MR measurement of ferritin and hemosiderin iron in patients with iron overload

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Introduction

To provide a clinically applicable MR technique for quantitative determination of tissue iron stores, we have developed a new method that independently measures the two principal forms of storage iron, ferritin and hemosiderin. In patients with iron overload, the amount of iron in functional and transport pools changes only slightly [1]. Virtually all of the excess is sequestered in storage forms of iron, as ferritin, a diffuse, soluble fraction, and as hemosiderin, an aggregate, insoluble fraction. The available data suggest that the amounts and distribution of these two forms of storage iron are influenced by the underlying disorder (such as hereditary hemochromatosis, thalassemia, sickle cell disease and other refractory anemia), by the duration and extent of iron loading, and by the type of therapy (phlebotomy, chelation). Moreover, hemosiderin iron may be more toxic than ferritin iron. The two storage forms of iron strongly affect signal intensity in both T_2 and T_2* weighted images [2-4] but influence MRI signal decay through different means [5]. In this study, we examine an MRI method for iron determination based on the measurement of two distinct relaxation parameters: the transverse relaxation rate R_2 and the "hemosiderin index" A. We hypothesize that iron measurements based on these two parameters will be both more accurate by taking account of the distinct effects on NMR relaxation and more clinically useful by providing new information about the partition of storage iron between ferritin and hemosiderin.

Theory

The NMR signal decay caused by ferritin solutions has a monoexponential form, and the transverse relaxation rate R_2 may be derived from monoexponential fitting of a multiple spin echo signal. The R_2 depends linearly both on the iron concentration and the applied field. In contrast, because hemosiderin iron is aggregated in insoluble clusters, the multiple spin echo NMR signal decay in liver is *not* monoexponential and has a strong dependence on the interecho time [5]. More precisely, the decay is predicted to approximately follow the analytic form $S= S_0\exp(-R_2\times TE) \times\exp(-A^{3/4}(\Delta t)^{3/4}(t-t_s)^{3/8})$, where $t_s=2\tau[1-(\tau/\Delta t)^2]$, 2τ is the first spin echo time, $2\Delta t$ is the interecho time, TE is the echo time, A is the hemosiderin index, and R_2 is the "reduced" transverse relaxation rate [5]. The parameter A is primarily sensitive to hemosiderin iron, and R_2 is primarily sensitive to the ferritin iron [5]. It is advantageous to set τ to be less than Δt in order better sample the initial part of the decay curve. The total iron concentration may be estimated as: $C = C_f + C_h$, where $C_f = Q_0+ Q_1\times R_2$, $C_h = Q_2 \times A$, and Q_0, Q_1, Q_2 are empirical calibration parameters, which can be determined from a best fit of the MRI measurements to independent iron estimates derived from biopsy or SQUID biosusceptometric [1] measurements. A unique feature of this approach for measurement of tissue iron by MRI is that it yields separate estimates for the ferritin (C_f) and hemosiderin (C_h) iron concentrations.

Methods

Six healthy subjects and 19 patients with transfusion-dependent thalassemia were examined at the Hatch NMR Research Center of Columbia Presbyterian Hospital using various multiple spin echo sequences on a Philips 1.5 T Intera scanner equipped with a five-element SENSE cardiac coil. For the measurement of iron in liver and myocardium, three slices of 10 mm thick with a matrix of 128×128 within a field of view of 37cm with an inter slice gap of 1 mm in an oblique orientation yielded a short axis orientation of the heart and sufficient cross sections of the liver. To estimate the two relaxation parameters: transverse relaxation rate R_2 and hemosiderin index A, three CPMG-based multi-echo spin echo sequences were used: a 25-echo with inter-echo time 4ms, a 15-echo (first echo 4ms, inter-echo 8ms), and a 10-echo (first echo 4ms, inter echo 15ms) sequence, each with ECG triggering (delay set to image at systole to minimize wall motion and blood flow artifacts) and respiratory navigator gating to compensate for cardiac and respiratory motion artifacts. The two parameters were estimated from global fitting of the 3 CPMG data sets.

Results

Figure 1 shows CPMG signal decay in the liver of a patient with iron overload and in the liver of a healthy control. The global fitting of the decays (solid line) found higher values for parameter A in iron-loaded than in healthy liver. Figure 2(a) shows the correlation between the total (ferritin + hemosiderin) storage iron as determined by our new method and measurements of total storage iron by biopsy or biomagnetic susceptometry (SQUID). Figure 2(b) shows the proportion of the total storage iron within hemosiderin as a function of the total storage iron concentration.

Conclusions and discussions

Using our new two parameter method, the modified multi spin echo sequences with three different inter-echo times, together with parallel imaging and a motion suppression gating system, provided high quality images yielding accurate estimates of the total storage iron concentration in the liver. As expected, the proportion of iron stored as hemosiderin, as determined by our method, increased as the total storage iron concentration increased. The ability to separately measure ferritin and hemosiderin iron may be clinically useful in evaluating patients with iron overload and in monitoring the results of treatment with phlebotomy or chelation.

References

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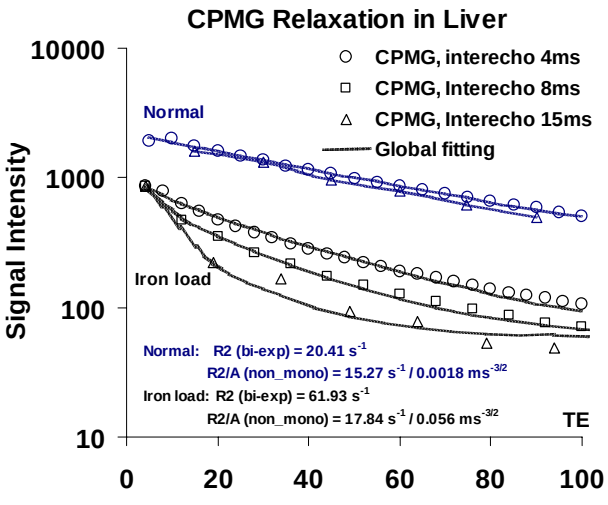

Figure 1. CPMG relaxation in healthy and iron-load liver.

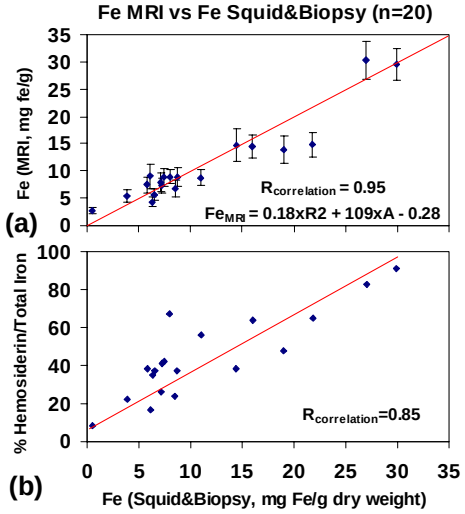

Figure 2. MRI iron concentration vs. estimated iron