Quantitative Assessment of Iron Content in the Body Using Fast Mappings of Relaxation Times

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Introduction

Numerous studies[1] have documented the sensitivity of MRI to iron deposition in the body, but a reliable method of quantitatively measuring tissue iron which is essential for the diagnosis and management of systemic iron overload disorders has not yet emerged for clinical practice. Preliminary studies conducted in different experimental settings have either used R_2 [2-4] or the signal intensity ratio (SIR) between liver and skeletal muscles for iron quantification. None, however, has proven itself sufficiently robust for routine clinical application. Particularly, in heavily iron loaded organs where T_2 can be as short as a couple of ms, the limited SNR and choices of echo time (TE) in clinical pulse sequences are critical for the accuracy of T_2 measurements. In this study, we implemented a number of optimized pulse sequences for efficient mappings of T_2, T_2*, and T_1 based on spiral acquisition and used them for iron quantification in different organs of the body.

Methods

The study was conducted using a GE Signa 1.5T LX 9.0 system. For T_2* and T_2 mapping with the shortest possible TE we used a delayed self-refocused RF pulse designed to refocus the magnetization at the end of the down-ramp of the slice selection gradient [5]. In combination with spiral readout, the GRE version can reach TE as short as 0.1ms. T_2* can be measured using either a dual-echo acquisition or a dynamic loop with incremental TEs. For T_1 mapping, we implemented the Look-Locker sequence in combination with spiral readouts which is schematically shown in Fig. 1.The design of the readout gradients was calculated on-line which allows flexible choice of spatial resolution and other scanning parameters. We used the above techniques for iron quantification in the brain and liver. For iron assessment in the brain, multiple slice T_2* and T_1 mappings were performed in 10 normal adults (35-42 years old) using the techniques described above to achieve a spatial resolution of 1×1×5 mm^3. For iron estimate in the liver, multiple slice T_2 and T_1 measurements with a spatial resolution of 2×2×8 mm^3 were conducted in 6 patients (40-50 years old) with hemochromatosis confirmed by biopsy.

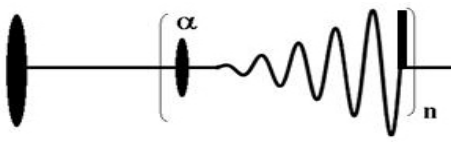

Fig.1 The Look-Locker sequence for fast T_1 imaging with spiral readouts. The essence of the sequence is an adiabatic 180° inversion pulse followed by a train of low flip angle (α=15°) pulses and readouts that generate a series of images at evenly spaced TI points during the recovery of the longitudinal magnetization. The following features were implemented into the sequence: (1) an adiabatic 180° inversion pulse with frequency offset- corrected (FOCI) slice selection gradient to improve the slice definition; (2) a variable length spoiler gradient after each readout; (3) minimized delay time between the α pulse and data acquisition using spiral out waveform.

Results

As shown in Fig. 2, there are significant linear correlations between R_2, R_2^*, and R_1 relaxation rates and iron contents in the body ($p<10^{-3}$). This agrees also with the vast majority of the MRI literature on body iron quantification in spite of the large differences in the employed techniques. Different MR relaxation times (T_1, T_2, and T_2*) differ significantly in their sensitivities to the iron concentration of the tissue, as expected from the differences of their underlying relaxation mechanisms. The estimated R_2* and R_1 relaxivities for iron in the normal brains were 0.4 and 0.024 s^{-1}/(mg iron/100 g fresh weight), respectively. The R_2 relaxivity for hepatic iron in the patients was about 5 s^{-1}/(mg iron/g dry tissue). The sensitivity to measure iron content in the brain using R_2* mapping is more than an order of magnitude higher than using R_1 relaximetry. But T_2* is not always the optimal choice because it can become too short to be accurately measured at high iron content. As shown in Fig. 1A, even in the normal subjects the measurement errors of R_2* in the regions with high iron content, such as in globus pallidus and red nucleus, are about twice of that in the regions with low iron content.

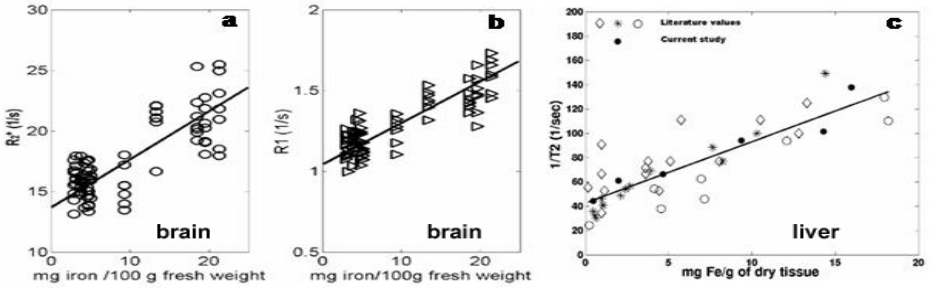

Fig.2 R_2, R_2', and R_1 relaxation rates as a function of iron content in brain and liver. The R_2' (a) and R_1 (b) relaxation results in the brain were average values from the different anatomical brain regions after co-registration of the extracted relaximetry maps with the standard Talairach template. The iron content in the brain was obtained from well-established autopsy literature[6]. The average R_2 values in the liver (c) were plotted against the hepatic iron content obtained from independent biopsy tests in the patients. For comparison, three sets of literature results [2-4] at 1.5T based on other types of relaximetry methods are also shown.

Discussion and Conclusions

The highly significant linear correlations and overall good agreements with literature results indicate that the MRI relaxation of water in tissues with iron overload can be approximated using a fast-exchange two-compartment model and iron quantification with MRI relaximetry is quite feasible. Once reliable calibration is established using a standardized relaximetry protocol, quantitative iron assessment in the body can be readily carried out. Comparing with the studies reported in the literature based on SIR approach or T_2 mapping using with long TE, our protocol for fast mapping of different relaxation times has the following advantages: (1) Reliable measurements of R_2* can be done in subjects with high iron overload because of the possibility to use TE as short as 0.1ms. (2) A wide range of iron content can be measured by taking advantages of the different sensitivities and accuracies of R_2*, R_2, and R_1. (3) Experimental errors and pathological changes can be detected by monitoring the relative ratios among R_2*, R_2, and R_1. Since T_1, T_2, and T_2* are affected differently by the structural and magnetic characteristics of the particles, measurements of T_1, T_2, and T_2*, and their relative changes can provide important information about the microstructure changes associated with pathological progression in the tissue. Any error in the measurements or pathological changes that alter the magnetic characteristics of the iron core or the interactions between water molecules and ferritin will be reflected by the variation of the relative ratios of relaxation times. Thus, simultaneous measurement of T_1, T_2, and T_2* may provide information about measurement errors or pathological changes. A robust protocol for fast mapping of different relaxation times can not only improve the accuracy of the estimate of iron content using established empirical calibration but can also provide a better understanding of how iron in tissue influences MR signal characteristics and yield insights into the relationships between organ iron deposition and iron toxicity.

References

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