Magnetic Resonance Elastography of Chronic Liver Disease
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Introduction

Hepatic fibrosis is an excessive accumulation of proteins, particularly collagen, in the extracellular matrix of the liver, resulting from chronic inflammation and cellular injury. Hepatic fibrosis alone does not affect liver morphology unless it causes extensive hepatocellular necrosis or scarring and cirrhosis. Conventional MR imaging may show surface nodularity, regenerative nodules, expanded hilar and gallbladder fossa spaces, liver volume changes, and evidence of portal hypertension in advanced liver fibrosis. All of these are signs of advanced disease and morphologic imaging is not sensitive for detecting less than stage 4 fibrosis.

MRI-based tissue characterization biomarkers that have proposed for assessing liver fibrosis include measurement of the apparent diffusion coefficient, (ADC), measurement of T1 or T1rho, and quantitative texture analysis without or with contrast material. Statistically significant changes from normal values have been demonstrated with all of these biomarkers advanced fibrosis is present. Like morphologic imaging, these biomarkers have not proved to be sensitive or specific for assessing fibrosis that is less than stage 4.

It has long been known that fibrotic liver tissue is mechanically stiffer than normal liver and the degree of increased stiffness correlates with the severity of fibrosis. More recently, it was demonstrated that in progressive liver disease, the stiffness of hepatic tissue actually increases prior to the onset of histological fibrosis. This is thought to represent the effects of early changes in the macromolecular composition of the extracellular matrix (ECM). It has also been shown that increased ECM stiffness actually promotes the development of hepatic fibrosis through a process known as mechanotransduction.

Magnetic resonance elastography (MRE) is an MRI-based technique for quantitatively assessing the mechanical properties of tissue [1,2,3]. The main clinical application at the present time is for non-invasive assessment of hepatic fibrosis. FDA-cleared upgrades to equip conventional MRI scanners for
MRE are available from GE Healthcare, Siemens, and Philips. MRE has been available since 2009, and approximately 800 MRI systems around the world are equipped to use the technique.

**Basic Principles**

MRE is based on the fact mechanical waves in tissue propagate at speeds determined by the mechanical stiffness of the medium. The technique consists of three steps: (1) generating mechanical waves in the region of interest, (2) imaging propagating mechanical waves, and (3) processing the information to calculate the mechanical properties. In commercially-available MRE systems, mechanical waves are typically generated at 60 Hz in the upper abdomen with a flat disk-shaped vibration source that is placed against the body wall. During imaging, synchronous cyclic motion-sensitizing gradients are used with a modified phase-contrast MRI pulse sequence to acquire snapshots of the propagating waves, depicting displacements as small as fractions of microns. The acquired data are then automatically processed with an inversion algorithm to generate cross-sectional images showing the mechanical properties of tissues (typically shear stiffness) on a color scale.

The MRE acquisition is performed during suspended respiration and takes 12-15 seconds. This acquisition is typically repeated four times, for a total acquisition time of less than one minute. MRE is usually added to a conventional abdominal MRI protocol (either full or limited) and adds very little additional time to the overall examination. Another protocol option is to perform a very limited exam consisting only of MRE and a ~30 sec Dixon-type sequence, which would provide quantitative estimates of fat fraction, iron content, and liver stiffness in an exam that could be accomplished in less than 10 minutes of scanner time, at very low cost.

After 1-3 minutes of automatic processing, the scanner produces gray scaled and color-scaled quantitative images ("elastograms") depicting tissue shear stiffness in units of kiloPascals (kPa). In addition, the algorithm provides anatomic images corresponding to each of the elastograms and "confidence images" that provide a measure of the reliability of the tissue stiffness measurement at each image location.

**Mechanical Properties Calculated**

The algorithm used by commercially-available MRE systems calculates the magnitude of the complex shear modulus of the tissue with simplifying assumptions that the tissue is isotropic, linear, viscoelastic, and locally-homogeneous. The real-valued component of the complex shear modulus is known as the storage modulus and the imaginary component is called the loss modulus. The magnitude of the complex shear modulus is often referred to as shear stiffness.

Many other parameters can be measured or calculated from MRE data. MRE data can be processed to estimate shear wave speed and attenuation. If local attenuation is small and tissue mass density is assumed to be unity, then shear stiffness can then be expressed in terms of wave speed squared.

MRE-based measurements of tissue stiffness typically increase with the frequency of the applied shear waves. Rheologic models, consisting of networks of elastic and viscous elements can be used to model the variation in the observed complex shear modulus with frequency. This yields many potential parameters that could be explored for characterizing tissue.
Clinical Indications for MRE

Hepatic elastography addresses a long-recognized need for a non-invasive alternative to liver biopsy for diagnosing and staging liver fibrosis. Liver biopsy has a risk of morbidity and mortality, is affected by sampling error and subjective histologic interpretation, and is much more expensive than imaging, including MRI.

At the Mayo Clinic, the most common indication for MRE is to assess possible hepatic fibrosis in patients who have conditions that are known to lead to this problem such as fatty liver disease and chronic viral hepatitis. Other indications include follow-up of previously diagnosed fibrosis, staging patients with known fibrosis, and evaluating patients with unexplained portal hypertension. Because the MRE acquisition can be added to a conventional abdominal MRI protocol with little or no impact on examination time, it does not require a high threshold of suspicion to be included in the protocol.

Diagnostic Performance of MRE in Assessing Hepatic Fibrosis

Since 2006, there have been more than 20 published studies assessing the diagnostic performance of MRE in detecting and staging hepatic fibrosis, using biopsy as the reference standard. An MRE-based measurement of hepatic stiffness that is in the normal range (< 2.5 kPa) has a very high negative predictive value for ruling out hepatic fibrosis of any stage. Excellent diagnostic performance for staging hepatic fibrosis has been reported in multiple studies. For instance, a recent meta-analysis concluded that the sensitivity, specificity, and AUROC of MRE for diagnosing advanced hepatic fibrosis and cirrhosis (≥F3) from less-advanced disease are 92%, 96%, and 0.98, respectively [4]. These metrics are probably at the limit of what is realistic to achieve, given the known limitations of using biopsy as a “gold standard”. Another pooled meta-analysis of 12 published studies [5], encompassing 697 patients, found that the sensitivity, specificity, and AUROC diagnostic performance for diagnosing stage F3 fibrosis and higher are 85%, 85%, and 0.93 respectively.

Several studies have compared the diagnostic performance of MRE with Transient Elastography (TE). A study of 141 patients found that AUROC values for TE to be: .80 for F≥1, .84 for F≥2, .91 for ≥F3, and .99 for F4, while with MRE the AUROC values were: .96 for F≥1, .99 for F≥2, .99 for ≥F3, and .99 for F4 [6]. The technical failure rate was 16% for TE and 6% for MRE. A comparative study that is currently being completed at the Mayo Clinic has shown the following preliminary results in a series of 113 patients: for TE the AUROC values are: .77 for F≥1, .82 for F≥2, .84 for ≥F3, and .90 for F4, while with MRE the AUROC values are: .80 for F≥1, .94 for F≥2, .94 for ≥F3, and .94 for F4. Technical failure rates were similar.

Confounding Factors

MRE is affected by the same confounding factors as quantitative ultrasound-based elastography. Liver stiffness is affected by chronic and acute inflammation. The presence of chronic inflammation can cause considerable overlap in stiffness values between patients with stage F0 and stage F1 fibrosis. Preliminary evidence suggests that measuring the phase angle of the complex shear modulus, as defined by the real and imaginary components may be helpful in distinguishing between chronic inflammation and early stage fibrosis. Acute hepatitis can be associated with very high liver stiffness
values without any degree of fibrosis. Portal hypertension, hepatic venous congestion, and malignant cellular infiltrates can elevate liver stiffness independent of the presence of fibrosis.

The most common reason for technical failure of MRE has been hepatic iron overload, which is not uncommon in patients with liver disease. With conventional gradient echo MRE sequences, very high liver iron content may cause the signal intensity of the liver to be too low to visualize the mechanical waves, resulting in a failure rate of ~4% in clinical populations. The newly-introduced SE-EPI MRE sequences are much less sensitive to iron overload, making these technical failures much less common. Clinical experience has shown that the technical success of MRE is not affected by obesity unless the patient is so large as not fit in the scanner. The presence of ascites, common in patients with liver disease, does not affect the technical success rate of MRE.

Accuracy and Precision

The accuracy of MRE-based measurements of semi-solid tissue-like materials has been assessed in a number of published studies, using bench-top mechanical testing devices as standards, generally showing excellent correlation. MRE-based measurements of phantom stiffness have also been demonstrated to compare favorably with TE-based measurements [7].

More than 10 published studies have assessed the test-retest repeatability of MRE in liver imaging. In general, they have shown that differences in MRE-derived liver stiffness of greater than about 20% represent meaningful longitudinal changes [8]. This is a useful level of repeatability because liver stiffness increases by more than 50% in the transition from no disease to clinical significant fibrosis.

Other Applications

MRE can be applied to evaluate tissue stiffness in most regions of the body, including pancreas, kidneys, prostate, uterus, skeletal muscle, breast, mediastinum, and heart. The most promising new application seems to be for assessment of intracranial lesions, especially preoperative evaluation of benign and malignant brain tumors. Preliminary studies indicate that MRE can be used to provide information that is useful in predicting the difficulty of surgical tumor resection.

References