Effect of Hepatocyte-Specific Gadolinium-Based Contrast Agents on Hepatic Fat-Fraction and R2*

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Introduction: Accurate quantification of fat-fraction (FF) and R2* as surrogate biomarkers of liver fat and iron overload, using chemical shift based water-fat separation methods, has been developed in recent years. When these methods use spectral modeling of fat, correct for T2* decay, and correct or avoid T1 related bias (typically through low flip angles), the resulting fat-fraction and R2* measurements are protocol and platform independent[1-4]. However, gadolinium based contrast agents (GBCA's) alter the underlying T1 and R2* of liver tissue and potentially impact FF and R2* measurements. Early investigations using conventional in/opposed phase imaging with extracellular fluid GBCA's have demonstrated an important influence of the GBCA, as well as the impact of the flip angle, on the apparent FF[5]. The purpose of this work is to investigate the effects of a hepatocyte-specific GBCA's on FF and R2* using a confounder corrected chemical shift based water-fat separation method.

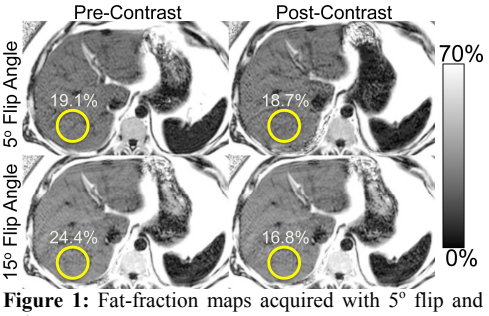

Figure 1: Fat-fraction maps acquired with 5° flip and 15° flip, before and after gadoxetic acid. FF increases at high flip angles pre-contrast, but decreases unexpectedly after contrast.

Materials and Methods: After obtaining institutional review board approval and informed written consent, 24 patients (M/F=12/12, 51.8 years (range 18-84)) were studied prospectively at 1.5T (Signa HDxt and Optima MR450w, GE Healthcare, Waukesha, WI). Imaging was performed with low (5°) and high (15°) flip angles, both before and after the IV administration of 0.05 mmol/kg of gadoxetic acid (Eovist, Bayer Health Care Pharmaceuticals Inc., Wayne NJ). Mean time after contrast was 19.9min (range=10-37min). We used an investigational version of a confounder corrected, chemical-shift based water-fat separation method to provide FF and R2* maps[6]. Imaging parameters included: axial slab, flip = 5° or 15°, TR/TE_1/ΔTE=13.5/1.2/2.0ms, ETL=6, matrix=224-256x160x32, FOV=36x32cm, slice=8mm, BW=±83-125kHz with ARC parallel imaging (R=3.2) for 21s scan time, covering the liver with 1.6 x 2.2 x 8mm^3 true spatial resolution.

Fat fraction and R2* were measured pre- and post-contrast, and at low and high flip angles, from regions-of-interest (ROIs) in all 9 Couinaud segments. Values were averaged across segments for each subject. The ROI's were copied to the corresponding R2* map and also to the other acquisition (adjusted to compensate for slight differences in breath-hold position). Linear regression was performed for correlation (r^2), slope and intercept.

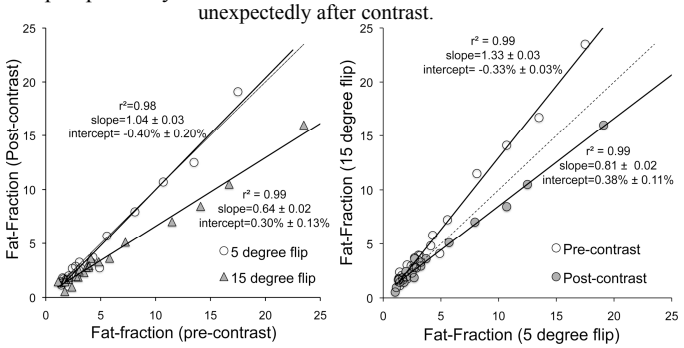

Figure 2: a) Fat-fraction is unaffected by gadoxetic acid, low flip angles are used to minimize T1 bias. **b)** Using higher flip angles, FF is over-estimated (pre-contrast) because the T1 of fat < T1 of water. Apparent FF decreases paradoxically post-contrast using high flip angle because the T1 of water must be shorter than water after contrast. Dashed lines = line of unity.

Results: Figure 1 illustrates an example from a 43-year-old man with steatosis. Good agreement between the pre- and post-contrast FF values was seen when a low flip angle was used. However, there is an apparent increase in FF using a high flip angle pre-contrast, due to T1 related bias (ref). After contrast, however, a high flip angle lead to an unexpected *decrease* in the FF. Figure 2 plots results from all subjects confirming this overall behavior.

Figure 3 shows an example of R2* maps acquired before and after contrast in a 68-year-old man. The apparent R2* increases within both the liver and the bile ducts. Figure 4 summarizes the R2* measured in all four acquisitions, demonstrating a general increase in the R2* after gadoxetic acid administration. There were no apparent differences in the apparent R2* between the two flip angles, as expected, Overall, R2* increased by an average of 10.1s^{-1} (mean R2* pre/post=33.1/43.2s^{-1}) resulting from gadoxetic acid.

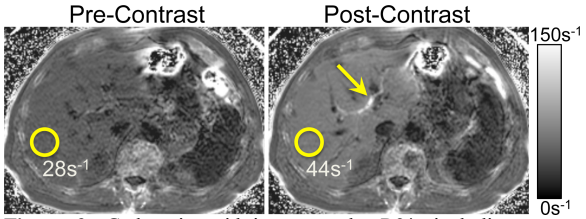

Figure 3: Gadoxetic acid increases the R2*, including severe increases in the bile ducts (arrow). Increases within the parenchyma may be clinical significant and R2* mapping after gadoxetic acid should be avoided.

Discussion: The presence of gadoxetic acid does not influence the quantification of hepatic fat-fraction, so long as low flip angles are used to minimize T1 bias. R2* measurements, however, should be avoided when gadoxetic acid is present due to an increased apparent R2* that could be misinterpreted as hepatic iron overload. Surprisingly, after contrast administration, the use of high flip angles leads to a decrease in the apparent fat-fraction. This demonstrates that intracellular gadoxetic acid has greater T1 shortening effect on tissue water than on triglycerides contained in intracellular vacuoles of fat. This may occur from reduced uptake of gadoxetic acid into steatotic cells or from limited influence of gadoxetic acid on fat vacuoles compared to tissue water.

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References: **1.** Yokoo et al Radiology 2009, **2.** Yokoo et al Radiology 2011, **3.** Meisamy et al Radiology 2011, **4.** Liu et al MRM 2007, **5.** Yokoo et al JMRI 2008, **6.** Yu et al MRM 2008.

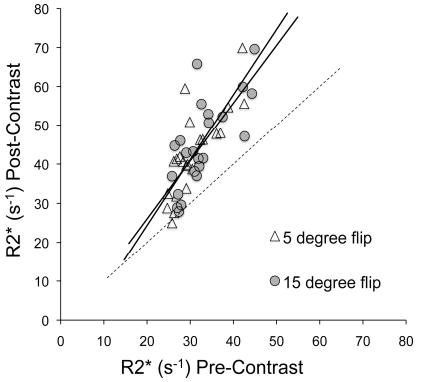

Figure 4: R2* increases after the administration of gadoxetic acid. There was no difference in R2* changes between low and high flip angles.