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Research Article

Implication of 2D-Speckle Tracking Deformation in Early Detection and Management of Anthracyclines Induced Left Ventricular Dysfunction in Pediatric Patients with Solid Tumors

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Abstract

Objectives: To evaluate the role of 2D-speckle tracking strain in early detection and management of subclinical impairment of left ventricular (LV) systolic function in anthracyclines treated pediatric patients with solid tumors.

Methods: Anthracyclines treated solid tumor patients between 1 - 14 years were included. Left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) were calculated by the standard equation. 2D-speckle global longitudinal strain (GLS) was recorded from the apical 4, 3 and 2 chamber views. These parameters were compared to the same parameters in 50 controls. Patients were divided depending on their LVEF into; group I with LVEF < 58% and group II with LVEF < 58%. All patients with impaired GLS (< -18%) whatever their LVEF and LVFS values underwent cardiac management (ACEI, spironolactone and B-blocker). Follow up echocardiography was done after each cycle of anthracyclines.

Results: The study included 110 patients with solid tumors (osteosarcoma 35.5%, Ewing sarcoma 20%, neuroblastoma 33.6%, hepatosarcoma 4.5% and Wilm's tumor 6.3%). The mean age was 11.04 ± 3.78 years. LVEF, LVFS and GLS were impaired in anthracyclines treated patients than in the control group (LVEF: 59.2 ± 4.10%, 62.23 ± 1.89% respectively, P < 0.001*), (LVFS: 29.59 ± 2.10%, 31.17 ± 0.70% respectively, P < 0.001*) and (GLS of -17.82 ± 3.40%, -21.77 ± 1.62%, P < 0.001*). Group I included 60 (54.55%) patients with LVEF of 54.65 ± 2.53%, LVFS of 27.27 ± 1.37% and GLS of - 13.22 ± 2.67%, all were significantly lower than in the control group (P < 0.001*). Group II included 50(45.45%) patients with LVEF of 61.32 ± 2.74%, LVFS of 30.67 ± 1.37% and GLS of -19.96 ± 2.36%.

Despite there was no difference in LVEF and LVFS between group II and control group, GLS was significantly impaired in group II (P = 0.002*). Patients with impaired GLS (52 patients) started cardiac treatment and showed improvement of LVEF from to 57.12 ± 4.1% to 63.18 ± 2.38% (P < 0.001*), LVFS from 29.82 ± 2.51% to 33.97 ± 2.58% (P < 0.001*) and GLS from -14.29 ± 2.07% to - 19.31 ± 0.45% (P < 0.001*).

Conclusions: 2D-speckle GLS is useful in early detection of LV endocardial dysfunction associated with anthracyclines especially in patients with good LVEF < 58%; in them despite their normal LVEF and LVFS, their GLS denotes early impairment of function. It is also useful in starting early management and salvage of cardiac function.

Keywords: *Anthracyclines Induced Dysfunction; Cardiotoxicity in Pediatrics; Speckle Tracking Strain; LV Strain; Speckled Strain*

Abbreviations

HF: Heart Failure; AIC: Anthracyclines Induced Cardiotoxicity; LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening; 2D: Two-Dimensional; LV: Left Ventricle; GLS: Global Longitudinal Strain; QS: Quantitative Strain; ACEI: Angiotensin Converting Enzyme Inhibitor

Introduction

Anthracyclines, especially doxorubicin and daunorubicin, are the main drugs in the management of patients with hematologic malignancies, soft-tissue sarcomas, and solid tumors [1]. Unfortunately, their use is limited by their dose-dependent cumulative effect, manifested as toxic cardiomyopathy with or without symptoms and signs of heart failure (HF) [2].

Anthracyclines-induced cardiotoxicity (AIC) are classified as acute or chronic, immediate or late, toxicity and this leads to increased morbidity and mortality. Even many children treated with less than 300 mg/m^2 doses of anthracyclines still can manifest with cardiac dysfunction [3]. Unfortunately, asymptomatic AIC is a serious problem in pediatric cancer patients and moreover may appear even after a long time in cancer survivors [4].

Echocardiography is the most common non-invasive diagnostic tool used for monitoring Anthracyclines induced cardiotoxicity. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) are the commonest Echo parameters for assessment of cardiac function. Several definitions of cardiotoxicity have been proposed [5]. The most commonly used definition is reduction in left ventricular ejection fraction (LVEF) more than 5% in symptomatic patients (or more than 10% in asymptomatic patients) from baseline or reduction of LVEF less than 55% [6]. Early detection of cardiotoxicity has mainly based on serial cardiac imaging at close follow up to identify any reduction in LV function without signs or symptoms of heart failure [7]. Unfortunately depending on LVEF has appreciated limitations; first, the measurement of LVEF is a technique and operator dependent which can carry many falsies [6,8], second, the reduction in LVEF is often a late phenomenon, with increased rate of failure to recover systolic function in up to 58% of patients despite intervention [9-13].

Reduced LV systolic strain after Anthracyclines treatment may indicate early impairment of myocardial function, before any detectable reduction in LVEF [14]. Thus, newer imaging techniques have been suggested to be more useful in detection of subclinical AIC. Two-dimensional (2D) speckle-tracking echocardiography is a technique that provides measurements of strain in three planes, by tracking patterns of ultrasound speckles in the myocardial wall all over the cardiac cycle. The most commonly used strain measure of left ventricular (LV) global systolic function is global longitudinal strain (GLS), which is more accurately assessed by speckle-tracking deformation imaging curves and describes the length change of the LV myocardium between end- diastole and end-systole [15]. Normal GLS for most echocardiography systems is recorded between -18 and -25% in healthy individuals, a variation, which in part may be explained by inter-software and intervendor variability. Good recordings can be achieved technically along any axis, but interpretation of radial and circumferential strains are still complicated by substantial transmural non-uniformity in the normal LV, which is related entirely to the geometric effect of the LV wall layers. However, for longitudinal strain, such geometrical effects are of less magnitude [16].

Hence, there has been a growing interest in markers of early myocardial changes (i.e. changes with normal LVEF) that may predict the development of subsequent LVEF reduction or the progression to HF, so that preventive strategies with established cardioprotective medications such as beta- blockers or angiotensin-converting enzyme inhibitors (ACEI) could be implemented [17].

Aim of the Study

The aim of this study is to evaluate the role of 2D-speckle tracking deformation imaging in early detection and management of subclinical impairment of LV systolic function in anthracyclines treated pediatric patients suffering from solid tumors.

Materials and Methods

One hundred and ten anthracyclines treated solid tumor patients who are less than 14 years and more than one year, receiving 35 - 50 mg/m^2/dose doxorubicin and who had structurally normal heart were recruited for this study. Informed written consent was obtained from parents of all the patients. After first dose of doxorubicin, LV ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were calculated using the standard equation. 2D-speckle tracking curves were used to assess the total myocardial deformation in the form of averaged global longitudinal systolic strain (GLS) from the apical four, three and two chamber views. These parameters were compared to the same parameters in 50 age matched controls.

Patients were divided depending on their global LVEF into two groups; group I with impaired LVEF < 58% and group II with good LVEF < 58%. GLS of the left ventricle was assessed for all patients included. All patients with impaired global LV systolic function defined as impaired GLS (impaired than -18 %) whatever their LVEF and LVFS values underwent continuous cardiac supportive management in the form of angiotensin-converting enzyme inhibitors (ACEI), spironolactone and sometimes B- blocker carvedilol (in absence of NYHA class III/IV heart failure). Follow up echocardiography by the same echo parameters was done after each cycle of anthracyclines. All data taken were collected and analyzed.

The work design has been approved by the local ethical committee and it conforms to the currently applied standards.

Statistical analysis

All analyses were performed using SPSS for Windows version 25.0 (SPSS Inc. Chicago, Illinois). Parametric measures were used. All results were expressed as mean ± SD. T- test was used to compare mean differences of measures between all patients and controls, ANOVA test were used to compare mean differences of measures between group I, group II and controls and paired test was used to compare mean differences of measures before and after cardiac supportive treatment. Significance was defined as $p < 0.05$* and highly significance was defined as $P < 0.001$*.

Results

The study included 110 patients with solid tumors with mean age at examination of 11.04 ± 3.78 years. Seventy six (69%) patients were males and 34 (31%) were females. Thirty nine (35.5%) patients had osteosarcoma, 22 (20%) patients had Ewing sarcoma, 37 (33.6%) patients had neuroblastoma, 5 (4.5%) patients had hepatosarcoma and 7 (6.3%) patients had Wilm's tumor.

LVEF and LVFS were significantly lower in anthracyclines treated patients than in the control group (LVEF was 59.21 ± 4.10% and 62.23 ± 1.89% respectively, $P < 0.001$*), (LVFS was 29.59 ± 2.10% and 31.17 ± 0.70% respectively, $P < 0.001$*). GLS was statistically significantly impaired in anthracyclines treated patients than in the control group (GLS = -17.82 ± 3.40% for patients and -21.77 ± 1.62% for controls, $P < 0.001$*), shown in table 1.

Patient		Groups		T-Test	
		Control	t	P-value	
LVEF (%)	Mean ± SD	59.21 ± 4.10	62.23 ± 1.89	-3.88	< 0.001*
LVFS (%)	Mean ± SD	29.59 ± 2.09	31.17 ± 0.7	-4.05	< 0.001*
GLS (%)	Mean ± SD	-17.82 ± 3.99	-21.77 ± 1.62	5.25	< 0.001*

Table 1: *Comparison of left ventricular systolic function by left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS) and speckle based global longitudinal strain (GLS) between patients and control group.*

LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening and GLS: Global Longitudinal Strain.

Group I included 60 patients (54.55%) who had LVEF of 54.65 ± 2.53%, LVFS of 27.27 ± 1.37% and GLS of -13.22 ± 2.67%; all were statistically highly significantly impaired than in the control group (P < 0.001*), shown in table 2. Group II included 50 patients (45.45%) who had LVEF of 61.32 ± 2.74%, LVFS of 30.67 ± 1.37% and GLS of -19.96 ± 2.36%. Despite there were no significant difference in LVEF and LVFS between group II and control group there was statistically significant impairment of GLS in group II than in the control group (P = 0.002*), also shown in table 2.

Group I		Groups			ANOVA	TUKEY'S Test		
		Group II	Control	P-value	I&II	I&C	II&C	
LVEF (%)	Mean± SD	54.65 ± 2.53	61.32 ± 2.74	62.23 ± 1.89	< 0.001*	< 0.001*	< 0.001*	0.243
LVFS (%)	Mean± SD	27.27 ± 1.37	30.66 ± 1.37	31.17 ± 0.7	< 0.001*	< 0.001*	< 0.001*	0.168
GLS (%)	Mean± SD	-13.22 ± 2.68	-19.96 ± 2.36	-21.77 ± 1.62	< 0.001*	< 0.001*	< 0.001*	0.002*

Table 2: *Comparison of left ventricular systolic function by left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS) and speckle based global longitudinal strain (GLS) between group (I), group (II) and the control group.*

LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening and GLS: Global Longitudinal Strain.

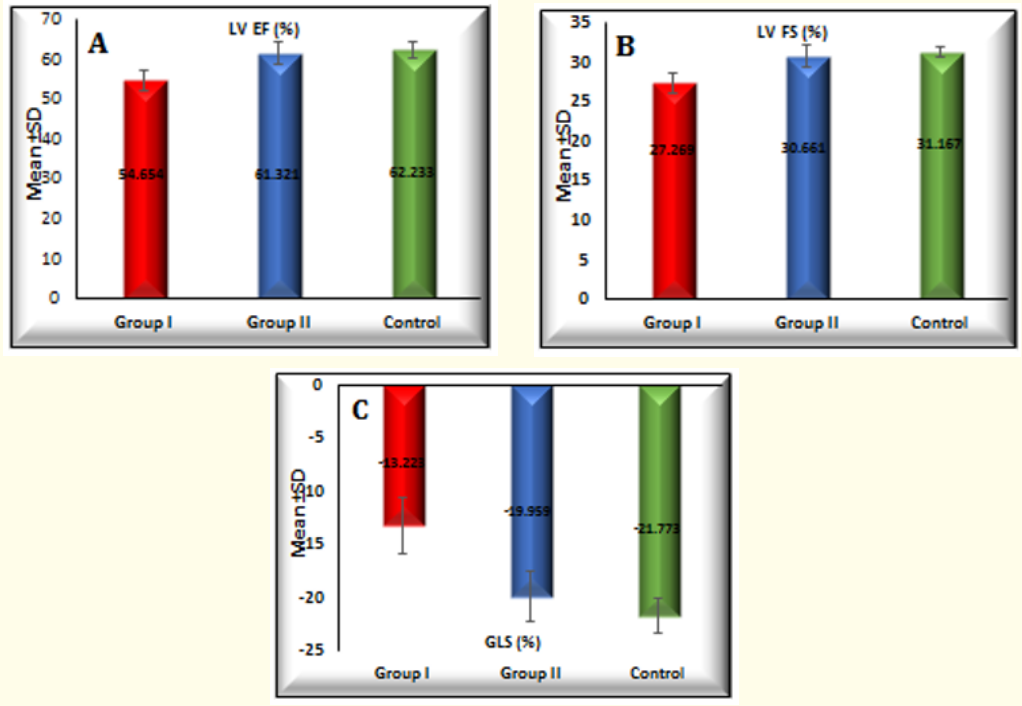

Figure 1: *Comparison of left ventricular systolic function by (A) left ventricular ejection fraction (LVEF), (B) left ventricular fractional shortening (LVFS) and (C) speckle based global longitudinal strain (GLS) between group (I), group (II) and the control group.*

LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening and GLS: Global Longitudinal Strain.

Fifty two patients; forty one (68%) of group I and 11 (22%) of group II showed impaired LV function with GLS impaired than -18%. These patients started cardiac supportive treatment, follow up of these 52 patients showed improvement of LVEF (LVEF increased from to 57.12 ± 4.1% to 63.18 ± 2.38%, P < 0.001*), LVFS (LVFS increased from 29.82 ± 2.51% to 33.97 ± 2.58%, P < 0.001*) and global longitudinal systolic strain (GLS) improved from - 14.29 ± 2.07 % to -19.31 ± 0.45%, P < 0.001*) as shown in table 3.

Before		Time		Differences		Paired Test	
		After	Mean	SD	t	P-value	
LVEF (%)	Mean ± SD	57.12 ± 4.1	63.18 ± 2.38	-6.06	3.10	-11.22	< 0.001*
LVFS (%)	Mean ± SD	29.82 ± 2.51	33.97 ± 2.58	-4.15	1.48	-16.1	< 0.001*
GLS (%)	Mean ± SD	-14.29 ± 2.08	-19.31 ± 0.45	5.02	1.93	14.99	< 0.001*

Table 3: *Comparison of left ventricular systolic function by left ventricular ejection fraction (LVEF), left ventricular, fractional shortening (LVFS) and speckle based global longitudinal strain (GLS) in patients with impaired left ventricular function before and after cardiac supportive therapy. LVEF: Left ventricular ejection fraction, LVFS: Left Ventricular Fractional Shortening and GLS: Global Longitudinal Strain.*

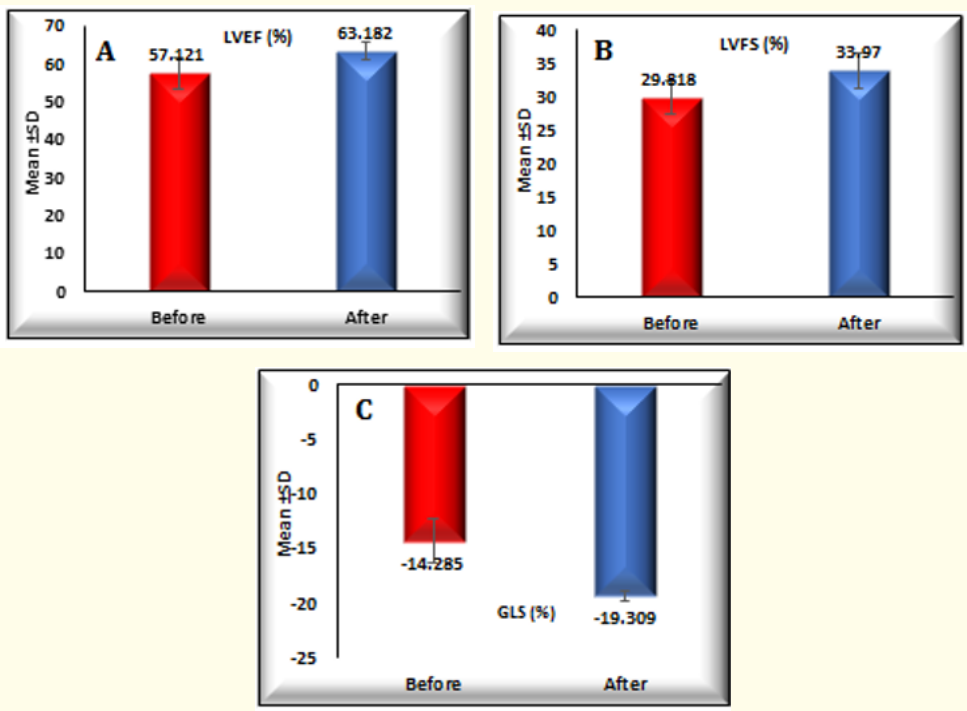

Figure 2: *Comparison of left ventricular systolic function by (A) left ventricular ejection fraction (LVEF), (B) left ventricular fractional shortening (LVFS) and (C) speckle based global longitudinal strain (GLS) in patients with impaired left ventricular function by impaired quantitative strain (QS) < -18% before and after cardiac supportive therapy.*

LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening and GLS: Global Longitudinal Strain.

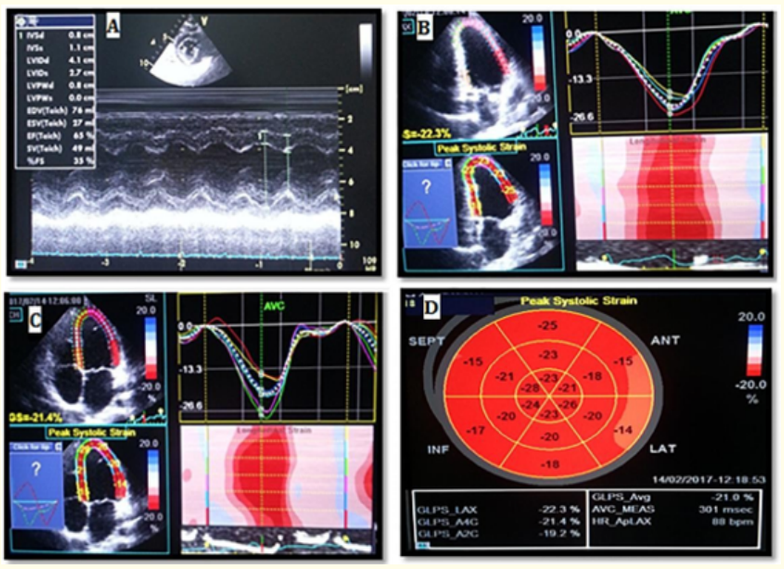

Figure 3: *Echocardiographic assessment of 10 years old boy with osteosarcoma before starting anthracyclines treatment. A: showed left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) assessed by the standard formula, B: showing global longitudinal strain (GLS) in apical 3 chamber view measuring -22.3%, C: showing GLS in apical 4 chamber view measuring -21.4% and D: showed average GLS of -21.0%.*

EF: Ejection Fraction; FS: Fractional Shortening and QS: Quantitative Strain; GLPS LAX: Global longitudinal strain in apical 3 long axis view; GLPS A4C: Global longitudinal strain in apical 4 chamber view; GLPS A2C: Global longitudinal strain in apical 2 chamber view and GLPS Avg: Average global longitudinal strain.

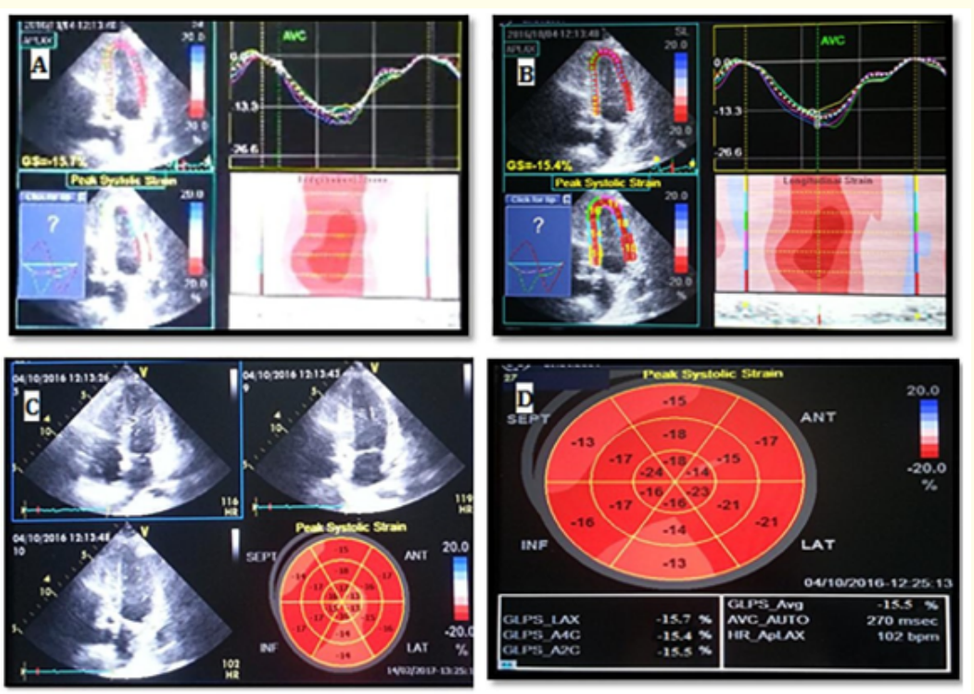

Figure 4: *Echocardiographic assessment of 16 years old girl with Ewing sarcoma showing anthracyclines induced cardiotoxicity after the fifth cycle of anthracyclines (185 mg/m2). A: showed global longitudinal strain (GLS) in apical 3 chamber view measuring -15.7%, B: showing GLS in apical 4 chamber view measuring -15.4%, C: showing Ball's eye of GLS in apical 3, 4 and 2 chamber views measuring and D: showed average GLS of the 3 views which was -15.5%, this patient started cardiac supportive management.*

QS: Quantitative strain; GLPS LAX: Global longitudinal strain in apical 3 axis view; GLPS A4C: Global longitudinal strain in apical 4 chamber view; GLPS A2C: Global longitudinal strain in apical 2 chamber view and GLPS Avg: Average global longitudinal strain.

Discussion

For both pediatric and adult patients undergoing cardiotoxic chemotherapy, the ACC/AHA/ASE guideline's recommends routine echocardiography as class I recommendation at baseline and on a yearly basis for adult survivors at recurrence and for patients with abnormal results [18].

The LV wall is not homogenous and is composed of three layers of fibers; with the endocardial layer is the first to be affected by different diseases. This layer is responsible for the long axis contraction, so reduction in longitudinal function has been found to be an early and accurate indicator of LV dysfunction with high susceptibility to ischemia, fibrosis, and hypertrophy [19,20]. The left ventricular longitudinal mechanics depends mainly on the subendocardium, which is more sensitive to the myocardial fibrosis. This suggests the use of other echocardiographic techniques for early detection of the subendocardial longitudinal function [21-23]. Based on this, there is a significant reduction in the GLS, with very low cumulative doses of anthracyclines, while other echocardiographic variables such as LVEF and mitral Doppler remain unchanged [24].

While the prevalence of LV dysfunction increases significantly when patients are given doxorubicin doses of ≥ 550 mg/m^2, still lower cumulative doses can also cause similar LV dysfunction [25]. Despite all these studies were done in adults, our study in children age group patients are consistent with the literature, where there was a significant reduction in the GLS after the end of anthracyclines cycles but it also can occur very early. Therefore, it should be noted, that GLS image modality warn us about the presence of subclinical ventricular dysfunction associated with anthracyclines chemotherapy, despite a preserved LVEF values.

However, anthracyclines-induced LV dysfunction was previously believed to be refractory to conventional pharmacological therapy, it is still associated with poor prognosis in relation to other types of cardiomyopathies [26-28]. Angiotensin-converting enzyme inhibitors (ACEI) or B-blockers have been shown to slow progression of impaired LV function [29,30]. In this study we started cardiac supportive therapy in the form of ACEI, spironolactone and B-blockers in all patients with impaired GLS irrespective of their LVEF and LVFS values and this supportive therapy showed significant improvement of GLS and preservation of LV systolic function.

We detected early minor LV endocardial dysfunction caused by anthracyclines even in patients with preserved global LV systolic function, and this dysfunction can eventually lead to impaired global LV performance. Because anthracyclines causes changes in LV performance over time, close observation is necessary for patients with preserved LV global function but with impaired LV endocardial function. Also, LV endocardial function can be reversed by early management implication and by close follow up of those patients.

Conclusions

2D-speckle tracking strain was found useful for early detection of minor LV endocardial dysfunction associated with the use of anthracyclines. This value was better recorded in patients with good LVEF < 58%; in them despite their normal LVEF and LVFS values, their GLS denotes early impairment of LV systolic function. Speckle based strain is not only useful for detection of early global LV dysfunction but also in starting early management and subsequently early salvage of cardiac function and improvement of cardiac prognosis.

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