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R_2 Imaging of Ferritin Iron in Thalassemic Patients Off and On Iron-Chelation Therapy

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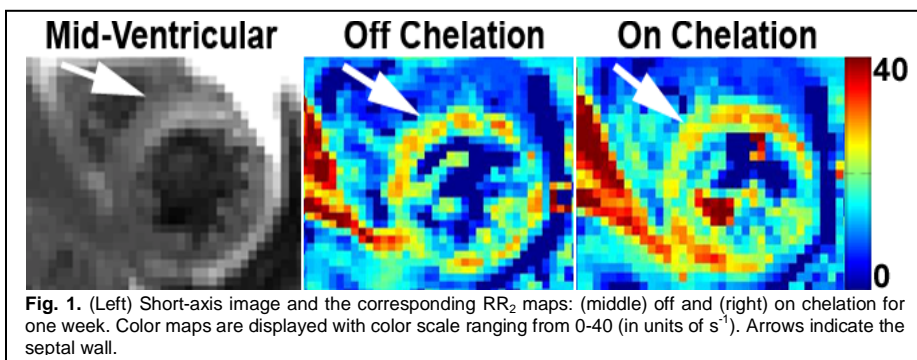
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Introduction: For patients with transfusional iron overload, improved non-invasive methods for monitoring iron-chelating therapy are needed. As transfusional iron overload develops, almost all the excess iron is sequestered intracellularly as *ferritin iron*, a dispersed, soluble fraction that can be rapidly mobilized, and *hemosiderin iron*, an aggregated, insoluble fraction that serves as a long-term reserve. Recent investigations provide compelling evidence that the intracellular ferritin iron concentration is in equilibrium with the low molecular weight cytosolic iron pool [1] accessed by iron chelators. Consequently, measurements of tissue ferritin iron concentrations could provide an indicator of the effectiveness of iron-chelating agents. MRI offers a means to non-invasively assess tissue iron concentrations in both liver and heart by exploiting the paramagnetic effects of iron on the relaxation rates of solvent protons, such as R_1, R_2, or R_2^*. At present, the most widely used method is breath-hold R_2^* imaging [2], which has been shown to detect myocardial [3] and hepatic [4] iron deposition. R_2^* is predominantly influenced by hemosiderin iron and changes very slowly even with intensive iron-chelating therapy [5]. We propose a breath-hold fast spin echo (FSE)[6] sequence for accurate imaging of myocardial and hepatic R_2 [7] that permits calculation of RR_2, a "reduced R_2" that provides a measure of ferritin iron that is independent of hemosiderin iron [8]. The purpose of our study was to compare the sensitivity of RR_2 (as a measure of ferritin iron) with that of conventional relaxation times, R_2 and R_2^*(as predominantly reflecting hemosiderin iron) in detecting changes in myocardial iron produced by one week of therapy with the oral iron-chelating agent, deferasirox.

Methods: The breath-hold R_2^* and FSE sequences were implemented on a 1.5T whole-body MR scanner (Avanto, Siemens) equipped with a 32-channel cardiac array coil. For pulse sequence details, please see references [2, 7], respectively. Relevant imaging parameters for the FSE sequence include: FOV = 340 x 276 mm, matrix = 128 x 78, slice thickness = 10 mm, GRAPPA acceleration factor = 1.8, BW = 500 Hz/pixel, ESP = 5.6 ms, echo-train duration ~ 120 ms, double-inversion black-blood preparation pulse, and breath-hold duration of 20-22 s. Image acquisition was repeated for two additionally different inter-echo spacing (ESP) of 7 (BW = 295 Hz/pixel; number of images =8) and 10 ms (BW = 155 Hz/pixel; number of images =6), respectively, in order to quantify non-monoexponential T_2 decay in the presence of soluble (ferritin) and particulate (hemosiderin) iron [8]. Relevant imaging parameters for the R_2^* sequence include: FOV = 340 x 276 mm, matrix = 128 x 78, slice thickness =10 mm, GRAPPA acceleration factor = 1.8, BW = 1500 Hz/pixel, ESP = 0.97 ms, number of images = 10, black-blood preparation pulse, flip angle = 15°, and breath-hold duration = 9-10 s. Five adult patients (4 males; 1 female) with thalassemia major were imaged in a mid-ventricular short-axis view of the heart, first after being off iron-chelating therapy for one week, and second after resuming iron-chelating therapy (deferasirox, 20 to 30 mg/kg daily) for one week. The region-of-interest (ROI) was manually drawn to segment the septal wall, as previously described [3]. R_2^* was calculated by performing monoexponetial fitting of its data set, and R_2 was calculated by performing monoexpoential fitting of the shorted ESP FSE data set. The reduced R_2 (RR_2) was calculated by non-linear least square fitting of the three sets of non-monoexponential relaxation curves with different ESPs [9]. RR_2 has been shown to be able to detect ferritin levels independently of hemosiderin levels [8]. The R_2^*, R_2, and RR_2 values were compared between off and on chelation states.

Results: Figure 1 shows a representative short-axis image (Subject 5) and the corresponding myocardial RR_2 maps after one week off iron-chelating therapy (middle panel) and one week after resuming iron chelation therapy (right panel). Table 1 shows the values for myocardial R_2^*, R_2, and RR_2 after one week off iron-chelating therapy (chelation off) and one week after resuming iron chelation therapy (chelation on). The effect of one week of iron-chelating therapy was reflected by a decrease of RR_2 from a mean of 27.4 to 24.8 s-1 (P = 0.006, using a paired t-test). No significant differences were found in myocardial R_2 or R_2^*.

Discussion: These results provide evidence that a single week of deferasirox iron-chelating therapy produces a decrement in myocardial iron detectable as a significant decrease in RR_2. This observation is consistent with the hypothesis that RR_2 measures myocardial ferritin iron which is in equilibrium with the low molecular weight cytosolic iron pool accessed by iron chelators. Conventional relaxation times, R_2 and R_2^*, predominantly influenced by hemosiderin iron, showed no significant change. Measurement of myocardial RR_2 may provide a new means of rapidly evaluating the effects of iron chelators on heart iron. Future work will thoroughly validate the RR_2 imaging method for monitoring iron-chelation therapy for both heart and liver iron.

Fig. 1. (Left) Short-axis image and the corresponding RR_2 maps: (middle) off and (right) on chelation for one week. Color maps are displayed with color scale ranging from 0-40 (in units of s^{-1}). Arrows indicate the septal wall.

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Table 1. R_2^*, R_2, and RR_2 values of all five patients: off and on chelation therapy for one week. Only the RR_2 (p < 0.006) was significantly different between the two chelation states.

Subject	R_2^* (s^{-1})		R_2 (s^{-1})		RR_2 (s^{-1})	
	Chelation Off	Chelation On	Chelation Off	Chelation On	Chelation Off	Chelation On
1	74.89	94.09	34.47	32.08	33.44	29.75
2	121.98	129.92	32.72	33.85	28.90	27.87
3	81.29	80.40	33.37	30.64	28.94	26.92
4	50.84	42.77	24.63	23.15	23.82	20.52
5	35.49	48.26	23.75	20.79	21.87	19.14