Liver Fibrosis Evaluation Using Ultrasound Shear Wave Imaging

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IRB Minimal Risk Protocol Template

General Study Information

Principal Investigator: Shigao Chen

Study Title: Liver Fibrosis Evaluation Using Ultrasound Shear Wave Imaging

Protocol version number and date: March 29, 2019

Purpose

Hypothesis: Liver stiffness measured by Ultrasound Shear Wave Imaging is correlated with liver stiffness measured by MRE (Magnetic Resonance Elastography).

Aims, purpose, or objectives: Liver stiffness measured by MRE can be used for noninvasive liver fibrosis staging. However, MRE is expensive and not widely available. This study will evaluate the efficacy of liver stiffness measured by ultrasound for fibrosis staging, using clinically indicated MRE as the gold standard. A secondary aim is to measure the fat content of liver using ultrasound and to study the correlation of liver fat and fibrosis.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):
Liver fibrosis/cirrhosis afflicts hundreds of millions of patients worldwide and 900,000 Americans. Liver biopsy, currently the gold standard for the diagnosis of liver fibrosis, is invasive and may occasionally cause significant complications, which limits the screening of at-risk populations, treatment monitoring, and follow-up. Liver stiffness measured by MRE (Magnetic Resonance Elastography) is used clinically at Mayo for non-invasive liver fibrosis staging. In MRE, small mechanical vibrations are applied at body surface and shear waves (mechanical waves due to vibration perturbation) thus introduced in liver is detected by Magnetic Resonance Imaging and used to calculate the stiffness of liver. However, MRI is expensive and not widely available. In this study, we will evaluate the feasibility of using ultrasound to detect shear waves introduced by small mechanical vibration for liver fibrosis staging. We expect that this new method will have better penetration compared to existing ultrasound elastography techniques, and therefore has more reliable measurements in obese patients. This is an important advantage considering prevalence of obesity in USA.

Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual: *Proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens,* ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Subject population: 325 patients (with clinically indicated liver MRE) and healthy volunteers.

Inclusion Criteria: Both male and female healthy volunteers or patients who are scheduled for clinically indicated liver MRE for fibrosis staging, age 18 to 80.

Exclusion Criteria: subjects lacking capacity to consent, or subjects with unreliable ultrasound or MRE measurements. Pregnant women will be excluded. Women of child baring potential will be asked by our study coordinator if they are pregnant. If not sure, a urine pregnancy test will be given to screen the subject at no cost to the subject.
Will a Certificate of Confidentiality be obtained? *If yes, provide an explanation*.
No.

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
Study on patients and volunteers will take place in the Radiology department using the GE Loqig E9 scanner (FDA approved), GE Logiq E10 (FDA approved), and the Verasonics ultrasound scanner. The first ultrasound scan will be about 10 minutes using the GE Logiq E9 scanner and optionally the GE Logiq E10 scanner to measure the stiffness of liver (used as a benchmark reference in this study). The seond ultrasound scan will be about 30 minutes using the Verasonics scanner. In the second scan, multiple miniature mechanical vibrators will be placed on the body surface of rib cage of the subject. An elastic strip (fibric covered neoprene) wrapped around the chest and sesured by hook-and-loop will be used to hold the mini-vibrators in contact with body surface. Alternatively, mechanical vibrations is introduced by an audio loudspeaker in contact with the subject's upper torso. Or mechanical vibration will be introduced through a miniature vibrator attached to the ultrasound probe. An experienced sonographer from Mayo will image the liver with an ultrasound transducer. The best intercostal window that shows an area of the hepatic lobe away from the diaphragm and adjacent vessels will be chosen. Repeated stiffness measurements will be made at different locations within the liver parenchyma while the mini-vibrators introduce shear wave in the liver, similar to an MRE examination. The subject will be instructed to briefly hold his/her breath during each measurement. This procedure will take about 30 minutes. The study is non-invasive and imposes no discomfort to the subject. Liver MRE results will be obtained from the medical record of the patient and compared with ultrasound results. Most healthy volunteers will not have liver MRE examination and therefore liver stiffness measured by mechanical vibrations will be compared with those obtained with the GE Logiq E9 scanner. Some healthy volunteers may be offered liver MRE examiniation so that we can compare the ultrasound and MRE measurements in the healthy cohort. Other clinical information relevant to liver diseases if available, such as results of liver biopsy or liver function tests, will also be obtained from medical records to assist data analysis. If a healthy volunteer were found to have abnormal liver stiffness by MRE performed as part of this research study, we will inform the healthy volunteer, and if requested, to his/her primary care provider. We will not communicate with patients on their MRE results, as their MRE examinations are clinically indicated and they should be aware of their MRE results from their clinical care provider. Reliability of the new ultrasound technology used in this study for liver disease diagnosis is not established yet. Therefore, participants will not be informed of research ultrasound measurement results. Incidental findings in subjects if noted (e.g if splenomegaly, adenopathy, or a mass) will be communicated to the subject, and if requested, to his/her primary care provider.

In addition to liver stiffness data, un-processed ultrasound data from conventional B-mode ultrasound imaging will be collected and analyzed offline to estimate the liver fat content. Completely de-identified data may be shared with GE to see if more advanced GE processing can improve the outcome. Correlation of liver stiffness (reflecting fibrosis) and liver fat content (reflecting steatosis) will be analyzed. Information from the patients' medical record about the status of liver disease may be used to help interpreting the results. We may screen potential patient candidates' MRE results to help select patients to enroll for this study, to ensure that we have a relatively uniform distribution of patient population to cover the full spectrum of the disease.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:
This project will be funded by a NIH R01 grant. Dr. William Sanchez (GI) and Dr. Matthew Callstrom (Radiology) are co-investigator of this project. We have commitments from all participating personnel and their efforts will be funded by the R01 grant.

Check all that apply. If none apply, leave blank:

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☐ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves audiotaping or videotaping

Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)_____

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. (*Example: 01/01/2000 to 12/31/2012*)

Date range: From _05__/_01__/__2013___ to __05_/_01__/_2025____

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☒ This study involves only data and/or specimens that will be collected after submission to the IRB.

☐ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained and check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol*.

IRB Number(s):

□Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study. When checked, provide all data sources:

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Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	x	
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	x	
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	x	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☒ None

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Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Statistical Considerations

Power Statement:

This protocol was initially approved as a pilot study to enroll 60 subjects to provide preliminary data for NIH grant applications. Our NIH R01 application is now funded. Therefore, we need to study 45 additional patients for Aim 2, and 220 patients for Aim 3 of the awarded NIH grant. Justification of sample size (45 and 220 patients) can be found in page 66-68 of the NIH application, which is attached to Section 47 (Supporting Documents) of this IRB application. Therefore, we will need to increase the target enrollment for this study by 265 (45+220) to meet the need of NIH award. This brings the total enrollment number to 325 (60+265).

Data Analysis Plan:
Detailed data analysis plan can be found in page 66-68 of the NIH application, which is attached to Section 47 (Supporting Documents) of this IRB application.

Endpoints

Primary: We study 325 subjects with successful MRE and ultrasound measurements.

Secondary: Some patients will have failed MRE or ultrasound measurements due to technical difficulties. We therefore will continue recruiting up to 400 subjects until we reach the primary end point.

Data Analysis Plan

Intraclass correlation coefficients (ICC) will be calculated from random effects models to evaluate the inter-sonographer agreement. For these models, subject and sonographer will both be included as random effects. The within subject variance components from the model will be used to obtain an estimate of the overall measurement variance for REVUE. In addition to the overall analysis, we will compare repeatability and reproducibility measures across subgroups defined according to subject BMI (<30 and ≥30) and perform supplemental analyses separately for each BMI category as appropriate. In all cases, findings will be presented using point estimates and 95% confidence intervals.

The primary objective is to demonstrate whether REVUE is an effective alternative to MRE for distinguishing patients with minimal fibrosis (MRE ≤ 2.9 kPa) and advanced fibrosis (MRE ≥ 5.0 kPa). To accomplish this objective, ROC curve analyses will be performed using logistic regression for these MRE cut points. Separate analyses will be performed to assess the performance of both REVUE and Aixplorer®. The results of these analyses will be summarized using the point estimate and 95% confidence interval for the area under the ROC curve (AUROC). In addition, we will compare the AUROC between ultrasound methods using the approach described by DeLong. Secondary analyses will be performed using Pearson product-moment correlation and linear regression to evaluate the association of REVUE and Aixplorer® measurements with MRE. The correlation coefficients obtained from these analyses will be summarized and compared (REVUE vs. Aixplorer®) using the method described in. To supplement the overall findings, we will repeat the analyses according to BMI (all BMI vs. BMI≥30) and, if appropriate, according to disease (chronic viral hepatitis and alcoholic/nonalcoholic fatty liver disease). In all cases, two-tailed p-values ≤ 0.05 will be considered statistically significant.