The relationship between the myocardial T2* value and left ventricular volumetric and functional parameters in thalassemia major patients

Selen Bayraktaroğlu, Yeşim Aydinok, Dilek Yıldız, Hatice Uluer, Recep Savaş, Hüdaver Alper

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halassemia major (TM) is an inherited hemoglobin disorder caused by impaired synthesis of the beta-globin chain, resulting in chronic hemolytic anemia (1). TM is particularly prevalent among individuals from Mediterranean countries. In Turkey, according to an official report, approximately 4000 transfusion-dependent patients have homozygous beta-thalassemia (2). Lifelong blood transfusions lead to iron overload and toxicity, which results in severe endocrine, liver, and cardiac dysfunctions (1, 3, 4). Cardiac involvement in TM is mainly characterized by left ventricular dysfunction caused by iron overload, which leads progressively to heart failure (5−8). Cardiac complications are reported to cause 50%−70% of deaths in patients with TM, making the heart the lethal target organ (8). Myocardial iron deposition leads to cardiomyopathy and heart failure, which can be reversed if aggressive chelation is begun early (9). Several methods for predicting heart failure have been used, such as time-averaged serum ferritin levels, the liver iron concentration, and echocardiographically measured left ventricular functions. However, these methods identify patients at risk at a late stage (8). Cardiovascular magnetic resonance (CMR) imaging is used as a noninvasive method to evaluate the amount of iron in the heart. Myocardial iron deposition can be assessed using the spin echo (T2) and gradient echo (T2*) techniques (10). The magnetic resonance imaging (MRI) relaxation parameters T2 and T2* are used to determine cardiac iron loading in patients with TM (11−13). Recently, T2* CMR imaging with a single slice approach has been validated as a quantitative method for evaluating myocardial iron overload (11, 12).

The aim of this study was to evaluate the relationship between the myocardial T2* value and left ventricular volumetric and functional parameters and to examine the associations between the degree of cardiac iron load and various clinical parameters.

PURPOSE
Cardiac involvement in thalassemia major (TM) is mainly characterized by left ventricular dysfunction caused by iron overload. Cardiovascular magnetic resonance imaging (MRI) including myocardial T2* measurement is becoming increasingly popular for quantitatively evaluating myocardial iron overload. The aim of this study was to evaluate the relationship between the myocardial T2* value and left ventricular functional parameters and to examine the associations between the degree of cardiac iron load and various clinical parameters.

MATERIALS AND METHODS
A retrospective analysis of 47 patients (25 males and 22 females; mean age, 23.0±5.4 years) with TM was performed. Myocardial iron load was assessed by T2* measurements, and volumetric functions were analyzed using the steady state free precession sequence.

RESULTS
In patients with myocardial iron deposition (T2* <20 ms), the mean left ventricular ejection fraction (LVEF) was 64.7±4.94%. The LVEF of patients with myocardial siderosis was significantly lower than that of patients without myocardial siderosis (r=0.35, P = 0.014). Inverse and significant correlations between both the left ventricular (LV) end-systolic volume index and the LV end-diastolic volume index and the myocardial T2* value (r=-0.32, P = 0.027 and r=-0.29, P = 0.046, respectively) were observed. There was an inverse correlation between the myocardial T2* value and the liver iron concentration (r=-0.31, P = 0.037). Cardiac T2* was not associated with serum ferritin levels, pre-transfusion hemoglobin levels or the annual red cell consumption rate.

CONCLUSION
Myocardial iron load assessed by cardiac MRI (T2*) is associated with deterioration in left ventricular function. Thalassemia major patients with myocardial siderosis may have LVEF values within normal limits, but this result must be interpreted cautiously.

Key words: • magnetic resonance imaging • iron overload • left ventricle

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therapy with DFO and DFP. Previous medical history of splenectomy was retrieved from medical records. Patient characteristics are summarized in Table 1. Patients with cardiac or vascular anomalies (congenital heart disease, valve disease, etc.) were not included in the study. Two patients had a prior history of heart failure and were taking cardiac medications. However, at the time of screening, they were scored as Class I according to the New York Heart Association Functional classification (14).

This study was approved by the local Research Ethics Committee.

Magnetic resonance imaging

All MRI examinations were performed with a 1.5 Tesla (T) scanner (Symphony, Siemens, Erlangen, Germany). The scans included measurement of the liver R2 value; the myocardial T2* value and left ventricular (LV) functions, volumes, and mass. The scan duration was 45 min. The T2* of heart was assessed by a cardiac-gated single breath-hold multiecho technique (FOV, 400 mm; TR, 135 ms; TE, 2.6–22.3 ms [8 echo times]; flip angle, 20; slice thickness, 10 mm; matrix, 192×75; number of averages, 1; bandwidth in Hz/pixel, 810).

Short axis cine images were acquired with a breath-hold steady state free precession (SSFP) sequence and were used for the ventricular volume and mass analysis. The heart was sectioned into 7-mm slices with a 3-mm gap from the atrioventricular ring to the apex.

Liver R2 values were assessed by the spin-density projection-assisted (SDPA) method (15). Phased array torso coils were used for signal detection. Axial images through the liver were acquired with a multislice single spin-echo (SSE) pulse sequence (FOV, 400; TR, 2500 ms; TE, 6 ms, 9 ms, 12 ms, 15 ms, 18 ms; slice thickness, 5 mm; interslice gap, 5 mm; resolution, 256×100; number of averages, 1). No fat suppression was used. A 1000-mL bag of normal saline solution was imaged with each subject to provide an external long T2 reference for the correction of instrumental gain drift. Slices covering the whole liver were collected for each subject. The MR scanner was validated using a FerriScan Phantom prior to study, and the validation procedure was repeated quarterly.

MRI analysis

T2* analysis was conducted using Thalassemia Tools (Cardiovascular Imaging Solutions, London, UK). A full-thickness region of interest (ROI) was drawn in the interventricular septum. The signal intensity of this region for each echo time was measured and plotted as an exponential signal decay curve (Fig. 1). The lower limit of normal for T2* in the detection of myocardial iron deposition has been reported as 20 ms, and this value was used as the cut-off in this study (10). Patients with T2* >20 ms were considered to be free of cardiac iron overload, while patients with T2* ≤20 ms were deemed to have cardiac iron overload.

Ventricular volumes, mass and ejection fractions were analyzed with CMRtools (CMRtools, Cardiovascular Imaging Solutions). The endocardial and epicardial borders were outlined during the cardiac cycle in the short axis slices, and then the mitral and aortic valve planes were tracked. Papillary muscles were subtracted by the program. LV end-diastolic and end-systolic volumes, ejection fraction (LVEF) and mass were measured. The body habitus may be below average in TM patients, so all parameters were indexed to the body surface area. The normal ranges for LV volumes and function were obtained from the published data for TM patients with normal myocardial iron (16). The lower limit of normal for EF was considered to be 59%, and normal ranges for the LV end-systolic volume index (LVESVi) was 13–34 mL/m² and that for the LV end-diastolic volume index (LVEDVi) was 45–152 mL/m².

To measure the liver iron concentration (LIC), the SDPA method was used (also known as FerriScan®) (15). The liver scans obtained from each patient were submitted online and analyzed by FAST (FerriScan® Analysis Services Tracking System). Determination of the liver iron concentration was performed by R2 MRI, using established methodology (17). An LIC >1.6 mg Fe/g of dry tissue is indicative of hepatic siderosis (18). The LIC measurement...
data were collected from the medical records. These data were available for 44 patients. Liver MRI scans and cardiac MRI examinations were performed on the same day.

Statistics

Statistical analysis was performed using a computer software (Statistical Package for Social Sciences version 15.0, SPSS Inc., Chicago, Illinois, USA). Except for T2*, each parameter was calculated as mean±standard deviation (SD). T2* is shown as a geometric mean (to normalize the data, a log transformation of the data was performed). Correlations between the myocardial T2* value and left ventricular functional parameters, the serum ferritin level and the LIC were calculated by Spearman’s rank test.

The parameters observed at different levels of T2* were compared using one-way ANOVA (analysis of variance). Statistical significance was set at P < 0.05.

Results

The mean cardiac T2* was 14.1 ms in this cohort of patients. Myocardial iron loading was observed in 30 of the 47 patients (63.8%). In TM patients with normal myocardial T2* values (T2* ≥20 ms), the LVEF was 68.94±4.71%, and was within the normal range for all patients. In patients with myocardial iron deposition (T2* <20 ms), the mean LVEF was 64.73±4.94% (Fig. 2), which was significantly lower (r=0.35, P = 0.014) compared to the LVEF in patients without myocardial iron loading.

An inverse and significant correlation between the LVESVi and the myocardial T2* value (r=-0.32, P < 0.05) was observed (Fig. 3). Similarly, a significant inverse correlation was present between the LV end-diastolic volume index and the myocardial T2* value (r=-0.29, P = 0.046). There was no significant correlation between cardiac T2* and the LV mass index.

There was an inverse correlation between the myocardial T2* value and the LIC (r=-0.31, P = 0.037). Cardiac T2* was not associated with the serum ferritin level, the pre-transfusion hemoglobin level or the annual red cell consumption rate.

Three of the 30 patients with myocardial siderosis (10%) had an LVEF below the lower limit of the normal range. The mean LVEF of these three patients was 57.33±1.1%, and the mean myocardial T2* value was 8.00±3.6 ms. All three patients had undergone a splenectomy. The LIC of these patients ranged from 22.8 to 18.4 mg Fe/g of dry tissue (mean LIC, 19.66±2.08 mg Fe/g of dry tissue). The serum ferritin level ranged from 1686 to 5055 ng/mL (mean serum ferritin, 3696±1776 ng/mL).

When the patients were divided into three categories based on their cardiac T2* values (>20, 10–20, <10), a decrease in the mean LVEF was correlated with an increase in myocardial siderosis (P = 0.018) (Fig. 4, Table 2). There was no difference between groups with respect to the serum ferritin level, the pre-transfusion hemoglobin level, the annual red cell consumption rate, the LIC, the LVEDVi, the LVESVi, or the LV mass index (Table 2).

The mean LIC was 25.5±27.5 mg Fe/g of dry tissue. The LIC derived from the R2 method was correlated with the serum ferritin level (r=0.650, P = 0.0001). However, an inverse correlation was observed between the myocardial T2* value and the LIC (see above); the LIC was not associated with the LVEF (r=0.005, P = 0.974).

Discussion

Cardiac complications such as heart failure and arrhythmias are the significant causes of death in TM patients. Although heart dysfunction in TM patients is multifactorial in origin, heart failure is mainly attributed to iron toxicity (19). In TM, the iron overload results from both excessive iron absorption from the gastrointestinal system and repeated blood transfusions. Transfusional iron is deposited in the reticuloendothelial system (RES); after the stores of the RES are saturated, iron deposition increases in parenchymal tissues such as endocrine glands, hepatocytes and the myocardium (20, 21). In the heart, intracellular lysosomes store the relatively nontoxic iron forms hemosiderin and ferritin; however, once this storage capacity is

### Table 1. Patient characteristics

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<td>Age (years)</td>
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<td>Body surface area (m²)</td>
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<th>Hematological profile</th>
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<td>Serum ferritin (ng/mL)</td>
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<td>Pre-transfusion hemoglobin (g/dL)</td>
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<td>Splenectomy (%)</td>
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<td>Mean splenectomy age (years)</td>
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<td>Annual red cell consumption (mL/kg/year)</td>
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<th>MRI parameters</th>
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<td>Cardiac T2* (ms), geometric mean</td>
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<td>LV ejection fraction (%)</td>
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<td>LV end-diastolic volume index (mL/m²)</td>
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<td>LV end-systolic volume index (mL/m²)</td>
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<td>LV mass index (g/m²)</td>
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<td>Liver iron concentration (mg Fe/g of dry tissue)</td>
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*All data are mean±standard deviation. T2* is shown as a geometric mean.

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exhausted, nontransferrin-bound iron, which is highly toxic, can be released, leading to hydroxyl radical formation and impaired function of the mitochondrial respiratory chain. This process manifests itself clinically as cardiac failure (5, 21). Left ventricular dysfunction and symptomatic heart failure develop at an advanced stage of cardiac siderosis. At that stage, the treatment is difficult, and the prognosis is poor (9, 22).

In the literature, there are reported echocardiographic studies evaluating several functional and volumetric parameters in thalassemia patients (23, 24). MRI techniques have recently been used to detect myocardial iron load and cardiac function (9, 10). In this study, we evaluated the relationship between myocardial iron loading and LV function. We used myocardial T2* and functional CMR imaging, which are considered to be the gold standard for assessment of cardiac iron loading and cardiac function. Myocardial iron loading was found in 63.8% of our patients. This finding is similar to those findings for Caucasian populations (10, 25).

The normal reference ranges of the left ventricular volumes and function in TM patients without cardiac iron load differ significantly from those values of healthy non-anemic controls. TM patients have greater left ventricular ejection fractions than controls (16). Thalassemia patients have impaired left ventricular function at higher values of LVEF than previously thought (9, 25). This factor is important in the interpretation of the impaired ejection fraction. We used a cut-off value for left ventricular impairment of 59%. We found a normal LVEF in patients with normal myocardial T2* values, but we detected a progressive decrease in the LVEF with increasing myocardial siderosis. Left ventricular dysfunction was present in three patients. In all of these patients, the myocardial T2* values were indicative of myocardial siderosis. The mean LVEF of our patients with myocardial siderosis was 64.73±4.94% and was within normal limits. Thus, the accepted normal LVEF value for the general population may represent myocardial siderosis in thalassemia patients. The LVEF results of thalassemia patients must be interpreted cautiously because patients with detectable cardiac iron but normal cardiac function are also at risk of developing heart failure if not treated. Anderson et al. initially described the progressive deterioration in LVEF when the cardiac T2* value fell below 20 ms (10). This finding was confirmed by Tanner et al. (9) and by this study.

In the literature, several reported echocardiography studies have measured the myocardial function in thalassemia patients. In those studies, a significant increase in the LV diameters (LV end-diastolic diameter and LV end-systolic diameter) was detected in thalassemia patients relative to the normal control group (26, 27). Our findings are in accordance with these studies. We detected an inverse correlation between the myocardial T2*
value and both LVESVi and LVEDVi. The increase in the left ventricular volume or diameter in these patients is mainly attributed to the high cardiac output state secondary to chronic anemia (26). The increase in the left ventricular end-systolic volume has been previously considered a precursor of subclinical left ventricular dysfunction (28). In this study, an increase in the LVESVi in TM patients with myocardial siderosis was also detected and may be a subclinical indicator of left ventricular dysfunction.

Serum ferritin levels are used as a major diagnostic tool in the identification and monitoring of iron overload. However, many unexplained deaths have occurred due to cardiac failure in TM patients despite low serum ferritin levels (29). The studies in the literature demonstrate that the relationship between the cardiac T2* value and the serum ferritin level is either non-significant or weak (10, 30). In our cohort, there was no relationship between serum ferritin levels and pre-transfusion hemoglobin levels or annual red cell consumption and between the cardiac T2* value and the LVEF.

These findings are consistent with the literature and suggest that myocardial iron levels cannot be predicted using these parameters. Cross sectional analysis has demonstrated a poor correlation between the cardiac T2* value and the LIC in the literature (10, 31, 32). Despite the significant negative correlation between the heart T2* value and the liver R2 value, the correlation was weak, with a wide scatter of values, indicating that cardiac T2* measurement is essential for predicting cardiac complications and the associated risk of death.

The presented data were analyzed retrospectively, which is a limitation of our study. In addition, these results were obtained using a 1.5 T scanner. Three-tesla magnets are becoming increasingly popular, and further studies using 3 T scanners may develop new approaches to conduct myocardial assessments.

In conclusion, it is important to identify the thalassemia major patients with a risk of iron overloaded cardiomyopathy. This study demonstrated that myocardial iron load assessed by CMR imaging (T2*) is associated with deterioration of the left ventricular function. Thalassemia major patients with myocardial siderosis may have LVEF values within normal limits, but this result must be interpreted cautiously.

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<th>Table 2. Clinical and MRI parameters for different categories of T2* values</th>
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<td>LVEDVi (mL/m²)</td>
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<td>LVESVi (mL/m²)</td>
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<td>LV mass index (g/m²)</td>
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<td>LIC (mg Fe/g of dry tissue)</td>
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LIC, liver iron concentration; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index

Data are presented as the mean±standard deviation.
Conflict of interest disclosure
The authors declared no conflicts of interest.

References
29. Kolnagou A, Economides C, Eracleous E, Kontogiorghes GJ. Low serum ferritin levels are misleading for detecting cardiac iron overload and increase the risk of cardiomyopathy in thalassemia patients. The importance of cardiac iron overload monitoring using magnetic resonance imaging T2 and T2*. Hemoglobin 2006; 30:219–227.