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Original Article

Paediatrics Section

Tissue Doppler Imaging and Focal, Late-Onset Anthracycline-Induced Cardiovascular Disease in Long Term Survivors of Childhood Cancer: A Research Article

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ABSTRACT

Introduction: In anthracycline-induced cardiomyopathy, the onset of diastolic dysfunction occurs before systolic dysfunction. Although, conventional echocardiogram is the standard method to assess cardiac function post anthracycline therapy, Tissue Doppler Imaging (TDI) may detect early onset cardiac diastolic dysfunction among anthracycline-recipient survivors of childhood cancers. There are limited data on the use of TDI in assessing anthracycline-associated cardiotoxicity in children.

Aim: To evaluate the role of Tissue Doppler Imaging (TDI) in assessing late-onset cardiotoxicity in survivors of paediatric cancers.

Materials and Methods: This was a single site, observational, blinded study of 11 long-term survivors of childhood cancer who had been treated with anthracyclines and 22 age-matched controls. The study group and the control group underwent conventional echo and TDI; operators were blind to study group. Conventional echo measurements were obtained. TDI was used to assess systolic and diastolic parameters at the mid-interventricular septum and lateral and medial annuli of the mitral valve; these parameters included: systolic wave (S'), early diastolic wave (E'), late diastolic wave (A'), Isovolemic Contraction Time (ICT), Isovolemic Relaxation Time (IRT) and Ejection Time (ET). Myocardial Performance Index (MPI) was also calculated.

Results: Conventional echo measurements were similar in both groups. Using TDI, cases had a lower mean E' velocity (9.7 ± 1.7 cm/s vs. 11.4 ± 1.3 cm/s, p=0.004) and a lower E'/A' (1.8 ± 0.5 vs. 2.2 ± 0.4, p=0.022) at the mid-interventricular septum than controls. The mean E' septum velocity in chemotherapy-recipients who also received chest radiotherapy was 8.5±0.5 cm/s in comparison to 10.2±1.7 cm/s in those that did not receive chest radiotherapy but this not achieve statistical significance. We did not find any additional associations between TDI parameters and patients' gender, age of diagnosis, length of follow-up and dose of anthracycline.

Conclusion: In long-term survivors of childhood cancer who received anthracyclines, diastolic dysfunction can be detected earlier by using TDI before overt systolic dysfunction. Further large-scale multicenter studies are needed.

Keywords: Cardiotoxicity, Diastolic dysfunction, Focal cardiomyopathy

INTRODUCTION

Anthracycline-Induced Cardiotoxicity (AIC) can occur in three categories: acute, early-onset chronic progressive and late-onset chronic progressive. It may manifest as subclinical and clinical heart failure. Subclinical refers to cardiac abnormalities in individuals without symptoms associated with myocardial dysfunction [1]. Cumulative toxicity is generally because of cardiomyocyte death and resultant dysfunction. Anthracycline-induced loss of myocytes is manifested first as diastolic dysfunction, followed by progressive systolic dysfunction [2].

Routine surveillance of long term survivors of childhood cancer who were treated with cardiotoxic drugs is recommended with the hope of detecting abnormalities early and providing potential life-saving interventions [2]. Guidelines from the Children's Oncology Group for childhood cancer survivors recommend the use of conventional echocardiography (echo) to monitor for myocardial toxicity [3,4]. Conventional echo detects changes in systolic function well; however, it is not sensitive in detecting early, subclinical diastolic dysfunction [5-7]. Tissue Doppler Imaging (TDI) is a modality that uses Doppler principles to measure the velocity of myocardial motion and to obtain systolic and diastolic time intervals [8]. Another measurement obtained by TDI is the Myocardial Performance Index (MPI), also known as Tei index. The MPI is considered to be a more reliable parameter to assess global ventricular function. MPI can also be calculated by conventional echocardiography, but unlike that obtained by TDI it is subject to variations with heart rate fluctuations. The other advantages of TDI are: 1) it is relatively independent from volume loading conditions; and 2) it allows the assessment of subclinical long-axis myocardial dysfunction that cannot be detected by LV systolic function measurements [8,9].

TDI has been used by various researchers to evaluate diastolic dysfunction in amyloidosis, diabetes, myocardial infarction, hypertrophic cardiomyopathy and subclinical hypothyroidism [10-13]. In iron-overloaded thalassaemia patients, TDI was sensitive and specific in predicting myocardial dysfunction. All these studies detected lower cardiac performance by TDI which was not identified by conventional echocardiography.

There are limited data on the use of TDI in assessing cardiac toxicity from anthracyclines in children with cancer. These studies included evaluation of acute and long-term anthracycline-associated cardiotoxicity in children with various childhood malignancies

[5-7,14,15]. We sought to investigate the utility of TDI in detecting early abnormalities in cardiac function and to determine the risk factors associated with detecting these abnormalities in long-term survivors of childhood cancers that received anthracyclines at our institution.

MATERIALS AND METHODS

This was a single site, observational, blinded, cohort study. The study group included long term (atleast three years from last chemotherapy dose) survivors of childhood cancer who were originally treated at the Meade Paediatric Haematology-Oncology Clinic at St. John Hospital and Medical Center (Detroit, MI) from 1990 to 2009. Thirty eight subjects met eligibility criteria but only 11 subjects agreed to participate from July 2013 to December 2013; the majority of those who did not participate could not be reached or failed to communicate intent of participation. The study subjects were recruited by either phone call or mail. The comparison group (controls) consisted of age-matched healthy adolescents seeing paediatricians for well visits, staff and resident physicians who volunteered to participate. A total of 22 controls were recruited to achieve a 2:1 control: subject ratio, for a total of 33 total participants.

Eligibility criteria for the study group included: Diagnosis of Hodgkin's lymphoma, non-Hodgkin's lymphoma, T-cell Leukaemia or osteogenic sarcoma, a minimum anthracycline dose of 50 mg/m^2, at least three years after final chemotherapy dose, and normal cardiac function prior to chemotherapy. Controls were included if there was no family history of cardiomyopathy. We excluded subjects who were treated with liposomal anthracycline. Controls were excluded if they had fever and/or anaemia at the time of study or history of systemic, vascular or cardiopulmonary disease.

Participant characteristics that were collected included age, race, gender, Blood Pressure (BP), Heart Rate (HR), anthropometric measurements and medications currently being used. A chart review was performed on the study group subjects to collect data pertaining to date of diagnosis, stage of disease, cumulative dose of anthracycline, date of last dose of anthracycline and Radiotherapy to chest (RT). Informed consent was obtained from the subject older than 18 years and from the parents or guardian if younger than 18 years. Assent was obtained in the latter group. Institutional review board approval was obtained at our institution.

Echocardiography

A conventional echo was performed with a Phillips iE33 ultrasound machine (Phillips, Andover, MA), with age appropriate probes. The echo was performed according to the guidelines of the American Society of Echocardiography, in the presence of an electrocardiogram recording [16]. The study was performed by one of two sonographers using a standard clinic protocol and was reviewed by a paediatric cardiologist well versed in the protocol. Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), Ejection Fraction (EF), and Fractional Shortening (FS) were measured. Normal EF and FS were defined as greater than 55% and 29%, respectively. Peak transmitral filling velocities in early diastole (E) and late diastole (A) was obtained by pulse wave Doppler at the tip of the mitral leaflets from the apical four chamber view and E/A ratio was calculated.

TDI was performed to obtain systolic wave (S'), early diastolic wave (E'), late diastolic wave (A'), Isovolemic Contraction Time (ICT), Isovolemic Relaxation Time (IRT) and Ejection Time (ET) [17]. These were measured at the level of the mid-portion of the inter-ventricular septum and at the medial and lateral annuli of the mitral valve. E' < 10 cm/s, A' < 4.5 cm/s, and S' < 5.5 cm/s were considered abnormal, based on the established normal values by age [18]. Myocardial performance index was calculated by dividing the sum of Isovolumetric Contraction Time (ICT) and Isovolumetric Relaxation Time (IRT) by the Ejection Time (ET). The technicians and the cardiologists were blinded to cumulative anthracycline dose. The cardiologist was blinded to the subject being studied.

STATISTICAL ANALYSIS

Data were analysed using SPSS v 21.0. Student's 't'-test was used to compare the data obtained by conventional echo and TDI between cases and controls. Chi-squared analysis was used for comparison of categorical variables. Pearson's correlation was used to analyse if there was a correlation between the TDI parameters values and other disease variables such as time since chemotherapy and dose of chemotherapy. A p-value <0.05 was considered to be statistically significant.

RESULTS

Eleven study subjects and 22 healthy volunteers had standard ECHO and TDI measurements done as per study guidelines. [Table/Fig-1] shows, a comparison of anthropometric measurements between study group and control subjects; there were no significant differences in age, gender, weight, BMI, heart rate and both systolic and diastolic blood pressures. Among the chemotherapy group, six had diagnoses of Hodgkin's lymphoma, three had NHL and two had T-cell ALL. The mean age at diagnosis was 12 ± 7.5 years with a mean anthracycline dose of 240 mg/m^2 and a mean follow up of 9.2 ± 4.9 years. Three patients with mediastinal mass (Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma and T Cell ALL) received chest radiotherapy. The two patients with T Cell ALL received cardio-protectant (ZinecardR, a chelating agent often used with doxorubicin) as part of the treatment protocol.

Conventional Echocardiogram and TDI Parameters

[Table/Fig-2] shows, conventional echo parameters for both control and study groups. There was no statistical difference in any of the parameters obtained. More importantly, none of the subjects in the study group demonstrated fractional shortening (FS) less than 29%. Also, of the 8 anthracycline-recipients in whom baseline FS was available, none had a decline of more than 10% at follow-up (data not shown).

TDI parameters did not reveal significant differences at the medial and lateral annuli of the mitral valve among the groups. At the mid portion of the inter-ventricular septum, however, there were significant differences with lower E' septum velocity in the study

	Study group Mean ± SD	Controls Mean ± SD	p-value
Gender (Males %/N)	63% (7)	32% (7)	0.08
Age	23.1 ± 7.8	23.6 ± 7.5	0.88
BSA	1.8 ± 0.18	1.7 ± 0.24	0.33
BMI	24.8 ± 3.7	23.9 ± 4.2	0.42
HR	69.7 ± 11.4	69.5± 13.8	0.36
SBP	111.5 ± 15.3	120.7 ± 15.0	0.57
DBP	63.8 ± 9.7	65.8 ± 6.8	0.96

[Table/Fig-1]: Comparison of controls and study subjects.

	Study group (n=11) Mean ± SD	Controls (n=20) Mean ± SD	p-value
LVEDD (mm)	50.1 ± 3.8	48.8 ± 5.5	0.49
LVESD (mm)	31.9 ± 2.9	31.6 ± 3.7	0.79
EF	65.5 ± 4.6	64.4 ± 2.6	0.47
FS	36.2 ± 3.5	35.6 ± 2.3	0.58
E (m/s)	0.87 ± 0.13	0.85 ± 0.15	0.60
A (m/s)	0.52 ± 0.15	0.48 ± 0.09	0.29
E/A ratio	1.7 ± 0.33	1.8 ± 0.43	0.55

[Table/Fig-2]: Conventional echo parameters for control and study groups.

group (9.7 ± 1.7 cm/s) compared to the control group (11.4 ± 1.3 cm/s) (p=0.004) and lower E'/A' (1.8 ± 0.51) compared to the control group (2.2 ± 0.45) (p= 0.022). We did not find a significant difference in the MPI at the medial and lateral mitral annuli or at the interventricular septum [Table/Fig-3]. Six out of the 11 study subjects (55 %) had a E' septum velocity values of <10 cm/s in comparison to two out of 22 control subjects (9%) (p=0.004).

The mean E' septum velocity in chemotherapy-recipients who also received chest radiotherapy was 8.5±0.5 cm/s in comparison to 10.2±1.7 cm/s in those that did not receive chest radiotherapy but this not achieve statistical significance (p= 0.146). All three study group subjects who received chest RT had E' septum velocity <10 cm/s compared to 37.5% in those that did not receive RT. There was no significant correlation between the E' septum velocity with anthracycline dose (r=-0.4, p=0.222), and time since last dose (r=-0.35, p=0.28). There was no correlation between E' septum velocity and age of diagnosis or gender.

	Study group (n=11) Mean ± SD	Controls (n=20) Mean ± SD	p-value
S' (cm/s)	6.0 ± 0.8	6.2 ± 0.7	0.45
E' (cm/s)	9.7 ± 1.7	11.3 ± 1.4	0.004
A' (cm/s)	5.6 ± 1.0	5.3 ± 0.9	0.360
E'/A'	1.8 ± 0.5	2.2 ± 0.5	0.022
ICT (ms)	63.6 ± 6.5	65.7 ± 7.7	0.46
IRT (ms)	63.7 ± 6.3	63.4 ± 9.1	0.92
ET (ms)	294.9 ± 39.9	283.4 ± 23.5	0.32
MPI	0.44 ± 0.08	0.46 ± 0.08	0.50

[Table/Fig-3]: TDI at mid-interventricular septum.

DISCUSSION

Cardiotoxicity is the main dose limiting effect of anthracyclines; it is associated with significant morbidity and mortality especially when administered during childhood. Such cardiotoxicity can present acutely or chronically, and symptomatically or asymptomatically. Late onset toxicity is defined as that manifesting at least one year after the last dose of anthracyclines [2]. Younger patients, female sex, those receiving higher anthracycline doses (more than 240 mg/m^2), and with cardiac exposure to ionizing radiation are at higher risk of developing cardiotoxicity [19-22].

There appears to be still a lot of controversy with regards to the incidence of cardiotoxicity at different cumulative doses of anthracyclines. Therefore, to be less vigilant with patients receiving lower doses of anthracyclines (e.g., 50 mg/m^2) does not appear to be prudent. This emphasizes the need for earlier detection by non-invasive methods. TDI appears to be the answer with minimal to no extra cost and non-invasive nature.

It has been shown that almost two thirds of childhood cancer survivors who received anthracyclines show cardiac structural as well functional abnormalities. Only 4 to 5% of exposed individuals develop clinically significant heart failure after 15 years of the initiation of therapy indicating that a significant percent of those exposed have subclinical disease [1,19,21]. The prognosis for those with clinical heart failure is poor [1]. Thus, strategies to prevent this toxicity and to intervene early in those with subclinical disease are imperative [2]. TDI may detect anthracycline induced cardiotoxicity early [8]. Our results confirm the notion that TDI may detect diastolic dysfunction before overt systolic dysfunction is seen by standard echocardiography [20].

We found significantly lower diastolic parameters at the mid portion of the interventricular septum only, thereby suggesting focal involvement of the myocardium. Focal abnormalities were also found by Kapusta [7]. In the study by Alehan, abnormalities in diastolic parameters were found at multiple locations. In addition, they found significantly lower systolic velocity which was consistent with the lower FS seen in their patients [15]. We did not find lower systolic velocities and none of our patients had abnormal FS. Our interpretation of these discrepancies is that their patients had more advanced and/or diffuse disease. We also demonstrated a lower E'/A' ratio at the mid-septum only, thereby corroborating the presence of focal diastolic dysfunction. We believe that the normal MPI values among our patients also indicate absence of global myocardial dysfunction. Regional abnormalities have been demonstrated acutely after anthracycline therapy in children [5]. Whether these acute changes correlate with long term focal changes should be investigated prospectively. The significance of these findings in relation to future development of systolic dysfunction is not known. In the study by Dorup et al., abnormally reduced E' was not strongly associated with future development of decreased FS [20]. Others suggest that even changes seen shortly after administration of anthracyclines predict future systolic dysfunction [5].

We did not find evidence of subclinical toxicity by standard echocardiography in contradiction with the findings of others who report significant abnormalities in a high percentage of cases [2,21,22]. One possible explanation is that the majority of our patients received less than the 300 mg/m^2, with only three subjects receiving over the 300 mg/m^2. Our findings are also in agreement with the findings of a systematic review that reported a very low incidence of subclinical cardiotoxicity in children receiving doses less than 300 mg/m^2 [22].

LIMITATION

The main limitation of this study was the small sample size of the study group, in part due to the inability to establish contact with many of the long-term survivors.

CONCLUSION

These results emphasize the need to establish long-term follow-up programs for survivors of childhood cancers. It is important to educate patients and parents about the importance of continued surveillance as they reach adulthood. An effort to orchestrate care of these patients with primary care physicians is also important. Given that the risk of cardiac mortality is higher among long-term survivors, continuous surveillance to detect abnormalities early is needed. Identification of early diastolic dysfunction may warrant medical therapy to prevent progression to systolic dysfunction. Routine assessment of diastolic and systolic dysfunction using TDI should be considered as part of the routine assessment of cardiac evaluation.

ABBREVIATIONS AND ACRONYMS

AIC = Anthracycline Induced Cardiotoxicity
BMI = Body Mass Index
BSA = Body Surface Area
DBP = Diastolic Blood Pressure
ET = Ejection Time
FS = Fractional Shortening
HR = Heart Rate
ICT = Isovolemic Contraction Time
IRT = Isovolemic Relaxation Time
LVEDD = Left Ventricular End Diastolic Diameter
LVESD = Left Ventricular End Systolic Diameter
MPI = Myocardial Performance Index
RT = Radiotherapy
SBP = Systolic Blood Pressure
TDI = Tissue Doppler Imaging

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