MR estimation of myocardial ferritin iron and hemosiderin iron in thalassemia major

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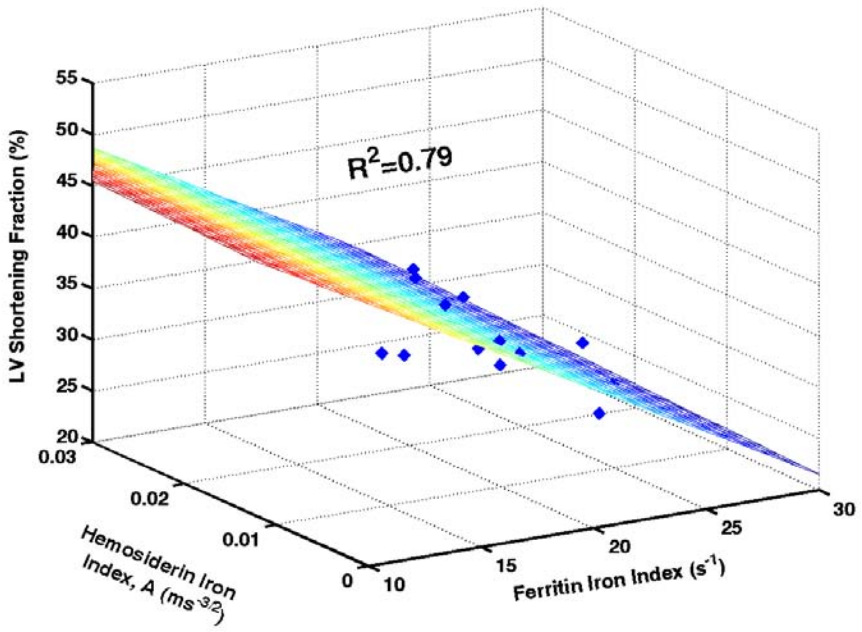
Introduction We have used a novel magnetic resonance (MR) method [1, 2] that separately estimates the two major forms of storge iron, ferritin and hemosiderin, to examine the relationship between myocardial storage iron fractions and left ventricular function in thalassemia major. New, non-invasive methods to directly measure heart iron are needed to improve the diagnosis and management of patients with the cardiac complications of iron overload [3]. Iron overload has little effect on the amount of iron in functional and transport pools; almost all of the excess is sequestered in paramagnetic storage forms of iron, as ferritin, a diffuse, soluble fraction, and as hemosiderin, an aggregate, insoluble fraction. Differences in the solubility and distribution of ferritin iron and of hemosiderin iron produce distinguishable effects on the T_2 and T_2* weighted MR images [1, 2, 4]. In this study, myocardial ferritin and hemosiderin iron were estimated in patients with thalassemia major and compared to the left ventricular shortening fraction as determined by concurrent echocardiography. A clinical summary of these data has been described elsewhere in abstract form [5].

Theory The T_2 signal in a CPMG multi-echo spin echo sequence in the presence of diffusely distributed soluble ferritin particles will have a monoexponential decay. Alternatively, the presence of aggregate and insoluble hemosiderin clusters causes significant deviation from monoexponential decay in a way that strongly depends on the interecho time. The T_2 decay curve of tissue containing both forms of storage iron is predicted to have the approximate analytic form:

$$S(t)= S_0 \exp(-RR_2 \times t) \times \exp(-A^{3/4} (\Delta t)^{3/4} (t-t_s)^{3/8}),$$

where $t_s=2\tau[1-(\tau/\Delta t)^2]$. 2τ is the first spin echo time, $2\Delta t$ is the interecho time, t is the time the echo is observed, A is the hemosiderin index, and RR_2 is the "reduced" transverse relaxation rate [1]. The parameter A is related to the concentration of hemosiderin iron, and RR_2 is related to the ferritin iron contained in the tissue [1]. The timing of the first 180 degree pulse is chosen to be shorter than subsequent echoes in order to better sample the critical initial part of the T_2 decay curve. A series of these sequences with different interecho times can be used to determine a value for RR_2 and A, which we refer to as the ferritin and hemosiderin indices given their respective dependences on the concentrations of these components.

Methods Thirteen patients with transfusion-dependent thalassemia were examined on a Philips 1.5 T (Philips Medical Systems, Best, The Netherlands) Intera scanner equipped with a five-channel SENSE cardiac coil. Three slices where acquired with a double oblique heart short-axis orientation with slice thickness 10mm, slice gap 1mm, resolution 128x128, and field of view 37cm. Three CPMG-based multi-echo spin echo sequences were used with the first echo at 4ms and subsequent interecho times of 4ms (25 echoes), 8ms (15 echoes), and 15ms (10 echoes). ECG triggering was used to minimize cardiac wall motion and real time navigator (RNAV) gating was used for free breathing data acquisition. The theoretical model of J.H. Jensen and R. Chandra [1] was used to estimate the parameter RR_2 and A from a global fitting of the 3 CPMG sequences. The fitting parameters RR_2 and A are determined by least squares minimization using the Levenberg-Marquardt method. Errors for these values are obtained from the covariance matrix of the resultant fit. The regions of interest were chosen in the ventricular septum to avoid cardiac great vessels. The left ventricular shortening fraction was measured using standard echocardiographic techniques.



Results The Figure shows a 3D plot of the relationship between the ferritin index (RR_2), the hemosiderin index (A) and the left ventricular shortening fraction. Multiple linear regression analysis found a highly significant relationship (R^2=0.79; $P < .0001$) between the ferritin iron index, RR_2, the hemosiderin index, A, and the left ventricular shortening fraction. Examination of the regression coefficients indicated that the ferritin index, RR_2, was responsible for almost all of the relationship ($P < 0.0001$); the contribution of the hemosiderin index, A, was not significant ($P > 0.9$).

Discussion and conclusion These findings suggest that the ferritin iron index, RR_2, is closely related to cardiac dysfunction with thalassemia major. Hemosiderin iron seems to have little direct effect on heart function. Magnetic resonance determinations of the partition of storage iron between ferritin and hemosiderin may be clinically valuable in the assessment of tissue iron toxicity in patients with transufsional iron overload.

References 1. Jensen JH, Chandra R. Magn Reson Med, 47:1131, 2002. 2. Sheth S, Tang H, et al. Ann. N.Y. Acad. Sci, 1054: 358-372 2005. 3. Brittenham GM and Badman DG. Blood, 101: 15, 2003. 4. Jensen PD, Br J Hæmatol 124: 697-711, 2004. 5. Sheth S, Tang H, et al. Blood 106; in press, 2005.

Figure 1. Three dimensional plot of MR determined Ferritin and Hemosiderin Iron Indices vs. left ventricular shortening fraction. The plane is the best linear regression fit to the two variables.