Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2021.20233

Evaluation of Cardiotoxic Effects of Anthracyclines by Tissue Doppler Imaging in Survivors of Childhood Cancer

Munise Caliskan[1,*], Pelin Kosger[2,*], Zeynep Canan Ozdemir[3], Birsen Ucar[2], Ozcan Bor[3]

[1]Department of Pediatrics, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
[2]Department of Pediatric Cardiology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
[3]Department of Pediatric Hematology and Oncology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
*These authors have contributed equally to this work.

What is already known on this topic?

- *Childhood cancer survivors (CCSs) are at risk for anthracycline induced cardiotoxicity which tends to be more prominent with long after completion of the chemotherapy.*
- *The early detection of asymptomatic but high-risk patients may reduce the progression of the cardiovascular disease with preventive strategies.*

What this study adds on this topic?

- *The present study, which biventricular myocardial functions were examined with tissue doppler echocardiography (TDI), revealed that the cumulative anthracycline doses > 300mg/m2 is a potential risk factor for development of long-term cardiotoxicity after chemotherapy, which was more prominent on left ventricle.*
- *TDI-derived myocardial performance index (MPI) can be a sensitive tool to reveal subtle signs of myocardial damage.*

ABSTRACT

Background: Childhood cancer survivors (CCSs) are at risk for anthracycline-induced cardiotoxicity which tends to be more prominent long after completion of the chemotherapy. The aim of this study was to examine echocardiographic parameters of anthracycline-induced subclinical cardiotoxicity in children who had received chemotherapy.

Materials and Methods: A cross-sectional single-center study was conducted in a tertiary level university hospital in Eskisehir, Turkey. A total of 50 CCSs and 40 healthy peers were included. The CCSs were divided into 3 subgroups according to cumulative anthracycline dose (100-200 mg/m^2, 201-299 mg/m^2, and ≥ 300 mg/m^2). Biventricular cardiac examination was performed with conventional echocardiography and tissue Doppler echocardiography imaging (TDI).

Results: The mean duration from termination of chemotherapy to echocardiographic assessment was 3.9 ± 2.2 years. The mean age of the CCSs was 11.6 ± 3.9 years. TDI-derived mitral annular isovolumetric relaxation time (IVRT) and myocardial performance index (MPI) were higher in the high-dose group of CCSs than in controls (P = .006, P = .007, P < .001, P = .0014, respectively). IVRT was also higher in patients with ≥ 300 mg/m^2 cumulative dose than in those with < 200 mg/m^2 (P = .007). TDI-derived mitral annular MPI and IVRT were significantly associated with cumulative anthracycline dose (r = 0.288, P = .006, r = 0.340, P = .001).

Conclusion: A cumulative anthracycline dose > 300 mg/m^2 may lead to subclinical cardiotoxicity, and is therefore a potential risk factor for late onset cardiac failure. TDI-derived MPI can be a sensitive tool to reveal subtle signs of myocardial damage, which may facilitate implementation of preventive therapies for patients suspected to be at risk.

Keywords: Anthracycline cardiotoxicity, children, diastolic dysfunction, myocardial performance index, tissue Doppler imaging

INTRODUCTION

The advances in chemotherapeutic regimen, radiotherapy, and surgery have led to an increase in survival rates in patients with childhood cancer. Unfortunately, the same treatments that cure cancer also increase the risk of adverse effects in other organ systems, especially the cardiovascular system.[1,2] Pediatric cancer survivors were revealed to have an 8-fold higher risk of death from cardiovascular diseases (CVD) than the general population, making CVD the leading cause of noncancer mortality in this population.[3] Anthracyclines, chemotherapeutic drugs widely used in oncological therapy, are known to be cardiotoxic. Risk factors for anthracycline-induced cardiotoxicity include: high cumulative anthracycline

Corresponding author:
Pelin Kosger
✉pelinkosger@gmail.com
Received: November 3, 2020
Accepted: April 15, 2021

Cite this article as: Caliskan M, Kosger P, Ozdemir ZC, Ucar B, Bor O. Evaluation of cardiotoxic effects of anthracyclines by tissue doppler imaging in survivors of childhood cancer. *Turk Arch Pediatr.* 2021; 56(5): 492-498.

doses, cancer treatment exposures at a young age, chest-directed radiation therapy, and longer length of follow-up.[4,5] Anthracycline-mediated cardiotoxicity can manifest at an early stage of therapy (during or immediately after treatment) or many years thereafter. Acute cardiotoxicity characterized by myocarditis-pericarditis syndrome or congestive heart failure is usually transient. In addition, pediatric cancer survivors also have long-term cardiotoxicity risk that includes a decrease in left ventricular wall thickness, mass, and contraction.[6-9] The cumulative anthracycline dose was indicated as the predominant determinant factor for late-onset cardiomyopathy.[10,11] In most of the asymptomatic children who survived, subclinical cardiac damage due to anthracyclines progresses and develops into a clinically evident disease after a long latency period.[5,9,12] The subclinical cardiac damage may lead to marked disability in survivors of childhood cancer which may often not be experienced by their adult malignancy survivor counterparts.[13,14] The early detection of these asymptomatic but high-risk patients may reduce the progression of the cardiovascular disease with preventive strategies. However, anticipating those patients that will develop cardiomyopathy (as a result of subclinical damage) is extremely difficult by conventional echocardiography. The great importance of early detection of subclinical damage in preventing cardiomyopathy has led to the use of novel diagnostic techniques such as tissue Doppler echocardiography imaging (TDI) and cardiac magnetic resonance imaging (MRI). TDI, which was known as superior to conventional echocardiography in detecting anthracycline-mediated cardiotoxicity, was also stated as more useful than cardiac MRI in detecting subclinical cardiac damage, since the myocardial fibrosis is a late onset cardiac adverse effect.[15,16]

The aim of the study was to investigate the evidence of long-term cardiotoxicity by conventional and TDI echocardiography in clinically asymptomatic childhood cancer survivors (CCSs). In order to reveal the presence of subclinical cardiac damage, we decided to compare the data obtained by examining healthy peers with the same methods. The identification of monitoring parameters shall optimize risk stratification, identify subclinical cardiovascular disease, and enable preventative treatment measures in time before overt clinical disease in CCSs becomes evident.

METHODS

Study Population

We analyzed data from a total of 60 patients who were diagnosed with childhood cancer (leukemia, lymphoma, or malignant solid tumors), received anthracycline as their chemotherapy between August 2007 and 2019, and were alive at the time of this study. This study includes only CCSs who received anthracyclines, did not undergo chest irradiation, had a gap of at least 1 year after the last anthracycline dose, and did not have congenital heart disease. The diagnostic methods used were bone marrow aspiration in leukemia patients, lymph node biopsy in lymphoma patients, and excisional biopsy in solid tumor patients, respectively. Ten of the 60 patients were excluded from the study due to factors such as having had chest radiotherapy, having congenital heart disease, being in the early period post-chemotherapy and having insufficient clinical information; thus, the study group consisted of 50 patients.

Information concerning patient characteristics, cancer diagnosis, chemotherapeutics received, and last date of therapy was obtained from the medical records. For each patient, the cumulative dose of anthracyclines and administration of additional chemotherapeutics was recorded.

A total of 40 children who were referred to the pediatric cardiology out-patient clinic for innocent heart murmur and who were not diagnosed with congenital heart disease constituted the control group.

The following formulas were used to convert to doxorubicin isotoxic equivalents, prior to calculating total cumulative anthracycline dose.[17] Doxorubicin: Multiply total dose × 1, Daunorubicin: Multiply total dose × 0.5, Idarubicin: Multiply total dose × 5, Mitoxantrone: Multiply total dose × 4. The patients were also divided in 3 subgroups as low-dose (100-200 mg/m^2), moderate-dose (201-299 mg/m^2), and high-dose ($\geq$300 mg/m^2) groups according to the initiated cumulative anthracycline dose.

Echocardiographic Evaluation

The transthoracic echocardiographic evaluations were all performed by the same expert pediatric cardiologist using a Philips Affinity (Philips, Botheli, USA) device with a 3-MHz probe under synchronous electrocardiography. The patients took at least a 10-minute rest before echocardiographic evaluation. All measurements were performed on 3 consecutive cardiac cycles. All patients were evaluated by two-dimensional and M-mode echocardiography, pulsed-wave Doppler for blood flow velocity through the mitral valve, and tissue Doppler imaging (TDI) for right and left ventricles, as recommended by the American Society of Echocardiography.[18]

Conventional Echocardiography

Two-dimensional echocardiography, including standard views as apical 4-chamber, parasternal short and long axis, suprasternal, and subcostal imaging planes was performed to evaluate cardiac structure and function.

The M-mode echocardiography was performed at parasternal long-axis view. The parameters measured were ejection fraction (EF), fractional shortening (FS), end-systolic (IVSs) and end-diastolic interventricular septum thickness (IVSd), left ventricular end-systolic (LVDs) and end-diastolic diameter (LVDd), end-systolic (LVPWs) and end-diastolic left ventricular posterior wall thickness (LVPWd), respectively. To assess the biventricular longitudinal systolic function, mitral (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were estimated at apical 4-chamber view. Right ventricular end-diastolic diameter (RVDd) at annular level was also obtained. The left ventricular diastolic mass (LVM) was estimated using the Devereux formula.[19] Left ventricular mass index (LVMI) was calculated as the ratio of the left ventricular mass to the body surface area.

In addition, antegrade mitral valve pulsed-wave Doppler was performed to evaluate left ventricular diastolic function. Therefore, the mitral inflow early diastolic velocity (E) was measured 1-2 mm above the mitral leaflets by a pulsed-wave Doppler.

Tissue Doppler Echocardiography

TDI was performed through the apical 4-chamber view, and the myocardial sample size was assessed as parallel as possible to the direction of maximum annular motion with a sample volume gate length < 5 mm. Biventricular TDI examination was performed at the lateral annulus of tricuspid and mitral valves. The velocities of diastolic and systolic peaks were measured on tissue Doppler tracings of annular motion with simultaneous electrocardiography. As for the assessment of systolic function, ejection time (ET), isovolumetric contraction time (IVCT) and systolic velocity (S') were measured. On the other hand, early- (E') and late-diastolic velocities (A') and isovolumetric relaxation time (IVRT) were measured for diastolic function. The velocity ratio of the blood flow Doppler-derived mitral inflow E wave to the tissue Doppler-derived E' wave were obtained to assess LV diastolic function. IVRT was measured from the end of the S' wave to the onset of the E' wave, and IVCT was measured from the end of the A' wave to the onset of the S' wave. Myocardial performance index (MPI), which is an indicator of the global ventricular systolic and diastolic function, was estimated using the Tei formula [MPI = (IVCT+IVRT)/ET].[20]

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences, Version 15 (SPSS, Chicago, USA). The sample size was determined by a priori two-sample *t*-test power analysis using G power software with an 85% statistical power at significance level of 0.05 and an effect size 0.56. The Kolmogorov–Smirnov test was used for assessment of normal distribution. All normally distributed data were shown as mean ± standard deviation, otherwise they were presented as median (minimum-maximum) value. Comparisons for continuous variables were analyzed with the independent samples *t*-test or Mann–Whitney *U*-test. For categorical variables, while 2 groups were compared using the chi-square test, multiple groups were compared using analysis of variance or Kruskal–Wallis tests. Correlations between variables were analyzed using Pearson's or Spearman's correlation coefficient. *P* values of < .05 were indicated as statistically significant.

RESULTS

Characteristics of CCSs and Controls

The mean age of the CCSs at the time of cancer diagnosis was 6.07 ± 4.33 years (8 months-17 years). The different diagnoses of CCSs were acute lymphoblastic leukemia ($n = 38$), acute myelogenous leukemia ($n = 5$), Hodgkin lymphoma ($n = 1$), non-Hodgkin lymphoma ($n = 3$), Wilms' tumor ($n = 2$), and renal cell carcinoma ($n = 1$). The mean duration of time from completion of chemotherapy to echocardiographic assessment was 3.9 ± 2.2 years (1-9.6 years). The mean age of the CCSs and controls at the time of evaluation did not reveal significant difference ($P = .964$). As for other demographic variables, there was no significant difference between the groups (Table 1). While the cumulative anthracycline dose was 246.5 ± 92.5 mg/m^2 overall, it was 153.2 ± 39.4 mg/m^2 in the low-dose group, 240 mg/m^2 in the moderate-dose group, and 371.8 ± 106.8 mg/m^2 in the high-dose group.

Echocardiography Findings of CCSs and Controls

Left ventricular systolic function, left and right ventricular (RV) dimensions, and biventricular longitudinal systolic functions of CCSs were normal and comparable with the controls (Table 2). In addition, the aforementioned echocardiographic measurements did not reveal significant differences according to the cumulative anthracycline dose (Table 3).

Tissue Doppler interrogation of the lateral mitral annulus revealed that the IVRT and MPI were significantly higher in CCSs than in controls ($P = .006$, $P = .007$). There was no difference between the groups in terms of E' and A' velocities, E'/A' ratio, S' velocity, ET, and IVCT ($P > .005$) (Table 4). In subgroup analysis of the lateral mitral annulus TDI, as revealed in Table 4, TDI-derived MPI and IVRT were significantly higher in CCSs who had received a higher cumulative anthracycline dose than controls ($P = .014$, $P < .001$ respectively), and this difference was derived between the high- and low-dose groups for IVRT (subgroup comparison revealed a *P* value of .007). According to the correlation analysis, the cumulative anthracycline dose was significantly associated with TDI-derived mitral annular MPI and IVRT ($r = 0.288$, $P = .006$, $r = 0.340$, $P = .001$). In addition, there was a negative correlation between TDI-derived MPI and early diastolic myocardial velocity (E') ($r = -0.276$, $P = .009$). TDI-derived myocardial functional parameters (MPI,

Table 1. Demographic Characteristics of the Groups

Variables	CCSs ($n = 50$)	Controls ($n = 40$)	*P*
Age (years)	11.45 (4.25-18)	12 (6-17)	.964[a]
Gender (male/female)	23/27	17/23	.740[b]
Height (cm)	147.5 (104-180)	147.4 (123-178)	.640[a]
Body weight (kg)	43.48±16.12	41.15 ± 15.61	.500[c]
BMI (kg/m^2)	19.68±3.91	18 ± 12.96	.060[c]

[a]Mann–Whitney *U*-test; [b]Chi-square test; [c]Independent samples *t*-test.
BMI, body mass index; CCS, childhood cancer survivor.

Table 2. Comparison of Two-Dimensional and M-Mode Echocardiographic Findings

Variable	CCSs ($n = 50$)	Controls ($n = 40$)	*P*
EF (%)	68.83 ± 6.22	69.63 ± 5.78	.532[c]
FS (%)	38.32 ± 5.11	38.97 ± 4.86	.542[c]
LVDs (mm)	26.28 ± 3.89	25.99 ± 3.82	.727[c]
LVDd (mm)	42.41 ± 4.70	41.98 ± 5.78	.877[c]
IVSs (mm)	8.65 ± 1.49	8.59 ± 1.96	.862[c]
IVSd (mm)	6.88 ± 1.44	6.82 ± 1.26	.838[c]
LVPWs (mm)	10.42 ± 1.60	11.12 ± 1.77	.052[c]
LVPWd (mm)	6.38 ± 1.35	6.84 ± 1.28	.106[c]
LVM (g)	84.96 ± 32.27	88.03 ± 33.18	.659[c]
LVMI (g/m^2)	63.90 ± 14.53	66.06 ± 13.70	.414[c]
RVDd (mm)	31.33 ± 4.60	31.69 ± 3.57	.681[c]
MAPSE	13 (7-24)	13.25 (9-20)	.646[a]
TAPSE	17.9 (12.2-28.7)	18.6 (11.8-28)	.261[a]

[a]Mann–Whitney *U*-test; [c]Independent samples *t*-test.
IVSd, end-diastolic interventricular septum thickness; IVSs, end-systolic interventricular septum thickness; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; LVPWs, left ventricular end-systolic posterior wall thickness; LVM, left ventricular diastolic mass; LVMI, left ventricular mass index; EF, ejection fraction; FS, fractional shortening; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; RVDd, right ventricular end-diastolic diameter.

Table 3. Comparison of the Two-Dimensional and M-Mode Echocardiographic Variables Between the Subgroups

Variables	Low-Dose group ($n = 13$)	Moderate-Dose Group ($n = 26$)	High-Dose Group ($n = 11$)	Controls ($n = 40$)	*P**
EF (%)	71.28 ± 4.26	67.68 ± 6.30	68.64 ± 7.60	69.63 ± 5.78	.322[d]
FS (%)	39.64 ± 4.41	37.58 ± 5.05	38.52 ± 6.14	38.97 ± 4.87	.606[d]
LVDs (mm)	23.97 ± 3.32	27.40 ± 3.47	26.37 ± 4.56	25.99 ± 3.83	.069[d]
LVDd (mm)	39.55 ± 4.64	43.80 ± 4.33	42.51 ± 4.49	41.98 ± 5.78	.076[d]
IVSs (mm)	8.30 ± 1.87	8.75 ± 1.38	8.85 ± 1.32	8.59 ± 1.96	.849[d]
IVSd (mm)	6.13 ± 1.50	7.37 ± 1.40	6.62 ± 1.12	6.82 ± 1.26	.166[d]
LVPWs (mm)	9.98 ± 1.78	10.6 ± 1.65	10.54 ± 1.26	11.23 ± 1.91	.129[d]
LVPWd (mm)	5.86 ± 1.60	6.71 ± 1.20	6.22 ± 1.31	6.84 ± 1.29	.097[d]
LVM (g)	66.75 ± 28.37	94.97 ± 32.71	82.82 ± 27.69	88.03 ± 33.18	.089[d]
LVMI (g/m^2)	60.48 ± 15.34	68.18 ± 14.48	57.82 ± 11.13	66.06 ± 13.70	.200[d]
RVDd (mm)	30.02 ± 4.47	32.09 ± 3.71	31.09 ± 6.46	31.70 ± 3.58	.479[d]
AOd/Lad	0.65 ± 0.11	0.65 ± 0.08	0.68 ± 0.14	0.67 ± 0.13	.887[d]
MAPSE	12.4 (8.5-18)	13.15 (7-18)	13 (11-24)	13.25 (9-20)	.595[e]
TAPSE	17 (12.5-24)	19.8 (13-28.7)	17.5 (12.2-23)	18.6 (11.8-28)	.15[e]

[d]ANOVA; [e]Kruskall–Wallis test.
IVSd, end-diastolic interventricular septum thickness; IVSs, end-systolic interventricular septum thickness; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; LVPWs, left ventricular end-systolic posterior wall thickness; LVM, left ventricular diastolic mass; LVMI, left ventricular mass index; EF, ejection fraction; FS, fractional shortening; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; RVDd, right ventricular end-diastolic diameter.

IVRT, E', and A') were not correlated with post chemotherapy duration (r = 0.105, $P = .469$, r = 0.245, $P = 0.086$, r = 0.124, $P = .392$, r = -0.169, $P = .241$, respectively). There was no statistically significant difference either between the CCSs and controls or between the subgroups in regard to lateral tricuspid annulus TDI ($P > .05$) (Table 5).

Table 4. Comparison of TDI Parameters Between Groups

Variables	CCSs ($n = 50$)	Controls ($n = 40$)	*P*
Left ventricle			
E (cm/s)	93.01 ± 15.38	99.24±16.60	.069[c]
E' (cm/s)	11.78 ± 2.53	12.44±2.09	.097[c]
E/E'	8.17 ± 2	8.11±1.48	.857[c]
A' (cm/s)	6.05 ± 1.58	6.13±1.78	.906[c]
E'/A'	2.01 ± 0.45	2.15±0.61	.204[c]
S' (cm/s)	7.56 ± 1.84	7.84±1.44	.078[c]
IVRT (ms)	56.26 ± 11.93	50.15±7.85	**.006**[c]
IVCT (ms)	48 (32-74)	49.5 (34-69)	.975[a]
ET (ms)	275 ± 19	282±26	.173[c]
MPI	0.38 ± 0.06	0.35±0.04	**.007**[c]
Heart rate	76.76 ± 12.92	77.67±12.96	.740[c]
Right ventricle			
E' (cm/s)	13.91 ± 2.64	14.26 ± 2.33	.520[c]
A' (cm/s)	9.32 ± 2.70	9.29 ± 2.33	.919[c]
E'/A'	1.58 ± 0.42	1.60± 0.30	.600[c]
S' (cm/s)	11.86 ± 2.48	11.7 ± 2.08	.612[c]
TV (m/s)	1.81 ± 0.30	1.77 ± 0.31	.555[c]
IVRT (ms)	47.18 ± 13.63	45.25 ± 12.20	.551[c]
IVCT (ms)	53 (32-71)	55 (26-74)	.428[a]
ET (ms)	272.9 ± 25.6	279.12 ± 24.13	.244[c]
MPI	0.36 ± 0.66	0.35 ± 0.06	.468[c]

[a]Mann–Whitney *U* test; [c]Independent samples *t*-test.
E, early diastolic ventricular inflow velocity; E', early diastolic myocardial velocity; A', late diastolic myocardial velocity; HR, heart rate; IVRT, isovolumetric relaxation time; IVCT, isovolumetric contraction time; ET, ejection time; MPI, myocardial performance index; S', systolic myocardial velocity; TV, tricuspid valve.

DISCUSSION

According to the present study, there was no marked cardiac dysfunction or myocardial remodeling in the long-term (between 1 and 9) years after the termination of the chemotherapy in CCSs who received anthracycline without mediastinal irradiation. However, tissue Doppler examination revealed findings consistent with subclinical cardiotoxicity in the left ventricle. While the presence of the subclinical cardiotoxicity was not correlated with follow-up length, it was significantly related with the cumulative anthracycline dose.

Cardiotoxicity resulting from anthracycline-induced cardiomyocyte damage is a chronic problem in CCSs and is the most common cause of death in these patients, other than cancer. The development process and predisposition to cardiotoxicity has been the area of interest for current and previous studies aiming to contribute to the development of preventive methods.[20-23] Over the years, significant progress has been reported in the decrease of left ventricular systolic function, cardiac output, and posterior wall thickness, which were first detected 6 years after completion of chemotherapy, in children who received anthracyclines.[21,22] Long-term follow-up results indicated that the cumulative anthracycline dose was not the single determinant of cardiotoxicity. The risk of cardiac damage persisted even in patients who received low cumulative dose.[22] Therefore, children who receive low cumulative doses are also at risk of developing cardiovascular disease in the long term. Furthermore, the detection of significant subclinical structural changes in the left ventricle in children with a cumulative dose of less than 100 mg/m^2 at least 6 years after treatment was consistent with this view.[23] In the current study, the mean duration between completion of chemotherapy and echocardiographic evaluation was 3.9 ± 2.2 years, and

Table 5. Comparison of TDI Parameters Between Subgroups

Variables	Low-Dose Group ($n = 13$)	Moderate-Dose Group ($n = 26$)	High-Dose Group ($n = 11$)	Controls ($n = 40$)	*P*
Left ventricle					
E (cm/s)	96.47 ± 13.63	93.73 ± 14.87	87.25 ± 18.18	99.24 ± 16.60	.147[d]
E/E'	8.77 ± 1.71	8.04 ± 2.16	7.79 ± 1.99	8.11 ± 1.48	.551[d]
E' (cm/s)	11.36 ± 2.59	12.14 ± 2.77	11.42 ± 1.87	12.44 ± 2.09	.217[d]
A'(cm/s)	5.46 ± 0.96	6.22 ± 1.60	6.37 ± 2.03	6.13 ± 1.78	.427[d]
E'/A'	2.10 ± 0.42	2.02 ± 0.46	1.89 ± 0.46	2.15 ± 0.61	.473[d]
S' (cm/s)	7.33 ± 1.70	7.85 ± 2.12	7.16 ± 1.18	7.84 ± 1.44	.239[d]
IVRT (ms)	50.61 ± 9.34	55.81 ± 11.47	64 ± 12.51**	50.15 ± 7.85	**<.001**[d]
IVCT (ms)	50 (42-74)	48 (32-74)	48 (34-66)	49.5 (34-69)	.932[e]
ET (ms)	267.31 ± 22.19	277.73 ± 18.19	280 ± 17.27	282.13 ± 26.06	.342[d]
MPI	0.41 ± 0.05	0.38 ± 0.06	0.40 ± 0.06***	0.36 ± 0.04	**.016**[d]
Right ventricle					
E' (cm/s)	13.92 ± 2.38	14.08 ± 2.73	13.55 ± 2.93	14.26 ± 2.34	.813[d]
A' (cm/s)	8.54 ± 2.79	9.62 ± 2.82	9.55 ± 2.31	9.29 ± 2.33	.496[d]
E'/A'	1.73 ± 0.43	1.56 ± 0.45	1.46 ± 0.35	1.60 ± 0.38	.345[d]
S' (cm/s)	11.65 ± 2.65	11.55 ± 2.58	12.85 ± 1.90	11.70 ± 2.08	.748[d]
TV (m/s)	1.86 ± 0.25	1.84 ± 0.32	1.69 ± 0.32	1.78 ± 0.32	.630[d]
IVRT (ms)	44 ± 10.86	48 ± 15.03	49 ± 13.62	45.53 ± 12.21	.698[d]
IVCT (ms)	50 (39-71)	54 (32-69)	50 (35-70)	55 (26-74)	.825[e]
ET (ms)	260.85 ± 21.69	278.69 ± 25.26	273.45 ± 28.21	279.13 ± 24.14	.122[d]
MPI	0.37 ± 0.06	0.36 ± 0.06	0.38 ± 0.09	0.36 ± 0.06	.697[d]

[d]ANOVA; [e]Kruskall–Wallis test.
**Subgroup comparison revealed a *P* value of .007 between group IC and group IA; <.001 between group IC and group II; ***Subgroup comparison revealed a *P* value of .014 between group IC and group II.
E, mitral inflow early diastolic velocity; E', early diastolic myocardial velocity; A', late diastolic myocardial velocity; S', systolic myocardial velocity; IVRT, isovolumetric relaxation time; IVCT, isovolumetric contraction time; ET, ejection time; MPI, myocardial performance index; TV, tricuspid valve.

the findings of left ventricular structure and systolic function did not reveal significant difference in comparison with their peers. In our cohort, where the mean cumulative dose was 246.5 ± 92.5 mg/m^2, the duration after the completion of the treatment may not be sufficient for marked cardiac damage, and cardiotoxicity might be more evident in the following years.

Considering the marked findings, anthracycline-induced cardiac damage has usually become evident over the long-term. Investigation of predictive parameters in the follow-up of individuals suspected to be at risk may be a useful tool. Determination of subclinical signs of cardiotoxicity may facilitate the use of pharmacological and/or non-pharmacological cardioprotective strategies to reduce the progression and severity of cardiac injury for patients who require them. Thus, TDI has begun to take its place in clinical practice as an imaging method to determine subclinical signs of myocardial damage. In 45 CCSs who completed anthracycline chemotherapy at least 1 year ago, although left ventricular morphology and functions were compatible with their healthy peers according to conventional echocardiography methods, the signs of myocardial deterioration were detected by TDI.[24] Moreover, according to another study, the findings consistent with subclinical myocardial diastolic impairment could be detected by TDI, even in patients with only a follow-up period of 2 years after the completion of chemotherapy.[25] It is known that diastolic dysfunction caused by cardiomyocyte damage related with systemic disorders may often progress to heart failure, in which systolic functions are preserved.[26,27] In the present study, the detection of longer duration of the TDI-derived IVRT in CCSs was consistent with the subclinical impairment in left ventricular diastolic functions. Similar to our results, Küpeli et al.[28] also reported prolonged IVRT measured by TDI as a consistent finding with subclinical diastolic dysfunction, in pediatric patients that received a high dose (>350 mg/m^2) of anthracycline. In addition, higher MPI values in CCSs were also consistent with subclinical global myocardial dysfunction in the present study. The MPI was previously reported as a non-invasive and sensitive indicator of subclinical anthracycline cardiotoxicity in CCSs.[29,30] Furthermore, a significant correlation was indicated between MPI and myocardial diastolic velocities.[29] Similar to the study by Karakurt C. et al.,[29] higher MPI values were established at the lower myocardial early diastolic velocities, as an indicator of subclinical diastolic dysfunction, in the current study.

Among the many risk factors of CVD in childhood, cumulative dose is one of the most prominent, associated with anthracycline cardiotoxicity.[31] The meta-analysis of 25 articles about the prevalence and risk factors of anthracycline-related cardiotoxicity stated that the frequency of an abnormal SF seemed to be higher for patients treated with a mean or median cumulative dose > 300 mg/m^2 anthracyclines (15.5-27.8%) than for patients treated with a cumulative dose < 300 mg/m^2 (0-15.2%).[11] It was reported in a study that the risk of systolic dysfunction increased 3-fold in patients who received chemotherapy and whose FS was found to be less than 29% in any follow-up period. Additionally, the risk of mortality was also stated to be increased 7-fold in these patients.[32] Similar to previous studies, the current study also revealed that consistent

with the subclinical left ventricular myocardial dysfunction, the TDI-derived MPI and IVRT values were higher in CCSs who received a cumulative dose > 300 mg/m^2.

The long-term detrimental effects of anthracyclines on left ventricular myocardial function in CCSs are well-known. In contrast, there are insufficient data on RV function in CCSs, particularly in the long term. Although there was no abnormality in RV size in adults with CCSs, a subclinical decrease in RV systolic functions was detected which was 3 times more common in those with LV dysfunction.[33] Identification of the harmful effects of anthracyclines on the right ventricle may require a long follow-up period, and the exposure to radiotherapy increases the risk significantly. Among the 33 leukemia or lymphoma patients who received lung toxic chemotherapy, 11 patients who suffered from radiotherapy-induced restrictive lung disease had decreased TAPSE and isovolumetric acceleration as an evidence of RV dysfunction.[34] Fifty CCSs who received anthracycline with various cumulative doses, but were not exposed to radiotherapy, were similar in RV structure and functions to healthy peers as examined by TDI and TAPSE, in the present study. Considering the previous studies, this may be related to the fact that harmful impact of chemotherapy on RV structure and function becomes evident in the long-term and more pronounced with a concomitant left ventricular dysfunction. Therefore, there is a need for longitudinal studies including a large number of cases to provide a more comprehensive understanding of the harmful effects of anthracyclines on the right ventricle.

Being single-centered, and having a limited number of cases seem to be the major limitations of our cross-sectional research study. The topic merits further investigation with more extensive and comparative study design with a higher number of cases and a longer follow-up period.

CONCLUSION

Cardiac impairment due to anthracyclines is more prominent with higher cumulative doses in children who received chemotherapy. However, more follow-up time may be required for significant myocardial dysfunction to become evident with decreased EF. TDI can be a useful method to reveal subclinical cardiotoxicity findings especially like restrictive physiology in asymptomatic children who received anthracycline chemotherapy for childhood cancer and were estimated normal according to conventional echocardiography.

Ethical Committee Approval: Ethical committee approval was received from the Institutional Ethical Committee of Eskisehir Osmangazi University on October 8, 2019. (Approval number: E.120185).

Informed Consent: Written informed consent was obtained from the patients' legal guardians.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – Ö.B., P.K., M.Ç., B.U.; Design - Ö.B., P.K., M.Ç., B.U.; Supervision - Ö.B., P.K.; Resource - M.Ç., P.K.; Materials - Ö.B., P.K., B.U.; Data Collection and/or Processing - P.K., M.Ç.; Analysis and/or Interpretation - P.K., M.Ç.; Literature Search - P.K., M.Ç.; Writing - P.K., M.Ç.; Critical Reviews - P.K., Ö.B., Z.C.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol.* 2014;32(12):1218-1227. [CrossRef]
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582. [CrossRef]
3. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: Part 1. *J Am Coll Cardiol.* 2017;70(20):2536-2551. [CrossRef]
4. Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. *J Clin Oncol.* 2018;36(21):2135-2144. [CrossRef]
5. Lipshultz SE. Exposure to anthracyclines during childhood causes cardiac injury. *Semin Oncol.* 2006;33(3)(Suppl 8):S8-14. [CrossRef]
6. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. *Future Cardiol.* 2012;8(4):647-670. [CrossRef]
7. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6-19 years after anthracycline therapy: a series of 15 patients. *Med Pediatr Oncol.* 1995;24(6):352-361. [CrossRef]
8. Lenaz L, Page JA. Cardiotoxicity of adriamycin and related anthracyclines. *Cancer Treat Rev.* 1976;3(3):111-120. [CrossRef]80018-7)
9. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol.* 2015;16(3):e123-e136. [CrossRef]70409-7)
10. Nysom K, Holm K, Lipsitz SR, et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. *J Clin Oncol.* 1998;16(2):545-550. [CrossRef]
11. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation.* 2013;128(17):1927-1995. [CrossRef]
12. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voûte PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. *Ann Oncol.* 2002;13(6):819-829. [CrossRef]
13. Bansal N, Amdani S, Lipshultz ER, Lipshultz SE. Chemotherapy-induced cardiotoxicity in children. *Expert Opin Drug Metab Toxicol.* 2017;13(8):817-832. [CrossRef]
14. Sundberg KK, Lampic C, Björk O, Arvidson J, Wettergren L. Positive and negative consequences of childhood cancer influencing the lives of young adults. *Eur J Oncol Nurs.* 2009;13(3):164-170. [CrossRef]
15. Xu XY, Huang MR, Tang JY, et al. Evaluation of early monitoring of cardiotoxicity induced by anthracyclines. *Zhongguo Dang Dai Er Ke Za Zhi.* 2011;13(6):490-494.
16. Wolf CM, Reiner B, Kühn A, et al. Subclinical cardiac dysfunction in childhood cancer survivors on 10-years follow-up correlates With cumulative anthracycline dose and is best detected by cardiopulmonary exercise testing, circulating serum biomarker,

speckle tracking echocardiography, and tissue Doppler imaging. *Front Pediatr*. 2020;8:123. [CrossRef]
17. Children's Oncology Group. *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers Version 5.0 (October 2018)*. Arcadia: Children's Oncology Group; 2018. (Available at: http://www.survivorshipguidelines.org/)
18. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23(5):465-95; quiz 576. [CrossRef]
19. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation*. 1977;55(4):613-618. [CrossRef]
20. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. *J Cardiol*. 1995;26(6):357-366.
21. Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. 1991;324(12):808-815. [CrossRef]
22. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2005;23(12):2629-2636. [CrossRef]
23. Leger K, Slone T, Lemler M, et al. Subclinical cardiotoxicity in childhood cancer survivors exposed to very low dose anthracycline therapy. *Pediatr Blood Cancer*. 2015;62(1):123-127. [CrossRef]
24. Yoldaş T, Yeşil Ş, Karademir S, et al. Evaluation of long-term cardiac side effects of anthracycline chemotherapy by conventional and non-conventional echocardiographic methods in childhood cancer survivors. *Cardiol Young*. 2019;29(7):904-909. [CrossRef]
25. Venturelli F, Masetti R, Fabi M, et al. Tissue Doppler Imaging for anthracycline cardiotoxicity monitoring in pediatric patients with cancer. *Cardiooncology*. 2018;4:6. [CrossRef]
26. Mesquita ET, Jorge AJ. Understanding asymptomatic diastolic dysfunction in clinical practice. *Arq Bras Cardiol*. 2013;100(1):94-101. [CrossRef]
27. Nicol M, Baudet M, Cohen-Solal A. Subclinical left ventricular dysfunction during chemotherapy. *Card Fail Rev*. 2019;5(1):31-36. [CrossRef]
28. Yağci-Küpeli B, Varan A, Yorgun H, Kaya B, Büyükpamukçu M. Tissue Doppler and myocardial deformation imaging to detect myocardial dysfunction in pediatric cancer patients treated with high doses of anthracyclines. *Asia Pac J Clin Oncol*. 2012;8(4):368-374. [CrossRef]
29. Karakurt C, Koçak G, Ozgen U. Evaluation of the left ventricular function with tissue tracking and tissue Doppler echocardiography in pediatric malignancy survivors after anthracycline therapy. *Echocardiography*. 2008;25(8):880-887. [CrossRef]
30. Ocal B, Oguz D, Karademir S, et al. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin-treated patients and its correlation to conventional echo/Doppler indices. *Pediatr Cardiol*. 2002;23(5):522-527. [CrossRef]
31. Perez IE, Taveras Alam S, Hernandez GA, Sancassani R. Cancer therapy-related cardiac dysfunction: an overview for the clinician. *Clin Med Insights Cardiol*. 2019;13:1179546819866445. [CrossRef]
32. Toro-Salazar O.H, Gillan E, Ferranti J, et al. Effect of myocardial dysfunction in cardiac morbidity and all-cause mortality in childhood cancer subjects treated with anthracycline therapy. *Cardiooncology*. 2015;1(1):1. [CrossRef]
33. Christiansen JR, Massey R, Dalen H, et al. Right ventricular function in long-term adult survivors of childhood lymphoma and acute lymphoblastic leukemia. *Eur Heart J Cardiovasc Imaging*. 2016;17(7):735-741. [CrossRef]
34. Patel A, Weismann C, Weiss P, et al. Association between right ventricular dysfunction and restrictive lung disease in childhood cancer survivors as measured by quantitative echocardiography. *Pediatr Blood Cancer*. 2014;61(11):2059-2064. [CrossRef]