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Cardiac Structural and Functional Changes Evaluated by Echocardiography and Two-Dimensional Strain in Patients with Beta Thalassemia

Norhan M. Sayed[1], Mohamed A. Mashahit[1], Noha M. El- Husseiny[2], Ragab A. Ali[1], Gomaa A. Ahmed[3], and Mostafa K.Ibrahim[3].

[1]Department of Internal Medicine, Faculty of Medicine, Fayoum University, Egypt.
[2]Department of Internal Medicine, Faculty of Medicine, Cairo University, Egypt.
[3] Department of Cardiology, Faculty of Medicine, Fayoum University, Egypt.
Email: nms03@fayoum.edu.eg

Abstract: Introduction: Assessment of cardiac function in thalassemia must be routinely performed to early diagnose various functional abnormalities, and to consider required therapeutic measures **so** the aim of this study was to evaluate cardiac abnormalities in thalassemia patients. **Methods:** The study included 80 patients subdivided into two groups **Group 1:** 40 patients of Beta thalassemia (major and intermediate) and **Group 2:** control group included 40 healthy subjects age and gender matched to the patient group. Both groups were subjected to detailed history,Clinical examination, laboratory investigations (CBC, lipid profile, serum ferritin) and imaging using Transthoracic Doppler echocardiography including Tissue Doppler imaging and two dimensional Strain echocardiography. **Results:** The global strain value was significantly lower in thalassemia patients than those of the controls **(p <0.0001)**. Thalassemia patients had higher serum uric acid than control. **Conclusions:** Evaluation of global strain was useful in assessing cardiac functions and predicting myocardial iron overload.

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1. Introduction

One of the most common hemolytic anemias in children and adolescents worldwide is beta-thalassemia. Regular blood transfusion and chelation therapy programmes have significantly increased the survival of thalassemia patients.. Nonetheless, secondary iron overload is a consequence of chronic transfusion therapy, which adversely affects the function of the heart, liver, and other organs, causing significant morbidity and shortening life expectancy **(1).**

Pericarditis, myocarditis, heart failure, and arrhythmias are forms of cardiac complications. However, pericarditis and myocarditis are now uncommon due to proper chelation therapy **(2).** Dilated cardiomyopathy (with restrictive features) and arrhythmia, most particularly atrial fibrillation, are the most common clinical features (AF) **(3).**

Longitudinal fiber motion abnormality is a sensitive marker of early myocardial dysfunction. In thalassemia patients, the edge between overt myocardial dysfunction and clinically silent left ventricular (LV) dysfunction is incredibly small. RV cardiomyopathy and pulmonary hypertension (PHT), in addition to LV abnormalities, are common complications in the disease's cardiopulmonary spectrum **(4).**

Using conventional echo-Doppler, previous studies revealed that the mean value of Left Ventricle End Diastolic Diameter (LVEDD) and Left Ventricle End Systolic Diameter (LVESD) for children with thalassemia major was significantly higher than in the control group **(5).**

Another study found that thalassemia major patients with no overt clinical cardiac dysfunction had abnormal right ventricular diastolic function, with higher atrial diastolic right ventricular velocity (tricuspid annular A ') and a low tricuspid annular E '/A' ratio compared to controls **(6).**For these reasons, our study conducted a comprehensive assessment of cardiac function investigating the value of using Two dimensional Strain echo in the detection of non-overt cardiac dysfunction in Egyptian adult patients with beta- thalassemia(major and intermediate) before the development of overt heart failure or cardiomyopathy.

2. Methods

Study Design and Patients

This study was a case-controlled, cross-sectional study conducted in Egypt (Fayoum). Faisal University's ethical committee approved the study. All participants gave informed consent. This study included 80 patients divided into two groups:

Group 1:

40 patients of both genders, with Beta thalassemia were divided into two groups;
Group 1a included 20 patients with thalassemia major.
Group 1b included 20 patients with thalassemia intermediate, aged 18 to 40 years, who attended the Fayoum University Hospital Outpatient Clinic of Internal Medicine for blood transfusions or medical follow-up during the study period (September 2019 to February 2020).

Group 2:

The control group included 40 healthy individuals with age and gender matched to the patient's group.

The exclusion criteria:

Cases with structural heart disease (congenital or rheumatic), cases with a history of smoking, hypertension, diabetes mellitus, dyslipidemia and obesity, a history of overt heart failure, and other causes of heart failure, rather than iron overload, including metabolic causes such as hypercalcemia and thyrotoxicosis.

All cases and controls were subjected to

- detailed history, including age, sex, frequency of blood transfusion, type of chelation therapy, symptoms of heart failure and history of
- Clinical examination including anthropometrics measurements, and presence of any complications of iron overload.
- Clinical signs of heart failure
- laboratory investigations (CBC, lipid profile, serum ferritin)
- Imaging using Transthoracic Doppler echocardiography. Digital media was used to store the images.

1. **Echo-Doppler examination included**

Transthoracic Doppler echocardiography was performed using (Philips Medical Systems, Epic 7 c). The images were saved on digital media.

- M-Mode and two dimensional echo: were performed according to the American Society of Echocardiography recommendations to measure LAi (left atrial diameter index), LAVi (left atrial volume index), LVDDi (left ventricle diastolic diameter index), LVSDi(left ventricle systolic diameter index), LVDVi (left ventricle diastolic volume index), LVSVi (left ventricle systolic volume index),ejection fraction by modified Simpson's method, right ventricle (RV) diameter and systolic fractional shortening area, and, RV free wall thickness.

2. Two-dimensional Speckle tracking

Patients of our sample were evaluated with 2D Strain, in which images of the LV in apical four-, two- and three-chamber views were obtained and made suitable for analysis. Longitudinal strain was assessed in all six LV walls in the three apical views using a software package (QLAB, Phillips, USA)., and the average value of each wall on each view and the global strain value was compared with the controls.

Statistical Analysis

- Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Simple descriptive analysis within the sort of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test:

For quantitative parametric data:

- In-depended student t-Test wont to compare measures of two independent groups of quantitative data.
- Bivariate pear son correlation test to check association between variables
- The level $P \leq 0.05$ was considered the cut-off value for significance.

3. Results

The study population's demographic data is shown in (Table 1). Age, sex and body surface area were statistically not significant between groups. Table 2 shows the clinical parameters of the study groups.

The laboratory parameters are illustrated in (Table 3).The mean haemoglobin level differed statistically between cases and controls. The mean haemoglobin level of the patients in group 1 a was 9.7 ± 0.6 g/L, and the mean level of the patients in group 1 b was 9.2 ± 0.7 g/L, while the mean level of the control group was 12.7 ± 0.8 g/L. Serum ferritin levels were significantly higher in thalassemia major patients than in thalassemia intermediate patients.

Group Ib had a higher frequency of blood transfusion, lower uric acid levels and higher serum

ferritin levels compared to group Ia (Table 1). The lipid profile did not differ statistically between groups (table 3).

The conventional echo-Doppler revealed that the mean value of the LAVi, LVDVi, LVSVi, and LVESDi for thalassemia patients was significantly higher than in the control, while there was no significant difference in EF between thalassemia major and intermediate, or between cases and the control group. Furthermore, the mean value of TAPSE for cases and controls was not statistically significant. (Table 4).

The assessment of RV diameter revealed statistically significant differences between patients (group 1 b) and controls, whereas there was no significant difference between cases and controls in terms of RV free wall thickness (Table 4).

By assessment of longitudinal strain in all six LV walls in the three apical views(apical four-, two- and three-chamber views), the study revealed statistically significant differences between the patients and the control subjects in all of them Apical four-, two- and three-chamber views were found to be significantly lower in thalassemia patients than controls. Also the global strain value was significantly lower in thalassemia patients than those of the controls. Left ventricular strain imaging data are detailed in **(Table 5).**

Table (1):Demographic and baseline characteristics of patients and controls.

Variable	Group 1a (N=20)		Group 1b (N=20)		Group 2 (N=40)		P-value
	Mean ± SD						
Age	27.0 ± 6.4		23.4 ± 6.2		24.5 ± 7.5		0.129
frequency of blood transfusion per year	3.6 ± 2.0		10.3 ± 2.1				**<0.0001**
Variable	**N**	**%**	**N**	**%**	**N**	**%**	
Sex							
Male	9	45.0%	11	55.0%	18	45.0%	0.740
Female	11	55.0%	9	45.0%	22	55.0%	
history of splenectomy							
No	18	90.0%	3	15.0%	40	100.0%	
Yes	2	10.0%	17	85.0%	0	0.0%	

values are expressed as means ± SD or number (%)

Table (2): clinical parameters of the study groups.

Variable	Group 1a (N=20)	Group 1b (N=20)	Group 2 (N=40)	P-value
	Mean ± SD			
BSA	1.5 ± 0.2	1.5 ± 0.2	1.6 ± 0.1	0.082
weight	55.3 ± 7.9	54.7 ± 9.5	59.8 ± 10.1	0.122
height	162.0 ± 11.1	159.6 ± 7.3	162.6 ± 7.7	0.425
SBP	120 ± 7.9	116.9 ± 25.4	120.9 ± 7.3	0.808
DBP	74.7 ± 6.1	76.3 ± 6.7	77.1 ± 6.8	0.176
HR	89.9 ± 6.7	89.2 ± 7.2	87.3 ± 7.8	0.391

Values are expressed as means ± SD or number (%). BSA – body surface area, HR – heart rate, bpm – beats per minute, SBP – systolic blood pressure,– diastolic blood pressure, DBP diastolic blood pressure

Table (3): laboratory investigations of the study groups.

Variable	Group 1a (N=20)	Group 1b (N=20)	Group 2 (N=40)	P-value
	Mean ± SD			
HB(gram/dL)	9.7 ± 0.6	9.2 ± 0.7	12.7 ± 0.8	**P1** 0.291 **P2 <0.0001** **P3 <0.0001**
UA(mg\dl	6.7 ± 1.5	5.7 ± 1.5	4 ± 0.9	**P1** 0.130 **P2 <0.0001** **P3 <0.0001**
Ferritin (ng|ml)	488.2 ± 330.9	1468.4 ± 830.3	40.3 ± 12.6	**P1 0.037** **P2 <0.0001** **P3 <0.0001**
Cholesterol (mg\dl)	82.8 ± 15.1	95.1 ± 14.9	90.9 ± 16.8	0.067
TG(mg\dl)	115.9 ± 35.5	130.3 ± 50.7	116.5 ± 48.5	0.680
LDL(mg\dl)	51.1 ± 29.5	54.2 ± 16.1	55.3 ± 22.2	0.100
HDL(mg\dl)	31 ± 10.7	31.6 ± 9.3	31.8 ± 9.4	0.922

values are expressed as means ± SD or number (%). HB_ Hemoglobin, UA _uric acid. TG- Triglyceride, LDL- low density lipoprotein, HDL- High density lipoprotein, P1=1a vs 1b, P2=1a vs 2, P3= 1b vs2

Table (4): Echocardiographic M-mode and two-dimensional Parameters in Cases versus Controls:

Variable	Group 1a (N=20)	Group 1b (N=20)	Group 2 (N=40)	P-value
	Mean ± SD			
LAi [cm/m²]	2.4 ± 0.5	2.6 ± 0.5	2.3 ± 0.3	**P1** 0.096 **P2** 0.391 **P3 0.005**
LAVi [ml/m²]	24.8 ± 4.8	33.2 ± 7.6	18.9 ± 4.7	**P1 0.025** **P2 <0.0001** **P3 <0.0001**
LVDDi [cm/m²]	3.0 ± 0.2	3.1 ± 0.3	2.8 ± 0.3	**P1** 0.956 **P2 0.005** **P3 0.004**
LVSDi [cm/m²]	2.0 ± 0.2	2.2 ± 0.2	1.9 ± 0.2	**P1 0.032** **P2** 0.116 **P3 <0.0001**
LVDVi [ml/m²]	65.0 ± 13.0	71 ± 15.6	49.2 ± 8.0	**P1** 0.380 **P2 <0.0001** **P3 <0.0001**
LVSVi [ml/m²]	26.9 ± 5.7	29.1 ± 5.9	20.7 ± 2.8	**P1** 0.400 **P2 <0.0001** **P3 <0.0001**
EF%	61.2 ± 4.2	62.1 ± 3.3	62.8 ± 3.8	0.461
RV diameter [cm]	3.3 ± 0.4	3.9 ± 0.3	3.2 ± 0.2	**P1 <0.0001** **P2** 0.252 **P3 <0.0001**
TAPSE [cm]	2.3 ± 0.4	2.4 ± 0.3	2.3 ± 0.3	0.149
RV free wall thickness	0.4 ± 0.1	0.5 ± 0.1	0.7 ± 1.0	0.051

P1=1a vs 1b,,P2=1a vs 2,,P3= 1b vs2

Values are expressed as means ± SD. LAi – left atrial diameter index, LAVi – left atrial volume index, LVDDi – left ventricle diastolic diameter index, LVSDi– left ventricle systolic diameter index, LVDVi – left ventricle diastolic volume index, LVSVi – left ventricle systolic volume index, EF – ejection fraction, RV – right ventricle, TAPSE– tricuspid annulus peak systolic excursion.

Table (5): Two-dimensional left ventricular strain echocardiographic parameters in patients versus controls.

Variable	Group 1a (N=20)	Group 1b (N=20)	Group2 (N=40)	P-value
	Mean ± SD			
A 4C –	-21.7 ± 2.5	-19.1 ± 2.6	-23.6 ± 1.9	**P1 0.029** **P2 0.005** **P3 <0.0001**
A 3C –	-21.0 ± 3.9	-16.2 ± 8.3	-24.3 ± 2.8	**P1 0.006** **P2 0.004** **P3 <0.0001**
A 2C –	-22.8 ± 2.9	-17.2 ± 8.6	-23.7 ± 1.4	**P1** 0.001 **P2** 0.217 **P3 <0.0001**
S Global	-21.7 ± 1.9	-19.4 ± 1.7	-24.7 ± 1.8	**P1 0.013** **P2 <0.0001** **P3 <0.0001**

P1=1a vs 1b,,P2=1a vs 2,,P3= 1b vs2

Values are expressed as means ± SD or number (%). A 4C – 4-chamber longitudinal strain, A 3C – 3-chamber longitudinal strain, A 2C – 2-chamber longitudinal strain, S Global – left ventricular global longitudinal strain

4. Discussion

Cardiac abnormalities are the most problematic transfusion related complications in thalassemia patients. Cardiac dysfunction precipitated by myocardial iron load may be detected early with the recent echocardiographic techniques but conventional echocardiography for EF detects damage at later stages of the disease. Previous studies have shown that tissue Doppler imaging (TDI) and speckle tracking echocardiography.(STE) may find early myocardial dysfunction in major patients with thalassemia. STE is also an echocardiographic technique for regional and global myocardial dysfunction studies (7). For these reasons, our study conducted a comprehensive assessment of cardiac function investigating the value of using Two dimensional Strain echo in the detection of non-overt cardiac dysfunction in Egyptian adult patients with beta- thalassemia(major and intermediate) before the development of overt heart failure or cardiomyopathy.

The present study showed that apical four-, two- and three-chamber longitudinal strains were found to be significantly lower in thalassemia patients than in controls. Also The global strain value (-21.7 ± 1.9 and - 19.4 ± 1.7 vs. -24.7 ± 1.8) were significantly lower in thalassemia patients than those of the controls. This result goes with the study of **Parsaeea et al. (7),** who reported that global longitudinal strain (GLS) in thalassemia patients was significantly reduced (−20.9 ± 1.9 vs. −22.2 ± 1.03) and there was also a significant decrease in longitudinal strain in the basal segments compared to the control group (−17.4 ± 2.7 vs. −19.6 ± 1.2) **(7).**

In this study, the conventional echo showed that the mean value the LAVi, LVDVi LVSVi and LVESDi for thalassemia patients were significantly higher than the control while there was no significant difference between cases and control group regarding LV systolic function (EF) by conventional echocardiography. These results are consistent with the results of **Ibrahim et al. (5)** who reported that conventional echocardiography detected LV dilatation and no affection in LV systolic function, although there was a considerable discrepancy between LVEDD and LVESD cases and controls **(5).**

Assessment of tricuspid annulus peak systolic excursion revealed no statistically significant differences between the patients and the control subjects. This goes hand in hand with the study that reported that there was no difference between the thalassemia patients and controls in TAPSE **(8)**. On the contrary, **Bornaun et al. (9)** found that there was significant difference between the thalassemia major patients and control subjects in TAPSE **(9).**This could be explained by the fact that our patients are chosen at the outset with non-overt cardiac dysfunction. Also, our patients with beta thalassemia were young, optimally transfused and their hemoglobin level was more than 9gm/ dL with mild and moderate iron overload. This finding is consistent with the findings of Agha et al., who found no pulmonary hypertension in transfusion-dependent thalassemia patients compared to controls. **(6).**

In our study, we found that thalassemia patients had higher serum uric acid than the control group. Because of chronic hemolysis and ineffective erythropoiesis, thalassemia patients have a high cell turnover rate, and, thus, hyperuricemia is expected. **(10)** Although elevated UA is associated with CV risk and events, this power is lost in different studies after adjusting for potential confounders, suggesting

that UA is not independent of other risk factors **(11).** These results are consistent with the study that reported that hyperuricemia was found in half of thalassemia patients, but gouty arthritis only occurred in ten percent, which can be explained by hyper excretion of uric acid **(12).**

In our study, there was no statistically significant difference in lipid profile between thalassemia patients and controls. These results are consistent with **Haghpanah et al. (13)** who reported that total cholesterol and LDL-cholesterol were lower in patients with thalassemia major and intermediate than in controls. These findings could be explained by increased erythropoiesis and cholesterol consumption in thalassemia intermediate (13), and iron overload and oxidative stress in thalassemia major **(13).**

Conclusions:

Speckle tracking echocardiography may be used as a valuable tool to determine subclinical myocardial dysfunction in thalassemia patients.

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