

Evaluation of diagnostic power of Tissue Doppler Echocardiography for assessment of cardiac iron overload in patients with thalassemia major

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Abstract

Background and Aim: Iron overload in patients with thalassemia major is one of the most important complications of this disease and its cardiac complications are the most important causes of death in these patients. MRI T2 is the perfect device to assess the amount of iron deposited in the heart of thalassemia patients, but it causes waste of time and also is an expensive diagnostic method. Tissue Doppler echocardiography is the newer method for this evaluation. Herein, this study was conducted to determine efficacy and specificity of tissue Doppler echocardiography in the assessment of heart iron overload in patients with thalassemia major.

Materials & Methods: It was a diagnostic power assessment research performed on 50 patients with thalassemia major aged ≥ 15 years old that had been visited in Bouali Sina Hospital in Sari, Iran. After the study was explained and patients agreed to participate, written informed consent was obtained. All the patients underwent MRI T2* and tissue Doppler echocardiography results were obtained. The collected data were processed with SPSS 16 and specificity and efficacy of tissue Doppler echocardiography were obtained. In all analysis, P value < 0.05 was considered statistically significant.

Result: Patients were divided into four groups: normal amount of iron in the heart tissue, mild, moderate and severe. There was a good compatibility between results of MRI T2* and tissue Doppler echocardiography.

Conclusion: we can offer that tissue Doppler echocardiography is a worthy method for evaluating cardiac complications of iron overload in patients with thalassemia major.

Keywords: Diagnostic power, Tissue Doppler Echocardiography, Cardiac Iron Overload, Thalassemia major

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Introduction

Thalassemia is a hereditary anemia characterized by anomalies in the synthesis of one or more of the globin chains of normal hemoglobin. (1) Beta- thalassemia characterized by reduced or absent of beta globin chain synthesis. There are more than 200 beta globin

gene mutations in beta- thalassemia². Based on type of mutations and the level of fetal hemoglobin production, blood transfusions could be started from the first few months to the second year of life in these patients. (2)

Blood transfusion is lifesaving in these patients, but it can be increased the risk of viral infection

and iron overload. (1) Congestive heart failure remains the main leading cause of death in thalassemia major patients. (3, 4)

Materials & Methods

This study was approved by the Ethic Committee of Mazandaran University of Medical Sciences and permissions were received from all participants. The aim of the study was to determine the diagnostic value of TDE in thalassemia major patients aged ≥ 15 years old followed by Bouali Sina Hospital Thalassemia Research Center, Sari/ Iran. Fifty samples were taken according to previous studies.(5) After the study was explained and patients agreed to participate, demographic data, blood levels of ferritin, the number of years the patient received blood transfusion, and other items were extracted from clinical records of the participants. Patients were then sent to the unique MRI T2* center that existed in Sari. MRI index is expressed in milliseconds. Index above the 20 ms means normal storage, 14-20 ms means low iron stores, 10-14 ms is considered medium storage of iron and less than 10 iron storage means severe iron deposition. After that, the patients underwent tissue Doppler echocardiography (TDE) using vivide3 set (Manufactured by GE Co.). The co-author cardiologist was blind to the results of the MRI. Some of the echocardiographic indices (indices of diastolic and systolic function) measured using TDE were as follows: E- Wave (blood flow through the mitral valve in early diastole), A- Wave (blood flow through the mitral valve during atrial contraction); DT (deceleration time), E- wave slope, E'- Wave (annulus movement of the mitral during early diastole), E / E '(ratio of E- wave to E'), LVEF (systolic function index) ¹⁸. Normal levels of echocardiography and LVEF indices are presented in Table- 1.

Data were analyzed using SPSS16 software. Measures of central tendency and dispersion, correlation between MRI parameters or echocardiographic indices with Pearson and Spearman correlation coefficient were calculated, and then the results were compared with serum ferritin levels. Sensitivity, specificity and efficiency of echocardiogram were calculated and Roc curve was drawn. P

value less than 0.05 was considered as statistically significant.

Table 1. Echocardiography and LVEF indices

Severity Indices		Normal	Mild	Moderate	sever
Echo	E/A	1-1.5	<1	1-1.5	2<
	DT(ms)	160-240	240<	160-240	<160
	E'(cm/s)	10<	<10	<7	<7
	E/E'	≤ 8	<8	8-14	15<
LVEF		55 \leq	45-55	35-45	≤ 35

Results

Of 50 eligible patients, 31 (62%) were females and 19 (38%) were males. The mean age was 5.5 ± 9.25 years, ranged between 16-40 years. Seventeen patients (34%) received desferal, 2 patients (% 4) used L1 medicine, 5 (10%) osveral and 23 (% 46) patients received both of the deferal and L1 as iron chelators. 3 patients (6%) used no medicines.

The minimum age for starting blood transfusion in patients was 3 months and maximum age of onset was 8 years (mean 1.9 ± 1.4 year). Average blood transfusion level was 9.1 ± 4.2 per year. Serum Ferritin levels of patients in the previous year were ranged from 300 to 6000 ng/ml with an average of 1437 ± 2304 . Mean hemoglobin level of patients in previous years was at a minimum of 8gr/dl and a maximum of 10gr/dl with an average of 9.8 ± 0.5 (Table 2.).

Table 2. Mean Serum Ferritin and Serum Hemoglobin levels of the patients

Variables	Frequency
Mean Serum Ferritin Level/y (ng/dl)	21437 \pm 423
Mean Serum Hemoglobin Level (gr/dl)	8.9 \pm 5

Findings of myocardial MRI T2 * showed ranging from minimum 4 ms to maximum 59 ms with an average of 22 ± 12.6 ms. Results were divided into four cardiac iron overload groups: normal, poor, moderate and severe. In 23 patients (46%), cardiac iron was within the normal range, 8 (16%) had a poor range, 6 (12%) were in the moderate range and 13

(26%) patients were placed in the severe cardiac iron overload group.

Based on TDE, patients were classified into four groups: normal, mild, moderate and severe. Twenty-four patients (48%) had normal iron storage in the heart, 12 (24%) had mild, 3 (6%) had moderate and 11 (22%) patients were in the severe group.

Mean serum ferritin levels in the patients with moderate and severe MRI T2 * was 2750±2000 and 2300±1300 ng/dl, respectively. There

was no significant association between these two variables (P=0.5).

Mean ferritin levels in people with moderate to severe echocardiography scale was 1100±655 and 2600±1400 ng/dl, respectively. There was no statistically significant relationship between these two variables (P=0.09).

The study results showed a statistically significant correlation between the results of the MRI T2 * and TDE (P=0.00). (Table 3)

Table 3. Distribution of patients as viewpoint of severity of disease based on echocardiography and MRI T2*

*TDE		**NL	Mild	Moderate	Sever	Total	P value
MRI T2*	NL	21	2	0	0	23	0
	Mild	3	3	1	1	8	00.00
	Moderate	0	3	1	2	6	00.00
	Sever	0	4	1	8	13	00.00
Total		24	12	3	11	50	

*LVEF: Left Ventricular Ejection Fraction; **NL: Normal

Ejection fraction of the patients indicated that they had systolic function of 40-60%. The comparison between and MRI T2 * revealed no

clear relationship between these two variables.(Table 4)

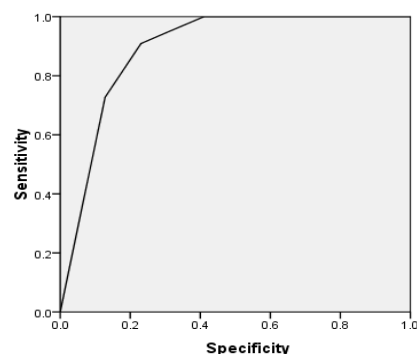
Table 4. Distribution of the patients as viewpoint of severity of the disease based on Ejection fraction and MRI

*LVEF		**NL	Mild	Moderate	Sever	Total	P value
MRI T2*	NL	23	0	0	0	23	0
	Mild	4	3	1	0	8	0.05<
	Moderate	2	3	1	0	6	0.05<
	Sever	7	4	2	0	13	0.05<
Total		36	10	4	0	50	

*LVEF: Left Ventricular Ejection Fraction; **NL: Normal

According to ROC curve, the sensitivity and specificity of TDE for the detection of cardiac complications in patients with cardiac disease is high (Diagram-1).

Diagram.1.ROC Curve of Sensitivity and specificity of Tissue Doppler Echocardiography



Discussion

This study investigated the relationship between indices of left ventricular systolic and diastolic function by TDE and iron deposition in the heart with cardiac MRI T2*. Our results indicated that diastolic cardiac dysfunction showed by TDE have a significant relationship with MRI results.

MRI T2* showed that there was no association between systolic dysfunction and an increased iron deposition. Previous studies have reported controversial results related to systolic function and iron deposition in MRI. (6) This controversy may be due to the sensitivity of cardiac systolic function, patient's age, and serum ferritin levels. Moreover, type and regular taking of iron chelators can be effective. Indices of diastolic function have a significant relationship with cardiac iron overload. Previous studies have showed that the cardiac diastolic echocardiography indexes in most cases were directly associated with iron overload in the heart. (7) While Leonardi reported that diastolic function parameters were poorly correlated with ejection fraction and cardiac MRI T2* in thalassemia patients (6), which was not similar with the results of our study. Early manifestation of diastolic to systolic dysfunction may be effective in this field since at the early onset of cardiac hemosiderosis, we expect it influences on cardiac diastolic function and systolic dysfunction to be added over the time.

In 2011, Marseille et al. evaluated the prognostic significance of several echocardiographic parameters on the occurrence of heart failure or arrhythmias in patients with beta thalassemia major. Their studied population was 37 asymptomatic patients with beta thalassemia and 25 age-matched healthy controls. All subjects underwent TDE and were followed for 22±8 months. The results of their study showed that conventional echocardiographic parameters of left ventricle were similar in both groups, whereas in TDE, the systolic and diastolic cardiac parameters were significantly abnormal in patients with thalassemia⁷. They also found that TDE can be faster than conventional echocardiography to show the heart failure in patients with thalassemia major.

In the present study, severe systolic dysfunction on echocardiography has not been observed. This effect can be observed and reflected in MRI with time and increased iron deposition.

Hamdi and colleagues in 2007 conducted a study on two age-matched case and control groups. The case group consisted of 27 patients with thalassemia and 14 patients of the control group were healthy population. All patients underwent tissue Doppler echocardiography and MRI T2*. Their findings indicated that even in the early stages of cardiac iron deposition in thalassemia patients, obvious changes have been made in the cardiac contractile function and cardiac wall motion. They concluded that TDE can be useful in cardiac evaluation of thalassemia patients who suffered from cardiac iron overload. In a study conducted in 2010 by Garada et al, with similar sampling and methodology of Hamdi's study, people with severe cardiac dysfunction had a higher rate of cardiac iron overload and low ejection fraction. (9)

Vogel et al. (2003) performed a study on 52 age-matched thalassemia major patients whose cardiac iron load was first measured by MRI T2* and then underwent TDE. Thirty-eight of patients had normal cardiac function by MRI T2* and 33 of whom had ventricular wall motion abnormalities detected in the ventricular septum. They concluded that wall motion abnormalities may represent an early sign of iron overload in cardiac muscle that can be easily detected by TDE and early diagnosis of cardiac complication due to iron overload is detectable by MRI T2* in thalassemia patients. (5)

In this study, most patients with normal systolic function on echocardiography have normal iron deposition too, but a significant number of patients with normal systolic function have shown severe iron deposition in MRI T2*. This finding indicates that normal cardiac systolic function is not a reliable predictor of the amount of iron deposition in the heart. This subject can explain the delayed onset of cardiac systolic dysfunction associated with a sudden rise in systolic dysfunction.

Therefore, it can be necessary used a more reliable indicators for cardiac monitoring iron deposition. The results of the present study indicate that TDE can be a noble alternative.

Serum ferritin levels had no significant relationship with systolic and diastolic cardiac dysfunction and rate of iron deposition in MRI T2*. These findings should be considered in the monitoring of patients, medical diagnosis and therapeutic management. Since ferritin acts as an acute phase reactant, increasing of serum ferritin in stressful events such as infection should be considered.

Therefore, high quantitative level of serum ferritin is not a reliable indicator of body iron storage. On the other hand, as quantitative level of serum ferritin is altered at different times, the quantitative description of the cross-sectional survey and even the average of annual storage level of ferritin cannot be fitted with the real level of iron stored in the body. However, low levels of serum ferritin and high iron tissue deposition are not clear and require monitoring and further study.

Although MRI T2* is the gold standard test for measuring of cardiac iron deposition, it is not available in all therapeutic centers and is expensive for patients. Therefore, it is recommended to use TDE for evaluating diastolic cardiac function as an early and more sensitive index to predict cardiac iron deposition. However, in the most of routine evaluation of patients, cardiac systolic function is evaluated.

In a study conducted by Ajeli in 2011, TDE was performed on 28 patients with thalassemia major who had been transfused and treated with chelators and 20 healthy subjects of the community. Cardiac dysfunction in patients with thalassemia major was clearly and significantly higher than healthy people and had a direct correlation with the amount of iron deposited in their hearts. The authors concluded that this method of echocardiography can be a new way for the detection of cardiac dysfunction in patients with thalassemia major when they are still asymptomatic. (10)

Gujja et al. (2010), in a meta-analysis study, compared their study results with the results of several previous studies on the subject of "Iron Overload Cardiomyopathy". They found that in previous studies, in all performed TDE, left atrial diastolic variables were used. So that, there was no significant correlation between the rate of iron deposited in the heart of patients and heart failure.

Furthermore, he stated that if the variables related to left atrial contraction phase were used, more accurate results could be obtained to be safely used in heart failure and early diagnosis of cardiac dysfunction. Also, a significant relationship between the amount of iron deposited in the heart and results MRI T2* technique was found. (11)

Conclusions

Finally, we can offer that TDE is a good method for the evaluation of cardiac complications of iron overload in patients with thalassemia major. Although the sample size of the present study was more than the similar previous study, more samples for further studies are needed. Furthermore, it seems that if patients match for chelators and equal duration of treatment and blood transfusion, more reliable results will be obtained.

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