Original Article

Role of Left Atrial Structure and Function in the Early Prediction of Cardiac Iron Overload in Transfusion-Dependent β-Thalassemia Patients

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ABSTRACT

Background: β-thalassemia is the most common monogenic disease caused by abnormalities in the synthesis of the β-chain of hemoglobin.

Methods: From January 2018 to September 2018, 90 patients (age >18 y) with β-thalassemia major or intermedia who referred to Rajaei Cardiovascular, Medical, and Research Center, Tehran, Iran, for the assessment of myocardial iron overload were enrolled. All the patients were receiving regular blood transfusions and chelating therapy. Comprehensive transthoracic echocardiographic studies consisting of 2D echocardiography, tissue Doppler imaging, and real-time 3D echocardiography were performed.

Results: A total of 90 patients were enrolled in the study. Cardiac iron toxicity (ie, T2* < 20 ms) was seen in 28 (31%) patients; whereas in 62 (69%) patients, the cardiac iron level was undetectable (ie, T2* > 20 ms). Patients with T2* < 20 ms had significantly higher serum ferritin levels than those with T2* > 20 ms (P = 0.02). No significant correlation was found between the serum ferritin level and T2* (r = −0.08, P = 0.41). The left ventricular ejection fraction was statistically similar in the 2D and 3D examinations. Left atrial end-systolic and end-diastolic volumes were greater in the patients with iron cardiotoxicity than in those with no detectable cardiac iron deposition (P = 0.01 and P <0.001, respectively). Left atrial strain was also significantly lower in the patients with critical iron overload. The patients with T2* < 20 ms also had lower left atrial ejection fractions than those with T2* >20 ms, both in 2D and 3D examinations (both Ps <0.001).

Conclusions: Our study showed that changes in the left atrial structure and function precede impairment in the left ventricular systolic function in thalassemia patients with critical myocardial iron loading. ***(Iranian Heart Journal 2020; 21(1): 27-33)***

KEYWORDS: Left atrium, Iron overload, β-thalassemia

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β-thalassemia is the most common monogenic disease caused by abnormalities in the synthesis of the β-chain of hemoglobin. [1, 2] Recent advances in available therapies have improved long-term prognosis in the affected individuals, with approximately 80% of patients surviving beyond 40 years. [3] Chronic hemolysis, enhanced iron absorption by the intestine, and frequent blood transfusions lead to iron overload in these patients, ultimately infiltrating various body organs including the heart, liver, glands, and skin. [4, 5] Excessive cardiac iron accumulation results in heart failure and cardiac arrhythmias, which constitute the major etiologies of death in patients with transfusion-dependent thalassemia. [6-8]

The gold standard technique to assess cardiac iron deposition is cardiac magnetic resonance imaging, [9] although its use is limited by high costs involved and less availability. Recently, echocardiographic modalities including conventional 2D echocardiography, Doppler echocardiography, tissue Doppler echocardiography, and 3D echocardiography have provided promising results in the diagnosis of iron overload in patients with transfusion-dependent thalassemia. Although most of these modalities have assessed left ventricular diastolic and systolic dysfunction as a surrogate marker of cardiac involvement in thalassemia patients, there is increasing evidence that ventricular dysfunction occurs late in the disease course. On the other hand, the data regarding the predictive role of the assessment of the left atrium in the early recognition of cardiac iron toxicity are still scarce.

Accordingly, in the present study, we aimed to investigate the association between the left atrial structure and function and critical cardiac iron deposition using conventional 2D echocardiography and real-time 3D echocardiography in patients with β-thalassemia receiving regular blood transfusions.

METHODS

Study Population

From January 2018 to September 2018, 90 consecutive adult patients (age >18 y) with β-thalassemia major or intermedia who were referred to Rajaei Cardiovascular, Medical, and Research Center, Tehran, Iran, for the assessment of myocardial iron overload were enrolled. All the patients were receiving regular blood transfusions and were on chelating therapy (deferoxamine mesylate).

All the patients provided written informed consent, and the Institutional Board Review at Rajaei Cardiovascular, Medical, and Research Center approved the study protocol.

Echocardiographic Examination

Comprehensive transthoracic echocardiographic studies comprised of 2D echocardiography, tissue Doppler imaging, and real-time 3D echocardiography were performed in all the patients by a single echocardiography specialist using a Philips EPIQ 7 ultrasound system for cardiology (Philips Ultrasound, Bothell, WA, USA) equipped with xMATRIX ultrasound transducer technology. All the echocardiographic examinations were performed in the left decubitus position and at least 4 days after a recent blood transfusion.

Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) scan was used to quantify myocardial tissue iron loading by Heart T2* measurements. All the scans were performed using a torso

coil on a 1.5 T General Electric CVi scanner via a single breath-hold multi-echo gradient technique. As described by Anderson et al, [7] critical iron loading was defined as a T2* value < 20 ms and values ≥ 20 ms were considered to be uncritical (no detectable cardiac iron).

Statistical Analysis

All the analyses were conducted using IBM SPSS Statistics 22 for Windows (IBM Inc, Armonk, NY, USA). The data were initially assessed for normality using the Kolmogorov–Smirnov test. The categorical variables were presented as numbers and percentages and were compared using the χ^2 test. The continuous variables were presented as the mean ± the standard deviation or the median and the interquartile range (IQR) and analyzed using the Student *t*-test, the Mann–Whitney test, and the Kruskal–Wallis test, depending on the data distribution. The relationships were assessed using the Pearson correlation coefficient (*r*) and the Spearman rank correlation coefficient (ρ), as appropriate. All the *P* values were 2-tailed and a *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 90 patients, including 42 females (46.6%), at a mean age of 29 ± 6 years were enrolled in the study. The median serum ferritin level was 693.50 µg/L (IQR, 309.00 to 1205.25) and mean cardiac T2* was 24.46 ± 7.91 ms. Cardiac iron toxicity (ie, T2* < 20 ms) was seen in 28 (31%) patients; whereas in 62 (69%) patients, the cardiac iron level was undetectable (ie, T2* > 20 ms). The baseline characteristics of the patients are summarized in Table 1.

Table 1. Baseline characteristics of the study population

Characteristic	*P* value
Age	29±6
Gender male female	 48 (53.4) 42 (46.6)
Dyspnea No Yes	 52 (57.8)
NYHA Function Class I II III IV	 31 (34.5) 7 (7. 4) 0 (0) 0 (0)
Electrocardiographic Findings Normal PAC PVC	 75 (83.3) 14 (15.6) 1 (1.1)
Laboratory Measurements	
Hemoglobin	10.4 (9.5-11.5)
Ferritin	693.5 (309-1205.25)
CMR data	
T2*	24 918-30.25)

Data are presented as the mean ± the standard deviation or the median (interquartile ranges) and numbers (percentage).
CMR, Cardiac magnetic resonance imaging; NYHA, New York Heart Association; PAC, Premature atrial contraction; PVC, Premature ventricular contraction

The patients with T2* < 20 ms had significantly higher serum ferritin levels than those with T2* > 20 ms (1150 [340–1750] vs 567 [300.75–886.50]; P = 0.02). However, no significant correlation was found between the serum ferritin level and T2* (r = −0.08, P = 0.41).

The left ventricular ejection fraction was statistically similar between the 2 study groups, both in 2D and 3D examinations (P = 0.29 and P = 0.20, respectively)

Left atrial end-systolic and end-diastolic volumes were greater in the patients with iron cardiotoxicity than in those with no detectable cardiac iron deposition (P = 0.01 and P < 0.001, respectively). Left atrial strain was also significantly lower in the patients with critical iron overload than in those without detectable cardiac iron deposition (P = 0.001). The patients with T2* < 20 ms also had lower left atrial ejection fractions than those with T2*>20 ms, both in 2D and 3D examinations (both Ps < 0.001). All the echocardiographic variables are compared between the 2 study groups in Table 2.

The correlations between serum ferritin, cardiac T2*, and echocardiographic indices are shown in Table 3.

Table 2. Echocardiographic indices in the patients with T2*< 20 ms and >20 ms

Variable	T2*<20 ms (Critical Iron Overload) (n=28)	T2*>20 ms (No Detectable Iron Overload) (n=62)	*P* value
LVEF (2D) (%)	55 (50-55)	55 (53.75-55)	0.29
LVEF (3D) (%)	50.5 (44.25-60.25)	53 (50-60)	0.20
RVEF (3D) (%)	43.5 (38.5-48.75)	48.5 (43.25-52.75)	0.01
LAESV (mL)	42.5 (33.5-53.75)	33 (28-43.25)	0.01
LAEDV (mL)	30 (22-38)	18 (14-22.12)	<0.001
LA Stroke volume (mL)	16 (12-22.5)	17.4 (14-23)	0.53
LA volume Normal Enlarged Mild Moderate Severe	 10 (35.7) 11 (39.3) 3 (10.7) 4 (14.3)	 48 (77.4) 11 (17.8) 2 (3.2) 1 (1.6)	0.001
LA strain	32 (25-38)	40 (33-44)	0.001
LAEF (2D) (%)	35.22±10.40	46.20±12.72	<0.001
LAEF (3D) (%)	35.89±12.25	45.40±13.48	0.002
SPAP (mm Hg)	35 (30-40)	30 (30-35)	0.11
RAEF (2D) (%)	29.88±10.71	40.57±10.92	<0.001
RAEF (3D) (%)	30±2.88	33.75±14.64	0.51

Data are presented as the mean ± the standard deviation or the median (interquartile ranges) and numbers (percentages).
LA, Left atrial; LAEF, Left atrial ejection fraction; LAEDV, Left atrial end-diastolic volume; LAESV, Left atrial end-systolic volume; LVEF, Left ventricular ejection fraction; RAEF, Right atrial ejection fraction; RVEF, Right ventricular ejection fraction; SPAP, Systolic pulmonary artery pressure

Table 3. Correlations between echocardiography-derived indices and serum ferritin levels and cardiac T2*

ENB'		Serum Ferritin	T2* ms
LVEF (2D)	R	0.04	0.19
	P	0.66	0.06
LVEF3D	R	0.25	0.22
	P	0.01	0.03
RV3DEF	R	0.20	0.20
	P	0.05	0.05
LAESV	R	0.18	-0.34
	P	0.07	0.001
LAEDV	R	0.12	-0.44
	P	.23	<0.001
SV	R	0.03	-0.03
	P	0.74	0.77
LA strain	R	-0.07	0.40
	P	0.51	<0.001
LAEF2D	R	-0.02	0.36
	P	0.79	.001
LAEF3D	R	-0.01	0.33
	P	0.91	0.001
SPAP	R	0.08	-0.19
	P	0.40	0.06
RA_EF2D	R	0.07	0.48
	P	0.48	<0.001
RAEF3D	R	0.62	0.69
	P	0.05	0.02

LA, Left atrial; LAEF, Left atrial ejection fraction; LAEDV, Left atrial end-diastolic volume; LAESV, Left atrial end-systolic volume; LVEF, Left ventricular ejection fraction; RAEF, Right atrial ejection fraction; RVEF, Right ventricular ejection fraction; SPAP, Systolic pulmonary artery pressure

DISCUSSION

Iron toxicity greatly affects the long-term prognosis in patients with β-thalassemia and is a major cause of morbidity and mortality in these patients. [3, 6-8] CMR is considered the gold standard method in the early recognition of iron deposition in the myocardium. However, its use is limited due to high cost and less availability, particularly in developing countries. As a result, echocardiography has been introduced as a less expensive, widely available, and reproducible method for this purpose, although its sensitivity and specificity in assessing cardiac iron accumulation are limited.

Assessments of the left ventricular function (ie, the ejection fraction) have been drawn upon as a marker of iron toxicity, even though an iron deposition level sufficient enough to affect the left ventricular function occurs late in the disease course. Moreover, high cardiac output due to chronic anemia masks proper detection of ventricular dysfunction. As a result, other echocardiographic indices have been investigated for the early recognition of iron accumulation in susceptible patients. A study by Rodrigues et al [11] showed that the left atrial volume index, the mitral septal E/Em ratio, the duration of reverse pulmonary vein flow, and the mitral E/A ratio were higher in patients with asymptomatic thalassemia major than in healthy individuals and patients with iron deficiency anemia. However, they found no significant differences in the left ventricular structures and systolic function indices among their 3 study groups. In contrast to our study, Rodrigues and colleagues did not evaluate cardiac iron accumulation CMR.

In the present study, to determine the predictive role of the left atrial structure and function in the early recognition of cardiac iron overload in patients with thalassemia, we employed conventional 2D echocardiography and real-time 3D echocardiography with a view to comparing relevant indices in patients suffering from thalassemia with and without critical iron deposition. All the patients were on chronic blood transfusion and were receiving iron chelation therapy (deferoxamine mesylate). Of note, all the participants had preserved left ventricular functions (ie, ejection fraction > 40%) and normal left and right ventricular sizes.

We found that the patients with and without critical myocardial iron deposition had statistically comparable left ventricular ejection fractions, reinforcing the limited role of the left ventricular function in the

early identification of myocardial iron loading, as previously described.

Cardiac involvement in infiltrating diseases primarily begins with diastolic dysfunction, causing gradual dilatation in atrial size and impairment in atrial contraction. [12-15] The progression of cardiac infiltration would eventually lead to the deterioration of the ventricular systolic function. Thus, changes in the left atrial structure and function might precede the development of overt pump failure. In accordance with this hypothesis, our results demonstrated that patients with iron cardiotoxicity had significantly lower left atrial ejection fractions than those without critical iron deposition, highlighting the predictive role of the left atrial function in the early prediction of iron toxicity in patients with thalassemia receiving chronic blood transfusions. In a case-control study, Aggeli et al [16] compared the left atrial performance in 28 patients with asymptomatic β-thalassemia who were on chelating therapy with 20 age- and sex-matched healthy controls using transthoracic real-time 3D echo. The thalassemia group had normal echocardiographic systolic and diastolic functions; however, unlike the patients in our study, there was no myocardial iron disposition according to MRI. They found that the left atrial active emptying fraction was reduced in the thalassemia group compared with the healthy controls.

We also found a significant correlation between T2* and the left atrial ejection fraction (both in 2D and 3D echocardiography, $r = 0.36$, $P < 0.001$ and $r = 0.33$, $P < 0.001$; respectively). Moreover, our results showed that the patients with critical iron loading had higher left atrial volumes (end-systolic and end-diastolic volumes) and lower left atrial strain than those with non-critical iron loading. However, in the study by Aggeli et al, [16] no significant differences were seen in the left atrial volumes (the left atrial maximum volume at end-systole, the left atrial volume just before the mitral valve opening, and the left atrial volume before atrial active contraction) between patients with thalassemia and healthy individuals. It should be noted, however, that the patients with thalassemia in the aforementioned study did have cardiac iron deposition, which might explain discrepancies seen in their results with our study.

CONCLUSIONS

In conclusion, our study showed that changes in the left atrial structure and function precede impairment in the left ventricular systolic function in patients suffering from thalassemia with critical myocardial iron loading. Larger left atrial systolic and diastolic volumes and poorer left atrial performance in these patients might be used as echocardiographic markers for the early identification of iron deposition, which, in turn, could affect management strategies such as the employment of more aggressive chelating therapies.

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