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

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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/m².

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 hematomal 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 monitoring (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.
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/m² (range, 60–360 mg/m²). 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 height².²³ (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
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 provide tracking quality using its algorithm. Once the aortic valve closure had been visually identified, frame-by-frame, in the apical 4CH view, 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 the mean values±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).

| 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 |
| LTPWD. 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 |
| LVM. g/m² | 35.5±7.4             | 34.0±14.7            | 0.679 |
| MAPSE. cm | 1.51±0.20            | 1.54±0.16            | 0.698 |

Data are presented as the mean values±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.).
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).

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
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/m²) (3). However, it was shown that even children who received a cumulative doxorubicin dose as low as 45 mg/m² 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 4. 2-D longitudinal strain in the study subjects | Patient group | Control group | P |
|-------------------------------------------------------|--------------|--------------|---|
| Longitudinal strain (%)                               | (n=23)       | (n=17)       |   |
| A4C septum                                            |              |              |   |
| Basal segment                                         | −16.5±2.8    | −19.3±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* |

| Table 5. 2-D Circumferencial strain in the study subjects | Patient group | Control group | P |
|-----------------------------------------------------------|--------------|--------------|---|
| Circumferencial strain, %                                 | (n=23)       | (n=17)       |   |
| 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    | −18.2±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
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 (21-23). In line with previously published data, our MPI values obtained from the septal mitral annulus were found to increase (21-23). In line with previously published data, our MPI values obtained from the septal mitral annulus were found to increase (21-23). In line with previously published data, our MPI values obtained from the septal mitral annulus were found to increase (21-23).

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. Ganne 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/m² 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-

**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) |
|----------|----------------------|----------------------|
| A4CH | –18.5±2.8 | –20.1±2.1 |
| A3CH | –18.6±3.0 | –21.3±2.5 |
| A2CH | –18.6±1.8 | –19.3±2.3 |
| Avg | –18.5±2.1 | –20.3±1.4 |

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

Section Title

Section Content

- 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. Ganne 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/m² had decreased 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-
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 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 interobserver-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.

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