Original Research

Influence of Myocardial Fibrosis and Blood Oxygenation on Heart T2* Values in Thalassemia Patients

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Purpose: To determine whether T2* measurements quantifying myocardial iron overload in thalassemia patients are influenced by myocardial fibrosis and blood oxygenation.

Materials and Methods: Multislice multiecho T2* was performed in 94 thalassemia patients in order to quantify myocardial iron overload. The left ventricle was automatically segmented into a 16-segment standardized heart model, and the T2* value on each segment as well as the global T2* were calculated. Delayed enhanced cardiovascular magnetic resonance (DE-CMR) images were obtained to detect myocardial fibrosis. The blood oxygenation was assessed by the noninvasive measurement of partial pressure of oxygen (pO2).

Results: Myocardial fibrosis was detected in 31 patients (33%). The global T2* value in patients with fibrosis was comparable with that of patients without fibrosis ($P = 0.88$) and T2* values in segments with fibrosis were comparable with those in segments without fibrosis ($P = 0.83$). The global T2* value was not correlated with the pO2 (Spearman's coefficient of correlation = 0.99).

Conclusion: Myocardial fibrosis and blood oxygenation did not significantly affect the T2* values. These data further support the use of heart T2* as equivalent of heart iron in the clinical arena.

Key Words: T2* magnetic resonance; myocardial fibrosis; blood oxygenation; thalassemia
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THALASSEMIA is the commonest genetic disorder worldwide (1). Although the survival of patients with beta thalassemia is good and has been improving in recent years, the prevalence of severe complications is still high and the main cause of morbidity and mortality remains heart failure secondary to iron overload (2). The iron-induced cardiomyopathy is treatable and reversible if intensive chelation treatment is instituted in time (3–5). Then, direct measurement of myocardial iron may allow earlier diagnosis and treatment and help to reduce the mortality due to iron-induced cardiomyopathy.

Magnetic resonance imaging (MRI) allows monitoring iron deposition in a safe and noninvasive way, exploiting the fact that superparamagnetic iron compounds produce susceptibility variability, shortening the T2 and the T2-star (T2*) relaxation time (6). T2* cardiac MRI, with a single measurement in the mid-ventricular septum (7–9) or with a multislice approach (10–12), has been validated as a quantitative evaluation of myocardial iron overload. However, only the multislice, multiecho T2* cardiovascular magnetic resonance (CMR) technique can assess for the detection of the distribution of iron within the whole myocardium (10).

However, T2* heart measurements, in order to quantify myocardial iron burden, could be susceptible to other factors besides tissue iron concentration as myocardial fibrosis and blood oxygenation (13).

Myocardial fibrosis is a common clinical finding in thalassemia patients (14–17) and it can be quantita-

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tively assessed by delayed enhancement (DE) CMR (18,19).

Moreover, in patients with thalassemia the deoxyhemoglobin concentrations and myocardial capillary densities could increase. The T2* is expected to decrease as the concentration of deoxyhemoglobin increases and those effects have been shown theoretically (20) and experimentally (21).

The absolute dominance of myocardial iron concentration over other factors is generally hypothesized in CMR studies of thalassemia patients (22). However, to our knowledge, still no systematic and quantitative study was performed on this issue. The aim of our study was to determine whether T2* measurements quantifying myocardial iron overload in thalassemia patients are influenced by myocardial fibrosis and blood oxygenation.

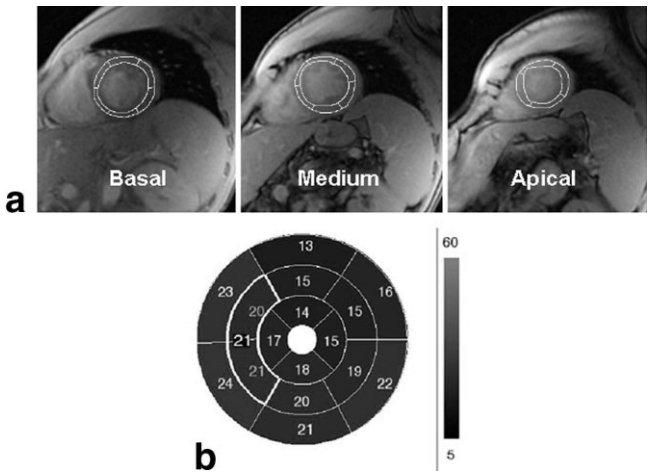

Figure 1. a: Automatic segmentation of each slice in the left ventricle. **b:** Bull's-eye representation of the 16 T2* segmental values in the myocardium.

MATERIALS AND METHODS

Study Population

Ninety-four thalassemia patients (78 with major and 16 with thalassemia intermedia) consecutively sent to our MRI Laboratory (38 males, 7–74 years old, mean age 28.9 ± 10.4 years) were studied retrospectively. All thalassemia major patients had been regularly transfused since early childhood and started undergoing chelation therapy from the mid-to-late 1970s, while patients born after the 1970s received chelation therapy from early childhood. Of the patients with thalassemia intermedia, 14 were regularly transfused, one received sporadic transfusions, and one has been never transfused. Over the last year, the mean serum ferritin level was 1642 ± 1137 ng/mL and the mean pretransfusion hemoglobin was 9.6 ± 0.7 g/dl in the whole population.

CMR scanning was performed within 1 week before the regularly scheduled blood transfusion. None of the patients had decompensated heart failure at the time of the scanning.

The study complied with the Declaration of Helsinki. All patients gave written informed consent to the protocol. The project was approved by the institutional ethics committee.

Cardiovascular Magnetic Resonance

CMR was performed using a 1.5 T MR scanner (GE Excite HD, Milwaukee, WI). An eight-element cardiac phased-array receiver surface coil with breath-holding in end-expiration and ECG-gating was used for signal reception.

For measuring the myocardial iron overload we used a multislice, multiecho T2* approach, as previously described (10–12). Three parallel short-axis views (basal, medium, and apical) of the left ventricle were obtained by a T2* gradient-echo multiecho sequence. Each single short-axis view was acquired at nine echo times (TEs 2.2–20.3 msec with an echo spacing of 2.26 msec) in a single end-expiratory breath-hold to ensure image alignment. The multiecho sequence parameters were as follows: flip angle 25°, matrix 192 × 256 pixels, field of view (FOV) 35 × 35 cm, bandwidth 62.5 kHz, slice thickness 8.0 mm, number of excitations 1, and views per segment 6–8 (depending on heart rate). The repetition time (TR) between the nine radio frequency (RF) pulses applied during each cardiac cycle was 25 msec. A delay time of 10 msec after the R-wave (the positive upward deflection in the QRS complex of an electrocardiogram that follows the Q wave) was chosen in order to obtain myocardial images in a consistent position in the cardiac cycle irrespective of the heart rate. After the delay time, only 20.3 msec were used for the acquisition of the nine k-space segments. This time covered the tele-diastolic phase, which was when heart motion can be negligible (12). Analysis on T2* images was performed by one experienced observer using dedicated software (HIPPO MIOT IFC-CNR) to provide the T2* value on each of the 16 segments of the left ventricle (according to the standard AHA/ACC model (23)) as well as the global T2* value averaged over all segmental T2* values and the T2* value in the mid-ventricular segment averaged over the mid-anterior septum and the mid-inferior septum (Fig. 1). As previously demonstrated, the developed procedure was able to correct for cardiac/visceral geometrical and susceptibility artifacts, exploiting an appropriate correction map (12). A T2* value > 20 ms was taken as the "conservative" normal value for all 16 segments and for the global T2* value (7–9,12).

Contrast delayed enhanced images were acquired 10–18 minutes after Gadobutrol (1.0 mol/L) (0.2 mmol/kg) intravenous administration using a fast gradient-echo inversion recovery sequence. Inversion times were adjusted to nullify the myocardium signal. The following parameters were used: slice thickness 8.0 mm, no gap between each slice, repetition time 5.4 msec, echo time 1.3 msec, flip angle 20°, field of view 36 × 36 cm, matrix 256 × 192 pixels, and reconstruction matrix 256 × 256. Depending on the left ventricle size, 10–14 short axis views were acquired for each subject (24). Also, vertical, horizontal, and oblique long-axis views were acquired.

The DE extent was first evaluated visually by two blinded, experienced observers using a two-point scale

(enhancement absent or present). Enhancement was considered present whenever it was visualized in two different views. In addition, the extent of the DE areas was quantified using semiautomatic, previously validated software (25). In each image the boundaries of myocardium and the DE areas were semiautomatically traced and manually corrected. A 17-segment model (according to the standard AHA/ACC model (23)) was adopted where 16 segments were derived from the short-axis images (same myocardium segmentation used to analyze the T2* sequences) and the 17th segment, corresponding to the apex, was obtained from the long-axis view. Each myocardial segment was subdivided into 100 radial chordae. The transmural extent of the DE was defined as the average number of chordae measured in each segment with >75% extent of the DE. The DE areas were expressed as percent of the entire left ventricle myocardium. The contrast-to-noise ratio (CNR) was calculated by objective pixel quantification as the contrast between the hyperenhanced tissue and the normal myocardium divided by the noise intensity evaluated in the image background. An appropriate correction factor was introduced to take into account the Rician distribution of the MRI noise in a multichannel system (26).

Measurements of Blood Oxygenation

The blood oxygenation was assessed by the noninvasive measurement of the partial pressure of oxygen (pO2). This peripheral measure was used to index coronary pO2, that is the closest physiologically accessible measure of the myocardial tissue oxygenation (27). We utilized a pulse oximeter (Bruker, Billerica, MA) that consists of a probe attached to the patient's finger which is linked to a computerized unit. The unit displays the percentage of hemoglobin (Hb) saturated with oxygen together with an audible signal for each pulse beat and a calculated heart rate (28). The acceptable normal ranges are from 95%–100% (29).

Statistical Analysis

All data were analyzed using SPSS v. 13.0 (Chicago, IL) and MedCalc v. 7.2 (Belgium) statistical packages. All continuous variables are expressed as the mean ± standard deviation. Correlation analysis was performed using Spearman's test. Comparisons between the groups were made by an independent-samples *t*-test. The Wilcoxon rank sum test was applied for continuous values with a nonnormal distribution (ie, T2* data). $P < 0.05$ was considered statistically significant.

RESULTS

Delayed Enhancement CMR

Myocardial fibrosis was detected in 31 (33%) patients (Fig. 2). Gender, age, mean serum ferritin level, and mean pretransfusion hemoglobin over the last year were not statistically significantly different between the fibrosis versus no-fibrosis group. The characteristics of all patients are summarized in Table 1.

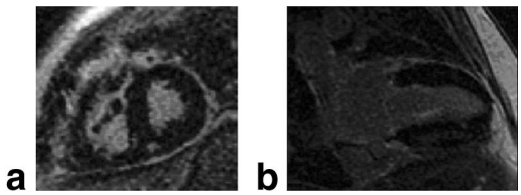

Figure 2. Thalassemia major patient with DE in the infero-septal junction visualized in the short axis view **(a)** and in the oblique plane **(b)**, acquired from the short axis view on the enhancement area.

The CNR was 5.87 ± 5.69. The extent of the DE areas was 4.6 ± 2.8% of the total left myocardial mass.

The myocardial fibrosis was predominantly patchy. Of the 31 patients with fibrosis, 10 had one focus of fibrosis, 10 had two foci of fibrosis, and 11 had more than two foci of fibrosis. Eight (26%) patients showed fibrosis in the infero- or anteroseptal junction. Fibrosis areas were detected more often at the mid-ventricular level (52%) compared with the basal (35%) and apical levels (13%). In all patients the location of fibrosis was epimesocardial, nontransmural, or otherwise similar to the enhancement in coronary artery disease. The mean number of DE segments per patient was 2.4 ± 1.3.

*Myocardial Fibrosis and T2**

The global heart T2* value in patients with enhanced tissue was comparable with that of patients without enhanced tissue (the fibrosis group 27.7 ± 12.9 msec vs. the no-fibrosis group 27 ± 12.7, $P = 0.88$) (Fig. 3a).

The T2* value in the mid-ventricular septum did not show a significant difference among patients with enhanced tissue and patients without enhanced tissue (the fibrosis group 32.1 ± 13.9 msec versus the no-fibrosis group 28.5 ± 14.8, $P = 0.43$) (Fig. 3b).

In addition, T2* values were comparable in segments with enhancement and segments without enhancement (the enhanced segments 28.0 ± 13.7 msec versus the no-enhanced segments 26.7 ± 13.8 msec, $P = 0.83$) (Fig. 3c).

We did not detect a significant correlation between the presence of fibrosis and the number of segments with normal T2* ($P = 0.19$).

Myocardial Fibrosis and Blood Oxygenation

There were no significant differences between the fibrosis group and the nonfibrosis group as to blood oxygenation (96.0 ± 1.9 vs. 95.4 ± 1.8, $P = 0.96$).

*Blood Oxygenation and T2**

Blood oxygenation did not significantly affect the global heart T2* value: the Spearman's coefficient of correlation was 0.99 (Fig. 4).

DISCUSSION

Precise and effective measurements of myocardial iron overload are critically needed for the early diagnosis, treatment, and follow-up of thalassemia patients. MRI

Table 1
Patient Characteristics

	Fibrosis group (N=31)	No-fibrosis group (N=63)	P-value
Age (years)*	31 ± 10.6	27.9 ± 10.2	0.44
M/F	13/18	25/38	0.69
Ferritin levels (ng/L)*	1533 ± 1761	1642 ± 1137	0.13
Hemoglobin pretransfusion (g/dl)*	9.5 ± 0.8	9.6 ± 0.7	0.57

*Data are mean values ± standard deviations.

represents the only noninvasive technique to quantify myocardial iron burden (30). In particular, iron overload in MRI is associated with an effect termed susceptibility-induced relaxation (31). The iron, when present in an intracellular location in the form of ferritin and hemosiderin, causes magnetic inhomogeneities that result in a considerable quickening of protons transverse relaxation time (6), which can be assessed by spin-echo (T2) techniques (32,33) or gradient-echo (T2*) techniques (7,10). The gradient-echo T2* technique is generally used in the clinical arena. In fact, the T2* approach allows for exploiting fast multiecho techniques that enable faster, more robust, and more sensitive data acquisition (ie, single breath-hold) and may be extended to measurements on the beating heart (11). A significant correlation between tissue iron concentrations and T2* values was demonstrated in calibration studies (7,34,35).

However, T2* values in the heart could be potentially affected by other factors besides tissue iron concentration, such as myocardial fibrosis and variations in blood oxygenation within the capillary networks of the myocardium (13). Although it was suggested that there was a high probability that myocardial iron concentration was the major factor that determined the T2* value of the tissue (22), the dominance of the myocardial iron concentration over other factors affecting T2* has not been experimentally proven.

Myocardial fibrosis has been shown in autopsy studies (14–16) as well as in studies based on cardiac biopsy or surgical specimens from living patients (17) with idiopathic hemochromatosis. Previous studies have investigated the influence of fibrosis on T2-weighted MRI images. Although different results have been reported, depending on the experimental or clinical model, there is general agreement that in extensive fibrosis such as postmyocardial infarct, T2 times drop (36,37). However, to our knowledge there are no studies about the influence of myocardial fibrosis on T2*-weighted images.

Moreover, the deoxyhemoglobin concentrations could increase in thalassemia patients. It has been shown experimentally that T2* decreases as the concentration of deoxyhemoglobin increases (21). This effect is also understood theoretically in terms of the geometry of the myocardial capillaries and the magnetic susceptibility differences between the blood within the capillaries and the surrounding tissue (20).

First, we tried to understand if T2* values in the heart were susceptible to fibrosis in addition to tissue iron concentration. We observed that fibrosis was a relatively common finding (33%) among thalassemia patients. We found a nonspecific, patchy, epimesocardial, nontransmural pattern of fibrosis (Fig. 2b). Moreover, the fibrosis involved a small percentage of the entire left ventricular myocardium (4.6 ± 2.8%). No significant association was found between myocardial fibrosis and myocardial iron overload (Fig. 3). The T2* values in segments with fibrosis were comparable to those in segments without fibrosis (P = 0.83). The global T2* value as well as the T2* value in the mid-ventricular septum in patients with fibrosis were comparable with that of patients without fibrosis (P = 0.88 and P = 0.43, respectively). We did not detect a significant correlation between the presence of fibrosis and the number of

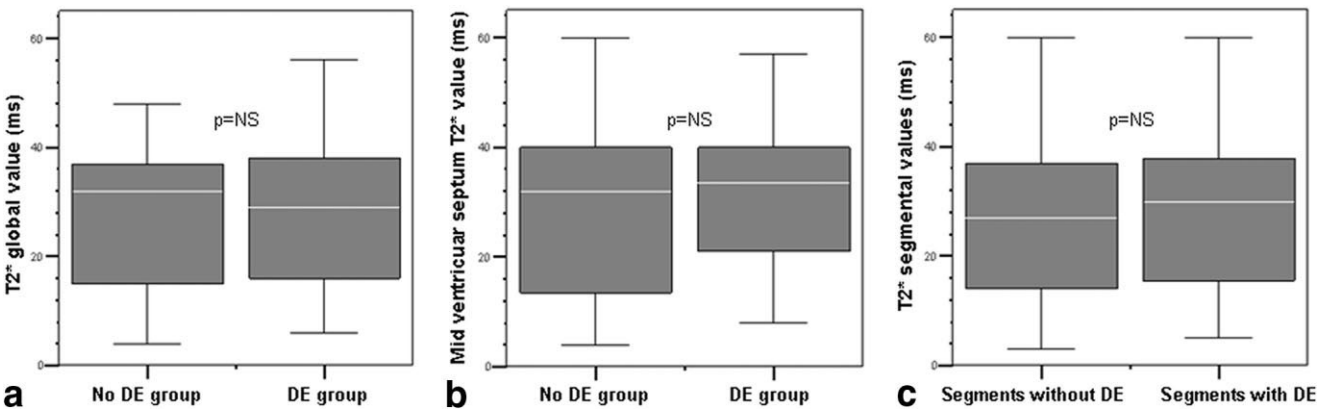

Figure 3. Simple boxplots. Each box shows the median (white line), quartiles, and extreme values within a category. Global heart T2* values **(a)** and mid-ventricular septum T2* values **(b)** in the fibrosis group and in the no-fibrosis group. Segmental T2* values **(c)** in segments with DE and in segments without DE. There were no significant differences.

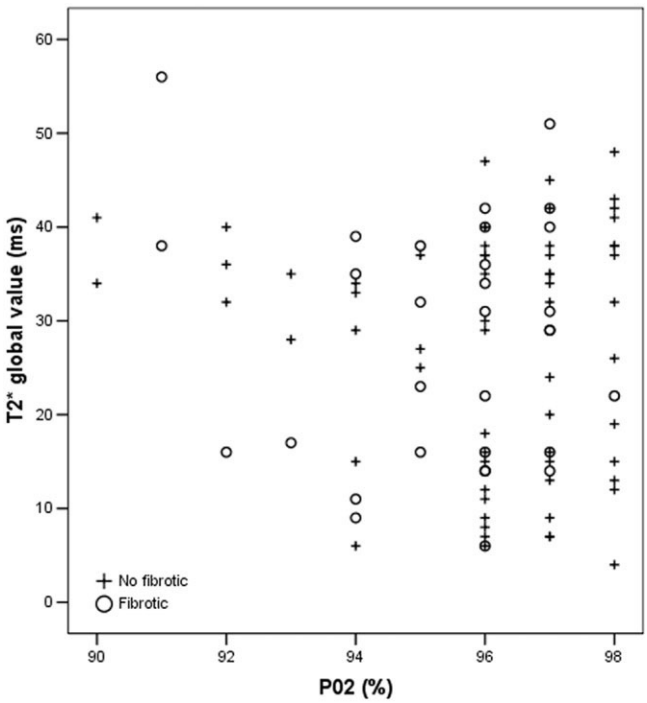

Figure 4. Plot of T2* global values vs. pO2.

segments with normal T2* ($P = 0.19$). Overall, myocardial fibrosis did not significantly affect T2* values, likely due to the small percentage of fibrosis within the left ventricular myocardium and its patchy distribution.

Second, we studied the effects of variations in blood oxygenation on the T2* values. Patients with thalassemia major can have varying deoxyhemoglobin concentrations and myocardial capillary densities (13). We found that blood oxygenation did not significantly affect global T2* values (Spearman's coefficient of correlation = 0.99). Thus, the role of blood oxygenation on T2* measurements seems to be clinically negligible with respect to the effect of iron burden. It can be speculated that myocardial blood volume is small, and consequently the deoxygenating effects in thalassemia patients are not significant.

In conclusion, myocardial fibrosis and blood oxygenation did not significantly affect the T2* values. These data further support the use of heart T2* as the equivalent of heart iron in the clinical arena.

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