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Evaluation of MRI Fat Fraction in the Liver and Spine Pre and Post SPIO Infusion

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Abstract

This study evaluates the robustness of a magnetic resonance (MR) fat quantification method to changes in $R2^*$ caused by an intravenous infusion of superparamagnetic iron oxide (SPIO) contrast agent. The $R2^*$ and proton density fat fraction (*PDFF*) were measured in liver and spine in 14 subjects using an investigational sequence (IDEAL IQ) provided by the MR scanner vendor. Measurements were made before and after SPIO infusion. Results showed SPIO significantly increased $R2^*$ in both liver ($p = 8.8 \times 10^{-8}$) and spine ($p = 1.3 \times 10^{-2}$) but *PDFF*s were not significantly different in either the liver ($p = 5.5 \times 10^{-1}$) or the spine ($p = 5.6 \times 10^{-1}$). These results confirm that the IDEAL IQ method of fat quantification is robust to changes in $R2^*$.

INTRODUCTION

The amount of fat in a tissue is an important biomarker of disease states and numerous magnetic resonance (MR) methods have been developed for estimating fat content (1,2). In clinical MR imaging, the quantity of interest is the proton density fat fraction (*PDFF*). The *PDFF* is so-named to differentiate it from the fat composition measured by other modalities, which may use a different physical unit or scale to quantify fat content (e.g. Hounsfield unit or percentage of cells containing a fat droplet).

The *PDFF* in a given sample is defined as the number of protons in fat (triglyceride) divided by the total number of protons (water plus triglyceride). However, some MR methods for measuring *PDFF* are confounded by signal relaxation, in the sense that the measured quantity depends on relaxation parameters as well as the fat content. The $R2^*$ is clinically relevant as a confounding factor since iron frequently accumulates in the liver and spine and causes rapid signal decay. $R2^*$ can also vary with MR scanner settings including field strength, voxel size and bandwidth, which can introduce variability into the *PDFF* measurement. For these reasons, an important consideration in evaluating methods of measuring *PDFF* is the robustness to $R2^*$.

A conventional method for *PDFF* estimation that clearly exhibits the confounding effect of $R2^*$ is the 2-pt Dixon method, which can be shown (3) to measure the quantity

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$$PDFF_{2-pt} = \frac{IP-OP}{2IP} \approx PDFF - \left(\frac{1}{2} - PDFF\right) R_2^* \Delta TE$$

where IP and OP are the in-phase and opposed-phase signal intensities and TE is the difference in echo time between the IP and OP acquisitions. Clearly $PDFF_{2-pt}$ is not a simple measure of $PDFF$, and so its use as a biomarker of the fat content in tissues is problematic.

Current state-of-the-art methods for measuring $PDFF$ take into account the R_2^* , as well as other confounds including field inhomogeneity, R_1 relaxation, fat spectrum, noise bias and eddy currents. The literature on the topic is large and the reader is referred to a recent review article and conference proceedings for a survey of contemporary methods (2). The method considered in the present study is based on Refs (4–6) and its implementation was provided as an investigational research sequence called IDEAL IQ by the vendor.

The goal of the present study is to assess whether a current state-of-the-art method for fat quantification (IDEAL IQ) is robust to changes in R_2^* induced by an intravenous infusion of superparamagnetic iron oxide (SPIO) contrast agent. The methodology serves as a model of iron overload in organs and is similar to that of previous studies (7,8).

METHODS

Study Design and Research Subjects

This was a cross-sectional observational research study, approved by our Institutional Review Board (IRB) and compliant with Health Insurance Portability and Accountability Act (HIPAA). We enrolled 14 adult subjects with underlying liver disease (eight with chronic hepatitis C viral infection, six with non-alcoholic fatty liver disease) to undergo a research MR examination of the liver and lumbar spine before and after SPIO infusion. The study sample included 12 men and two women, ranging in age from 19 to 63 years (mean age 39 years). All subjects gave written informed consent prior to participating in the study.

MR Imaging

Subjects were scanned at 3.0T (Signa HDx, GE Healthcare, Milwaukee, WI) in axial or sagittal planes with an 8-element torso phased-array coil centered over the liver after at least two hours fasting. Respiratory bellows were applied to monitor breathing and subjects were instructed to breath-hold during the image acquisition. A dielectric pad was placed between coil and the abdominal wall.

A 3D multiple echo spoiled gradient echo sequence was used with a flyback echo train of 3, interleaved twice, to give a total of 6 echos. The TR/first TE/ ΔTE were approximately 8/1/1 ms (precise timings varied depending on field of view since minimum values were automatically selected). Other parameters were: field of view 35–45 cm, matrix 256×160×16, slice thickness 8 mm, bandwidth 1500 Hz/pixel and Array Spatial Sensitivity Encoding Technique (ASSET) parallel imaging factor 2. Scan times were approximately 25 seconds. A low flip angle of 5° was used to reduce the effects of R_1 relaxation (including those induced by SPIO contrast agent).

A SPIO contrast agent (Feridex, Bayer Healthcare, Wayne, NJ) was prepared as a suspension diluted in 100 ml of 5% dextrose and infused intravenously through a 5 micron filter over 30 min (iron dose 10 μ mol/kg of body weight) at a rate of 2–4 ml/min. Imaging was performed before and after the SPIO infusion (typical time interval 120 min).

Image Analysis

After acquisition, maps of the $R2^*$ and fat fraction were calculated using an investigational method supplied by the MR vendor (IDEAL IQ). The maps were transferred offline and measurements taken using custom-written Matlab software (The Mathworks, Natick, MA). A radiology resident (2 months experience in clinical MR and 4 years experience in research MR) selected representative axial or sagittal slices of the liver and of the spine in each subject.

Two regions of interest (ROIs) were selected for each subject, one in the liver, and another in the spine. Each ROI contained approximately 170 to 180 voxels. The liver ROIs were selected to include liver parenchyma and avoid focal lesions, biliary or vascular structures, and imaging artifact. The spine ROIs were selected in the center of a lower thoracic or upper lumbar (T12 to L3) vertebral body for each subject, and was positioned to include vertebral body bone marrow and avoid areas of partial voluming and image artifact.

Each ROI was inspected and manually adjusted, when necessary, to account for subject motion between scans. The mean signal intensity within the ROIs was recorded giving eight numbers per subject: liver $R2^*$ pre, liver $R2^*$ post, liver $PDFF$ pre, liver $PDFF$ post, spine $R2^*$ pre, spine $R2^*$ post, spine $PDFF$ pre, and spine $PDFF$ post.

Visual inspection of data showed extensive breathing motion artifact in Subject 13's data, and the liver data for this subject was not included in the analysis. Subject 13's spine data was not affected by the motion artifact and was included.

Statistical Analyses

The difference of the estimated $PDFF$ before and after the administration of SPIO was calculated in the liver (liver $PDFF$ post – liver $PDFF$ pre) for each subject. A one sample t -test was performed on the difference values to determine if SPIO significantly changed $PDFF$ estimation. This was repeated for the liver $R2^*$ measurements. The entire process was then repeated for the spine values.

RESULTS

Figure 1 shows data from a representative subject (Subject 3), with the white circles in panels (a) and (e) indicating the liver and spine ROIs respectively. The top row shows representative axial slices of liver $R2^*$ measurements before (a) and after (b) the administration of SPIO. The liver parenchyma shows dramatically increased $R2^*$ after administration of SPIO, consistent with the known effect of SPIO. The second row shows representative axial slices of liver $PDFF$ measurements before (c) and after (d) the administration of SPIO. Qualitatively, the liver $PDFF$ maps are very similar, suggesting that $PDFF$ estimates are unaffected by $R2^*$. The third row shows representative axial slices of spine $R2^*$ measurements before (e) and after (f) the administration of SPIO. The vertebral body $R2^*$ maps appear similar before and after administration of SPIO, suggesting SPIO has little effect on the spine's $R2^*$. Axial slices showing the spine $PDFF$ before (g) and after (h) the administration of SPIO are also visually similar (bottom row).

Table 1 gives the mean $R2^*$ and $PDFF$ in liver and spine for each subject before and after the administration of SPIO. The second to last row shows the mean difference computed across subjects and the last row shows the results of the one sample t -test on the difference (post – pre) across subjects. Consistent with Figure 1, SPIO significantly increases the liver $R2^*$ ($p = 8.8 \times 10^{-8}$; mean difference 104.7 s^{-1}). The Bland-Altman plot in Figure 2a shows the liver $R2^*$ difference for every subject is positive. Despite the dramatic increase in liver $R2^*$, the liver $PDFF$ measurements are not significantly different ($p = 5.5 \times 10^{-1}$; mean

difference -0.27%). This is depicted in the Bland-Altman plot in Figure 2b, which shows relatively symmetric distribution of liver *PDFF* difference values about zero.

Although a change in $R2^*$ with SPIO administration was not visually appreciable in the spine in Figure 1, SPIO was found to significantly increase $R2^*$ in the spine ($p = 1.3 \times 10^{-2}$; mean difference 22.7 s^{-1}). As depicted in the Bland-Altman plot in Figure 2c, most but not all subjects showed an increase in spine $R2^*$ after SPIO (the majority of spine $R2^*$ differences are positive). The spine *PDFF*, however, was not significantly different pre- and post- SPIO ($p = 5.6 \times 10^{-1}$; mean difference = 0.37%), which is indicated in the Bland-Altman plot in Figure 2d.

DISCUSSION

Fat fraction measurements typically rely on multiecho methods that attribute the signal change during an echo time interval to chemical shift interference between water and fat. However $R2^*$ decay also causes a signal change over this same interval and $R2^*$ is traditionally a confound for estimating fat using clinical IP/OP imaging.

In this study, we experimentally increased both the liver $R2^*$ and spine $R2^*$ using SPIO contrast agent and measured the proton density fat fraction (*PDFF*) measurements pre- and post- infusion using a recent MR fat quantification method (IDEAL IQ). Correction for $R2^*$ employed by IDEAL IQ assumes a monoexponential signal decay, which has been shown in previous studies to provide robustness to $R2^*$ variability (7–10). The *PDFF* measured by IDEAL IQ was not significantly affected by SPIO in either liver or spine, indicating that this method is robust to differences in $R2^*$.

One interesting observation was the $R2^*$ in the spleen did not change as much as the liver. The spleen signal is sometimes used to correct liver signal to normalize for non-fat related differences between IP and OP images (11,12). While not specifically noted in the above studies, spleen correction will also partly compensate for $R2^*$ decay. A relatively minor point to make is that, since the $R2^*$ can differ between spleen and liver (at least in the case of SPIO particles), a spleen correction may not fully correct for $R2^*$ decay in the liver and should not substitute for $R2^*$ correction.

A limitation of this study is the absence of a fat fraction measurement gold standard, given we did not perform biopsies to obtain histologic quantification of fat fraction. This should not affect interpretation of our study since each subject serves as his independent control and comparison of the pre and post SPIO values would mitigate the effect of any systemic bias. In addition, several prior studies have evaluated the accuracy of MR fat fraction estimation in the absence of SPIO (13,14), and found the approach (i.e. with corrections for known confounding factors) to be accurate with respect to independent references. Taking the pre SPIO *PDFF* as a reference, the present study can be considered to validate the IDEAL IQ method in the presence of $R2^*$ decay.

A second limitation of the present study was a variation in protocol across subjects; specifically, eight subjects were scanned in axial sections and six subjects were scanned in sagittal sections. The plane of image acquisition is not thought to significantly affect the interpretation of results because careful visual evaluation of the raw data showed comparable data quality in both axial and sagittal data. Analysis performed using only the eight subjects acquired in axial section (not shown) gave very similar findings, except that the increase in spine $R2^*$ with SPIO was no longer statistically significant ($p = 9.2 \times 10^{-2}$, mean difference = 26.1 s^{-1}).

In conclusion, we have tested whether the proton density fat fraction (*PDFF*) measured in the liver and spine using an investigational MR technique (IDEAL IQ) is significantly affected by changes in $R2^*$. Our findings were that the *PDFF* is not significantly affected by $R2^*$ and hence the technique is robust to $R2^*$ variability.

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Figure 1.

Axial data from Subject 3 before (left column) and after (right column) the administration of SPIO. The first and third rows are measurements of $R2^*$ (s^{-1}), and the second and fourth rows are measurements of proton density fat fraction ($PDFF$) (%). The axial slices from the top two rows were selected to evaluate the liver, and the bottom two rows were selected to evaluate the spine. Circles in panels (a) and (e) indicate regions of interest in the liver and spine.

Figure 2.

Bland-Altman plots of R2* (left column) and proton density fat fraction (right column) measurements for each subject from the liver (top row) and spine (bottom row). The difference (y-axis) versus mean (x-axis) of the signal intensities in the regions of interest of each subject are shown. The mean difference (solid horizontal line) and ± 1.96 standard deviation (dash lines) are also shown.

R2* and fat fraction (*Pdff*) in the liver and spine before and after SPIO administration. The liver data for subject 13 was not included due to breathing motion artifact.

Table 1

Subject	Liver R2* (s ⁻¹)		Liver <i>Pdff</i> (%)		Spine R2* (s ⁻¹)		Spine <i>Pdff</i> (%)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	85.5	190.6	5.4	7.7	156.6	195.3	39.4	45.0
2	16.2	178.8	8.5	7.5	128.1	198.1	46.5	46.9
3	55.0	178.6	22.0	20.2	144.9	146.9	31.1	27.9
4	57.9	127.3	1.0	0.8	199.4	275.1	57.1	57.6
5	49.1	127.1	33.3	33.5	123.8	162.0	24.4	27.3
6	47.3	158.4	3.2	4.8	160.3	188.1	34.7	36.4
7	39.0	186.7	6.1	4.8	159.4	194.1	38.0	40.3
8	49.2	169.6	11.9	12.0	166.3	164.9	29.9	29.1
9	48.5	134.5	14.8	14.3	198.6	221.7	38.2	37.9
10	37.0	80.1	9.5	7.1	116.5	141.8	40.5	37.7
11	35.4	155.2	1.9	2.8	133.9	149.3	52.1	51.8
12	38.6	113.9	3.8	5.1	286.8	303.1	38.6	39.8
13	-	-	-	-	148.6	138.4	53.0	52.5
14	92.4	212.0	10.9	8.2	291.5	254.3	45.2	43.9
Mean Difference	104.7		-0.27		22.7		0.37	
p-value	8.8 × 10 ⁻⁸		5.5 × 10 ⁻¹		1.3 × 10 ⁻²		5.6 × 10 ⁻¹	