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Relationship between color M-mode echocardiography flow propagation and cardiac iron load on MRI in patients with thalassemia major

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PURPOSE
Myocardial iron overload remains an important problem and results in cardiac dysfunction in patients with thalassemia major (TM). The ratio of color M-mode flow propagation velocity to early diastolic transmitral flow velocity (E/Vp) in echocardiography is a marker of increased left ventricular filling pressure, which is independent of preload, afterload, and heart rate. We examined the relationship between E/Vp and iron loading in patients with TM using cardiac magnetic resonance imaging (MRI).

MATERIALS AND METHODS
Twenty-one TM patients and 21 age-matched healthy controls were enrolled in the study. Transmitral flow, pulmonary vein velocities, and Vp were obtained by two blinded echocardiographers. Left ventricular isovolumetric relaxation time (IVRT) was measured in the apical long axis by echocardiography. All patients also underwent MRI for cardiac T2* evaluation of iron overload. An increased E/Vp was defined as >1.5.

RESULTS
The E/Vp ratio was increased in TM patients compared with control subjects (1.7±0.4 and 1.2±0.2, $P < 0.01$, respectively). There was no correlation between E/Vp and cardiac T2* value. E/Vp was significantly correlated with IVRT (r=0.51, $P = 0.02$). In addition, the cardiac T2* value was comparable in patients with an E/Vp >1.5 and E/Vp ≤1.5 (21.1±9.8 ms vs. 22.3±8.0 ms, $P = 0.80$, respectively).

CONCLUSION
E/Vp may be a marker of diastolic abnormality that is independent from myocardial iron load in TM patients with preserved left ventricular function.

Key words: • *thalassemia major* • *iron overload* • *magnetic resonance imaging* • *Doppler echocardiography*

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Beta-thalassemia, or thalassemia major (TM), is an inherited hemoglobin disorder and usually requires regular and frequent blood transfusions (1). As a consequence of frequent blood transfusions, iron deposition in the heart may cause severe cardiac complications (2). Despite advances in chelation therapy, cardiovascular complications remain the main cause of mortality and morbidity in TM patients (3).

Previous studies have shown that diastolic functions are impaired in the early phase of TM, despite normal systolic functions (4). Transthoracic echocardiography may be helpful in evaluating diastolic functions. Evaluating diastolic dysfunction by transmitral flow patterns and tissue Doppler imaging (TDI) methods is limited because of dependence on age, heart rate, and loading conditions (5). However, the ratio of color M-mode flow propagation velocity to early diastolic transmitral flow velocity (E/Vp) has been proposed as a preload-independent measure for estimating left ventricular (LV) filling pressures (6). An E/Vp of >1.5 is highly specific and sensitive for estimating pulmonary capillary wedge pressure (PCWP) and left ventricular end-diastolic pressure in heterogeneous groups, including patients with heart failure, coronary heart disease, cardiomyopathies, and atrial fibrillation (7–10).

Cardiac T2* is a magnetic resonance imaging (MRI) based measurement of iron loading and is more sensitive and specific for predicting iron loading than plasma ferritin levels and liver T2* values (11). The main disadvantage of the cardiac T2* method is its limited availability and high cost. Although previous studies have evaluated the relationship between cardiac T2* MRI and echocardiographic measurements, such as mitral inflow parameters and TDI, the association of E/Vp with cardiac T2* values has not been investigated. One study evaluated E/Vp in TM patients and found a positive correlation between E/Vp and brain natriuretic peptide (BNP) levels (12). The purpose of the study described herein was to determine whether E/Vp is affected by iron load and to describe the relationship between E/Vp and cardiac T2* values in TM patients.

Materials and methods

Study population

Twenty-one patients (13 males; mean age, 23±8 years) with a diagnosis of TM and 21 age-matched healthy control subjects were prospectively enrolled in the study. Informed consent was obtained from all participants, and the study was approved by the local ethical committee. The diagnosis of TM was based on hemograms, blood smears, hemoglobin electrophoresis data, and clinical evaluations. The patients had been regularly transfused (every 3–4 weeks) and had received chronic chelation therapy (desferoxamine or deferiprone).

Exclusion criteria

None of the patients enrolled in the study had diabetes mellitus, hypertension, systolic heart failure, or documented coronary heart disease. Patients who had restrictive, hypertrophic or dilated cardiomyopathies, congenital heart disease, or atrial fibrillation were not included in the study.

Echocardiography

Echocardiographic examinations were performed with a Philips EnVisor C HD ultrasound machine (Royal Philips Electronics, Bothell, Washington, USA) with a 2.5 MHz transducer. Timing of echocardiography was adjusted to the last blood transfusion and was performed at least two weeks after blood transfusion.

Conventional echocardiography

Cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography (ASE) by M-mode, two-dimensional echo and Doppler (13). Ejection fraction was measured using a modified Simpson method from the apical four-chamber view. LV diastolic filling patterns were determined by mitral inflow pulsed wave (PW) Doppler examination. In the apical four-chamber view, the Doppler sample was placed in the middle of the LV inflow tract 1 cm below the plane of the mitral annulus between the mitral leaflet tips, where maximal flow velocity in the early diastole was recorded (14). Peak E and late A transmitral filling velocities, the E/A ratio, and deceleration time (DT) were assessed by PW Doppler echocardiography. Isovolumetric relaxation time (IVRT) was measured from the apical long axis as the time from the aortic valve closure in pulsed Doppler to the onset of diastolic flow velocity. Pulmonary venous flow velocity was routinely recorded by placing a sample volume of approximately 1 cm^3 into the right superior pulmonary vein (15). Pulmonary vein systolic (Ps), diastolic (Pd), S/D ratio, atrial reversal (Ra), and duration of flow at atrial contraction (Ra) were recorded. When a biphasic Ps was detected, the highest peak velocity was used (11).

Color M-mode propagation velocity

The propagation velocity (Vp) of early flow into the LV cavity was measured using color M-mode, from the four-chamber view, after aligning the cursor in the direction of the inflow jet from the mitral annulus in the early diastole to 4 cm distal to the LV cavity. The E/Vp was defined as the ratio of mitral peak E-wave velocity to Vp (Fig. 1). Two echocardiographers who were blinded to the patients' clinical and laboratory data interpreted each echocardiographic examination independently. To assess intra-observer variability, echocardiographic measurements of 20 patients were repeated the following day. Intra- and inter-observer variability for E/Vp were calculated to be 5.9% and 7.2%, respectively. All echocardiographic recordings were obtained during normal respiration in dim light.

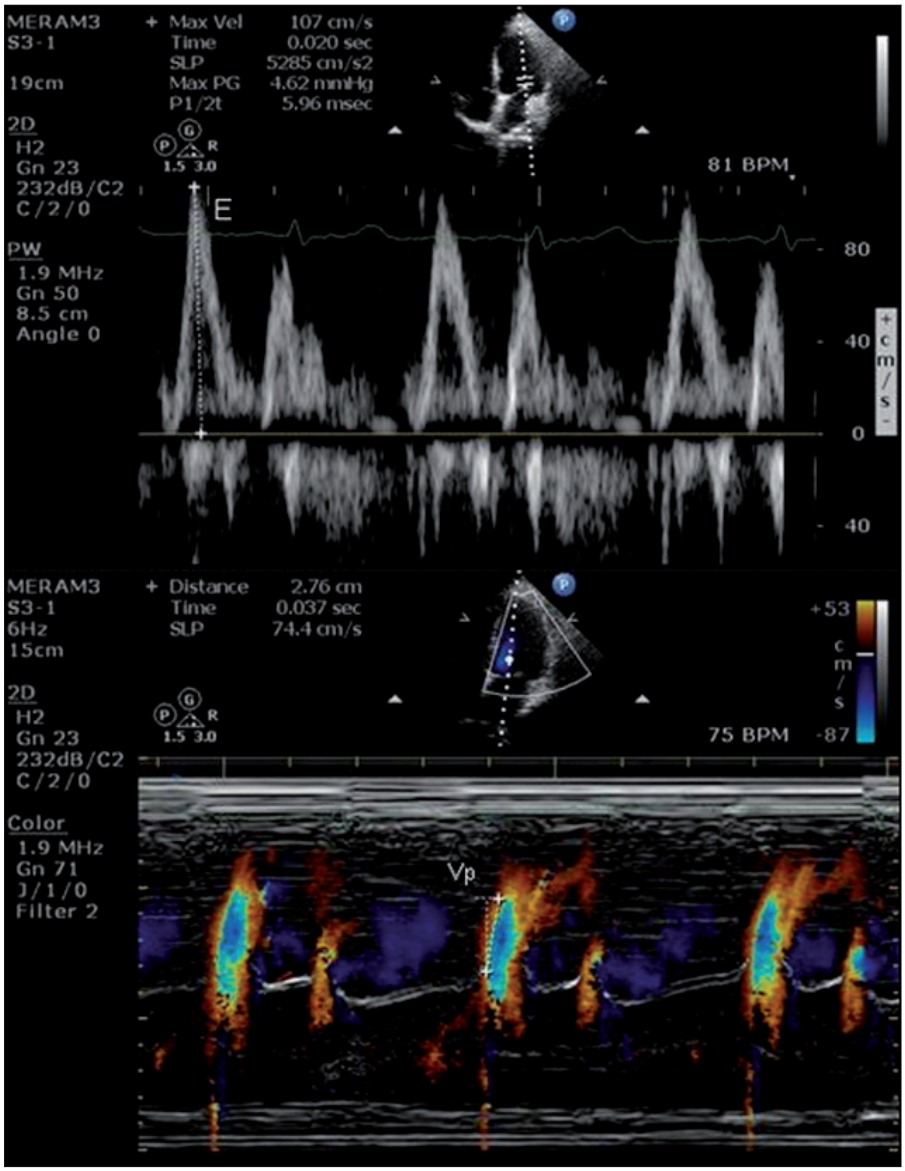

Figure 1. Measurement of color M-mode flow propagation velocity and the E/Vp ratio (E/Vp ratio=107/74=1.45).

Cardiac MRI

Iron loading in the heart was evaluated using MRI T2* property. MR images were acquired for all patients with a single imager equipped with a 1.5 T magnet (Siemens Medical Solutions, Symphony, Erlangen, Germany). Body phased array coils to image a single 10 mm mid-ventricular short axis slice at eight echo times (ranging from 3 ms to 21 ms, with increments of 2.6 ms) with ECG gating and breath hold were also utilized. A gradient-echo sequence was used (flip angle, 35°; matrix, 128×256). Double inversion recovery pulses were

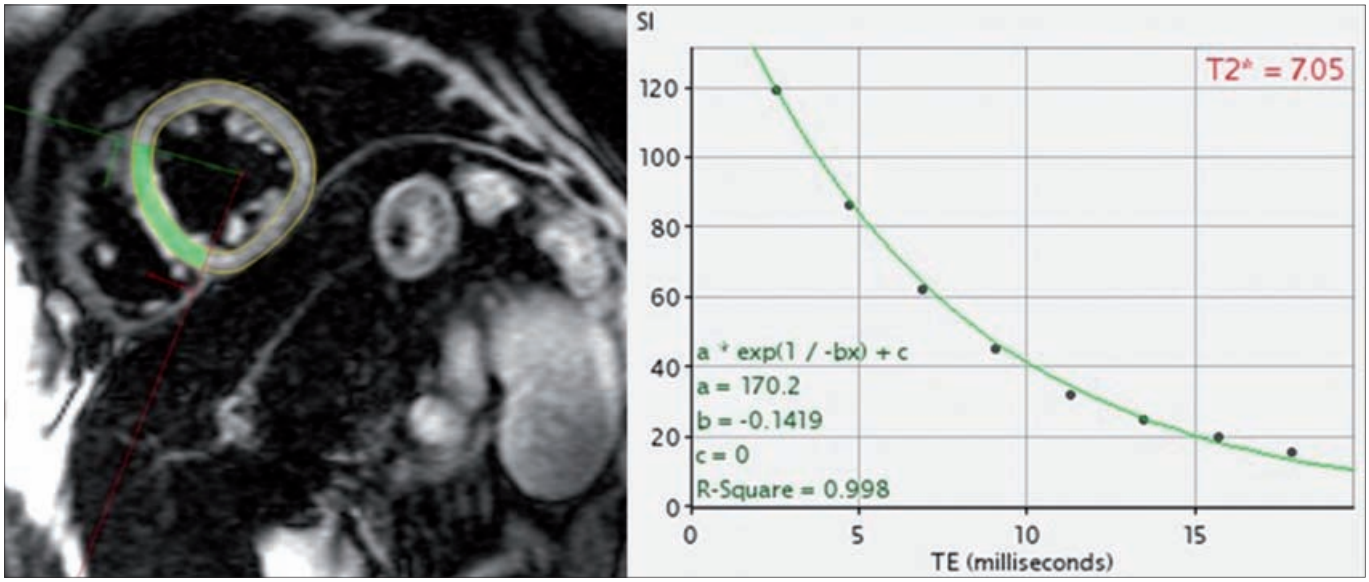

Figure 2. A short axis midventricular cardiac MR image. A full-thickness region of interest was measured in the left ventricular myocardium, encompassing both epicardial and endocardial regions. The T2* value is 7.05 and represents iron overload.

applied to suppress the blood signal, and data were acquired every other cardiac cycle. The monoexponential decay model and the nonlinear curve fitting algorithm were used to fit the curve to obtain T2 measurements (Fig. 2). We used cardiac MR Tools software (http://www.cmrtools.com) for quantification.

Statistical analysis

All statistical analyses were performed with a software (Statistical Package for Social Sciences, version 15.0, SPSS Inc, Chicago, Illinois, USA). All data are expressed as the mean±standard deviation. Differences between parametric variables of two groups were assessed using Student *t* test. The linear association between parametric variables was assessed using Pearson's correlation analysis. A x^2 test was used for comparing categorical variables in two groups. A *P* value <0.05 was considered statistically significant.

Results

The baseline characteristics of the patients and control group are listed in Table 1. There were no significant differences between the TM group and healthy subjects in terms of age, gender, body-mass index, or blood pressure levels. Hemoglobin (Hb) and hematocrit (Hct) levels were significantly lower in the TM group than in the control group (Table 1). The heart rate was significantly elevated in TM patients compared with controls (86±9 bpm vs. 75±8 bpm, *P* = 0.001) (Table 1).

Conventional echocardiographic parameters

LV dimensions and systolic functions performed by two-dimensional echocardiography were similar in both groups (Table 2). Left atrial diameters were enlarged in TM patients compared with controls (3.6±0.3 mm vs. 3.3±0.5 mm, *P* = 0.04, respectively). E waves were higher in the TM group than in the control group (114±17 cm/s vs. 83±16 cm/s, *P* = 0.01). The E/A ratio was also greater in the TM group compared with the control group (1.7±0.5 vs. 1.2±0.2, *P* = 0.01). LV IVRT was significantly prolonged in patients with TM compared with controls (71±12 ms and 54±9 ms, *P* = 0.01). Pulmonary peak systolic velocity (Ps) and reverse atrial velocity (Ra) were similar in both groups, whereas peak pulmonary diastolic velocity was significantly elevated in the TM group compared with the control group (59±16 ms vs. 49±7 ms, *P* = 0.05). The Ps/Pd ratio was similar between groups. There were no significant differences between the groups with regard to the

Table 1. The clinical, demographic, and laboratory characteristics of the study population

	TM (n=21)	Control (n=21)	*P*
Age (years)	27±8	29±3	NS
Gender (female/male, n)	13/8	16/5	NS
BMI (kg/m^2)	23±2.0	24±1.6	NS
SBP (mmHg)	120±14	121±12	NS
DBP (mmHg)	82±5	71±4	NS
Heart rate (bpm)	86±9	75±8	0.01
Hemoglobin (g/dL)	10.4±1.3	13.3±1.2	0.001
Hematocrit (%)	34.3±6.6	44.2±2.6	0.001
Cardiac T2* (ms)	21.7±9.3		
Chelation therapy (%)	100		

TM, thalassemia major; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

other conventional echocardiographic parameters (Table 2).

Color M-mode flow propagation velocity

Vp was similar between groups (73±18 cm/s vs. 68±13 cm/s, $P = 0.56$). The E/Vp ratio was significantly higher in TM patients compared with healthy subjects (1.7±0.4 vs. 1.2±0.2, $P = 0.01$) (Fig. 3). Increased E/Vp (>1.5) was found in 52.4% (n=11) of the TM patients, whereas only one patient had an increased E/VP in the control group. E/Vp was significantly correlated with IVRT (r=0.51, $P = 0.02$) (Fig. 4) and was positively correlated with both transmitral A velocity and pulmonary reverse atrial velocity (Ra) (r=0.56, $P = 0.01$ and r=0.50, $P = 0.02$, respectively). In addition, E/Vp was negatively correlated with Ra duration (r=-0.65, $P = 0.01$).

Table 2. The conventional and color M-mode echocardiographic parameters in patients with TM and healthy controls

	TM (n=21)	Control (n=21)	*P*
IVS (cm)	0.9±0.15	0.9±0.14	NS
PW (cm)	0.9±0.16	0.9±0.11	NS
LVEDD (cm)	4.8±0.5	4.6±0.3	NS
LVESD (cm)	2.8±0.3	2.7±0.3	NS
LA diameter (mm)	3.6±0.3	3.3±0.5	0.04
EF (%)	62±2	63±3	NS
E (cm/s)	114±17	83±16	<0.01
A (cm/s)	69±20	67±11	NS
E/A	1.7±0.5	1.2±0.2	<0.01
DT (ms)	149±27	168±40	NS
Vp (cm/s)	68±13	73±18	NS
E/Vp	1.7±0.4	1.2±0.2	<0.01
Ps (cm/s)	59±9	56±7	NS
Pd (cm/s)	59±16	49±7	0.05
Ps/Pd	1.0±0.3	1.1±0.1	NS
Ra (cm/s)	30±3.0	29±3.3	NS
Ra duration (s)	108±31	93±15	0.07
PAP (mmHg)	27±5	25±3	NS
LV IVRT (ms)	71±12	54±9	0.01

TM, thalassemia major; IVS, interventricular septum; PW, posterior wall; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrium; EF, ejection fraction; DT, deceleration time; PAP, pulmonary arterial pressure; LV IVRT, left ventricular isovolumetric relaxation time; NS, not significant.

Table 3. Correlation and statistical significance of the echocardiographic parameters to cardiac T2* values

Echocardiography findings	r	*P*
Mitral E	-0.26	0.24
Mitral A	-0.21	0.41
E/A	-0.24	0.36
DT	0.21	0.36
E/Vp	0.03	0.86
IVRT	0.16	0.28

DT, deceleration time; IVRT, isovolumetric relaxation time.

Cardiac T2 MRI values*

Cardiac T2* MRI revealed abnormal myocardial iron load (T2* <20) in 40% of the TM patients, with a mean cardiac T2* value of 21.7±9.3 ms. The cardiac T2* was below 20 ms in 11 patients and below 10 ms in four patients. There was no linear association between cardiac T2* value and E/Vp ratio (Fig. 5). Furthermore, the cardiac T2* values were not correlated with IVRT or other Doppler findings (Table 3). The mean cardiac T2* value of TM patients with an elevated E/Vp was similar to that from the normal E/Vp groups (21.1±9.8 ms vs. 22.3±8.0 ms, $P = 0.80$).

Discussion

The present study demonstrated that the E/Vp ratio in patients with TM was impaired and that it was not related with the cardiac T2* value. The IVRT was significantly correlated with the E/Vp. Thus, the E/Vp was associated with LV diastolic function independently from myocardial iron load in patients with TM. To the best of our knowledge, this is the first study to assess the relationship between the cardiac MRI T2* value and echocardiography flow propagation properties in TM patients.

Cardiac disorders start early in TM patients' lives, and early detection of cardiac involvement is important. TM patients require regular and frequent blood transfusions, which may cause excessive iron load in the heart and lead to cardiovascular events (16). The cardiac T2* MRI technique is a unique and sensitive method for determining iron overload in the heart (17). A cardiac T2* value of less than 20 ms indicates iron overload (18). In a cross-sectional study of 30 patients presenting with heart failure, 89% of cases had a cardiac T2* <10 ms (19). There is a progressive decline in myocardial systolic and diastolic functions below this value. The mean cardiac T2* value was above 20 ms and the number of patients with severe iron load (T2* <10

ms) was limited in the present study (20). However, cardiovascular involvement may develop in patients with TM without cardiac iron overload (21).

Cardiac involvement can also be monitored by echocardiography (M-mode, PW Doppler, and TDI). Diastolic dysfunction usually precedes systolic dysfunction and is mainly attributed to iron deposition in the heart (22). Iron overload may lead to apoptosis, fibrosis, and oxidative stress in the myocardial tissues, and therefore, diastolic functions may be impaired (2). It has been demonstrated that despite worsening relaxation, E waves increase as a result of increasing filling pressures (pseudonormalization), but Vp does not (6). This phenomenon suggests preload independence. The first Vp studies were performed in canines, and significant preload alterations did not significantly change propagation velocity (23). Recently, preload independence has also been demonstrated in human patients with and without left ventricular systolic dysfunction (22). Invasive studies in humans have also shown a consistent high-inverse correlation between the isovolumetric time constant of relaxation (τ) and Vp (22). E/Vp is the most widely used index for estimating PCWP and is load independent (24). The positive and negative predictive values for an E/Vp >1.5 at predicting PCWP greater than 12 mmHg have been reported as 93% and 70%, respectively (7). In the present study, more than 50% of patients had an E/Vp >1.5, but were asymptomatic. A possible explanation for this condition was related to compensation of increased LV filling pressure by a higher heart rate.

Chryshoou et al. (12) have investigated the value of the E/Vp ratio in patients with TM. However, their study did not examine cardiac iron load using MRI. They found a strong positive linear relationship between the E/Vp ratio and BNP levels, reflecting diastolic abnormalities in young patients with increased preload but preserved systolic function. With regard to the present study, IVRT was positively correlated with the E/Vp ratio. Along with the increase in the E/Vp ratio, transmitral A velocity and pulmonary Ra velocity, which are indirect indicators of increased left atrial pressure, were increased. In addition, a negative correlation of the E/Vp with Ra duration

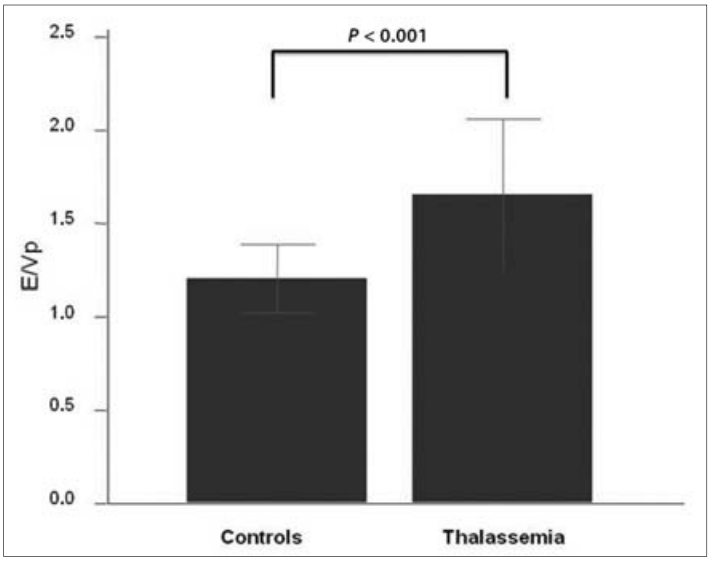

Figure 3. Comparison of E/Vp values between thalassemia patients and healthy controls.

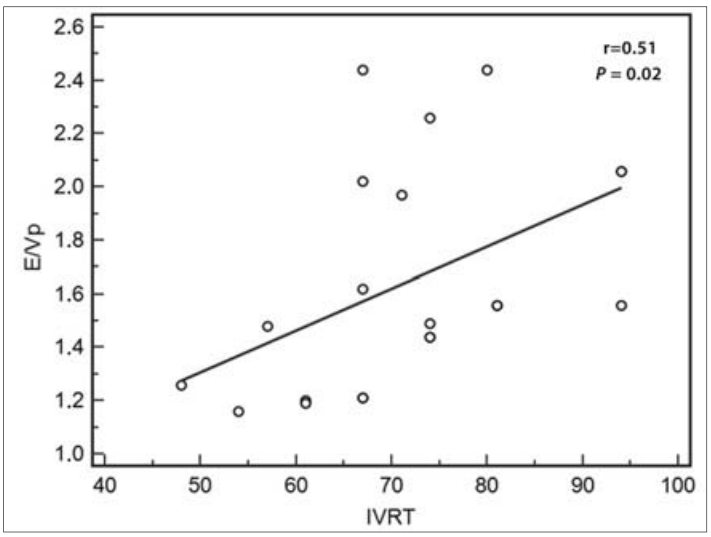

Figure 4. Correlation between the E/Vp and IVRT.

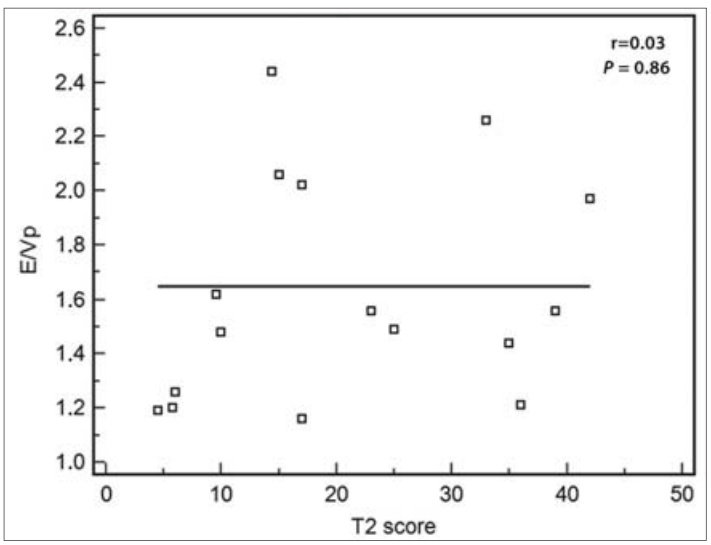

Figure 5. Correlation between the E/Vp and T2* values.

was related to the compensation of increased LV filling pressure by a higher heart rate. A possible explanation for increased Pd velocity in the TM group may be attributed to increased left atrial pressure, which may lead to shortened pulmonary systolic emptying. Although E/Vp consistently correlated with indirect indicators of LV filling pressure, there was no correlation with cardiac iron load using MRI.

Controversial results were found in TDI studies in terms of relationship between TDI and cardiac T2* in TM patients. Although some of these studies have demonstrated a significant correlation (25–27), others have not (11, 28). The main limitation of TDI parameters is their dependence on heart rate. Because of the anemic state of patients with TM, the heart rate is usually increased and TDI parameters are affected. Therefore, we used the E/Vp because it is independent of load and heart rate and analyzed the relationship between the E/Vp with cardiac MRI T2* values. One limitation of our analysis is the heterogeneity of the above-mentioned studies. We speculate that the different ratios of TM patients with overt heart failure, impaired mild to moderate LV systolic dysfunction and preserved LV systolic function may have influenced the iron load assessments and echocardiographic measurements. The small sample size used in these studies did not allow for subgroup identification. Therefore, we preferred to study a homogenous group that did not include patients with LV impairment. However, we did not find any relationship between the E/Vp and iron load by cardiac MRI in patients with preserved LV functions. These results should be tested in moderate and severe LV dysfunction groups. Lastly, all TM patients in our study were undergoing chelation therapy. Although chelation therapy may reduce iron overload, there is no evidence regarding fibrosis reversal in these patients. It is unknown whether fibrosis due to iron overload is a reversible event. Therefore, diastolic functions may be impaired because of iron overload even in asymptomatic TM patients (T2* ≥20 ms).

A few potential limitations of this study should also be mentioned. The main limitation is that this study was a cross-sectional study with a small sample size. Despite detection of impaired E/Vp ratios in TM patients when compared with controls, our study did not look at clinical outcomes. Thus, longitudinal, follow-up studies with larger sample sizes to investigate whether abnormal E/Vp ratios translate into clinical outcome and predict future heart failure and cardiac events are needed. Also, the E/Vp was evaluated in patients with preserved LV functions according to echocardiographic evaluation. These results should be tested in patients with moderate or severe LV dysfunction. The present study may be accepted as a pilot study in this area.

In conclusion, we showed that the E/Vp is markedly impaired in patients with TM compared with controls, despite the asymptomatic status of the patients. The impaired E/Vp ratio was independent from cardiac T2* values obtained using MRI in patients with preserved LV systolic functions. The E/Vp may be a useful marker of abnormal LV filling and early diastolic impairment in patients with TM.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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