Fat Fraction Quantification:

A Quantitative Technique for Proton Density Fat Fraction (PDFF) Measurement in the Liver

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming an increasingly prevalent problem throughout the globe. In the United States, the prevalence of NAFLD increased from 15% in 2005 to 25% in 2010.[1] Therefore, it is very important to detect and quantify liver fat in order to precisely initiate and prescribe a treatment.

Imaging is rapidly becoming the standard for fat and iron quantification—replacing the invasive, but highly accurate, process of liver biopsy. Proton Density Fat Fraction (PDFF) measurement using Magnetic Resonance Imaging (MRI) can be employed to quantify hepatic fat content for diagnosis, severity grading, disease monitoring, or treatment response assessment, on a per-subject basis, in those with suspected or known hepatic steatosis of any etiology.[2]

Similar to fatty liver disease, biopsy is the standard diagnostic test for estimation of iron overload. However, due to invasive procedure and limitations with biopsy, an alternative imaging technique is indispensable. MRI has shown significant potential as a non-invasive, accurate, and reproducible method for R2* quantification as an image-based surrogate for liver iron quantification.[3]

As fat and iron contents in the liver can both impact PDFF and iron quantification, an imaging technique to simultaneously quantify fat and iron contents in one scan, while it corrects the influence of iron concentration on PDFF quantification and vice versa, can be advantageous. Recently, several MR imaging approaches were developed for simultaneous PDFF and R2* quantification.[4,5] Canon has implemented Fat Fraction Quantification, a technique which can simultaneously, in a single breath-hold exam, provide quantitative maps of the liver to measure corrected PDFF and R2* (a surrogate of iron concentration). In this article, the technical details and some clinical applications of Fat Fraction Quantification technique are described.

Technical Description

Pulse Sequence and Reconstruction

In general, a dual-echo FE sequence can be used for water/fat separation and PDFF measurement. Further, a multi-echo FE sequence can be employed to estimate R2* and iron level. However, it has been established that for higher levels of iron, prolonged R2* (fast T2* decay) yields errors in PDFF estimates; similarly, R2* is influenced by higher fat levels, leading to errors in R2* estimates; hence there is a need for simultaneous PDFF and R2* quantification. Fat Fraction Quantification is a reliable technique to simultaneously estimate PDFF and R2* maps based on multi-echo FE imaging. Fat Fraction Quantification can be performed in a single breath-hold scan using a properly engineered multi-echo FE sequence. Canon has implemented a six-echo breath-hold 3D FE sequence to estimate PDFF and R2* maps. A standard liver image scan can be acquired with a single breath-hold (approx. 20 seconds), making wide use in clinical examinations possible. In addition to In-Phase, Opposed-Phase, Water, and Fat images, which are available in conventional WFS imaging, PDFF image and R2* quantification images can be obtained at the same

time using Fat Fraction Quantification.

Figure 1 shows the flowchart of Fat Fraction Quantification reconstruction, where the six echoes are employed to calculate PDFF and R2*. The first two echoes (TE1 and TE2) can be used to calculate IP and OP images. Alternatively, any combination of two echoes can be used to calculate IP and OP images.

Next, the reconstruction algorithm decomposes the signal from IP and OP images into fat and water images. B0 field inhomogeneity interferes with an accurate creation of water and fat images. B0 field inhomogeneity can cause water/fat swap artifact, which is one of the common artifacts in water/fat shift (WFS) imaging techniques resulting in incorrect water and fat separation. Water/fat swap can impact PDFF and R2* quantification depending on the severity and location of the swap.

In order to achieve an accurate water/fat separation, B0 field map is initially estimated using different combinations of the source images, as shown in Figure 1. Similarly water and fat images are initially estimated using different pairs for the source images. Based on the initial estimation information, the final estimated values are obtained, suppressing the frequency of occurrence of water/fat swapping to a level lower than for conventional WFS imaging. Additionally, for more accurate B0 field, an FFE-based shim can be used. The FFE-based shim also reduces the impact of motion and susceptibility on the shim performance. In quantitative imaging, there are several confounding factors that impact accurate estimation of PDFF and R2*. Those confounding factors impacting PDFF (e.g., R2* and multi-peak fat model) can be addressed at this point in the image reconstruction to

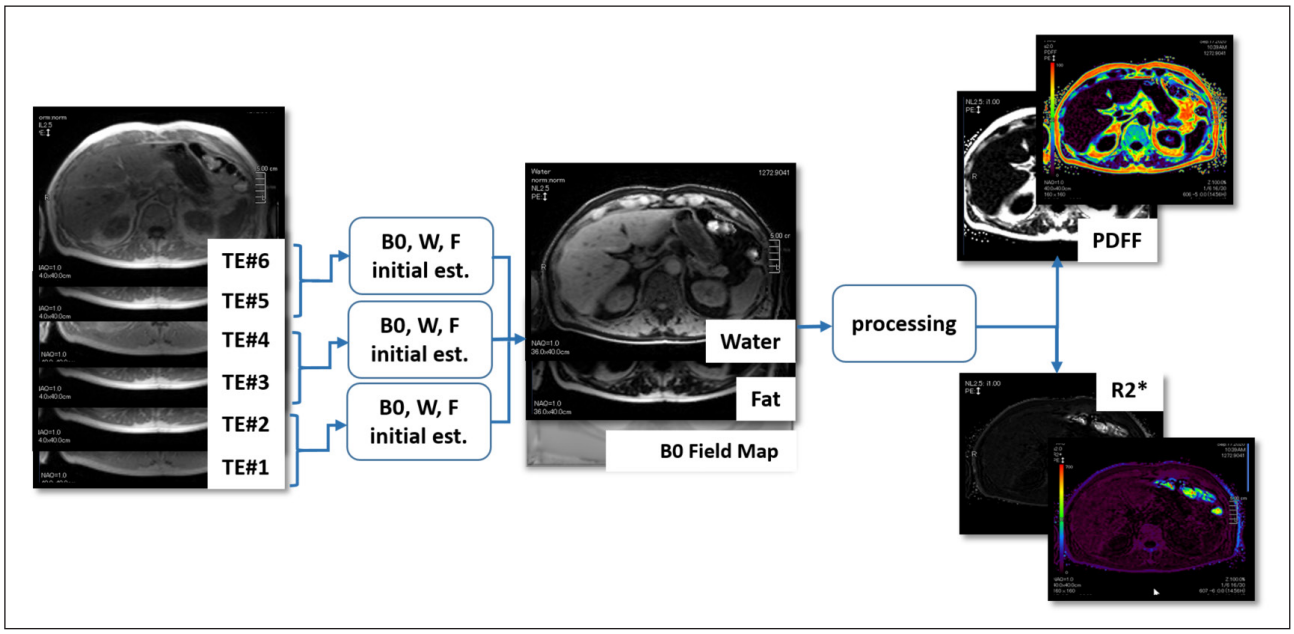

Figure 1 Flowchart of Fat Fraction Quantification reconstruction. 6 echoes are used as source images to reconstruct fat and water images as well as estimate R2* map. PDFF is calculated by using water and fat images, after addressing the confounding factors.

Parameters	Fat & Mild Iron	High Iron
FOV (cm x cm)	40 x 40	40 x 40
Slice thickness (mm)	6	6
Matrix Size	144 x 192	144 x 192
Resolution (mm x mm)	2.8 x 2.1	2.8 x 2.1
Number of slices	32	32
Base TE (steps) (msec)	1.2 (1.0)	0.9 (0.9)
TR (msec)	7.8	6.8
Acq. Time (sec)	20	17
BW (hz/pixel)	1302	1562
Flip angle (degree)	5	12

Table 1 Two protocols designed for fat & mild iron and high iron situations.

achieve accurate water and fat images. After calculation of water and fat images, the PDFF is measured as the ratio of MR-visible fat protons to the sum of water and fat protons.

Areas with a high concentration of fat will appear bright, whereas areas of low fat concentration will appear dark.

Table 1 shows the parameters for two typical Fat Fraction Quantification pulse sequences on Vantage Orian 1.5T. Two different base TEs are considered for accurate PDFF and R2* quantification based on the contributions of fat and iron. The sequence with base TE of 1.2 msec uses echo times that are derived from the chemical shift of water and fat. Therefore, it is well suited for PDFF quantification in the typical situation. The sequence with base TE of 0.9 msec acquires echoes with short first echo time and echo spacing. It is well suited for a rapidly decaying signal, such as is the case when R2* is high due to increased levels of iron. Rapidly decaying signal can cause reduced SNR and hence a larger flip angle (FA) may be used to compromise the lower SNR. However, larger FA introduces T1 bias effect in the Fat Fraction Quantification and consequently impacts an accurate PDFF quantification. Therefore, it is recommended to use sequences with shorter TE (and larger FA) only for R2* quantification when the iron concentration is expected to be high in the liver. One should note that the sequence with base TE of 0.9 msec is not supported on Vantage Galan 3T.

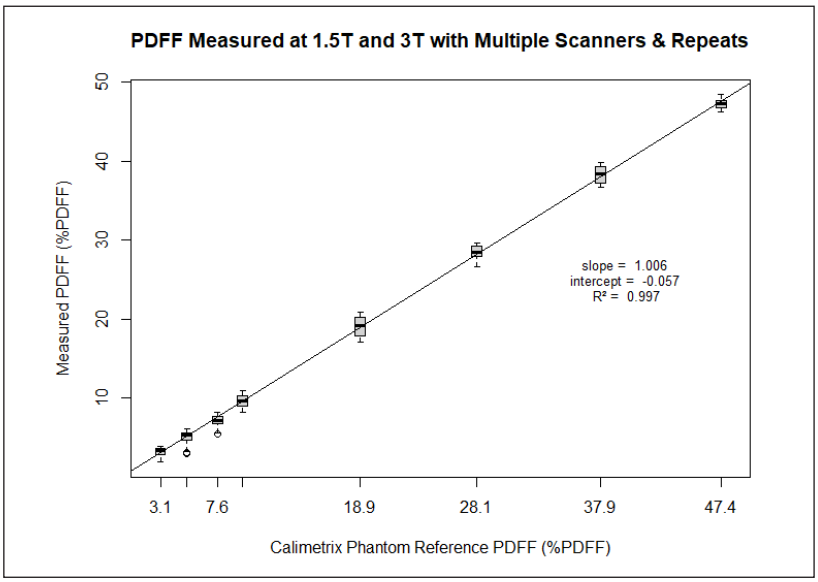

Figure 2 Accuracy of PDFF quantification using Fat Fraction Quantification compared to known values in a Phantom at 1.5T and 3T with multiple scanner and repeats.

Phantom Study

To evaluate the accuracy, repeatability and reproducibility, a study was performed using a Calimetrix (https://www.calimetrix.com/) combination phantom. The study included the same phantom on 4 different Canon Scanners, two Vantage Orian 1.5T scanners and two Vantage Galan 3T scanners, with five intra-exam repeats, then repeated on three separate days, each. The results of all the data combined (n=480) are plotted in figure 2, showing the accuracy of the measured PDFF value as compared to the known values (tolerance = 1.5 %PDFF) contained within the phantom (slope=1.006, intercept=-0.057 %PDFF, and coefficient of

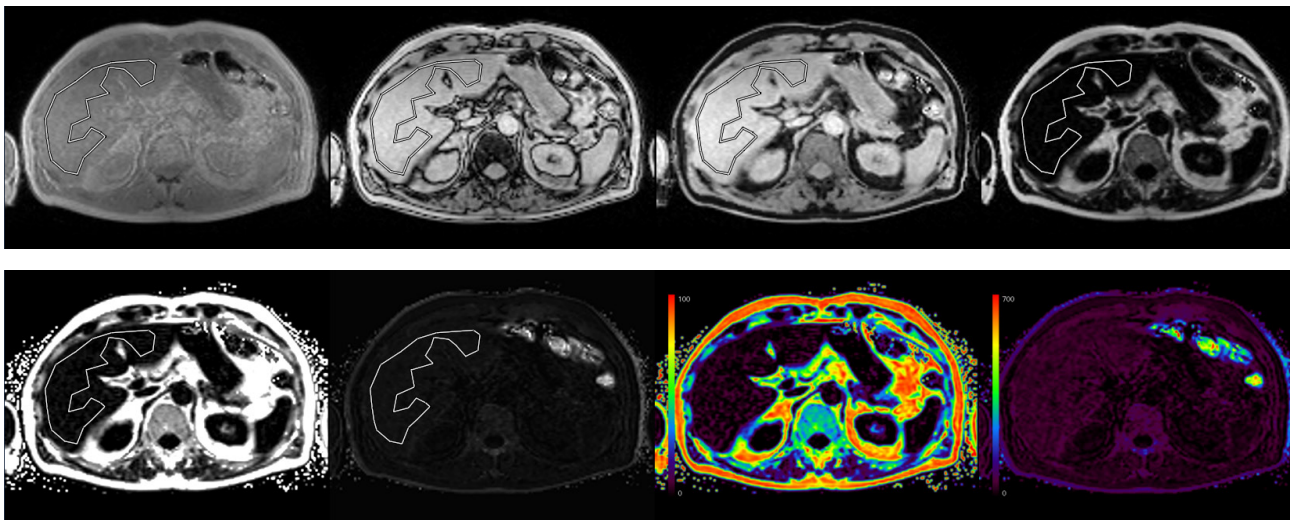

Figure 3 Fat Fraction Quantification scan in a normal volunteer on Vantage Orian using a sequence with TE=1.2 msec. IP, OP, water, and fat images are shown in the top tow. In the bottom row, PDFF, R2* maps, and color maps of PDFF and R2* are demonstrated. The dark signal in liver in PDFF map is due to low FF in liver in a healthy volunteer.

determination=0.997). Additionally, Bland-Altman analysis (not shown) for all permutations of test-retest comparisons across days, scanners, etc., suggest that reproducibility and repeatability of PDFF measurements are < ±3 %PDFF.

In-Vivo Study

Several volunteers were scanned at Canon facility (MR Research Center) to evaluate Fat Fraction Quantification technique and optimize the sequence. Figure 3 shows a result of Fat Fraction Quantification in a healthy volunteer on Vantage Orian. As explained in technical description, two protocols were designed on Vantage Orian 1.5T for either mild or high iron deposition in the liver. In Figure 3, the protocol with TE =1.2 msec was selected as normal level of iron in the liver was expected. The first row demonstrates IP, OP, water, and fat images, respectively. Bottom row shows PDFF map, R2* map, and color mapped PDFF and R2* maps. Fat Fraction (FF) was measured in an ROI in the liver tissue but away from the edge of the liver, large ducts, and vessels as shown in figure 3. In order to draw the ROI accurately, a clinical Axial T2W scan was used. The measured FF in this ROI was 3% which is in agreement with FF level in a healthy liver.

Figure 4 shows the results of Fat Fraction Quantification scan on the same volunteer with TE=0.9 msec. The measured FF in the same ROI as figure 3 was 6.8% which is higher than the normal range for liver fat fraction (0-5%). This result was expected as the protocol with 0.9 msec is optimized for patients with high level of iron concentration

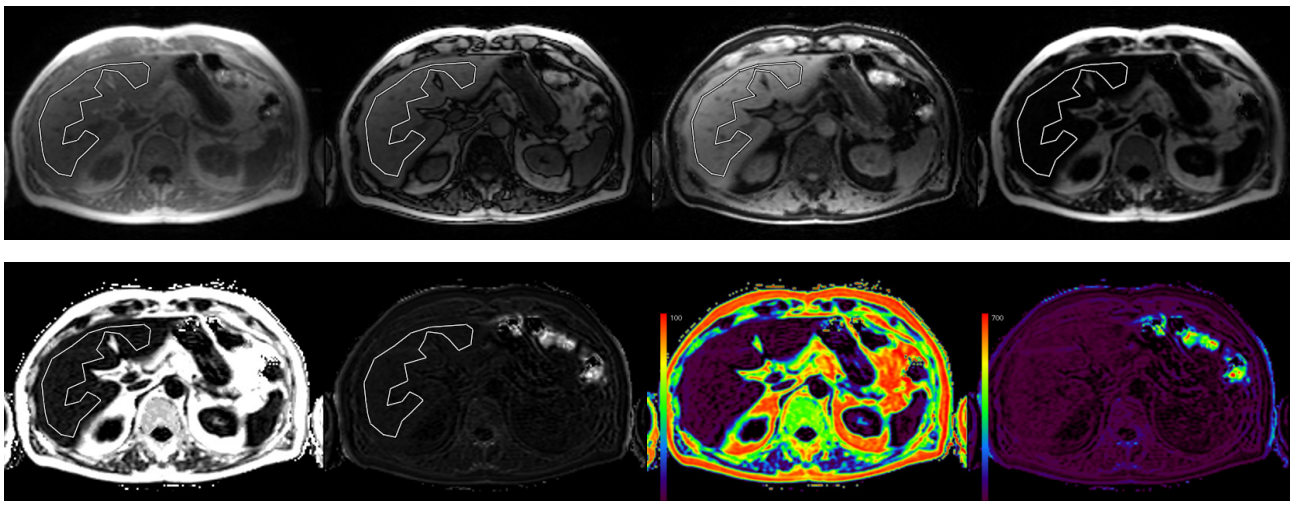

Figure 4 Fat Fraction Quantification scan in a normal volunteer on Vantage Orian using a sequence with TE =0.9. IP, OP, water, and fat images are shown in the top tow. In the bottom row, PDFF, R2* maps, and color maps of PDFF and R2* are demonstrated. The signal in liver in PDFF map is brighter which is due overestimation of FF.

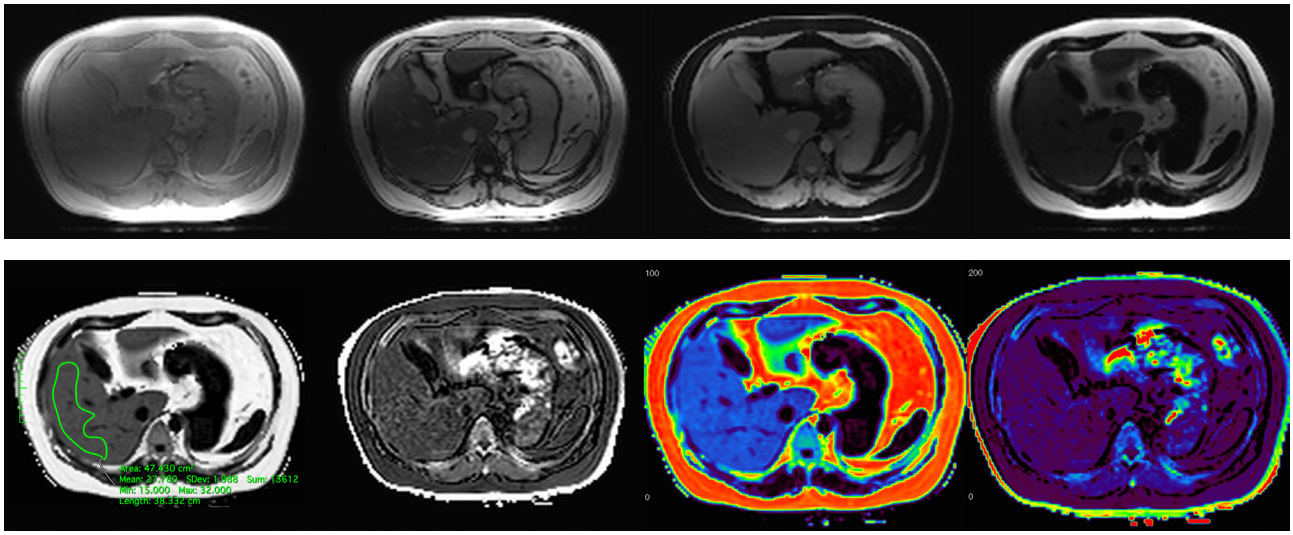

Figure 5 Fat Fraction Quantification scan in a volunteer with fatty liver disease on Vantage Galan 3T using a sequence with TE=1.2 msec. IP, OP, water, and fat images are shown in the top tow. In the bottom row, PDFF, R2* maps, and color maps of PDFF and R2* are demonstrated. The signal in liver in PDFF map is brighter than the normal volunteer in figure 3 due to fat overload in the liver.

in the liver and is known to overestimate the FF in the liver due to T1 bias caused by higher FA in the protocol.

Figure 5 shows the result of Fat Fraction Quantification scan with 1.2 msec TE on Vantage Galan 3T in a volunteer with fatty liver disease. The measured FF in the illustrated ROI in the liver is ~28% which is significantly higher than FF in a normal volunteer.

Discussion

The results of in-vivo study in normal volunteers were in good agreement with expected values for a healthy liver. The FF quantification in a normal volunteer correlated with the reported FF values for a healthy liver in the literature. On Vantage Orian 1.5T, the two protocols with higher and lower TEs were used to evaluate the impact of TE in quantifications. The results confirms that TE = 1.2 msec is appropriate for scanning a healthy liver or liver with mild iron concentration as described in figure 3 and 5. The TE=0.9 msec led to overestimation of FF as shown in figure 4 and is not recommended for subjects with normal to mild iron concentration. This sequence is intended to measure R2* map on Vantage Orian 1.5T in patients with suspected high level of iron concentration. In these patients, it is recommended to also acquire PDFF map using the protocol with TE = 1.2 msec, in addition to the sequence with TE=0.9 msec. In this case, the R2* map generated by protocol with TE=0.9 msec is more accurate while the sequence with TE=1.2 msec can provide more accurate PDFF map. Also, there is noticeable contrast difference between images acquired with TE =0.9 msec and TE =1.2 msec. This is mainly due to the increased T1 weighting in the sequence with TE=0.9 msec due to higher FA. The higher FA in TE=0.9 msec protocol is used to compromise the SNR drop due to shorter TEs.

In patients with lower level of fat it the liver (e.g. figure 3), the liver tissue appears darker in PDFF maps compared to the cases with fatty liver disease (e.g. figure 5). This is more distinct if the patient suffers from liver diseases such as NAFLD. Note that in the color mapped PDFF, the area with subcutaneous adipose tissue appears as red which indicates very high concentration of fat, as expected. In R2* map, the liver appears dark in both volunteers shown here as the level of iron concentration in both volunteers appears to be normal. In case of patients with high iron overload, the liver tissue would appear brighter in R2* map.

There were no water/fat swaps in any of these scans which indicates reasonable homogeneity of magnetic field after shimming and robust image reconstruction to generate water and fat images.

One limitation for in-vivo study was that the record of volunteers' health history was not available and there was no other FF quantification available (such as biopsy or spectroscopy) to employ as a ground-truth for our quantifications.

Conclusion

Fat Fraction Quantification is an accurate, reproducible, and repeatable quantification method which can be used to measure FF in the liver. Fat Fraction Quantification also provides R2* map which, in addition to the built-in correction of PDFF, may be useful in evaluating the effects of iron deposition in the liver. Further clinical study on patients with liver disease is required to evaluate clinical application of Fat Fraction Quantification.

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The clinical results, performance and views described in this paper are the experience of the author(s). Results may vary due to clinical setting, patient presentation and other factors. Many factors could cause the actual results and performance of Canon's product to be materially different from any of the aforementioned.

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