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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 ineffective 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). Because cellular ferritin iron is in close equilibrium with the cytosolic iron pool involved in cellular injury, 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. Our study examined a new transverse relaxation index, the reduced R2 (RR2) that is estimated from non-monoexponential changes only slowly, after months of iron-chelating therapy. We used a new transverse relaxation index, the reduced R2 (RR2) that is estimated from non-monoexponential changes only slowly, after months of iron-chelating therapy. In brief, the non-monoexponential CPMG signal decay in the presence of soluble and particulate iron is predicted to approximately follow:

\[
S_{(TE)} = S_0 \cdot \exp(-RR2\cdot TE) \cdot \exp(\frac{-A^3}{4}\cdot(\frac{ESP}{2})^{3/4}\cdot TE^{3/8})
\]

where S(TE) is the signal amplitude at time TE, S0 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.

MRI

A single-breathhold ECG-triggered turbo multi-echo spin-echo (MESE) sequence 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 = 128x96, turbo factor = 2, SENSE factor = 2, partial Fourier factor = 0.6, TR = 750-1200 ms, FOV = 370 mm, and slice thickness = 10 mm for 90° excitation and 30 mm for 180° 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). The sequence was first validated by measuring R2 in phantoms of varying concentrations of MnCl2 (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 MnCl2 concentrations, indicating the robustness of R2 measurement by the turbo MESE protocol implemented. The transverse relaxivity was measured as 103.5 ± 5.3 s⁻¹mM⁻¹ at 3T (in contrast to 73.6 s⁻¹mM⁻¹ previously reported for 1.5T for aqueous MnCl2). Figure 1 shows typical septum ROI delineation and the corresponding CPMG MESE signal decay of five repeated scans.

Results and Discussions

The sequence was first validated by measuring R2 in phantoms of varying concentrations of MnCl2 (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 MnCl2 concentrations, indicating the robustness of R2 measurement by the turbo MESE protocol implemented. The transverse relaxivity was measured as 103.5 ± 5.3 s⁻¹mM⁻¹ at 3T (in contrast to 73.6 s⁻¹mM⁻¹ previously reported for 1.5T for aqueous MnCl2). Figure 1 shows typical septum ROI delineation and the corresponding CPMG MESE signal decay of five repeated scans.

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.

References