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Early detection of myocardial dysfunction in poorly treated pediatric thalassemia children and adolescents: Two Saudi centers experience

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HIGHLIGHTS

- Cardiac complications are among the most serious complications in Beta Thalassemia Major Patients.
- Tissue Doppler imaging can detect cardiac dysfunction in pediatric thalassemics before development of overt heart disease.
- Patients with normal global functions, by conventional echo, have abnormal ventricular functions detected by TDI.
- TDI is superior to Echo-Doppler in detection of early myocardial damage in asymptomatic thalassaemic patients.

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ABSTRACT

Background & Objective: Cardiac complications are among the most serious complications in Beta Thalassemia Major Patients. Our aim was to evaluate the value of tissue Doppler imaging (TDI) for early detection of myocardial dysfunction in pediatric and adolescent patients with B-TM before development of overt heart failure or cardiomyopathy.

Patients and methods: 100 thalassemic patients below 18 years old and 100 healthy, age & sex matched controls were enrolled in our case-control study. Cases were selected from those attending outpatient clinics and inpatient wards, King Abdulaziz University hospital and Alhada Armed Forces Hospital, Saudi Arabia, between January 2014 and January 2015. They were subjected to echo-Doppler examination for both septal and lateral walls of the basal mitral and tricuspid annuli assessing the systolic myocardial velocity (S wave), early diastolic myocardial velocity (Ea wave) and late diastolic myocardial velocity (Aa wave).

Results: Patients with thalassemia have RV and LV dysfunction on the basis of abnormal TDI derived myocardial velocities. There was a statistically significant differences between patients and controls regarding (Aa) and (S) of the septal wall of the basal mitral annulus and (Ea) of the lateral wall of the mitral annulus. Also patients with thalassemia have significantly higher (S) of the basal tricuspid annulus. These abnormalities were not detected by conventional echo-Doppler.

Conclusion: Clinically asymptomatic thalassemic children and adolescents who had normal global functions by conventional echo-Doppler were found to have abnormal left ventricular and right ventricular dysfunctions detected by TDI. TDI is superior to Echo-Doppler in detection of early myocardial damage in asymptomatic thalassaemic patients.

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1. Introduction

Beta thalassemia major is the most common chronic hemolytic anemia among children and adolescents across the world [1]. Beta-thalassemia is prevalent in Mediterranean countries, the Middle East, including Saudi Arabia, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia [2–3]. The high prevalence in the Middle East can be attributed the high prevalence (25–60%) of consanguineous marriages [4].

About 1.5% of the global population are carriers of beta thalassemia, with about 60,000 symptomatic individuals born annually. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world [5]. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world [6].

Regular blood transfusion programs and chelation treatment have considerably improved the survival of patients with thalassemia. However, a consequence of chronic transfusion therapy is secondary iron overload, which adversely affect function of the heart, liver and other organs, causing severe morbidity and shorten the life expectancy [1].

Despite improved survival after the use of iron chelators, the cardiac complications are still the primary leading cause of death for young adults with β-thalassemia major [7]. Cardiac dysfunctions in β-thalassemia major have traditionally been attributed to iron-overload [8] related to repeated transfusions and increased intestinal absorption rate combined with a sustained state of increased cardiac output [9].

Cardiac complications, include pericarditis, myocarditis, HF, and arrhythmias [10,11]. However, with proper chelation treatment, pericarditis and myocarditis are now rare [12]. The most common clinical features are dilated cardiomyopathy (with restrictive features) and arrhythmia, primarily atrial fibrillation (AF). In severe cases, ventricular arrhythmias become more common, and ectopic atrial tachycardia, flutter, and chaotic atrial rhythms may also occur [13].

The age of cardiac death depends primarily on the access to transfusions and chelation. In transfused, but unchelated patients, the typical age at death was 10 years, primarily of cardiac causes [14].

One unit of transfused red blood cells contains approximately 250 mg of iron [15], while the body cannot excrete more than 1 mg of iron per day. A patient who receives 25 units per year, accumulates 5 g of iron per year in the absence of chelation [16].

Although iron chelation therapy can prevent and delay myocardial dysfunction due to the progressive increase of heart iron burden, once dysfunction has become clinically evident it is difficult to reverse [17,18].

Long term control of serum ferritin has been related to protection from cardiac involvement and with improved survival if levels are less than 2500 μg/L [19] with even better outcomes at levels <1000 μg/L [20]. However, serum ferritin is a poor marker of iron balance because ferritin levels change with inflammation/infection, or ascorbate deficiency, and depends on the intensity of blood transfusion, making its reliability uncertain [20].

Detection of early cardiac abnormality is difficult [18,21]. Symptoms and echocardiographic abnormalities arise late in the course of the disease. Usually, patients have normal exercise capacity, with systolic dysfunction occurring in the final stage of disease [21]. Abnormality of longitudinal fiber motion is a sensitive marker of early myocardial dysfunction. Hence, tissue Doppler imaging can be beneficial in the quantitative assessment of regional myocardial function [22,23].

Magnetic resonance imaging (MRI) with the T2* technique is the best method for the detection of tissue iron deposition worldwide. It is noninvasive, and suitable for moving organs like heart [18,24,25]. In children with hemoglobinopathy who received transfusion and chelation, the cardiac T2* was <20 ms only after 10 years of age [26,27]. However, younger onset of cardiac iron, as young as 7 years, has been occasionally reported in TM, especially when poorly chelated [28].

The aim of this study was to investigate the value of using Tissue Doppler Imaging in the detection of non-overt cardiac dysfunction in pediatric and adolescent patients with beta thalassemia major.

2. Patients and methods

We carried a multicenter case-control study on pediatric and adolescent patients of β-TM. Patients were selected from those attending outpatient clinics and inpatient wards, King Abdulaziz University Hospital and Alhada Armed Forces Hospital, Saudi Arabia, between January 2014 and January 2015. It included 100 patients with β-TM aged below 18 years old. Patients were prescribed oral iron chelator; Deferasirox in dose of 20–40 mg/kg. Patients were considered as poorly treated if they were not compliant to their oral iron chelator. We excluded cases with congenital or rheumatic heart disease to exclude structural cardiac disease, including regurgitant valvular lesions, as detected by echocardiography, which may cause ventricular dilatation. We also excluded cases with history of smoking, hypertension, present or past history of overt heart failure. In addition, we excluded other causes of heart failure, other than iron overload, including biochemical causes such as hypercalcemia and thyrotoxicosis. The control group had one hundred age and sex matched apparently healthy individuals with normal cardiovascular status. The study was approved by the research and ethical committees of the contributing hospitals. Written informed consents were obtained from participants or their parents.

All cases and controls were subjected to full history taking (for symptoms of heart failure, co-morbid diseases, drug history and history of transfusions), thorough clinical examination (for signs of heart failure such as gallop rhythm, raised jugular venous pressure and delayed capillary refill), laboratory investigations (CBC and serum ferritin) and imaging using Echo-Doppler and TDI. All echocardiography examinations were done to the patients after receiving blood transfusion as anemia can affect the echocardiographic findings (e.g. marked anemia can cause high cardiac output heart failure).

2.1. Echo-Doppler examination included

(A) M-Mode and two dimensional echo to measure left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter LVEDD, left ventricular mass (LVM), ejection fraction (EF%), fractional shortening (FS%), and tricuspid annular plane systolic excursion (TAPSE).
(B) Conventional Doppler.
(C) Tissue Doppler imaging.

2.2. Echo-Doppler technique

By using ATL 5000 echocardiography machine, tissue Doppler imaging data were acquired transthoracically using a 2.5 or 3.5 MHZ transducer. The mitral inflow velocity pattern was recorded in the apical 4-chamber view with the pulsed wave Doppler sample volume positioned at the tip of mitral leaflets during

diastole. In Doppler tissue imaging, the sample volume was positioned at the medial (septal) end of the mitral annulus, lateral end of the mitral annulus and tricuspid annulus in apical four chamber view with proper alignment of the examined area with the Doppler beam. The velocities of different waves then determined (S, Ea, Aa). Isovolumic contraction time (IVCT) was calculated from mitral valve closure to the aortic valve opening (end of Aa to onset of S wave). Ejection time (ET) was calculated from onset of (S) to end of (S). Isovolumic relaxation time (IVRT) was calculated from aortic valve closure to mitral valve opening (end of S to onset of Ea). Then, myocardial performance index (MPI) or (LV Tei index) was calculated as the sum of IVCT and IVRT, dividing it by ET. The same was applied on the tricuspid valve to assess the right ventricular MPI (RV Tei index) [29].

Pulmonary capillary wedge pressure (PCWP) was assessed using the mitral E velocity to early diastolic myocardial velocity of the septal wall of the mitral annulus (Ea) ratio, with the formula PCWP = 1.9 + 1.24 (E/Ea).

Measurements of the myocardial velocities were performed on three consecutive heart beats and the average of the three measurements was calculated. All patients were in sinus rhythm at the time of examination.

3. Statistical analysis

Data are shown as mean ± standard deviation (SD) and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t*-test for independent samples in comparing two groups when normally distributed and Mann–Whitney *U* test for independent samples when not normally distributed. P-values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

4. Results

We included 100 patients with B thalassemia with non-overt cardiac disease and 100 age and sex matched controls. Both patients and controls were evaluated using Echo-Doppler imaging, including Tissue Doppler Imaging modality. Demographic data of the study population are shown in Table 1.

Twenty two percent (22%) of patients were receiving oral iron chelators regularly; while 78 patients (78%) were non-compliant.

The mean hemoglobin level of the patients was 91 ± 23 g/Lwhile the mean level of the control group was 115 ± 15 g/L (p-value < 0.05). Serum Ferritin level was significantly higher in the thalassemic patients compared to control group (Table 1).

The conventional echo-Doppler showed that the mean value of the LVEDD, LVESD and LVM for cases were significantly higher than the control group while there was no significant difference between cases and control group regarding FS and EF. Also mean value of the transmitral E/A ratio for cases and control group was not statistically significant (Table 2).

By assessment of the mitral valve by TDI, we found statistically significant differences between the patients and the control subjects in late diastolic myocardial velocities (Aa) and systolic myocardial velocities (S) at the basal mitral annulus of the septal wall, also patients with thalassemia have significantly higher early diastolic myocardial velocities (Ea) at the basal mitral annulus of the lateral wall by tissue velocity imaging. Pulmonary capillary wedge pressure was found to be significantly higher in thalassemic patients than controls. The Tissue Doppler imaging data are detailed in Table 3.

Assessment of the tricuspid valve showed significant difference for only systolic myocardial velocity (S) at the basal tricuspid annulus by tissue Doppler imaging.

The left ventricular Tei index was significantly lower in thalassemic patients than those of the controls.

These alterations in myocardial velocities detected only by TDI might indicate earlier left and right ventricular dysfunction before being detected by conventional echocardiography.

5. Discussion

The present study aimed to investigate the diagnostic value of using Tissue Doppler Imaging in the detection of non-overt cardiac dysfunction in pediatric and adolescent patients with beta thalassemia major.

Conventional echocardiography has reported increased EF, FS and left ventricular dimensions, which were associated with high cardiac output of chronic anemia state [30]. These changes, apart from increased left ventricular dimensions and mass, might not be apparent in younger thalassemia patients [31]. Cases of thalassemia show evidence of ventricular systolic dysfunction only in those with congestive heart failure, which occur at a late stage [32].

In our study, conventional echocardiography showed LV dilatation and no abnormalities in LV systolic function. There was significant difference between cases and controls regarding LVEDD and LVESD. In accordance with our results other investigators found that the ventricles were dilated in thalassemia patients than control subjects [33,34]. Similarly, Khalifa and coworkers showed a significant increase of all cardiac dimensions by echocardiography [35]. They stated that these cardiac structural changes are due to chronic anemia more than siderosis. More recently, Agha and coworkers found no difference in LV systolic function and increase in left ventricular dimensions by conventional echocardiogram in thalassemia patients compared to controls [36].

The mean LVM was increased in thalassemia patients than the control group and there was a highly significant difference between cases and control group. This finding coincides with other studies that reported a significant increase in LVM in beta thalassemia patients than controls [34,37,38].

Table 1
Demographic data of the study patients and control group.

Parameter	β-TM	Control	P-value
Age (Years)	12.1 ± 4.1	11.5 ± 4.0	>**0.05**
Male/female	70/30	70/30	>**0.05**
Weight (kg)	35.7 ± 12.7	40 ± 10.5	>**0.05**
Serum Ferritin (ug/L)	2.876 ± 1.189	230 ± 22	**0.000**[a]
Hemoglobin (g/L)	91 ± 23	115 ± 15	**0.000**[a]

[a] Significant p value.

Table 2
Conventional echocardiographic data.

Parameter	β-TM	Control	P-value
LVEDD (in cm)	4.4 ± 0.7	4 ± 0.52	**0.000**[a]
LVESD (in cm)	2.8 ± 0.6	1.42 ± 0.42	**0.000**[a]
LVM (in gm)	108.9 ± 50.4	75 ± 20.5	**0.000**[a]
FS (%)	36.5 ± 6.03	35 ± 5.15	>**0.05**
EF (%)	66 ± 8.03	67 ± 6.5	>**0.05**
Mitral E/A ratio	2.2 ± 0.8	2.3 ± 0.7	>**0.05**
TAPSE (cm)	2.41 ± 0.42	2.24 ± 0.36	>**0.05**

[a] Significant p value, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVM left ventricular mass, FS fractional shortening, E/A ratio: the ratio of the early (E) to late (A) ventricular filling velocities, TAPSE: tricuspid annular plane excursion.

Table 3
Tissue Doppler imaging data.

Parameter	β-TM	Control	P-value
Mitral valve, septal wall			
Ea (cm/s)	12.7 ± 2.10	13.2 ± 2.41	>**0.05**
Aa (cm/s)	7.70 ± 2.50	5.72 ± 1.41	**0.000**[a]
S (cm/s)	10.70 ± 1.75	7.90 ± 1.23	**0.000**[a]
Septal E/Ea ratio	8.10 ± 1.31	6.55 ± 1.60	**0.000**[a]
PCWP	11.9 ± 1.6	10.0 ± 1.95	**0.000**[a]
Mitral valve, lateral wall			
Ea (cm/s)	18.2 ± 2.41	15.8 ± 1.82	**0.000**[a]
Aa (cm/s)	7.30 ± 1.41	6.60 ± 1.72	>**0.05**
S (cm/s)	10.3 ± 2.30	9.61 ± 1.80	>**0.05**
LV Tei index	0.32 ± 0.11	0.41 ± 0.10	**0.000**[a]
Tricuspid valve			
S (cm/s)	14.8 ± 2.63	12.6 ± 1.30	**0.000**
Ea (cm/s)	15.9 ± 2.24	13.8 ± 3.00	>**0.05**
Aa (cm/s)	10.4 ± 2.54	8.83 ± 2.74	>**0.05**
RV Tei index	0.24 ± 0.09	0.18 ± 0.08	>**0.05**

[a] Significant p value, Ea: early diastolic myocardial velocity, Aa: late diastolic myocardial velocity, S: systolic myocardial velocity, Ea: early diastolic velocity of the mitral annulus, LV Tei: left ventricle myocardial performance index, RV Tei: right ventricle myocardial performance index.

We found that the LV EF, FS, and TAPSE, in thalassemic patients were comparable to those of the control group. This was suggestive of preserved systolic function, as assessed by conventional echocardiography.

These results are similar to other reports which also demonstrated preserved left ventricular systolic function in spite of cardiac dilatation with no significant difference between the studied cases and controls as regards the mean values of EF and FS [35,39–41]. However, other studies reported a significantly lower LVEF in thalassemia patients in comparison with healthy age and sex-matched individuals [42,43]. However, the mean values of EF in these studies were more than 55% in the studied thalassemia patients.

Compared with controls, the diastolic indices of LV in beta thalassemia patients (trans-mitral E/A ratio) showed no significant difference between cases and controls which indicates preserved global diastolic function of the L.V. This is consistent with reports from other studies [36,43,44]. Absence of a significant difference in E/A ratio in thalassemic patients in comparison to the control subjects could be explained by the exclusion of patients with heart failure symptoms. It could be declared that the E/A ratio alone is not enough to diagnose diastolic dysfunction [45].

On the contrary, other investigators found diastolic dysfunction of restrictive pattern with increased E/A ratio in patients with beta-thalassemia compared to the control group [17,46]. It has been assumed that myocardial iron deposition in some thalassemic patients may not directly affect left ventricular systolic function, but it may rather cause diastolic dysfunction with left ventricular myocardial restriction [47].

Serum ferritin does not correlate with myocardial iron load [48]. Also, systolic dysfunction was not correlated with serum ferritin and occurred at a late stage of the disease [39]. This is why we did not correlate the echo-Doppler findings with serum ferritin levels.

Echocardiography is a substantial imaging technique for diagnosis of ventricular function [49], that allows exclusion of overt LV systolic dysfunction (left ventricular EF < 50%) [50]. Nevertheless, changes of segmental wall motion, the early sign of myocardial dysfunction in thalassemia patients, may be subtle that can not be detected by conventional echocardiography which may remain normal until later stages of the disease [51].

Tissue Doppler Imaging (TDI) is a relatively new Doppler ultrasound modality that records regional systolic and diastolic velocities within the myocardium. It allows quantitative measurement of both systolic and diastolic velocities directly from the ventricular myocardium with the determination of the extent of mitral annular displacement in systole and diastole [52].

This new technique can show additional information compared with other echocardiography techniques, detecting even minor changes before the occurrence of abnormal indices of global ventricular dysfunction [45].

In our study assessment of the mitral valve with pulsed Doppler tissue imaging showed statistically significant differences between the patients, with no overt cardiac clinical impairment, and the control subjects in late diastolic myocardial velocities (Aa) and systolic myocardial velocities (S) at the basal mitral annulus of the septal wall. Additionally, patients with thalassemia have significantly higher early diastolic myocardial velocities (Ea), at the basal mitral annulus of the lateral wall, than controls.

In accordance with these findings, other authors had reported significant lower tissue Doppler systolic velocity in the β-TM group compared to controls [42,45]. On the contrary, Iarussi et al. [44] found that all Doppler tissue imaging systolic and diastolic parameters of the mitral annulus were similar in patients with beta thalassemia major before and after transfusion to those of healthy subjects. Nevertheless, significantly lower early diastolic velocity was reported by some investigators [42,45,53]. These conflicting results might be due to different age of the studied groups, as it is known that age and body surface area are the most important factors affecting isovolumic relaxation and deceleration times [54].

Iron loading of the heart can be patchy, mainly affecting the ventricles with deposition predominantly in the septum with other areas of the ventricles and heart being affected later in the disease process and these can explain the index findings [55].

An interesting finding, albeit not that accurate like cardiac catheterization, is that pulmonary capillary wedge pressure (PCWP) estimated by echo-Doppler was higher in the thalassemia patients than in the control group which correlates with higher left ventricular end-diastolic pressure and left ventricular dysfunction. This result coincides with the result of another study which stated increased PCWP in thalassemia patients as compared to iron deficiency anemia and healthy control groups [56]. Similarly, they correlated this finding with left atrial volume that was found significantly higher in the thalassemia patients than control group.

We found that Septal E/Ea ratio was significantly higher in thalassemia patients when compared with controls. This was in agreement with authors [57], who found that there was a significant elevation in E/E′ in the TM patients compared to the control group. On the contrary this difference was not significant in the other studies [36,53]. The difference from our findings can be explained by enrollment of different age groups, difference in iron load, or different compliance to chelation therapy.

The E/Ea ratio has a special diagnostic importance for diastolic dysfunction among thalassemic patients due to its load independent nature, its unaffection by elevated LA pressure and linear correlation with LV end diastolic pressure [57,58].

Assessment of the tricuspid valve showed significant difference in only systolic myocardial velocity (S) at the basal tricuspid annulus by tissue Doppler imaging. These alterations in myocardial velocities by TDI might indicate earlier left and right ventricular dysfunction.

Iarussi et al. [44] found that lateral tricuspid annulus velocities in the beta thalassemia patients before transfusion was significantly reduced than controls. More recently, Abdelmoktader and Azer, found comparable (S) wave velocity at lateral margin of the tricuspid annulus in thalassemic patients when compared to control group [42].

The myocardial performance index (Tei index) of LV of patients was significantly higher than control group. The impaired Tei index

as detected by TDI in patients with normal conventional echocardiographic parameters, particularly EF, supports the idea that TDI can be an early sensitive indicator of cardiac dysfunction in asymptomatic beta-TM. This finding was in agreement with the report of authors who studied 55 asymptomatic beta-thalassemia patients with median age of 20 years [59].

Hence, among our patients, with beta thalassemia, and asymptomatic cardiac dysfunction showing preserved global systolic function as detected by conventional echocardiography, tissue Doppler imaging technique has shown latent systolic and diastolic cardiac dysfunction. This denotes the importance of this modality for evaluation of beta thalassemia children and adolescents to detect asymptomatic cardiac dysfunction before being detected by conventional echocardiography. This is particularly important in developing countries where the Magnetic Resonance Imaging (MRI T2*), the gold standard diagnostic modality of early detection of iron cardiac load, is still not convenient for mass screening due to its cost and limited availability.

6. Limitations

The small number of patients and non-availability of the more recent modalities of TDI like strain, strain rate, and speckle tracking were the major limitations of our study. These modalities can display intrinsic cardiac deformation and is superior to TDI due to its independence of cardiac translational motion and tethering effect of the adjacent segments. Another limitation is that the use of T2-weighted MRI as a diagnostic marker of body iron load was beyond the scope of our study. Our study was based on the echocardiographic parameters. Future studies can be conducted using cardiac catheterization and correlating the findings with the echocardiographic parameters.

7. Conclusion

Tissue Doppler imaging is superior to conventional echocardiography in giving an early evidence of systolic and diastolic myocardial dysfunction in non-symptomatic thalassemic patients. Hence, TDI can be applied as an integrated part of assessment of children and adolescents with beta-thalassemia.

Ethical approval

The study was approved by the research and ethical committees of the contributing hospitals.

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Author contribution

Mohamed H. Ibrahim, Naglaa M. Kamal, Enas A.A. Abdallah:

- Substantial contributions to the conception and design of the work.
- Drafting the work and revising it critically for important intellectual content.
- Final approval of the version published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mostafa A Salama, Soha A Ebrahim, Ahmad A Azab:

- Acquisition, analysis, and interpretation of data.
- Drafting the work.
- Final approval of the version published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- Final approval of the version published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest

Authors declare no conflicts of interest.

Guarantor

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