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Validation of a Motion-Robust 2D Sequential Technique for Quantification of Hepatic Proton Density Fat Fraction during Free Breathing

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Abstract

Background—Current chemical-shift encoded (CSE) MRI techniques for measuring hepatic proton density fat fraction (PDFF) are sensitive to motion artifacts.

Purpose—Initial validation of a motion-robust 2D-sequential CSE-MRI technique for quantification of hepatic PDFF.

Study Type—Phantom study and prospective in vivo cohort.

Population—50 adult patients (27 women, 23 men, mean age 57.2 years).

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Conflicts of Interest

All authors have no relevant disclosures unless otherwise stated. Dr. Reeder has no relevant disclosures, although has the following unrelated disclosures: ownership interests in Collectar Biosciences, Reveal Pharmaceuticals, and Elucent Medical, and is a founder of Calimetrix, LLC.

Ms. Shimakawa discloses that she is an employee of GE Healthcare. The authors note that while Ms. Shimakawa was integral in development of the experimental MR sequence evaluated in this manuscript as well as study methodology, she did not participate directly in data collection or analysis in order to maintain study integrity and minimize conflicts of interest.

Dr. Reeder is the guarantor of this submission and affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Field Strength/Sequence—3D, 2D-interleaved, and 2D-sequential CSE-MRI acquisitions at 1.5T.

Assessment—Three CSE-MRI techniques (3D, 2D-interleaved, 2D-sequential) were performed in a PDFF phantom and in vivo. Reference standards were 3D CSE-MRI PDFF measurements for the phantom study and single voxel MR spectroscopy hepatic PDFF measurements (MRS-PDFF) in vivo. In vivo hepatic MRI-PDFF measurements were performed during a single breath hold (BH) and free breathing (FB), and were repeated by a second reader for the FB 2D-sequential sequence to assess inter-reader variability.

Statistical Tests—Correlation plots to validate the 2D-sequential CSE-MRI against the phantom and in vivo reference standards. Bland-Altman analysis of FB versus BH CSE-MRI acquisitions to evaluate robustness to motion. Bland-Altman analysis to assess inter-reader variability.

Results—Phantom 2D-sequential CSE-MRI PDFF measurements demonstrated excellent agreement and correlation ($R^2 > 0.99$) with 3D CSE-MRI. In vivo, the mean ($\pm$ SD) hepatic PDFF was $8.8 \pm 8.7\%$ (range 0.6–28.5%). Compared with BH acquisitions, FB hepatic PDFF measurements demonstrated bias of +0.15% for 2D-sequential compared with +0.53% for 3D and +0.94% for 2D-interleaved. 95% limits of agreement (LOA) were narrower for 2D-sequential ($\pm 0.99\%$), compared with 3D ($\pm 3.72\%$) and 2D-interleaved ($\pm 3.10\%$). All CSE-MRI techniques had excellent correlation with MRS ($R^2 > 0.97$). The FB 2D-sequential acquisition demonstrated little inter-reader variability, with mean bias of +0.07% and 95% LOA of $\pm 1.53\%$.

Conclusions—This motion-robust 2D-sequential CSE-MRI can accurately measure hepatic PDFF during free breathing in a patient population with a range of PDFF values of 0.6–28.5%, permitting accurate quantification of liver fat content without the need for suspended respiration.

Keywords

magnetic resonance imaging; hepatic steatosis; motion; proton density fat fraction; motion artifact; liver

Introduction

As obesity rates in the United States rise, non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent in both adult^{1, 2} and pediatric³ populations. At the cellular level, NAFLD results from intracellular deposition of triglycerides within hepatocytes, *i.e.* hepatic steatosis. Patients with hepatic steatosis are at elevated risk of necroinflammatory changes in the form of non-alcoholic steatohepatitis (NASH) and ultimately cirrhosis and end stage liver disease.^{4, 5} This same progression of disease also increases the risk of hepatocellular carcinoma in patients with NAFLD/NASH.⁶

Historically, direct pathologic analysis of tissue obtained from liver biopsy was the only reliable method widely available to diagnose and quantify NAFLD.⁷ Due to the invasiveness of this procedure, it is difficult to justify the risk and discomfort to the patient inherent in using liver biopsy to monitor liver fat content over time. Furthermore, random liver biopsy only samples a very small fraction of the liver parenchyma. MR spectroscopy (MRS) is

another available method for determining liver fat content and can serve as a useful reference standard,⁸ but only samples a small fraction of the liver parenchyma—similar to biopsy—but is generally limited in availability and requires complicated processing that may not be feasible in the clinical setting. Fortunately, chemical shift-encoded (CSE) MRI techniques have been developed which accurately and noninvasively measure liver proton density fat fraction (PDFF), a quantitative imaging biomarker of liver fat content.^{9–12} Current CSE-MRI techniques, which are based on multi-echo spoiled gradient echo (SGRE) using either 3D or 2D slice-interleaved acquisitions, are susceptible to motion-related artifacts. Unfortunately, these techniques require a prolonged breath hold to avoid motion-related artifacts, which is often challenging for ill patients and children. In previous studies, respiratory-gating and navigator based methods have been shown to enable accurate hepatic PDFF quantification without the need for suspending respiration.¹³ Gated methods, however, require longer scan time, and the resulting images still contain moderate residual motion artifact.

To address this issue, we describe below the use of a sequentially-acquired 2D CSE-MRI technique that can be used to assess liver fat content during free breathing. This technique represents an improvement over predecessors in that it has an extremely short temporal footprint (1–2 seconds/slice), which essentially negates breathing motion without the need for respiratory gating. The purpose of this study is to demonstrate the feasibility and validity of this 2D-sequential CSE-MRI technique for motion-robust quantification of liver fat content.

Materials and Methods

Phantom Study

A PDFF phantom consisting of 11 cylindrical vials with varying peanut oil concentrations in an agar-based emulsion with nominal PDFF values of 0, 2.5%, 5%, 7.5%, 10%, 15%, 20%, 30%, 40%, 50% and 100% was constructed as previously described.^{14, 15} The phantom was scanned using three different CSE-MRI techniques (2D-sequential CSE-MRI, 2D-interleaved CSE-MRI and 3D CSE-MRI) using acquisition parameters shown in Table 1. 3D CSE-MRI was used as the reference standard for MRI-PDFF. 3D CSE-MRI has been previously validated in phantoms as an accurate biomarker of fat concentration.^{14, 15}

Patient Population and In Vivo Study Design

This prospective observational study was approved by our institutional review board and maintained full compliance with the Health Insurance Portability and Accountability Act (HIPAA). Signed informed consent was obtained from all study participants. Over 7 months (August 1, 2016 through February 28, 2017) adult patients undergoing clinically indicated diagnostic abdominal MRI were prospectively enrolled to undergo CSE-MRI to measure hepatic PDFF as an adjunct to the clinical scan. Patients were eligible for inclusion if they were 18 years of age or older and were undergoing an abdominal MRI protocol requiring the use of a phased-array torso coil. As the aim of this study was to demonstrate the general feasibility of 2D-sequential CSE-MRI for the quantification of hepatic PDFF during free breathing, there were no specifically defined exclusion criteria.

Once enrolled, patients underwent acquisitions using three different CSE-MRI techniques (2D-sequential CSE-MRI, 2D-interleaved CSE-MRI and 3D CSE-MRI) using acquisition parameters shown in Table 2, each performed once during a single breath hold (BH) and once during free breathing (FB), for a total of six CSE-MRI scans. Single voxel MR spectroscopy (MRS) was also performed in the right lobe of the liver (Couinaud segment 6/7) using a stimulated echo acquisition mode (STEAM) technique as an independent reference measurement of hepatic PDFF for each patient. These six CSE-MRI and one MRS acquisitions resulted in a total of seven acquisitions per patient.

CSE-MRI Technique and PDFF Analysis

All phantom and human subject imaging was performed on a clinical 1.5T MRI system (MR450w v25.0, GE Healthcare, Waukesha, WI) using a 12-channel phased-array torso coil. Imaging was performed using investigational versions of a complex-based quantitative CSE-MRI method (IDEAL IQ, GE Healthcare), to quantify PDFF. This CSE-MRI method corrects or minimizes confounding factors that introduce error in PDFF measurement in conventional MRI, including T1 related bias,¹⁶ noise bias,¹⁶ R2* signal decay,¹⁷ multi-frequency interference effects of fat,¹⁸ and the effects of eddy currents.¹⁹ Scan parameters for the individual acquisitions (2D-sequential, 2D-interleaved, and 3D) are provided in Table 2. Parameters between corresponding FB and BH sequences for each acquisition were identical. No respiratory gating was used for any sequence.

The CSE-MRI sequence uses both magnitude and phase information from images acquired at multiple echo times to facilitate independent estimation of fat water signals. When these signals are corrected for the above confounding factors, the ratio of corrected fat signal to the total corrected signal of water and fat provides an accurate estimation of fat and water signals. The method automatically reconstructs water-only and fat-only images, and PDFF maps. The latter depict the spatial distribution of PDFF, pixel by pixel, throughout the scanned volume.

Reconstructed PDFF maps were then transferred to a standalone workstation for analysis using OsiriX (Pixmeo SARL, Geneva, Switzerland). For phantoms, a single circular ROI (2 cm diameter) was positioned in a central slice of the phantom, sufficiently large to cover the majority of the cross-section of each vial, while avoiding the edges and potential volume averaging artifacts. For the human study, we used a previously validated method,² with regions of interest (ROI) placed by a trained analyst (Reader 1, BDP, abdominal imaging clinical fellow with 5 years of MRI interpretation experience) in each of the nine Couinaud segments of the liver in order to sample representative portions of the entire liver. The PDFF in each of the nine ROIs was averaged as a single composite hepatic PDFF value for every patient and acquisition.

Multi-echo T2-corrected single-voxel STEAM MRS measurements of hepatic PDFF for each patient were also made using a previously proposed algorithm for T2-corrected spectroscopic quantification of water and multi-peak fat signals.^{20, 21} Single-voxel measurements were taken from Couinaud segment 6/7 within the right lobe of the liver. Six spectra were acquired in consecutive TRs, using stimulated echo times of 10, 10, 15, 20, 25, and 30 ms, respectively, with the first TR discarded in order to reach steady state. MRS

parameters are summarized in Table 3. Note that with at TR of 3500 ms, T1 effects are minimal given a previously reported average liver T1 of approximately 586 ms at 1.5 T.²²

MRS processing was performed off-line using a previously described fully automated algorithm²¹ implemented in Matlab (MathWorks, Natick, MA). Six metabolites were included with resonances [-3.40, -3.80, -2.60, -1.94, -0.39, 0.60] ppm relative to the water peak. Voigt line shapes were used for fitting these peaks. For stability, a single T2 was considered for all the fat peaks.

Inter-reader Variability

In order to evaluate the inter-reader variability of the free breathing 2D-sequential CSE-MRI technique, a subset of 24 patients from the original 50-patient cohort were randomly selected for analysis by a second reviewer. The 2D-sequential FB images for these patients were analyzed by a second trained analyst (Reader 2, HI, medical student without significant MRI experience), who performed OsiriX analysis using the previously described method while blinded to the results of the analysis performed by Reader 1. Of note, both readers performed ROI measurements on 5 practice cases prior to data collection for this study.

Statistical Analysis

At the conclusion of the study period, all CSE-MRI and MRS data were collected and collated. For phantom data, linear regression was performed to compare the sequential and interleaved 2D-CSE-MRI method, using 3D CSE-MRI as the reference. The Pearson correlation coefficient was calculated, as well as the slope and intercept, each with 95th percentile confidence intervals.

For the human study, Bland-Altman analysis²³ of FB vs BH acquisitions was performed for each CSE-MRI technique to determine bias and limits of agreement (LOA). Correlation plots of MRS-PDFF and MRI-PDFF were performed for BH techniques to demonstrate the validity of the CSE-MRI measurements. As reference MRS measurements were made from the posterior right lobe of the liver (Couinaud segments 6 or 7), the average hepatic PDFF from Couinaud segments 6 and 7 by CSE-MRI was compared with the single-voxel MRS-PDFF measurements. Paired Student's t-test was used to compare mean MRI-PDFF values with those of MRS-PDFF and one-way ANOVA was used to assess for differences among the CSE-MRI techniques.

For inter-reader comparison, Bland-Altman analysis of the 2D-sequential FB acquisitions for Reader 1 versus Reader 2 was performed. Numerical data was collated using Microsoft Excel (2010 version, Microsoft, Redmond, WA, USA) and statistical calculations were performed using SPSS (version 23, IBM, Armonk, NY, USA).

Results

Figure 1 plots MRI-PDFF measured using the sequential and interleaved 2D-CSE-MRI methods, compared to 3D CSE-MRI, which served as the reference standard. Very strong correlation with slope and intercept very close to 1.0 and 0.0, respectively demonstrate

excellent agreement between both 2D-CSE-MRI methods with 3D CSE-MRI to quantify PDFF.

50 subjects (27 women and 23 men) were recruited, with a mean [$\pm$ SD] age of 57.1 ± 12.1 years (range 23–81 years). Example in vivo PDFF maps with ROIs are shown in Figure 2. All patients successfully completed the BH and FB acquisitions for the three CSE-MRI sequences, although the 2D-sequential FB series for one patient was lost during data transfer. All patients also underwent MRS-PDFF measurements, although in 10 cases the MRS data were not properly transferred from the MR scanner and were lost. The MRS data from two additional patients were excluded from the final analysis. In the first case, a spurious PDFF value was produced due to patient motion during the MRS acquisition. In the second case, the data was excluded after the difference between CSE-MRI and MRS failed the Grubbs' test for statistical outliers for all three CSE-MRI techniques (z -score >3.0 for all techniques); upon further review the liver parenchyma in question was markedly heterogeneous in fat content, and the MRS was found to have been sampled from a region of liver which was substantially lower in fat at CSE-MRI (approximately 5–6% for all acquisitions) than the liver average at CSE-MRI (approximately 10–11% for all acquisitions).

By MRS, mean hepatic PDFF for the cohort was $8.8 \pm 8.7\%$ (range 0.6–28.5%). Mean hepatic PDFF was $8.8 \pm 8.5\%$ for 3D BH, $8.3 \pm 8.9\%$ for 3D FB, $8.9 \pm 8.4\%$ for 2D-interleaved BH, $8.0 \pm 8.8\%$ for 2D-interleaved FB, $8.3 \pm 8.2\%$ for 2D-sequential BH, and $8.0 \pm 8.1\%$ for 2D-sequential FB, none of which were significantly different than mean hepatic PDFF by MRS (P -value range, 0.67–0.99). Furthermore, by one-way ANOVA, no significant difference was observed among the six CSE-MRI groups ($P=0.99$)

Strong correlation (Figure 3) was observed between mean MRI-PDFF and MRS-PDFF, with R^2 values of at least 0.97 for each of 3D, 2D-interleaved, and 2D-sequential sequences. Corresponding slope values were 0.92 (95% CI [0.87, 0.96]), 0.92 [0.87, 0.98], and 0.99 [0.93, 1.05], respectively. Corresponding y -intercept values were 0.51 [−0.08, 1.10], 0.76 [0.07, 1.45], and −0.02 [−0.75, 0.70], respectively.

Bland-Altman analysis comparing FB versus BH acquisitions (Figure 4) demonstrated a mean bias of +0.15% (95% CI [0.00%, +0.30%]) for the 2D-sequential acquisition, compared with +0.53% (95% CI [−0.01%, +1.07%]) for 3D and +0.94% (95% CI [+0.49%, +1.39%]) 2D-interleaved acquisitions. The 95% limits of agreement (LOA) were narrower for the 2D-sequential acquisition ($\pm 0.99\%$) compared with 3D ($\pm 3.72\%$) and 2D-interleaved ($\pm 3.10\%$) acquisitions. Furthermore, confidence intervals for the LOAs were narrower for the 2D-sequential acquisition ($\pm 0.25\%$) when compared with 3D ($\pm 0.93\%$) and 2D-interleaved ($\pm 0.78\%$) acquisitions.

Bland-Altman analysis performed to assess inter-reader variability by comparing 2D-sequential FB acquisitions for Reader 1 versus Reader 2 (Figure 5) demonstrated a mean difference between the two readers (bias) of +0.07% (95% CI [−0.26%, +0.40%]) with 95% limits of agreement of $\pm 1.53\%$ and 95% CI of LOA of $\pm 0.57\%$.

Discussion

This study demonstrated that a 2D-sequential quantitative complex-based CSE-MRI method can accurately evaluate liver fat content in the form of PDFF without the need for the patient to suspend respiration. We observed very strong correlation and agreement with both 2D-sequential and interleaved CSE-MRI methods compared to 3D CSE-MRI in a phantom study. Further, we observed very strong in-vivo correlation with MRS for PDFF values obtained from all CSE-MRI sequences, including the 2D-sequential CSE-MRI sequence (the primary method of interest in this study), as well as very strong agreement between MRS and the 2D-sequential sequence, indicating high technical accuracy of 2D-sequential CSE-MRI to quantitative liver fat content.

In order to achieve increased robustness to motion, the 2D sequential acquisition features a reduction in TR compared to the 2D interleaved sequence (from 300 ms to 10.2 ms), substantially reducing the temporal footprint of each slice. In order to avoid T1 bias with reduced TR, the flip angle is also reduced (from 20° to 5°). In addition to a reduced temporal footprint, the combined effect of shortened TR and reduced flip angle also results in lower SNR. In order to avoid excessive noise, this lower SNR can be ameliorated by limited the in-plane spatial resolution. The resulting SNR is still somewhat lower than with the 3D or 2D interleaved acquisitions, but is adequate for liver PDFF measurement with excellent robustness to respiratory motion.

Beyond exhibiting high accuracy when compared to the MRS reference standard, the 2D-sequential acquisition also offered much more consistent performance across a wide range of liver fat content values during free-breathing when compared to the 3D and 2D-interleaved acquisitions. Using the breath hold acquisitions as a reference, the 2D-sequential free breathing acquisitions demonstrated minimal bias which was significantly less than that of the 2D-interleaved acquisition and less than that of the 3D acquisition, although confidence intervals between the two did overlap. Additionally, the limits of agreement for the 2D-sequential free breathing acquisition compared to the 2D-sequential breath-hold acquisition were substantially narrower, indicating superior reproducibility between breath-holding and free-breathing. This behavior reflects the observation that nearly no motion artifact was observed with the 2D-sequential acquisition during free-breathing owing to the motion insensitivity of this approach. This is especially impressive when considering that previously studied respiratory-gated CSE-MRI had clear residual motion artifact with a much longer scan time (approximately 80 seconds for respiratory-gated CSE-MRI compared with 20 seconds for 2D-sequential).¹³ Finally, the 2D-sequential free breathing acquisitions also demonstrated excellent inter-reader variability.

Previous studies have suggested that it is feasible to use CSE-MRI in the clinical setting to both diagnose liver fat content and monitor liver fat content over time, given the non-invasive nature of the examination, relatively short examination time, and potential widespread availability.^{9, 11, 12, 24} Given the nature of abdominal MRI examinations in general, artifacts related to motion are a concern with any new MRI technique. This study augments the mounting research in favor of CSE-MRI as a useful clinical tool for measuring liver fat content, as the performance of the 2D-sequential acquisitions in this study

demonstrates that artifacts related to motion during patient breathing can be largely mitigated for CSE-MRI. Consequently, this technique represents a viable method for quantifying and monitoring liver fat content even in patients who cannot reliably hold their breath, including pediatric patients and patients with orthopnea, and obviates the need for sedation or general anesthesia in these cases.

We acknowledge some limitations to this study. While we did not include pediatric patients in this study, we have clinically applied this technique to patients under the age of 18 with success, and have no evidence to suggest these results shouldn't generalize to this patient population. Furthermore, the motion-robust 2D-sequential acquisition was primarily intended to be used to assess diffuse hepatic steatosis—with many aspects of its design (such as the 2 mm gap between slices and reduced in-plane resolution) predicated on this purpose—and presume relative homogeneity of the liver parenchyma. Consequently, application of this technique may be limited in patients with focal or heterogeneously distributed liver disease. In addition, the signal-to-noise ratio (SNR) performance of 2D-sequential gradient echo acquisitions is generally low, due to the use of a short TR that limits T1 recovery, low flip angles to avoid T1 bias, and the lack of depth encoding that boosts SNR performance for 3D acquisitions. Further work evaluating the noise performance of sequential methods and the potential impact on the accuracy of PDFF quantification is warranted.

Another potential limitation of this work is the apparent distribution of PDFF values in this population. Specifically, we observed a mean PDFF value of 8.8% over a range of 0.6–28.5% with a standard deviation of 8.7%. We note that Yokoo et al recently published a meta-analysis of CSE-MRI compiling results from 23 studies in 1679 unique subjects with 3191 measurements.²⁴ In this summary analysis, the average reported PDFF value reported was 9.6% (range of average values = 5.0–16.8%), with a standard deviation of 8.8%. We do note, however, that the meta-analysis had an overall range of –2.8 – 55.4%. Although the range of PDFF values in the meta-analysis included extreme liver fat concentrations, the average PDFF and general distribution (based on standard deviation) was very similar to our current study. Thus, while our prospective study did not observe the full range of PDFF values that have been reported in the literature, the overall distribution is nearly identical to the majority of published studies. Furthermore, our phantom study demonstrated high accuracy for the proposed 2D CSE-MRI method across a wide range of PDFF values (0–100%). Future work may be needed to evaluate the proposed motion insensitive CSE-MRI method in patients with more severe liver fat concentrations.

In conclusion, our findings demonstrated that CSE-MRI can be successfully used to measure hepatic PDFF during free breathing using a motion-robust 2D-sequential technique, as assessed in a patient population with a range of PDFF values of 0.6–28.5%. This sequence permits the accurate quantification of liver fat content without the need for the patient to suspend respiration, and has important potential clinical application in patients who are unable to hold their breath.

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References

1. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *American Journal of Physiology-Endocrinology and Metabolism* 2005;288:E462–E8. [PubMed: 15339742]
2. Campo CA, Hernando D, Schubert T, Bookwalter CA, Pay AJV, Reeder SB. Standardized Approach for ROI-Based Measurements of Proton Density Fat Fraction and R2* in the Liver. *AJR Am J Roentgenol* 2017;1–12.
3. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006;118:1388–93. [PubMed: 17015527]
4. Gramlich T, Kleiner DE, McCullough AJ, Matteoni CA, Boparai N, Younossi ZM. Pathologic features associated with fibrosis in nonalcoholic fatty liver disease. *Human Pathology* 2004;35:196–9. [PubMed: 14991537]
5. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. *Gastroenterology* 1999;116:1413–9. [PubMed: 10348825]
6. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. *Gastroenterology* 2005;129:113–21. [PubMed: 16012941]
7. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313–21. [PubMed: 15915461]
8. Hamilton G, Middleton MS, Bydder M, et al. Effect of PRESS and STEAM Sequences on Magnetic Resonance Spectroscopic Liver Fat Quantification. *Journal of Magnetic Resonance Imaging* 2009;30:145–52. [PubMed: 19557733]
9. Bannas P, Kramer H, Hernando D, et al. Quantitative magnetic resonance imaging of hepatic steatosis: Validation in ex vivo human livers. *Hepatology* 2015;62:1444–55. [PubMed: 26224591]
10. Hines CDG, Yu HZ, Shimakawa A, et al. Quantification of Hepatic Steatosis with 3-T MR Imaging: Validation in ob/ob Mice. *Radiology* 2010;254:119–28. [PubMed: 20032146]
11. Idilman IS, Aniktar H, Idilman R, et al. Hepatic Steatosis: Quantification by Proton Density Fat Fraction with MR Imaging versus Liver Biopsy. *Radiology* 2013;267:767–75. [PubMed: 23382293]
12. Reeder SB, Hu HCH, Sirlin CB. Proton density fat-fraction: A standardized mr-based biomarker of tissue fat concentration. *Journal of Magnetic Resonance Imaging* 2012;36:1011–4. [PubMed: 22777847]
13. Motosugi U, Hernando D, Bannas P, et al. Quantification of liver fat with respiratory-gated quantitative chemical shift encoded MRI. *Journal of Magnetic Resonance Imaging* 2015;42:1241–8. [PubMed: 25828696]
14. Hernando D, Sharma SD, Ghasabeh MA, et al. Multisite, Multivendor Validation of the Accuracy and Reproducibility of Proton-Density Fat-Fraction Quantification at 1.5T and 3T Using a Fat-Water Phantom. *Magnetic Resonance in Medicine* 2017;77:1516–24. [PubMed: 27080068]
15. Hines CDG, Yu HZ, Shimakawa A, McKenzie CA, Brittain JH, Reeder SB. T-1 Independent, T-2* Corrected MRI With Accurate Spectral Modeling for Quantification of Fat: Validation in a Fat-Water-SPIO Phantom. *Journal of Magnetic Resonance Imaging* 2009;30:1215–22. [PubMed: 19856457]
16. Liu CY, McKenzie CA, Yu H, Brittain JH, Reeder SB. Fat quantification with IDEAL gradient echo imaging: Correction of bias from T-1 and noise. *Magnetic Resonance in Medicine* 2007;58:354–64. [PubMed: 17654578]

17. Yu HZ, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T2*estimation. *Journal of Magnetic Resonance Imaging* 2007;26:1153–61. [PubMed: 17896369]
18. Yu HZ, Shimakawa A, McKenzie CA, Brodsky E, Brittain JH, Reeder SB. Multiecho Water-Fat Separation and Simultaneous R-2* Estimation With Multifrequency Fat Spectrum Modeling. *Magnetic Resonance in Medicine* 2008;60:1122–34. [PubMed: 18956464]
19. Yu HZ, Shimakawa A, Hines CDG, et al. Combination of Complex-Based and Magnitude-Based Multiecho Water-Fat Separation for Accurate Quantification of Fat-Fraction. *Magnetic Resonance in Medicine* 2011;66:199–206. [PubMed: 21695724]
20. Hamilton G, Yokoo T, Bydder M, et al. In vivo characterization of the liver fat H-1 MR spectrum. *Nmr in Biomedicine* 2011;24:784–90. [PubMed: 21834002]
21. Hernando D, Artz NS, Hamilton G, A R-A, Reeder SB. Fully automated processing of multi-echo spectroscopy data for liver fat quantification *Proceedings of the 22th Annual Meeting of ISMRM* 2014.
22. de Bazelaire CM, Duhamel GD, Rofsky NM, Alsop DC. MR imaging relaxation times of abdominal and pelvic tissues measured in vivo at 3.0 T: preliminary results. *Radiology* 2004;230:652–9. [PubMed: 14990831]
23. Giavarina D Understanding Bland Altman analysis. *Biochemia Medica* 2015;25:141–51. [PubMed: 26110027]
24. Yokoo T, Serai SD, Pirasteh A, et al. Linearity, Bias, and Precision of Hepatic Proton Density Fat Fraction Measurements by Using MR Imaging: A Meta-Analysis. *Radiology* 2017:170550.

Fig. 1—.
Both sequential and interleaved 2D CSE-MRI techniques result in accurate PDFF quantification in phantoms, over the entire PDFF range 0–100%, using a previously validated 3D CSE-MRI technique as the reference.

Fig. 2—.

2D-sequential CSE-MRI is robust to motion, unlike 2D-interleaved and 3D CSE-MRI methods. Representative PDFF maps from a 54-year-old female patient with hepatic steatosis. Images from the 3D, 2D-interleaved, and 2D-sequential scans are shown during breath-hold [BH, *top row*] and free breathing [FB, *bottom row*] acquisitions. Note the lack of motion artifact in the 2D-sequential FB [*bottom right*] acquisition compared to the 3D FB [*bottom left*] and 2D-interleaved FB [*bottom middle*] acquisitions. Note also the lack of ghosting artifact in the background regions of the 2D-sequential acquisitions, even during free-breathing. Circular regions of interest (ROI, yellow circles) for PDFF measurement are shown. A PDFF fat content scale is provided to the right of the images.

Fig. 3—.
 Correlation plots of PDFF values from MR Spectroscopy (MRS) and CSE-MRI during breath hold. All CSE methods, including the 2D CSE-MRI method, show excellent correlation and good agreement with MRS.

Fig. 4—
Bland-Altman analysis shows minimal variability between free breathing (FB) and breath hold (BH) acquisitions for 2D-sequential CSE-MRI [*bottom*], demonstrating insensitivity to motion artifact, unlike 3D [*top*] and 2D-interleaved [*middle*] CSE-MRI. Note the small bias and comparatively narrow limits of agreement (LOA) and 95% confidence intervals for the 2D-sequential acquisition.

Fig. 5—
 Bland-Altman analysis of free breathing 2D-sequential CSE-MRI shows little variability between Reader 1 (R1) and Reader 2 (R2) with a mean difference between the two readers (bias) of 0.07% with 95% limits of agreement (LOA) of $\pm 1.53\%$

Table 1:

Scan Parameters for phantom CSE-MRI acquisitions

Parameter	3D	2D-interleaved	2D-sequential
Field of view	44 × 35 cm	44 × 35 cm	44 × 35 cm
Slice thickness	4 mm	4 mm/0 mm gap	4 mm/0 mm gap
Slices	20 slices	22 slices	22 slices
Matrix size	224 × 160	192 × 144	192 × 144
TR	16.5 ms	300 ms	14.3 ms
TE1/ TE	1.1 ms/2.0 ms	1.7ms/2.1 ms	1.7 ms/2.1 ms
Flip angle	5°	20°	5°
Echo train length	6 (single train)	6 (single train)	6 (single train)
Receiver bandwidth	±111 kHz	±62.5 kHz	±62.5 kHz
Parallel imaging	N/A	N/A	N/A
Scan Time	52 s	74 s	38 s

Table 2:

Scan Parameters for in vivo CSE-MRI acquisitions

Parameter	3D	2D-interleaved	2D-sequential
Field of view	44 × 36 cm	44 × 36 cm	44 × 36 cm
Slice thickness	8 mm	8 mm/2 mm gap	8 mm/2 mm gap
Slices	28 slices	22 slices	22 slices
Matrix size	224 × 160	192 × 144	128 × 100
TR	16.3 ms	300 ms	10.2 ms
TE1/ TE	1.1 ms/2.0 ms	1.3ms/2.0 ms	1.1 ms/1.5 ms
Flip angle	5°	20°	5°
Echo train length	6 (single train)	6 (single train)	6 (single train)
Receiver bandwidth	±111 kHz	±62.5 kHz	±62.5 kHz
Parallel imaging (R)	2.5	N/A	N/A
Acquisition Time	20 s	23 s	20 s

Table 3:

Scan Parameters for Single-Voxel STEAM MR Spectroscopy (MRS)

Parameter	MRS Value
Voxel size	$20 \times 20 \times 20 \text{ mm}^3$
TR	3.5 s
TE1/ TE	10.0 ms/5.0 ms
Readout points	2048
Bandwidth	$\pm 2.5 \text{ kHz}$
Mixing time	5 ms
Acquisition Time	18 s