Assessment of Left Ventricular Function in Childhood Cancer Survivors by 2D Conventional Echocardiography

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Abstract: Objective: To assess left ventricular function in childhood cancer survivors by 2D conventional echocardiography. **Background:** Two-dimensional echocardiography is considered one of the most widely used methods for detection of cardiotoxicity in childhood cancer survivors (CCS). **Patients and Methods:** In this case-control study, left ventricular functions were assessed by 2 D conventional echocardiography in 40 pediatric childhood cancer survivors and 20 healthy children as controlled. All of the participants were subjected to complete history taking and thorough clinical examination. **Results:** Most of the survivors (25 children) were diagnosed as ALL, 8 as NHL and 7 as HL. Their age at diagnosis of cancer ranged between 2 and 16 years. All of our survivors were treated with anthracycline based protocols of chemotherapy and the cumulative dose of anthracycline ranged between 75 and 400 mg/m^2. The systolic and diastolic blood pressures were significantly higher in the survivors group than the control group. the EF and FS (which represents the LV systolic function) were significantly lower in the survivors group than the control group though still within the normal values while no significant difference in LVEDD and LVESD. Also, the mitral E/A ratio (which represents the LV diastolic function) was significantly lower in the survivors group than the control group. **Conclusion:** Childhood cancer survivors are at higher risk of developing cardiac complications. Thus follow up of cardiac condition is mandatory in CCS.
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1. Introduction

Cancer therapies are used worldwide; yet, although chemotherapy is beneficial by destroying malignant cells, it can simultaneously cause injury or death to myocardial cells or, in other words, cardiotoxicity. The resulting paradox for cancer patients is, frequently, premature death without treatment and, possibly, irreversible myocardial cell dysfunction, potentially leading to heart failure (HF) and death, with treatment, if not recognized early. Presently, chemotherapy-induced cardiotoxicity limits the ability to reduce morbidity and mortality associated with cancers throughout the world **(Oreto et al., 2012).**

Chemotherapy-induced cardiotoxicity has forced both cardiologists and oncologists to deal with the early detection of cardiotoxicity to set up strategies to prevent irreversible cardiac damage and heart failure **(Mele et al., 2015).**

Most survivors of childhood malignancies had received anthracyclines (a class of drugs whose cardiotoxicity has been known for more than 40 years) as a part of their treatment. These drugs are used to treat both hematological malignancies and solid tumors **(Lipshultz et al., 2015).**

The most commonly hypothesized mechanism for anthracycline-induced cardiotoxicity is the generation of free radicals and superoxides. Anthracycline-induced loss or damage to a critical number of cardiomyocytes decreases the number of residual myocardial cells, which are required to generate a normal myocardial mass, despite the marked hypertrophy of the remaining cardiomyocytes **(Lipshultz et al., 1991).** Cardiomyocyte loss leads to LV wall thinning and, with early to intermediate follow-up during the first six years after anthracycline therapy, to progressive LV dilation. Cardiomyocyte mitochondrial structure and function are particularly affected by anthracycline exposure, and these effects may be persistent **(Lipshultz et al., 2012).**

Late-occurring cardiotoxicity related to anthracycline treatment is initially subclinical, often progressive, potentially severe, and sometimes fatal. More than half of survivors have subclinical cardiac abnormalities 5–10 years after chemotherapy **(Lipshultz et al., 2015).**

Echocardiography is one of the most widely used noninvasive methods for early detection and monitoring of doxorubicin-induced cardiotoxicity in

childhood cancer survivors (CCS)**(Al-Bitagi et al., 2012).**

Echocardiography has the advantage of being a non-invasive method that does not involve the use of radiation. In addition to reporting the LVEF, it provides other information on cardiac morphology, chamber size, and valvular and diastolic function**.** However, the measurement of LVEF presents a number of challenges related to image quality, assumption of left ventricular geometry, load dependency, and expertise **(Plana, 2011).**

2. Methods

This study was performed on 40 pediatric patients who finished their chemotherapy treatment in the Hematology and Oncology Unit of the pediatric department in the Menoufia University Hospitals during their follow up visits. All the patients were treated by chemotherapy according to the approved protocol of the unit.

The study was done over the period from October 2014 to March 2016.

Also, the study included 20 healthy children with matched age and sex as control.

Written informed consent was obtained from each patient's legal guardians as well as permission from the faculty ethical committee.

The following broad inclusion and exclusion criteria were used:-

- **Inclusion criteria:**

Pediatric Childhood Cancer survivors (CCS) who received anthracycline in the form of Doxorubicin as part of their treatment protocol.

- **Exclusion criteria:**

1. Presence of any cardiac disease either congenital or acquired.
2. Presence of any associated systemic disease that can affect the cardiac function, and/or medication that can affect cardiac function, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or beta-blockers.

Study design:

Study population

This is a comparative case-control study. The studied children were categorized into the following groups:

Group (A): Included 40 childhood cancer survivors (24 males & 16 females) who finished their treatment from 6 months to 8 years before starting the study. Their age ranged between 4 and 17 years with median age 12 years.

Group (B): Included 20 healthy children of matched age and sex with no history of medical problems who served as controls.

Both groups were subjected to:

I-Full history taking: including:

1- Personal history (name, age, sex & residence).

2- History of past illness of group A.

3- Drug history of group A: all of them were treated with chemotherapy, but none of them was exposed to radiotherapy.

II-Examination:

General examination:

- **Vital signs:**
  - **Arterial Blood Pressure (ABP):** measured with standard mercury sphygmomanometer after the subjects had rested at least for 10 minutes with the arm at heart level **(Bickley et al., 2013).**
  - **Heart Rate**: assessed by measuring the radial pulse in one minute **(Bickley et al., 2013).**
- **Chest examination.**
- **Abdominal Examination.**
- **Neurological Examination.**

Local Examination:

- **Cardiac Examination:** included inspection, palpation and auscultation of the heart.

III-Imaging:

- **Conventional Echocardiography.**

Methods:

Our survivors were previously diagnosed with childhood cancer (ALL, HL and NHL). They were treated with anthracycline based protocols of chemotherapy. They all received doxorubicin (adriamycin) in their protocol of therapy. The cumulative dose of adriamycin ranged from 75 to 400 mg/m^2 according to the corresponding protocol used in our unit. Our ALL survivors were treated by: CCG protocol with dose of adriamycin ranged from 75 to 175 mg/m^2 according to risk stratification and by St. Jude Total XV protocol with dose 110 mg/m^2 for low risk and 230 mg/m^2 for standard risk. Our HL survivors were treated by ABVD protocol with a dose ranged from 200 to 400 mg/m^2. While our NHL survivors were treated by modified FAB/LMB 96 protocol with dose ranged from 120 to 240 mg/m^2.

Both groups were subjected to cardiac assessment by 2D conventional echocardiography.

- **Conventional Echocardiography:**

Echocardiographic exams performed in the left lateral decubitus, in the parasternal long, short-axis, apical 2 & 4-chamber views using standard transducer positions. GE vivid9 Norton Norway equipped with multi-frequency 1.7-4 MHz MS5 transducer utilized. Left ventricular (LV) end diastolic diameter (EDD), end systolic diameter (ESD), Ejection Fraction (EF %) and Fractional shortening (FS) measured in accordance with the recommendations of the **American Society of Echocardiography and the European Association of Cardiovascular Imaging**

(Mor-Avi et al., 2011). Peak early (E) and late (A) transmitral filling velocities measured to calculate (E/A ratio) for mitral inflow velocities.

Statistical Analysis

The results were collected, tabulated and statistically analyzed by SPSS (Statistical Package for Social Science) version 22.0 on IBM compatible computer. Two types of statistics were used: mean and standard deviation (SD) were used for descriptive statistics e.g. percentage (%). Chi-squared test (χ^2), Fisher's exact test, Student t-test, Mann-Whitney test (U), Pearson's correlation and Spearman's correlation for analytic statistics. A p-value of <0.05 was considered statistically significant and a p-value of <0.0001 was considered statistically highly significant.

3. Results

Table (1): Demographic characteristics of cases

Characteristics	**Total number of cases = 40**	
Age at study (years) Mean ± SD Range	 11.2±3.9 4 – 17	
Age at diagnosis (years) Mean ± SD Range	 7.02±3.2 2 – 16	
Gender Male Female	**No.** 24 16	**%** 60.0 40.0

SD = standard deviation.

The age of children survivors at time of our study ranged between 4 and 17 years. While their age at diagnosis ranged between 2 and 16 years. Twenty four (60%) of them were males and 16 (40%) were females.

The age of children survivors ranged between 4 and 17 years. Twenty four (60%) of them were males and 16 (40%) were females. The control group has matched age and gender.

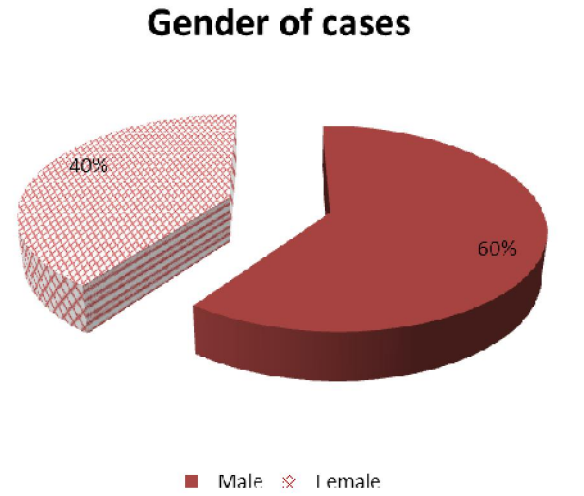

Figure 1: The gender of the survivors group

Table (2): Comparison of the Demographic characteristics of studied groups

Studied variables	**Cases (n=40)**		**Controls (n=25)**		**Mann Whitney Test**	**P value**
Age (years) Mean ± SD Range	11.2±3.9 4 – 17		9.4±4.1 3.7 – 17		1.70	0.09 NS
	No.	**%**	**No.**	**%**	**χ^2 test**	**P value**
Gender Male Female	24 16	60.0 40.0	12 13	48.0 52.0	0.89	0.34 NS

χ^2 test = Chi square test, SD = standard deviation; NS= non-significant (P-value > 0.05)

Regarding the types of malignancies in the study group, most of survivors were diagnosed as ALL (62.5%), (17.5%) diagnosed as HL and (20%) diagnosed as NHL. The most frequent clinical presentation at diagnosis was fever in 26 (65%) survivors followed by pallor in 23 (57.5%), lymphadenopathy in 21 (52.5%), hepatomegaly in 17 (42.5%), splenomegaly and bleeding each in 14 (35%), respiratory infection in 13 (32.5%), abdominal mass in 6 (15%), then lastly mediastinal mass in 2 (5%) of survivors. They received their chemotherapy with different protocols according to their diagnosis. Eight ALL survivors on CCG protocol [5 (12.5%) as standard risk and 3 (7.5%) as high risk], 18 survivors (17 ALL & 1 T-cell NHL) on St. Jude Total XV protocol [14 (35%) as standard risk and 4 (10%) as low risk], 7 HL survivors (17.5%) were treated according ABVD protocol and lastly 7 NHL survivors (17.5%) on Modified FAB/LMB 96 protocol. Their duration of chemotherapy ranged between 1 and 46 months. All of our survivors were treated with anthracycline based protocols of chemotherapy and none of them received radiotherapy in their treatment. The cumulative dose of anthracycline to the survivor

group ranged between 75 and 400 mg/m^2. The cumulative dose of anthracycline for ALL survivors ranged between 75 and 230 mg/m^2 and for HL survivors between 200 and 400 mg/m^2. While for NHL survivors, it ranged between 120 and 240 mg/m^2.

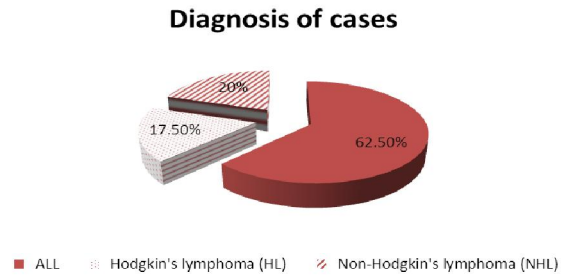

Figure 2: Types of malignancies among the survivors group

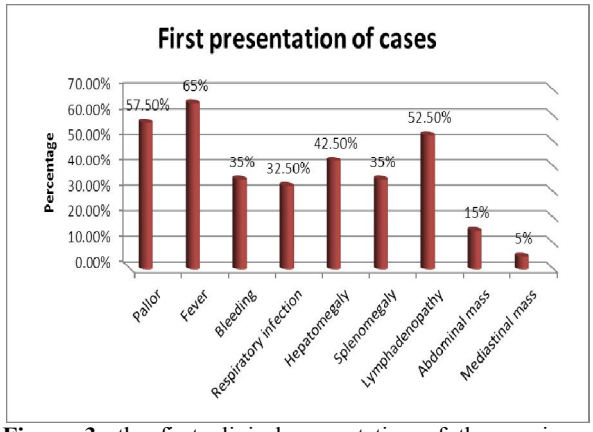

Figure 3: the first clinical presentation of the survivors group at diagnosis

Table (3): Clinical characteristics of cases

Characteristics	**Total number of cases = 40**	
Diagnosis		
Acute lymphoblastic leukemia (ALL)	25	62.5
Hodgkin's lymphoma (HL)	7	17.5
Non-Hodgkin's lymphoma (NHL)	8	20.0
First presentation at diagnosis	**No.**	**%**
Pallor	23	57.5
Fever	26	65.0
Bleeding	14	35.0
Respiratory infection	13	32.5
Hepatomegaly	17	42.5
Splenomegaly	14	35.0
Lymphadenopathy	21	52.5
Abdominal mass	6	15.0
Mediastinal mass	2	5.0
Duration of chemotherapy (months)		
Mean ± SD	25.2±16.1	
Range	1 – 46	
Protocol	**No.**	**%**
CCG high	3	7.5
CCG standard	5	12.5
Total XV low	4	10.0
Total XV standard	14	35.0
ABVD	7	17.5
Modified FAB/LMB 96	7	17.5
Cumulative dose of adriamycin(mg/m^2)		
Mean ± SD	198.8±77.1	
Range	75 – 400	
Cumulative dose of adriamycin(mg/m^2)		
• **For ALL survivors:**		
Mean ± SD	179.2±59.4	
Range	75 – 230	
• **For HL survivors:**		
Mean ± SD	300±75.6	
Range	200 – 400	
• **For NHL survivors:**		
Mean ± SD	171.3±45.1	
Range	120 – 240	

SD = standard deviation, **ABVD**= [(A) driamycin, (B) leomycin, (V) inblastine, (D) acarbazine], **CCG**= Children's Cancer Group

Table (4): Blood pressure and heart rate of studied groups

Parameters	Cases (n=40)	Controls (n=25)	t-Test	P value
SBP (mmHg)				
Mean ± SD	107.9±8.7	100.4±10.1	**t**=3.16	0.002
Range	80 - 125	80 – 120		S
DBP (mmHg)				
Mean ± SD	66.8±7.6	61.8±7.2	**t**=2.59	0.01
Range	50 - 80	50 - 80		S
HR (bpm)				
Mean ± SD	83.9±8.4	84.4±7.5	**t**=0.23	0.82
Range	75 - 114	70 - 101		NS

t= student's t test U=Mann-Whitney Test
SBP: systolic blood pressure, **DBP:** diastolic blood pressure, **HR:** heart rate, **bpm:** beats per minute
NS= non-significant (P-value > 0.05), S = significant (P-value ≤ 0.05)
HS= highly significant (P-value ≤ 0.001).

Regarding the blood pressure, the systolic and diastolic blood pressures were significantly higher in the survivors group than the control group. But regarding heart rate there was no significant difference between survivors and control groups

Table (5): Conventional Echocardiographic findings of studied groups

Parameters	Cases (n=40)	Controls (n=25)	t-Test	P value
LVEDD				
Mean ± SD	38.8±3.9	38.9±5.6	0.09	0.93
Range	30 - 48	30 – 49		NS
LVESD				
Mean ± SD	26.1±3.1	25.1±4.9	0.85	0.40
Range	18 - 30	18 - 34		NS
EF (%)				
Mean ± SD	64.6±4.2	67.6±2.5	3.73	<0.001
Range	56 - 73	63 – 72		HS
FS (%)				
Mean ± SD	32.1±2.4	33.8±1.2	3.79	<0.001
Range	28 - 41	31.5 – 36		HS
E/A				
Mean ± SD	1.5±0.17	1.6±0.15	3.36	0.001
Range	1.11 – 1.94	1.32 – 1.83		HS

t= student's t test
LVEDD: left ventricular end diastolic diameter, **LVESD:** left ventricular end systolic diameter, **EF:** ejection fraction, **FS:** fractional shortening, **E:** early transmitral flow velocity, **A:** atrial transmitral flow velocity
NS= non-significant (P-value > 0.05), HS= highly significant (P-value ≤ 0.001).

Regarding Echocardiographic data of survivors and control groups, the Ejection Fraction (EF %) and Fractional shortening (FS)(which represents the LV systolic function) were significantly lower in the survivors group than the control group though still within the normal values while no significant difference in LVEDD and LVESD. Also, the mitral E/A ratio (which represents the LV diastolic function) was significantly lower in the survivors group than the control group.

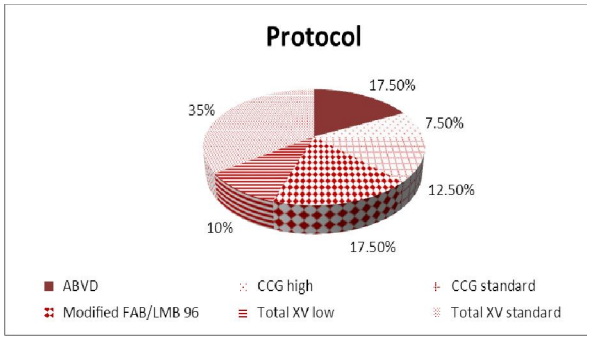

Figure 4: Different protocols of chemotherapy received by the survivors group

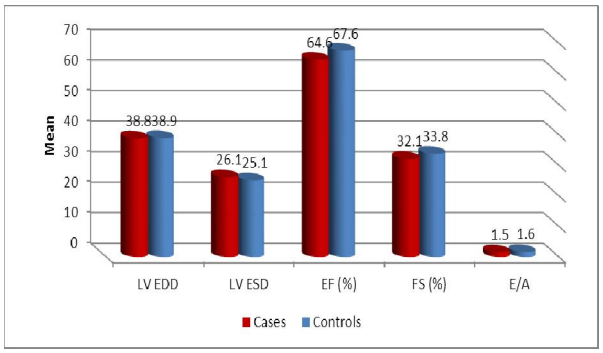

Figure 5: Conventional Echocardiographic findings among studied groups

4. Discussion

Advancements in therapies for childhood cancer have increased their survival, but the cardiovascular related health burden is increasing. Optimal monitoring strategies and preventive treatments still need to be identified. Treatment-related cardiovascular effects may appear decades after treatment and are often progressive and irreversible. Thus, screening, preventing, or reducing treatment-related cardiovascular damage, screening for risk factors, and implementing serial cardiac monitoring are important for survivors of childhood cancer **(Lipshultz et al., 2015).**

Cardiotoxicity is generally evaluated by assessing the LV ejection fraction (LV-EF), which is defined as the LV (end-diastolic volume minus the end-systolic volume)/end-diastolic volume. Generally, the LV-EF is obtained using 2-D echocardiography, which has the advantage of being a widespread technique **(Bovelli et al., 2010).**

The aim of this study was to evaluate left ventricular function in childhood cancer survivors by 2D conventional echocardiography.

The demographic data of the study showed that the age of survivors at study ranged between 4 and 17 years and their age at diagnosis of cancer ranged between 2 and 16 years. Twenty four of them were males (60%) and 16 were females (40%). The control group has matched age and gender**.**

This agrees with the study ofcancer incidence of the **Middle East Cancer Consortium (MECC) (2006)** in four member countries (Cyprus, Egypt, Israel, and Jordan). The Gharbiah Regional Cancer Registry collected data from all governmental, non-governmental, and private centers and laboratories dealing with cancer patients mainly from the National Cancer Institute in Cairo and Gharbiah government. The study reported that, in Egypt from 1996 to 2001, total diagnosed new cases with childhood cancer below age of 20 years were 1813. Males were 1063 (58.6%) and 750 (41.4%) were females.

Regarding the diagnosis of the patients, 25 children (62.5 %) patients were diagnosed as ALL, while 7 children (17.5%) as Hodgkin's lymphoma and 8 children (20.0 %) were diagnosed as non-Hodgkin's lymphoma.

Our result is consistent with **Ward et al., (2014)**, who stated that ALL is considered the most common cancer in children in USA and accounting for 26%, followed by Non-Hodgkin's Lymphoma 6% and Hodgkin's Lymphoma 4 % for estimated cases of childhood cancer.

Regarding the presenting symptoms and signs of our survivors at the time of their diagnosis with cancer, we found that the most frequent clinical presentations were fever in 26 (65%) of them followed by pallor in 23 (57.5%), lymphadenopathy in 21 (52.5%), hepatomegaly in 17 (42.5%), splenomegaly in 14 (35%), bleeding in 14 (35%), respiratory infection in 13 (32.5%), abdominal mass in 6 (15%), then lastly mediastinal mass in 2 (5%) of survivors.

Our results were in accordance with that reported by **Clarke et al., (2016).** They performed a meta-analysis of 33 studies (number of patients=3084). They could identify 95 presenting signs and symptoms. Five features were present in >50% of children: hepatomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%) and bruising (52%). An additional eight features were present in a third to a half of children: recurrent infections (49%), fatigue (46%), limb pain (43%), hepatosplenomegaly (42%), bruising/petechiae (42%), lymphadenopathy (41%), bleeding tendency (38%) and rash (35%). In addition, 6% of children were asymptomatic on diagnosis.

All of our cases were treated with anthracycline based protocols of chemotherapy and none of them received mediastinal radiotherapy in their treatment. They received their chemotherapy according to their diagnosis. Eight ALL survivors on CCG protocol [5 (12.5%) as standard risk and 3 (7.5%) as high risk], 18 survivors (17 ALL & 1 T-cell NHL) on St. Jude Total XV protocol [14 (35%) as standard risk and 4 (10%) as low risk], 7 HL survivors (17.5%) were treated according ABVD protocol and lastly 7 NHL survivors (17.5%) on Modified FAB/LMB 96 protocol. Their duration of chemotherapy ranged between 1 and 46 months. The cumulative dose of anthracycline to the survivor group ranged between 75 and 400 mg/m^2. The cumulative dose of anthracycline for ALL survivors ranged between 75 and 230 mg/m^2 and for HL survivors between 200 and 400 mg/m^2. While for NHL survivors, it ranged between 120 and 240 mg/m^2**.**

Regarding the blood pressure, we found that the systolic and diastolic blood pressures were significantly higher in the survivors group than the control group. However, regarding heart rate there was

no significant difference between survivors and control groups**.**

Our results are in consistence with that reported by **Gunn et al., (2016).** They recorded the blood pressure for 269 survivors. They found that 19.0% (n=51) had hypertension (hypertension prevalence in survivors <18 years 11.3% and 28.7% in those >18 years old).

Armstrong et al., (2015) performed a study to determine the prevalence of cardiac dysfunction in adult survivors of childhood malignancies by echocardiographic evaluation of cardiac function. The study included 1,820 CSS (946 males & 874 females). They were treated at St. Jude Children's Research Hospital (SJCRH). Median age at evaluation was 31 years (range 18-65). They were exposed to either anthracycline chemotherapy (N=1,050), chest directed radiotherapy (N=306), or both therapies (N=464). The anthracycline cumulative dose ranged from 100 to 600 mg/m^2. They found that patients with hypertension (systolic blood pressure ≥ 130 mmHg, diastolic ≥ 85 mmHg or treatment for hypertension) were 816 survivors (45.2%).

In 2014, **Nottage et al.,** performed a study to evaluate cardiovascular risk factors among Long-Term Survivors of ALL from the St. Jude Lifetime Cohort. The study included 784 survivors of median age 31.7 years; they were evaluated and compared with 777 matched controls in age, sex and race from the National Health and Nutrition Examination Survey (NHANES). They found that hypertension was identified among 364 survivors (46.4%).

It is well established that long-term survivors of childhood cancer have an increased risk of cardiac disease and cardiac-specific mortality **(Brouwer et al., 2011).** Chemotherapy is associated with higher systolic blood pressure; the exact mechanism is unclear, but it may be due to damage of the vascular endothelium, resulting in vascular alterations **(Casco and Soto, 2016).** Additionally, radiotherapy could have a damaging effect on the endothelium **(Van Waas et al., 2010).**

Regarding Echocardiographic data of the studied groups, the Ejection Fraction (EF %) and Fractional shortening (FS)(which represents the LV systolic function) were significantly lower in the survivors group than the control group **(p value <0.001)** though still within the normal values while no significant difference in LV end diastolic diameter (EDD) **(p value=0.93)** and LV end systolic diameter (ESD) **(p value=0.40).** Also, the mitral E/A ratio (which represents the LV diastolic function) was significantly lower in the survivors group than the control group **(p value =0.001).**

This is in agreement with the following studies:

In 2016, **Ylänen et al.,** performed a study to detect the decrease in cardiac function in anthracycline-exposed CCS. The study included 75 (34 male & 41 female) survivors from Finland. Their mean age was (14.3 ± 3.1) years. They were compared to 75 matched healthy children as controls. The median cumulative anthracyclines dose received by the survivors group was 223 mg/m^2. They found that that the survivors group had lower EF and FS compared to the control group (P<0.001).

Bayram et al., (2015) performed a study for evaluation of cardiotoxicity by Tissue Doppler Imaging in leukemia CCS treated with anthracycline. The study included 60 ALL survivors (31 male and 29 female) treated in Turkey. They were compared to 30 age- and gender-matched healthy children (15 male and 15 female). Median age of patients was 11.7 years. All patients were treated with a low cumulative dose of adriamycin (100 mg/m^2). They found that there were not any significant differences between the patient and control groups in terms of LVEDD. Also, the EF and FS were normal in the patient and control groups, even though EF values were significantly lower in the patients (P < 0.01).

In 2013, **Mavinkurve-Groothuis et al.,** performed a study to investigate myocardial 2D strain echocardiography and cardiac biomarkers for assessment of cardiac function in children with acute lymphoblastic leukemia (ALL) during and shortly after treatment with anthracyclines. The study included 60 (37 male & 23 female) children with ALL and compared with 60 healthy age-matched controls. The median age of patients at diagnosis was 6 years. The first cardiac evaluation was done in the first week of ALL treatment (before the first anthracycline dose) (T=0). The second cardiac evaluation was performed at the end of the induction phase of the ALL treatment (10 weeks after start of treatment and 5 weeks after the latest anthracycline dose) (T=1). The third cardiac evaluation was performed 1 year after start of ALL treatment (at least 2 weeks after the last anthracycline dose) (T=2). All patients had received anthracycline and the range of cumulative anthracycline dose was (120–300 mg/m^2). They found that none of the patients showed clinical signs of cardiac failure or abnormal FS. However, FS decreased significantly after the first dose of anthracyclines (P<0.0001). Also, the patients group at T=2 showed significantly decreased FS compared to control group (p=0.002). Also, they found that E/A ratio was significantly lower in patients group T=2 than control group (p=0.03).

Also in 2012, **Poterucha et al.,** performed a study that aimed to assess the changes in LV longitudinal peak systolic strain (LPSS) and their correlation with parameters of LV systolic dysfunction associated with Anthracycline chemotherapy in

adolescents. The study included 19 prospectively enrolled pediatric patients (12 male and 7 female) with a mean age at cancer diagnosis of (15.3 ± 30 years. The mean cumulative anthracycline dose was (296 ± 103 mg/m^2). They were compared to 19 controls matched for age and gender. For patients, echocardiography was performed at baseline, mid, and final treatment points (0, 4, and 8 months). They found that there was no significant difference in LVEDD and LVESD at 4 and 8 months compared with baseline. Also they found that the percentage change in EF showed a statistically significant decrease at 8 months (P= 0.044). Also there was a significant difference between the patients group and controls identified for E/A ratio at the 4-month ($p < 0.01$) and 8-month ($p < 0.001$) time points.

Although the molecular and genetic mechanisms of anthracycline-induced cardiotoxicity are not completely understood, the innate presence of quinone groups is believed to cause anthracyclines to produce free radicals in both normal and malignant cells that react with oxygen to produce superoxide anion radicals, causing cardiotoxicity **(Raj et al., 2014).**

Other pathophysiologic considerations include decreased adenosine triphosphate (ATP) production, direct damage to mitochondria, mitochondria-dependent apoptosis in the heart and cardiomyocytes, and lipid peroxidation of the cardiac myocyte membrane **(Rebbaa et al., 2001).**

Anthracyclines also affect mitochondrial metabolism due to iron accumulation and changes in mitochondrial gene expression. This causes further oxidative damage and affects myocardial energy metabolism. Cell membrane changes and other mechanisms influence calcium metabolism resulting in increased intracellular calcium levels. This activates the pathways resulting in apoptosis and cardiac cell death in certain more vulnerable cells **(Rajic et al., 2009).**

While normal myocardium has some regenerative capacity, recent studies showed that anthracyclines influence cardiac repair mechanisms by reducing the pool of cardiac stem cells and possibly through inhibiting other regenerative pathways **(De Angelis et al., 2010).**

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