Monitoring Iron Chelation Effect in Hearts of Thalassaemia Patients with Improved Sensitivity Using Reduced Transverse Relaxation Rate (RR2)

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Introduction

Accurate MRI characterization of myocardial iron is needed to improve the diagnosis and management of thalassaemia patients with transfusional iron overload. To prevent iron toxicity from inadequate chelation therapy and avoid the adverse effects of excessive chelator administration, reliable and sensitive monitoring of tissue iron is needed. In patients with iron overload, virtually all of the excess iron is sequestered within cells as short-term storage iron in ferritin (soluble nanometer-sized particles, dispersed and relatively uniformly distributed) and as long-term storage iron in hemosiderin (insoluble and clumped in irregular micron-sized clusters within siderosomes)[1]. Because cellular ferritin iron is in close equilibrium with the cytosolic iron pool involved in cellular injury[2], measurement of myocardial ferritin iron may be valuable in assessing iron toxicity. Myocardial R2* is predominately influenced by hemosiderin iron and changes only slowly, after months of iron-chelating therapy[3]. Our study examined a new transverse relaxation index, the reduced R2 (RR2) that is estimated from non-monoexponential multi-echo CPMG signal decay[4-6] and provides a measure of cellular ferritin iron. In thalassaemia patients examined at 3T, we found that RR2 could detect changes in myocardial ferritin iron after as little as 1 week (wk) of iron-chelating therapy.

Methods

Theory: In brief, the non-monoexponential CPMG signal decay in the presence of soluble and particulate iron is predicted to approximately follow:

$$S(TE) = S_0 \cdot \exp(-RR2 \times TE) \cdot \exp(-A^{3/4} \times (ESP/2)^{3/4} \times TE^{3/8}),$$

where S(TE) is the signal amplitude at time TE, S_0 is the initial signal amplitude and ESP is the interecho spacing. In tissues loaded with both ferritin and hemosiderin iron, RR2 is primarily sensitive to ferritin iron while A is predominately sensitive to hemosiderin iron[4-6].

MRI: A single-breathhold ECG-triggered turbo multi-echo spin-echo (MESE) sequence[7-9] was implemented to measure CPMG signal decay on a 3T Philips MRI scanner with a 6-channel cardiac coil. One mid-ventricular short-axis slice with double-inversion black blood preparation was acquired with acquisition matrix = 128×96, turbo factor = 2, SENSE factor = 2, partial Fourier factor = 0.6, TR = 750-1200 ms, FOV = 370 mm, and slice thickness = 10 mm for 90º excitation and 30 mm for 180º refocusing. CPMG echo signal decays with 3 different interecho spacings (ESPs) (5, 9 and 13 ms; 6 echo images each) were acquired to estimate RR2. The acquisition was repeated five times, and RR2 measurements were averaged. For comparison, R2* measurement was performed in the same slice location using a single-breathhold ECG-triggered multi-echo gradient-echo sequence (MEGE)[7,10] with first TE = 1.55 ms, echo spacing 1 ms, echo number = 25, flip angle = 20º, turbo field echo factor = 4 and black-blood preparation.

Patients and 1-wk suspension of iron chelation: Thalassaemia patients with transfusional iron overload (N = 8; mean age = 29.3 ± 8.6 yrs) receiving regular iron chelation (deferoxamine, 30 to 50 mg/kg for 2 to 5 days weekly +/- deferiprone, 55 to 95 mg/kg daily) were recruited. Cardiac MR was performed immediately before discontinuing iron chelation for 1 wk (Day 0), after 1-wk suspension of chelation (Day 7), and one week after resuming chelation (Day 14).

Data Analysis: Identical ROIs in septum were used with slight position adjustments to account for motion among different breathholds. CPMG MESE signal decays of 3 different ESPs were fitted to the non-monoexponential equation above with floating noise for RR2 measurement. R2 and R2* were measured by monoexponential fitting of signal decays (5 ms ESP for R2) with floating noise.

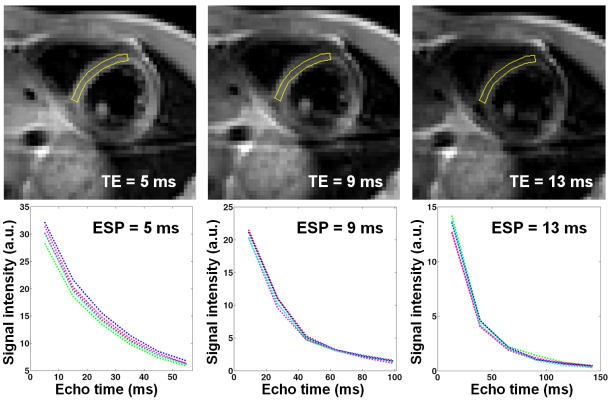

Fig. 1. Typical ROI delineation in ventricular septum and the corresponding CPMG MESE signal decay of five repeated scans.

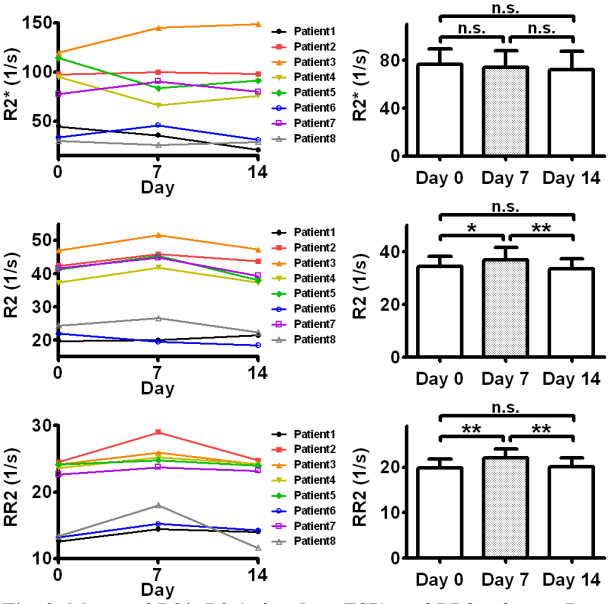

Fig. 2. Measured R2*, R2 (using 5 ms ESP), and RR2 values at Day 0 (on regular chelation), Day 7 (off chelation for 1 wk), and Day 14 (on chelation again for 1 wk). Repeated measures ANOVA was performed with * for $P < 0.05$, ** for $P < 0.01$, n.s. for insignificance.

Results and Discussions

The sequence was first validated by measuring R2 in phantoms of varying concentrations of $MnCl_2$ (0 to 1 mM with 0.1 mM increments) in 2% agarose gel, with 1s TR and 5 ms ESP. R2 increased linearly (R = 0.99) with $MnCl_2$ concentrations, indicating the robustness of R2 measurement by the turbo MESE protocol implemented. The transverse relaxivity was measured as 103.5 $s^{-1}mM^{-1}$ at 3T (in contrast to 73.6 $s^{-1}mM^{-1}$ previously reported for 1.5T for aqueous $MnCl_2$[11]). Fig. 1 shows typical septum ROI delineation and the corresponding MESE signal decays from the 5 repeated scans. Fig. 2 shows the R2*, R2, and RR2 changes in patients before (Day 0), and after chelation suspension (Day 7) and then 1 wk after resuming iron chelation (Day 14). Significant differences in R2 and RR2 were observed between Day 0 and 7, and between Day 7 and 14, with RR2 yielding stronger significance. This finding indicates that transverse relaxation rate R2 and RR2, especially RR2, are more sensitive in detecting changes in myocardial iron. This is likely a result of their superior sensitivity to soluble ferritin iron that is in close equilibrium with the cytosolic iron pool that is expected to change during the 1-wk suspension of chelation. Note that no significant difference was found in R2 computed with other ESPs (i.e., 9 and 13 ms) as well as the average of 3 R2 values computed from 3 ESPs. For comparison, no significant differences in R2* were found. R_2* is predominantly determined by hemosiderin iron that would be little changed by the brief suspension of iron-chelating therapy. These results are qualitatively consistent with a recent study by Kim et al at 1.5T.[12]

Conclusion

The experimental findings in this study demonstrated that RR2 measurement could detect myocardial iron changes associated with a brief (1 wk) suspension of iron-chelating therapy in thalassaemia patients. Therefore, MRI measurement of myocardial ferritin iron using RR2 may provide a new means of rapidly monitoring the effectiveness of iron-chelating therapy in transfusional iron overload.

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