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Limits of Liver Fat Quantification with Chemical Shift Encoded MRI in the Presence of Iron Overload

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Abstract

Background—CSE-MRI-based tissue fat quantification is confounded by increased $R2^*$ signal decay rate caused by the presence of excess iron deposition.

Purpose—To determine the upper limit of $R2^*$ above which it is no longer feasible to quantify proton density fat fraction (PDFF) reliably, using chemical shift encoded magnetic resonance imaging (CSE-MRI).

Study Type—Prospective

Population—Cramér–Rao lower bound calculations, Monte Carlo simulations, phantom experiments, and a prospective study in 26 patients with known or suspected liver iron overload.

Field Strength/Sequence—Multiecho gradient echo at 1.5T and 3.0T

Assessment—CRLB calculations were used to develop an empirical relationship between the maximum $R2^*$ value above which PDFF estimation will achieve a desired number of effective signal averages. A single voxel multi-TR, multi-TE Stimulated Echo Acquisition Mode Magnetic Resonance Spectroscopy acquisition was used as a reference standard to estimate PDFF. Reconstructed PDFF and $R2^*$ maps were analyzed by one analyst using multiple regions of interest drawn in all nine Couinaud segments.

Statistical Tests—None

Results—Simulations, phantom experiments, and in vivo measurements demonstrated unreliable PDFF estimates with increased $R2^*$, with PDFF errors as large as 20% at an $R2^*$ of 1000s^{-1} . For typical optimized Cartesian acquisitions ($TE_1=0.75\text{ms}$, $TE=0.67\text{ms}$ at 1.5T, $TE_1=0.65\text{ms}$,

TE=0.58ms at 3.0T), an empirical relationship between PDFF estimation errors and acquisition parameters was developed that suggests PDFF estimates are unreliable above an $R2^*$ of $\sim 538s^{-1}$ and $\sim 779s^{-1}$ at 1.5T and 3T, respectively. This empirical relationship was further investigated with phantom experiments and in vivo measurements, with PDFF errors at an $R2^*$ of $1000s^{-1}$ at 3.0T as large as 10% with TE1=1.24ms, TE=1.01ms compared to 3% with TE1=0.65ms, TE=0.58ms.

Data Conclusion—We successfully developed a theoretically-based empirical formula that may provide an easily calculable guideline to identify $R2^*$ values above which PDFF is not reliable in research and clinical applications using CSE-MRI to quantify PDFF in the presence of iron overload.

Keywords

liver; fat; iron; proton density fat fraction; PDFF; $R2^*$ chemical shift encoded magnetic resonance imaging

Introduction

Intracellular accumulation of triglycerides within hepatocytes is the earliest and hallmark feature of nonalcoholic fatty liver disease (NAFLD) (30). Affecting an estimated 100 million Americans, NAFLD is now the leading cause of liver disease in the western world (1). Over the past decade, emerging quantitative confounder-corrected chemical shift encoded MRI (CSE-MRI) methods have been developed for the detection, grading, and treatment monitoring of liver fat. When all relevant confounding factors such as T1(2), noise related bias (2,3), spectral complexity of fat (4–6), eddy currents (7,8), concomitant gradients (9), and $R2^*$ signal decay (2) have been addressed, unbiased and precise measurements of the proton density fat fraction (PDFF) can be obtained (10). Indeed, confounder-corrected CSE-MRI methods have been shown to be highly reproducible across protocols, vendors, and even field strength (10,11).

Abnormal accumulation of iron in the liver is common in patients with genetic hemochromatosis, transfusional hemosiderosis, dysmetabolic iron overload syndrome (29), and other forms of systemic iron overload (12–14). Importantly, iron overload is also common with chronic liver disease and commonly coexists with hepatic steatosis in patients with NAFLD (15–17). In CSE-based liver PDFF quantification, correction for $R2^*$ signal decay is known to be of particular importance in those patients with elevated liver iron content (6,18,19). Increased $R2^*$ decay is known to cause linewidth broadening in the frequency domain and rapid signal decay in the time domain. These effects obscure the interference pattern of fat and water signal evolution and can only be corrected in cases with mild to moderate iron overload.

The level of bias and/or variability that causes PDFF estimates to be classified as unreliable will depend on specific applications and specific performance requirements. Further, the ability to separate water and fat signals depends heavily on the underlying signal to noise ratio (SNR) or the desired effective number of signal averages (NSA) (which is independent of SNR) and choice of acquisition parameters (echo times, number of echoes, flip angle, etc). Therefore, the purpose of this work is to determine upper limit of $R2^*$, above which it

is no longer feasible to quantify PDFF reliably by CSE-MRI methods for a desired NSA and given acquisition parameters.

Theory

Increasing $R2^*$ signal decay rates can cause dramatic differences in the signal evolution for tissues containing fat, as shown in Figure 1. In this figure, the time evolution of the simulated signal at 1.5T from tissue with 40% fat fraction (modeled with a 6 peak fat model (20)) and four $R2^*$ values ($25\text{-}1000\text{s}^{-1}$) is shown in Figure 1A. Figure 1B plots the corresponding frequency spectrum of the same signals. The interference pattern between water and fat signals in the time domain is more conspicuous for low $R2^*$ values, as shown in Figure 1a, and well-defined fat and water peaks are evident in the frequency domain (Figure 1B). However, as $R2^*$ increases (with increasing tissue iron content), the evolution of the water and fat signal components become nearly indistinguishable. This effect can also be observed in the frequency domain as shown in Figure 1B, where there is marked linewidth broadening, making it difficult to distinguish water and fat signals. Consequently, at severely elevated $R2^*$ levels, severe linewidth broadening leads to coalescing of the water and fat peaks rendering it impossible for a CSE-MRI method to separate the water and fat signals reliably. This work focuses on this effect and will determine a threshold $R2^*$ above which estimates of PDFF are no longer reliable.

Methods

Cramér–Rao lower bound (CRLB)

The signal equation for simultaneous water, fat, $R2^*$ quantification, is given by:

$$S(TE_n) = (\rho_w + \rho_F C_F(TE_n)) e^{-R2^* TE_n} e^{i2\pi f_0 TE_n}. \quad [1]$$

The complex signal S , measured at the n^{th} echo time TE_n ($n=1, \dots, N$) is a function of the complex water (ρ_w) and fat (ρ_F) signals, and $C_F(TE)$ which is the sum of weighted complex exponentials of a unit spectrum of fat with multiple peaks (4,5), and the frequency shift (Hz) attributed to B_0 inhomogeneity (f_0). This is the signal equation for complex quantitative confounder corrected CSE-MRI for PDFF and $R2^*$ quantification. Based on this equation, the CRLB was formulated for unbiased estimation of PDFF. The CRLB provides the lower theoretical bound on the variance of the estimated PDFF and is a useful analytical tool to analyze the noise performance of estimation techniques that are commonly used with many estimation techniques including that combined with CSE-MRI. Details of the mathematical formulation of the CRLB used in this work can be found in the previous analysis of CSE-MRI (21).

An empirical relationship between the imaging parameters and the maximum $R2^*$ where PDFF estimates are still reliable was derived by fitting a polynomial regression model to the CRLB simulations. These equations were determined by fitting CRLB simulation data, for each field strength, across a 0-20% range of PDFF values (most clinically relevant), for echo combinations of $0.1 < TE_1 < 2\text{ms}$, for echo spacings between $0.5 < TE < 2\text{ms}$, and the effective number of signal averages of $0.1 < NSA < 0.25$.

Monte Carlo Simulations

Monte Carlo simulations were performed over a physiological range of $R2^*$ (0-1000 s^{-1}) and PDFF (0-20%) values experienced in patients with known or suspected NAFLD. Computer simulations were performed to confirm the noise performance of PDFF quantification in the presence of varying $R2^*$ values, as predicted by the CRLB, by generating the signal as expressed in Equation 1, with the addition of complex Gaussian zero-mean noise.

Monte Carlo simulations with PDFF values of 0, 10, and 20%, and $R2^*$ values ranging from 0-1000 s^{-1} were compared to the CRLB at 1.5T and 3.0T with an SNR of 20 (defined as the ratio of the fat and water signal combined at time=0 to the variance of the noise). Two commonly used clinically feasible acquisition protocols were investigated, one with an early first echo and short echo spacing, and another with a later first echo and longer echo spacing (Table 1).

Phantom Experiments

Vials that mimic the simultaneous presence of fat and iron were constructed using a recently developed procedure (22). Three groups of 5 mL vials, with nominal fat fractions 0%, 15%, and 30%, were constructed with varying iron concentrations (with desired $R2^*$ = 200, 400, 600, 1000 s^{-1}). The iron concentration in each group of vials was obtained by varying the concentration of microspheres (2.9 μm diameter magnetite spheres COMPEL, Bangs Labs, Fishers, IN).

Vials were scanned in a custom designed spherical housing that was filled with deionized water to create a homogeneous magnetic field and avoid fat-water swaps. The two protocols listed in Table 1 were used to scan the phantom on a clinical 1.5T MRI system (GE Healthcare Signa HDxt, Waukesha, WI) using an 8-channel head coil (MRI Devices, Harrogate, UK) and on a clinical 3.0T MR system (Discovery MR750, GE Healthcare, Waukesha, WI) using a 32-channel torso coil (NeoCoil, Pewaukee, WI). All sequences were a commercial quantitative complex confounder-corrected CSE-MRI method (IDEAL IQ, GE Healthcare, Waukesha, WI).

In Vivo Experiments

A prospective study was performed in patients with known or suspected iron overload. Patients were recruited after obtaining approval from our local Institutional Review Board (IRB), and after obtaining informed written consent. Inclusion criteria included patients referred from the local hematology clinic with known or suspected iron overload and included all patients above the age of 10. Exclusion criteria included patients with known contraindications to MRI.

Subjects were imaged on a clinical 1.5T MR system (GE Healthcare Signa HDxt, Waukesha, WI) using an 8-channel cardiac coil (Signa HDxt, GE Healthcare, Waukesha, WI) and on a clinical 3.0T MRI system (Discovery MR750, GE Healthcare, Waukesha, WI) using a 32-channel torso coil (NeoCoil, Pewaukee, WI). The two imaging protocols listed in Table 1 were acquired using a commercial quantitative complex confounder-corrected CSE-MRI

method (IDEAL IQ, GE Healthcare, Waukesha, WI). Complex source echo images were collected for subsequent off-line reconstruction of PDFF and $R2^*$ maps.

In addition, a single voxel multi-TR, multi-TE Stimulated Echo Acquisition Mode (STEAM) Magnetic Resonance Spectroscopy (MRS) acquisition (23) was used as a reference standard to estimate PDFF in the liver of each subject. For each subject, a single voxel was placed in the right lobe of the liver, avoiding large vessels, bile ducts, any liver lesions, as well as the dome of liver. Acquisition parameters for the MRS acquisition included: 28 echoes acquired with varying TR (150-2000ms) and TE (10-110ms), 5ms mixing time, 20x20x20mm voxel size, and 20s acquisition duration, as previously described (20).

Complex echo images acquired as part of the CSE-MRI acquisition were reconstructed offline using a non-linear maximum likelihood estimator algorithm (24). Separate water, fat, PDFF, and $R2^*$ maps were generated as part of this reconstruction. The MRS signal was reconstructed and T2-corrected by fitting the signal of each peak to a monoexponential decay (25). The spectral complexity of fat was accounted with the MRS signal using the AMARES algorithm in the JMRUI software as previously described (25). This provided a T2-corrected MRS-based estimate of PDFF.

Reconstructed PDFF and $R2^*$ maps were analyzed by one analyst using multiple regions of interest. ROIs were drawn in all nine Couinaud segments as large as possible while trying to avoid any obvious artifacts, as described by Campo et al (26).

Results

Cramér–Rao Lower Bound (CRLB)

Figure 2 plots an example of the maximum acceptable $R2^*$ value where PDFF can be estimated reliably based on CRLB simulations with an NSA for fat signal estimation of at least 0.2. This minimum NSA threshold was based on simulations assuming a baseline SNR of 20 for the total water and fat signal from a single echo image at a putative echo time of zero. With this SNR, it is straightforward to demonstrate that NSA=0.2 for fat signal estimation corresponds to a pixel-wise PDFF standard deviation of approximately 10% (in absolute PDFF). For region-of-interest (ROI) measurements containing 100 voxels, this corresponds to a standard deviation of 1% due solely to noise propagation. Figure 2 contains both 1.5T and 3.0T for representative fat fractions, for different combinations of first echo time and echo spacing.

A polynomial regression model was then fit to CRLB calculations in order to develop an empirical relationship between the maximum $R2^*$ value (units = s^{-1}), the choice of echo combinations (units = ms), and the desired NSA, as summarized in equation 2 for each field strength ($R^2 = 0.94$ and 0.98 , respectively).

$$\begin{aligned}
 \mathbf{1.5T:} \quad & \text{Max } R2^*(TE_1, \Delta TE, NSA) = 978.52 - 355.72 \cdot TE_1 - 0.65 \cdot \Delta TE + 98.2 \\
 & \cdot TE_1 \cdot \Delta TE + 19.16 \cdot TE_1^2 - 78.79 \cdot \Delta TE^2 - 989.53 \cdot NSA \\
 \mathbf{3.0T:} \quad & \text{Max } R2^*(TE_1, \Delta TE, NSA) = 1562.8 - 781.25 \cdot TE_1 - 335.01 \cdot \Delta TE + 243.84 \\
 & \cdot TE_1 \cdot \Delta TE + 123.25 \cdot TE_1^2 - 109.61 \cdot \Delta TE^2 - 946.56 \cdot NSA
 \end{aligned} \quad [2]$$

For example, the two protocols listed in Table 1 for 1.5 T and a desired NSA of 0.2 would have a maximum $R2^*$ of $538s^{-1}$ and $308s^{-1}$ (Protocol 1 and Protocol 2, respectively), above which PDFF estimates are not reliable. At 3.0T, the two protocols with a desired NSA of 0.2 would have a max $R2^*$ of $779s^{-1}$ and $449s^{-1}$ (Protocol 1 and Protocol 2, respectively).

As can be seen in the CRLB results, the precise $R2^*$ value above which PDFF can be reliably estimated depends on the specific protocol, field strength, as well as other factors such as the PDFF. We note, however that the echo times (first echo and echo spacing) and NSA are the most important consideration that impact the maximum acceptable $R2^*$ value.

Monte Carlo Simulations

Figure 3 summarizes the CRLB and Monte Carlo simulations that plot both the absolute PDFF error with increasing $R2^*$, as well as the variance of PDFF estimates with increasing $R2^*$ values. As can be seen in Figure 3, the variance in fat estimates as a function of $R2^*$ depend on imaging protocol and field strength. It can be appreciated from this plot the two echo time combinations provide a different range over which PDFF estimates are reliable. Figure 3 also shows good subjective agreement between Monte Carlo simulations and CRLB estimates of PDFF variance for small $R2^*$ but diverge as the rapid signal decay creates additional variance in the fitting algorithm. As can be seen in this plot, there is a steady increase of variance as the $R2^*$ increases, as expected, as well as improved noise performance with the shorter echo times used in protocol 1.

Phantom Experiments

Figure 4 plots the average value and the standard deviation, in a $3cm^2$ ROI, of phantom measurements where the same set of vials with increasing $R2^*$ were imaged at both 1.5T and 3.0T for all the protocols listed in Table 1. $R2^*$ fits demonstrate good agreement between the different protocols and field strengths. Figure 5 plots the corresponding PDFF estimates of the same vials. The PDFF estimates vary depending on protocol, field strength, and $R2^*$ in the vial. Vials with high $R2^*$ show increasing variance and overall error in PDFF estimates, especially in Protocol 2 with longer echo spacing and first echo.

In Vivo Experiments

A total of 26 patients were successfully recruited, with an average age of 43 (10-73 range) and 18:8 men:women, each patient was scanned at 1.5T and 3.0T with the protocols listed in Table 1. Among the 26 patients in this study, causes for known or suspected iron overload included hemochromatosis (9), transfusional hemosiderosis due to chronic non-malignant (5) and malignant (8) conditions, and liver iron overload associated with chronic liver disease (4). Representative $R2^*$ and PDFF maps from two patients, one with elevated liver iron and one without is shown in Figure 6. Note that the MRS estimate and MRI-PDFF

agree in Patient 1 but in Patient 2 the MRS estimate of PDFF was 10.9% while the MRI-PDFF estimate was 26.0%. This disagreement is larger in Patient 2 than in Patient 1 due to the elevated $R2^*$ of approximately 667s^{-1} . This example explicitly illustrates the effect of $R2^*$ on PDFF estimation for this protocol.

Figure 7 plots the absolute error in PDFF as measured by the absolute difference between PDFF estimated by the two CSE-MRI protocols and MRS. As can be seen in this figure, the acquisition, which has shorter first echo and echo spacing, has markedly lower PDFF error as $R2^*$ increases. In this example, using an NSA of 0.2, a threshold of approximately $555/780\text{s}^{-1}$ (1.5T/3.0T) for acquisition protocol 1 and $327/397\text{s}^{-1}$ for acquisition protocol 2 can be observed from these in vivo data. These limits correspond to the theoretical results shown in Figure 2 and Equation 2.

Discussion

In this work we have investigated the effect of $R2^*$ on the ability of CSE-MRI to quantify PDFF in the liver in the presence of excess iron accumulation. As a result of signal decay and linewidth broadening, it becomes increasingly difficult to separate water and fat signals and therefore estimate PDFF reliably at high $R2^*$ values. We also have characterized the threshold $R2^*$ value above which estimation of PDFF becomes unreliable. Further, we developed an empirical formula that provides a practical guideline for use in clinical and research application of CSE-MRI to quantify PDFF.

Clinical Relevance

The relevance of this work in a clinical population depends on the frequency of abnormal liver fat and iron content, and the specific clinical or research question to be answered. Concomitantly elevated liver fat and iron is commonly encountered in patients with liver disease. Further, given the estimated prevalence of hepatic steatosis at 30 percent of the US population (31), statistically, those patients with elevated iron overload have a relatively high prevalence of hepatic steatosis. Therefore, this work may be particularly relevant in patients with known or suspected iron overload who have an elevated risk of elevated liver fat in addition to liver iron overload.

Practical Guideline

This work provides an easily calculated guideline for estimation of PDFF in this setting of iron overload. We note that the specific criteria for unreliable estimates of PDFF is application specific although our expression allows for calculations based on different required levels of reliability through the selection of the desired NSA. Physicians are increasingly using CSE-MRI methods to quantify liver fat and iron and are met with the highly clinically relevant question of when PDFF estimates are reliable, especially in the setting of iron overload. This work provides potential guidelines for interpreting CSE-MRI of liver fat and iron content. and provides a framework for patients with concomitant iron and fat overload. Further work may also include incorporating a theoretical maximum $R2^*$ threshold that could be calculated in real time for every unique exam at the time of imaging.

This could aid an iterative process to design CSE-MRI acquisition protocols depending on the specific application and expected iron levels.

Limitations

We only assessed one vendor and one set of platforms at 1.5T and 3.0T. The reference standard used in in vivo imaging (i.e. STEAM MRS) is also sensitive to the levels of iron so the reliability of MRS at high levels of iron needs to be characterized. Liver biopsy would have been another standard reference for the fat fraction, but it was not included in this study due to its invasive nature. Multiple analysts were also not used to analyze the images of this work but previous studies have investigated the intra- and inter-reader variability of the technique used (26) so only one analyst was used in the work. Also, the $R2^*$ threshold criteria developed in this work is context/application specific that limits the generalizability of these results to every application. Further, this work has focused on complex-based PDFF estimation with $R2^*$ correction. Although most vendors use complex-based or complex-magnitude hybrid PDFF estimation, the use of magnitude-based PDFF is common, particularly for research applications (27, 28). Future work should consider the addition of a similar analysis for magnitude-based PDFF estimation based on the framework laid out above. We also note that CRLB calculations describing the noise performance of PDFF estimates agreed closely with Monte Carlo simulations at low and moderate $R2^*$ values. At higher $R2^*$ values, Monte Carlo simulations demonstrated higher variability than predicted by the CRLB. The deviation from the CRLB is commonly observed at low SNR, which occurs at higher $R2^*$ values.

Conclusion

This work has evaluated the effect of elevated $R2^*$ on the ability of CSE-MRI to quantify liver fat content. Specifically, we have developed a paradigm for determining the threshold $R2^*$ values above which PDFF estimation becomes unreliable at both 1.5T and 3.0T using CRLB simulations, Monte Carlo simulations, phantom experiments, and in vivo patient scans. We have developed a practical empirical guide for the maximum $R2^*$ above which PDFF estimation is unreliable, with the goal of providing practical clinical and research guidelines for PDFF estimation.

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Conflict of Interest

None of the authors have any relevant conflicts of interest. The University of Wisconsin receives research support from GE Healthcare and Bracco Diagnostics. Drs. Reeder and Hernando are founders of Calimetrix, LLC. Dr. Reeder has an ownership interest in Elucent Medical, Reveal Pharmaceuticals, Celectar Biosciences and HeartVista.

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Figure 1:

Increasing iron content results in linewidth broadening that obscures the presence of fat.

The signal evolution across time (A) is shown for tissue with 40% PDFFF and different R_2^* values (units of s^{-1}). The frequency spectrum (B) for 40% PDFFF (using a six peak fat model) and water at different R_2^* values.

Figure 2:

CRLB estimates for the maximum $R2^*$ where PDFF can be reliably estimated. The top row is the maximum $R2^*$ where an NSA of 0.2 is achieved at 1.5T with a PDFF of 0% (left), 10% (middle) and 20% (right). The bottom row is for 3.0T and a PDFF of 0% (left), 10% (middle) and 20% (right).

Figure 3:

CRLB and MC simulations that demonstrate that the variance in fat estimation depends on $R2^*$ and the acquisition protocol. The first row is the variance in PDF estimates for the two protocols at 1.5T for 0% (left), 10% (middle), and 20% PDFF (right). The second row is the variance in PDF estimates for the two protocols at 3.0T for 0% (left), 10% (middle), and 20% PDFF (right).

Figure 4:

Phantom results confirm that $R2^*$ for values less than 1000 s^{-1} can be estimated accurately for different echoes and different field strengths. The estimated $R2^*$ values are plotted for both protocols as a function of $R2^*$ at 1.5T (top row) and 3.0T (second row) for vials containing different fat fraction values. Only a small variance is seen in both protocols and field strengths for the highest $R2^*$ value with each fat fraction. Error bars represent the standard deviation in a 1.8cm² ROI placed in the center of the vial and the dashed line represent the nominal value for the fat fraction.

Figure 5:

Phantom results confirm that PDFF estimates vary depending on choice of echo times and field strength. The estimated PDFF values are plotted for both protocols as a function of R2* at 1.5T (top row) and 3.0T (second row) for vials containing different fat fraction values. Increasing amounts of variance in the fat estimates can be seen for Protocol 2 but less variance is seen in Protocol 1. Error bars represent the standard deviation in a 1.8cm² ROI placed in the center of the vial.

Figure 6:

Errors on in vivo PDFF estimates increase with large R2* values. Representative R2* and PDFF maps, acquired with the same protocol and fitting algorithm, are shown for patients with low (A-B) and high (C-D) R2*. The estimated R2* and MRS PDFF are shown for each patient along with the estimated PDFF values in the right lobe of the liver.

Figure 7:

Errors in PDF estimates for patients with suspected iron overload that depend on the imaging protocol and the iron concentration. Shown are errors in ROI based PDF measurements relative to MRS at 1.5T (top row) and 3T (bottom row) for the two protocols. The dashed line denotes our threshold for when PDF estimates will no longer be reliable ($NSA > 0.2$) (Equation 2).

Table 1.

Acquisition parameters for two protocols at 1.5T and 3T with different echo spacings.

	1.5 T		3.0 T	
	Protocol 1	Protocol 2	Protocol 1	Protocol 2
# Echoes	8	6	8	6
TE ₁ (ms)	0.75	1.19	0.65	1.24
TE (ms)	0.67	1.97	0.58	1.01
Spatial resolution (mm ³)	2.5x3.1x8.0	1.7x2.5x8.0	2.8x3.1x8.0	1.6x2.8x8.0
TR (ms)	9.6	14.6	6.0	8.0
Flip angle (°)	5	5	3	3