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DETECTION OF EARLY ANTHRACYCLINE – INDUCED CARDIOTOXICITY IN CHILDHOOD CANCER WITH DOBUTAMINE STRESS ECHOCARDIOGRAPHY*

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SUMMARY: Lenk MK, Zeybek C, Okutan V, Özcan O, Gökçay E. (Department of Pediatrics, Gülhane Military Medical Academy, Ankara, Turkey). Detection of early anthracycline-induced cardiotoxicity in childhood cancer with dobutamine stress echocardiography. Turk J Pediatr 1998; 40: 373-383.

Asymptomatic long-term survivors of childhood cancer treated with anthracyclines may have latent cardiac dysfunction which is undetected by commonly used echocardiographic methods. A more sensitive echocardiographic screening test, dobutamine stress echocardiography, was performed on 22 patients (mean age 9.10 ± 3.79 years) treated with 75 to 450 mg/m^2 of anthracyclines (mean 210.45 ± 127.34) and results were compared with 22 healthy age-matched control subjects. Echocardiographic Doppler studies were performed after each dobutamine infusion of 0.5, 2.5, 5 and 10 µg/kg/min.

Although left ventricular mass was decreased and end-systolic wall stress increased in the patient group when compared with the control subjects ($p < 0.01$ and $p < 0.05$, respectively), no differences were found between shortening fraction and ejection force in control subjects and patients, at rest and during each dobutamine infusion. A decreased mitral E/A ratio (ratio of early-to-late peak filling velocity) was demonstrated in anthracycline-treated patients only during dobutamine infusion ($p < 0.01$).

Our data showed left ventricular diastolic dysfunction during inotropic stimulation with dobutamine, and suggest that dobutamine stress echocardiography is a useful technique for evaluating the cardiac status of anthracycline-treated patients on a long-term basis.
Key words: dobutamine stress echocardiography, anthracyclines, cardiotoxicity, childhood cancer.

The anthracycline antibiotics (doxorubicin and daunorubicin) are known to be effective cancer chemotherapeutic agents, but their high incidence of cardiac toxicities limits their effective usage. These side effects can occur acutely, during or shortly after treatment; subacutely, within days or weeks of treatment; chronically, manifesting weeks or months after drug administration, usually as a cumulative dose response; or as late sequelae, many years after termination of therapy[1-4]. To date, several noninvasive methods, including radionuclide

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scintigraphic monitoring and echocardiographic determinants of systolic and diastolic function[1-6], and invasive methods, such as endomyocardial biopsy[7], have been used to detect these cardiac toxicities. Dobutamine stress echocardiography was reported to be a useful noninvasive technique as it unmasks the echocardiographic abnormalities that are not detected by rest echocardiography in asymptomatic doxorubicin-treated patients[8].

In this study we report the effects of anthracycline antibiotics on systolic and diastolic cardiac function in 22 patients using dobutamine stress echocardiography.

Material and Methods

Study Subjects: The study group consisted of children previously treated with anthracyclines (daunorubicin and doxorubicin) in the Pediatric Hematology and Oncology Unit, Gülhane Military Medical Academy, for childhood cancers. Control subjects were healthy age-matched volunteers. Excluded from the study were patients with cardiac failure or arrhythmias and those taking cardiac drugs or chemotherapeutic agents other than anthracyclines known to be associated with chronic or late cardiotoxic effects. Written informed consent was obtained from parents before the study. During the study, heart rate and rhythm were monitored with simultaneous electrocardiogram; blood pressure was measured every five minutes by sphygmomanometry. Age, weight, height and body surface area were obtained from every subject before the study.

Echocardiographic Studies: Echocardiograms were recorded using Hewlett-Packard Sonos 2500 Color Doppler ultrasound system with 3.5 and 5 Mhz transducers. Echocardiographic measurements were based on measurement of three consecutive cardiac cycles (averaged) in each subject. Recordings were obtained at the rate of 100 mm/s. A baseline two-dimensional echocardiographic study was performed to rule out structural heart disease. M-mode echocardiograms of the left ventricle from the parasternal long axis were recorded as described previously[9]. Apical four-chamber views that provided good visibility of the mitral annulus and leaflets were obtained by placing subjects in the left lateral decubitus position. Doppler examination of mitral flow velocity was performed with pulsed Doppler technique, with the sample volume positioned at the level of the tips of the mitral valve leaflets to record maximum transvalvar velocities[10]. Doppler flow velocities in the ascending aorta and aortic diameter were obtained from the suprasternal notch to assess systolic ventricular function, using the indices of peak velocity (PkV), acceleration time (AT), ejection time (ET), pre-ejection period (PEP), and velocity time integral (VTI)[11].

Dobutamine Infusion: After baseline values were obtained by resting echocardiography, continuous dobutamine infusion was initiated at 0.5 μg/kg/min and increased to 2.5, 5 and 10 μg/kg/min. To attain sufficient dobutamine

concentration, dobutamine was infused for 15 minutes at each rate before the echocardiographic study[12], and the echocardiogram was performed after the 15th minute, within five minutes. The infusion rate of dobutamine was increased after the completion of the echocardiographic study at each dobutamine dose.

Echocardiographic Measurements: Left ventricular cavity and thickness of interventricular septum and posterior free wall at end-diastole (LVIDd, IVSd, LVPWd) and end-systole (LVIDs, IVSs, LVPWs) were measured in cm according to standards recommended by the American Society of Echocardiography[13]. Left ventricular shortening fraction (FS) was evaluated according to the method of Gutgesell et al.[14] with the equation: FS (%) = LVIDd-LVIDs/LVIDd x 100.

Left ventricular volume at end-diastole (LVEDV) and end-systole (LVESV) were calculated according to the Teichholz method[15] with the equation: $V = (7.0/2.4 + D)(D)^3$.

The ejection fraction (EF) was calculated as the FS by substituting volume-derived data for the pure dimension data using the formula: EF (%) = LVEDV-LVESV/LVEDV x 100.

Left ventricular wall mass (LVWM) was calculated by M-mode echocardiography using the formula described by Devereux et al.[16] and indexed by body surface area[17]: $LVWM = 0.80\ [1.04\ (IVSd + LVPWd + LVIDd)^3-(LVIDd)^3]+0.6$.

Left ventricular posterior wall percent thickening (%LPWT) was calculated by the equation[18]: %LVPWT = (LVPWs-LVPWd)/LVPWd x 100.

Left ventricular end-systolic meridional wall stress (LVESS) was calculated in g/cm^2 according to the method of Grossman et al.[19] by the equation: LVESS = [(1.35)(MBP)(LVIDs)]/[(4)(LVPWs)(1+LVPWs/LVIDs)]. In this equation, 1.35 is the factor to convert pressure to g/cm^2 and MBP (mean blood pressure), as an estimate of end-systolic pressure in mm Hg, was calculated by the equation, MBP = (2 Diastolic BP + Systolic BP)/3.

Left ventricular ejection force (F), expressed in kilodynes, was calculated from aortic velocity curves described by Isaaz et al.[20] using the principles expounded in Newton's second law of motion (force = mass x acceleration). The accelerated blood mass that passed through the aortic cross-section was calculated in grams as M = p x CSA x VTI and mean acceleration in cm/s^2 as Mac = PkV/AT, where M was the mass of blood, p the mass density of blood (1.06 g/cm^3), CSA the cross-sectional aortic area [$\pi/4$ x (aortic annulus diameter)^2], VTI the velocity time integral, PkV the peak velocity during acceleration and AT the acceleration time.

Diastolic Function: For the determination of left ventricular filling dynamics, without making specific correction for the respiratory phase, only maximal velocities were measured in all patilents, which in the steady state should negate such a periodic variable. The following parameters were obtained from the spectral display:

Peak early filling velocity (peak E) and peak late (atrial) filling velocity (peak A) were measured according to the method of Nishimura et al.[21], from which a peak E/A ratio was derived. Mitral acceleration time (AT) was measured from the onset of diastolic flow to peak E, and deceleration time (DT) from peak E to the point where the deceleration velocity crossed baseline. Left ventricular isovolumetric relaxation time (IVRT) was measured from the closure of the aortic valve determined from phonocardiogram to the first upstroke of diastolic mitral flow velocity.

Statistical Analysis : All data are reported as mean values ± SD. Data for the study group are compared with those for the control group by using Student's t test.

Results

Patient data are summarized in Tables I and II. The study group was composed

Table I: Patient Data

Patient No.	Age (Year)	Sex	BSA (m^2)	Diagnosis
1	6.5	F	0.81	ALL
2	15.7	M	1.61	ALL
3	8.5	M	1.09	ALL
4	4.2	F	0.7	ALL
5	5.5	F	0.83	ALL
6	11.08	M	1.38	ALL
7	9.8	M	1.12	ALL
8	11.25	F	1.15	Hodgkin's lymphoma
9	15	M	1.31	Hodgkin's lymphoma
10	9.5	M	1.04	ALL
11	12	F	0.98	Leiomyosarcoma
12	3.08	M	0.7	Neuroblastoma
13	11.1	M	1.18	ALL
14	12.5	M	1.54	Hodgkin's lymphoma
15	10	F	1.16	ALL
16	5.5	M	0.79	Ewing's sarcoma
17	3.6	F	0.62	ALL
18	10.1	F	0.98	ALL
19	6.5	F	0.79	ALL
20	3.5	F	0.66	Wilms's tumor
21	13.5	F	1.1	Osteosarcoma
22	12	M	1.28	Osteosarcoma
Mean ± SD	9.10 ± 3.79	1.03 ± 0.28		

ALL: acute lymphoblastic leukemia, BSA: body surface area, F: female, M: male.

Table II: Patient Data (Continued)

Pt No.	Anthracyclines (Total Dose mg/m²)			Age During Rx (Year)	Duration of Rx (Year)	Time Since Rx (Year)
	Doxorubicin	Daunorubicin	Total			
1	–	75	75	2	1.83	2.67
2	75	–	75	12	2.5	1.2
3	–	75	75	6	1.66	0.84
4	–	75	75	1.5	2.58	0.12
5	75	–	75	2	2.66	0.84
6	90	–	90	2	1.08	8
7	90	–	90	4	2.91	2.89
8	160	–	160	8	0.08	3.17
9	160	–	160	11	1.08	2.92
10	–	170	170	4	3.66	1.84
11	180	–	180	10	0.16	1.84
12	–	180	180	2	0.5	0.58
13	120	120	240	10	0.5	0.6
14	240	–	240	9	0.41	3.09
15	120	120	240	9	0.5	0.5
16	240	–	240	3	0.83	1.67
16	240	–	240	3	0.83	1.67
17	120	120	240	2	0.58	1.02
18	90	200	290	3	7.08	0.02
19	295	120	415	2	2.25	2.25
20	420	–	420	2	0.75	0.75
21	450	–	450	11	0.83	1.67
22	450	–	450	11	0.75	0.25

Pt: patient, Rx: therapy.

of 22 patients (11 boys, 11 girls) aged 3.08 to 15.7 years (mean 9.10 ± 3.79, median 9.9), who had been previously treated with anthracycline group antibiotics. Seventeen patients received doxorubicin therapy at a mean cumulative dose of 198.52 ± 131.32 mg/m² (range 75 to 450) and 10 patients daunorubicin at a mean cumulative dose of 125.5 ± 45.05 mg/m² (range 75 to 200). Five patients received both doxorubicin and daunorubicin. The total mean cumulative dose of anthracyclines was 210.45 ± 127.34 mg/m² (range 75 to 450, median 180). The time elapsed since the last dose of therapy ranged from 0.02 to eight years (mean 1.76 ± 1.72, median 1.43). The control group consisted of 22 healthy subjects (13 boys, 9 girls) aged four to 16 years (mean 9.13 ± 3.88). Mean weight was 30.75 ± 11.91 kg for the study group and 31.31 ± 13.43 kg for the control group. Mean body surface area was 1.03 ± 0.28 m² for the study group and 1.05 ± 31 m² for the control group. Age,

weight and body surface area were not significantly different between the patient and control groups. No arrhythmia or symptoms were observed with the increasing infusion rates of dobutamine in any study or control subject.

The mean difference in left ventricular posterior wall end-systolic and end-diastolic dimensions between anthracycline-treated patients and control subjects was only 0.2 and 0.03 cm, respectively, at rest and during each dobutamine infusion (Table III). Though individual changes in percent left ventricular posterior wall thickening from baseline to lower doses of dobutamine infusion (0.5 and 2.5 µg/kg/min) were decreased in patient group when compared with changes in control subjects, the difference in the mean percent left ventricular posterior wall thickening between the two groups was not significant ($p > 0.05$) (Table IV). However, a significant reduction in left ventricular myocardial muscle mass was seen in the patient group ($p < 0.01$) (Table III). The mean left ventricular shortening fraction and ejection force were not different between the patient and control groups at rest and at each dobutamine infusion. Mean end-systolic wall stress was significantly higher at rest and during each dobutamine infusion in the patient group when compared with mean values in the control group ($p < 0.05$) (Table IV). Early (mitral E) and late (mitral A) peak filling velocities in the anthracycline-treated subjects were not different from that in control subjects at rest but demonstrated significantly greater amplitudes compared with those of control subjects during each dobutamine infusion ($p < 0.05$ and $p < 0.01$, respectively) (Table V). The mean mitral E to mitral A ratio was significantly different between the study and control groups only during dobutamine infusion ($p < 0.01$). Although left ventricular isovolumetric relaxation time did not differ significantly between the study and control subjects at rest and at 0.5 µg/kg/min infusion rate of dobutamine, it was significantly decreased in the patient group at 2.5, 5 and 10 µg/kg/min infusion rates of dobutamine ($p < 0.05$).

Table III: Left Ventricular Dimensions and Wall Mass

Dobutamine Dose	LVIDd (cm)	LVPWd (cm)	LVIDs (cm)	LVPWs (cm)	LVM (g)	LVMI (g/m²)
Baseline						
Patient	3.85 ± 0.54	0.47 ± 0.20	2.44 ± 0.44	0.88 ± 0.20	50.20 ± 29.05*	46.34 ± 16.53
Control	4.26 ± 0.38	0.50 ± 0.09	2.21 ± 0.11	1.08 ± 0.12	79.60 ± 23.34	76.53 ± 6.41
0.5 µg/kg/min						
Patient	3.84 ± 0.58	0.46 ± 0.18	2.39 ± 0.47	0.91 ± 0.17	49.44 ± 26.18*	46.26 ± 15.08
Control	4.28 ± 0.31	0.51 ± 0.08	2.52 ± 0.16	1.11 ± 0.10	80.54 ± 20.90	78.22 ± 7.33
2.5 µg/kg/min						
Patient	3.88 ± 0.56	0.48 ± 0.20	2.33 ± 0.55	0.88 ± 0.26	48.55 ± 26.95*	45.22 ± 16.74
Control	4.2 ± 0.29	0.56 ± 0.09	2.49 ± 0.18	1.15 ± 0.09	81.62 ± 20.27	79.52 ± 6.98
5 µg/kg/min						
Patient	3.92 ± 0.51	0.48 ± 0.28	2.23 ± 0.45	0.94 ± 0.22	50.38 ± 32.52*	45.90 ± 16.53
Control	4.11 ± 0.35	0.54 ± 0.08	2.45 ± 0.16	1.21 ± 0.06	77.81 ± 20.67	75.63 ± 8.49
10 µg/kg/min						
Patient	3.92 ± 0.58	0.51 ± 0.25	2.26 ± 0.50	0.99 ± 0.23	51.32 ± 27.75*	47.72 ± 14.22
Control	4.33 ± 0.31	0.58 ± 0.08	2.27 ± 0.15	1.26 ± 0.06	87.24 ± 20.67	85.23 ± 7.86

LVIDd: left ventricular end-diastolic dimension, LVPWd: left ventricular end-diastolic posterior wall thickness, LVIDs: left ventricular end-systolic dimension, LVPWs: left ventricular end-systolic posterior wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass index. *$p < 0.01$ relative to values in control subjects.

Table IV: Systolic Function

Dobutamine Dose	EF (%)	FS (%)	% LVPWT	LVESS (g/cm²)	Ejection Force (Kilodynes)
Baseline					
Patient	66.95 ± 7.12	36.68 ± 5.43	101.22 ± 68.96	58.18 ± 20.55*	24.65 ± 13.65
Control	79.37 ± 3.82	37.42 ± 0.42	121.79 ± 47.40	37.69 ± 7.81	24.98 ± 13.45
0.5 µg/kg/min					
Patient	67.86 ± 8.93	35.76 ± 7.53	110.00 ± 46.73	52.68 ± 17.63*	31.19 ± 19.76
Control	71.67 ± 4.95	36.89 ± 3.47	122.87 ± 42.75	42.96 ± 8.52	31.01 ± 19.25
2.5 µg/kg/min					
Patient	70.65 ± 10.2	34.07 ± 7.94	92.99 ± 49.70	58.63 ± 35.93*	33.09 ± 16.06
Control	71.33 ± 5.39	36.04 ± 3.24	108.30 ± 37.27	40.18 ± 6.11	33.98 ± 18.55
5 µg/kg/min					
Patient	74.63 ± 6.49	33.19 ± 5.57	126.69 ± 87.26	47.78 ± 15.99*	42.29 ± 19.86
Control	71.12 ± 5.15	35.21 ± 0.38	125.52 ± 35.57	36.82 ± 5.90	44.86 ± 20.93
10 µg/kg/min					
Patient	73.61 ± 9.03	36.53 ± 7.41	119.84 ± 90.18	47.68 ± 23.39*	43.04 ± 20.38
Control	78.78 ± 3.88	38.07 ± 3.40	121.38 ± 34.38	31.73 ± 5.87	44.59 ± 20.83

EF: ejection fraction, FS: shortening fraction, %LPWT: percent left ventricular posterior wall thickening, LVESS: left ventricular end-systolic wall stress. * $p < 0.05$ relative to values in control subjects.

Table V: Diastolic Function

Dobutamine Dose	Peak E (cm/s)	Peak A (cm/s)	E/A ratio	IVRT (ms)	DT (ms)
Baseline					
Patient	84.79 ± 12.35	45.82 ± 4.27	1.85 ± 0.25	49.31 ± 21.45	88.40 ± 24.70
Control	81.68 ± 9.95	43.50 ± 5.20	1.88 ± 0.15	50.81 ± 13.99	91.81 ± 23.65
0.5 µg/kg/min					
Patient	90.90 ± 13.15*	62.81 ± 14.29†	1.52 ± 0.44†	52.27 ± 24.23	92.50 ± 26.53
Control	82.36 ± 10.33	41.04 ± 5.26	2.00 ± 0.05	51.54 ± 13.95	95.81 ± 25.93
2.5 µg/kg/min					
Patient	94.10 ± 12.85*	65.73 ± 16.12†	1.50 ± 0.37†	39.75 ± 27.31*	99.31 ± 33.46
Control	82.81 ± 7.98	41.04 ± 3.99	2.01 ± 0.04	49.13 ± 9.98	102.36 ± 33.12
5 µg/kg/min					
Patient	97.20 ± 16.57*	64.40 ± 16.17†	1.58 ± 0.40†	30.90 ± 21.58*	92.04 ± 29.94
Control	84.90 ± 6.61	43.59 ± 5.03	1.96 ± 0.15	46.45 ± 9.73	99.09 ± 29.32
10 µg/kg/min					
Patient	100.37 ± 14.50*	62.75 ± 18.74†	1.71 ± 0.45†	23.00 ± 16.09*	99.09 ± 31.07
Control	91.31 ± 6.64	45.09 ± 3.32	2.02 ± 0.10	45.86 ± 13.70	102.81 ± 30.56

Peak E: peak early filling velocity, Peak A: peak late (atrial) filling velocity, E/A ratio: ratio of early-to-peak filling velocity, IVRT: isovolumetric relaxation time, DT: deceleration time. *$p < 0.05$ and †$p < 0.01$ relative to values in control subjects.

Discussion

The anthracyclines, doxorubicin and daunorubicin, are well-known cancer chemotherapeutic agents with their high incidence of cardiac toxicities[1,2]. The most prominent toxic effect occurs as a cardiomyopathy, resulting from chronic, cumulative, dose-related myocardial injury as demonstrated by abnormal endomyocardial biopsy findings[7]. Endomyocardial biopsy studies have demonstrated histologic changes in almost all patients who had received a total dose of ≥ 240 mg/m^2 of doxorubicin, and histologic damage was reported to be directly proportional to the total cumulative dose of doxorubicin between doses of 100 and 600 mg/m^2[2,22]. However, in accordance with the significant variability in the degree of morphologic changes, severe damage has been reported with cumulative doses as low as 45 mg/m^2. It has also been reported that cardiac

function is not impaired in proportion to the degree of histologic damage, indicating that a critical threshold of myocyte injury is necessary before cardiac function becomes abnormal[22].

The global indices of systolic left ventricular function with echocardiography derived either from M-mode measurements (the left ventricular ejection and shortening fraction), or from the aortic velocity curves. Show that ejection force generally decrease with higher levels of anthracycline doses. Bu'Lock et al.[4] reported that patilents with a shortening fraction < 30 percent at any stage, < 32 percent at > 200 mg/m^2, or those with a fall in shortening fraction of > 2-3 absolute percent per 100 mg/m^2 would have appeared to be at increased risk of significant cardiotoxicity. However, they are reported to be in the normal range unless cardiotoxicity is severe[23]. Although eight of our 22 study patients had a shortening fraction < 30 percent at > 200 mg/m^2, in general they were in normal levels at rest and during each dobutamine infusion. Left ventricular end-systolic wall stress, which better reflects the inotropic state of the myocardium by taking the loading conditions into account, increases in doxorubicin-treated patients[1]. We found this index increased in the study group, at rest and during dobutamine infusion, but the levels were not as high as seen in congestive heart failure secondary to cardiomyopathies[24].

Lipshultz et al.[1] hypothesized that in younger patients, cardiac afterload was more adversely affected by doxorubicin because more myocardial growth is required for young children to reach adult proportions. Furthermore, loss of cardiac myocytes during doxorubicin therapy in childhood might result in inadequate left ventricular mass and clinically important heart disease in later years. The results of our study were consistent with this work confirming the finding of reduced myocardial mass in relation to body surface area in our anthracycline-treated patients.

The reduction in muscle mass may be considered as a pattern of cardiac dysfunction. As a result of reduced muscle mass, left ventricular wall stress significantly increases. Individual changes in left ventricular end-systolic wall stress from baseline to 10 µg/kg/min dobutamine infusion were accompanied by a reduction in myocardial muscle mass in our study group. Our patients can be considered to be in a compensated state before the evident cardiac dysfunction.

Changes in left ventricular diastolic function with normal systolic indexes have been reported in anthracycline-treated patients and prolonged isovolumetric relaxation time and decreased mitral E/A ratio have been shown[5]. Our results of diastolic function demonstrated augmented early and late filling velocity during dobutamine infusion. The decreased early-to-late filling ratio during dobutamine infusion in anthracycline-treated patients when compared to the ratio in control subjects shows diastolic dysfunction in the patient group with dobutamine stress echocardiography.

Congestive heart failure, ventricular tachycardia and sudden death occurring more than five years after doxorubicin treatment have been reported[25]. Recent reports have focused on sex and the dosage of doxorubicin before limiting the cumulative dose of the agent. In children, girls especially were reported to have a greater susceptibility to anthracycline-induced cardiotoxicity[26]. More than 40 percent of patients with significant abnormalities of cardiac function ≥ 15 years after anthracycline treatment has been reported[27]. A more intensive evaluation has identified abnormal cardiac function in up to 74 percent of patients at a mean length of follow-up of only seven years[1] and with dobutamine stress echocardiography at a mean follow-up of only 6.1 ± 3.6 years[8].

Dobutamine is a short-acting $beta_1$ agonist with primarily inotropic action at low doses and seems an ideal drug for evaluating cardioselective responses to catecholamines. Dobutamine stress echocardiography is reported to be a new methodology used to identify early anthracycline toxicity[8]. With this technique, we found the diastolic function minimally affected. Systolic function was preserved in our study populatilon, and they had no clinical manifestations.

The authors could not comment on the suitability of this test for younger cancer patients in a previous study[8], as the youngest study subject was reported as nine years old and as 10 μg/kg/min infusion rate of dobutamine is associated with a high incidence (50%) of adverse effects. In our study, we applied dobutamine to children with a mean age of 9.1 ± 3.79 years, with the youngest being three years old, at 10 μg/kg/min dose for 15 minutes without observing any adverse effects.

Our investigation had an important limitation. As we do not have an extented follow-up time, we cannot derive clearly significant clinical implications from the echocardiographic findings. We believe that future evaluation of the clinical status of these patients is necessary.

Asymptomatic anthracycline-treated cancer patients may have cardiac dysfunction undetected by commonly used rest echocardiography. Left ventricular systolic function was preserved in our patient group. Mitral E, mitral A and E/A ratio were abnormal only during inotropic stimulation by dobutamine in our asymptomatic anthracycline-treated patients. Our data suggest that dobutamine stress echocardiography is a useful technique for monitoring the cardiac functions of these patients in the follow-up period.

REFERENCES

1. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 324: 808-815.

2. Leandro J, Dyck J, Poppe D, et al. Cardiac dysfunction late after cardiotoxic therapy for childhood cancer. Am J Cardiol 1994; 74: 1152-1156

3. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6-19 years after anthracycline therapy: a series of 15 patients. Med Pediatr Oncol 1995; 24: 352-361.
4. Bu'Lock FA, Mott MG, Oakhill A, Martin RP. Early identification of anthracycline cardiomyopathy: possibilities and implications. Arch Dis Child 1996; 75: 416-422.
5. Marchandise B, Schroeder E, Bosly A, et al. Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J 1989; 118: 92-98.
6. Stashun AM, Goldsmith SJ, Horowitz SF. Gated blood pool scintigraphic monitoring of doxorubicin cardiomyopathy: comparison of cancer and computerized probe results in 101 patients. J Am Coll Cardiol 1986; 8: 1082-1087.
7. Friedman MA, Bozdeck MJ, Bilingham ME, Rider AK. Doxorubicin cardiotoxicity: serial endomyocardial biopsies and systolic time intervals. JAMA 1978; 240: 1603-1606.
8. Klewer SE, Goldberg SJ, Donnerstein RL, Berg RA, Hutter JJ Jr. 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.
9. Sahn DJ, De dMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072-1083.
10. Courtois M, Kovács SJ Jr, Lindbrook PA. Transmitral pressure flow velocity relations. Importance of regional pressure gradients in the left ventricle during diastole. Circulation 1988; 78: 661-671.
11. Sabbah HN, Khaja F, Brymer JF, et al. Noninvasive evaluation of the ventricular performance based on peak aortic blood acceleration measured with a continuous-wave Doppler velocity meter. Circulation 1986; 74: 323-329.
12. Padbury JF, Habib DM, Martinez AM. Thresholds for the physiologic effects of adrenergic agents: a methodologic appraisal. Dev Pharmacol Ther 1990; 14: 115-124.
13. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation 1980; 62: 1054-1061.
14. Gutgesell HP, Paguet M, Duff DF, McNamara DG. Evaluation of left ventricular size and function by echocardiography: results in normal children. Circulation 1977; 56: 457-462.
15. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976; 37: 7-11.
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450-458.
17. Daniels R, Meyer RA, Liang Y, Bove KE. Echocardiographically determined left ventricular mass index in normal children, adolescents and young adults. J Am Coll Cardiol 1988; 12: 703-708.
18. Henry WL, Ware J, Gardin JM, Hepner SI, McKay J, Weiner M. Echocardiographic measurements in normal subjects: growth-related changes that occur between infancy and early adulthood. Circulation 1978; 57: 278-285.
19. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975; 56: 56-64.
20. Isaaz K, Ethevenot G, Admant P, Brembilla B, Pernot C. A new Doppler method of assessing left ventricular ejection force in chronic congestive heart failure. Am J Cardiol 1989; 64: 81-87.
21. 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.

22. Bristow MR, Mason JW, Bilingham ME, Daniels JR. Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. Ann Intern Med 1978; 88: 168-175.

23. Hutter JJ Jr, Sahn DJ, Woolfenden JM, Carnahan Y. Evaluation of the cardiac effects of doxorubicin by serial echocardiography. Am J Dis Child 1981; 135: 653-657.

24. Borrow KM, Green LH, Grossman W, Braunwald E. Left ventricular end-systolic stress-shortening and stress-length relatilons in humans. Normal values and sensitivity to inotropic state. Am J Cardiol 1982; 50: 1301-1308.

25. Goorin AM,m Chauvent AR, Perez-Atayde AR, Cruz J, McKone R, Lipshultz SE. Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. J Pediatr 1990; 116: 144-147.

26. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995; 332: 1738-1743.

27. Steinherz LJ, Steinherz PG, Sklar C, Wollner N, Tan C. Cardiac status of 42 patients ≥15 years post anthracy therapy. Med Pediatr Oncol 1994; 23: 176.