Compartmental Analysis of R2 measurements of Hepatic Lipid and Iron In Vivo using Breath-hold Multi-Echo ^{1}H Spectroscopy (HISTO)

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Introduction: The presence of iron with hepatic steatosis is a common manifestation of diffuse liver disease. The etiological significance of hepatocellular iron remains an area of continued investigation. Single-voxel magnetic resonance spectroscopy (MRS) is technique known to accurately measure lipid fraction in the liver. Whereas imaging displays the weighted contribution of metabolic species within a voxel, an advantage of MRS for lipid quantification is the separate display of water and lipid spectral peaks, allowing analysis of the individual component behavior. Since the transverse relaxation rate, R2 or R2*, is related to hepatic iron content, T2-corrected lipid quantification additionally provides an estimation of iron content. Liver phantom studies have shown that R2 of the water component ($R2_{water}$) using MRS is linearly related to iron level, while R2 of the lipid component ($R2_{fat}$) remains generally unaffected [1]. However, this influence of iron-related susceptibility effects on $R2_{water}$ and $R2_{fat}$ remains unexplored in vivo.

Purpose: The objective is to investigate the compartmental dependence of R2 on iron deposition in vivo using breath hold single-voxel T2-corrected (HISTO-MRS) spectroscopic analysis. The water/lipid-iron interactions observed in liver phantoms with MRS will be examined in human subjects with known hepatic steatosis and iron deposition, and implications on MRI-based iron estimation delineated.

Methods: This study protocol was IRB approved and HIPAA compliant. All MRI and MRS acquisitions were performed on a Siemens 1.5T Avanto system, using phase-array body coils. ***Patients –*** All participating subjects signed informed consent. 27 patients (12 male, 52.9 ± 13.4yrs) with known steatosis, iron deposition, or combined disease (based on prior T1 in/opposed-phase MRI), who were scheduled for routine contrast-enhanced abdominal MRI, underwent an additional breath hold HISTO-MRS acquisition to quantify R2 (of water and lipid) and lipid fraction. As a primary evaluation of the presence of hepatic iron, a 2pt 3D gradient-echo (GRE) sequence was also acquired. ***HISTO analysis –*** The multi-echo HISTO-MRS technique has been described previously [2]. The adjustable TE was fixed to {12, 24, 36, 48, 72}ms. Other pertinent parameters were TR=3000ms, 1200Hz bandwidth, 1024 acquisition points, and mixing time (TM) = 10ms. A 27cm^3 voxel was placed in a region fully within the liver, away from edges and avoiding major hepatic vessels. Overall scan duration was 15 secs. Data was exported off-line for processing (Matlab, Mathworks, Natick, MA), where water and lipid spectra at each TE were analyzed automatically by determining peak area over a user-defined frequency range (water peak: 4.6ppm; lipid peak: 1.3, 2.0ppm). Least-squares mono-exponential fitting of integrated peak areas allowed estimation of T2 and equilibrium signal (M_0) of each metabolite. The T2-corrected lipid content was calculated from: %lipid = M_{0lipid} / (M_{0lipid} + M_{0water}). ***MRI-R2* Analysis –*** A fast 3D GRE sequence was acquired using 2 in-phase echoes (4.5ms and 9.0ms) for R2* estimation via least-squares fitting. The acquisition consisted of approximately 46 slices at 3mm thick, TR=11.7ms, FA = 10 deg, field-of-view = 400 x 300mm, matrix 256 x 160, bandwidth = 500Hz/px, and parallel acquisition (factor=2). In this study, measurements of MRI-derived R2*, within the MRS voxel region-of-interest, were used as an empirical reference for the existence and extent of hepatic iron. R2 of water and fat from MRS analysis was compared to R2* by linear regression.

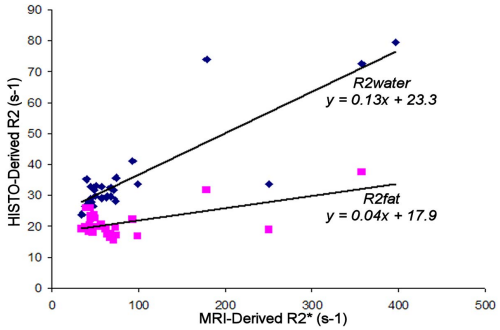

Figure 1. Relationship between HISTO-R2 and MRI-R2*

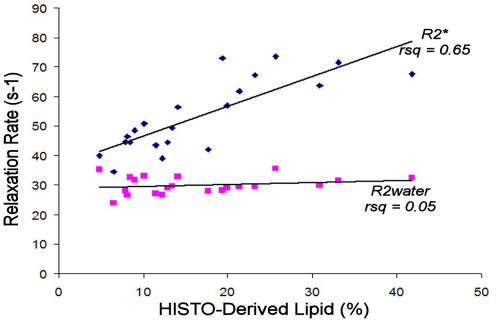

Figure 2. Relationship between relaxation rates and measure lipid%

Results: Hepatic lipid was detected in all subjects except one, who had iron deposition exclusively. The range of hepatic lipid measured by HISTO-MRS was 0% to 41.8%. The presence iron, which was estimated empirically by MRI-derived R2* values, spanned 34.5s^{-1} (low) to 396.8s^{-1} (very high). In all MRS cases, $R2_{water} > R2_{fat}$, with larger differences evident for increasing R2* values. Figure 1 compares HISTO-derived $R2_{water}$ and $R2_{fat}$ against R2*. Considering all subjects, there existed a significant correlation between R2 and R2*, with r=0.86 and r=0.59 for $R2_{water}$ ($p<0.001$) and $R2_{fat}$ ($p<0.01$), respectively. However, there was also a significant difference between the $R2_{water}$ and $R2_{fat}$ regression lines themselves ($p<0.0001$), which suggests higher $R2_{water}$ sensitivity for iron, than for $R2_{fat}$. Furthermore, 92.3% (24/26) of $R2_{fat}$ measures were less than 26.0s^{-1} (20.0s^{-1} +/- 2.8), with the two higher values associated with broad spectral widths and very high corresponding R2* values. Considering only low to moderately-high empirical levels of iron (R2* < 80.0s^{-1}), $R2_{water}$ did not significantly correlate with R2* (n=21, r=0.39, p=0.07). This may be due to the integrated R2* contributions from water and lipid metabolites within an MRI-voxel at lower iron, or higher hepatic lipid levels. Figure 2 depicts the relationship between relaxation rate (R2 and R2*) and HISTO-derived lipid%. Despite the greater inherent dynamic range of R2* for iron, higher values of R2* were significantly associated with higher levels of hepatic lipid ($p<0.001$), while this was not found for $R2_{water}$ (p=0.30).

Conclusions: The results in this clinical investigation of HISTO-MRS-derived R2 measures closely parallel phantom results observed previously [1], which demonstrate that there is low variance of $R2_{fat}$ for low to moderately-high tissue iron levels, while $R2_{water}$ demonstrates a high positive correlation with iron. This suggests a dominant water-compartmental dependence to hepatic iron deposition. In contrast to MRS, our data suggest that MRI measures of R2*show some sensitivity to hepatic lipid% in addition to iron, which can be accounted for by voxel averaging of water and lipid R2* components on MRI. In conclusion, HISTO-MRS provides a technique for measuring hepatic lipid and iron concurrently, with advantages over MRI in livers that have both iron and lipid accumulation.

References: [1] Sharma P, et al. ISMRM 18, 2010, #555. [2] Pineda N, et al Radiology 2009: 252(2):568-76