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Early diagnosis of anthracycline toxicity in asymptomatic long-term survivors: dobutamine stress echocardiography and tissue Doppler velocities in normal and abnormal myocardial wall motion

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Aims Asymptomatic long-term cancer survivors treated with anthracycline were investigated for late anthracycline cardiotoxicity using dobutamine stress echocardiography (DSE) and tissue Doppler (TD) velocities.

Methods and results The study comprised 20 asymptomatic patient and 18 healthy children as the control group. Twenty patients were divided into two groups according to the myocardial wall motion during DSE: Group 1 (normal myocardial wall motion; six girls and five boys) and Group 2 (abnormal myocardial wall motion: nine boys). Intravenous dobutamine infusion was started at a dose of 5 μg/kg/min (D5) and gradually increased to 10 (D10), 15 (D15) and 20 μg/kg/min (D20). Echocardiographic assessment was performed at rest and after each dose of dobutamine infusion. Abnormal myocardial wall motion was observed at rest in 3 patients and during DSE in six patients. There were no significant differences between the patients and control groups at rest except the end systolic wall stress and mitral deceleration time measured by conventional methods; however, both patients group showed significant differences of systolic and diastolic functions at D20. In patients groups, systolic and diastolic functions of interventricular septum (IVS) and systolic function of left ventricle (LV) and right ventricle (RV) TD velocities showed significant changes compared with control group at rest. Significant differences of diastolic functions of IVS and RV were noted during dobutamine infusion in abnormal myocardial wall motion compared with other groups.

Conclusion LV, RV and IVS TD velocities systolic function at rest and during DSE can provide valuable information for early detection of subclinical cardiac toxicity. TD velocities of diastolic functions during DSE are a valuable parameter for assessment of subclinical cardiac toxicity in patient with abnormal wall motion.

Keywords Dobutamine stress echocardiography • Tissue Doppler velocities • Anthracycline late cardiotoxicity • Early diagnosis

Introduction

Almost 60% of children with cancer are currently being treated with anthracycline and more than 70% of these children are expected to be cured. Cardiotoxicity due to anthracycline may occur early or in later stages of treatment, even several years after completion of the treatment for childhood cancer. Although anthracycline-induced cardiotoxicity is a well recognized, its mechanism of action is not

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completely understood. Anthracycline-induced cardiotoxicity can present as an asymptomatic decline in cardiac function or as clinical heart failure beginning as diastolic dysfunction and progressing to include systolic dysfunction.[1] Subclinical cardiac toxicity can be diagnosed in children with various diagnostic methods (e.g. functional tests, biomarker, magnetic resonance imaging, isotope imaging), demonstrating significant abnormalities related to the heart.[1–4]

Echocardiography is a noninvasive and effective tool in the assessment of anthracycline cardiotoxicity. Echocardiographic parameters that are frequently used for the evaluation of cardiac functions include left ventricular shortening fraction (SF), ejection fraction (EF), left ventricular posterior wall thickening (LVPWt), left ventricular end-systolic wall stress (ESWS), and mitral deceleration time (DT).[3,4] None of these parameters have been proven to be a reliable indicator for early diagnosis of cardiotoxicity. Tissue Doppler imaging (TDI), a novel echocardiographic method used in the diagnosis of anthracycline cardiac toxicity, has been proven to be an effective tool in the assessment of regional systolic and diastolic functions.[5,6] Some derangements in cardiac functions are usually not evident at rest and can be revealed only during exercise. Dobutamine stress echocardiography (DSE) has successfully been used for the diagnosis of subclinical cardiotoxicity.[3,7]

In our study our primary goal is to investigate the presence of subclinical anthracycline cardiotoxicity (defined as echocardiographic abnormalities in asymptomatic patients in comparison to healthy control subjects) using conventional echocardiography, TDI and DSE. Our secondary goal was to investigate the wall motion abnormalities by using DSE study and for this purpose we divided the patients into two groups depending on their wall motion functions and compared the patients with abnormal and normal myocardial wall motion.

Patients

This study included 20 asymptomatic patients who had been treated with anthracycline for childhood cancer. Patients were divided into two groups according to the myocardial wall motion during DSE. Group 1 had normal myocardial wall motion (six girls and five boys, mean age: 18.5 $\pm$ 3.0, mean cumulative dose of anthracycline: 295.5 $\pm$ 90 mg/m^2), and Group 2 had abnormal myocardial wall motion (nine boys, mean age: 18.1 $\pm$ 3.2, mean cumulative dose of anthracycline: 266 $\pm$ 122 mg/m^2). The control group consisted of 18 healthy volunteers (14 boys, 4 girls, mean age: 19.2 $\pm$ 4.0 years). Mean age at the time of diagnosis was 7 $\pm$ 3.8 (median: 6, 4–15) years in Group 1 and 6.5 $\pm$ 3.2 (median: 6.1, 5–14) in Group 2. The follow-up period after completion of anthracycline treatment ranged from 7 to 14 years (mean: 10 $\pm$ 2 years, median: 10 years). Patients received anthracycline treatment doses for a period of 6 h via infusion with the diagnosis of lymphoma, angiosarcoma, hepatoblastoma, rhabdomyosarcoma, Willm's tumour, or ganglioneuroblastoma. One patient received additional mediastinal radiotherapy at nontoxic doses (2000 cyg) in group 2.

Methods

After establishing baseline values at rest by echocardiography, intravenous dobutamine infusion was initiated at a dose of 5 μg/kg/min (D5) and this dose was increased to 10 (D10), 15 (D15) and 20 (D20) μg/kg/min at 5 min intervals. Blood pressure, heart rate, respiratory rate, oxygen saturation, arrhythmia, and clinical symptoms were continuously monitored during the test. Dobutamine infusion was prematurely terminated if any of the following complications occurred: arrhythmia, a sudden increase or decrease in blood pressure and a severe feeling of discomfort. Pulse oximeter, ECG monitor, and a manual blood pressure monitoring device were used for measurements.

Echocardiography

Echocardiographic evaluation was performed by General Electric Vivid 3 Pro equipped with 3 MHz transducer and dedicated software for dobutamine stress test. Myocardial segmental analysis was performed by stress echocardiography as previously described.[8] All patients were examined in supine or left lateral decubitus position. Images were obtained during parasternal short- and long-axis views, apical 2 chamber and apical 4 chamber positions. Assessments of systolic and diastolic functions, TD velocities, and myocardial wall motions were performed both at rest and during dobutamine infusions. Wall motion is graded for each of the 16 segments by examining both endocardial excursion and myocardial thickening during systole using the baseline image as a reference standard. Wall motion is graded in worsening degrees as normal, hypokinetic, akinetic, dyskinetic, aneurysmal, akinetic with scar, or dyskinetic with scar.[8] After obtaining the baseline recordings, continuous dobutamine infusion was initiated at 5 μg/kg/min (D5) and gradually increased to 10 (D10), 15 (D15), and 20 μg/kg/min (D20). Echocardiographic measurements were repeated after each dose increment, if the patient could tolerate the specified dose for 5 min. Three consecutive images were recorded at rest and during dobutamine infusions. At the end of the test these images were evaluated by the same investigators (A.Y. and F.S.T.). Mean values of all measurements were used for statistical analysis. Measurements were performed according to the American Echocardiographic Society guidelines.[9] Peak mitral E and A wave filling velocities were measured according to the method described by Nishimura *et al.*[10] and ESWS was calculated according to the method described by Grossman *et al.*[11] Mitral acceleration time (AT) and the mitral DT were also measured. Left ventricular posterior wall percent thickening was calculated by the following formula: [% LVPWt = 100 $\times$ (LV posterior wall end systolic thickness − LV posterior wall end diastolic thickness)/LV posterior wall end diastolic thickness].[3,9–11] The measurements used in TD studies were annular (Sa) and middle systolic (Sm), early annular, and middle diastolic (é and ém, respectively), late annular and middle diastolic (á and ám respectively), myocardial velocities at the LV and RV free wall and IVS by apical 4 chamber position. TD é/á wave ratios were calculated. Images obtained during stress echocardiography were evaluated for any abnormal movement in the myocardium.

Statistical analysis

Windows SPSS 15.0 computer software was used for the statistical analysis of the data and quantitative values were presented as mean $\pm$ SD, and qualitative values were presented as frequency distribution or percentage. Mann–Whitney *U*-test was used to evaluate the difference between the groups. Spearman's nonparametric correlation test was used to examine the correlation between the cumulative anthracycline dose and all of echocardiographic measurements. A *P*-value <0.05 was considered statistically significant.

Ethics

The study protocol was approved by the local ethical committee. Informed consent was obtained from all participants and/or their guardians.

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Results

There were no significant differences between patient and control groups for age, weight, blood pressure, and heart rate recorded at rest or during dobutamine infusions (*Table 1*, $P > 0.05$). There were no significant differences between both patients groups and the control group at rest except ESWS and DT measured by conventional methods. As the dose of dobutamine was gradually increased, the patients groups demonstrated some abnormalities in EF, SF, LVSd, LVDd, % LVPWt, interventricular septum systolic thickening (IVSSt), and AT values compared with the control group (*Tables 2* and *3*).

Table 1 The measurements of blood pressure and heart rates during dobutamine stress echocardiography, mean ± SD

	Rest	D5	D10	D15	D20
Systolic blood pressure (mmHg)					
Group 1*	108.7 ± 11.0	120.0 ± 15.2	131.1 ± 18.5	142.0 ± 13.0	147.6 ± 13.8
Group 2*	111.2 ± 12.1	126.8 ± 16.9	141.8 ± 18.0	146.8 ± 16.2	149.8 ± 14.6
Control	112.7 ± 10.4	126.0 ± 11.0	139.0 ± 14.7	146.0 ± 14.0	149.5 ± 17.2
Diastolic blood pressure (mmHg)					
Group 1	65.8 ± 7.0	66.2 ± 5.7	70.0 ± 6.2	76.3 ± 9.3	77.2 ± 10.7
Group 2	64.7 ± 10.1	67.9 ± 12.9	69.2 ± 8.4	73.3 ± 8.0	70.5 ± 8.7
Control	66.3 ± 6.5	66.9 ± 9.8	73.0 ± 11.0	72.0 ± 10.0	73.9 ± 11.6
Heart rate (min)					
Group 1	69.4 ± 9.5	79.8 ± 17.0	84.4 ± 18.7	98.9 ± 21.8	117.7 ± 28.4
Group 2	71.7 ± 14.7	81.6 ± 21.1	97.0 ± 13.5	110.0 ± 19.5	121.0 ± 16.1
Control	73.0 ± 11.4	81.0 ± 11.2	93.0 ± 12.0	113.0 ± 15.0	138.7 ± 11.8

*$P > 0.05$: Group 1–Group 2, $P > 0.05$: Group 1–control, $P > 0.05$: Group 2–control.

Table 2 The measurements of left ventricular systolic functions during dobutamine stress echocardiography, mean ± SD

		Rest	D5	D10	D15	D20
EF (%)	Group 1	69.0 ± 2.8	72.7 ± 6.9	72. 8 ± 5.2	72.0 ± 4.6	73.4 ± 6.8
	Group 2	68.7 ± 3.6	71.8 ± 7.8[a]	68.6 ± 11.7[a]	71.4 ± 8.8	68.4 ± 9.6[a]
	Control	71.0 ± 6.5	78.0 ± 15.0	78.2 ± 5.62	77.2 ± 5.5	78.7 ± 5.8
SF (%)	Group 1	38.0 ± 2.5	42.2 ± 6.6	40.2 ± 4.7	41.5 ± 3.9	43.7 ± 8.3
	Group 2	36.5 ± 2.8	41.1 ± 6.2	38.3 ± 9.5[a]	40.8 ± 6.8	37.9 ± 7.7[a]
	Control	39.1 ± 6.1	44.2 ± 5.4	46.2 ± 4.6	45.9 ± 2.5	47.8 ± 5.8
ESWS (g/cm^2)	Group 1	91.0 ± 11.0[b]	93.2 ± 12.6[b]	95.0 ± 14.6[b]	97.6. ± 12.8[b]	99.4 ± 16.5[b]
	Group 2	98.5 ± 12.9[a]	97.5 ± 16.9[a]	101.6 ± 15.3[a]	104.2 ± 13.2[a]	107.8 ± 12.8[a]
	Control	74.7 ± 11.5	73.6 ± 15.5	64.3 ± 12.8	63.1 ± 19.2	62.3 ± 8.5
%LVPWt	Group 1	51.3 ± 12.0	55.0 ± 13.0	50.8 ± 19.3	46.8 ± 14.1	43.4 ± 12.5[b]
	Group 2	53.4 ± 17.8	54.0 ± 16.6	47.8 ± 15.5[a]	49.7 ± 10.0	48.9 ± 13.2[a]
	Control	62.8 ± 16.0	67.9 ± 11.0	66.3 ± 14.8	65.4 ± 17.9	69.6 ± 12.2
IVSSt (mm)	Group 1	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2[b]
	Group 2	1.4 ± 0.1	1.4 ± 0.3	1.5 ± 0.5	1.5 ± 0.3	1.4 ± 0.2[a]
	Control	1.5 ± 0.2	1.5 ± 0.3	1.5 ± 0.2	1.5 ± 0.3	1.7 ± 0.2
LVDd (mm)	Group 1	4.1 ± 0.4	4.2 ± 0.5	4.2 ± 0.8	4.1 ± 0.4	4.2 ± 0.5
	Group 2	4.1 ± 0.8	4.3 ± 4.1	4.4 ± 0.6	4.4 ± 0.8	4.4 ± 0.5[a]
	Control	4.1 ± 0.4	4.1 ± 0.4	4.0 ± 0.4	4.0 ± 0.5	3.9 ± 0.4
LVSd (mm)	Group 1	2.4 ± 0.2	2.4 ± 0.3	2.5 ± 0.3	2.3 ± 0.3	2.4 ± 0.4[b]
	Group 2	2.7 ± 0.4	2.6 ± 0.6	2.7 ± 0.7[a]	2.7 ± 0.8[a]	2.6 ± 0.6[a]
	Control	2.4 ± 0.3	2.4 ± 0.6	2.3 ± 0.3	2.2 ± 0.3	2.0 ± 0.4

EF, ejection fraction; SF, shortening fraction; ESWS, end systolic wall stress; %LVPWt, percent of left ventricle posterior wall thickening; IVSSt, interventricular septum systolic thickening; LVDd, left ventricle diastolic diameter; LVSd, left ventricle systolic diameter.
[a]Group 2–control, $P < 0.05$.
[b]Group 1–control, $P < 0.05$.

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Table 3 The measurements of diastolic functions during dobutamine stress echocardiography, mean ± SD

		Rest	D5	D10	D15	D20
ME (m/s)	Group 1	1.1 ± 0.1	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.2	1.4 ± 0.2
	Group 2	1.0 ± 0.2	1.3 ± 0.2	1.2 ± 0.3	1.3 ± 0.2	1.4 ± 0.3
	Control	1.1 ± 0.1	1.2 ± 0.2	1.3 ± 1.7	1.3 ± 0.2	1.4 ± 0.1
MA (m/s)	Group 1	0.6 ± 0.1	0.6 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	1.0 ± 0.3
	Group 2	0.6 ± 0.1	0.7 ± 0.2	0.7 ± 0.1	0.9 ± 0.1	1.0 ± 0.3
	Control	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.2
M E/A	Group 1	1.6 ± 0.1	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.6	1.5 ± 0.4
	Group 2	1.6 ± 0.4	1.7 ± 0.5	1.7 ± 0.4	1.6 ± 0.6	1.5 ± 0.4
	Control	1.6 ± 0.3	1.7 ± 0.3	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2
AT (s)	Group 1	57.0 ± 20.5	64.0 ± 18.8	64.0 ± 12.8[a]	66.5 ± 14.2[a]	61.6 ± 15.6[a]
	Group 2	61.0 ± 17.7	67.9 ± 16.6	67.2 ± 18.0[b]	69.2 ± 10.0[b]	69.6 ± 2.1[b]
	Control	61.0 ± 15.0	56.0 ± 13.0	53.0 ± 15.0	53.0 ± 10	47.0 ± 10.3
DT (s)	Group 1	131.0 ± 15.0[a]	128.5 ± 19.6[a]	124.6 ± 15.8[a]	115.1 ± 11.7[a]	110.6 ± 12.7[a]
	Group 2	132.4 ± 12.9[b]	129.1 ± 18.4[b]	128.3 ± 12.2[b]	117.4 ± 17.1[b]	111.0 ± 19.8[b]
	Control	109.0 ± 11.0	105.3 ± 13.0	96.3 ± 18.0	84.1 ± 14.6	75.6 ± 16.0
T E (m/s)	Group 1	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.3
	Group 2	0.8 ± 0.1	0.9 ± 0.2	0.8 ± 0.1	1.1 ± 0.2	1.1 ± 0.1
	Control	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.2	1.0 ± 0.1	1.2 ± 0.2
T A (m/s)	Group 1	0.5 ± 0.1	0.6 ± 0.1	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
	Group 2	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.9 ± 0.4	0.8 ± 0.2
	Control	0.6 ± 0.1	0.7 ± 0.2	0.7 ± 0.1	0.9 ± 0.3	0.9 ± 0.3
T E/A	Group 1	1.5 ± 0.7	1.4 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.4
	Group 2	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	1.2 ± 0.3
	Control	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.2	1.4 ± 0.3	1.3 ± 0.3

AT, acceleration time; DT, deceleration time.
[a]Group 1–control, $P < 0.05$.
[b]Group 2–control, $P < 0.05$.

TD velocities of IVS

There were no significant differences between the three groups for IVS Sa velocity during the test; however, both patient groups demonstrated lower IVS Sm velocities compared with control group at rest and at the end of the test ($P > 0.05$). In Group 2, the IVS é velocities were lower at rest and during dobutamine infusion compared with other groups, and the IVS á velocity was higher compared with control group both at rest and at the end of the test. In Group 2, é/á ratio was lower compared with other groups at rest and during the dobutamine infusion, and only ém/ám ratio was lower compared with control group at the end of the test (*Table 4*).

TD velocities of LV

Both patients groups demonstrated lower LV Sa velocities compared with the control group at rest and during dobutamine infusions. LV é, LV é/á, LVSm, LV ém, and LV ém/ám velocities of Group 2 were lower compared with the control group at rest and during the dobutamine infusion (*Table 5*).

TD velocities of RV

In patient groups, RV Sa and Sm velocities were lower compared with the control group at rest, whereas no significant differences were found between the three groups at the end of the test. In Group 2, RV é and RV é/á velocities were lower and RV ám velocities were higher compare with the control group at the end of the test (*Table 6*).

Abnormal myocardial wall motion was determined in nine patients (all of them hypokinetic segments); however, only three of them showed abnormal findings at rest. In the remaining six patients, abnormal myocardial findings were detected at D20. Abnormal wall motion was observed at the IVS in eight of nine patients, and at the LV apex of one patient.

Evaluation of IVS, RV, and LV TD é/á ratios at rest showed é/á <1 in three patients (15%) of Group 1 and in four patients (20%) of Group 2 in annular and middle myocardial segments. These figures were seen in four patients (20%) and seven patients (35%) in the groups, respectively, at the end of the test. Abnormal é/á ratios in Group 2 demonstrated substantially larger differences compared with Group 1 at the end of the test. In the Group 2, abnormal é/á ratio (é/á <1) of RV and IVS were observed at rest and after dobutamine infusion these changes were intensified (*Figures 1, 2 and 3*).

Correlations between anthracycline cumulative dose and TDI velocities at rest and at the end of the test

We observed a strong correlation between cumulative anthracycline dose and RV Am velocities at rest and at the end of the test ($P = 0.04$ $r = 0.47$). RV ám velocities were increased as the

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Table 4 The measurements of TD velocities of IVS (m/s) during dobutamine stress echocardiography, mean ± SD

TDI velocities		Rest	D5	D10	D15	D20
IVS Sa	Group 1	7.5 ± 1.8	9.7 ± 2.4	13.4 ± 2.9	14.5 ± 4.5	15.3 ± 4.6
	Group 2	8.9 ± 1.2	10.7 ± 1.8	12.3 ± 2.5	15.1 ± 2.7	16.4 ± 5.3
	Control	10.1 ± 1.6	11.09 ± 3.3	13.7 ± 2.4	15.4 ± 3.3	16.9 ± 2.6
IVS é	Group 1	14.3 ± 1.5[a]	14.7 ± 1.6[a]	14.7 ± 3.8[a]	14.7 ± 2.8[a]	14.8 ± 3.4[a]
	Group 2	11.8 ± 2.6[b]	12.5 ± 2.4[b]	12.4 ± 3.2[b]	12.4 ± 2.8[b]	12.5 ± 3.2[b]
	Control	15.8 ± 2.4	15.9 ± 2.7	15.2 ± 3.1	16.1 ± 3.2	16.8 ± 2.3
IVS á	Group 1	6.8 ± 0.9[a]	6.9 ± 1.3	8.4 ± 3.1	9.6 ± 4.2	9.4 ± 3.7
	Group 2	7.6 ± 2.0[b]	7.6 ± 2.2	8.3 ± 1.6	9.9 ± 2.0	10.6 ± 2.1[b]
	Control	6.7 ± 1.5	7.2 ± 1.6	7.9 ± 2.1	7.3 ± 2.0	8.3 ± 1.9
IVS é/á	Group 1	2.4 ± 0.6[a]	2.5 ± 0.6[a]	2.5 ± 0.7[a]	2.1 ± 1.0[a]	1.9 ± 0.6[a]
	Group 2	1.6 ± 0.6[b]	1.8 ± 0.6	1.5 ± 0.5[b]	1.2 ± 0.4[b]	1.2 ± 0.7[b]
	Control	2.4 ± 0.6	2.3 ± 0.9	2.3 ± 0.6	2.2 ± 0.7	2.1 ± 0.4
IVS Sm	Group 1	6.0 ± 0.9[c]	8.1 ± 2.4[c]	9.9 ± 4.3	10.7 ± 6.1[c]	11.6 ± 2.5[c]
	Group 2	6.8 ± 1.8[b]	8.3 ± 2.1	9.2 ± 3.8	11.7 ± 3.0[a]	11.9 ± 5.4[a]
	Control	8.5 ± 1.8	9.9 ± 2.1	11.2 ± 3.1	12.2 ± 2.7	14.5 ± 3.3
IVS ém	Group 1	10.7 ± 3.4	12.3 ± 2.6	13.8 ± 5.0	13.8 ± 3.8	12.2 ± 3.5
	Group 2	10.4 ± 3.7	11.6 ± 3.4[b]	11.0 ± 3.6	11.0 ± 3.6	10.5 ± 4.5
	Control	13.7 ± 2.6	14.9 ± 2.7	13.6 ± 2.8	12.4 ± 3.0	12.6 ± 3.2
IVS ám	Group 1	5.9 ± 0.8	6.3 ± 1.1	7.2 ± 2.4	9.1 ± 3.7	8.9 ± 3.6
	Group 2	6.0 ± 1.9	6.2 ± 0.9	7.3 ± 1.7	9.0 ± 6.3	7.4 ± 2.2
	Control	6.2 ± 1.5	6.1 ± 1.5	7.1 ± 1.8	7.9 ± 1.9	8.3 ± 1.5
IVS ém/ám	Group 1	2.1 ± 1.2	2.1 ± 0.9	1.9 ± 0.6	1.6 ± 0.6	1.6 ± 0.7
	Group 2	1.9 ± 0.7	1.9 ± 0.7	1.6 ± 0.8	1.4 ± 0.5[b]	1.5 ± 1.0[b]
	Control	2.3 ± 0.7	2.4 ± 1.1	2.0 ± 0.6	1.9 ± 0.5	1.8 ± 0.4

TDI, TD imaging; IVS, interventricular septum; S, systolic myocardial velocity; é, early diastolic myocardial velocity; á, late diastolic myocardial velocity; a, annular; m, middle.
[a]Group 1–Group 2, $P < 0.05$.
[b]Group 2–control, $P < 0.05$.
[c]Group 1–control, $P < 0.05$.

anthracycline cumulative dose was increased. There was a negative correlation between anthracycline cumulative dose and RV ém/ám ratio, which was determined only at rest ($P = 0.001$, $r = -0.35$). We found a negative correlation between anthracycline cumulative dose RV Sm ($P = 0.004$, $r = -0.46$) and LV é/á ($P = 0.003$ $r = -0.43$) only at the end of the test.

Side effects

Sudden headache and tingling sensation on certain parts of the face developed in one subject of the control group on the fifth minute of dobutamine infusion at the dose of 5 μg/kg/min, which caused premature termination of the test.

Discussion

Nearly 60% of the children with cancer are currently being treated with anthracyclines. Cardiotoxic effects of anthracyclines are the most frequent and serious adverse effects of cancer treatment in children. Pediatric cardiologists have demonstrated subclinical cardiac toxicity among survivors of childhood cancer by echocardiographic findings. In the literature it has been reported that echocardiographic changes can be observed in up to 57% of the patients.[1]

In our study, the most significant finding is the demonstration of the use of TDI and DSE in the detection of subclinical cardiac toxicity. Conventional 2D and M-mode echocardiographic measurements showed no significant differences in echocardiographic parameters of the patients group compared with the control group except for increase of ESWS and prolongation of DT. However, unlike the conventional method, the subclinical cardiac toxicity was demonstrated in 15% of patients by the presence of abnormal myocardial wall motion at rest. Additionally, IVS-RV é/á and ém/ám ratio of <1 at rest was observed in 35% of the patients during TDI measurements. The ventricular elasticity is usually impaired by the loss of myocytes in anthracycline toxicity and this event causes impairment in relaxation and diastolic dysfunction.

Previous DSE studies on long-term survivors treated with anthracycline have shown significant differences in % LVPWt and ESWS values at rest and these abnormalities were intensified during dobutamine infusion. Revelation of latent cardiac dysfunctions following dobutamine infusion (decreased SF, increased ESWS and decreased mitral E/A) have been reported.[3,7,12] In our study, abnormal wall motions were observed in 15% of the patients at rest, this figure raised to 45% by the end of the test. The patient with abnormal myocardial wall motion showed a decline in systolic response to dobutamine stress and their EF and FS were not increased as compared with the control group. At rest, patients groups showed significant differences in only DT and ESWS measurements compared with the control group; however,

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Table 5 The measurements of TD velocities of left ventricle (m/s) during dobutamine stress echocardiography, mean ± SD

TDI velocities		Rest	D5	D10	D15	D20
LV Sa	Group 1	9.4 ± 3.1	12.3 ± 2.8	16.0. ± 5.6[a]	19.7 ± 6.0	18.0 ± 6.3[a]
	Group 2	8.2 ± 2.2[b]	11.3 ± 2.0[b]	15.4 ± 5.5[b]	17.9 ± 4.8	18.7 ± 5.5[b]
	Control	11.8 ± 4.5	15.6 ± 4.8	20.3 ± 5.8	21.1 ± 5.7	24.9 ± 4.7
LV é	Group 1	18.0 ± 4.3	19.9 ± 2.8	21.1 ± 2.7	19.1 ± 4.6	18.4 ± 5.6
	Group 2	16.0 ± 4.3[b]	17.7 ± 5.3[b]	21.0 ± 4.5	19.8 ± 5.0	16.5 ± 4.3[b]
	Control	21.4 ± 3.1	23.4 ± 4.5	21.8 ± 3.6	21.3 ± 3.6	21.1 ± 3.4
LV á	Group 1	6.4 ± 1.9	8.4 ± 3.4	8.8 ± 2.0	9.4 ± 2.5	9.4 ± 4.4
	Group 2	7.2 ± 3.0	6.8 ± 1.8	8.8 ± 2.9	9.6 ± 2.9	11.1 ± 5.3
	Control	6.8 ± 2.1	7.4 ± 2.1	8.5 ± 2.6	10.1 ± 3.0	9.9 ± 2.4
LV é/á	Group 1	2.9 ± 0.8	2.7 ± 1.1	2.4 ± 0.5	2.3 ± 1.2	2.3 ± 1.3
	Group 2	2.7 ± 2.1[b]	2.7 ± 1.2[b]	2.7 ± 1.3	2.2 ± 1.0	1.8 ± 0.8[b]
	Control	3.4 ± 1.2	3.4 ± 1.2	2.8 ± 0.8	2.7 ± 4.4	2.8 ± 0.9
LV Sm	Group 1	8.0 ± 3.0[a]	10.6 ± 2.9[a]	16.7 ± 7.1	19.3 ± 7.1	21.0 ± 8.6
	Group 2	6.4 ± 2.3[b]	10.2 ± 3.2[b]	11.8 ± 4.6[b]	17.7 ± 6.2	16.3 ± 7.5[b]
	Control	12.7 ± 4.1	16.5 ± 6.7	19.6 ± 5.6	22.0 ± 4.4	22.0 ± 3.2
LV ém	Group 1	18.0 ± 5.0	19.9 ± 4.6	19.8 ± 5.9	19.9 ± 6.3	20.4 ± 7.9
	Group 2	13.5 ± 5.4	15.6 ± 5.8[b]	16.2 ± 5.4[b]	16.0 ± 3.4[b]	16.8 ± 4.3[b]
	Control	19.0 ± 2.9	20.6 ± 2.4	20.7 ± 4.5	21.4 ± 4.0	21.8 ± 3.9
LV ám	Group 1	5.7 ± 1.7	6.3 ± 1.8	7.6 ± 2.9	8.1 ± 1.8	7.6 ± 1.6
	Group 2	5.9 ± 2.0	5.9 ± 2.1	6.9 ± 2.6	9.0 ± 3.4	10.3 ± 7.0
	Control	6.0 ± 2.1	6.9 ± 2.0	8.7 ± 2.6	9.2 ± 2.3	8.9 ± 1.9
LV ém/ám	Group 1	3.2 ± 1.1	3.3 ± 1.3	2.7 ± 1.0	2.6 ± 1.2	2.7 ± 1.1
	Group 2	2.5 ± 1.5[b]	2.9 ± 1.5	2.3 ± 1.2	2.1 ± 0.9	1.9 ± 0.7[b]
	Control	3.5 ± 1.2	3.2 ± 1.0	2.9 ± 0.9	2.8 ± 0.7	2.9 ± 0.9

TDI, TD imaging; LV, left ventricle; S, systolic myocardial velocity; é, early diastolic myocardial velocity; á, late diastolic myocardial velocity; a, annuler; m, middle.
[a]Group 1–control, $P < 0.05$.
[c]Group 2–control, $P < 0.05$.

during dobutamine infusion AT, %LVPWt, IVSSt, LVDd, and LVSd (D20) measurements also showed significant differences compared with the control group.

Myocardial damage as a result of myocytes loss results in an abnormal thickening of ventricular wall. Contrary to conventional Doppler echocardiography, TDI measures myocardial tissue velocities, which directly reflect contractile and relaxation properties of myocardium.[13] Therefore, in our study, TDI utilized for early detection of subclinical cardiotoxicity. In the patients groups were demonstrated more significant differences in the systolic and diastolic functions at rest (IVS é, IVS á, IVS é/á, IVS Sm, LVSa, LV é, LV é/á, LVSm, LV ém/ám, RVSa, RV é/á, RVSm). However, some other significant differences in the systolic and diastolic functions appeared after the dobutamine stress test (IVS ém/ám, LVSa, LV E ém, RV é, RV E ém, RV A ám, RV ém/ám). We observed stress response LV and RV systolic function: LVSm (group 1), RVSa and RVSm (group 1, 2). This might be due to the viability of the segment. The severity of anthracycline effects on the myocardium may vary: with low dobutamine doses, we observed viability in the segments but viability deteriorated at high doses (IVS á, group 2; IVS é/á, group 2; IVS Sm, groups 1 and 2, LVSa, groups 1 and 2, LV é–LV é/á, group 2; LVSm, group 2; and LV ém/ám, group2). The increase in the dose of dobutamine of the systolic functions improved however, as the dose increases gradually differences in functions reappear in the following parameters; EF, SF, IVS Sm, LV Sa and LV Sm. The patient groups showed a decline in the response to stress because of myocyte injury and this is attributed to the antracycline cardiotoxicity.

In our study, similar to the study by Stapleton *et al*.,[6] most significant difference was observed at the diastolic functions represented by decreased é and é/á, increased á. Tassan-Mangina *et al*.[14] observed early changes following anthracycline therapy and showed that changes in diastolic LV functions were more significant with decreased é velocities in adults; whereas diastolic changes were more pronounced and they were associated with alteration of systolic functions (LV EF and Sa) in late period after anthracycline therapy.[14]

Abnormal myocardial wall motion may persist after completion of the anthracycline therapy. These regional abnormalities usually recover 6 months after the end of the therapy. However, it has been shown to persist in 20% of the patients.[5,15] In the study of Kaputsa *et al*.[5] no statistically significant difference was observed in IVS systolic and early diastolic velocities between the patients that have regional LV wall motion abnormalities. In contrast to the study by Kaputsa *et al*.[5] we observed wall motion abnormalities by the use of DSE in our study. Abnormal myocardial wall motion was present only at the IVS region in 15% of patients (three patients) at rest whereas, this ratio increased to 45% (five patients in IVS and one patient in LV-free wall) at the end of the test. Although between normal and abnormal myocardial wall motion

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Table 6 The measurements of TD velocities of RV (m/s) during dobutamine stress echocardiography, mean ± SD

TDI velocities		Rest	D5	D10	D15	D20
RV Sa	Group 1	13.0 ± 2.0[a,b]	17.2 ± 2.2[b]	20.9 ± 5.7	24.6 ± 3.9	23.3 ± 2.8
	Group 2	15.0 ± 4.9[c]	17.4 ± 3.1[c]	20.0 ± 6.1	21.0 ± 5.4	21.3 ± 6.3
	Control	18.2 ± 2.3	21.2 ± 2.5	23.3 ± 6.6	24.2 ± 3.5	22.6 ± 4.7
RV é	Group 1	15.7 ± 2.1	18.8 ± 3.1	18.1 ± 4.5	18.2 ± 6.0	19.4 ± 8.6[a]
	Group 2	14.0 ± 5.1[c]	16.9 ± 6.3	16.7 ± 7.3	17.1 ± 8.6[c]	15.8 ± 9.5[c]
	Control	18.1 ± 3.4	18.3 ± 3.6	18.5 ± 4.2	19.9 ± 7.3	19.9 ± 4.6
RV á	Group 1	10.8 ± 3.7	13.6 ± 5.9	17.4 ± 6.0	18.1 ± 9.8	20.1 ± 7.9
	Group 2	12.5 ± 3.0	16.1 ± 3.2	20.6 ± 5.2	20.3 ± 5.5	19.6 ± 6.3
	Control	10.9 ± 4.6	15.1 ± 5.3	17.5 ± 5.3	17.8 ± 6.3	17.3 ± 8.2
RV é/á	Group 1	1.6 ± 0.8[a]	1.7 ± 1.0[a]	1.2 ± 0.5	1.4 ± 1.0[a]	1.3 ± 0.6[a]
	Group 2	1.1 ± 0.5[c]	1.0 ± 0.4[c]	0.8 ± 0.3[c]	0.8 ± 0.4[c]	0.8 ± 0.7[c]
	Control	1.4 ± 1.0	1.4 ± 0.7	1.2 ± 0.5	1.3 ± 0.6	1.3 ± 0.5
RV Sm	Group 1	11.0 ± 1.8[b]	13.5 ± 3.8[b]	16.1 ± 6.0	18.1 ± 4.0	18.5 ± 5.1
	Group 2	11.8 ± 3.6[c]	13.7 ± 3.8[c]	15.7 ± 5.0	16.3 ± 5.6	17.7 ± 9.3
	Control	14.7 ± 3.4	17.9 ± 2.9	17.8 ± 3.1	18.1 ± 5.0	18.5 ± 4.3
RV ém	Group 1	12.4 ± 2.0	13.8 ± 1.5	14.5 ± 3.7	15.7 ± 5.2	15.1 ± 4.4
	Group 2	13.1 ± 4.6	13.9 ± 5.8	13.7 ± 5.4	14.7 ± 5.3	12.0 ± 5.4[c]
	Control	13.1 ± 3.4	14.5 ± 3.5	14.1 ± 3.4	15.1 ± 4.2	16.3 ± 5.6
RV ám	Group 1	9.9 ± 2.9	12.1 ± 4.4	16.0 ± 6.5	17.6 ± 7.2	19.3 ± 8.9
	Group 2	11.5 ± 3.3	13.0 ± 3.8	19.3 ± 5.5[c]	19.4 ± 7.2[c]	20.0 ± 9.2[c]
	Control	10.6 ± 4.4	14.1 ± 4.0	14.4 ± 4.5	15.5 ± 4.2	16.1 ± 8.1
RV ém/ám	Group 1	1.1 ± 0.4	1.3 ± 0.4	1.2 ± 0.5	0.7 ± 0.4	0.9 ± 0.6
	Group 2	1.3 ± 0.4	1.1 ± 0.5	0.7 ± 0.2[c]	0.7 ± 0.3[c]	0.6 ± 0.3[c]
	Control	1.4 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	1.2 ± 0.6	1.4 ± 0.5

TDI, TD imaging; S, systolic myocardial velocity; é, early diastolic myocardial velocity; á, late diastolic myocardial velocity; a, annuler; m, middle.
[a]Group 1–Group 2, $P < 0.05$.
[b]Group 1–control, $P < 0.05$.
[c]Group 2–control, $P < 0.05$.

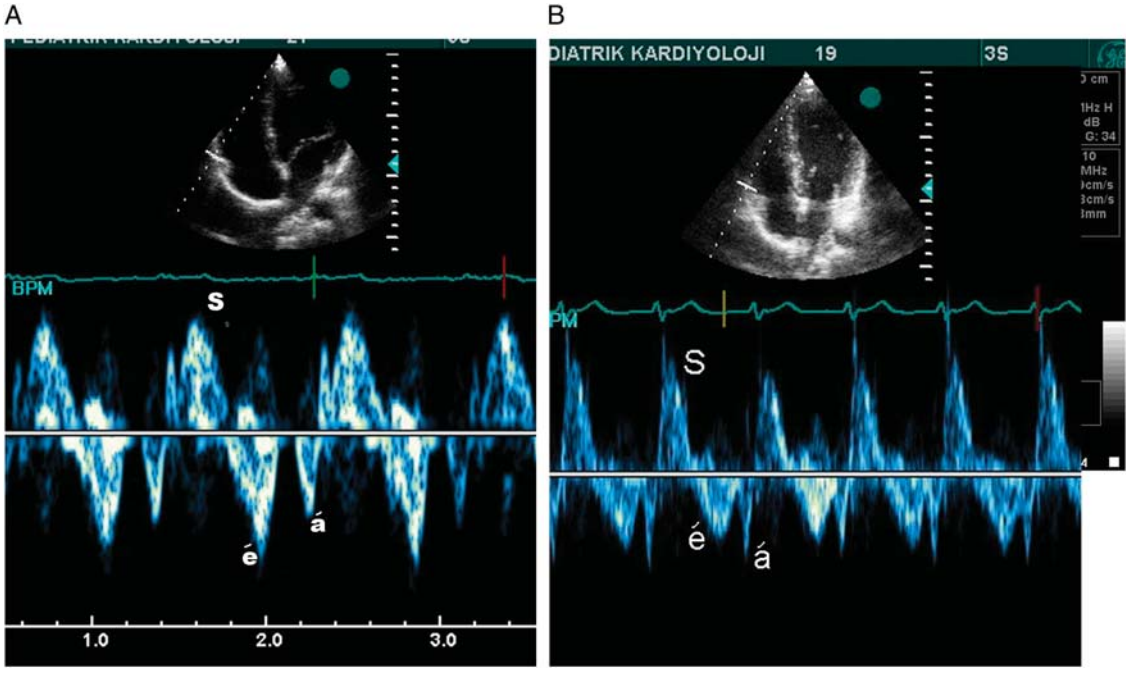


Figure 1 TD RV annular é and á curves: (*A*) at the beginning, é/á >1; (*B*) in D20, é/á <1.

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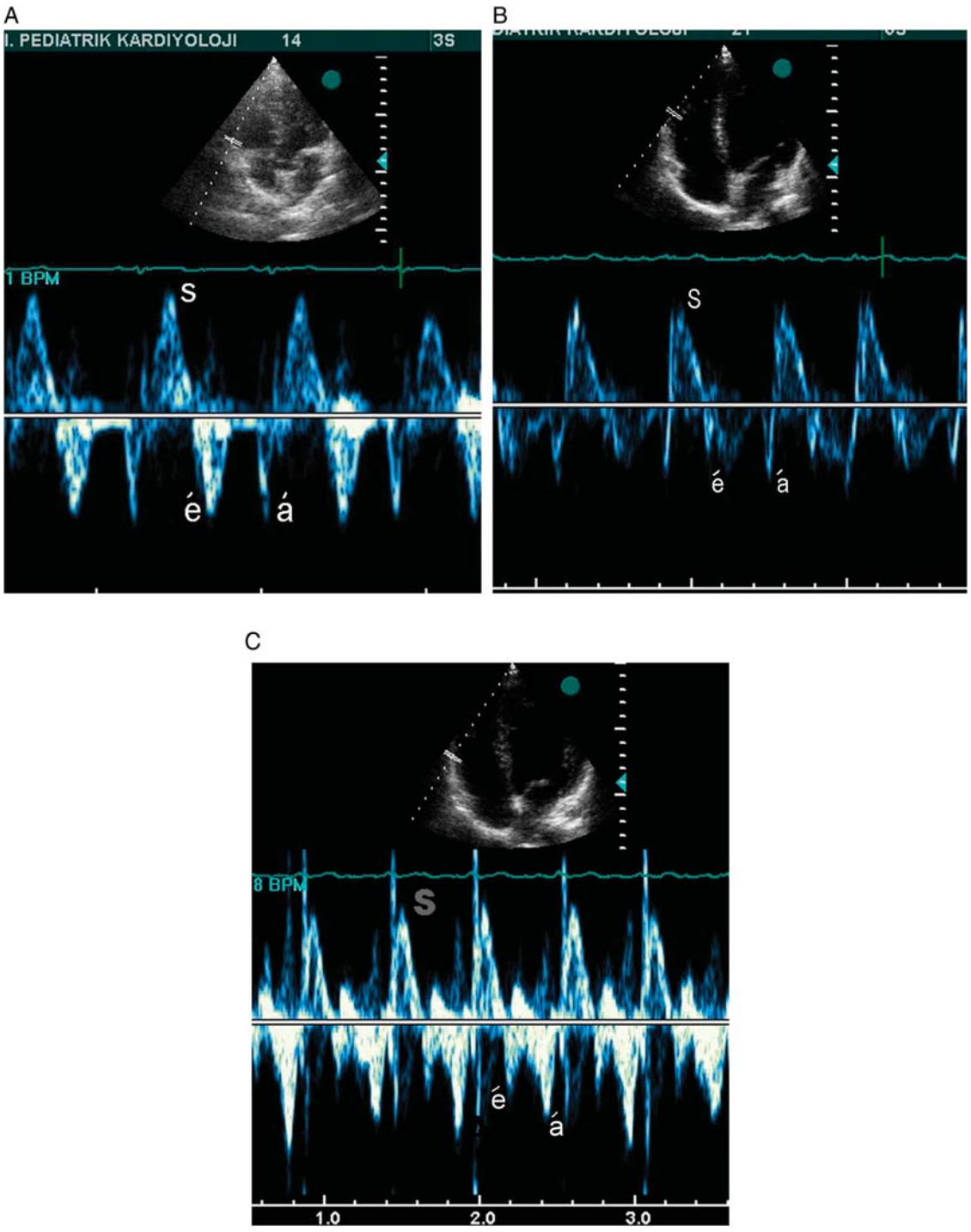


Figure 2 TD RV annular and middle é and á curves: (*A*) at the beginning, é/á = 1; (*B*) at the beginning ém/ám ≤1, C:D20'de ém/ám <1.

groups showed no significant differences for abnormal TDI é/á ratios at rest, abnormal TDI é/á ratios in abnormal myocardial wall motion group were significantly increased towards the end of the test compared with the normal myocardial wall motion group. Patients with abnormal myocardial wall motion demonstrated more significant differences in the diastolic functions compared with patient with normal wall motion during the test.

In our study, we failed to demonstrate any relationship between the cardiac functions assessed by conventional echocardiographic findings and the cumulative anthracycline doses. TDI studies showed that strong correlation between cumulative anthracycline dose and diastolic velocities at rest and during DSE (increased RV ám and decreased RV ém/ám). We found a negative correlation between anthracycline cumulative dose RV Sm and LV é/á only at the end of the test.

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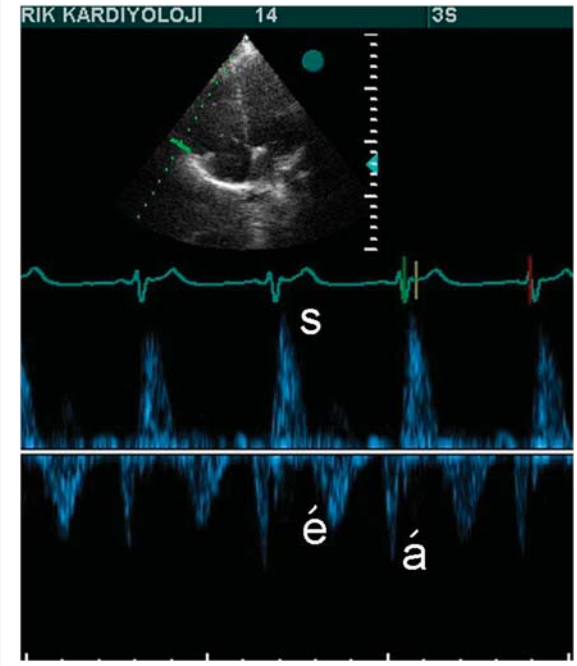


Figure 3 At the beginning of the test: RV middle ém/ám <1.

Anthracyclines have been shown to damage myocytes. Therefore, this study investigated the presence of subclinical anthracycline cardiotoxicity using TD velocities and segmental analysis of myocardial wall motion in addition to other echocardiographic parameters obtained at rest and during dobutamine infusion test. Early diagnosis is encouraged to take necessary measures to increase the quality of life, to arrange the children's daily activities of life and help choosing their profession as well.

Conclusion

Cardiac toxicity observed in many childhood cancer patients that received anthracycline therapy cannot be underestimated. These patients should be periodically evaluated by DSE and TDI studies for the presence of any type of cardiotoxicity. DSE and TD velocities are safe and effective parameters that were found to be useful in detecting subclinical cardiac toxicity. Our findings suggest that systolic and diastolic dysfunctions in LV and IVS by TDI at rest and during dobutamine infusion and RV diastolic dysfunction only dobutamine infusion. During DSE, the evaluation of annular and mid-wall TDI velocities may contribute to the early diagnosis of subclinical cardiotoxicity more than the conventional methods and may be considered as useful markers. In addition, especially the diastolic function deteriorates in patients with TDI é/á <1 and for this reason abnormal wall motion should be investigated during DSE studies for early detection of anthracycline-related cardiotoxicity.

Conflict of interest: none declared.

References

1. Kremer LCM, Caron HN. Anthracycline cardiotoxicity in children. *N Engl J Med* 2004;120–1.
2. Giantris A, Abdurrahman L, Hinkle A, Asselin B, Lipshultz SE. Anthracycline-induced cardiotoxicity in children and young adults. *Crit Rev Oncol/Hematol* 1998;**27**:53–68.
3. Klewer SE, Goldberg SJ, Donnerstein RL, Berg RA, Hutter JJ. Dobutamine stress echocardiography: a sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. *J Am Coll Cardiol* 1992;**19**:394–401.
4. Sorensen K, Levitt GA, Bull C, Dorup I, Sullivan ID. Late anthracycline cardiotoxicity after childhood cancer. *Am Cancer Soc* 2003;**98**:1991–8.
5. Kapusta L, Groot-Loonen J, Thijssen JM, DeGraaf R, Daniels O. Regional cardiac wall motion abnormalities during and shortly after anthracyclines therapy. *Med Pediatr Oncol* 2003;**41**:426–35.
6. Stapleton GE, Stapleton SL, Martinez A, Ayres NA, Kovalchin JP, Bezold LI *et al.* Evaluation of longitudinal ventricular function with tissue doppler echocardiography in children treated with anthracyclines. *J Am Soc Echocardiogr* 2007;**20**:492–7.
7. Hamada H, Ohkubo T, Maeda M, Ogawa S. Evaluation of cardiac reserved function by high-dose dobutamine- stress echocardiography in asymptomatic anthracycline- treated survivors of childhood cancer. *Pediatr Int* 2006;**48**:313–20.
8. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D *et al.* Stress Echocardiography Expert Consensus Statement–Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;**30**:278–89.
9. Shan DJ, Demaria A, Kisslo J, Weyman A. The commitee on M-mod standardization of than American Society of Echocardiography recommendation regarding quantitation in M-mod echocardiography: results of a survey of echocardiographic measurement. *Circulation* 1978;**58**:1072–83.
10. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II. Clinical studies. *Mayo Clin Proc* 1989;**64**:181–204.
11. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975;**56**:56–64.
12. Elbl L, Hrstkova H, Chaloupka V, Novotny J, Michalek J. The evaluation of left ventricular function in childhood cancer survivors by pharmacological stress echocardiography. *Neoplasma* 2003;**50**:191–7.
13. Aranda JM Jr, Weston MW, Puleo JA, Fontanet HL. Effect of loading conditions on myocardial relaxation velocities determined by Doppler tissue imaging in heart transplant recipients. *J Heart Lung Transplant* 1998;**17**:693–7.
14. Tassan-Mangina S, Codorean D, Metivier M, Costa B, Himberlin C, Jouannaud C *et al.* Tissue Dopper imaging and conventional echocardiography after anthracycline treatment in adults; early and late alterations of left ventriculer functions during prospective study. *Eu J Echocardiography* 2006;**7**:141–6.
15. Berry GJ, Jorden M. Pathology of radiation and anthracycline cardiotoxicity. *Pediatr Blood Cancer* 2005;**44**:630–7.

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