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ORIGINAL ARTICLE

Speckle Tracking Echocardiography for Detection of Myocardial Dysfunction in β- Thalassemic Children

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ABSTRACT

Background: β-Thalassemia is known to be one of the most severe inherited hemoglobin disorders triggered by decreasing β-globin chain synthesis, resulting in inadequate erythropoiesis, resultant chronic hemolytic anemia and iron overload. This study aimed to evaluate myocardial function in children with β-thalassemia by Speckle tracking echocardiography.

Methods: A case-control study was conducted at Pediatric haematology and cardiology units, Pediatric Department, Zagazig University Hospital performed on 68 subjects divided into two groups: group 1: 34 patients well diagnosed as B-thalassemia. Group 2: 34 age and sex matched healthy children as a control group in the period between from February to July 2019. Complete examination was done with stress on anthropometric measurements and vital signs. Laboratory investigations (Complete blood count (CBC), Haemoglobin level (Hb%), Serum iron and Serum ferritin). Echocardiographic measurements of conventional left ventricular (LV) systolic and diastolic function performed and LV longitudinal global and segmental strain measured by 2D speckle tracking echocardiography.

Results: Significant reduction in median global longitudinal strain (GLS) in thalassemic patients compared to control (16.9 vs. 26.03) and significant correlation between left ventricular global longitudinal strain , serum ferritin , haemoglobin level and age of β- Thalassemic patients.

Conclusion: Speckle tracking Echocardiography is superior to conventional echocardiography when providing early evidence of myocardial dysfunction in patients with non-symptomatic thalassemia. Therefore, STE can be used as an integrated part of the assessment of beta-thalassemic children.

Keywords: speckle tracking echocardiography (STE), β-Thalassemia, myocardial.

INTRODUCTION

β-Thalassemia is considered as one of the most common inherited hemoglobin disorder caused by the declined synthesis of β-globin chains, resulting in ineffective erythropoiesis, subsequent chronic hemolytic anemia and iron overload [1] **.** Transfusions of the blood together with increased absorption of intestinal iron and chronic hemolysis determine progressive iron overload with secondary hemochromatosis in different tissues. The heart is a target organ in the pathological phase, and iron-mediated cardiomyopathy has previously been shown to be the leading cause of death and morbidity in patients with thalassemia major (TM) [2]**.** The occurrence of dilated cardiomyopathy in β-thalassemia is postulated to be multifactorial, including immune-inflammatory and genetic components [3]**.** Most patients with thalassemia may experience no symptoms until they become decompensated. But only 50 per cent of patients will survive with development of overt heart failure. Global ventricular function and ability to exercise can remain within normal value until late in the disease process [4]**.**Today, cardiovascular magnetic resonance imaging, especially T2* imaging, is used for precise myocardial and hepatic iron load assessment and therapeutic advice [3]**.** Echocardiographic stress analysis could however define subclinical cardiac involvement in many heart diseases [5]**.** Advanced imaging techniques such as speckle tracking echocardiography (STE) may be required to

determine ventricular structures and functions adequately. The new imaging modality speckle tracking echocardiography (STE) has recently proven to be comparable in reproducibility and precision to the cardiac magnetic resonance [6]**.** Recently, speckle tracking echocardiography (STE) has arisen as a computational technique for accurately measuring myocardial activity. By analyzing the movement of speckles in the two-dimensional ultrasonic image, this technique enables a non-Doppler angle-independent objective analysis of myocardial deformation, with the possibility of quantifying cardiac dynamics of thickening, shortening and rotation [7,6].

Longitudinal left ventricular (LV) strain, which originates predominantly in the subendocardial region, is the most sensitive component of LV strain in myocardial disease [8]**.**

This study aimed to evaluate myocardial function in children with β-thalassemia by Speckle tracking echocardiography

METHODS

A case-control study was conducted at Pediatric haematology and cardiology units, Pediatric Department, Zagazig University Hospital performed on 68 subjects divided into two groups**:** group1**:**34 patients well diagnosed as B-thalassemia. Group 2**:**34 age and sex matched healthy children as a control group in the period between from February to July 2019.

Inclusion criteria: **Age:** 6 to 15 years **,** Sex: both sexes are included , Children who were previously diagnosed as beta-thalassemia major by hemoglobin electrophoresis, and received at least ten blood transfusions, and were on chelation therapy for 6 months or more were included in the study. **Exclusion criteria were** inability to obtain adequate 2D image quality, children with hypertension, newly diagnosed or treated patients, symptoms of heart failure or Left ventricular dysfunction defined as ejection fraction <50% and Children with arrhythmia which may affect the image analysis Our patients underwent a questionnaire interview for collection of personal data, sociodemographic data and complete history followed by complete examination was done with stress on anthropometric measurements and vital signs. Laboratory investigations (complete blood count, hemoglobin level, Serum iron and Serum ferritin). Echocardiographic measurements of the conventional LV systolic and diastolic function and LV longitudinal global and segmental strain measured by echocardiography of 2 D speckle tracking. All cases were examined using multiple frequencies transducer ranging from 3 to 8 MHZ. with simultaneous electrocardiographic recording to allow timing of flow. The imaging planes consisted of the parasternal long- and short-axis views followed by the apical four and two-chamber views. Cardiac dimensions: The interventricular septum (IVS), the posterior left ventricular wall (LVPW), the length, the diastolic left ventricular end (LVED), and the systolic end (LVES). The percentage of left ventricular ejection and the shortening of the fraction is determined from tracings in M-mode. Strain analysis is based on combined speckle tracking algorithms that are applied to ultrasonic images of high frequency. Through nature, strain shows how much of a deformed myocardial tissue, i.e. Strain (S)= (L1-L0)/L0, and strain rate (SR) represents how easily myocardial tissue deforms **[9].** In 2D echocardiographic images, B-mode cine loops were selected and then three to four consecutive cardiac cycles are selected to analyze the strain. Endocardial boundary tracing was performed. The strain was then analyzed to obtain regional and global measures, respectively **[10].** Our thalassemic patients were subdivided according to their Global Longitudinal Strain (GLS%) into: Normal GLS>-17 %, Borderline GLS from -17% to -15%, Clearly abnormal GLS < -15%.

Ethical declaration:

Approval for performing the study was obtained from Pediatrics Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval and also informed written consent was taken from patients and/or their caregivers. This Work was performed according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans**.**

STATISTICAL ANALYSIS:

All data was collected, tabulated and statistically analyzed for Windows using SPSS 20.0 (SPSS Inc., Chicago, IL, USA 2011). Quantitative data

were expressed as mean±SD & (minimum-maximum) and qualitative data as absolute frequencies (number) & relative frequencies (percentage) were expressed. By using the Shapiro Walk method continuous data is tested for normality. Independent samples (t) a test was used to compare normally distributed variables between two independent groups. Mann-Whitnney u test was used to compare the variables normally not distributed between two independent groups. F-test has been used to evaluate naturally distributed component classes of more than two. While Kruskall Wallis test was used for variables which are not normally distributed. The rank correlation coefficient of Spearman was calculated to evaluate the relationship between different study variables, (+) indicate direct correlation, and (-) indicate inverse correlation, as well as values close to 1 indicate strong correlation, and values close to 0 indicate weak correlation. All testing was two-sided. P-value < 0.05 was deemed statistically significant (S), and p-value 0.05 was deemed statistically insignificant (NS).

RESULTS

There was non-significant differences between cases and controls as regards age, sex. However, there were statistically significant decrease of body mass index among Thalassemic patients compared to controls. **Table (1)** This study showed that Beta thalassemic patients had highly significantly lower RBCS count and Hb% than controls . However, RDW and serum ferritin among thalassemic patients were highly significantly increased than controls. **Table (2)** There was a statistical significant difference of Speckle Tracking Echocardiography of all LV strain% among B-Thalassemic patients versus controls while as regards basal septal, mid septal strain%, there was non statistical significant difference. **Table (3)** There was a statistical significant differences of LVEDD and PW among B- Thalassemic patients in relation to Global longitudinal strain (GLS) %. **Table (4).**This study showed that Global longitudinal strain (GLS) % had statistically significant relation to other Speckle Tracking Echocardiography parameters among B-Thalassemic patients. **Table (5)**There was statistically highly significant relation between Global longitudinal strain (GLS) % and serum ferritin in B- Thalassemic patients . **Table (6)**This study showed that Haemoglobin level was negatively correlated to BAS LAT strain% and Global longitudinal strain(GLS)% among B-Thalassemic patients. **Table (7)**

Table (1): Socio-demographic characteristics and Body mass index among Thalassemic patients in comparison to controls.

Items	Thalassemic patients n=34	Control n=34	MW	p
Age (years) median (range)	12(6-15)	11.5(11-12)	0.97	0.33
Sex no (%)				0.81
Female	16(47.1)	17 (50)	χ^2=0.06	
Male	18(52.9)	17 (50)		
Body mass index(kg/m2) median(range)	17.5(13.2-24.2)	21.6(21.4-21.8)	5.7	0.0001

χ^2 Chisquare test MW = Mann-Whitney U

Table (2) : Laboratory parameters among B- Thalassemic patients in comparison to controls.

Laboratory parameters	Thalassemic patients n=34	Control n=34	t	p
RBCS count /million mean± SD	3.4±0.7	5.5±0.5	13	0.00001
Hb g/dl mean± SD	7.9±0.8	13±1	22.6	0.00001
RDW% median(range)	13 (11-20.6)	12.3 (12-12.5)	MW=3.5	0.0003

Laboratory parameters	Thalassemic patients n=34	Control n=34	t	p
Ferritin ng/ml median(range)	2800 (1500-6221)	90 (80-100)	MW=7.2	0.00001

Hb: haemoglobin% , RDW: red cell distribution width

Table (3) : Speckle Tracking Echocardiography of LV strain % among B- Thalassemic patients in comparison to controls.

Speckle Tracking Echocardiography of LV strain %	Thalassemic patients	Control	MW	P
BAS Sep strain% median(range)	16(2.08:48.8)	-18.2(14.5-22)	0.21	0.83
MID SEP strain% median(range)	16.1(.4-29.1)	15.6(9.6-21.6)	0.42	0.67
Apic SEP strain% median(range)	13.5(.1-29.1)	22.9(18.9-26.9)	4.7	0.0001
Apic LAT strain% median(range)	15(0-29.6)	29.2(28.8-29.6)	6.6	0.0001
Mid LAT strain% median(range)	14(0.1-36.5)	32.2(31.5-32.8)	5.1	0.0001
BAS LAT strain% median(range)	15.7(0-38.5)	31.4(31.3-31.6)	5.1	0.0001
Global longitudinal strain (GLS) % median(range)	16.9(0-29.9)	26.03(22.2-29.9)	4.9	0.0001

MW= Mann Whitnney test

Table (4): Global longitudinal strain (GLS) %grading among B- Thalassemic patients in relation to Conventional Echocardiographic parameters.

Conventional Echocardiographic parameters	Thalassemic patients GLS category			f	p
	Abnormal n=11	Border line n=6	Normal n=17		
LVEDD.mm mean± SD	48.6±6.7	46.9±5.6	40.7±7.4	3.7	0.036(S)
LVESD.mm mean± SD	33.6±5.5	26.3±5.02	33.6±8.4	2.6	0.09
IVS.mm Median(range)	6.5(2.1-8.6)	7.7(2.9-9.7)	5.1(3.4-12.6)	KW=2.99	0.22
PW.mm Median(range)	6.9(3.7-10.1)	9.6(5.9-10.9)	5.5(3.5-12.6)	KW=6.1	0.047(S)
LVEF% mean± SD	58.3±6.8	65.5±5.3	60.3±12.6	1.04	0.38
LVFS% mean± SD	31±4.7	36.2±3.7	33.1±8.9	1.03	0.38
E.ms mean± SD	0.7±0.1	0.8±0.1	0.8±0.2	1.17	0.32
A.ms mean± SD	0.4±0.04	0.4±0.1	0.4±0.1	3.7	0.13
E.A ratio mean± SD	2.1±0.4	1.9±0.4	0.2±0.3	1.07	0.58

F Anova test KW =Kruskall wallius test S= significant

*LVEDD left ventricular end diastolic diameter, LVESD left ventricular end systolic diameter, IVS interventricular septum- PW posterior wall – LVEF ejection fraction- LVFS fractional shortening- E left

ventricular E wave peak velocity transmitral flow in early phase- A left ventricular A wave peak velocity transmitral flow during atrial systole.

Table (5): Global longitudinal strain (GLS) %grading of B- Thalassemic patients in relation to other Speckle Tracking Echocardiography parameters.

Speckle Tracking Echocardiography parameters	Thalassemic patients GLS category			KW	P
	Abnormal n=11	Border line n=6	Normal n=17		
BAS Sep. strain% Median (range)	9.7(2.08-21.29)	21.4(6.41-31.3)	22.3(5.8-48.8)	11.602	0.003(s)
MID SEP.strain% median(range)	8.15(0.38-16.5)	17.7(5.4-20.75)	18.4(6.4-29.1)	11.209	0.004(s)
Apic SEP strain% median(range)	9.5(0.1-14.4)	9.4(4.09-20.47)	18.9(3.41-29.11)	10.834	0.004(s)
Apic LAT strain% median(range)	6.6(0-15.03)	12.1(6.59-20.26)	21.9(8.08-29.55)	17.954	0.0001(H.s)
Mid LAT. strain% median(range)	12.1(0.1-12.57)	13.4(9.62-19.42)	23.6(9.44-36.51)	18.799	0.0001(H.s)
BAS LAT strain% median(range)	12.3(0-15.82)	12.76(9.63-20.68)	24.7(5.89-38.5)	15.246	0.0001(H.s)

KW =Kruskall wallius test S= significant H.S= highly significant

Table (6): Echocardiographic parameters of B- Thalassemic patients in relation to serum ferritin level

Echocardiographic parameters	ferritin level of B- Thalassemic patients		t	P
	<2500(n=12)	≥2500(n=22)		
LVEF% mean± SD	64.9±10.4	58.2±9.3	1.9	0.062
LVFS% mean± SD	36±7.5	31.3±6.4	1.8	0.08
E.ms mean± SD	0.82±0.16	0.74±0.12	1.7	0.09
A.ms mean± SD	0.39±0.07	0.38±0.073	0.7	0.48
E.A ratio mean± SD	2.1±0.3	2±0.36	0.8	0.42
Global longitudinal strain(GLS)% median(min-max)	21.77(0.36-29.87)	16.3(0-24.53)	MW=3.8	0.001

MW= Mann- Whitnney u test

Table (7): Correlation between Haemoglobin level and Speckle tracking Echo parameters among B-Thalassemic patients.

Speckle tracking Echo parameters	Haemoglobin level g/ml	
	r	p
BAS SEP strain%	-.033	0.851
MID SEP strain%	-.039-	0.825
Apic SEP strain%	-.317-	0.067
Apic LAT strain%	-.289-	0.098
MID LAT strain%	-.329-	0.058
BAS LAT strain%	-.37	0.031*
Global longitudinal strain(GLS)%	-.35	0.045*

(r) correlation coefficient *significant<0.05 **highly significant <0. 01

DISCUSSION

The study was case-control study include 68 participants (34 patients with B-thalassemia and 34 age and sex matched healthy children as a control group).Their median age was 12 and 11.5 years for cases and controls respectively. Male to female ratio was 1.1:1 and 1:1 in cases and controls respectively.

Narayana et al., [11] reported in their study that the mean age of patients with beta-thalassemia was 7.02 ± 3.00 and 5.06 ± 3.62 of controls. The proportion of participants with male: female ratio was 13:1 and 12:1 respectively.

These results showed non-significant differences between cases and controls as regards age and sex because of proper matching of both groups regarding sex, but BMI was 21.6 among controls and 17.5 among thalassemic patients with significant difference.

These results were in agreement with **Cheung et al., [12]** Who stated that Thalassemic patients correlated with controls were lighter (48.2 ± 8.9 kg vs. 58.0 ± 12.1 kg, P < 0.001) and had a smaller body mass index (19.2± 2.3 kg/m2 vs. 21.7 ± 3.7 kg/m2, P=0.004).

In this study, there were statistically significant decrease of RBCs count, Hb**%** among thalassemic patients compared to control group. Median serum Ferritin level was significantly higher in the thalassemic patients (2800ng/ml) compared to control group (90ng/ml).

These results were in agreement with **Ibrahim et al.,[13]** who reported that patients mean hemoglobin level was 9.1 ± 2.3 g / L while control group mean level was 11.5 ± 1.5 g / L (p-value < 0.05). Also, our results were agreed with **Narayana et al., [11]** who found that the mean hemoglobin of beta thalassemic children was 5.54 ±1.30 and 10.96±1.36 of Control group statistically significant for P < 0.001.

These results showed statistical significant differences of speckle tracking echocardiography of all LV strain % among B- Thalassemic patients in comparison to controls except basal septal and mid septal strain. These results were in agreement with **Monte et al., [14]** who conducted a case–control study with 27 patients with thalassemia major and 27 healthy controls. Standard echocardiography was performed for evaluating LV rotation and longitudinal mechanics. Echocardiography was used to track the speckle. The study found that LV rotational dynamics are negatively related to iron overload in patients with thalassemia major.

The study by **Hyder et al., [15]** was done to evaluate the LV function in patients with thalassemia major using echocardiography. The study included fifty cases of major beta thalassemia and thirty controls with normal pattern of hemoglobin and electrophoresis. The patients age ranged from 1 to 25 years. 2D echocardiography, M-mode and Doppler echocardiography were performed in all cases and the participants in control. Results showed that 19 (38%) patients had LV dysfunction, of which isolated systolic dysfunction was found in 2 (4%), isolated diastolic dysfunction in 15 (30%) and global dysfunction in 2 (4%) patients, and LV measurements, stroke length and E/A ratio were significantly impacted in the study group as measured by standard echocardiography.

This results showed statistical significant differences of LVEDD and PW thickness among B- Thalassemic patients in relation to GLS, GLS had statistically significant differences in relation to other Speckle Tracking Echocardiography examination parameters among B- Thalassemic patients.

This results showed that there was statistically high significant difference of Echocardiographic GLS parameters among B- Thalassemic patients in relation to age, Hb level and serum ferritin.

These findings were in line with **Parsaee et al.,[16]** who stated that GLS can be useful in predicting myocardial iron overload in thalassemic patients with normal LVEF by correlating T2* CMR with the STE results. These findings were consistent with **Hamdy's[17]** findings, which stated that strain imaging could diagnose LV function problems before conventional echocardiography becomes abnormal. In addition, the vital point of this finding was that a moderate overload of iron in cardiac problems can lead to longitudinal ventricular deformation. As the results revealed, GLS indirectly demonstrated iron overload and consequent systolic dysfunction using speckle tracking. This finding was in line with several previous studies carried out by **Seldrum et al.,[18]** and **Mentz & Khouri,[19]** which showed that there was not only a significant correlation between GLS and LVEF, but also that GLS had a quantitative analytical ability to detect systolic dysfunction in patients with steady EF at the early stages of cardiomyopathy .

There was statistically high significant difference of Echocardiographic GLS parameters among B- Thalassemic patients in relation to age, Hb level and serum ferritin in agreement with **Parsaee et al., [16]**. Haemoglobin level was negatively correlated to BAS LAT strain% and Global longitudinal strain(GLS)% among B- Thalassemic patients.

Limitations: The study had some limitations including small sample size and there was no estimation of the global radial strain of the six segments in the short axis as averaging was not feasible even with the current version of the software, we did not assess the impact of volume load on stress analysis. There are two-dimensional STE limitations, which include potential under sampling due to a relatively low frame rate of 50–70/sec for optimum speckle tracking, failure to take into account scatterer movement out of plane, and axial and lateral resolution differences. Speckle detection was feasible on all of our samples in the present study.

CONCLUSION

Although the conventional echocardiographic functions of Thalassemic patients were apparently normal, Two dimensional speckle tracking echocardiographic study revealed subclinical left ventricular dysfunction which is correlated to older age, low haemoglobin % and high serum ferritin levels.Hence, STE can be applied as an integrated part of assessment of children with beta-thalassemia.

RECOMMENDATIONS

We recommend to conduct this study on larger sample size for further documentation of the proposed assumption and to determine their prognostic significance on using different new therapeutic strategies among patients with thalassemia.

Declaration of interest

no conflicts of interest.

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