Quantification of Ferritin Iron in Presence of Hemosiderin

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Introduction

To improve the MRI measurement of ferritin iron in the presence of hemosiderin iron, we extend our earlier theoretical approach [1] by incorporating an additional fitting parameter and examine the feasibility and validity of the modified method in studies of phantoms. In patients with iron overload, virtually all of the excess iron is sequestered as storage iron, in ferritin, a diffuse, soluble fraction that can be rapidly mobilized, and in hemosiderin, an aggregate, insoluble fraction that serves as a long-term stockpile. We hypothesize that the readily mobilizable iron in ferritin is in closer equilibrium with the putative toxic pool of low molecular weight iron than are the long-term deposits of iron in hemosiderin. In iron-loaded tissue, such as heart or liver, conventional relaxation rate parameters, such as R_2 and R_2*, typically are affected primarily by hemosiderin iron. Our new method should improve the measurement of ferritin iron in the presence of hemosiderin iron and may provide a clinically useful means for the detection and monitoring of iron-induced tissue damage.

Theory

The method is an extension of a previously proposed technique based on the non-monoexponential signal decay induced by hemosiderin iron for multiple spin echo (MSE) sequences [1-4]. Consider a shifted MSE sequence with a first (n = 1) echo at a time 2τ and subsequent echoes at 2τ + $2\Delta t(n - 1)$, for n = 2, 3, … The signal intensity, S, of an echo at a time t can then be fit to the functional form

$$S(t) = S_0 \exp\left\{RR_2 t - A^{3/4}\left(\Delta t\right)^{3/4}\left(t - t_s\right)^{3/8}\left[1 + W\left(t/\tau, \Delta t/\tau, z\right)\right]\right\}, \quad (1)$$

where S_0 is the initial signal intensity, A is the "hemosiderin index," RR_2 is the "reduced relaxation rate," $t_s \equiv 2\tau[1 - (\tau/\Delta t)^2]$, and $z \equiv D\tau^{1/3}/(q\gamma KB_0)^{2/3}$ with D being the water diffusion coefficient, q being the mean iron mass/particle, γ being the proton gyromagnetic ratio, K being the iron mass specific magnetic susceptibility, and B_0 being the applied field. For W = 0, Eq. (1) corresponds to the fitting form upon which our previous iron quantification approach is based [1-4]. The added function W is a correction term that includes a fourth fitting parameter, z. Although we do not possess an exact analytic expression for W, it is straightforward to calculate this function with numerical Monte Carlo techniques. By fitting experimental data to Eq. (1), one derives estimates for S_0, RR_2, A, and z. Iron concentrated in particles, such as hemosiderin, with a mean separation comparable to or larger than the diffusion length, $(6Dt)^{1/2}$, affects mainly A, while more uniformly distributed iron, such as ferritin, affects mainly RR_2. The parameter z depends on the mean iron mass per particle, q, but not on the iron concentration.

Methods

Eighteen bottles were prepared containing 2% agarose, 5.8 μm iron oxide (magnetite) microspheres (4.4×10^{-9} mg Fe/particle), and $MnCl_2$. The microspheres were chosen to simulate hemosiderin iron, while the uniformly distributed $MnCl_2$ was chosen to simulate ferritin iron. The $MnCl_2$ concentrations were 0.135, 0.405, and 0.675 mM, and for each $MnCl_2$ concentration there were six bottles with iron particle concentrations ranging from 0 to 0.1 mg Fe/cm^3. The phantoms were imaged at room temperature on a Philips 1.5 T Intera scanner with three different MSE sequences. All the sequences had τ = 2 ms, but differing values for Δt (2, 4, and 8 ms), and the final echo occurred at 100 ms in each case. The signal decay data for the even order echoes (i.e., n = 2, 4, 6 …) were fit globally to the form of Eq. (1) using the Marquardt method. The use of three different MSE sequences significantly improved the accuracy of the parameter estimates, and the restriction to even echoes reduced the effect of refocusing pulse imperfections. A conventional R_2 estimate based on a monoexponential fit of the signal decay data to the MSE sequence with Δt = 2 ms was also obtained as a reference. In addition, a multiple gradient echo sequence with 17 echoes and an interecho time of 0.91 ms was used to estimate R_2*.

Results and Discussion

The hemosiderin index A was found to be highly correlated (r^2 = 0.957) with the particulate iron concentration, while being independent of the $MnCl_2$ concentration ($r^2 < 10^{-4}$), suggesting that this parameter can be used to quantify hemosiderin iron. Figures 1-3 show R_2, R_2* and RR_2 as functions of the $MnCl_2$ concentration, C_{Mn}. Fewer data points appear in Fig. 2, since meaningful R_2* values for two of the bottles could not be determined due to a low signal-to-noise ratio. As can be seen for both R_2 (r^2 = 0.495) and R_2* (r^2 = 0.024), the values for different particulate iron concentrations vary considerably, while those obtained for RR_2 (r^2 = 0.935) are essentially independent, showing that this parameter can be used to estimate the $MnCl_2$ concentration even in the presence of particulate iron. Therefore, use of the reduced relaxation rate RR_2 should result in improved estimates for ferritin iron concentrations in iron overload patients.

Fig. 1

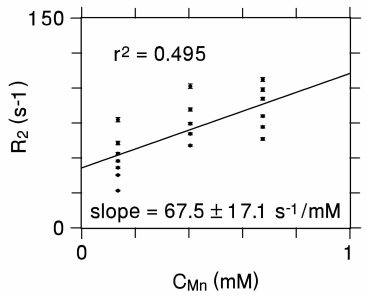


Fig. 2

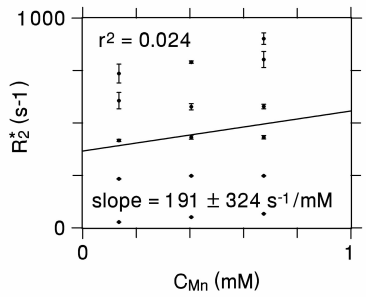
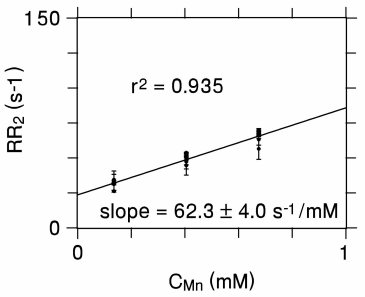


Fig. 3



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