R2* Quantitation Reveals That Serum Ferritin is an Unreliable Surrogate for Tissue Iron Concentration in Myocardium and Liver

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INTRODUCTION Humans do not have an effective mechanism to excrete iron. Iron overload is caused by increased intestinal absorption or by parenteral iron administration as blood transfusions. The prevalence of hereditary hemochromatosis in Northern European descendents is 1 per 200, with 10% heterozygous for HFE-variant.[1] Excess iron results in hepatic, endocrine, and cardiac dysfunction, arthritis, and susceptibility to specific infections. Management of iron overload requires frequent evaluation of body iron stores, most commonly by measurement of serum ferritin. Determination of the liver iron concentration by tissue biopsy is still regarded as the best predictor of total body iron, but the procedure is invasive and has risks. In the heart, non-uniform distribution of iron renders endomyocardial biopsy an unreliable and invasive measure. Alternatively, R2* (R2* = 1/T2*) quantitation can provide estimates of tissue [Fe], calibrated for specific tissues via tissue biopsies.[2-5] This project acquires R2*-based estimates of the actual liver and myocardium [Fe] in patients with expected iron overload for comparison with serum ferritin levels. Because serum ferritin is acute phase reactant, we hypothesize that it is not a reliable predictor of tissue iron concentration.

METHODS Patients were eligible if they had hemochromatosis or transfusional iron overload (received ≥50 units of RBC transfusions), and were ≥18 years old. IRB approval was obtained, and informed consent was given by each participant prior to study entry. Images were acquired using a research multiple-gradient-echo pulse sequence designed specifically for quantitative R2* imaging, *mfgre*, and a 8-channel body coil array at 1.5T (GE Healthcare, 1.5T Excite HD 12.0 M4). The first echo was acquired as a partial echo to minimize the first TE. ECG-gated heart acquisitions were obtained during 1 breath-hold for 21 heart beats. Other common parameters: 10 mm slice thickness (oblique orientation for left ventricle short-axis views), 45º FA, 1 NEX, 0.7-1.0 phase FOV,; Cardiac: 62-125 kHz bandwidth, 192 x 128 matrix, 22.5 TR, 2.57 ms echo spacing, and 6 views per segment. Liver acquisitions were done using: 1 breath hold, 256x128, 150 TR, echo spacing 1.0-2.5 ms, 100 kHz. Custom Matlab applications were employed to compute and analyze the liver and myocardium. For each slice location, R2*(x,y) was computed at each voxel location by fitting to Equation 1, where *S0* = unknown SI at time 0 ms, *R2**= unknown tissue value, and *C* = unknown noise level. Figure 1 shows fitted results producing an estimated R2* map for liver and myocardium. Tissue [Fe] as a function of ROI R2* has been experimentally determined to be Equation 2, and will be tabulated in the presentation.[6] ROI analysis is supported: drawing the desired ROI, display of ROI statistics, graphical display of the curve fit (seen in Figure 2), and the histogram of the ROI voxel values.

$$SI(TE) = S_0 e^{-R2^* \cdot TE} + C \quad (1)$$

$$[Fe]_{R2^*} = 0.0254 \cdot R2^* + 0.202 \quad (2)$$

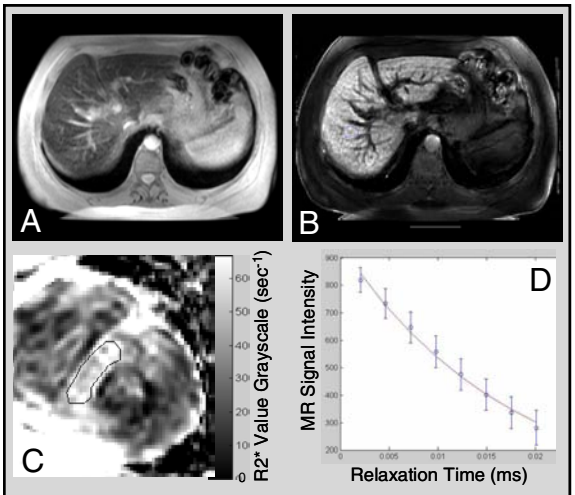

Figure 1 Original and Parametric R2* Images
Figure A is the original 2nd echo image of 8 for liver R2* computation. B shows the resulting parametric R2* image. Liver R2* = 262 sec-1. C shows the R2* map of LV myocardium, revealing remarkable heterogeneity of [Fe]. R2* for the indicated ROI is 58 sec-1. D shows the fitted data for the septal ROI shown in C.

RESULTS and DISCUSSION Fifteen patients and 2 volunteers have been enrolled in the study to date. Study data will be tabulated in the presentation. Table 1 provides the core results--pair-wise correlations for liver R2*, myocardium R2*, and serum ferritin. Myocardium R2*, and hence myocardial [Fe], does not correlate significantly with either serum ferritin or liver R2*. Thus myocardial [Fe] and hepatic [Fe] are not tightly coupled. This suggests that the processes of iron pathophysiology in liver and myocardium differ in clinically significant ways.

Table 1. Correlations

		Liver R2*	Heart R2*
Ferritin	Pearson Correlation	0.874	0.049
	Sig. (2-tailed)	0.048	0.003
	N	15	16
Heart R2*	Pearson Correlation	-0.097	
	Sig. (2-tailed)	0.012	
	N	15	

The patterns of heterogeneity of myocardial [Fe] indicated in the parametric R2* images varied remarkably. Figure 1C shows the extreme example of this. Spatial variations in [Fe] can be both slowly varying—by a factor of 4 in Figure 1C, as well as small localized regions of high [Fe] with concentrations as high as ~0.2 mg/g in our patient series. Importantly, note that no other means for clinically observing regional myocardial [Fe(x,y,z)] exists. R2* quantitation enables investigation into the roles of iron in congestive heart failure, idiopathic arrhythmias, and pericarditis, and any other organ of interest. The noninvasiveness of R2* methods enables effective monitoring of therapeutic response and clinical case management without biohazard.

Liver R2* did correlate significantly with serum ferritin. The data suggests an exponential relationship between serum ferritin and liver [Fe] at high concentrations. There is a large amount of variability in the serum ferritin measures, which range from 38 to 3100 mg/dL. Given our small sample and the very large standard deviation for ferritin, these results must be interpreted with caution as potential spurious results. The constant 'C' term in Equation 2 has not been included in most published studies employing R2* quantitation. At higher tissue [Fe], fitting with the 'C' term results in a better intuitively appearing result, and in generally higher R2* estimations. One recent publication on this specific topic strongly advocates including the constant.[6]

The preliminary findings from this limited clinical series suggest that serum ferritin may not be an accurate surrogate of the concentration of iron in either liver or myocardium as measured by MRI.

REFERENCES

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