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ORIGINAL ARTICLE

Dual-echo TFE MRI for the assessment of myocardial iron overload in beta-thalassemia major patients

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PURPOSE
Cardiac failure due to myocardial iron overload is the most common cause of death in beta-thalassemia patients. Multi/two echo times-turbo field echo (TE-TFE) magnetic resonance imaging (MRI) is considered the gold standard technique in the evaluation of myocardial iron accumulation. However, multi TE-TFE technique is not available in all scanners. The aim of our study was to show the role of black blood dual-echo cardiac triggered TFE in the assessment of myocardial iron overload.

MATERIALS AND METHODS
Sixteen beta-thalassemia major patients (10 males) with a mean age of 19 years who were receiving parenteral deferoxamine and oral deferiprone treatment were included in this study. Baseline measurement of myocardial T2* values were <20 ms in all patients. Cardiac MRI was performed after 6 months, 12 months, and 18 months with the same technique.

RESULTS
The average baseline value of T2* was 8.2 ± 3.6 ms. After treatment of combined deferoxamine and deferiprone, the average measurements of myocardial T2* at 6, 12, and 18 months were 11.3 ± 6.0, 13.6 ± 7.5, and 15.7 ± 7.4 ms, respectively ($P < 0.05$). The basal ejection fraction (EF) value was 49 ± 8.7%. The EFs were 54.4 ± 11% at 6 months, 54.8 ± 6.9% at 12 months, and 58.6 ± 3.6% at 18 months of follow-up ($P > 0.05$).

CONCLUSION
Cardiac MRI with dual TE-TFE technique can be used to determine myocardial iron accumulation and response to the chelation treatment.

Key words: • *beta-thalassemia* • *iron overload* • *myocardium* • *magnetic resonance imaging*

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Beta-thalassemia major (beta-TM) is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. Regular blood transfusions are necessary in these patients to suppress extramedullary hematopoesis and cardiac decompensation caused by marked anemia (1). The lack of physiological mechanisms to eliminate the excessive iron causes its deposition in tissues. When the iron-binding capacity of iron binding proteins such as transferrin and ferritin is exceeded, non-transferrin bound iron can generate harmful free radicals and cause tissue and multiorgan damage (2). In the absence of adequate chelation therapy, cardiomyopathy caused by iron overload and heart failure remains the leading cause of death in patients with beta-TM. Almost 70% of adult patients with beta-TM suffer from hypogonadism, osteoporosis, and other endocrine disorders (1–3). The use of iron chelators is the mainstay of treatment in beta-TM patients to ameliorate the inevitable complications of iron overload caused by regular transfusions.

A number of factors contribute to the high cardiac-related mortality of beta-TM patients, including the poor compliance of patients with deferoxamine chelation and myocardial iron loading despite deferoxamine chelation (4, 5). Eventually, left ventricular dysfunction which is resistant to treatment develops late in the disease; identification of asymptomatic preclinical iron overload, however, is problematic (6, 7).

Quantifying myocardial iron accumulation is important not only to prevent cardiomyopathy, but is also crucial in planning and monitoring iron chelation therapy. Direct measurement of myocardial iron allows diagnosis and treatment of iron overload before the stage of heart failure. Since myocardial biopsy to quantify cardiac iron load is invasive, alternative methods for detection and quantification of cardiac iron overload are needed. Therefore for the early assessment of myocardial iron load, cardiovascular T2* magnetic resonance imaging (MRI), which is a noninvasive method, has been developed (8, 9). Cardiovascular MRI permits highly reproducible measurements of myocardial iron (T2*) and ventricular function, making this modality the gold standard in assessment of cardiovascular response to chelation treatments in patients with beta-TM (5, 7–13).

In conventional cardiovascular MRI, the myocardial iron concentration is measured using multiecho turbo field echo (TFE) technique (8, 11). Myocardial T2* values have previously been studied using two echo times (14). The aim of our study was to show the role of dual-echo TFE (black blood dual-echo cardiac triggered TFE) in the assessment of myocardial iron overload.

Materials and methods

Patients

The inclusion criteria were diagnosis of beta-TM currently maintained on subcutaneous deferoxamine monotherapy; age ≥10 years; and main-

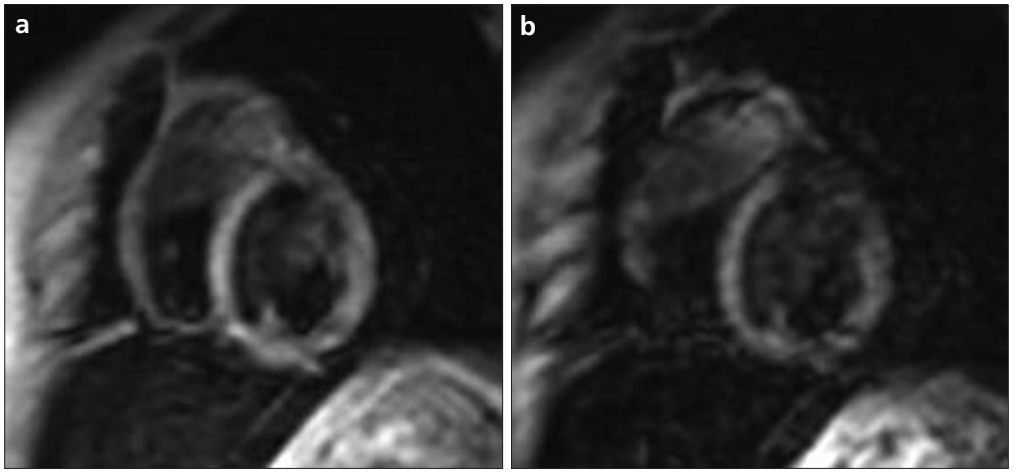

Figure 1. a, b. MR images taken from the short axis midventricular line using black blood dual-echo TFE. TE is either 4.6 ms **(a)** or 9.2 ms **(b)**.

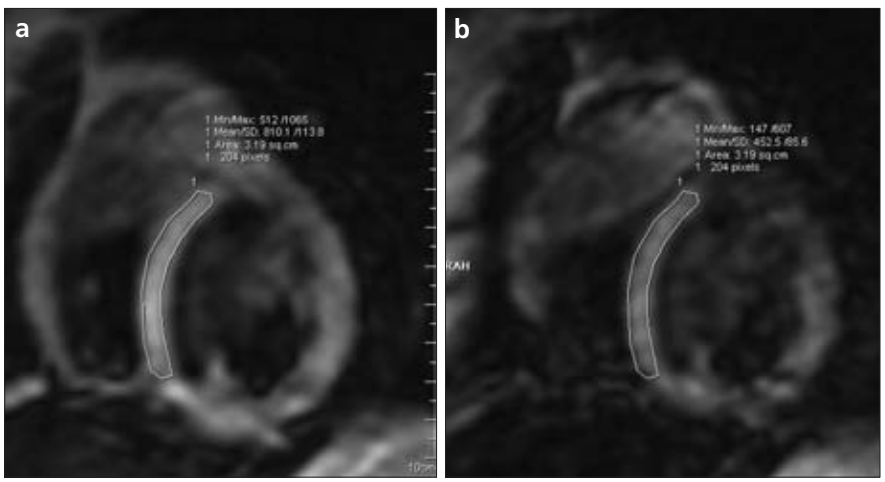

Figure 2. a, b. MR images showing the contour drawn over the septum for the calculation of T2*.

taining pre-transfusion hemoglobin >9 g/dL. Exclusion criteria were previous initiation of deferiprone, neutropenia (ANC $<1.5 \times 10^9$/L), thrombocytopenia ($<50 \times 10^9$/L), and liver enzymes >3 times upper limit of normal. Of 48 patients screened, 16 (29%) had significant myocardial iron load (T2* <20 ms) and were included in the study. These 16 patients were started on combined therapy with oral chelator deferiprone three times daily (20–25 mg/kg/dose), in addition to subcutaneous deferoxamine 3–5 times a week, 30–40 mg/kg/day. None of the 16 patients had a condition incompatible with MRI, including pacemaker or claustrophobia.

The study was approved by our institutional review board, and informed consent was obtained from the patients for MRI screening. All 16 patients were prospectively scanned at baseline and and at six months. The number of patients decreased to eight by 12-month follow-up and to seven by 18-month follow-up; patients who dropped out declined radiologic evaluation follow-up, although they continued hematology follow-up visits.

Cardiac MRI and T2 evaluation*

The 16 patients who had a baseline MRI study with a T2* value <20 ms were initially scheduled for cardiac MRI follow-up at 6, 12, and 18 months with 1.5 Tesla MRI system (Philips Intera Achieva; Philips Medical Systems, Best, The Netherlands). Patients were scanned in the supine position with ECG and breath follow-up pad. A 5-element phased array cardiac coil was used for signal collection. For T2* evaluation, images were taken from the short axis midventricular line, using black blood dual-echo cardiac triggered TFE sequence, by using two echo times (TE) (Fig. 1). The parameters were as follows: TR, 12; TE_1, 4.6 ms; TE_2, 9.2 ms; flip angle (FA), 30°; FOV, 320 mm; RFOV, 100%; slice thickness, 10 mm. To calculate the T2*, a contour was drawn over the septum on one image and copied to the other echo (Fig. 2) The mean value of both ROIs was taken to do the calculation. The T2* value (in ms) was the time between the two echoes (delta TEs) divided by the natural logarithm of the division of signal intensity at TE_2 by the intensity at TE_1.

For ejection fraction calculation, short axis cine turbo field echo was used. The parameters were as follows: TR/TE, 3.0/1.52 ms; slice thickness, 8 mm; gap, 3 mm; SENSE factor, 2; FOV, 320 mm; RFOV, 100%; FA, 60°. Endocardial and epicardial borders were contoured manually, and functional analysis was performed with a dedicated software (ViewForum Cardiac Package Program, Version 3.4; Philips Medical Systems, Best, The Netherlands).

All calculations were done by the same radiologist (TH) who had seven years' experience in cardiovascular imaging.

Statistical analyses

The mean value and standard deviation were acquired for each parameter. Friedman test was used for analyzing the change in MR measurements in patient group, and Wilcoxon signed ranks test with Bonferroni correction was used for pairwise comparison. $P < 0.05$ was considered statistically significant. The Statistical Package for Social Sciences (SPSS Inc, Chicago, USA) Standard Version 11.5.0 for Windows was used as the statistical software program.

Results

Mean age of the 16 patients with significant myocardial siderosis (T2* <20 ms) was 19 years (ten males; range, 10–25 years). Scanning times of the examinations were between 17–25 min. The average baseline value of T2* was 8.2±3.6 ms (range, 4–15.8). After chelation with combined deferoxamine and deferiprone, the mean myocardial T2* values at 6, 12, and 18 months were 11.3 ± 6.0, 13.6 ± 7.5, and 15.7 ± 7.4 ms, respectively. The increase in T2* values were found to be significant ($P < 0.05$) (Table). The basal ejection fraction (EF) values were 49 ± 8.7%. On follow-up, EFs were 54.4 ± 11% at 6 months, 54.8 ± 6.9% at 12 months, and 58.6 ± 3.6% at 18 months. The differences in EFs during subsequent MRI screens were found to be insignificant ($P > 0.05$).

No patient required permanent cessation of deferiprone; however, two patients developed transient neutropenia which resolved after interruption of medication for one visit and did not recur. None of the patients developed thrombocytopenia or elevation in liver enzymes requiring drug cessation or dose adjustment. All the patients were alive at the end of the 18-month follow-up period of the study.

Discussion

Prevention of iron toxicity and iron-induced morbidity and mortality is the main objective of iron chelation therapy in transfusion-dependent patients. Despite the availability of deferoxamine, a third of patients develop an excessive body iron load, not only because of the compliance problems cumbersome subcutaneous self-administration brings about, but also due to failures in diagnosis of preclinically myocardial iron-overloaded patients who are at risk for future therapy-resistant left ventricular heart failure (15).

Table. T2* measurements of the individual patients in milliseconds (ms) at baseline, 6th, 12th, and 18th months

Patient number	Baseline T2* (ms)	6th month T2* (ms)	12th month T2* (ms)	18th month T2* (ms)
1	5.6	6.2	7.6	8.4
2	5.7	5.2	6	8.3
3	8.6	8.7	-	-
4	4	25.8	-	-
5	6.9	9.4	-	-
6	6.6	8.5	-	-
7	11.8	13.2	17.1	-
8	6.4	6.6	8	9.5
9	6.4	14.6	23	27
10	11.9	16.1	17.7	22.2
11	5.6	5.5	6.1	6.9
12	15.8	18.8	-	-
13	15.1	18.1	23.5	27.7
14	6.8	6.5	-	-
15	11.1	13.2	-	-
16	4.5	5.5	-	-

Measurement of iron stores is crucial for evaluation and management of chelation therapy. Assessment of body iron can be done by measuring the serum ferritin level and also by directly measuring the liver iron content. However, it has been shown that neither serum ferritin level nor liver iron concentration correlate with myocardial iron overload (5). Myocardial biopsy would be the most precise way of determining the amount of iron in the heart; however, it is invasive and cannot be used in daily practice. Therefore, for early assessment of myocardial iron, noninvasive cardiac MRI has been introduced.

Deferiprone, an orally administered iron chelator, is superior in preventing myocardial iron, as it is lipophilic and crosses cell membranes. It has been shown that combination therapy with deferoxamine and deferiprone is effective in reduction of myocardial iron and maintaining left ventricular function (5, 7, 13, 16–18). In the present study, all patients were administered combined therapy (proven effective in reducing myocardial iron overload and improving cardiac function) to test the reliability of dual-echo TFE instead of multiecho TFE.

Magnetic resonance imaging methods for assessing tissue iron can be separated into two groups: signal intensity ratio (SIR) methods and relaxometry methods. SIR methods require shorter acquisition times but lack a wide range of iron assessment. Relaxometry methods, mainly the T2* method, by using multiple echoes create in- and out-of-phase effects between water and fat transverse magnetization. Relaxometry methods, although taking longer, are preferable because they achieve a better sampling of the time domain in which relaxation mechanisms take place and lead to more precise results (19–21).

Iron overload causes signal loss in affected tissues as they become magnetized in the scanner. They induce local irregularities in the magnetic field which cause water protons around these deposits to lose phase coherence (22). T2* is a relaxation parameter arising from local magnetic field inhomogeneities, which increase with iron accumulation. Anderson et al. measured myocardial T2* by using gradient echo sequence at eight separate echo times (8). The transferability of multi-breathhold T2* technique with eight separate

echo times was validated with a multicenter research study (11). Recently, single breathhold multi-echo T2* technique has been described and used widely because it offers the advantage of being faster (23). However, this technique is not supported by all vendors. Therefore we have shown the role of single breathhold dual-echo black blood cardiac triggered TFE, which our scanner supported. Li et al. studied myocardial T2* values of normal myocardium using two echo times (14). Inspired by that study, we used two echo times to measure T2* values on beta-TM patients.

In dual-echo TFE protocol, the resolution was kept low for the best possible signal to noise ratio. Because the T2* values are derived from two sample points only, the signal-to-noise ratio needs to be good. To avoid intra voxel water and fat dephasing, the dual TEs were chosen such that water and fat were in-phase. It has been shown that black blood sequences are superior to bright blood techniques by suppressing blood signals and minimizing partial volume errors, thus providing a more homogeneous image of the myocardium (24). The scan is cardiac triggered to avoid cardiac motion artifact and performed in a single breathhold.

It is clear that using multi echoes will increase sensitivity, but we have showed that dual-echo is capable of determining the changes related to iron overload or response to treatment. However, the limitation of dual-echo TFE is that the normal and abnormal ranges of myocardial T2* values for dual-echo TFE are not defined. Also, it is not known if T2* value ranges differ from the multi-echo technique; therefore, a comparative study needs to be done with the multi-echo technique. Further studies with higher patient numbers are needed, including a multi-center study, because we do not yet know the inter-study and inter-center variability of the dual-echo technique.

In conclusion, T2* can be measured with dual-echo instead of eight echo times on scanners that do not support the multi-echo single breathhold sequence for the follow-up of patients with myocardial iron overload to show the efficiency of the treatment. However, further detailed and multicenter studies are needed to determine the sensitivity of the technique.

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