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Evaluation of the Left Ventricular Function with Tissue Tracking and Tissue Doppler Echocardiography in Pediatric Malignancy Survivors after Anthracycline Therapy

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Although the anthracyclines have gained widespread use in the treatment of childhood hematological malignancies and solid tumors, cardiotoxicity is the major limiting factor in the use of anthracyclines. The aim of this study was to assess the mitral annular displacement by tissue tracking in pediatric malignancy survivors who had been treated with anthracycline groups chemotheraphy and compare with the tissue Doppler and conventional two dimensional measurements and Doppler indices. In this study, 32 pediatric malignancy survivors and 22 healthy children were assessed with 2D, colour-coded echocardiography. Left ventricular ejection fraction, fractional shortening, stroke volume, cardiac output, cardiac index and diastolic functions were measured. All subjects were assessed with tissue Doppler echocardiography, mitral annular displacements, and also with tissue tracking method. We detected that peak velocity of the early rapid filling on tissue Doppler (E′) was lower ($p < 0.05$) and the ratio of early peak velocity of rapid filling on pulse Doppler to tissue Doppler (E/E′) values were statistically higher in patient group than control group ($p < 0.05$). Myocardial performance index values were also higher in patient group than the control group ($p < 0.01$). It appears that MPI is a useful echocardiograghic method than tissue tracking of mitral annular displacement in patients with pediatric cancer survivors who had subclinical diastolic dysfunction. (ECHOCARDIOGRAPHY, Volume 25, September 2008)

anthracycline cardiotoxicity, tissue Doppler, tissue tracking, myocardial performance index

Although anthracyclines have gained widespread use in the treatment of childhood hematological malignancies and solid tumors, cardiotoxicity is a limiting factor in the use of anthracyclines.[1] Studies of long-term pediatric survivors have shown that the incidence of cardiotoxicity increases with time.[2]

The assessment of the diastolic function by Doppler echocardiography or radionuclide angiocardiography may help to detect early myocardial damage, but these functional approaches have inherent limitations in sensitivity. Several of the conventional echocardiography methods are time-consuming and their use may be limited in setting of poor endocardial visibility.

Myocardial performance index (MPI) and tissue tracking are relatively new echocardiographic modalities. MPI, a recently proposed index that evaluates the combined ventricular systolic and diastolic functions, is defined as the ratio of the sum of isovolumic relaxation time and isovolumic contraction time, over the ejection time. Changes in MPI values occur before changes in other conventional measures of left ventricular systolic and diastolic functions and appear to be a more sensitive noninvasive technique for detecting subclinical anthracycline cardiotoxicity.[3,4]

Tissue tracking is a new echocardiographic modality based on tissue Doppler imaging. It allows rapid visual assessment of the systolic basoapical displacement of each myocardial segment in apical views by a graded

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color display.[5] Tissue tracking and strain rate echocardiography are proposed as highly sensitive tools for monitoring anthracycline cardiotoxicity.[6]

The aim of this study was to assess the mitral annular displacement by tissue tracking in patients who had been treated with anthracyclines and compare the results with the tissue Doppler and conventional two-dimensional measurements and Doppler indices.

Materials and Methods

There were 54 people studied in this analysis: 32 pediatric malignancy survivors after anthracycline therapy (15 males, 17 females) and 22 healthy children (13 males, 9 females). Patients who had structural heart disease and rhythm disturbances were excluded. All patients and healthy children had a normal sinus rhythm. Medical history, age, weight, height measurements were obtained from all observed persons. Total daunorobicine, adriamycine, amsacrine, and mitoxantrone doses were calculated.

M-Mode and Two-Dimensional Echocardiography

Patients and healthy children were assessed with 2D and color coded echocardiography (Vivid Pro 7, GE). Systolic and diastolic left ventricular dimensions were measured from the long-axis view at the level of papillary muscle. Left ventricular ejection fraction and fractional shortening were calculated with Teicholz's formula by using the M-mode echocardiography. Ejection fraction above 55% was considered normal. Stroke volume and cardiac output were also measured for each subject. The cardiac index was calculated as cardiac output/ body surface area for each subject.

Doppler Measurements

The peak velocity of the early rapid filling (E), peak velocity of the late filling (A), and the E/A ratio were measured by using pulsed wave Doppler techniques. The sample volume was placed at the tip of the mitral leaflet from the apical four-chamber views. Deceleration time (DT) was measured as the interval from the peak of the E velocity to its extrapolation to baseline. After that, the Doppler sample volume was placed below the aortic valve from the parasternal long axis and then izovolumic relaxation time was measured. Tissue Doppler imaging was obtained with the sample volume placed at the lateral corner of the mitral annulus from the apical four-chamber view. The wall filter settings were adjusted to exclude

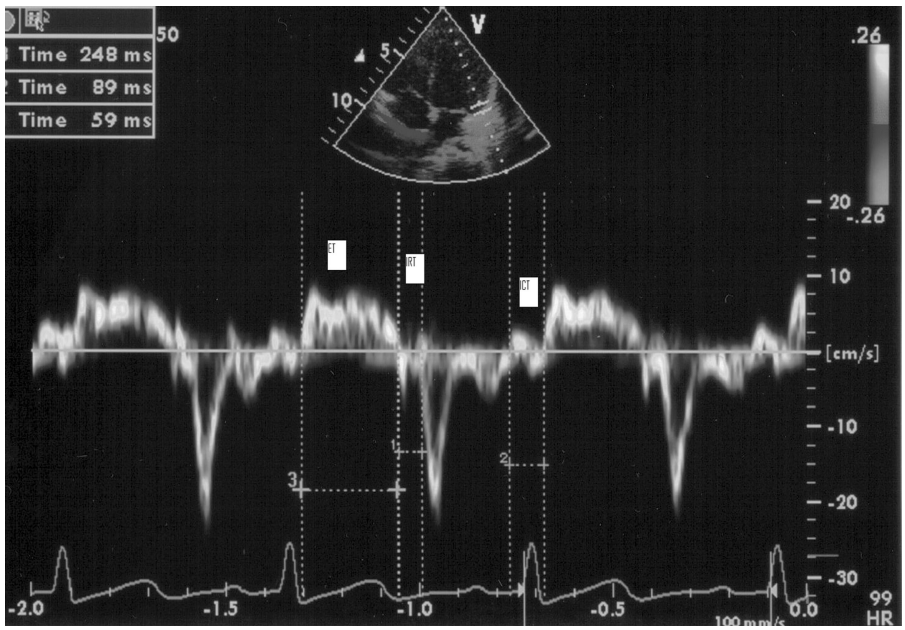

Figure 1. *Calculation of myocardial performance index (MPI) on tissue Doppler imaging. MPI: isovolumic relaxation time (IRT) + isovolumic contraction time (ICT)/ejection time (ET).*

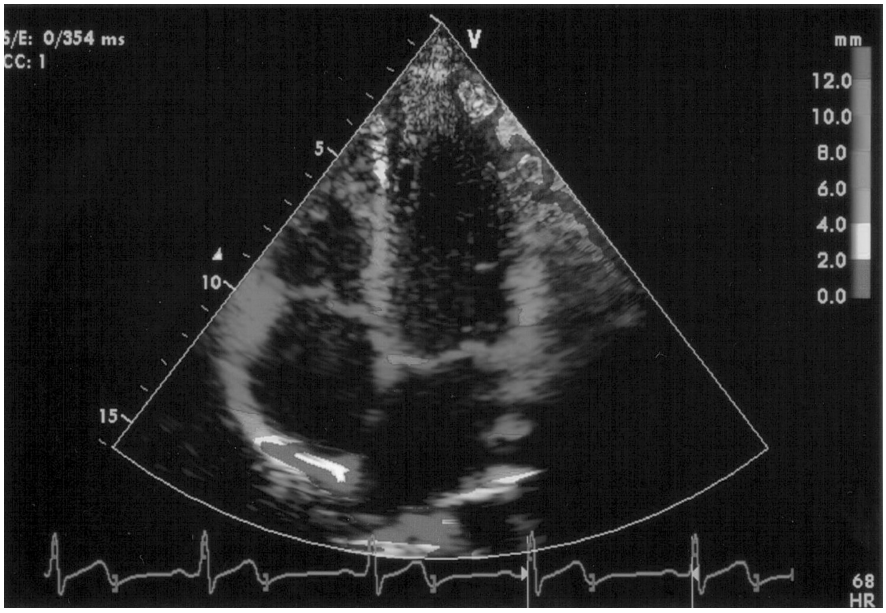

Figure 2. *Apical four-chamber view images with tissue tracking.*

high-frequency signals and the gain was minimized. On the flow Doppler images Mitral E′ and A′ were measured. MPI (Tei index) was measured by using the isovolumic contraction time (IVCT) + isovolumic relaxation time (IVRT)/ ejection time (ET) (Fig. 1). The ratio of mitral E′/A′ and E/E′ were also calculated for each subject.

Tissue Tracking

In tissue tracking, a by-product of tissue imaging, basoapical views of each ventricular segment are displayed as seven color bands, with each color representing a particular distance the tissue moves during the systole. The range of the distance of motion is displayed

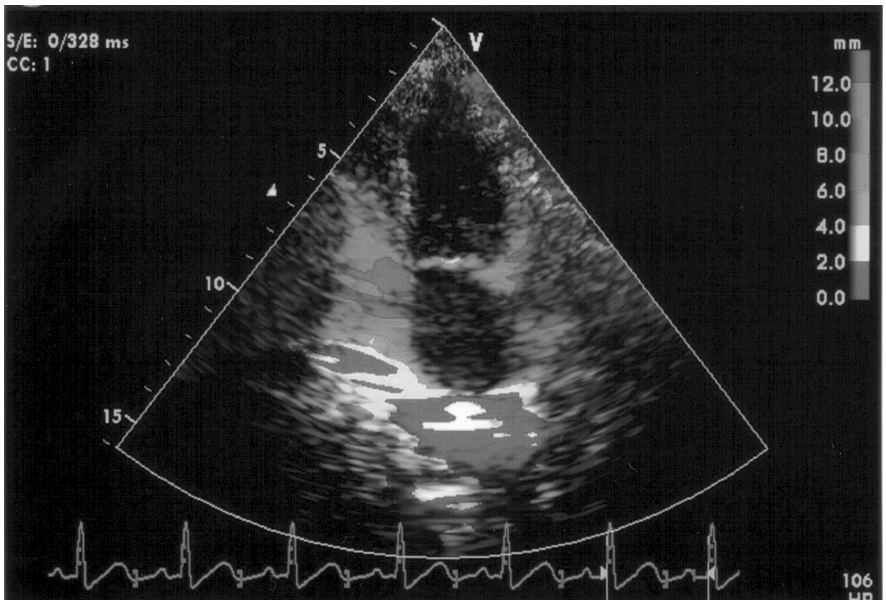

Figure 3. *Apical two-chamber view with tissue tracking.*

by seven color bands. The maximal distance of tissue motion during the systole was adjusted depending on the left ventricular function, to stretch the seven color bands between the apex and the greatest distance at the mitral annulus. Thus, tissue tracking provides a rapid assessment of systolic motion.[7] The filter and gain settings were adjusted at the minimal optimal level to minimize noise and eliminate the signals produced by transmitral flow. The interval of the systole and gain of the ECG were adjusted on the ECG monitoring system. Tissue tracking measurements were completed under the simultaneous electrocardiographic monitoring. Systolic mitral annular displacements were measured in the apical four-chamber, two-chamber, and three-chamber views and were recorded for the septal, lateral, inferior, anterior, posterior, and anteroseptal part of the mitral annulus. Mitral annular displacement was measured by M-mode echocardiography from apical four-chamber, two-chamber and three-chamber views for the septal, lateral, inferior, anterior, posterior, and anteroseptal part of the mitral annulus (Figs. 2 and 3). Three consecutive cycles were analyzed and averaged for all echocardiographic parameters.

Statistical Analysis

Statistical analysis was performed using SPSS package 11.0. The clinical and echocardiographic data between the two groups were compared by the independent-sample*t*-test. All data were expressed as mean ± standard deviation. A two-tailed P-value <0.05 was considered statistically significant. Correlation analysis was used to examine the interrelationship of the variables.

Results

Fifty-four people were studied in this analysis. A total of 32 pediatric malignancy survivors after anthracycline therapy (15 males, 17 females) made up the patient group and 22 healthy children (13 males, 9 females) made up the control group. The mean age was 8.82 ± 4.59 years in the patient group and 9.75 ± 2.78 years in the control group. There was no statistical significant difference between the two groups ($P > 0.05$). In total, the patient group consisted of 21 patients with acute lymphoblastic leukemia, 6 with acute myeloblastic leukemia, 4 with non-Hodgkin lymphoma, and one with neuroblastoma who had been

TABLE I

Clinical Data, Left Ventricular Systolic and Diastolic Functions of Pediatric Malignancy Patients and the Control Group

	Patient (n = 32)	Control (n = 22)	P Value
Age (years)	8.82 ± 4.59	9.75 ± 2.78	>0.05 (0.40)
Gender			
Male	15 (46%)	13 (59%)	>0.05 (0.38)
Female	17 (54%)	9 (41%)	
Weight (kg)	28.43 ± 14.13	30.93 ± 9.58	>0.05 (0.47)
Height (cm)	121.64 ± 29.20	129.45 ± 16.78	>0.05 (0.26)
LVEF (%)	68.90 ± 6.31	67.81 ± 6.74	>0.05 (0.54)
LVSF (%)	38.18 ± 5.21	37.68 ± 5.80	>0.05 (0.73)
SV (ml)	44.43 ± 16.45	53 ± 14.90	>0.05 (0.056)
CO (lt/minute)	4.03 ± 1.47	4.04 ± 0.89	>0.05 (0.98)
CI (CO/BSA)	4.16 ± 1.06	3.86 ± 0.99	>0.05 (0.23)
Mitral E	1.03 ± 17	1.07 ± 0.15	>0.05 (0.39)
A	0.64 ± 0.11	0.62 ± 15	>0.05 (0.49)
E/A	1.64 ± 0.31	1.74 ± 0.31	>0.05 (0.27)
DT (msec)	119.62 ± 29.26	107.31 ± 12.93	>0.05 (0.07)
IRT (msec)	55.87 ± 15.86	63.90 ± 14.57	>0.05 (0.065)

LVEF = Left ventricular ejection fraction; LVFS = Left ventricular shortening fraction; SV = Stroke volume; CO = Cardiac output; CI = Cardiac index; DT = Deceleration time; IRT = Isovolumic relaxation time.

TABLE II

Tissue Doppler and Tissue Tracking Measurements of Patient and Control Groups

	Patient (n = 32)	Control (n = 22)	P Value
Tissue Doppler			
E′	0.18 ± 0.03	0.20 ± 0.03	<0.05 (0.015)
A′	0.06 ± 0.01	0.07 ± 0.01	>0.05 (0.23)
E′/A′	2.78 ± 0.76	2.92 ± 0.84	>0.05 (0.051)
E/E′	5.76 ± 1.11	4.93 ± 1.42	<0.05 (0.02)
MPI	0.49 ± 0.09	0.44 ± 0.09	<0.05 (0.04)
Tissue tracking			
Apical four-chamber			
MAD-septal	9.84 ± 2.05	10.01 ± 1.39	>0.05 (0.71)
MAD-lateral	10.51 ± 2.34	10.73 ± 1.74	>0.05 (0.73)
Apical two-chamber			
MAD-inferior	10.48 ± 2.38	11.14 ± 1.58	>0.05 (0.26)
MAD-anterior	10.46 ± 2.01	10.97 ± 1.84	>0.05 (0.35)
Apical three-chamber			
MAD-anteroseptal	10.42 ± 2.30	10.51 ± 1.30	>0.05 (0.87)
MAD-posterior	9.91 ± 2.48	10.02 ± 1.70	>0.05 (0.86)

MAD = Mitral annular displacement, E′ = Early peak velocity of the early filling in tissue Doppler; A = Peak velocity of the late filling in tissue Doppler.

treated with anthracycline group chemotherapy including daunorobicine, adriamycine, amsacrine, and mitoksantrone.

In total, 28 patients had received a total dose of 162.85 mg/m^2 ± 87.72 (100–300 mg/m^2) daunorobicine, 30 patients had received a total dose of 82 ± 34.02 mg/m^2 (50–240 mg/m^2) adriamycine, 6 patients had received amsacrine 500 mg/m^2, and one patient had also received mitoksantrone 50 mg/m^2. Twenty-two patients received daunorobicine together with adriamycine, 5 patients received daunorobicine, adriamycine, and amsacrine, 2 patients received only adriamycine, and 1 patient received daunorobicine together with amsacrine and mitoksantrone. There was no mediastinal irradiation history in pediatric malignancy group. The mean follow-up period after anthracycline chemotherapy was 26.86 ± 20.7 months (1–79 months, median 28 months). The mean weight and height of the two groups were statistically similar (P > 0.05).

In the echocardiographic evaluation the mean left ventricular ejection fraction was 68.9% ± 6.3% in the patient group and 67.8% ± 6.7% in the control group (P > 0.05). The mean shortening fraction was 38.1% ± 5.2% in the patient group and 37.6% ± 5.8% in the control group. There was no statistical difference between the two groups (P > 0.05). Stroke volume and cardiac output values were also similar in two groups. On pulse Doppler evaluation, mitral E, mitral A, DT, IRT values, and E/A ratio were statistically similar in the two groups. The results of the left ventricular systolic and diastolic functions are shown in Table I.

On tissue Doppler evaluation, the mean mitral E′ value of the patient group was 0.18 ± 0.03 and 0.20 ± 0.03 msec in the control group (P < 0.05). The mean A′ value was 0.06 ± 0.01 msec in the patient group and 0.07 ± 0.01 in the control group. The mean E′/A′ ratio was 2.78 ± 0.76 and 2.92 ± 0.84 in patient and control groups, respectively. Mitral A′ values and E′/A′ ratios were similar in the two groups (P > 0.05). The mean E/E′ ratio was 5.76 ± 1.11 in the patient group and 4.93 ± 1.42 in the control group (P < 0.05) (Table II).

MPI was 0.49 ± 0.09 in the patient group and 0.41 ± 0.09 in the control group (P < 0.05). Negative correlation was found between the MPI and E/A ratio (r = −0.36, P = 0.03) and the MPI and E′/A′ ratio (r = −0.397, P = 0.02). A statistical correlation was found only between the MPI and total adriamycine dose (r = 0.365, P = 0.047).

Tissue tracking measurements including apical four-chamber (mitral annular displacement—lateral and septal), apical two-chamber (mitral annular displacement-inferior and anterior), and three-chamber (mitral annular displacement-anteroseptal and posterior) measurements were similar in the two groups (P > 0.05).

Discussion

A growing number of patients treated with aggressive chemotherapy modalities including anthracyclines may have the potential for substantial morbidity and mortality due to anthracycline cardiotoxicity.[8] Childhood cancer survivors exposed to anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone) or thoracic radiation therapy are at risk for long-term cardiac toxicity. The factors considered to be related to cardiotoxicity include the total dose of anthracycline >550 mg/m^2, high infusion rate, method of administration, age, and concomitant chest irradiation.[9]

Echocardiography is a useful and noninvasive tool for detection of cardiotoxicity. The most common method to evaluate the heart function is standard 2D and M-mode echocardiography. Early and late cardiotoxicity is mainly characterized by the deterioration of cardiac functions. Subclinical cardiomyopathy is more prevalent than symptomatic heart failure. Significant abnormalities of left ventricular diastolic filling patterns are associated with previous anthracycline treatment.[10] Lee et al. (1987) demonstrated that abnormalities of diastolic function in adult patients resulted when patients received lower doses of anthracyline than those producing significant changes in systolic function.[11] Bu'Lock et al. (1995) showed that significant abnormalities of diastolic function were related to anthracycline treatment, but these were not linearly related to the anthracycline dose.[10] The authors concluded that, although the overall clinical significance of diastolic dysfunction is uncertain, some individual abnormalities may have significant management and therapeutic implications. In our study, we found no statistical difference between the pediatric malignancy and control groups according to the conventional left ventricular diastolic functions. However, mitral E′ values were lower and the E/E′ ratio was statistically higher in the patient group than in the control group ($P < 0.05$). The P-value of the E′/A′ ratio was close to 0.05 (0.051). E′ velocity reflected relaxation of the myocardium, while a decrease in E′ was one of the earliest markers for diastolic dysfunction.[12] It has been also demonstrated that the E/E′ ratio correlates well with the left ventricular filling pressure.[13] Rathe et al. (2007) demonstrated that even low to moderate doses of anthracycline might lead to progressive cardiac dysfunction.[14] They recommended that the children who were treated with anthracyclines receive lifelong follow-ups for signs of cardiomyopathy. In our study, the clinical means of these tissue Doppler findings are unclear, but it may be related to the subclinical diastolic dysfunction and some patients may demonstrate decreased left ventricular systolic functions and heart failure. For this reason, our patients required closely monitored follow-ups for anthracycline cardiomyopathy.

Tissue Doppler imaging is a new echocardiographic modality based on assessed myocardial velocities; therefore, it is a more sensitive method than the conventional Doppler measurements. MPI has been reported as a useful method and parameter for the detection of cardiac dysfunction related to anthracyclines.[3,4,15] MPI has been correlated well with other invasive and noninvasive measures of left ventricles in adults.[16] Gaibazzi et al. (2005) compared MPI and conventional method or mitral annulus tissue Doppler in patients with heart failure and healthy adults.[17] They found that MPI that measured by conventional and pulse wave tissue Doppler method had high diagnostic accuracy for congestive heart failure. It also seems to be a more sensitive noninvasive technique for detecting subclinical left ventricular dysfunction than conventional echocardiographic measurements in children.[3] Senju et al. (2007) examined 23 patients at least twice during the anthracycline treatment.[18] They showed that change in the DeltaTei-index is a more sensitive indicator of early cardiotoxicity induced by anthracyclines than LV ejection fractions (LVEF) regardless of its value before treatment. Studies of long-term pediatric survivors have shown that the incidence of cardiotoxicity increases with time. MPI changes occur before changes in other conventional measures of left ventricular systolic and diastolic functions and appear to be a more sensitive noninvasive technique for detecting subclinical anthracycline cardiotoxicity. The mean follow-up period of our patients after anthracycline chemotherapy was 26.86 ± 20.7 months (1–79 months, median 28 months). MPI appears to be a sensitive noninvasive echocardiographic method for evaluating pediatric malignancy survivors. Positive correlation was found between the myocardial performance index and E′/A′ and E/E′ ratios. Yilmaz et al. (2007) assessed isovolumic relaxation time (IVRT), IVCT, LVET, ratio of IVCT/LVET, and MPI. ([IVRT+IVCT]/LVET) were measured via Doppler echocardiography. They investigated the relationship between the

ratio of isovolumic contraction time/left ventricular ejection time (IVCT/LVET), MPI, and LV systolic function in a total of 43 adult patients with LV ejection fractions (LVEF) <55% and 43 adult patients with LVEF values >55% (control group).[19] They found that the mean value of MPI and the ratio of ICT/LVET were significantly higher in the patient group. The value of the ratio of ICT/LVET was found to have a significant negative correlation with the value of LVEF and a significant positive correlation with the value of MPI. In our study, mean ICT/ET ratio were found as 0.15 ± 0.1 in patient group and 0.17 ± 0.04 in control group ($P = 0.2$). The mean IRT/ET ratio of patient group were 0.33 ± 0.1 and 0.24 ± 0.07 ($P < 0.01$). Higher MPI values of the pediatric malignancy group appear to be related to increased IRT on tissue Doppler measurements. This finding reflects subclinical diastolic dysfunction that was detected with tissue Doppler measurements.

Tissue tracking is a new echocardiographic modality on the basis of tissue Doppler imaging, which allows the assessment of the systolic longitudinal contraction of the myocardium. Tissue track analysis can be performed within a short time, with a reasonable reproducibility, and longitudinal ventricular function.[6,7] In our study, we did not find a statistical difference between the patient and control group according to the tissue track analysis of mitral annular displacement. It appears that tissue tracking echocardiography assesses the myocardial systolic function, but it is not a useful modality that assesses the subclinical anthracycline cardiotoxicity. Tissue track analysis may be useful in the case of systolic dysfunction. Takenaka et al. (2001) proposed that the measurement of the systolic thickening of the subendocardial layer (delta Endo), subepicardial layer (delta Epi), and whole wall (delta Total) of the left ventricular posterior with the tissue Doppler echo tracking system (M-mode) results in the most distinct difference and the least overlap of the data between normal subjects and patients; whereas, the delta Total failed to show significant differences. The myocardial strain rate imaging (B-mode) measurement of integrated strain rate endo/epi showed the most distinct difference and the least overlap of the data between control subjects and patients, but the ejection fraction failed to show statistically significant differences.[20] Myocardial strain rate imaging is a sensitive method to use, but it is a time-consuming echocardiographic method. Therefore, it can be considered after the detection of systolic and diastolic dysfunction in patients with anthracycline cardiotoxicity.

Study Limitations

In our study, the mean follow-up period after anthracycline chemotherapy was 26.86 ± 20.7 months (1–79 months, median 28 months). Some patients have short follow-up period and we do not know if MPI, E′, and E/E′ changes over time after chemotherapy. Our patients should be follow-up with tissue Doppler echocardiography further follow-up period.

In summary, we evaluated pediatric malignancy survivors with conventional systolic and diastolic measurements, tissue Doppler measurements, tissue tracking of mitral annular displacement and compared the results to the measurements from the healthy patients. We detected that on tissue Doppler evaluation mitral E′ values were lower and the E/E′ ratio was statistically higher in the patient group than in the control group. MPI values are also higher in the patient group than the control group. It appears that MPI is a useful echocardiographic method for the tissue tracking of mitral annular displacement in patients with pediatric cancer survivors who had subclinical diastolic dysfunction. Tissue tracking may be also useful in the case of systolic dysfunction. Therefore, clinicians should take into consideration the late anthracycline cardiotoxicity and follow-up with pediatric cancer survivors several years after treatment completion for late cardiotoxicity.

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