Original Article

Evaluation of tissue doppler echocardiography and T2* magnetic resonance imaging in iron load of patients with thalassemia major

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Abstract

Background: Iron-mediated cardiomyopathy is the main complication of thalassemia major (TM) patients. Therefore, there is an important clinical need in the early diagnosis and risk stratification of patients. The aim of this study was to evaluate the efficacy of tissue doppler imaging (TDI) to study cardiac iron overload in patients with TM using T2* magnetic resonance (MR) as the gold-standard non-invasive diagnostic test.

Methods: A total of 100 TM patients with the mean age of 19±7 years and 100 healthy controls 18.8±7 years were evaluated. Conventional echocardiography, TDI, and cardiac MRI T2* were performed in all subjects. TDI measures included myocardial systolic (Sm), early (Em) and late (Am) diastolic velocities at basal and middle segments of septal and lateral LV wall. The TM patients were also subgrouped according to those with iron load (T2* ≤ 20 ms) and those without (T2* > 20 ms), and also severe (T2* ≤ 10 ms) versus the non-severe (T2* ≤ 10 ms).

Results: Using T2* cardiovascular MR, abnormal myocardial iron load (T2* ≤ 20 ms) was detected in 84% of the patients and among these, 50% (42/84) had severe (T2* ≤ 10 ms) iron load. The mean T2* was 11.6±8.6 ms (5–36.7). A negative linear correlation existed between transfusion period of patients and T2* levels (r = -0.53, p=0.02). The following TDI measures were lower in patients than in controls: basal septal Am (p<0.05), mid-septal Em and Am (p<0.05), basal lateral Am (p<0.05), mid-lateral LV wall Sm (p<0.05) and Am (p<0.05).

Conclusion: Tissue doppler imaging is helpful in predicting the presence of myocardial iron load in Thalassemia patients. Therefore, it can be used for screening of thalassemia major patients.

Keywords: Thalassemia major, MRI, Tissue doppler imaging, Iron overload, T2* MRI

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Beta-thalassemia major (TM) is a chronic hemolytic anemia, and cardiac complications including congestive heart failure (CHF) and arrhythmia are the most common causes of death in this disease (1-3). In thalassemia syndromes, there is an important clinical need to risk stratifying patients and early detection for the development of iron-mediated cardiomyopathy so that chelation therapy can be adjusted and cardiac morbidity averted and improve prognosis (4, 5). Myocardial iron content cannot be predicted with organ biopsy (an invasive procedure) or serum ferritin (changes with many variables) and conventional assessments of cardiac function can only detect those with advanced disease (6-8). Magnetic resonance imaging (MRI) offers the best way for the detection of tissue iron deposition worldwide. It is a noninvasive, readily available, suitable for moving organs like heart and reproducibly quantified using myocardial T2* (6). T2* is a unique magnetic resonance parameter measured in milliseconds and shortened in relation to the level of iron in the heart (9, 10). However, T2* MRI is expensive, not widely available in many centers and interpretation needs an expert.

Therefore, MRI is still unsuitable for screening of patients with TM. In TM, iron overload may lead to wall motion abnormalities as an early sign of myocardial involvement despite good global ventricular function. Conventional echocardiographic techniques have failed to accurate assessment of ventricular functions (3). Recent advances in echocardiography like tissue doppler imaging (TDI) technique has been found to be both sensitive and specific in predicting the presence of myocardial iron load in TM patients (11, 12). We aimed to assess the efficacy of TDI in predicting myocardial iron load in TM patients using T2* MRI as the gold-standard non-invasive diagnostic test.

Methods

Between February 2012-2013, one hundred patients with TM from Thalassaemia Unit of Babol University of Medical Sciences, Babol, Iran (Northern Iran) were enrolled. The patients had regular examinations and were on regular blood transfusions to maintain serum hemoglobin levels above 10 gr/dl and long term chelation therapy with desferrioxamine or combined desferioxamine and oral deferiprone. The exclusion criteria were documented arrhythmias, pacemaker, evidence of congenital heart disease, use of medications altering myocardial functions, history of smoking, and evidence of hypertension, renal disease, thyroid and parathyroid diseases and diabetes.

The control group had age and sex matched without any problems and normal cardiovascular status. For all patients and controls, conventional echocardiographic and TDI measures and cardiovascular T2* MR examinations were performed. The Local Ethics Committee approved this study and the informed consents were obtained from the patients and or their parents. The study complied with the ethical rules for human experimentation stated in the declaration of Helsinki.

Conventional and tissue-Doppler echocardiography: They were performed in all the patients approximately few days after blood transfusions, serum ferritin measurement and MR acquisition, without sedation state, during normal respiration in supine or left lateral decubitis position with simultaneous ECG tracings. All the patients were in normal sinus rhythm during the examination. The same cardiologist blinded to the results of MRI did the measurements. An echocardiography machine (Vivid 3, GE, Horten, Norway, and 2–4 mHz phased array transducer, interfaced with a system (aV sector scanner with pulsed Doppler tissue imaging software) that performed the study.

Conventional echocardiographic evaluation from the parasternal long axis view included LV end-diastolic (LVEDD), end-systolic diameters (LVESD), septum and LV posterior wall thicknesses in diastole and systole, LV ejection fraction (EF) by Simpson's rule and fractional shortening (FS). Transmittal flow patterns were obtained by pulsed-wave doppler echocardiography from apical four-chamber view. Peak early (E) and late (A) diastolic velocities, E/A ratios, E wave deceleration time (DT) were measured. A PW Doppler tracing was placed at the level of basal and middle segments of septal and lateral LV wall and peak myocardial systolic (Sm), early (Em) and late diastolic (Am) velocities were measured from apical four-chamber view. All data were obtained according to the recommendations of the American Society of Echocardiography (13, 14).

T2* cardiovascular MRI: Each scan included the measurement of myocardial and hepatic iron. All T2* cardiovascular MRI examinations were performed at the Radiology Department. Imaging was made during the late cardiac cycle diastole phase using ECG synchronization. Myocardial and hepatic iron were assessed performed on a GE 1.5 tesla MR device using a 5-channel cardiac coil. In patients who can tolerate, imagings were made by breath-holding technique and a navigator sequence was used in the rest. The same radiologist blinded to the echocardiographic and the TDI results evaluated all MR studies. T2* $\leq$ 20 ms represented abnormal myocardial iron load and T2* $\leq$ 10 ms was considered as severe myocardial iron load (15, 16).

Statistical analysis: All statistical calculations were assessed using SPSS Version 11.5. The numeric data are presented as mean ± standard deviation. We used the unpaired student t test to assess the significance of differences between the studied parameters and calculated the relationships between different variables with the Pearson correlation coefficient. The one-sample Kolmogorav– Smirnov test was used to define the distribution of variables. A p value < 0.05 was considered statistically significant.

Results

The demographic and clinical features of the patients with TM and controls are presented in table 1. The serum

hemoglobin level at the time of study was 12.0±1.3 (10.1-14.6) g/dl, and serum ferritin level was 2863±1509 ng/ml. They had history of blood transform for 18±7 years. 78 of the patient received desferioxamine and deferiprone in 26 patients. Conventional echocardiographic examinations revealed that patients with TM had larger LVEDD, LVESD, lower LV EF and lower E/A ratio measurements than controls (tables 2 and 3). Using T2* cardiovascular MR, abnormal myocardial iron load (T2* ≤ 20 ms) was detected in 84% (84/100) of the patients and among these, 50% (42/84) had severe (T2* ≤ 10 ms) iron load. The mean T2* was 11.6±8.6 ms (5–36.7). A negative linear correlation existed between transfusion period of patients and T2* levels (r=−0.53, p=0.02).

The following TDI measures were lower in patients than in controls: basal septal Am (p<0.05), mid-septal Em and Am (p<0.05), basal lateral Am (p<0.05), mid-lateral LV wall Sm (p<0.05) and Am (p<0.05) (table 3).

Table 1. Demographic and clinical characteristics of patients with beta-thalassemia major (TM) and controls

Variables	Patients with TM (n=100)	Controls (n=100)	P-value
Age (mean±SD)	19±7	18.8±7	NS
Gender (female/male)	56.44	57.43	NS
Body weight (kg)	39±12 (23–61)	48.9±13.7 (25–71)	< 0.05
Height (cm)	152±19 (121–173)	156±13 (121–170)	NS
Body mass index (kg/m^2)	18±4 (13–25)	19±4 (13–28)	NS

Data were expressed as mean ± SD

Table 2. Conventional echocardiographic measures of patients with beta-thalassemia major (TM) and healthy controls

Variables	Patients with TM (n = 100)	Group 2 (Controls) (n = 100)	P-value
LVEDD (mm)	47.6±5.2 (39–59)	45.5±5.4 (36–53)	<0.05
LVESD (mm)	28.1±5.2 (23–38)	25.2±3.7 (19–30)	<0.05
IVS (d) (mm)	8.9±2.2 (7.7–13.1)	8.4±1.7 (4.7–11.4)	Ns
IVS(s) (mm)	12.1±3.2 (6.9–16)	10.9±1.9 (8–12.9)	Ns
LVPWD (d) (mm)	8.3±1.9 (7.8–12/1)	7.9±2.3 (6.5–12.8)	Ns
LVPWD(s) (mm)	11.3±3.1 (7.9–13.9)	11.1±1.3 (9.8–12.9)	Ns
FS (%)	40.6±6.1 (34–52)	45.8±7.3 (40–58)	Ns
EF (%)	54.8±9.3 (45–68)	78.5±5.8 (69–81)	<0.05
Mitral E (m/s)	1.1±0.4 (0.83–1.5)	1.01±0.21(0.9–1.6)	NS
Mitral A (m/s)	0.8±0.5 (0.5–1.4)	0.7±0.8 (0.5–0.8)	Ns
E/A ratio	1.4±1.01 (0.9–1.8)	1.8±0.8 (1.2–2.9)	<0.05
DT (ms)	128±27 (83–179)	132±30 (91–180)	Ns

NS, None Significant LVEDD, Left ventricular end-diastolic diameter LVESD Left ventricular end-systolic diameter IVS(s) Interventricular septum diameter in systole IVS (d) Interventricular septum diameter in diastole LVPWD(s) Left ventricular posterior wall diameter in systole LVPWD (d) Left ventricular posterior wall diameter in diastole FS Fractional shortening EF Ejection fraction Mitral E Peak early diastolic wave Mitral A Peak late diastolic wave DT E wave deceleration time

Table 3. Comparison of Tissue Doppler imaging measurements in patients with beta-thalassemia major (TM) and healthy controls

Variables	Group 1 (Patients with TM) (n=100)	Group 2 (Controls) (n=100)	P-value
Basal septal wal			
Sm (cm/s)	7.9±1.5 (5.8–11.4)	8.9±1.7 (5.9–12.6)	NS
Em (cm/s)	13.2±3.3 (9.8–18.1)	14.2±3.3 (11.5–16.3)	NS
Am (cm/s)	5.6±1.6 (3.8–10.7)	7.9±1.8 (5.4–8.9)	<0.05*
Mid-septal wall			
Sm (cm/s)	6.1±1.3 (4.4–9.7)	6.8±1.7 (4.8–9.3)	NS
Em (cm/s)	9.9±1.6 (7.2–12.3)	11.8±2.4 (7.9–14.9)	<0.05*
Am (cm/s)	4.9±1.3 (3.4–9.1)	5.4±1.9 (3.9–7.9)	<0.05*
Basal lateral LV wall			
Sm (cm/s)	10.8±2.8 (6.9–16.9)	11.9±2.5 (8.3–15.9)	NS
Em (cm/s)	16.9±3.06 (13.1–25.3)	17.5±3.04 (12.1–22.9)	NS
Am (cm/s)	6.7±1.7 (3.8–10.9)	9.8±2.8 (7.1–11.7)	<0.05*
Mid-lateral LV wall			
Sm (cm/s)	9.7±2.8 (4.9–15.5)	12.8±2.9 (7.9–14.9)	<0.05*
Em (cm/s)	17.9±2.9 (11.3–21.7)	19.7±3.8 (12.8–19.7)	NS
Am (cm/s)	5.5±1.6 (3.2–17.8)	5.9±1.9 (4.1–9.8)	<0.05*

Data were expressed as mean ± SD

NS, None Significant LV, left ventricle Sm, peak myocardial systolic velocity Em, peak myocardial early diastolic velocity Am, peak myocardial late diastolic velocity

Discussion

The present study demonstrated that TDI could detect myocardial abnormalities like regional wall abnormalities and diastolic dysfunction in patients with TM. Our findings also support the severity of iron overload with MRI and myocardial tissue involvement. The diastolic and systolic dysfunctions detected by conventional echocardiography in patients with TM were related to intensity of iron status with MRI T2*. The systolic myocardial velocities of the basal septal and lateral walls were lower in thalassemic patients compared to normal subjects.

Cardiac overload by MRI was higher in our group than the reports of other researchers (6, 9, 10, 17, 18). MRI offers a non-invasive and readily available approach for the quantitative estimation of iron concentration within different organs (16). The parameter can be used for screening hemochromatosis patients and to guide chelation therapy in those with established cardiac hemochromatosis (4, 19, 20). Like the previous studies, TM patients showed larger chamber diameters for chronic anemia, higher mitral E wave as a marker of increased preload and more diastolic dysfunction than controls like the results of the other researchers (3, 21-23). Like our findings, other groups stated regional systolic dysfunction of lateral and septal walls of left ventricle, even if they did not have overt heart failure (1, 5, 24-26). Like Pepe et al. significant correlations were found between TDI values T2* measurements (27). We have some small differences with the results obtained by Hamdy. He compared 27 patients with TM with a mean age of 12±5 years and 14 age-matched controls using TDI (24). The basal segments of septal and lateral LV and right ventricular free walls were assessed. The patients with TM were found to have regional systolic dysfunction in lateral LV wall and regional diastolic dysfunction in septum and RV wall. We observed septal wall motion changes.

Balci et al. showed that conventional echocardiographic techniques have failed to distinguish ventricular functions of patients with TM but TDI should be used for screening patients with TM (3). Apar et al. showed that TDI is both sensitive and specific for predicting the presence of myocardial iron load in TM patients with normal LV global systolic function. Therefore, it can be used for screening of TM patients (11).

Ucar et al. revealed that TDI is an adjunctive parameter to conventional echocardiography for detecting early myocardial damage like diastolic dysfunction and regional wall velocitites (29). In conclusion, magnetic resonance imaging (MRI) offers the best way for the detection of tissue iron deposition which is noninvasive, reproducibly reliable test but is expensive, not widely available in many centers and interpretation needs an expert. TDI technique is also reliable, noninvasive, widely available in many centers and easy to perform as a screening test and can help for chelation therapy.

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