Tissue Doppler Imaging and Electrocardiography Reliability in Predicting Severity of Myocardial Siderosis in β-Thalassemic Children

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ABSTRACT

Background: Cardiac complications, heart failure, and arrhythmias remain as the major causes of death in thalassemia major. **Aim:** The aim was to detect the early cardiac involvement in patients with β-thalassemia major. **Patients and Methods:** 56 patients with β-thalassemia major and transfusion burden ≥12 times/year aged 6-16 years were included in our study and classified into 3 groups according to serum ferritin, Group I: Consisted of 21 patients with serum ferritin level <2500 ng/mL, Group II: Consisted of 23 patients with serum ferritin level 2500-5000 and finally, Group III: Consisted of 12 patients with serum ferritin level >5000 ng/mL. They were subjected to a thorough history taking, routine laboratory investigations and serum ferritin level, electrocardiography, echocardiography, and tissue Doppler imaging (TDI). **Results:** There was significant increase in septal wall thickness in Group II and Group III compared to Group I, where (P = 0.002, 0.0001), respectively, also, there were significant increase in posterior wall thickness in Group II and Group III compared to Group I, where (P = 0.012, 0.001), respectively. QTc and QT dispersion (QTd) intervals were significantly increased in Group III in comparison to Group I (P = 0.01) while in Group II, QTc and QTd intervals increased in comparison to Group I but were not statistically significant. Left ventricular (LV) diastolic function (E/A ratio) by both standard and tissue Doppler was significantly impaired in Group III and II compared with Group I. Furthermore, left atrial (LA) active emptying fraction was significantly impaired in Group III compared with Group I (P = 0.001) while LV systolic function parameters by TDI were impaired significantly in Group III and II compared to Group I but by standard echocardiography, LV systolic function showed insignificant difference between different groups. **Conclusion:** The increase in LV septal and posterior wall thickness precedes changes in QTc and QTd as a precursor of arrhythmias in β-thalassemia major. Furthermore, LV diastolic function by both methods, impaired LA active emptying fraction and impaired LV systolic function parameters by TDI precedes changes in LV systolic function by standard echocardiography.

Keywords: β-thalassemia major, tissue Doppler, ECG changes

INTRODUCTION

An important complication of β-thalassemia major is iron deposition in cardiac tissue resulting in degeneration, fibrosis, and dysfunction.[1] Cardiac disease is the primary cause of death.[2] Iron-chelation therapy may prevent myocardial dysfunction and early death from cardiac disease.[3] Despite adequate iron chelation, myocardial function is still worsening due to iron deposition, fibrosis, and chronic anemia. In clinical practice, serum ferritin has been used to assess the effectiveness of treatment. In several studies, diastolic ventricular dysfunction demonstrated in these patients preceded the onset of systolic impairment.[4] Many of the previous data support cardiovascular disorders such as structural changes and thicknesses of septum and posterior wall and reduction of shortening fraction and ejection fraction (EF).[5] It has been shown that ventricular wall-thickening may be altered by pathologic factors such as iron deposition. It has been suggested that QT dispersion (QTd) reflects regional variation in ventricular recovery.[6] It is an index of inhomogeneity of repolarization. It is usually expressed as the difference or the range of the various repolarization measurements obtained from a

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heart.[7] Increased QTd is a predictor of sudden death and ventricular arrhythmias in the patients with chronic heart failure.[8] The aim of this study was to detect the early cardiac involvement in patients with β-thalassemia major.

PATIENTS AND METHODS

Our study was carried out on 56 patients with β-thalassemia major who had regular follow-up in pediatric hematology outpatient's clinic, children university hospital, Al Minia University from February 2009 to April 2011. For the purpose of this study, severity of iron overload was defined by serum ferritin level, and patients were classified accordingly into the following 3 Groups: Group I included 21 patients with serum ferritin level <2500 ng/mL, Group II included 23 patients with serum ferritin level 2500-5000 ng/mL, and Group III included 12 patients with serum ferritin level >5000 ng/mL.

Inclusion criteria

1. Age between 6 and 16 years old
2. Transfusion burden ≥12/year
3. Last blood transfusion was <4 days ago.

Exclusion criteria

1. Patients younger than 6 years old
2. Transfusion burden <12/year
3. Any cardiac disease (e.g., rheumatic, congenital, heart failure etc.).

The studied groups were subjected to; thorough history taking, clinical examination, and laboratory investigations including complete blood count by sysmex and serum ferritin by ELISA based on a monoclonal antibody sandwich to ensure an optimal sensitivity and specificity (normal range was 18-323 ng/mL).[9] Furthermore, electrocardiography (ECG) was performed; standard 12-lead ECGs were recorded at a speed of 25 mm/s. Heart rate was calculated from the average RR interval of the tracings. QT intervals were measured manually in blinded fashion from the onset of QRS complex to the end of the T wave on the isoelectric line by the same physician. For each lead, three consecutive QT intervals were measured and averaged. QTd was defined as the difference between the longest and shortest QT intervals. QT intervals were corrected by heart rate according to Bazett's formula ($QTc = QT/\sqrt{RR}$).[10] Finally, standard echocardiography and tissue Doppler imaging (TDI); all examinations were performed in the left lateral decubitus position by using general electric vivid 3 ultrasound unit equipped with 2.5-3.5 MHz transducers and a pulsed wave TDI program with simultaneous ECG tracing. The measurements represent a mean of at least three consecutive cardiac cycles. Doppler parameters as transmitral, transtricuspid early and late diastolic velocities were obtained, and then E/A ratio was calculated. Furthermore, deceleration time (DT) was measured. Septal and posterior wall thickness was measured, and EF was obtained by M-mode approach.[11] Left atrial (LA) volumes was measured by biplane area-length method in mL.[3] LA volume measurements were done at the onset of atrial systole (LAVp) −P-wave at ECG - and the closure of mitral valve (LAVmin), then LA active emptying fraction was calculated: LA active emptying fraction = LAVp−LAVmin/LAVp. The pulsed wave TDI was performed by activating the TDI function in the same echo machine. Images were acquired using a variable frequency phased-array transducer. The filter settings were kept low (50), and gains were adjusted at the minimal optimal level to minimize noise and eliminate the signals produced by the transmitral flow. Two different sites at the mitral annulus were selected. In the apical 4-chamber view, the TDI cursor was placed at the septal side as well as lateral site of the mitral annulus. A Doppler velocity range of −20-20 cm/s was selected for this study. Three major velocities were recorded: The positive systolic velocity (S) and 2 negative diastolic velocities (one during the early phase of diastole [Ea] and another in the late phase of diastole [Aa]). Time elapsed from the inscription of the Q-wave on the surface ECG to the peak of the S-wave (Q-S peak) in photothermal deformation techniques was determined.[12]

Statistical methodology

Standard computer program SPSS for windows, release 13.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation. Comparison of different variables in various groups was done using Student's *t*-test and ANOVA test. A significant *P*-value was considered when $P < 0.05$.[13]

RESULTS

Table 1 shows description of the β-thalassemic patients as regarding some demographic data. Patients in different groups showed nonstatistical significant differences between them as regard weight, height, systolic blood pressure, diastolic blood pressure, and heart rate where ($P > 0.05$) and were summarized in Table 2.

Concerning ECG findings, QTc and QTd intervals were significantly increased in Group III in comparison to Group I while, in Group II, QTc and QTd intervals

Table 1: Description of the β-thalassemic patients as regarding some demographic data

Datum	Group I with serum ferritin<2500 ng/mL *N* (21)	Group II with serum ferritin 2500-5000 ng/mL *N* (23)	Group III with serum ferritin>5000 ng/mL *N* (12)
Sex			
Male *N* (%)	12 (57.14)	12 (52.17)	8 (66.66)
Female *N* (%)	9 (42.86)	11 (47.83)	4 (33.34)
Age (years)			
Range	6-16	6-12	7-16
Mean±SD	9.35±4.591	10.5±2.432	12.33±2.934
Age of onset (months)			
Range	6-48	6-48	6-18
Mean±SD	9.52±8.92	8.87±7.97	7.83±4.02
Similar conditions in the family *N* (%)	10 (47.62)	7 (30.43)	4 (33.34)
Consanguinity *N* (%)			
Positive	6 (28.57)	8 (34.78)	4 (33.34)
Negative	15 (71.43)	15 (65.22)	8 (66.66)
Residence			
Urban *N* (%)	7 (33.34)	6 (26.08)	3 (25)
Rural *N* (%)	14 (66.67)	17 (73.91)	9 (75)
Frequency of transfusion/year			
Range	12-18	12-24	12-24
Mean±SD	12.87±2.68	14.48±4.81	17±5.62

SD: Standard deviation

Table 2: Comparison between different groups of β- thalassemic patients as regarding some clinical data

Clinical data	Group I *N* (21)	Group II *N* (23)	Group III *N* (12)	*P* value
Wieght (kg)				
Mean±SD	24.7±16.2	21.8±10.39	21.42±9.28	0.38
Percentile				
<5 (%)	5 (23.8)	8 (34.78)	7 (58.34)	
5-95 (%)	16 (76.19)	15 (65.21)	5 (41.66)	
>95 (%)	0 (0)	0 (0)	0 (0)	
Height (cm)				
Mean±SD	137.25±25.4	135.36±15.84	136±11.89	0.45
Percentile				
<5 (%)	4 (19.04)	5 (21.73)	6 (50)	
5-95 (%)	16 (76.19)	18 (78.26)	6 (50)	
>95 (%)	1 (4.76)	0 (0)	0 (0)	
Systolic BP (mmHg)				
Mean±SD	100.25±13.4	104.85±11.88	110.83±6.337	0.26
Percentile				
5-95 (%)	21 (100)	23 (100)	12 (100)	
>95 (%)	0 (0)	0 (0)	0 (0)	
Diastolic BP (mmHg)				
Mean±SD	67±8.796	67.08±7.79	73.33±4.924	0.97
Percentile				
5-95 (%)	21 (100)	23 (100)	12 (100)	
>95 (%)	0 (0)	0 (0)	0 (0)	
Heart rate (beat/min)				
Range	70-97	75-105	70-120	0.1
Mean±SD	85.5±17.532	91.79±11.463	99.5±7.574	

BP: Blood pressure, SD: Standard deviation

increased in comparison to Group I but were not statistically significant (Table 3).

Table 3: Comparison of QTc and QTd in different groups

	Group I	Group II	Group III	*P1*	*P2*
QTc (ms)	366.85±428.24	369.61±25.41	427.01±27.82	0.63	0.01
QTd (ms)	37.43±11.55	39.32±10.58	44.94±11.66	0.44	

P1: I versus II, *P2*: I versus III, QTd: QT dispersion

There was a significant increase in septal wall thickness in Group II and Group III compared to Group I, where ($P = 0.002$, 0.0001), respectively, also, there were a significant increase in posterior wall thickness in Group II and Group III compared to Group I, where ($P = 0.012$, 0.001), respectively (Table 4).

Diastolic function parameters

1. There was a significant increase in E/A ratio in Group II and Group III compared to Group I. These changes were present in both transmitral and transtricuspid flows by standard echocardiography and TDI (Table 5).
2. DT of both mitral and tricuspid flow was significantly decreased in group III compared to Group I while Group II showed an insignificant decrease in DT compared to Group I (Table 6).

Left ventricular (LV) systolic function parameters

As regarding systolic function by M mode (EF%, fractional shortening%), there were insignificant differences between Group II and III compared to Group I (Table 7). Group III and II had a significant lower peak S wave ($P = 0.00$) and a significant prolongation of Q-S duration at the sepal and lateral walls compared to Group I (P = 0.01) (Table 8). Finally, Group III showed a significant impairment in LA active emptying function in Group III compared to Group I (P = 0.001) while Group II showed insignificant difference when compared with Group I (P = 0. 252) (Table 9).

Table 4: Comparison of septal and posterior walls in different groups

	Group I	Group II	Group III	*P1*	*P2*
Septal wall thickness (mm)	58±13	65±3	69±8	0.002	0.0001
Posterior wall thickness (mm)	57±12	64±11	65±10	0.012	0.001

*P*1: I versus II, *P*2: I versus III

Table 5: Comparison of E/A ratio of mitral and tricuspid valve between different groups

	Group I	Group II	Group III	*P1*	*P2*
M E/A	1.6±0.28	1.9±0.29	2.25±0.38	0.001	0.001
T E/A	1.6±0.27	1.85±0.39	2.12±0.16	0.04	0.001
Septum E/A	1.97 (1.2-2.5)	2.0 (1.2-2.5)	2.49 (1.6-3.6)	0.001	0.001
Lateral wall E/A	1.8±0.57	1.9±0.3	2.6 (1.56-4.5)	0.001	0.001

M: Mitral flow, T: Tricuspid flow, *P*1: I versus II, *P*2: I versus III

Table 6: Comparison of DT of mitral and tricuspid flow between different groups

	Group I	Group II	Group III	*P1*	*P2*
M DT	150.75±17.15	134.08±21.48	97.5±12.33	0.87	0.001
T DT	153.4±19.18	143.33±19.76	102.8±27.86	0.87	0.001

M: Mitral flow, T: Tricuspid flow, DT: Deceleration time, *P*1: I versus II, *P*2: I versus III

Table 7: Comparison between different studied groups as regarding systolic function by M mode echocardiography

	Group I	Group II	Group III	*P1*	*P2*
EF%	66.28±5.53	67.35±5.52	65±4.52	0.13	0.26
FS%	35.52±4.32	36.22±4.6	34.5±2.54	0.19	0.21

EF%: Ejection fraction, FS%: Fractional shortening, *P*1: I versus II, *P*2: I versus III

Table 8: Comparison between different studied groups as regarding systolic function by TDI

	Group I	Group II	Group III	*P1*	*P2*
Peak S-wave cm/s (septum)	8±0.31	6.88±0.44	6.75±0.61	0.01	0.0001
Q-S duration ms (septum)	145.23±6.84	160.86±12.28	163±4	0.01	0.0001
Peak S-wave cm/s (lateral wall)	8.23±0.51	7.06±0.32	6.83±0.1	0.03	0.001
Q-S duration ms (lateral wall)	132.4±4.38	143.86±7.05	145.5±3.9	0.01	0.001

*P*1: I versus II, *P*2: I versus III, TDI: Tissue Doppler imaging

Table 9: Comparison between different studied groups as regarding LA emptying function

	Group I	Group II	Group III	*P1*	*P2*
LA active emptying fraction	44.46±3.26	43±5.91	38.38±1.66	0.252	0.001

LA: Left atrium, *P*1: I versus II, *P*2: I versus III

DISCUSSION

Life expectancy in patients with thalassemia major is still limited by development of congestive heart failure due to a cardiomyopathy associated with iron overload. Aggressive chelation therapy may prevent, delay, or even reverse myocardial dysfunction, but once overt heart failure is present, only 50% of patients survive.[14]

The goal, therefore, is to begin treatment while the cardiomyopathy is still reversible. However, early recognition of patients at risk of heart failure has been difficult because global LV function and exercise capacity in chronically transfused patients with iron overload may remain normal until late in the disease process.[15] We, therefore, under took this study to detect the early cardiac involvement in these patients.

In the current study, QTc was prolonged significantly in thalassemic patients with serum ferritin >5000 ng/mL compared to Group I while septal and posterior wall thickness was increased significantly in Group III and II compared to Group I. The increase in LV wall thickness can be explained by that iron deposition in the myocytes causes them to hypertrophy which may partly contribute to the increased QTd.[16] These results were similar to the results obtained by Kocharian *et al*., who found a significant difference in QTd in thalassemia major patients and normal persons. QTc was significantly broader in LV hypertrophy (LVH) + patients (patients with LVH) compared with LVH-patients (without patients). On the other hand, local ischemia of the hypertrophied ventricular myocyte may be one potential mechanism for the increased dispersion of repolarization and it is shown that QTa interval (measured from the onset of QRS to the apex of T wave) tended to be longer in LVH + patient as compared with LVH - patients. This hypertrophy of myocytes may partly contribute to the increased QTd.[17] Some studies showed an increase in the thickness of posterior wall, dimension of atrium, and aortic root and LV systolic and diastolic dimensions in thalassemic patients. They can be some reasons of increased QTd in thalassemic patients.[5] Taysir *et al*.[18] found that The QTc interval and the QTd dispersion on ECG were increased in thalassemia major patients with no significant difference.[12] These results are in accordance with our results in Group II that showed prolongation in QTc and QTd compared to Group I but not statistically significant.[18] The results of Taysir *et al*. were in contrast to our results concerning with Group III compared to other groups. This is may be explained by the difference in serum level of ferritin in Group III and with its level in thalassemia major patients in Taysir *et al*.

study which in not too high to produce significant changes in QTc and QTd intervals.

As regard to diastolic function parameters, the current study found that diastolic function parameters (E/A ratio and DT) were significantly impaired in Group III by both standard and TDI. Our results are in accordance with results of Silvilairat *et al*.[19] Their findings support the hypothesis that pulsed wave Doppler and TDI patterns of diastolic LV dysfunction reflect the severity of iron overload in which these Doppler parameters significantly correlated to the serum ferritin as diastolic LV dysfunction was absent in all patients with serum ferritin <2500 ng/mL and was present in all patients with serum ferritin >5000 ng/mL. These Doppler parameters were significantly correlated to the serum ferritin.[19] Olivieri *et al*., reported that the cardiovascular prognosis in patients with homozygous b thalassemia was excellent if serum ferritin was below 2500 ng/mL.[1] In 1991, Spirito *et al*., reported a restrictive pattern of transmitral flow in a group of young adults with normal systolic function.[20] and no alteration in LV compliance was reported in the early stage of the disease by Kremastinos *et al*.[16] The filling pattern previously reported was explained by increased volume overload caused by the hyperdynamic state. A strongly restrictive pattern of transmitral flow was reported only in the final stages of the disease.[15]

As regards systolic evaluation, the current study found that there was insignificant difference between the different groups as regard LV systolic function by M mode (EF%) where $P > 0.05$, while LV systolic function parameters by TDI (peak S-wave velocity and peak Q-S duration) showed that the Group III had lower peak S-wave and a significant prolonged Q-S duration at the septum and lateral walls. Silvilairat *et al*., reported that TDI may be the early detection of systolic ventricular dysfunction.[19]

This study accords to Vogel *et al*. whose had failed to distinguish LV function of patients with thalassemia and iron overload from that of normal controls by conventional M-mode technique but with TDI had shown that iron overload affects systolic and diastolic function as TDI allows the evaluation of regional ventricular function.[21]

Uçar *et al*.,[22] and Aypar *et al*.,[23] confirmed that TDI seems to be an early sensitive parameter of cardiac dysfunction in thalassemic patients. However, Bosi *et al*., found a weak, but significant correlation between LVEF and serum ferritin concentration, where patients with a high ferritin concentration (>2500 ng/mL) had a lower EF than those patients with a low ferritin concentration (<1000 ng/mL).[24] The higher mean age of the patients in Bosi's study might be the responsible factor for detection of changes in LV systolic function by M mode echocardiography as well as by TDI. Furthermore, Wood *et al.,* found that cardiac risk is conveyed by positive iron balance over a prolonged period of time.[25] The cause of the systolic dysfunction is owed to decrease in LV systolic performance due to an increase in the after load and a reduced contractile state which is probably secondary to iron toxicity.[19] Furthermore, our results were in agreement with results of Magrì *et al*., who reported that even in a population of young, asymptomatic, and well-chelated patients with thalassemia major, there is an impairment of myocardial function and that this condition could be easily detected by more advanced ultrasound techniques such as TDI.[26]

Concerning LA emptying function, this study revealed that LA emptying function was decreased in Group III compared Group I. Arbab-Zadeh *et al*., reported that diastolic dysfunction precedes systolic function in many systemic diseases and leads to LA dilation and impaired atrial contraction.[27] Furthermore, Li *et al*., postulated that LA dilation and dysfunction would be earlier markers of iron cardiotoxicity than depressed ventricular function in thalassemia major subjects and that LA EF was a more sensitive marker of cardiotoxicity than LVEF.[28] Furthermore, Li *et al*. demonstrated that atrial volume and function were decreased by cardiac iron overload. Decreased atrial EF probably represents a combination of increased atrial after load (through ventricular stiffening) as well as direct poisoning of the atrial muscle.[28] Autopsy studies suggested greater iron deposition in the ventricles, compared with the atria, but the thin walls and relative muscular paucity of the left atrium may make it more vulnerable to even small amounts of tissue iron.[29] Regardless of the mechanism, depressed LAEF was 2.5-3.5 times more sensitive than depressed ventricular EF in identifying subjects with heavy cardiac iron burden.[28] Therefore, atrial EF may serve as a valuable marker of pre-clinical cardiac dysfunction in the developing world; this is in accordance with Shabanian *et al*., who found that combining the atrial ejection force with the transmitral-derived echocardiographic assessment is a feasible way to detect early stages of myocardial iron overload in patients with beta thalassemia major.[30]

CONCLUSION

The increase in LV septal and posterior wall thickness precedes changes in QTc and QTd as precursors of arrhythmia's. Furthermore, the decrease in LA active emptying fraction and parameters of LV systolic function by TDI as well as diastolic dysfunction precede changes in LV systolic function by standard method.

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