Echocardiography in Thalassemic Patients on Blood Transfusions and Chelation without Heart Failure

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Abstract

Background: Patients with thalassemia major present chronic hemolysis and require regular blood transfusions which may cause iron overload cardiomyopathy and chronic heart failure. Hemochromatosis is characterized by excessive iron accumulation in tissues, and heart involvement is the main cause of death in patients with thalassemia.

Objective: The aim of this study was to evaluate cardiac structure and function by conventional Doppler echocardiography and tissue Doppler imaging in patients with TM and no clinical evidence of heart failure.

Methods: This is a prospective observational study including 18 patients with thalassemia major (TM) receiving regular blood transfusion. To separately evaluate anemia and blood transfusion effects, two gender, age, weight, and height-matched control groups were included: one with healthy individuals (Healthy, n=18) and one with iron deficient anemia patients (Anemia, n=18). Statistical analysis was performed using ANOVA followed by Tukey's test or Kruskal-Wallis's and Dunn's test.

Results: The following echocardiographic variables presented significantly higher values in TM than the Anemia and Healthy groups: left atrium volume index (Healthy: 16.4±6.08; Anemia: 17.9±7.02; TM: 24.1±8.30 cm^3/m^2); mitral septal E/Em ratio (Healthy: 6.55±1.60; Anemia: 6.74±0.74; TM: 8.10±1.31); and duration of reverse pulmonary vein flow [Healthy: 74.0 (59.0-74.0); Anemia: 70.5 (67.0-74.0); TM: 111 (87.0-120) ms]. The mitral E/A ratio was higher in TM than Anemia (Healthy: 1.80±0.40; Anemia: 1.80±0.24; TM: 2.03±0.34). No differences were found in left ventricular structures and systolic function indexes.

Conclusions: Conventional Doppler echocardiography and tissue Doppler allow changes in left ventricular diastolic function to be identified in asymptomatic patients with thalassemia major. (Arq Bras Cardiol. 2013;100(1):75-81)

Keywords: Echocardiography, Doppler; beta-Thalassemia / complications; Blood Transfusion; Iron Chelating Agents; Ventricular Function.

Introduction

Thalassemia major, also known as Mediterranean anemia, is considered the most common single gene disorder. Beta gene homozygosis usually causes relevant clinical signs and symptoms[1]. Patients with thalassemia major present a state of chronic hemolysis, elevated iron absorption by the intestine, and require frequent blood transfusions leading to iron overload in organs and tissues including the heart, liver, glands, and skin[2,3]. Hemochromatosis is part of a group of storage diseases and is characterized by excessive iron accumulation in tissues. Heart involvement in the disease is the main cause of death in regularly transfused thalassemia major patients[3-7].

Patients with thalassemia major remain asymptomatic with normal left ventricular function for a long period of time. Early identification of ventricular dysfunction, before the appearance of symptoms, can alter the prognosis of these patients because it reinforces the need to optimize the therapy with chelators, drugs that alleviate iron overload in the organism[8-11]. Some reports indicate Doppler-echocardiogram with tissue Doppler as a promising technique for this situation[12-19]. However, data obtained by this method are still scarce, particularly in relation to left ventricular diastolic function and right ventricular structure and function.

The aim of this study was to evaluate cardiac structure and function by conventional Doppler-echocardiogram and tissue Doppler imaging in patients with thalassemia major and regular blood transfusions with no signs or symptoms of heart failure.

Methods

This is an observational and cross sectional study including 18 patients with thalassemia major receiving regular blood transfusion with no signs or symptoms of heart failure. The study was conducted at Faculdade de Medicina de Marília (FAMEMA), Brazil, after approval by the institution Research Ethics Committee. Written informed consent was obtained from all participants or their parents. To separately evaluate anemia and blood transfusion effects, two gender, age, weight, and height-matched control groups were included: one with healthy individuals (Healthy, n=18) and one with iron deficient anemia patients (Anemia, n=18).

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This study included thalassemia major patients of both genders under frequent blood transfusions for more than two years. The diagnosis of thalassemia major was based on clinical evaluation, hemogram, blood smear, and hemoglobin electrophoresis. The patients had been regularly receiving red blood cells transfusion (approximately 250 mL) every three to four weeks. Target pretransfusion hemoglobin levels ranged from 9.0 to 10.0 g/dL. All patients had received chronic chelation therapy with subcutaneous deferoxamine (40 - 60 mg/kg/day, 5 to 7 days per week) and/or oral deferiprone (50-70 mg/kg/day in 3 divided doses) according to serum ferritin levels and tolerance.

In the Anemia group, investigation of comorbidities did not reveal any other diseases and anemia etiology was considered to be chronic iron deficiency caused by inadequate dietary intake. No patient presented evidence of acute anemia.

Patients presenting one or more of the following conditions were excluded: signs or symptoms of heart failure; acquired or congenital heart disease; systemic abnormalities that can affect cardiac structure and function such as systemic arterial hypertension, diabetes mellitus, thyroidopathies, obesity, and renal or hepatic dysfunction; cardiac arrhythmia; use of cardiotoxic drugs; and inadequate echocardiographic image. All individuals were submitted to clinical evaluation by the same cardiologist and laboratory exams with measurements of hemoglobin levels. In thalassemia major patients, ferritin, serum iron, transferrin, and iron fixation capacity were also measured.

The echocardiographic study was performed using a General Electric VIVID 3 device, equipped with a multifrequency probe (1.7-4.5 MHz), with second harmonic imaging and conventional Doppler associated with tissue Doppler (General Electric Medical Systems Ultrasound, Milwaukee, WI, USA), under simultaneous electrocardiographic recording. All exams were performed by the same cardiologist who carried out the clinical evaluation at least 4 hours after blood transfusion. All patients and controls were in normal sinus rhythm during the examination. Echocardiographic evaluation included left ventricle (LV) end-diastolic and end-systolic diameters, septum and LV posterior wall thicknesses in diastole and systole, LV end-diastolic and end-systolic volumes, and LV ejection fraction by Simpson's method. Left atrial (LA) volume was calculated using the biplane area-length method from two and four chamber views. Transmitral flow patterns were obtained by pulsed-wave Doppler echocardiography from apical four chamber views. Mitral peak early (E) and late (A) diastolic velocities, E/A ratio, E wave deceleration time, and isovolumetric relaxation time were measured. For tissue Doppler imaging (TDI), the filter was adjusted to prevent high frequency signals, and Nyquist limit was adjusted to 15-20 cm/s. Gains were minimized to allow for a clear tissue signal with minimal background noise. TDI was evaluated at the level of basal segments of anterior, septal, lateral and inferior LV wall and peak myocardial systolic, and early and late diastolic velocities were measured from apical two and four chamber views. All pulsed-wave Doppler and TDI parameters were measured at the end of expiration at a sweep speed of 100 mm/s on three consecutive heart beats with the average for each taken. Pulmonary capillary wedge pressure (PCWP) was assessed using the mitral E velocity to early diastolic mitral annulus velocity (Em) ratio, with the formula PCWP=1.9+1.24(E/Em)[20]. All images and structural and functional measurements were performed according to American Society of Echocardiography recommendations[21].

Data are expressed as mean ± standard deviation or median and 25th and 75th percentiles depending on normal or non-normal distribution. Comparison between groups was by analysis of variance (ANOVA) and complemented by the Tukey's or Kruskal-Wallis and Dunn's tests for normal and non-normal distributions, respectively. SigmaStat for Windows 2.0 statistics package (Jandel Co., San Rafael, CA, USA) was used for the tests. Statistical significance was accepted at the level of $p < 0.05$.

Results

Table 1 shows the general characteristics of individuals belonging to the three groups: Healthy, Anemia, and Thalassemia. Hemoglobin levels in the Thalassemia group were lower than the Healthy and higher than the Anemia group. There was no difference between groups for the following variables: age, gender proportion, weight, height, body mass index, blood pressure, and heart rate. The following blood tests were performed only in thalassemic patients: serum iron 199 (138-206) μg/dL, ferritin 3289±2331 ng/mL, transferrin 163±44 mg/dL, and iron fixation capacity 318±61 μg/dL.

Echocardiographic data related to left ventricular structural and systolic function evaluation are shown in Table 2. LV diastolic and systolic diameters and volumes, and diastolic wall thickness were not different between groups. Also, no consistent differences in LV systolic function were found between groups. Only the percentage of LV systolic wall thickening was lower in the Thalassemia group. LV diastolic function indices are presented in Table 3. The main variables that were statistically different in Thalassemia group compared to Healthy and/or Anemia groups are illustrated in Figure 1. Pulmonary capillary wedge pressure was higher in the Thalassemia group than the other two groups. Structural and functional right ventricle evaluation showed no significant differences between groups (Table 4).

Discussion

Cardiac structure and function in thalassemia major patients are mainly affected by two factors: increased cardiac output and iron overload. In thalassemia major patients, anemia and bone marrow expansion cause hemodynamic alterations characterized by volume overload and increased cardiac output, with consequent development of eccentric ventricular hypertrophy. Chronic maintenance of this state can evolve into heart failure[22-25]. Also, iron deposition in the myocardium mainly results in decreased left ventricular function.

Previous studies assessed cardiac function in thalassemia major patients by comparing them to a healthy control group, without considering the isolated effects of anemia on the heart. To the best of our knowledge, this is the first study to compare thalassemia major patients with groups comprised by healthy

control individuals or anemic patients. Anemia is known to cause cardiovascular structural and/or functional alterations. In our study, individuals with thalassemia major presented lower levels of hemoglobin at the moment of echocardiographic exam (at least 4 hours after blood transfusion) in relation to healthy controls. When compared to the Anemia group, thalassemia major patients presented higher hemoglobin levels. We also observed that thalassemia major hemoglobin level before blood transfusion on the day of echocardiographic evaluation was not significantly different from the Anemia group (data not shown). Therefore, we can assume from our study that cardiac alterations found in the Thalassemia group, compared to Anemia group, are caused by iron overload and not by anemia.

In our study, left atrium volume indexed by body surface area was significantly higher in Thalassemia than the two control groups. This suggests an increase in left ventricular end diastolic pressure, reflecting an alteration in diastolic property,

Table 1 - General characteristics of individuals from the Healthy, Anemia, and Thalassemia Groups

Variables	Healthy (n=18)	Anemia (n=18)	Thalassemia (n=18)
Age (years)	18.1 ± 7.27	18.6 ± 10.6	18.3 ± 7.50
Gender male/female	15/3	15/3	15/3
Weight (Kg)	63.0 (49.0-70.0)	58.0 (44.0-63.0)	59.0 (40.0-66.0)
Height (m)	1.67 (1.56-1.71)	1.62 (1.51-1.72)	1.60 (1.47-1.68)
Body mass index (Kg/m²)	21.2 ± 3.39	22.0 ± 4.17	21.0 ± 3.01
Hemoglobin (g/dL)	14.5 ± 1.75	10.5 ± 1.03*	13.0 ± 0.83*#
Systolic blood pressure (mmHg)	107 ± 10.2	107 ± 12.6	102 ± 8.80
Diastolic blood pressure (mmHg)	70.0 (60.0-80.0)	70.0 (60.0-80.0)	65.0 (60.0-70.0)
Heart rate (bpm)	68.2 ± 12.5	75.1 ± 11.1	73.1 ± 16.7

*Values expressed as mean and standard deviation or median and 25th and 75th percentiles. Kg: kilograms; m: meters; mmHg: millimeters of mercury; bpm: beats per minute. *: p<0.05 vs. Healthy; #: p<0.05 vs. Anemia (ANOVA and Tukey or Kruskal-Wallis and Dunn).*

Table 2 - Left ventricular structures, systolic function, and hemodynamic variables of individuals from the Healthy, Anemia, and Thalassemia Groups

Variables	Healthy (n = 18)	Anemia (n = 18)	Thalassemia (n = 18)
LV EDV 4C (cm³)	91.3 ± 34.4	85.9 ± 32.2	103 ± 35.1
LV ESV 4C (cm³)	38.9 ± 17.1	35.7 ± 15.2	38.3 ± 14.6
LV EDV 2C (cm³)	98.2 ± 37.7	96.4 ± 35.0	99.3 ± 34.6
LV ESV 2C (cm³)	41.3 ± 18.0	36.0 ± 14.7	37.2 ± 12.8
LV mass index (g/m²)	77.4 ± 14.9	80.4 ± 20.2	86.0 ± 15.6
Ejection fraction LV Simpson	0.59 ± 0.07	0.61 ± 0.05	0.62 ± 0.04
Cardiac output (L/min)	3.60 ± 1.03	4.21 ± 1.46	4.01 ± 1.45
Cardiac index (L/min/m²)	2.36 ± 0.54	2.86 ± 0.76	2.70 ± 0.73
LV Tei index	0.41 ± 0.10	0.33 ± 0.11	0.32 ± 0.11 *
Sm sep (cm/s)	7.90 ± 1.23	8.83 ± 1.15	8.70 ± 1.75
Sm lat (cm/s)	9.61 ± 1.80	10.1 ± 2.20	10.3 ± 2.30
LV End-SS (g/cm²)	60.9 ± 8.91	61.2 ± 10.0	66.8 ± 11.1
LV systolic thickness (%)	75.2 ± 16.1	74.2 ± 20.1	50.8 ± 16.6 *#
PCWP (mmHg)	10.0 ± 1.95	10.3 ± 0.92	11.9 ± 1.63 *#

*Values expressed as mean and standard deviation or median and 25th and 75th percentiles. LV: left ventricle; EDV: end diastolic volume; ESV: end systolic volume; 4C: four chambers; 2C: two chambers; Sm sep: systolic myocardial velocities at the basal mitral annulus of the septal wall by Tissue velocity imaging; Sm lat: systolic myocardial velocities at the basal mitral annulus of the lateral wall by Tissue velocity imaging; End-SS: end-systolic wall stress; PCWP: pulmonary capillary wedge pressure. *: p<0.05 vs. Healthy; #: p<0.05 vs. Anemia (ANOVA and Tukey or Kruskal-Wallis and Dunn).*

Table 3 - Left ventricular diastolic function of individuals from the Healthy, Anemia, and Thalassemia Groups

Variables	Healthy (n=18)	Anemia (n=18)	Thalassemia (n=18)
LA Volume (cm³)	23.7 ± 4.88	28.0 ± 8.21	33.9 ± 7.46 *#
LA Volume/BSA (cm³/m²)	16.4 ± 6.08	17.9 ± 7.02	24.1 ± 8.30 *#
Mitral E (cm/s)	84.2 ± 16.4	93.6 ± 14.0	101 ± 15.4 *
Mitral A (cm/s)	47.4 ± 7.60	53.7 ± 8.23	50.9 ± 8.80
E/A ratio	1.80 ± 0.40	1.80 ± 0.24	2.03 ± 0.34 #
DT (ms)	226 ± 51.4	223 ± 39.1	231 ± 33.6
A duration mitral (ms)	126 (104 - 130)	104 (96 - 111)	128 (120 - 144) #
IVRT (ms)	72.4 ± 10.8	63.2 ± 15.1	74.1 ± 9.55 #
Ard (ms)	74.0 (59.0 - 74.0)	70.5 (67.0 - 74.0)	111 (87.0 - 120) *#
Em sep (cm/s)	13.2 ± 2.41	14.0 ± 2.30	12.7 ± 2.10
Am sep (cm/s)	6.60 ± 1.72	7.11 ± 1.60	7.30 ± 1.41
Em lat (cm/s)	15.8 ± 1.82	16.9 ± 2.84	18.2 ± 2.41 *
Am lat (cm/s)	5.72 ± 1.41	6.30 ± 1.70	7.70 ± 2.50 *
Mean Em (cm/s)	15.3 ± 2.00	15.6 ± 2.20	15.3 ± 2.00
Septal E/Em ratio	6.55 ± 1.60	6.74 ± 0.74	8.10 ± 1.31 *#
Mean E/Em	5.60 ± 1.24	6.10 ± 1.10	6.70 ± 1.02 *

*Values expressed as mean and standard deviation or median and 25th and 75th percentiles. LA: left atrium; BSA: body surface area; Mitral E and Mitral A: peak early and late diastolic filling velocities, respectively; E/A ratio: ratio between E and A mitral waves; DT: deceleration time of mitral E wave; IVRT: isovolumetric relaxation time; Ard: duration of reverse flow of atrial systole to the pulmonary vein; Em sep and Am sep: early and late diastolic myocardial velocities at the basal mitral annulus of the septal wall by Tissue velocity imaging, respectively; Em lat and Am lat: early and late diastolic myocardial velocities at the basal mitral annulus of the lateral wall by Tissue velocity imaging, respectively; Septal E/Em ratio: ratio between mitral E and Em waves. *: p<0.05 vs. Healthy; #: p<0.05 vs. Anemia (ANOVA and Tukey or Kruskal-Wallis and Dunn).*

most probably caused by iron overload in the heart. An important observational study with 6,657 individuals without history of atrial fibrillation or valve disease showed that a left atrium volume/body surface area ratio ≥ 34 ml / m² is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke[26]. There is a significant association between left atrium remodeling and diastolic function indices obtained by Doppler-echocardiogram. Furthermore, the increase in left atrium volume reflects the cumulative effect of alteration in left ventricular filling pressure[27-29]. Another interesting finding is that pulmonary capillary wedge pressure, estimated by Doppler echocardiography, was higher in Thalassemia than the two control groups. This result reinforces the findings already discussed in relation to the left atrium. Patients with left ventricular dysfunction present elevated left ventricular end diastolic pressure and left atrium pressure, with a consequent increase in left atrium volume and pulmonary capillary wedge pressure[27,30,31].

In left ventricular systolic function evaluation, the percentage of systolic posterior wall thickening was lower in Thalassemia than the two control groups; this was the only index that suggested some degree of left ventricular systolic dysfunction. Tissue Doppler, a recently introduced method in echocardiographic study, is known to permit early identification of systolic dysfunction even when left ventricular ejection fraction is still preserved. Reduced systolic velocity of mitral annulus displacement (Sm) is considered a sensitive marker of light left ventricular systolic dysfunction in individuals with preserved left ventricular ejection fraction[32-35]; but we identified no alterations in this variable in our sample.

In our study, the echocardiographic evaluation obtained by conventional Doppler associated with tissue Doppler imaging showed differences in parameters of ventricular diastolic function between Thalassemia and the two other groups, Control and Anemia. According to literature[11], iron can affect all cardiac structures including papillary muscles, conduction system, and pericardium. The epicardial region of the left ventricular free wall is the most affected. Histological evaluation of individuals with iron overload has demonstrated myocyte hypertrophy with iron deposition in cytoplasm and macrophages. Furthermore, myocyte disruption, reduced myofiber numbers, and dense nuclei and cytoplasmic granules containing iron were demonstrated. These alterations are commonly found in subjects with elevated iron overload and clinical features of heart failure. Diastolic dysfunction generally appears before systolic dysfunction in the natural history of ventricular dysfunction; therefore, diastolic dysfunction secondary to iron overload can be explained by the initial phase of the structural heart alterations described above.

Recent advances in echocardiography have enabled this technique to be used for early identification of ventricular

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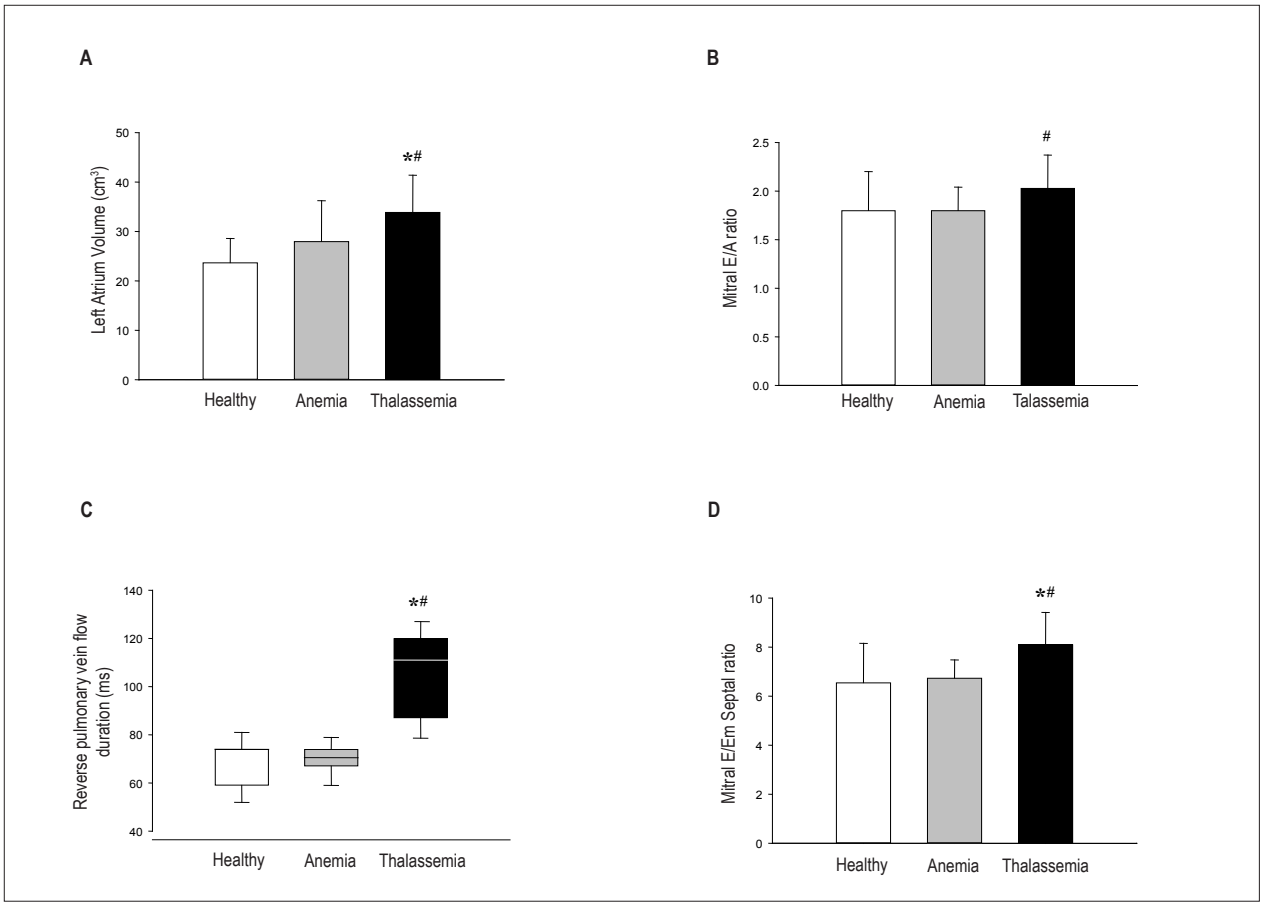

Figure 1 - *Left atrium volume (A), ratio of early to late diastolic mitral inflow velocities (B), reverse pulmonary vein flow duration (C), and ratio of early diastolic mitral inflow velocity to early diastolic myocardial velocity at the basal mitral annulus of the septal wall by tissue Doppler imaging (D) for individuals from Healthy, Anemia, and Thalassemia groups. *: p<0.05 vs. Healthy; #: p<0.05 vs. Anemia; ANOVA and Tukey (A, B, and D); Kruskal-Wallis and Dunn (C).*

Table 4 - Right ventricular structures, systolic function, and hemodynamic variables for individuals from the Healthy, Anemia, and Thalassemia Groups

Variables	Healthy (n=18)	Anemia (n=18)	Thalassemia (n=18)
RV EDV (cm³)	38.6 ± 16.7	34.8 ± 16.1	35.8 ± 14.8
RV ESV (cm³)	16.4 ± 7.91	13.2 ± 6.44	16.8 ± 8.30
RV Ejection Fraction	0.57 ± 0.08	0.62 ± 0.09	0.53 ± 0.07 #
RV Tei index	0.18 ± 0.08	0.19 ± 0.09	0.24 ± 0.09
TAPSE (mm)	2.24 ± 0.36	2.45 ± 0.39	2.41 ± 0.42
St (cm/s)	12.6 ± 1.30	14.2 ± 2.53	14.8 ± 2.63 *
Et (cm/s)	13.8 ± 3.00	15.8 ± 3.20	15.9 ± 2.24
At (cm/s)	8.83 ± 2.74	9.50 ± 3.40	10.4 ± 2.54
PAS (mmHg)	23.6 ± 5.52	25.4 ± 5.93	24.4 ± 4.27
IVC (cm)	1.30 (0.90 - 1.40)	1.40 (0.80 - 1.60)	1.40 (1.20 - 1.60)

Values expressed as mean and standard deviation or median and 25th and 75th percentiles. RV: right ventricle; EDV: end diastolic volume; ESV: end systolic volume; TAPSE: tricuspid annular plane systolic excursion; St: myocardial systolic velocity at the basal tricuspid annulus by tissue Doppler imaging; Et and At: early and late myocardial diastolic velocity at the basal tricuspid annulus by tissue Doppler imaging, respectively; PAS: pulmonary artery systolic pressure; IVC: inferior vena cava diameter.: p<0.05 vs. Healthy; #: p<0.05 vs. Anemia (ANOVA and Tukey).*

dysfunction secondary to hemochromatosis in thalassemia major patients. Although magnetic resonance with the T2* technique remains the gold standard for early diagnosis of cardiac hemochromatosis[3,6,7,36], echocardiography can be used as a screening method. Due to its low cost and widespread availability, echocardiography is also a valuable instrument for monitoring patient evolution by permitting structural and functional cardiac parameter comparisons at different moments.

Our study presents some limitations such as the small number of individuals and no availability of strain and speckle tracking data; however, inclusion of a control group with iron deficient anemic patients, to differentiate the effects of anemia and iron overload in the heart, strengthens the already high probability that the alterations found in the Thalassemia group are due to cardiac hemochromatosis.

In summary, conventional Doppler echocardiography and tissue Doppler allow to identify left ventricular diastolic alterations in asymptomatic patients with thalassemia major.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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