Subclinical reduction in left ventricular function using triplane and 2D speckle tracking echocardiography after anthracycline exposure in children

Erman Çilsal, Ayşe Deniz Oğuz[1], Fatma Sedef Tunaoğlu[1], Serdar Kula[1], Ayhan Pektaş[2]

Department of Pediatric Cardiology, Adana Numune Training and Education Hospital; Adana-*Turkey*
[1]Department of Pediatric Cardiology, Gazi University Hospital; Ankara-*Turkey*
[2]Department of Pediatric Cardiology, Afyon Kocatepe University Hospital; Afyon-*Turkey*

Abstract

Objective: Speckle tracking echocardiography (STE) enables global and regional evaluation of the left ventricle (LV); therefore, it is the most useful method for detecting subclinical dysfunction in patients exposed to cardiotoxic agents. A novel technique triplane (3P) echocardiography also allows single beat assessment of LV global longitudinal strain values. We firstly aimed to demonstrate both two-dimensional (2D)- and 3P-STE-derived LV global longitudinal strain measurements in children after anthracycline exposure.

Methods: This study included 23 cross-sectionally enrolled asymptomatic pediatric cancer patients who received anthracycline chemotherapy and 17 healthy controls matched by age, gender, and body surface area. All subjects underwent detailed 2D, Doppler, 2D-STE, and 3P-STE for assessment of LV function. The patients had received a median cumulative dose of 150 mg/m^2.

Results: 1. From "Pulsed" Doppler-based measurements, only pulmonary vein flow ratio showed a significant difference between the groups. 2. When measurements were taken from the interventricular septum, the patients' ejection time values decreased significantly and their myocardial performance index values increased significantly; when the measurements were taken from the LV free wall, the peak systolic velocities showed a statistically significant difference. 3. Both 2D- and 3P-STE-derived longitudinal myocardial deformation values of LV were lower in the patient group. 4. 2D-STE-derived LV circumferential strain values were decreased in the patient group, whereas radial strain values were not significantly different compared with matched controls.

Conclusion: Using Doppler and 2D- and 3P-STE methods, this study confirmed the subclinical LV dysfunction in patients after anthracycline exposure. *(Anatol J Cardiol 2018; 19: 58-66)*

Keywords: anthracycline, cardiotoxicity, tissue Doppler imaging, global longitudinal strain, 2D-STE, 3P-STE (Speckle Tracking Echocardiography)

Introduction

Anthracyclines are one of the most common chemotherapeutic agents having antineoplastic activity against various tumors. These agents have been commonly used for many years in the treatment of hematological malignancies (leukemia, lymphoma) and solid tumors. Cardiotoxicity of these agents, however, still threaten cardiac function in children despite the fact that they were recognized more than 40 years ago. Anthracycline cardiotoxicity is classified into three groups. Acute and subacute toxicity occurs immediately within 24 h following exposure, with an incidence of <1% (1). Early onset chronic progressive toxicity is defined as the deterioration of cardiac function within the first year after exposure. Late clinical cardiotoxicity, which occurs after the first year of anthracycline chemotherapy in children, varies from 0% to 16% (2). Late subclinical cardiotoxicity incidence in children was reported to be 57% (1). According to this information, children who have received anthracycline therapy are recommended lifelong cardiac monitorization (3). Echocardiography is the most useful and applicable imaging method for assessing cardiotoxicity. Basically, traditional M-mode and "Pulsed" Doppler techniques are used for the measurement of the left ventricular (LV) systolic and diastolic functions. The tissue Doppler imaging method, which has been used for a few decades, gives detailed information about LV functions; however, the angle dependency has limited the clinical application in practice. Strain echocardiography, a more sensitive imaging method, is an emerging technique that provides a global and regional assessment of systolic and diastolic functions, and it started to be used in clinical practice after tissue Doppler imaging.

Address for correspondence: Dr. Erman Çilsal, Serinevler Mah. Ege Bağtur Cad. Yüreğir/Adana-*Türkiye*
Phone: +90 322 355 01 01 Fax: +90 322 355 01 55 E-mail: ermancilsal@gmail.com

Accepted Date: 26.10.2017 **Available Online Date:** 08.01.2018

DOI:10.14744/AnatolJCardiol.2017.7944

After improvements in both hardware and software of two-dimensional (2D)-speckle tracking echocardiography (STE) method in the last couple of years, detection of regional LV myocardial systolic and diastolic dysfunctions became easier and more feasible. After transition from Doppler-based to 2D-STE method, strain analysis has improved with the use of this technology in most clinics. Multiple studies have shown the accuracy and reliability of strain techniques in the pediatric age group, particularly within the last few years (4-6). Compared with conventional imaging methods, regional ventricular deformation is more sensitive in detecting subclinical myocardial dysfunction at the earlier stages.

2D-STE strain measurements can also be performed by triplane (3P)-2D datasets in the same cardiac cycle using a 3D probe. 3P echocardiography has been validated for the measurement of strain analysis with a faster and better standardization of the apical views (7). There is still limited data on the analysis of 2D strain using STE in the serial echocardiographic assessment of children after anthracycline chemotherapy. Recent reports on pediatric and adult patients have shown the association of anthracycline chemotherapy with impaired LV myocardial deformation (8, 9). The primary goal of this study was to assess standard 2D strain measurements of all three directions (longitudinal, radial, and circumferential) and 3P longitudinal strain after anthracycline exposure in pediatric patients.

Methods

Informed consent

The study was approved by the institutional review board of Gazi University Hospital. Informed written consent was obtained from all patients/parents.

Study design and population

We cross-sectionally evaluated 23 patients (13 females and 10 males; median age, 14 years; range, 6–19 years), followed at the Pediatric Oncology Department of the Gazi University Hospital in Ankara, Turkey. This study was conducted between January 2013 and December 2013, and 23 patients were selected throughout the study period. Age- and gender-matched 17 patients were selected from patients who were referred for evaluation of a cardiac murmur, and they were found to have normal intra-cardiac structural anatomy and function. Oncologists identified patients who received anthracycline treatment and required echocardiograms in the part of their follow-up period. All patients met the following inclusion criteria: (1) <20 years old; (2) received or have completed chemotherapy; (3) LV ejection fraction (LVEF) >50%; and (4) at least three weeks down from their last dose. During evaluation, all patients were asymptomatic from a cardiovascular standpoint and were not on cardiac medications. All patients had received anthracycline treatment (doxorubicin, epirubicin) as a part of the chemotherapy protocol for Hodgkin lymphoma (n=9), Ewing sarcoma (n=8), non-Hodgkin lymphoma (n=2), osteosarcoma (n=2), Wilms tumor (n=1), or Rhabdomyosarcoma (n=1). The patient group had received a median cumulative dose of 150 mg/m^2 (range, 60–360 mg/m^2). We used the formula to convert dosage to doxorubicin isotoxic equivalents (10). The patients were monitored at a median of 328 days after the last dose of anthracycline.

Standard echocardiographic assessment

Parasternal long-axis views provided 2D M-mode images. All children's interventricular septal wall thickness, left ventricular internal diameters, and left ventricular posterior wall thickness measurements were obtained. Using shortening fraction, we evaluated the LV systolic functions. Teichholz method was utilized for calculating EF (11). LV mass (LVM) was calculated using the Devereux formula at end-diastole, as described by Lang et al. (12), and relative wall thickness (RWT) was calculated using the formula: RWT=2x (posterior wall thickness/left ventricular end-diastolic volume) (12). LVM index (LVMI) was obtained by dividing individuals' left ventricular mass by their height$^{2.7}$ (13).

''Pulsed'' Doppler measurements were performed with the transducer from the apical 4-chamber view. The LV-inflow pattern at the tips of the mitral valve provided peak early (E) and late (A) filling velocities, E/A ratio, and deceleration time (DT). Placing a 3–4-mm ''pulsed'' Doppler sample volume into pulmonary vein from the apical 4-chamber view, we obtained pulmonary venous inflow velocities: peak systolic pulmonary venous (PV) flow velocity (PV S), peak diastolic PV flow velocity (PV D), and PV S/D ratio.

Measurements of ''pulsed'' tissue Doppler were attained with the transducer from the apical 4-chamber view by aligning the Doppler beam perpendicular to the plane of the lateral and septal mitral annulus. Peak systolic (S'), early diastolic (E'), and late diastolic (A') myocardial velocities at the lateral and septal mitral annulus were determined using tissue Doppler imaging (TDI).

The isovolumic contraction time (IVCT: interval between the end of A' wave to the beginning of the S' wave) and the isovolumic relaxation time (IVRT: interval between the end of S' wave to the beginning of the E' wave) were measured for both sides of the mitral annulus using TDI. The following formula was used with a view to calculate the myocardial performance index (MPI): MPI=isovolumic relaxation time + isovolumic contraction time/LV ejection time (defined as the duration of the S' wave) (14).

2D- and 3P-STE Assessment

All subjects underwent complete transthoracic echocardiographic (TTE) examination. General Electric Vivid E9 (GE Health Medical, Horten, Norway) device was used for the assessment. EchoPAC 11 [automated function imaging (AFI); GE Health Medical] was used as the respective post-processing analysis software. Initially, we obtained TTE with an M5S 1.5/4.6 MHz transducer for conventional 2D-STE imaging and a 3V 1.7/3.3 MHz

Anatol J Cardiol 2018; 19: 58-66
DOI:10.14744/AnatolJCardiol.2017.7944

Table 1. Clinical features of study groups

Clinical data	Patient group (n=23)	Control group (n=17)	*P*
Age, years	13.4±3.4	11.7±4.2	0.153
Sex, M/F	10/13	10/7	0.350
Weight, kg	49.1±21.1	46.1±22.7	0.670
Height, cm	152.3±21.2	151.4±26.8	0.904
BSA, m^2	1.42±0.38	1.38±0.45	0.788
Heart rate, /min	88.3±15.5	77.4±10.1	0.016*
SBP, mm Hg	104.5±13.8	108.8±14.0	0.347
DBP, mm Hg	67.1±8.6	67.8±9.3	0.655

Data are presented as the mean values±SD

BSA-body surface area, DBP-diastolic blood pressure, SBP-systolic blood pressure, *Student t-test, Mann-Whitney U test *P*<0.05 considered statistically significant

Table 2. M-mode echocardiographic parameters of study groups

Variables	Patient group (n=23)	Control group (n=17)	*P*
IVSS. mm	8.0±1.7	8.9±2.6	0.334
IVSD. mm	9.5±2.5	10.3±2.8	0.212
LVEDD. mm	42.1±4.7	42.5±5.7	0.786
LVESD. mm	26.8±3.4	26.4±4.0	0.739
LVPWD. mm	7.7±1.6	7.9±2.0	0.732
LVPWS. mm	11.0±2.3	10.3±3.5	0.738
EF. %	65.9±6.1	67.7±4.5	0.317
FS. %	36.2±4.7	37.4±3.9	0.399
LVM. g	104±37.7	121±66	0.308
LVMI. $g/m^{2.7}$	35.5±7.4	34.07±14.7	0.679
RWT	0.36±0.07	0.37±0.07	0.885
MAPSE. cm	1.51±0.20	1.54±0.16	0.698

Data are presented as the mean values±SD

Student t-test *P*<0.05 considered statistically significant

EF-ejection fraction, FS-fractional shortening, IVSS-interventricular septum systolic thickness, IVSD-interventricular septum diastolic thickness, LVEDD-left ventricular end-diastolic diameter, LVESD-left ventricular end-systolic diameter, LVM-left ventricle mass(diastolic), LVMI-left ventricle mass index, LVPWD-left ventricle posterior wall diastolic dimension, LWPWS-left ventricle posterior wall systolic dimension, MAPSE-mitral annular plane systolic excursion, RWT-relative wall thickness

transducer for 3P-STE imaging. With M5S probe, we respectively and sequentially obtained the conventional parasternal and LV apical 2-, 3-, and 4-chamber (A2CH, A3CH, and A4CH) views, and then with 3V probe placed apically under the "triplane" mode. One ultrasonic view enabled to demonstrate these three views.

Three consecutive cardiac cycles belonging to the three apical views were obtained at a frame rate of 40–80 MHz and stored digitally as raw data for subsequent post-processing analysis. Using AFI, Peak Global Longitudinal Strain (PGLS) was automatically calculated from the saved data. At the septal and lateral mitral annulus and at the apical endocardium, three sampling points were manually placed for each apical view (2CH, 3CH, and 4CH). A Region of interest (ROI) was used with a view to draw the trace between the epicardial and endocardial borders of the LV myocardium. ROI was also manually adjusted so that optimal tracking could be provided. One representative cycle provided longitudinal 2D speckle tracking strain values, which avoided premature beats. The GE Health Medical software enables to assess tracking quality using its algorithm. Once the aortic valve closure had been visually identified, frame-by-frame, in the apical long-axis (3CH) view, PGLS values were estimated. American Society of Echocardiography's 17-segment LV model formed base for segmental longitudinal strain values (12).

PGLS was calculated as the average of regional strains. A single bull's eye summary was used to document the segmental longitudinal strain results of all three planes. The calculation of PGLS could only be performed with the software package EchoPAC 11 (GE Health Medical, Horten, Norway) (AFI method) when tracking quality was adequate in at least five of six segments in each apical view. We also obtained myocardial circumferential and radial strain values. Average strain values were determined with 17 segments from the short-axis views.

3P-STE

Strain analysis conducted with 3P-STE resembles the conventional method in that it starts from the A4CH view and is followed by A2CH and A3CH views, with the exception that the software recognizes and automatically starts the analysis from A4CH view, and the three apical views had the same cycle. All images were digitally stored for offline analysis and 3P-STE data were analyzed by the software EchoPAC 11 (GE Health Medical).

Statistical analysis

Data are presented as mean±SD. Comparisons between the groups were calculated using nonparametric tests (Mann–Whitney U-test) for non-normally distributed data and parametric tests (Student's t-test) for normally distributed data. A p-value of <0.05 was considered to be significant. All statistical analyses were performed using Statistical Package for Social Science (version 22.0, SPSS, Inc.).

Results

Clinical features

Overall, 23 children (10 males, 13 females) and 17 healthy controls (10 males, 7 females) were recruited. The mean age of the patients and controls were 13.4±3.4 and 11.7±4.2 years, respectively. Table 1 summarizes the sample characteristics of the children enrolled in the study. There were no statistically significant differences between the patient and control groups in terms of the systolic and diastolic blood pressures. Heart rate values were higher in the patient group (p=0.016).

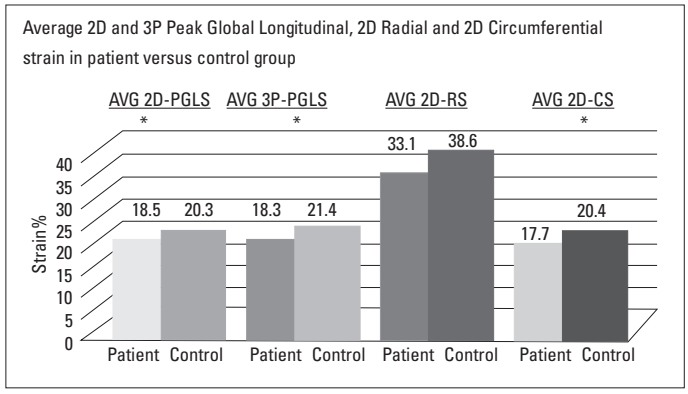

Figure 1. Average 2D and 3P Peak Global Longitudinal, 2D Circumferential strain in patient versus control group *P>0.005

Conventional and Doppler echocardiographic parameters (standard echocardiographic evaluation)

There were no statistically significant differences between the groups in LV M-mode diameters and functions (EF and fractional shortening). LVM, LVMI corrected for height[2.7], and RWT values were similar in both groups. M-mode measurements are shown in Table 2. Comparison of the standard transmitral Doppler parameters yielded similar E-wave, A-wave, E/A ratio, and E-wave DTs for the two groups. Analysis of the diastolic function of LV only shows reduced PV S/D ratio in the control group (Table 3).

TDI

Comparison of TDI parameters measured from the septal mitral annulus demonstrated similar S', E', and A' velocities for the two groups (Table 3). MPI measured from the septal mitral annulus was significantly prolonged in patients compared with the controls. Ejection time measured from the septal mitral annulus was reduced in patients compared with the controls. S' velocities derived from the lateral mitral annulus were significantly lower in the control group, whereas E' velocity, A' velocity, MPI, and ejection time were similar.

2D-STE

Longitudinal myocardial deformation of LV was significantly reduced in the anthracycline group. The global average of PGLS, PGLS-4CH, and PGLS-3CH measurements in the patient group were lower than the control group, but there was no difference in PGLS-2CH values (Table 4, Fig. 1).

The average circumferential myocardial deformation of LV was significantly reduced in the anthracycline group (Table 5, Fig. 1).

Although there was a significant reduction of radial strain at the papillary muscle level of anteroseptal, anterior, and lateral wall of LV, there were no differences in average radial deformation of LV between the two groups (Table 6, Fig. 1).

3P-STE

Longitudinal strain values measured with 3P-STE were found to reduce significantly in the anthracycline group. 3P-STE measurements of the global average PGLS, PGLS-4CH, PGLS-3CH, and PGLS-2CH values in the patient group were found to be significantly lower than the control group (Table 7).

Table 3. Conventional and tissue Doppler echocardiographic parameters of study groups

Variables	Patient group (n=23)	Control group (n=17)	*P*
Mitral E, cm/s	1.03±0.18	1.08±0.17	0.405
Mitral A, cm/s	0.64±0.18	0.60±0.10	0.436
Mitral E/A	1.66±0.37	1.81±0.32	0.203
Mitral DT, ms	188.0±24.2	186.9±27.5	0.894
PV S, cm/s	0.66±0.14	0.59±0.09	0.095
PV D, cm/s	0.60±0.16	0.66±0.12	0.197
PV S/D	1.18±0.37	0.92±0.23	0.018*
PV A, cm/s	0.37±0.08	0.39±0.09	0.475
PV Ad, ms	128±22.2	131±21.0	0.654
S'm , cm/s	0.13±0.03	0.10±0.02	0.001*
E'm, cm/s	0.17±0.04	0.20±0.03	0.051
A'm , cm/s	0.08±0.02	0.08±0.01	0.960
ETm , ms	255±31.8	267±20.7	0.192
IVCTm , ms	44.6±11.3	47.5±10.2	0.398
IVRTm, ms	45.7±8.8	50.1±10.3	0.154
MPI m, ms	0.36±0.08	0.36±0.06	0.836
E/E'	6.2±2.05	5.3±0.75	0.095
S's , cm/n	0.09±0.01	0.09±0.01	0.784
E's, cm/s	0.14±0.02	0.15±0.02	0.614
A's, cm/s	0.08±0.19	0.07±0.13	0.337
ETs, ms	244±28.0	263±19.1	0.022*
İVCTs, ms	46.3±11.8	42.8±9.6	0.329
İVRTs, ms	49.0±10.3	47.6±6.2	0.625
MPIs, ms	0.39±0.09	0.34±0.04	0.042*
E/E's	7.2±1.66	7.2±1.31	0.989

Data are presented as the mean values±SD

*Student t-test P<0.05 considered statistically significant

DT-deceleration time, ET-ejection time, IVCT-isovolumetric contraction time, IVRT-isovolumetric relaxation time, m-lateral mitral annulus, MPI-myocardial performance index, PV Ad-pulmonary vein A wave duration, s-septal mitral annulus

Discussion

To the best of our knowledge, this is the first published study on the evaluation of cardiac function measured with both 2D- and 3P-STE methods in children after anthracycline therapy. We demonstrate significantly decreased LV strain indices of cancer patients after chemotherapy compared with healthy subjects.

Diagnoses of childhood cancers are gradually increasing in our country as well as worldwide. Ever since they were first

Anatol J Cardiol 2018; 19: 58-66
DOI:10.14744/AnatolJCardiol.2017.7944

Table 4. 2-D longitudinal strain in the study subjects

Longitudinal strain (%)	Patient group (n=23)	Control group (n=17)	*P*
A4C septum			
Basal segment	–16.5±2.8	–19.2±3.0	0.006*
Mid segment	–18.8±2.9	–21.0±2.5	0.015*
Apical segment	–21.2±4.2	–24.3±3.0	0.006*
A4C lateral wall			
Basal segment	–17.5±3.8	–16.7±5.2	0.665
Mid segment	–18.7±3.9	–18.7±3.6	0.766
Apical segment	–19.9±4.4	–22.6±4.5	0.085
A4C average	–18.5±2.8	–20.1±2.1	0.024*
A3C posterior wall			
Basal segment	–15.8±5.6	–18.5±3.0	0.149
Mid segment	–17.2±3.8	–19.5±2.2	0.032*
Apical segment	–20.9±4.6	–23.1±3.6	0.182
A3C anterior septum			
Basal segment	–17.3±3.7	–20.9±3.7	0.003*
Mid segment	–19.8±4.1	–23.6±3.5	0.001*
Apical segment	–22.4±5.8	–24.9±5.3	0.126
Average A3C	–18.6±3.0	–21.3±2.5	0.003*
A2C inferior wall			
Basal segment	–15.4±8.8	–17.9±5.1	0.498
Mid segment	–18.0±4.7	–18.1±2.9	0.850
Apical segment	–21.7±4.6	–21.1±4.5	0.850
A2C anterior wall			
Basal segment	–16.7±4.4	–18.7±3.3	0.066
Mid segment	–19.7±3.1	–21.8±2.6	0.051
Apical segment	–22.9±4.2	–22.9±4.6	0.829
Average A2C	–18.6±1.8	–19.3±2.3	0.371
GLOBAL AVERAGE	–18.5±2.1	–20.3±1.4	0.003*

Data are expressed as mean±SD

*Student t-test *P*<0.05 considered statistically significant

A2C-Apical two-chamber. A3C-Apical three-chamber. A4C-Apical four-chamber

Table 5. 2-D Circumferencial strain in the study subjects

Circumferencial strain, %	Patient group (n=23)	Control group (n=17)	*P*
Mitral valve level			
Anteroseptal wall	–23.8±4.7	–25.6±4.4	0.201
Anterior wall	–16.6±5.6	–18.2±5.9	0.302
Lateral wall	–8.0±14.7	–11.6±6.0	0.432
Posterior wall	–5.6±14.2	–11.7±5.0	0.062
Inferior wall	–11.9±7.1	–16.2±6.2	0.071
Septal wall	–20.3±7.5	–22.6±5.6	0.588
Papillary muscle level			
Anteroseptal wall	–21.6±3.9	–24.5±6.2	0.221
Anterior wall	–17.0±5.1	–18.1±8.3	0.221
Lateral wall	–11.6±5.8	–12.8±5.6	0.464
Posterior wall	–11.0±6.9	–12.2±5.0	0.386
Inferior wall	–16.6±5.2	–17.3±4.5	0.432
Septal wall	–22.1±4.7	–24.3±4.9	0.080
Apical level			
Anteroseptal wall	–24.3±5.5	–28.4±8.2	0.090
Anterior wall	–23.5±7.0	–24.8±8.8	0.829
Lateral wall	–19.4±10.3	–22.4±9.0	0.705
Posterior wall	–18.7±7.2	–21.0±13.3	0.126
Inferior wall	–20.5±6.0	–25.8±8.4	0.030*
Septal wall	–23.4±6.5	–30.1±6.1	0.004*
AVERAGE	–17.7±2.9	–20.4±2.9	0.010*

Data are expressed as mean±SD

*Student t-test *P*<0.05 considered statistically significant

recognized about 50 years ago, anthracyclines including doxorubicin, daunorubicin, epirubicin, and idarubicin have been effectively utilized for the treatment of various solid tumors and leukemia. Although they have been used with successful results in cancer treatment for many years, they should be cautiously used due to cardiotoxic potency. Echocardiographic screening is recommended every 2–3 years in the long-term follow-up of cardiac asymptomatic childhood cancer survivors at a high risk of anthracycline-induced cardiotoxicity (cumulative doses >250 mg/m^2) (3). However, it was shown that even children who received a cumulative doxorubicin dose as low as 45 mg/m^2 had reduced LV mass, implying the absence of a safe dose that was free of cardiotoxicity (15). Although LVEF and fractional shortening have been traditionally used for the assessment of cardiac toxicity, their accuracy is insufficient for early detection of myocardial dysfunction (16).

In this study, heart rate changes in pediatric cancer patients were also demonstrated compared with the control group. Some of the factors such as dehydration, poor appetite, anemia, pain, and anxiety could be reasons for the increase in heart rate. Interestingly, it was found that cancer patients had a resting heart rate of ≈30% higher than controls before any treatment, and it was presumed that the patients were in an elevated adrenergic state (8).

In our study, there were no significant differences in the LV systolic functions measured by traditional TTE methods between the patient and control groups, which is in line with literature (17, 18). Various pediatric and adult studies have described changes in mitral inflow Doppler, with increased isovolumic relaxation time, decreased early filling velocity, increased late diastolic velocity, and decreased E/A ratio. Al-Biltagi et al. (19) did not show any significant differences in LV diastolic functions reflected by mitral

Table 6. Radial strain in the study subjects

Radial strain, %	Patient group (n=23)	Control group (n=17)	*P*
Mitral valve level			
Anteroseptal wall	26.3±14.0	36.9±19.2	0.075
Anterior wall	26.5±17.3	32.7±16.7	0.221
Lateral wall	28.6±19.1	30.7±14.8	0.464
Posterior wall	30.1±18.9	32.3±14.7	0.356
Inferior wall	29.5±16	34.9±15.5	0.232
Septal wall	28.3±12.5	37.5±17.1	0.071
Papillary muscle level			
Anteroseptal wall	33.8±16.2	47.2±16.0	0.016*
Anterior wall	39.4±18.6	51.9±15.1	0.024*
Lateral wall	44.8±20.9	55.4±16.7	0.039*
Posterior wall	46.9±21.4	55.0±17.2	0.156
Inferior wall	44.4±19.6	51.9±16.5	0.126
Septal wall	38.9±17.2	47.7±17.3	0.058
Apical level			
Anteroseptal wall	29.2±20.2	28.7±17.2	0.808
Anterior wall	31.4±24.2	28.3±18.8	0.850
Lateral wall	30.8±22.7	29.8±22.0	0.850
Posterior wall	30.0±20.7	31.8±24.3	0.935
Inferior wall	28.9±18.1	31.3±23.7	0.871
Septal wall	27.2±15.0	31.2±20.9	0.607
AVERAGE	33.1±11.3	38.6±14.2	0.201

Data are expressed as mean±SD.

*Student t-test $P<0.05$ considered statistically significant

Table 7. Peak Global Longitudinal Strain values of patient versus control group

GLPS	Patient group (n=23)		Control group (n=17)	
(%)	2-D	Triplane	2-D	Triplane
A4CH	−18.5±2.8§	−18.1±3.3§	−20.1±2.1	−19.8±1.7
A3CH	−18.6±3.0§	−18.1±3.1§	−21.3±2.5	−21.6±2.7
A2CH	−18.6±1.8	−18.8±3.5§	−19.3±2.3	−22.6±2.4
Avg	−18.5±2.1§	−18.3±2.8§	−20.3±1.4	−21.4±1.5

Data are expressed as mean±SD

§ $P<0.05$ between the patient and control group

Avg-global average; A2CH-apical 2 chamber view; A3CH- apical 3 chamber view; A4CH-apical 4 chamber view; PGLS-peak global longitudinal strain

inflow Doppler parameters mitral E and A waves, E/A ratio, DT of the mitral valve, pulmonary vein S-, D-, A-waves, and duration of A-wave of the pulmonary vein in cancer children before and after receiving chemotherapy. In our study, we only showed the difference in the pulmonary vein S/D ratio measured by "Pulsed" Doppler echocardiography between patients and healthy subjects. The difference in this ratio could not clearly be adopted as a diastolic dysfunction due to previous studies showing that this ratio increases with age (20). When the groups were compared with regard to isovolumetric contraction and relaxation time, a statistically significant difference was not established. In addition, increases in the MPI values obtained from TDI have been reported to demonstrate significant changes in global ventricular performance that could indicate anthracycline-induced impairment of LV function after acute and chronic period of exposure (21-23). In line with previously published data, our MPI values obtained from the septal mitral annulus were found to increase in the anthracycline group.

Global strain values have been used for many years with a view to determine the dysfunction with respect to the assessment of the LV systolic function, which was reported in previous studies (24-27). The priority of the 2D strain analysis over EF was explained by a model of regional cardiac effect in anthracycline cardiotoxicity. In recent years, there has been an increase in the number of published articles about the myocardial strain in the pediatric population. Poterucha et al. (2) demonstrated that LV longitudinal peak systolic strain values decreased before the reduction of EF following anthracycline therapy in children. Ganame et al. (28) found a decline in tissue Doppler-derived LV longitudinal strain in children after low-dose anthracycline therapy. Cheung et al. (15) showed impaired LV myocardial mechanical dyssynchrony with 2D-STE despite normal shortening fractions in children after anthracycline exposure. Based on these previous reports, our study showed impairment of 2D-STE-derived LV longitudinal strain indices after chemotherapy. Expert consensus of American Society of Echocardiography concluded that PGLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction and suggested that reductions in average PGLS of <8% compared with baseline values would not be meaningful, whereas those of >15% are very likely to have a clinical importance (29). In our study, distinct from other studies, we compared patients with healthy controls, and we did not demonstrate clinical significance of the deformation change between the PGLS values. However, we showed a decline of PGLS values in the patient group, which was statistically significant. Low cumulative anthracycline dosage may be a reason for clinically insignificant changes in deformation parameters. However, it was shown that even children who received a cumulative doxorubicin dose as low as 45 mg/m^2 had reduced LV mass, implying the absence of a safe dose that was free of cardiotoxicity (15). Our study showed that several subtle abnormalities in diastolic dysfunction with "'Pulsed'' and tissue "Pulsed'' Doppler and in LV regional myocardial deformation could be detected in asymptomatic pediatric cancer patients after anthracycline exposure.

In this study, we also showed statistically significant difference in average circumferential strain, despite no difference in average radial strain, in patients compared with controls. A pos-

Anatol J Cardiol 2018; 19: 58-66
DOI:10.14744/AnatolJCardiol.2017.7944

sible explanation of the reduction in radial strain at the papillary muscle level of LV could be that circumferential fibers dominantly locate in the mid-part of LV (30). In agreement with our results, a recent report showed no significant differences in average radial strain values (31). In contrast, Kang et al. (15, 32) demonstrated significant reduction in PGLS, RS, and CS after anthracycline exposure, which was also in concordance with various previous studies. There are several reasons to explain these divergent radial strain analysis results. Firstly, despite the fact that it could be affected by the angle-dependent Doppler-based one-dimensional methods, but still the most commonly used strain modality, this study used STE, which enables to track speckles independent of angle. However, because radial strain has the opposite polarity of longitudinal and circumferential strains, the measurements are still angle-dependent. Hence, the increasing deviation from the major axis will result in progressive reduction in absolute strain (33). Secondly, different software variations among vendors may have caused the different results in the measurements of radial strain in our study compared with previous studies (34). Thirdly, it is complicated to interpret radial and circumferential strain because of the transmural non-uniform geometrical shape of LV; however, such geometrical effects are of less magnitude for PGLS (33). Reant et al. (35) suggested that strains in the longitudinal and circumferential directions may be more sensitive to changes in regional deformation than radial direction. Dallaire et al. (4) indicated that longitudinal strain is more reliable than radial and circumferential strain in detecting the early injury of myocardial fibers. It was also thought that normal EF measurements may be caused by the compensatory increase in the radial strain values (36). Despite reduction in longitudinal and circumferential strain measurements, the radial strain increment was demonstrated in children with diagnosis of familial hypercholesterolemia with preserved EF, and it could be explained with the compensatory development of myocyte hypertrophy in LV (37). Although our study indicated a decrease in circumferential strain measurements, no compensatory radial strain was monitored.

Subtle cardiac dysfunction in pediatric cancer patients prior to chemotherapy has been recently reported, whereas that in adult patients with colorectal cancer has been documented before (26). This dysfunction was manifested by strain abnormalities, and the mechanism was unexplained but thought to be due to underlying diseases with increased inflammatory cytokines or loading conditions. Due to the lack of baseline strain values in our study, we could not demonstrate this alteration.

AFI is a user-friendly process for speckle tracking assessment. Using AFI to assess 2D-STE reduced the average of interobser-ver-intraobserver variability more than that of biplane LVEF demonstrated in previous studies (38). This method has overcome the angle dependency of TDI-derived strain and has become a more accurate method for evaluating cardiac deformation in practice. Zhang et al. (39) have recently showed that 3D strain analysis may help overcome the limitations of 2D strain analysis on LV in children. Also, they demonstrated that 3D strain analysis is feasible and reproducible in pediatric population; it is not easily and routinely performed compared with 2D and 3P techniques. 3P-STE also allows single beat assessment of LV PGLS in patients after using cardiotoxic agents. In our study, we also demonstrated both 2D- and 3P-STE-derived LV PGLS measurements in childhood population. The results of our study suggested that both 2D- and 3P-STE appear to be useful methods for detection of myocardial dysfunction after anthracycline exposure. Because the AFI-capable echo machines will be more accessible, 3P techniques will become reproducible in the daily practice of echocardiography in children.

Study limitations

The small sample size of each group and single-centered study design are the main limitations of the present study. Another limitation is that the patients' echocardiographic assessment should have been done before the treatment, because it is important to obtain baseline strain measurements to observe subsequent changes after chemotherapy. In our study, the patients' low dosage of cumulative anthracycline exposure can be considered a disadvantage.

Conclusion

We presented an investigation of myocardial strain analysis in pediatric cancer patients after anthracycline chemotherapy. The main original findings of this study include the following: 1) 2D- and 3P-STE-derived LV average PGLS values were decreased in the patient group compared with matched controls. 2) 2D-STE-derived LV circumferential strain values were decreased in the patient group compared with matched controls. 3) 2D-STE-derived LV radial strain values were not significantly different between the groups.

Funding: None declared.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – E.Ç., A.D.O.; Design – E.Ç., A.D.O.; Supervision – E.Ç, A.D.O, F.S.T., S.K.; Fundings – E.Ç., A.D.O., F.S.T., S.K.; Materials – E.Ç., A.P.; Data collection &/or processing – E.Ç., A.P.; Analysis &/or interpretation – E.Ç, A.D.O, F.S.T., S.K.; Literature search – E.Ç., A.P.; Writing – E.Ç., A.D.O.; Critical review – E.Ç., A.D.O.

References

1. Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med 1977; 62: 200-8. [CrossRef]
2. Poterucha JT, Kutty S, Lindquist RK, Li L, Eidem BW. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in

adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr 2012; 25: 733-40. [CrossRef]
3. Wallace WH, Thompson L, Anderson RA, Guideline Development Group. Long term follow-up of survivors of childhood cancer: summary of updated SIGN guidance. BMJ 2013; 346: f1190. [CrossRef]
4. Dallaire F, Slorach C, Bradley T, Hui W, Sarkola T, Friedberg MK, et al. Pediatric Reference Values and Z Score Equations for Left Ventricular Systolic Strain Measured by Two-Dimensional Speckle-Tracking Echocardiography. J Am Soc Echocardiogr 2016; 29: 786-93 e8.
5. Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013; 26: 185-91. [CrossRef]
6. Elkıran O, Karakurt C, Kocak G, Karadağ A. Tissue Doppler, strain, and strain rate measurements assessed by two-dimensional speckle-tracking echocardiography in healthy newborns and infants. Cardiol Young 2014; 24: 201-11. [CrossRef]
7. Trache T, Stobe S, Tarr A, Pfeiffer D, Hagendorff A. The agreement between 3D, standard 2D and triplane 2D speckle tracking: effects of image quality and 3D volume rate. Echo Res Pract 2014; 1: 71-83.
8. Moon TJ, Miyamoto SD, Younoszai AK, Landeck BF. Left ventricular strain and strain rates are decreased in children with normal fractional shortening after exposure to anthracycline chemotherapy. Cardiol Young 2014; 24: 854-65. [CrossRef]
9. Agha H, Shalaby L, Attia W, Abdelmohsen G, Aziz OA, Rahman MY. Early Ventricular Dysfunction After Anthracycline Chemotherapy in Children. Pediatr Cardiol 2016; 37: 537-44. [CrossRef]
10. American Academy of Pediatrics Section on Hematology/Oncology Children's Oncology Group: Long-term follow-up care for pediatric cancer survivors. Pediatrics 2009: 123: 906-15. [CrossRef]
11. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976; 37: 7-11. [CrossRef]
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography. J Am Soc Echocardiogr 2005; 18: 1440-63.
13. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 2009; 22: 709-14. [CrossRef]
14. Cui W, Roberson DA. Left ventricular Tei index in children: comparison of tissue Doppler imaging, pulsed-wave Doppler, and M-mode echocardiography normal values. J Am Soc Echocardiogr 2006; 19: 1438-45. [CrossRef]
15. Cheung YF, Hong WJ, Chan GC, Wong SJ, Ha SY. Left ventricular myocardial deformation and mechanical dyssynchrony in children with normal ventricular shortening fraction after anthracycline therapy. Heart 2010; 96: 1137-41.
16. Eidem BW. Identification of anthracycline cardiotoxicity: left ventricular ejection fraction is not enough. J Am Soc Echocardiogr 2008; 21: 1290-2. [CrossRef]
17. Pınarlı FG, Oğuz A, Tunaoğlu FS, Karadeniz C, Gökçora N, Elbeg S. Late cardiac evaluation of children with solid tumors after anthracycline chemotherapy. Pediatr Blood Cancer 2005; 44: 370-7. [CrossRef]
18. Mornos C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Can J Physiol Pharmacol 2013; 91: 601-7.
19. Al-Biltagi M, Abd Rab Elrasoul Tolba O, El-Shanshory MR, Abd El-Aziz El-Shitany N, El-Sayed El-Hawary E. Strain echocardiography in early detection of Doxorubicin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. ISRN Pediatr 2012; 2012: 870549. [CrossRef]
20. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009; 10: 165-93. [CrossRef]
21. Brown TR, Vijarnsorn C, Potts J, Milner R, Sandor GG, Fryer C. Anthracycline induced cardiac toxicity in pediatric Ewing sarcoma: a longitudinal study. Pediatr Blood Cancer 2013; 60: 842-8. [CrossRef]
22. 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 anthracyc-lines. J Am Soc Echocardiogr 2007; 20: 492-7. [CrossRef]
23. Yıldırım A, Tunaoğlu FS, Pınarlı FG, İlhan M, Oğuz A, Karadeniz C, et al. The role of dobutamine stress echocardiography in early diagnosis of cardiac toxicity in long-term survivors of asymptomatic children treated with anthracycline. Anatol J Cardiol 2010; 10: 154-62. [CrossRef]
24. D'Hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J echocardiogr 2000; 1: 154-70. [CrossRef]
25. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004; 17: 630-3. [CrossRef]
26. Sato Y, Maruyama A, Ichihashi K. Myocardial strain of the left ventricle in normal children. J Cardiol 2012; 60: 145-9. [CrossRef]
27. Black DE, Bryant J, Peebles C, Godfrey KM, Hanson M, Vettukattil JJ. Tissue motion annular displacement of the mitral valve using two-dimensional speckle tracking echocardiography predicts the left ventricular ejection fraction in normal children. Cardiol Young 2014; 24: 640-8. [CrossRef]
28. Ganame J, Claus P, Uyttebroeck A, Renard M, D'Hooge J, Bijnens B, et al. Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. J Am Soc Echocardiogr 2007; 20: 1351-8. [CrossRef]
29. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014; 15: 1063-93. [CrossRef]
30. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci (Lond) 2004; 106: 53-60. [CrossRef]
31. Ho E, Brown A, Barrett P, Morgan RB, King G, Kennedy MJ, et al. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. Heart 2010; 96: 701-7.
32. Kang Y, Cheng L, Li L, Chen H, Sun M, Wei Z, et al. Early detection of anthracycline-induced cardiotoxicity using two-dimensional speckle tracking echocardiography. Cardiol J 2013; 20: 592-9. [CrossRef]
33. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016; 37: 1196-207. [CrossRef]
34. Biaggi P, Carasso S, Garceau P, Greutmann M, Gruner C, Tsang W, et al. Comparison of two different speckle tracking software systems:

Anatol J Cardiol 2018; 19: 58-66
DOI:10.14744/AnatolJCardiol.2017.7944

does the method matter? Echocardiography 2011; 28: 539-47. [CrossRef]
35. Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, et al. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol 2008; 51: 149-57. [CrossRef]
36. Sawaya H, Plana JC, Scherrer-Crosbie M. Newest echocardiographic techniques for the detection of cardiotoxicity and heart failure during chemotherapy. Heart Fail Clin 2011; 7: 313-21. [CrossRef]
37. Di Salvo G, D'Aiello AF, Castaldi B, Fadel B, Limongelli G, D'Andrea A, et al. Early left ventricular abnormalities in children with heterozygous familial hypercholesterolemia. J Am Soc Echocardiogr 2012; 25: 1075-82. [CrossRef]
38. Tran JC, Ruble K, Loeb DM, Chen AR, Thompson WR. Automated Functional Imaging by 2D Speckle Tracking Echocardiography Reveals High Incidence of Abnormal Longitudinal Strain in a Cohort of Pediatric Oncology Patients. Pediatr Blood Cancer 2016; 63: 1075-80.
39. Zhang L, Gao J, Xie M, Yin P, Liu W, Li Y, et al. Left ventricular three-dimensional global systolic strain by real-time three-dimensional speckle-tracking in children: feasibility, reproducibility, maturational changes, and normal ranges. J Am Soc Echocardiogr 2013; 26: 853-9.