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NON-INVASIVE MYOCARDIAL IRON ASSESSMENT IN THALASSAEMIC PATIENTS

T2 relaxometry and magnetization transfer ratio measurements

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Abstract

Purpose: To compare T2 relaxometry and magnetization transfer ratio (MTR) measurements of myocardial tissue in normal volunteers and thalassaemic patients for assessment of the myocardial iron levels.

Material and Methods: All examinations were done on a 1 T MR system using a multi-echo spin-echo sequence with 8 echoes for T2 measurements and a gradient echo sequence for MTR measurements. Diastolic cardiac triggering was used in both sequences. Ten patients and 10 normal subjects were included in the study. T2 and MTR measurements were correlated with serum ferritin levels.

Results: Regression analysis between T2 and MTR measurements and ferritin demonstrated a reversed linear relationship, ($r=-0.932$, $p<0.05$) and ($r=-0.824$, $p<0.05$), respectively. Mean T2 relaxation time and mean MTR of the normal subjects (57.95 ± 4.9 ms and $43.70\pm3.3\%$) was significantly higher than that of the thalassaemic patients (38.8 ± 6.2 ms and $26.40\pm6.1\%$) ($p<0.01$), respectively.

Conclusion: MTR measurements can be used to complement T2 measurements for non-invasive myocardial iron assessment.

Key words: Thalassaemia, MR T2 relaxometry; iron; magnetization transfer ratio.

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Iron deposits in various tissues have been well correlated with 1/T2 relaxation rate. Liver 1/T2 values were found to be linearly dependent on iron tissue concentration in patients with haemosiderosis (7, 10, 14). Brain iron deposits were also correlated with 1/T2 values in basal ganglia in normal subjects (1, 18). Despite the technical difficulties to estimate the T2 constant with high accuracy, several groups have proved the clinical potential of MR relaxometry in the evaluation of iron deposits in several tissues.

Magnetization transfer ratio (MTR) measurements were used in several clinical applications like differentiation between active and chronic multiple sclerosis lesions (5), brain and hepatic tumour characterisation (11, 13). Magnetization transfer (MT) effect is most prominent in tissues with macromolecular biochemical composition, including muscle, myocardium, liver, white and grey matter (17).

In thalassemic patients, iron deposits are more pronounced in liver and myocardial tissue. Serum ferritin test has been used to monitor iron levels in such patients but it suffers from high inaccuracy especially when an inflammation is present. Another approach to quantify the iron in liver is by biopsy which is an accurate, but invasive, technique.

Since one of the major complications in thalassaemic patients is cardiac insufficiency due to ex-

tensive iron deposits in the myocardial tissue, a technique capable of monitoring the iron levels would be desirable.

In this study we have made T2 and MTR measurements of the myocardial tissue in normal subjects and thalassaemic patients in order to evaluate these techniques for monitoring myocardial iron levels.

Material and Methods

Ten patients with thalassaemia and 10 normal subjects were investigated. Patients' mean age was 24 years (19–32 years) while normal subjects' mean age was 28 years (24–35 years). Serum ferritin values were recorded in all patients. T2 measurements were obtained by using a multiecho spin-echo sequence with 8 echoes (20, 40, 60, 80, 100, 120, 140 and 160 ms). All measurements were done using a 1.0 T MR system (Gyroscan NT-T10, Philips Medical Systems). One slice was acquired in double oblique plane (Fig. 1) and the slice thickness was 10 mm. The field-of-view was 230×350 mm^2 while the matrix was 128×256. TR ranged from 1,800 to 2,500 ms depending on patient heartbeat. The MTR measurements were done using a dynamic gradient echo sequence (fast field echo) with TRs ranging from 700 to 1,000 ms depending on patient heartbeat, TE of 7 ms and flip angle of 30°. This acquisition consisted of two identical dynamic scans. The only difference between the first and the second scan was that in the second an additional on-resonance MT prepulse was added. Ten slices were acquired with a slice thickness of 6 mm and an interslice gap of 0.6 mm. Both sequences were cardiac-synchronized with a delay time of 400 ms from the R-pulse, resulting in diastolic triggering. We used diastolic triggering in order to reduce the motion artefacts from cardiac pulsation. Additionally, a flow compensation gradient scheme was used to reduce ghosting from blood pulsation in the left ventricle. Acquisition time was 10 to 12 min due to the use of cardiac and respiratory triggering techniques.

Image analysis, T2 calculation: Signal intensity measurements were done using a region-of-interest (ROI) placed in myocardial tissue in all 8 echoes. The background signal was also measured by placing a ROI in the air (avoiding ghost artefacts) and the noise level was measured using the SD-value of the air. The background signal intensities were subtracted from the myocardial signal intensities and a noise-weighted non-linear least squares fitting algorithm was used to calculate the T2 constant of the myocardial tissue.

MTR calculation: Signal intensity of the myocardial tissue was recorded by placing a ROI (Fig. 1) in both dynamic images (with and without MT prepulse). MTR was calculated using the following formula:

$$MTR = 100*(SIa - SIb)/SIa$$

where SIa represented the myocardial signal intensity without an MT prepulse and SIb represented the myocardial signal intensity with an MT prepulse.

Statistical analysis: Mean T2 and MTR values were calculated for patients and normal subjects. A Student's *t*-test was used to compare T2 and MTR mean values between patients and normal subjects with a *p*-value less than 0.01 considered as significant. A linear regression analysis with serum ferritin values was performed for both measurements on patients and a correlation coefficient was recorded. Statistical analysis was done on a personal computer using Instat Software (GraphPad Software Inc.).

Results

Mean myocardial T2 value and SD in patients was 38.84±6.2 ms while in normal subjects it was 57.95±4.9 ms ($p<0.01$). The mean MTR value and SD in patients was 26.4±6.1 while in normal subjects it was 43.7±3.3 ($p<0.01$) (Fig. 2). Mean

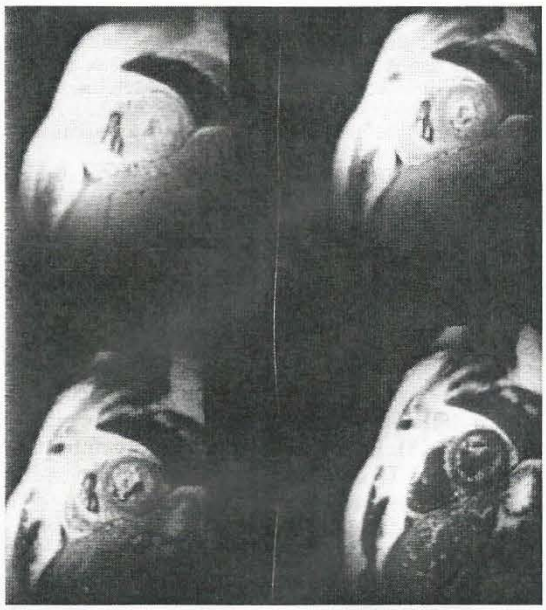

Fig. 1. Four images of the multiecho spin-echo acquisition corresponding to echo times of 20 ms (upper left), 40 ms (upper right), 100 ms (lower left) and 140 ms (lower right).

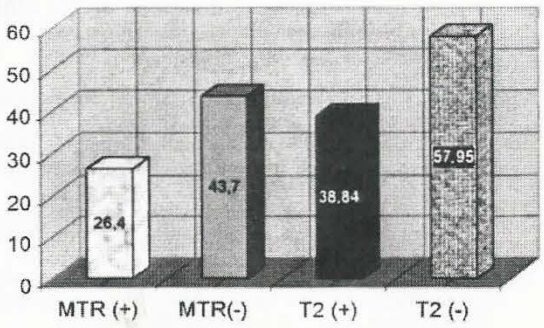

Fig. 2. Mean myocardial MTR, T2 values and SD of the patient group (+) and the control group (−).

serum ferritin level and SD for the patient group was 2128.7±801 μg/l. Linear regression analysis showed a very good reversed linear relationship between serum ferritin levels and T2 value with a correlation coefficient r=–0.932 ($p<0.01$), and serum ferritin levels and MTR value also showed a very good reversed linear relationship with a correlation coefficient r=–0.824 ($p<0.05$).

Discussion

The presence of iron in myocardium results in T2 shortening. The effect is caused by dephasing of water protons as they diffuse through local field gradients induced by iron. This effect depends linearly on the amount of iron (9). Several investigators have tried to quantify iron in various tissues *in vitro* by utilizing T2 relaxometry (3, 12, 16) with successful results using NMR spectrometers. Other groups (7, 10, 14) have utilized whole-body imagers to quantify *in vivo* iron deposition. The main problem of this approach is the low accuracy of the measurements.

The systematic errors include radio frequency pulse imperfections, susceptibility artefacts and timing errors responsible for low accuracy of T2 measurements in a whole-body imager (6, 8). Another major limitation of T2 relaxometry is the fact that human tissues have large intrinsic variation of the T2 values. The limitations of accurate T2 calculations in patients with high-grade haemosiderosis performed on a standard whole-body imager compared to a NMR spectrometer were reported by Dixon & Styles (4). The main drawbacks of using a whole-body unit are low signal-to-noise ratios, limited number of echoes (less than 32) and long inter-echo intervals.

Bottomley et al. reported normal myocardial T2 to be around 57±16 ms (2) while the myocardial T2 constant in thalassaemic patients could go down to 10 ms. The prerequisite to accurately quantify high iron levels was the use of a large number of echoes at the first 50 ms in order to sample the exponential T2 decay of the iron-rich tissue with better accuracy.

MTR measurements were made by utilizing a gradient recalled sequence with and without an magnetic transfer constant on-resonance prepulse. This approach proved less susceptible to artefacts and more robust than T2 relaxometry, while the correlation coefficient with serum ferritin levels in thalassaemic patients was comparable to that of T2 relaxometry. MTR values in iron-rich tissues are reduced (15) since iron possibly destroys the normal myocardial macromolecules which are subjected to MT effects. The reduction in MTR values seems to be linearly dependent on the iron concentration.

In conclusion, MTR measurements may be used instead of or in addition to T2 relaxometry in the evaluation of myocardial iron deposition using a whole-body unit. However, an extended study is necessary to confirm our preliminary findings.

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