm/s)	44 ± 9 (43)	46 ± 8 (46)	n.s.
A – stress (cm/s)	46 ± 9 (47)	44 ± 10 (43)	n.s.
E/A – rest	1.96 ± 0.41 (1.95)	1.97 ± 0.32 (1.88)	n.s.
E/A – stress	2.24 ± 0.43 (2.21)*	2.35 ± 0.42 (2.41)*	n.s.
DT – rest (ms)	143 ± 24 (146)	137 ± 27 (132)	n.s.
DT – stress (ms)	127 ± 30 (128)*	123 ± 18 (120)*	n.s.
IRT – rest (ms)	64 ± 10 (64)	60 ± 7 (59)	0.05
IRT – stress (ms)	52 ± 8 (52)*	47 ± 6 (47)*	0.04

Data are expressed as a mean ±1 SD and median (in parenthesis).
* – p <0.001 statistical significance for the changes of the variable in the individual subgroup, ** – statistical significance between subgroups, E – velocity of early filling, A – velocity of atrial contraction, E/A – index of diastolic filling, DT – deceleration time, IRT – isovolumic relaxation time.

in a particular variable. All controls revealed physiological response in EF, FS, $mVcf_c$, ESS and IRT. Surprisingly, an abnormal response (0–5% improvement) in the myocardial performance index, E/A ratio, and DT was found in 16%, 28%, and 25% of controls (Tab. 3), respectively. All patients reached the physiological response only in EF and FS parameters (Tab. 3). In summary, the results demonstrated the pathological response of one or more variables tested in 63% of patients. Fourteen % of patients responded abnormally and 23% physiologically. Controls did not reveal any pathological response in any of the parameters

Table 3. Number of patients with physiological response to the low-dose dobutamine (10 μg/kg/min) stress test

Variables	Patients	Controls	p-value**
EF	100	100	n.s.
FS	100	100	n.s.
$MVcf_c$	88	100	0.01
ESS	94	100	0.05
MPI_c	55	84	0.0001
E/A	66	72	0.05
DT	77	75	n.s.
IRT	94	100	0.05

Values are expressed as percentages.
EF – ejection fraction FS – fractional shortening, $mVcf_c$ – mean velocity of circumferential fiber shortening, MPI_c – myocardial performance index, ESS – endsystolic stress of left ventricle, E/A – index of diastolic filling, DT – deceleration time, IRT – isovolumic relaxation time.

Table 4. Linear regression analysis between risk factors of late cardiotoxicity and parameters of left ventricular function

Variables (%)	Age at the diagnosis	Age at the examination	Cumulative dose of doxorubicin	Time of follow-up
EF	R = –0.1	R = –0.1	R = 0.1	R = –0.24*
FS	–0.05	–0.4*	0.05	–0.44*
$MVcf_c$	–0.2	–0.24	–0.03	–0.14
ESS	0.22	0.24	0.03	0.55*
MPI_c	–0.14	–0.53*	0.06	–0.22*
E/A	0.2	0.44*	0.36*	0.24*
DT	–0.04	0.22	0.33*	0.17
IRT	0.22	–0.57*	0.17	0.17

* – statistical significance p <0.05. EF – ejection fraction, FS – fractional shortening, $mVcf_c$ – mean velocity of circumferential fiber shortening, MPI_c – myocardial performance index, ESS – endsystolic stress of left ventricle, E/A – index of diastolic filling, DT – deceleration time, IRT – isovolumic relaxation time.

tested. Abnormal and physiological responses were present in 45% and 55% of controls, respectively (Fig. 2).

Linear regression analysis. The following risk factors of late cardiotoxicity were selected: the age at diagnosis of cancer, the age at examination, the length of follow-up, and the cumulative dose of anthracycline. A linear regression analysis with exercise induced changes of LV function parameters was performed. Relatively week correlation was found among tested variables (Tab. 4).

Discussion

The number of long-term survivors of childhood cancer is increasing due to highly effective anticancer treatment. By the year 2010, approximately one of every 250 adults (age 20 to 45 years) in the United States may be a survivor of malignant disease in childhood or adolescence [1]. Many of them

have been exposed to the potential cardiotoxic chemotherapy containing anthracyclines, namely doxorubicin [1].

Long-term cancer survivors represent one of the largest groups of patients at risk for premature cardiovascular disease. The results completed by the Pediatric Cardiomyopathy Registry in the USA showed that approximately 15% of all patients diagnosed with cardiomyopathy weres previously treated for cancer in childhood or adolescence [9]. The same problem will be also expected in the future in Europe.

Anthracycline-induced cardiotoxicity in children and adolescents can be broadly classified by clinical presentation into three categories: acute (or subacute), early-onset chronic progressive cardiomyopathy and late-onset chronic cardiomyopathy [7].

Late-onset is defined as cardiomyopathy that manifests itself after a latency period of more than one year after the completion of anticancer therapy. This type of cardiotoxicity has been characterized with an asymptomatic period without cardiac dysfunction or arrhythmia and normal clinical status [7, 9, 23].

The pathological mechanism of early and late chronic cardiotoxicity differs. In children, early onset is presumed to be due to the cardiomyocyte damage or death, which subsequently results in diminished LV contractility. On the contrary, late onset is presumably due to diminished LV contractility and inappropriately thin LV wall resulting in elevated endsystolic wall stress, which precedes the ventricular dysfunction [7, 20].

Late clinical cardiotoxicity following anthracycline chemotherapy for childhood cancer has been described in 10–15% of long-term survivors 5–10 years after the treatment [23, 24]. The most detailed studies found abnormal changes in the LV structure, parameters of systolic and diastolic function in otherwise asymptomatic patients [5, 7, 8, 12, 17, 29, 25].

The prevalence of subclinical cardiotoxicity varies widely between studies. Lipshultz et al [19] found an elevated afterload in 65% of long-term survivors. The mean cumulative dose of anthracycline was 360 mg/m^2. In another study Bu'lock et al [2] demonstrated reduced fractional shortening in 23% of patients treated with a median dose of 300 mg/m^2 of anthracycline. Leonardo et al [21] reported reduced LV mass, decreased fractional shortening, and pathologically increased ESS in 21% childhood cancer survivors. Children received a mean dose of 335 mg/m^2 of doxorubicin and were followed for 7 years. In the study from Johnson et al, 14% of children had abnormal decrease of fractional shortening 3 years after completion of chemotherapy with a mean dose of 291 mg/m^2 of anthracycline [13].

The introduction of stress tests has increased the presence of pathological or abnormal findings [29]. Low-dose dobutamine stress test enables to discover latent decreased cardiac performance in cancer patients. Klewer et al [16] have found significantly decreased LV wall dimension and thickening at the baseline in 21 patients (mean age 16 years) 1–17 years after the treatment. The application of dobutamine has decreased FS and pathologically increased ESS. DeWolf et al [5] presented abnormal response to dobutamine in 85% of asymptomatic children, adolescents and young adults. Both systolic and diastolic functions were affected. The systolic dysfunction in this study was not related to diminished contractility but to an elevated systolic wall stress due the inadequate cardiac wall thinning.

In the comparison to presented data, Lanzarini et al [18] have not found the difference in LV functional response to the low-dose dobutamine between controls and cancer patients. Moreover, currently accepted risk factors for cardiotoxicity had no influence on stress test results.

Main risk factors for late cardiotoxicity are: the age at cancer treatment, time of follow-up, female sex, cumulative dose of administered anthracycline and mediastinal irradiation involving the heart [7]. However, their clinical significance for the development of subclinical cardiotoxicity is not yet established and published data are controversial [9, 23]. Our data support the results from Lanzarini's study [18]. Because of a small number of patients we have not assessed the relation between sex and LV dysfunction. The influence of cyclophosphamide on such late disturbances is negligent. Small subset of patients with radiation therapy revealed no significant difference in LV function in the comparison to others. Standard protocols were used for the treatment without fundamental differences in administered cumulative doses of doxorubicin in respect to the neoplastic disease. We assume that relatively short time of follow-up is the main factor responsible for weak correlations. Main factors influencing the frequency of subclinical cardiotoxicity are diagnostic modality used and variable tested. FS and EF are widely accepted parameters of LV systolic function, unfortunately, both of these indexes are sensitive to load conditions, heart rate and age [4]. The stress-velocity index has been recently successfully used for the detection of LV impairment after chemotherapy at rest as well as by the dobutamine test [5, 20].

Dobutamine increases the value of EF, FS, mVcf$_c$, decreases ESS by a relatively more important increase in systolic wall thickness compared to the minimal increase of SBP in normal subjects [5, 6, 16]. Despite normal findings in LV posterior wall enddiastolic diameter, the systolic thickening at rest and stress was impaired in patients in our study. Then, the disturbance in systolic wall thickness was responsible for increased ESS.

Similarly, positive lusitropic effect of dobutamine accelerates the relaxation and enhances the filling of normal left ventricle. The delay in IRT shortening after dobutamine may reflect an early impaired relaxation due the doxorubicin-induced changes in calcium handling, ATP metabolism

or due to the presence of fibrotic changes in myocardium [7]. The importance of the changes in IRT after anthracycline administration for late development of late systolic heart failure has been described [26].

Recent studies have documented frequent coexistence of systolic and diastolic dysfunction in the presence of various cardiac diseases. Global left ventricular performance is a function of both ventricular filling and ejection and can be assessed exactly by means of Doppler echocardiography. Index of global myocardial function (Tei index) seems to be a useful noninvasive means that correlates with clinical symptoms, is relatively independent of loading conditions and can stratify patients with poor EF [27]. Myocardial performance index of LV may serve as a predictor of moderate cardiac rejection in pediatric cardiac transplant patients [22]. Three variables that are utilized for calculations of the index are shortened after catecholamine stimulation in controls. In the absence of loading changes during low-dose dobutamine, only the quality of both contraction and relaxation is responsible for the final value of the index. Therefore, this index showed most significant difference in the response of LV to the dobutamine stimulation between both groups.

There is no consensus which change of the parameter of left ventricular function represents the gold standard for the physiological response to the stress test. Some authors defined it as a change of a value >5% [6]. Surprisingly, 45% of controls did not reach the threshold at the rate of 10 μg/kg/min of dobutamine. All these subjects revealed only inappropriate response between 0–5% in one or two parameters. These findings must be interpreted with caution. The biological variability of measured parameters in young people and the fact, that we have not administered higher doses of catecholamine, should be taken into consideration. The findings in control and patient groups differ. The results of 63% pathological responses in one or more parameters are not negligent and evidently characterize the differences between both groups.

In conclusion, low-dose dobutamine stress echocardiography is safe and feasible diagnostic tool in children and adolescents. Dobutamine significantly increases the differences in cardiac variables between healthy population and asymptomatic survivors for childhood cancer. Compared to the controls most asymptomatic patients revealed subclinical myocardial damage at the test. It is unclear, how to interpret these findings in the clinical setting. Undoubtedly, late subclinical cardiotoxicity influences survival minimally. The predictive value for the development of clinical symptoms and complication must be assessed in a large prospective study. Accordingly to previous studies, our data suggest that low-dose dobutamine stress echocardiography is a useful noninvasive approach for examining the cardiac status of doxorubicin-treated patients.

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