ENDRA LIFE SCIENCES

A First Clinical Feasibility Study Employing Thermoacoustics to Estimate Liver Fat Fraction as Determined by MRI-PDFF

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ABSTRACT

A feasibility study comparing ENDRA Life Sciences' Fatty Liver Imaging Probe (FLIP) thermoacoustic measurements of liver fat fraction, to MRI-PDFF (magnetic resonance imaging - proton density fat fraction), was recently completed. The aims of the study were to estimate: the sensitivity of FLIP measurements in detecting fatty liver disease, and the correlation of FLIP measurements to MRI-PDFF. In a limited sample size of 19 healthy volunteer subjects with BMI ranging from 22.2 - 40.6 kg/m^2, FLIP measurements had a sensitivity of 0.88 and specificity of 0.82, at an MRI-PDFF threshold of 6%. At an MRI-PDFF threshold of 15%, the sensitivity was 0.82 with specificity of 0.85. The Area Under the Receiver Operating Characteristic (AUROC) was 0.91 and 0.88 at MRI-PDFF values of 6% and 15%, respectively. The Pearson correlation coefficient (r) of FLIP thermoacoustic measurements with MRI-PDFF was 0.75.

INTRODUCTION

Current biomarkers and imaging tools that are routinely used in the management of liver disease have sensitivity and specificity ranging from 0.68-0.96, and 0.50-1.0, respectively, while the C statistic (AUROC) ranges from 0.61-0.99[1-5]. A first clinical feasibility study was conducted with an investigational FLIP development system, by investigators at the Robarts Research Institute in London, Ontario, Canada, in collaboration with ENDRA Life Sciences. The study objectives included the development of a workflow for obtaining useful thermoacoustic measurements in the liver, and to estimate the sensitivity and specificity of FLIP measurements in detecting clinically relevant liver fat fraction (>6% MRI-PDFF)[6]. Measurements were obtained at several anatomical sites in order to evaluate their suitability for routine clinical use with the FLIP system.

The study included three procedures: conventional ultrasound imaging, quantitative Magnetic Resonance Imaging (MRI) to determine liver fat fraction by Proton Density Fat Fraction (PDFF), and thermoacoustic measurement with an ENDRA development FLIP system. Conventional ultrasound imaging was used to locate access to the liver for FLIP measurements, while MRI-PDFF was used to obtain true, volumetric liver fat fraction measurements for each subject. ENDRA Life Sciences employees participated in the collection and analysis of data in this study.

STUDY DESIGN

TEST SUBJECTS

The study was conducted in two parts. In the first part, 33 healthy volunteer subjects were scanned to develop a FLIP measurement protocol, and to identify suitable anatomical sites for FLIP measurements. Only 5 of the 33 subjects had clinically relevant (elevated) liver fat fraction (>6%) by MRI-PDFF). In the second part of the study 17 additional subjects were recruited, and 9 subjects from part 1 of the study were rescanned for a total of 26 subjects. The cohort of 26 subjects spanned a range of liver fat fraction that mimicked the target population for FLIP applications, with liver fat fraction ranging from 2 - 26% by MRI-PDFF. The height, weight, and alcohol consumption, along with lifestyle information (diet and exercise), was collected for each study participant.

MRI IMAGING

MRI scans were performed with a GE 3T MRI system equipped with a 32 channel (phased-array) receive only torso coil (Discovery MR750, GE Healthcare, Waukesha WI). Pulse sequences were acquired with a commercially available quantitative fat imaging application IDEAL IQ (GE Healthcare) that employs 3D gradient echo series with a multi-point Dixon parametric fitting technique to compute a quantitative map of fat fraction. An IDEAL IQ pulse sequence is obtained with a single 22 second breath hold. The entire MRI procedure was approximately 30 minutes.

ULTRASOUND IMAGING

An abdominal liver ultrasound examination was performed with a GE Logiq E-9 ultrasound system for each study subject. Intercostal B-mode images of the liver were obtained with a curved linear array (GE Healthcare C1-6 probe) to locate suitable anatomical sites for thermoacoustic measurement. Once the anatomical site was identified with conventional ultrasound, the skin was marked with a surgical pen and the FLIP device was positioned at the same anatomical location in order to collect thermoacoustic measurements.

OBTAINING MEASUREMENTS WITH FLIP

The FLIP data acquisition was initiated once proper coupling of the FLIP transducer to the skin was indicated. A single FLIP measurement consists of acoustic signals induced by a series of 480 radio frequency pulses obtained over 1.2 seconds. The thermoacoustic data was stored on a computer located on the FLIP cart, independent from the conventional ultrasound system.

ANALYSIS

QUALIFICATION OF LIVER FAT FRACTION BY MRI-PDFF

MRI-PDFF analysis was performed with the GE CDViewer (GE Healthcare) analysis software. The analysis steps included the selection of an MRI-FatFrac IDEAL IQ image slice between the superior pole of the right kidney and the right lung. Three circular regions of interest (ROI) ranging 500mm^2 to 800mm^2 were placed at the lateral edge of the right lobe. Large vessels were excluded in the selection of each ROI. The average and standard deviation of fat fraction within each selected ROI was recorded (fig. 1).

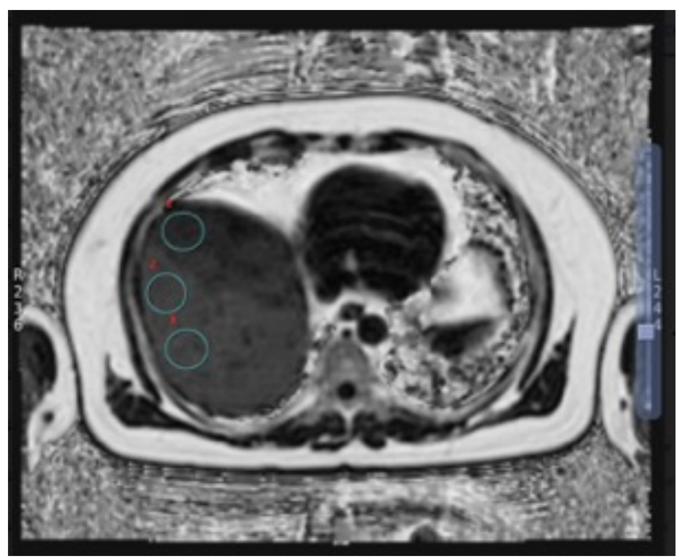

Figure 1

MRI-PDFF ROI positioning. Three selected ROIs are displayed the corresponding mean and standard deviation of fat fraction is recorded.

FLIP MEASUREMENT ANALYSIS

Each data set was inspected manually to select acquisitions with thermoacoustic signals that corresponded to the fat, muscle, and liver capsule locations as measured by conventional ultrasound (fig. 2). Each data set consisted of multiple acquisitions obtained from more than one anatomical site. The criteria for a valid flip measurement was:

1. Contiguous data with no anomalous data acquired over the 1.2 secs duration of the FLIP measurement
2. Agreement between FLIP measurements and conventional ultrasound, of the location of: fat, muscle, and the liver capsule.
3. If multiple acquisitions satisfy the criteria above, the measurement with the highest signal to noise ratio was selected.

FLIP measurement data was processed by averaging the 480 individual thermoacoustic pulse acquisitions, followed by low and high pass filtering to remove signal noise outside of the FLIP sensor bandwidth. Processed data was beamformed (reconstructed) with a delay-and-sum algorithm and signal amplitudes at fat-muscle and muscle - liver interfaces were extracted (fig. 3). Compensation for non-uniform electric field was applied to the extracted thermoacoustic measurements, with subject specific anatomy obtained from conventional ultrasound images of the subject's fat, muscle and liver anatomy. The FLIP liver fat metric was calculated for each subject based on the electric field compensated extracted thermoacoustic signals.

FLIP measurements were rejected if: (i) measurements had low or undetectable signal at the relevant anatomical locations, (ii) there was a mis-match between the anatomical location of the fat, muscle, and liver capsule, in FLIP measurements compared to the conventional ultrasound image, and (iii) measurements contained artifacts induced by system or operator error.

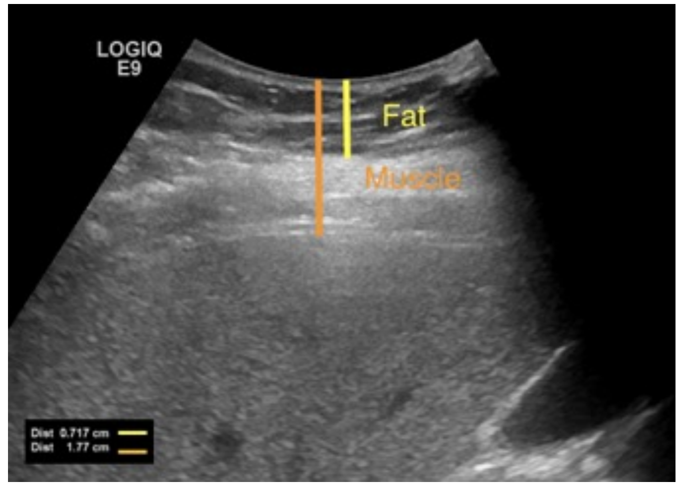

Figure 2

A conventional ultrasound image was obtained to determine the depth of the subcutaneous fat, and the depth of the liver capsule.

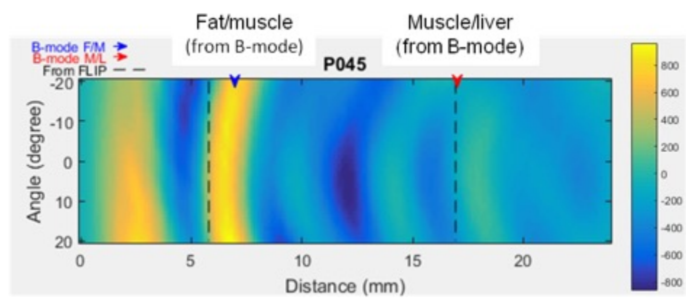

Figure 3

Beamformed FLIP thermoacoustic measurements (left) coincide with the anatomical locations of the fat, muscle, and liver capsule. The overlaid dashed lines represent the depth of subcutaneous fat and the liver capsule, as determined by conventional ultrasound. The color bar (right) provides the mapping of thermoacoustic signal amplitude to display color

Thermoacoustic measurements in 19 subjects were successfully acquired, analyzed, and included in statistical analysis. Measurement data from 7 subjects were rejected based on one or more of the rejection criteria.

RESULTS

FLIP measurements for 19 of 26 subjects met the inclusion criteria for inclusion. 11 of the 19 subjects included had liver fat fraction > 6% as determined by MRI-PDFF. Linear regression was performed, individually, to determine the correlation coefficient with MRI-PDFF for: FLIP measurements, BMI, and abdominal fat thickness. The Pearson coefficient of correlation (r) of FLIP thermoacoustic measurements with MRI-PDFF was 0.75 (fig. 4). The correlation of BMI and abdominal fat thickness with MRI-PDFF was weak, r = 0.17 and r = 0.38, respectively.

FLIP measurements had a sensitivity of 0.88, and specificity of 0.82 in detecting fatty liver at an MRI-PDFF threshold of 6% (fig. 5). At MRI-PDFF of 15%, the sensitivity was 0.82 with a specificity of 0.85. The C statistic (AUROC) was 0.91 and 0.88 at MRI-PDFF values of 6% and 15%, respectively.

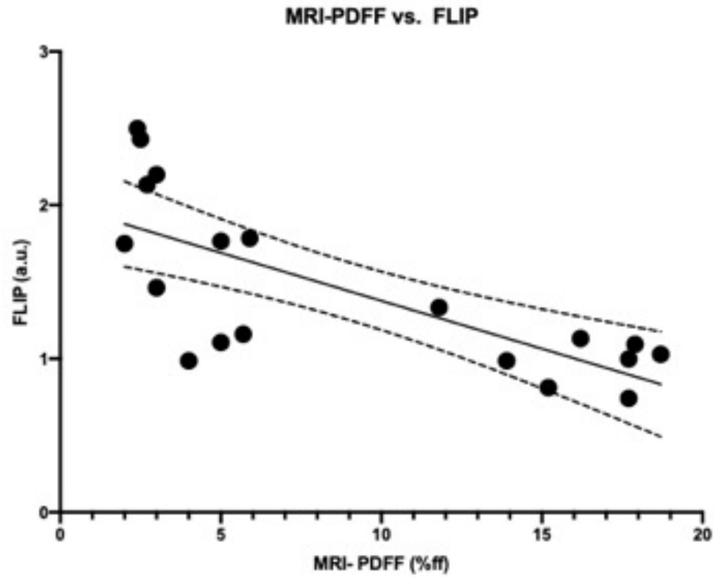

Figure 4

MRI-PDFF vs TAEUS FLIP regression analysis for 19 study subjects, Pearson linear correlation coefficient r=0.75. The dashed lines represent the 95% confidence interval for the linear regression.

	Sensitivity	Specificity	FLIP signal
0	0.000	1.000000	-0.2587
1	0.125	1.000000	0.7413
2	0.375	1.000000	0.9856
3	0.375	0.909091	0.9857
4	0.750	0.909091	1.0934
5	0.750	0.818182	1.1057
6	0.875	0.818182	1.1308
7	0.875	0.727273	1.1598
8	1.000	0.727273	1.3330
9	1.000	0.000000	2.4981

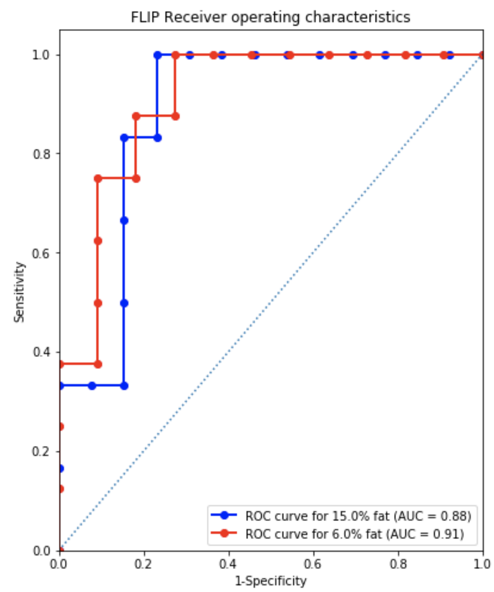

Figure 5

The receiver operating characteristic, with an NAFLD threshold of 6% by MRI-PDFF, is shown in tabular form (left), the graph (right) has ROC for MRI-PDFF thresholds of 6 and 15%.

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