Indian J Hematol Blood Transfus (Oct-Dec 2019) 35(4):750–757
https://doi.org/10.1007/s12288-019-01117-6

ORIGINAL ARTICLE

Left Ventricular Regional Function in Children with Beta Thalassemia with No Cardiac Manifestations (Four-Dimensional Echocardiographic Study)

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Received: 31 October 2017 / Accepted: 15 March 2019 / Published online: 22 March 2019

Abstract Early detection of myocardial dysfunction is essential for the management of patients with thalassemia. Four-dimensional echocardiography imaging technique may be useful for detecting subclinical cardiovascular disease. To evaluate the 4-dimensional echocardiographic strain in children with beta thalassemia major with no cardiac manifestation and correlate it with other echocardiographic parameters. This is a prospective cross-sectional cohort Study included 200 children, 1–18 years-old. They were divided into: One hundred children with p-Thalassemia major with no clinical cardiac manifestations and 100 healthy children as a control group. They were subjected to the following investigations: Complete blood count, serum ferritin and Four-dimensional echocardiographic strains (Longitudinal, Circumferential, Radial and Area strains). There was no significant difference between the two groups as regard mitral annulus systolic velocity (S wave), E/A ratio and iso-volumic acceleration, but there was a significant difference as regard to ejection fraction, left ventricle mass, sphericity index and myocardial performance index. The mean values of Left Ventricular Strains (Longitudinal, Circumferential, Radial and Area strains) were significantly lower in patients with thalassemia (-14.86 ± 12.13, -8.01 ± 3.829, 33.13 ± 10.61, -19.45 ± 6.866) than controls (-19.13 ± 1.502, -16.32 ± 1.34, 37.28 ± 4.209, -22.94 ± 3.06) than controls respectively with a positive correlation with 2-Dimensional strain. Strain parameters of the left ventricle obtained by four-dimensional.

Keywords Speckle tracking · Four-Dimensional Echocardiography · β-thalassemia major

Introduction

β-thalassemia (β-TM) is considered a very critical public health issue in Egypt [1]. The main treatment of β-TM is regular blood transfusion; which is necessary to maintain the life of the patient's due to profound anemia. Because of that together with increased iron absorption from the intestinal tract, iron overload occurs, and this excess iron accumulates in body tissues, especially heart, the liver and endocrine system causing tissue destruction and organ malfunction or even failure [2, 3]. Chronic anemia together with iron overload play the major role in the pathogenesis of cardiac affection in patients with thalassemia. The process of heart disease is gradual, and the heart muscle is affected a while before the appearance of manifestations of heart failure which is the full-blown picture of cardiomyopathy [4].

Cardiomyopathy is considered a well-known complication of β-thalassemia and the main cause of death in β-thalassemia is congestive heart failure due to iron overload [5].

The global left ventricular function can be maintained in thalassemia patients and remain with no cardiac symptoms till the late stages of the disease. Hence, early detection of myocardial dysfunction may be useful in the management of thalassemia cases. The earliest sign of myocardial dysfunction is the affection of segmental wall motion. This may be subtle and can be missed by conventional echocardiography modes which may reveal no changes till the late stages of the disease [6].

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Strain analysis is a new advancement that evolved for objective quantification of regional myocardial function. It was at the start introduced as a post-processing feature of tissue Doppler imaging (TDI) at which velocity data are converted to strain and strain rate. Recently, strain analysis information has also been extracted from speckle tracking through processing by computer [7, 8]. Strain analysis can detect impaired left ventricular segmental systolic function even if global left ventricular ejection fraction is preserved [9].

Strain analysis includes longitudinal, circumferential, radial and area strains. Area Strain combines the longitudinal and circumferential strains. Some authors reported it as a very useful tool for evaluating ventricular function [10].

The aim of this work is to evaluate the 4-dimensional strain using echocardiography in children with β-TM and correlate it with other echocardiographic parameters.

Subjects and Methods

This is a cross-sectional cohort study was carried out on 100 children diagnosed with beta thalassemia major with no clinical cardiac manifestations. Each patient received blood transfusion every 2–3 weeks to maintain the hemoglobin level above 8 g/dl, with iron chelation by deferasirox in a dose of 30 mg/kg/day was prescribed for all patients with serum ferritin more than 1000 ng/ml. They were chosen from those attending the Hematology Unit, Pediatrics Department of Tanta University Hospital before they receive their regular blood transfusion. One hundred healthy children matched for age and sex were served as a control group. An informed consent was obtained from the guardian of all children and the study was conforming the declaration of Helsinki. Any children with congenital or acquired heart diseases, were excluded. The study was approved by the ethical committee of the Faculty of Medicine, Tanta University.

Full history taking, general and regional examinations were done in all subjects. Serum ferritin and Complete blood count were the laboratory investigations made. Echocardiographic studies were performed using a commercially available ultrasound transducer and equipment (Vivid 7 or Vivid 9, GE Healthcare, Horten, Norway). Data acquisition was performed with a 3.5-MHz transducer, S7, and V3 matrix real-time 3-dimensional probes.

Digital loops were stored on the hard disk of the echocardiography machine, and transferred to a workstation (Echo PAC PC, 113; GE, and Horten, Norway) for offline analysis. Transthoracic 2DE Examination (TTE) was performed for all patients using the standard apical, parasternal and subcostal views to obtain all quantitative and qualitative complete studies according to the American Society of Echocardiography guidelines.

The displaying mode of real time three-dimensional echocardiography (RT-3DE) includes 3D Live and full volume and color Doppler mapping. RT-3D-TTE with faster and more highly automated image processing provides a 60° × 30° cake-like 3D image.

The 4D Strain tracking is performed starting from a region of interest (ROI) defined at the end of systole. 4D Strain analysis is integrated as the last step in the 4D Auto Left Ventricular Quantification tool, which also includes volume and LV mass measurements. The meshes created for these two measurements are re-used for the 4D Strain ROI. The 4D Strain ROI is automatically generated in the end-systolic frame and is built up from an endocardial and an epicardial mesh. The endocardial mesh is based on the one used for the end-systolic volume measurement. The epicardial mesh is automatically generated from the epicardial mesh used in the LV mass stage, by propagating it from end diastole to end systole. The user can correct the ROI shape by placing attractor points to pull the nearby ROI border towards where the user wishes it to go. From the tracking results, 4D Strain derives several parameters, including area strain [11]. Detection of longitudinal strain is shown in Fig. 1.

Inter- and Intra-observer Variability Analysis

Two echocardiographers, blinded to clinical data, independently measured the Speckle Tracking 4D analysis of 10 randomized subjects (five patients and five controls) for inter-observer variability analysis. One observer measured the Speckle Tracking 4D analysis twice in the 10 randomized subjects on two consecutive days for intra-observer variability analysis.

Statistical Analysis

Quantitative data were presented as mean ± standard deviation. The independent t-test was used to compare the means of the two groups. Qualitative data were presented as count and appropriate proportion. The chi-square test was used to compare the two independent proportions. Pearson's correlation coefficient was used to test the association between two variables. Significant results were considered with $P \leq 0.05$. Statistical Package for Social Sciences (SPSS) version 13 was used in data entry and analysis (IBM Corp, Armonk, NY, USA).

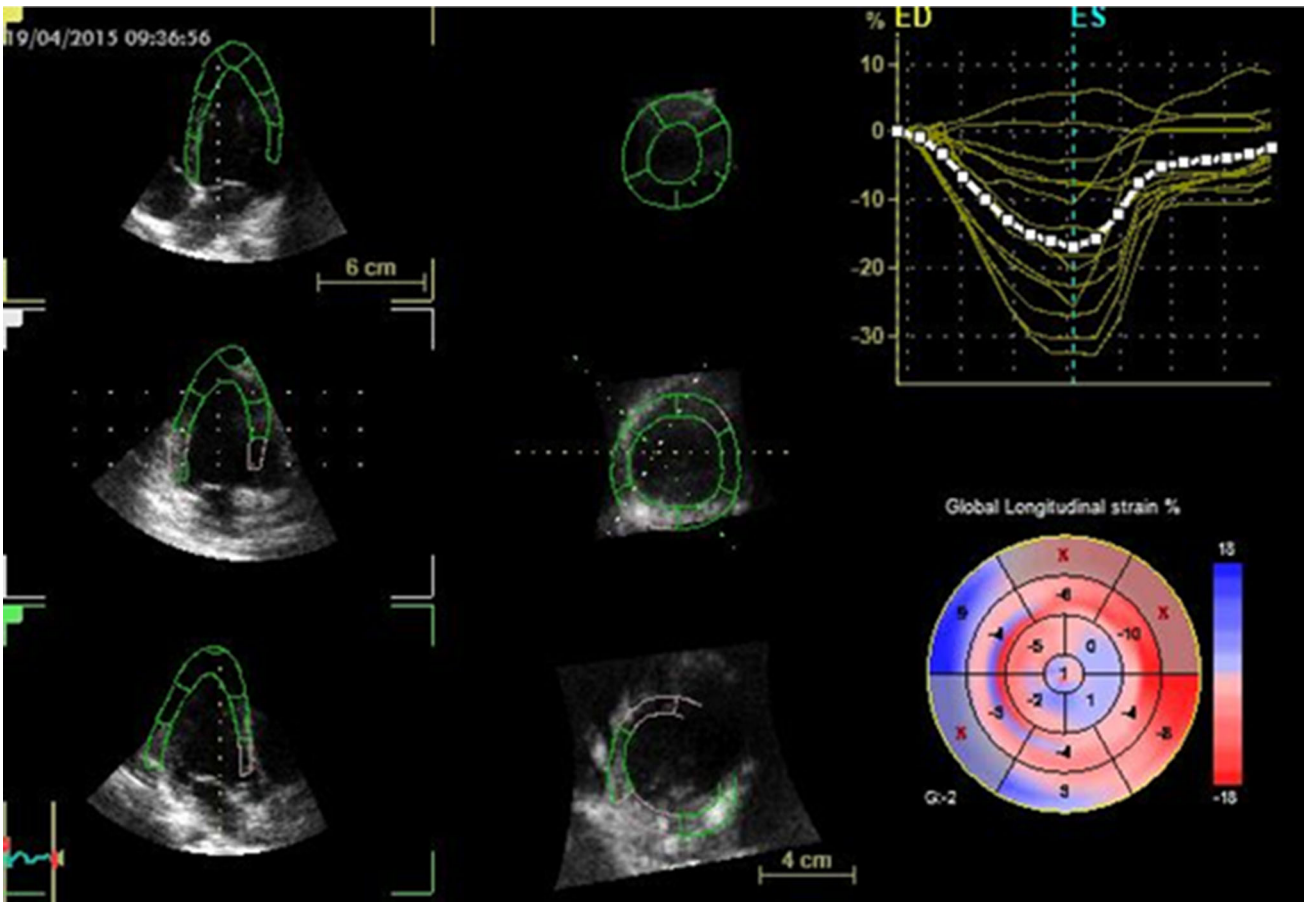

Fig. 1 Global longitudinal strain in a patient thalassemia

Results

The mean age of the patient group was 7.97 ± 3.75 years and that of control group was 7.86 ± 3.63 years. Forty-nine males and 51 females comprised the patient group. Family history of thalassemia was positive in 44 patients and 57 patients were products of consanguineous marriage.

The body mass index of patients was 17.81 ± 4.97 kg/m^2 which was not significantly lower than that of the control group 18.48 ± 4.77 kg/m^2.

Hemoglobin level of patients was 7.85 ± 1.70 gm/dl and their serum ferritin level was 1794 ± 511.74 ng/ml; both are significantly different from those of the control group which were 11.75 ± 1.12 gm/dl and 63.82 ± 7.4 ng/ml respectively.

Conventional echocardiographic data revealed a significant differences decrease between in EF, LV Mass and Sphericity index in patient group when compared to control group.

Conventional tissue Doppler revealed statistically significant difference between the two groups as a regard myocardial performance index (MPI), with no significant difference between the two groups as regard mitral annulus systolic velocity, E/A ratio and ISO-volume acceleration (IVA) (Table 1).

RT-3DE demonstrated significant differences between both groups as regard LV strains {longitudinal, circumferential, radial and area strains} (Table 2). There was a positive correlation between longitudinal strain and 2-Dimensional strain (2DS) with statistically significant difference. While a negative correlation between longitudinal strain and EF with statistically significant difference. Also, there was a weak positive correlation between circumferential strain and (2DS, IVA and EF) with statistically significant difference. Concerning Area strain there was a positive correlation between area strain and 2-Dimensional strain with statistically significant difference. While a weak negative correlation between area strain and mitral annulus systolic velocity with statistically significant difference and negative correlation between area strain and ejection fraction (EF) with statistically significant difference. As regards, radial strain; there was a positive correlation between radial strain and (S, 2DS and EF) with statistically significant difference (Table 3).

Table 1 Comparison between patients with thalassemia and control group as regard S, E/A ratio, IVA and MPI measured by tissue Doppler imaging (TDI)

Variable	Patients	Control	t-test	*P* value
S (cm/s)				
Range	4–8	6–8	− 1.868	0.063
Mean ± SD	6.72 ± 0.854	6.92 ± 0.646		
E/A ratio				
Range	0.6–2.6	1.1–1.9	1.039	0.300
Mean ± SD	1.595 ± 0.404	1.55 ± 0.156		
IVA (m/s^2)				
Range	1–5	2–4	− 0.575	0.566
Mean ± SD	2.82 ± 0.619	2.87 ± 0.652		
MPI				
Range	0.33–0.74	0.3–0.5	8.129	< 0.0001*
Mean ± SD	0.4772 ± 0.1051	0.376 ± 0.0669		

S mitral annulus systolic velocity, *IVS* isovolumic systole, *MPI* myocardial performance index

*Defined as significant *P* value

Table 2 Comparison between patients with thalassemia and control group as regard all strains measured by 4-dimensional speckle tracking echocardiogram

Strains	Range	Mean ± SD	*P* value
Longitudinal			
Patients	− 25 to − 97	− 14.86 ± 12.131	< 0.0001*
Control	− 22 to − 17	− 19.13 ± 1.502	
Circumferential			
Patients	− 19 to − 2	− 8.01 ± 3.829	< 0.0001*
Control	− 20 to − 15	− 16.32 ± 1.34	
Area			
Patients	− 30 to − 25	− 19.45 ± 6.866	< 0.0001*
Control	− 28 to − 20	− 22.94 ± 3.064	
Radial			
Patients	10 to 56	33.13 ± 10.613	< 0.0001*
Control	30 to 45	37.28 ± 4.209	

*Defined as significant *P* values

Discussion

Cardiomyopathy is a leading cause of deaths in beta thalassemia. The early detection of these complications is markedly needed. In our study, we stressed on the utility of echocardiography as a diagnostic tool in the pre-symptomatic stage of cardiomyopathy. We used all available modalities; including conventional echo Doppler, 2D tissue Doppler and interestingly, we presented the modality of strain analysis focusing on the help of real time 3D echocardiography as a valuable modality for cardiac diagnosis.

In this study, we found that there was no significant difference between both groups regarding age and gender ($P \leq 0.257$, $P \leq 0.884$ respectively). This agrees with a study conducted by Noori and Mehralizadeh [12] and Garadah et al. [13].

Table 3 Correlation between 4D strains (longitudinal, circumferential, area and radial strains) and other echo parameters

	LS		CS		AS		RS	
	r	*P* value	r	*P* value	R	*P* value	r	*P* value
S (cm/s)	0.097	0.340	− 0.166	0.101	− 0.213	0.033*	0.262	0.009*
E′/A′	0.088	0.384	0.016	0.872	0.021	0.838	− 0.028	0.781
IVA (ms)	− 0.144	0.154	0.228	0.024*	0.165	0.102	0.006	0.956
MPI	− .047	0.640	0.103	0.312	0.045	0.659	0.002	0.981
2DS	0.603	< 0.0001*	0.203	0.044*	0.336	0.001*	0.333	0.001*
EF%	− 0.423	< 0.0001*	0.273	0.006*	− 0.435	< 0.0001*	0.543	< 0.0001*
SpI	− 0.094	0.354	− 0.159	0.117	− 0.148	0.141	0.163	0.105
Mass (g)	0.086	0.406	− .034	0.725	− 0.070	0.498	0.020	0.848

LS longitudinal strain, *CS* circumferential strain, *RS* radial strain, *AS* area strain, *S* mitral annulus systolic velocity, *IVS* isovolumic systole, *MPI* myocardial performance index, *2DS* two dimensional strain, *EF* ejection fraction, *LV* left ventricle

*Defined as significant *P* values

In the present study, the mean value of MPI of patients with thalassemia group was higher than the control group with high significant difference between both groups which means that left ventricular systolic and diastolic functions of patients with thalassemia group was affected without showing any symptoms of heart failure. This was in accordance with many findings reported by multiple investigators; Uçar et al. [14], Noori and Mehralizadeh [12] and Noori et al. [15]. Uçar et al. [14]. They reported that mean MPI of the patients with thalassemia was significantly higher than that of control group and concluded that MPI taken by TDI can be an early parameter for early detection of left ventricular dysfunction. On the other hand, Siddammanahalli et al. [16] reported that MPI was normal in the thalassemia group in comparison to control group. But in the same study when dividing the patients with thalassemia into subgroups according to serum ferritin level, it showed that patients with serum ferritin less than 1000 μg/L had normal MPI but it becomes prolonged if serum ferritin exceeds that level.

Regarding mitral annulus systolic velocity (S (there was no statistically significant difference between both groups. Ragab et al. [6] in a study conducted on 25 asymptomatic patients with thalassemia using TDI to evaluate non-overt cardiac dysfunction in β-TM was in agreement with our results. On the other hand, Abdelmoktader et al. [17] reported on their study of the value of pulsed tissue Doppler imaging in early detection of the left ventricular dysfunction in asymptomatic β-thalassemia patients that S was significantly lower in patients with thalassemia group compared to control group which means that there was subclinical myocardial dysfunction in patients with thalassemia group.

The present results showed that there was no significant difference between both groups as a regard E/A ratio denoting preserved diastolic function and no restrictive pattern of the left ventricle. This was consistent with what Gharzuddine et al. [18] and Piccione et al. [19]. Also, similar results were published by Abdelmoktader et al. [17]. On the other hand, Noori et al. [15] in a study conducted on 80 asymptomatic beta thalassemia patients to evaluate diastolic and systolic function of the left ventricle showed that E/A ratio was significantly lower than control group of 80 age and sex matched healthy individuals. This denoted left ventricular diastolic dysfunction due to impaired ventricular relaxation. Moreover, E/A ratio was found to be increased in thalassemia patients in the study done by Garadah et al. [13]. This can be due to restrictive diastolic dysfunction of the left ventricle.

Iso-volumic acceleration (IVA) in this study showed no significant difference between both groups. Cheung et al. [20] was not in agreement with our results and showed in their study significant increase in IVA denoting myocardial contractility impairment.

The mean value of ejection fraction (EF) of the thalassemia group was significantly lower than the control group. This means that patients with thalassemia suffered from left ventricular systolic dysfunction, which is the early sign of heart failure. This was in accordance to Abdelmoktader et al. [17] who reported on their study of the value of pulsed tissue Doppler imaging in early detection of the left ventricular dysfunction in asymptomatic β-thalassemia patients that EF was lower in patients with thalassemia than control but with no significant difference between both groups.

On the other hand, Ragab et al. [6] reported that asymptomatic patients with thalassemia had no significant difference regarding EF comparable to the control group suggesting preserved systolic function. Also, Arshad and Hyder [21] reported that EF was significantly higher in patients with thalassemia than control. Hyder et al. [22] also reported that having a normal EF is not surprising as anemia causes hyperdynamic circulation, which can maintain EF within normal range until late in the disease.

The present study also showed that LV mass of our patients with thalassemia was significantly higher than controls which means that there was LV hypertrophy in asymptomatic β-thalassemia patients.

Uçar et al. [14] in a study of LV and RV functions of 36 pediatric patients with thalassemia reported that, the LV mass was significantly higher in patients with thalassemia group than in controls due to the increased cardiac output caused by the chronic anemia. Also in a study conducted by Bilge et al. [23] on 32 adult patients with β-thalassemia major showed that LV mass in patients with thalassemia group was significantly higher than controls.

It is well known that the shape of the LV is an additional useful parameter to assess in patients with LV dysfunction. As function deteriorates and LV size increases, the ventricle assumes a more globular rather than elliptical shape [24]. The LV sphericity index was defined by the ratio of LV short-axis length to long-axis length [25].

To our knowledge, there is deficient literature concerning 4DE sphericity index (SpI) parameter and the correlation between it and conventional echocardiography parameters in children with thalassemia.

In our study, there was a highly significant increase between two groups as regard SpI indicating an alteration of the left ventricular shape from elliptical shape to more spherical shape which is an early sign of left ventricular failure.

In a case report study conducted by Sadeghpour et al. [26] a 28-year old female with thalassemia major whose clinical assessment, including two-dimensional Doppler echocardiography demonstrated severe left ventricular hypertrophy with severe biventricular enlargement and systolic dysfunction as well as severe diastolic dysfunction.

Her LV SpI was much higher than normal (1.69) indicating LV shape changing from being elliptical to spherical. This result resembles most patients with thalassemia cases in our study.

This study showed that there was a significantly lower longitudinal strain (LS) in patients with thalassemia compared to controls which means that there was left ventricular dysfunction as regard the longitudinal epicardial and endocardial muscle layer of LV in patients with thalassemia without any cardiac symptoms. Also, there was a positive correlation between LS in and (2DS) with statistically significant difference. But there was a negative correlation between longitudinal strain and EF with statistically significant difference.

Cheung et al. [20] conducted a study on 42 young adult patients with thalassemia (24.4 ± 6.4 years) using 2D-STE showing that patients with thalassemia had significantly low LS if compared to controls. Also in a study conducted by Piccione et al. [19] on 32 young adult patients with thalassemia using 2DE, there was a statistically significant difference between both groups as a regard LS denoting impaired LV function as a regard longitudinal axis. On the other hand, Monte et al. [27] in a study conducted on 27 asymptomatic young adult patients with thalassemia using STE, reported that there was no statistically significant difference between both groups about LS.

Regarding our study there was highly significant difference between both groups as regard circumferential strain (CS) which means that there was LV dysfunction as a regard to circumferential muscle layer in the mid-wall of LV in patients with thalassemia without any cardiac symptoms. Also, there was a weak positive correlation between circumferential strain and (2DS, IVA and EF) with statistically significant difference.

Monte et al. [27] in a study conducted on 27 asymptomatic young adult patients with thalassemia (29.76 ± 8.4 years) using speckle tracking echocardiography (STE), reported that there was statistically significant difference between both groups about CS. However, Cheung et al. [20] was not in agreement with our result and found no significant difference between patients with thalassemia and control groups in his study as regard CS. Also in a study conducted by Piccione et al. [19] on 32 young adult patients with thalassemia using 2DE, there was no statistically significant difference between both groups as regard CS denoting preserved LV function as a regard circumferential axis.

Our results showed that there was a highly significant low RS in patients with thalassemia than controls which means that there were left ventricular dysfunction in patients with thalassemia concerning radial axis without any cardiac symptoms. Also, there was a positive correlation between Radial strain and (S, 2DS and EF) with statistically significant difference.

Monte et al. [27] who conducted a study on 27 asymptomatic young adult patients with thalassemia using STE, agreed to us and reported that there was statistically significant difference between both groups as regards LS. However, Cheung et al. [20] was not in agreement with and found significant increase in RS in patients with thalassemia compared to control group. Also in a study conducted by Piccione et al. [19] on 32 young adult patients with thalassemia using 2DE, there was no statistically significant difference between both groups as regard RS denoting preserved LV function as a regard radial axis.

This new parameter area strain (AS) enables us to combine the analysis of left ventricular longitudinal and circumferential strains. The first area of the endocardium to be affected in several different cardiopathies is the subendocardial surface which can be monitored through the estimation of the subendocardial surface deformation by the help of that new parameter (AS) [28].

In the present results, there was a highly significant low AS in thalassemia patients than control. Also, there was a highly significant correlation between AS and EF. Li et al. [29] conducted a study on 24 young adult thalassemia patients to evaluate global LV myocardial mechanics using 3DSTE at which he agreed with our results concerning area strain and also showed higher correlation with LVEF which coincide with our results.

The low AS in patients with thalassemia, approved left ventricular dysfunction concerning subendocardial surface.

Lastly; we would like to stress on the importance of real time 3 D echocardiography and it's all evolving parameters that can give an accurate picture of the left ventricular functions; adding our findings to the expectations of Monaghan [24]. About what we have introduced newly in this study; it is the detection of left ventricular deformation by speckle tracking in its four parameters. Previous similar studies have been performed. But they have detected just one parameter. The study of Bay et al. [30]; have studied the left ventricular deformation in thalassemia patients, but only by detecting the longitudinal strain and strain rate.

Echo findings are proposed as early markers of cardiac dysfunction, but the study is limited by cross-sectional design. A follow up would tell us if patients with evidence of strain ultimately go on to develop overt cardiac dysfunction. Another limitation of this study, is the assessment of iron overload by measuring the serum ferritin rather than magnetic resonance imaging (MRI).

Conclusion

Collaboration of 4DE Strain parameters of the left ventricle obtained by four-dimensional echocardiography can be a novel and promising technique for early detection of left ventricular dysfunction in patients with thalassemia.

Author's Contribution The conception and design of the study by OAE, MRE. Acquisition of data by WAE. Analysis and interpretation of data by OAER, MRES. Drafting the article by AME, AMF, EAE. Revising it critically for important intellectual content by MRE, OAE and NMH. Final approval of the version to be submitted all authors.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the ethical committee of the Faculty of Medicine, Tanta University. An informed consent was obtained from the guardian of all children and the study was conforming the declaration of Helsinki.

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