Fat Quantification Using SPIO as a Surrogate Marker for Iron Accumulation in the Liver

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INTRODUCTION: The differing precessional frequencies of water and lipid protons can be used to construct in-phase (IP) and out-of-phase (OP) images whereby the magnetization vector of water is aligned with or opposed to the magnetization vector of fat, respectively. When there is loss of signal intensity on OP images compared to IP images, an admixture of water and lipid within tissue can be inferred. Quantitative comparison of OP and IP signals can be used to estimate the fat signal fraction in tissues such as liver. However, the sequential OP-then-IP acquisition order causes an underestimation of true fat content since both water and fat undergo T2* decay during the inter-echo interval. This can be expressed in terms of the measured fat fraction (FF_{meas}) compared to the true fat fraction (FF_{true}) in the following equation [1].

$$FF_{meas} = (IP - OP) / (2IP) \approx (1 - \delta)\, FF_{true} \quad \text{where} \quad \delta = (\Delta TE/T2^*)\, [1 / (2FF_{true}) - 1]$$

The effect of T2* relaxation is even more pronounced in iron-containing tissue, in which T2* is shortened [2], thereby exacerbating the underestimation of true fat content. In this study, 11 patients with known or suspected fatty liver disease were administered ferumoxides, a super paramagnetic iron oxide (SPIO) MR contrast agent, to experimentally induce the T2* shortening associated with endogenous hepatic iron accumulation.

PURPOSE: We hypothesize that accounting for the T2* decay of water and fat allows for stable measurements in FF despite experimental perturbations in T2*. The model of the signal included water and fat, each undergoing T2* decay, and was curve-fitted to 6 data points at different TE (6-point method), as described in [1]. Conversely, we expect FFs obtained with the traditional 2-point method to steadily decline under the same SPIO-induced perturbations. Secondarily, we hypothesize that a significant difference between FFs obtained by the two methods will be observed even prior to the administration of SPIO.

METHODS: This was a prospective, experimental study of 11 patients (ages 18-54) with known or suspected fatty-liver disease who underwent MR imaging at 1.5Tesla.The study was IRB-approved and HIPAA-compliant. All subjects signed informed consent. Subjects were given SPIO as a suspension diluted in 100 ml of 5% dextrose, which was infused intravenously through a 5 micron filter over 30 minutes (dose, 0.5 mL ferumoxides/kg) at a rate of 2-4 ml/min. A multiple gradient echo sequence was performed at intervals of 1-2 minutes before, during, and after administration of the contrast agent. Imaging parameters were TR 122ms, flip angle 10° and TE 2.3–13.8ms. In 6 subjects, single voxel spectroscopy was performed prior to SPIO using STEAM with TR 3000ms and TE 20ms. A trained reader then selected one image per sequence, and within each of these images, delineated 3 representative regions of interest (≥ 100mm^2) within the liver. In the six subjects in whom MRS was performed, one region of interest was manually co-localized to the MRS voxel. A 2-point and a 6-point FF were calculated and recorded from each region of interest. Processing and data handling were performed in MATLAB. Using fixed-effects linear regressions, FF was modeled as a function of SPIO infusion time. The slopes (measures of the rate of change in FF during SPIO infusion) and intercepts (measures of FF at baseline prior to SPIO infusion) of the two techniques were calculated. Statistical comparisons included one sample and paired two sample t-tests as appropriate.

RESULTS: The T2* of the water and fat components of liver were shortened by SPIO administration [Table 1]. FF measurements obtained with the 2-point method showed a large decline during SPIO infusion (mean regression slope = -7.9, p<0.0003), whereas FF measurements obtained with the 6-point method showed a minimal decline (mean regression slope = -0.6, p<0.03). Pre- and post-SPIO FF estimates were in close agreement using the 6-point method [Table 2], whereas the post-SPIO FF estimates were an average of 8.3 percentage points lower than the pre-SPIO FF estimates using the 2-point method [Table 2]. Moreover, the pre-SPIO FF estimates using the 2-point method were an average of 4.9 percentage points lower than those using the 6-point method (p<0.001). Figures 1 (2-point data) and 2 (6-point data) show FF estimates over time in five subjects representing a spectrum of liver fat content. In subjects with MRS, there was close agreement between the spectroscopic FF and the 6-point FF, but not the 2-point FF [Figs. 1, 2]. Shown in Figure 3 are FF maps pre-and post-SPIO using the 6-point method as well as maps showing the corresponding T2* values of water.

Figure 1. 2-point Fat Fraction: Pre- and Post-SPIO

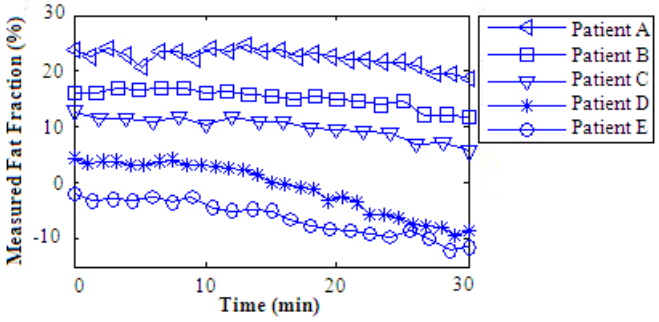

Figure 2. 6-point Fat Fraction: Pre- and Post-SPIO

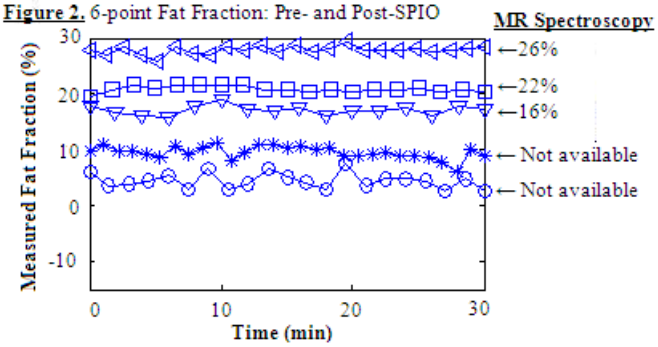

Figure 3 In vivo maps of the fat fraction from the 6-point method (A and C) and the T2* of liver (B and D). Note the uniform fat distribution in the liver apart from hemangiomas that have long T2*s and no fat.

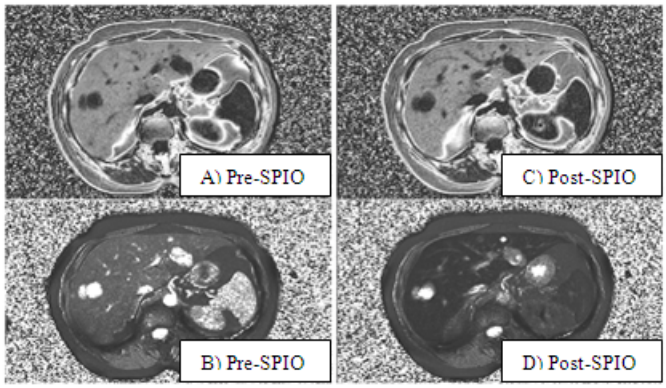

Table 1. Mean T2*

	Pre-SPIO	Post-SPIO
T2* Water	29.6 (sd=6.0)	10.6 (sd=6.4)
T2* Fat	11.4 (sd=4.0)	6.8 (sd=3.1)

Table 2. Mean Measured Fat Fraction

	Pre-SPIO	Post-SPIO
6-point	14.8 (sd=7.1)	13.6 (sd=8.0)
2-point	9.9 (sd=7.0)	1.6 (sd=11.1)

CONCLUSIONS: The 6-point method provides stable fat fraction measurements despite experimentally induced perturbations in T2*. Compared to the 6-point method, the 2-point method underestimates fat content, and the degree of underestimation increases as the T2* is shortened.

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