Original Article

Association between Diastolic Function Parameters and MRI T2 Measurements in a Sample of Iranian Patients with Major Thalassemia*

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ABSTRACT

Background: The aim of the present study was to investigate the relationship between the echocardiographic indices of diastolic dysfunction and MRI T2* measurements, indicating myocardial iron loadings, in patients with thalassemia major and normal left ventricular ejection fractions.

Methods: A series of consecutive patients with known thalassemia major under treatment with regular blood transfusions and iron chelation therapy were enrolled in the current study between July 2012 and June 2015 at Baharlou Hospital, Tehran, Iran. All the patients underwent cardiac MRI with the measurement of T2* for the liver and heart, echocardiographic examination with tissue Doppler assessment, and serum ferritin assay. The correlation between diastolic function parameters and T2* measurements was assessed using statistical software. Standard diastolic indices, comprising early (E) and late (A) transmitral peak flow velocities and early deceleration time (DT), were recorded.

Results: The mean E/A, mean E/E′, and mean E′ were 2.09±0.54, 0.07±0.011, and 14±1.40 cm/s, respectively. The mean deceleration time (dt) was 190.97±35.89. The average serum ferritin level was 1498±783.08 ng/mL (range =212.7 to >3000 ng/mL). The mean cardiac T2* derived from MRI was 26.58±7.54 ms. The frequencies of the different severities of myocardial iron loading based on myocardial T2* were as follows: 44 (80%) normal, 4 (7.3%) mild, 2 (3.6%) moderate, and 5 (9.1%) severe. MRI T2* did not have a significant correlation with E/A (r=0.091; P=0.508), E′ (r=0.130; P=0.345), E/E′ (r=0.005; P=0.971), and dt (r=0.028; P=0.838). Hepatic iron loading based on the MRI T2* values also did not have any correlation with the echocardiographic indices of left ventricular diastolic dysfunction—namely E/A (r=0.151; P=0.270), E′ (r=0.034; P=0.804), E/E′ (r=0.083; P=0.547), and dt (r=0.128; P=0.351).

Conclusions: None of the echocardiographic diastolic function parameters examined in this study were found to be suitable for cardiac surveillance in transfusion-dependent patients affected by thalassemia major. Longitudinal studies are needed to evaluate the utility of echocardiographic and MRI parameters to predict cardiac events. At the moment, we cannot recommend the replacement of cardiac MR and T2* measurements, indicating myocardial iron loading, by Doppler echocardiography in patients with a normal systolic function. ***(Iranian Heart Journal 2016; 17(3):12-17)***

Keywords: Diastolic dysfunction ■ Thalassemia major ■ Hemoglobin disorders ■ Iron overload

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INTRODUCTION

β-thalassemia, first described by Cooley and Lee, represents a group of autosomal recessive hemoglobin disorders with the impaired synthesis of β-globin chain. The homozygous state, so called thalassemia major, brings about severe anemia.[1] Due to numerous consanguineous marriages in Iran, major thalassemia is more frequent than in other developed countries—with about 14000 affected individuals mostly residing in the northern and southern parts of the country.[2] Patients suffering from major thalassemia need regular blood transfusions to survive. However, with the longer lifespan of these patients, iron deposition throughout the body—especially in the heart and endocrine tissues—consequently forms a secondary devastating condition.[3] Myocardial iron loading is the leading cause of death in transfusion-dependent thalassemia patients.[4] Cumulative and progressive deposition of iron in the myocardium—albeit silent in the beginning—could further cause systolic and diastolic dysfunction, arrhythmias, and congestive heart failure. These symptoms usually present in the 2nd or 3rd decade of life.[5] Iron deposition-induced cardiomyopathy in thalassemic patients can be reversible if the diagnosis has been made early followed by intensive chelation therapy.[6] Previous conventional studies such as ECG, conventional echocardiography, and Holter monitoring failed to help detect the cardiac involvement in early stages.[7] Recently, cardiac magnetic resonance imaging (CMR) has gained popularity in diagnosing preclinical iron-overload cardiomyopathy in transfusion-dependent thalassemia. Although the MRI-derived relaxation time parameter, T2*, has been shown to be associated with left ventricular function,[8] the availability and cost of such MRI examinations have limited the clinical impact of T2*—especially in less developed countries. Thus, less expensive diagnostic methods are more desirable. One of these recently highlighted techniques is the echocardiographic assessment of left ventricular diastolic function, which might be a more sensitive marker than systolic function for detecting excess myocardial iron-induced adverse effects. We, therefore, aimed to investigate the correlation between the echocardiographic indices of diastolic function and myocardial T2* in a series of Iranian patients with transfusion-dependent thalassemia.

Study Population

Our subjects were a consecutive series of all patients with thalassemia major who were referred for cardiac function assessment and underwent both echocardiography and CMR between July 2012 and June 2015 at Baharlou Hospital, Tehran, Iran. All the patients were transfusion dependent and had been under chelation therapy with deferoxamine from childhood. Additionally, all the patients had undergone regular ferritin assay to assess the outcome of chelation therapy. None of the patients had decreased left ventricular ejection fractions at the time of imaging assessment.

MRI Techniques and Data Analysis

MRI examinations were routinely performed within 10 days of transfusion. Iron in the

myocardium was quantified by measuring T2* (1/R2*), an MR relaxation parameter that has been shown to vary inversely with tissue iron concentrations.[9] The MRI measurements were performed using a 1.5-T clinical MRI scanner (Philips Achieva, Philips Medical System, Best, the Netherlands) and a torso surface coil. ECG-gated CMR images were obtained for T2*. Short-axis images were prepared in different sequences, similar to the technique described by Westwood et al.[10] The T2* and iron-load values were calculated using "CMR Tools" software. Liver T2* was also assessed similarly to myocardial values. In the myocardium, the loading of iron was categorized into 4 groups according to the corresponding myocardial T2* as follows: normal (>20 ms), mild (14–20 ms), moderate (10–14 ms), and severe (<10 ms). In the liver, hepatic iron loading was divided based on both hepatic T2* (in ms) and mg of iron in each gram of liver dry weight (mg/g/dw). The 4 groups were as follows: normal (>6.3 ms or <2 mg/g/dw), mild (2.8–6.3 ms or 2–5 mg/g/dw), moderate (1.4–2.7 ms or 5–10 mg/g/dw), and severe (<1.4 ms or >10 mg/g/dw).

Echocardiography

Complete 2D, Doppler, and tissue-Doppler echocardiography was performed. Left ventricular end-diastolic and end-systolic volumes were calculated using a modified Simpson algorithm based on long- and short-axis images, and the ejection fraction was calculated. Left ventricular diastolic function was assessed using the pulsed-Doppler samples of the mitral inflow and pulsed-tissue Doppler at the level of the lateral wall of the mitral annulus. Standard diastolic indices, comprising early (E) and late (A) transmitral peak flow velocities and early deceleration time (DT), were recorded. Deceleration time was measured as the time between the peak E velocity and the point where the velocity returns to 0. The peak velocities (cm/s) of the myocardial systolic wave and of the early (E′) and late (A′) diastolic tissue Doppler signals were measured, and the E/E′ ratio was calculated.

Statistical Analysis

The correlations between myocardial and hepatic T2* and the indices of left ventricular systolic and diastolic functions were calculated using the linear regression analysis. A *P* value <0.05 was considered statistically significant.

RESULTS

Patients

A total of 55 patients (27 male, mean age =20.4±4.55 y, age range =4–27 y), who were referred to our medical center, underwent both echocardiography and MRI T2* assessment. The average serum ferritin level was 1498±783.08 ng/mL (range =212.7 to >3000 ng/mL).

Echocardiographic Findings

There were 55 echocardiograms collected over our study period. None of the subjects had left ventricular ejection fractions <50%–55%. The mean E/A, mean E/E′, and mean E′ were 2.09±0.54, 0.07±0.011, and 14±1.40 cm/s, correspondingly. The mean deceleration time (dt) was 190.97±35.89.

MRI Findings

There were 55 CMR images obtained within 1 month of an echocardiogram. The mean cardiac T2* derived from MRI was 26.58±7.54 ms, while the mean hepatic T2* and the mean hepatic iron loading per grams of liver dry weight were 4.32±2.76 ms and 4.59±2.14 mg/g/dw, respectively. The frequencies of the different severities of myocardial iron loading based on myocardial T2* were as follows: 44 (80%) normal, 4 (7.3%) mild, 2 (3.6%) moderate, and 5 (9.1%) severe. The frequencies of normal, mild, and moderate amounts of liver iron loading based on hepatic T2* were 8 (14.5%), 34 (61.8%), and 12 (21.8%), respectively. However, in 1

case, hepatic iron loading was severe (1.8%). In addition, based on the presence of iron in liver dry weight, the prevalence of normal, mild, moderate, and severe hepatic iron loading was similar.

Relationship between MRI and Echocardiographic Findings

MRI T2* did not have a significant correlation with E/A (r=0.091; P=0.508), E′ (r=0.130; P=0.345), E/E′ (r=0.005; P=0.971), and dt (r=0.028; P=0.838). Hepatic iron loading based on the MRI T2* values also did not have any correlation with the echocardiographic indices of left ventricular diastolic dysfunction—namely E/A (r=0.151; P=0.270), E′ (r=0.034; P=0.804), E/E′ (r=0.083; P=0.547), and dt (r=0.128; P=0.351).

DISCUSSION

In the present study, we sought to investigate the correlation between the echocardiographic indices of diastolic function and myocardial and hepatic T2*, which are allied to iron loading in transfusion-dependent thalassemia patients. We found that all the patients had normal left ventricular ejection fractions. The parameters of E/A, E′, E/E′, and the dt index did not correlate with myocardial or hepatic iron concentration (1/T2*).

The main role of a cardiac surveillance program in patients with thalassemia major is to prevent the development of cardiac dysfunction and arrhythmia while avoiding chelator-associated toxicities through the optimal titration of iron chelator medications. The systolic function, although being normal, may rapidly deteriorate and is not adequately sensitive; thus, a periodic monitoring of systolic function is not satisfactory in this setting.[11] The fact that, in ischemic cardiomyopathy, left ventricular diastolic dysfunction precedes the onset of systolic dysfunction has led some researchers to assume that left ventricular diastolic function, as an early marker of myocardial iron overload, may be more sensitive and, thus, serve as a guide for adjusting chelator therapy. To assess left ventricular diastolic function in thalassemia major, investigators have developed several noninvasive techniques in clinical practice. These include the Doppler echocardiography of the transmitral flow, tissue-Doppler imaging, and radionuclide ventriculography.[12–14] Although in the absence of systolic dysfunction, the abnormalities of diastolic function are often noted—as was seen in our study—the clinical significance of these abnormalities has yet to be elucidated. The identification of patients at greater risk for systolic dysfunction and heart failure is the potential clinical usage of subclinical diastolic functional abnormalities. In transfusion-dependent patients, the importance of diastolic function indices to identify at-risk subjects for heart failure has not been shown by others[12–14] and is not supported by our data. In the present study, diastolic function indices, regardless of systolic function, were abnormal in our series.

Investigating the correlation between diastolic function parameters and myocardial MRI T2* measurements would be another efficient approach to assess the potential utility of echocardiographic cardiac surveillance in thalassemia major. In the literature, it has been shown that myocardial T2* correlates well with biopsy-derived iron levels in the heart muscular tissue.[15,16] However, we were unable to detect a significant correlation between the diastolic function parameters of E/A, E′, E/E′, and dt and myocardial T2*—suggesting that among our studied patients, these parameters were a poor reflection of myocardial iron concentration. There are only a few other reports comparing echocardiographic diastolic function indices with myocardial T2*. Aessopos et al.[17] studied the relationship between a variety of parameters—including E, A, and E/A, but not tissue-Doppler indices—and myocardial T2*. The authors found statistically significant but weak (r<0.5) correlations between A and E/A

and T2*; these, however, lacked discriminatory powers to identify patients with myocardial iron overload but with a normal systolic function. Vogel et al.[13] found that despite commonly seen anomalies in tissue-Doppler measurements among thalassemia patients with myocardial iron overload, they were also present in 35% of the patients with a normal T2*, which means that this method was only 65% specific in the setting of iron overload. Westwood et al.[10] used MRI-derived ventricular volume-time curves to measure early and atrial peak filling rates and found that diastolic parameters were weakly correlated with myocardial iron loading. Leonardi et al.[7] also failed to show a significant correlation between myocardial T2* measurements and the echocardiographic parameters of diastolic function. In summary, the above reports overall are consistent with our findings in that abnormal diastolic function indices are frequently seen in patients with thalassemia major but have unsatisfactory specificity to categorize patients into low and high risk of iron overload-induced cardiomyopathy.

Study Limitations

The essential limitation of our study is its relatively small sample size, which decreases its power to detect correlations between echocardiographic diastolic parameters and myocardial T2*. We could not assess the left ventricular ejection fraction by CMR due to high expenses and poor equipment, an issue which was addressed in earlier related reports.

CONCLUSIONS

None of the echocardiographic diastolic function parameters examined in the current study was found to be suitable for cardiac surveillance in transfusion-dependent patients affected by thalassemia major. Longitudinal studies are needed to evaluate the utility of echocardiographic and MRI parameters to predict cardiac events. At the moment, we cannot recommend the replacement of CMR and T2* measurements, indicating myocardial iron loading, by Doppler echocardiography in patients with a normal systolic function.

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