Development of a Diaphragmatic Motion-Based Elastography Framework for Assessment of Liver Stiffness

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ABSTRACT

Evaluation of mechanical stiffness imaging biomarkers, through magnetic resonance elastography (MRE), has shown considerable promise for non-invasive assessment of liver stiffness to monitor hepatic fibrosis. MRE typically requires specialized externally-applied vibratory excitation and scanner-specific motion-sensitive pulse sequences. In this work, we have developed an elasticity imaging approach that utilizes natural diaphragmatic respiratory motion to induce deformation and eliminates the need for external deformation excitation hardware and specialized pulse sequences. Our approach uses clinically-available standard of care volumetric imaging acquisitions, combined with offline model-based post-processing to generate volumetric estimates of stiffness within the liver and surrounding tissue structures. We have previously developed a novel methodology for non-invasive elasticity imaging which utilizes a model-based elasticity reconstruction algorithm and MR image volumes acquired under different states of deformation. In prior work, deformation was external applied through inflation of an air bladder placed within the MR radiofrequency coil. In this work, we extend the methodology with the goal of determining the feasibility of assessing liver mechanical stiffness using diaphragmatic respiratory motion between end-inspiration and end-expiration breath-holds as a source of deformation. We present initial investigations towards applying this methodology to assess liver stiffness in healthy volunteers and cirrhotic patients. Our preliminary results suggest that this method is capable of non-invasive image-based assessment of liver stiffness using natural diaphragmatic respiratory motion and provides considerable enthusiasm for extension of our approach towards monitoring liver stiffness in cirrhotic patients with limited impact to standard-of-care clinical imaging acquisition workflow.

Keywords: mechanical properties, elastography, parameter reconstruction, mechanical model, liver

1. INTRODUCTION

Percutaneous liver biopsy is currently considered the gold-standard and is essential to the diagnosis of liver disease, but it is an invasive procedure that includes risk of complication [1]. Up to 18% of percutaneous liver biopsy procedures are associated with complications; while most complications are mild, up to 1% of procedures experience serious complications, including hemorrhage, hemothorax, biliary peritonitis, and even death [1]. The risk of complication is also significantly correlated to increased hepatic fibrosis [1]. Due to this, among other drawbacks including intra- and inter-observer variability and sampling error, there has been significant interest in the development of novel non-invasive imaging modalities that aim to assess the fibrotic state of the liver. One attractive method is to exploit the phenomenon of elevated tissue mechanical stiffness that occurs during fibrosis as a means for diagnostic assessment. As a result of this link between tissue mechanics and disease, the field of 'elastography' (non-invasive imaging based assessment of tissue mechanical properties) has developed. Assessment of liver fibrosis through elastography was one of the earliest elastographic imaging applications, and has already generated commercially available technologies in the clinic for liver stiffness assessment [2, 3] (in addition to several other tissues). As a form of 'palpation-by-imaging', elastography is a means to quantitatively evaluate the mechanical stiffness of tissue, even in the

case of tissues that are non-palpable. In the case of liver fibrosis assessment, elastography is rapidly emerging as a successful non-invasive image-based alternative to tissue biopsy; magnetic resonance elastography (MRE) has even begun to replace tissue biopsy as a reference standard for assessment of hepatic fibrosis in some centers [4]. With respect to the source of deformation for MRE reconstructions (and elasticity imaging in general), externally-applied mechanical excitation is traditionally applied and imaging is used to visualize the displacement response of tissue.

While MRE of the liver has previously undergone significant development for assessing hepatic stiffness for fibrosis staging, these measurements require proprietary MR sequences and external deformation devices placed upon the patient during the magnetic resonance (MR) examination. External deformation sources are known to exhibit significant attenuation with increasing penetration depth. As spatial resolution and accuracy are dependent upon sufficient wave signal in the presence of measurement noise, limited spatial resolution/accuracy is suffered in areas distant to the driver or other areas experiencing significant wave attenuation. Attenuation is also exacerbated by adipose tissue positioned between the wave driver and the tissue of interest, such as that found in significantly obese patients. This is potentially problematic for assessing liver stiffness, especially in patients with nonalcoholic steatohepatitis, which is associated with obesity. Further, clinical workflow requirements limit available scanner time for additional imaging sequences as well as patient repositioning required to place external deformation devices. Therefore the development of elasticity imaging approaches that can take advantage of broadly clinically available MR pulse sequences that eliminate external devices and are clinically workflow amenable would facilitate broader clinical implementation of image-based elasticity assessment.

Our underlying hypothesis for this work is that respiratory motion is a sufficient deformation source for elastographic imaging of the liver, and thus we can decouple liver elastography from the need for external deformation excitation sources and their associated challenges. In this work, we investigate the use of harnessing the natural thoracic diaphragmatic respiratory motion experienced between end-inspiration and end-expiration in order to induce tissue deformation. We present an extension to a previously described quasi-static model-based elasticity imaging methodology, modality independent elastography (MIE), for the assessment of liver stiffness. Our approach uses a model-based inverse image-analysis methodology to reconstruct elasticity images using anatomical MR image volumes from end-inspiration and end-expiration breath hold image acquisitions. This approach eliminates the need for proprietary motion-sensitive pulse sequences and specialized external deformation application devices. The fundamental advantages to this approach are simplicity, workflow-ease, and adaptability to standard of care imaging methods.

2. METHODS

2.1 MR Imaging

MR imaging was performed on healthy volunteers on a research-dedicated 3T Phillips scanner (Phillips Healthcare, Best, The Netherlands) and on patients with cirrhosis undergoing routine clinical standard-of-care MR imaging on a clinical Phillips 1.5T MR scanner (Phillips Healthcare, Best, The Netherlands). A clinically available modified DIXON (mDixon) sequence was used to acquire fat, water, in-phase, and out-of-phase image volumes with a $1.339 \times 1.339 \times 3.0$ mm voxel resolution over a sagittal field of view. Two breath-hold image volumes were acquired (< 15 second acquisition time) for each subject, representing end-inspiration and end-expiration diaphragmatic deformation states. All volunteer and patient data was collected and analyzed as a part of Institutional Review Board approved studies.

2.2 MIE Method

Elastography images were generated though the use of a modality independent elastography reconstruction [5-13], whereby diaphragmatic respiratory motion was used to induce deformation in the liver. A schematic of the MIE method is shown in Figure 1. Briefly, the method is a quasi-static image-based automated elastography approach which utilizes biomechanical model-based image processing techniques to generate estimates of mechanical elasticity based on two anatomical image volumes acquired under differing states of mechanical loading. Computer models of the abdominal cavity for each subject were built from end-inspiration image volumes by segmenting liver, visceral adipose tissue, and other surrounding abdominal organs within the abdominal cavity from the image volume, removing the

subcutaneous adipose tissue, abdominal wall, and peritoneal surfaces. Following image segmentation, a tetrahedral FE mesh was created. Regions within the mesh were assigned to one of three material types: liver, visceral adipose tissue, and 'other abdominal tissue' (which includes the kidney). The liver tissue was semi-automatically segmented and visceral adipose tissue and 'other' tissues material type assignment was aided by mDixon fat/water imaging, shown in Figure 2, which separates the MR signal generated from fat and water, based on principles of chemical shift. Following tissue assignment within the model, regions for material property reconstruction were created by geometrical k-means clustering in 300 spatially discreet sub-domains. Following region assignment, deformation boundary conditions necessary to drive the biomechanical model displacement are generated through the use of a diffeomorphic demons non-rigid image registration between the end-expiration image volume and the end-inspiration image volume, as previously described [10]. Following boundary condition assignment, mechanical properties are iteratively reconstructed through the use of a gradient-based reconstruction algorithm with a penalty term based on identified tissue type [12]. For more detail on the general MIE method, the reader is directed to [12].
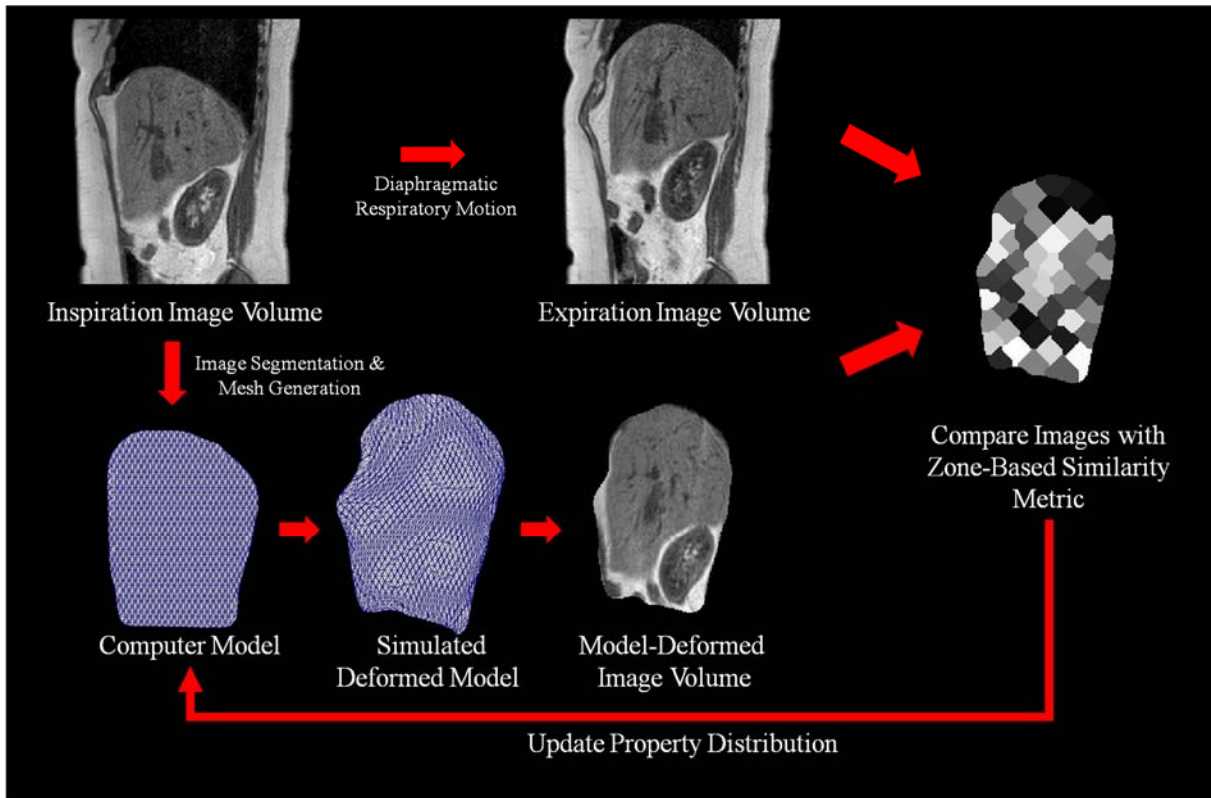

Figure 1. Schematic of the diaphragmatic respiratory motion based MIE approach. Computer models of the abdominal cavity are created from end-inspiration image volumes. A biomechanical model is then used to simulate the tissue displacement that occurs during diaphragmatic respiratory motion to the end-expiration state. The model-deformed end-expiration image volume is compared to the acquired end-expiration image volume, and estimates of the mechanical property distribution are iteratively updated using a zone-based image similarity metric.
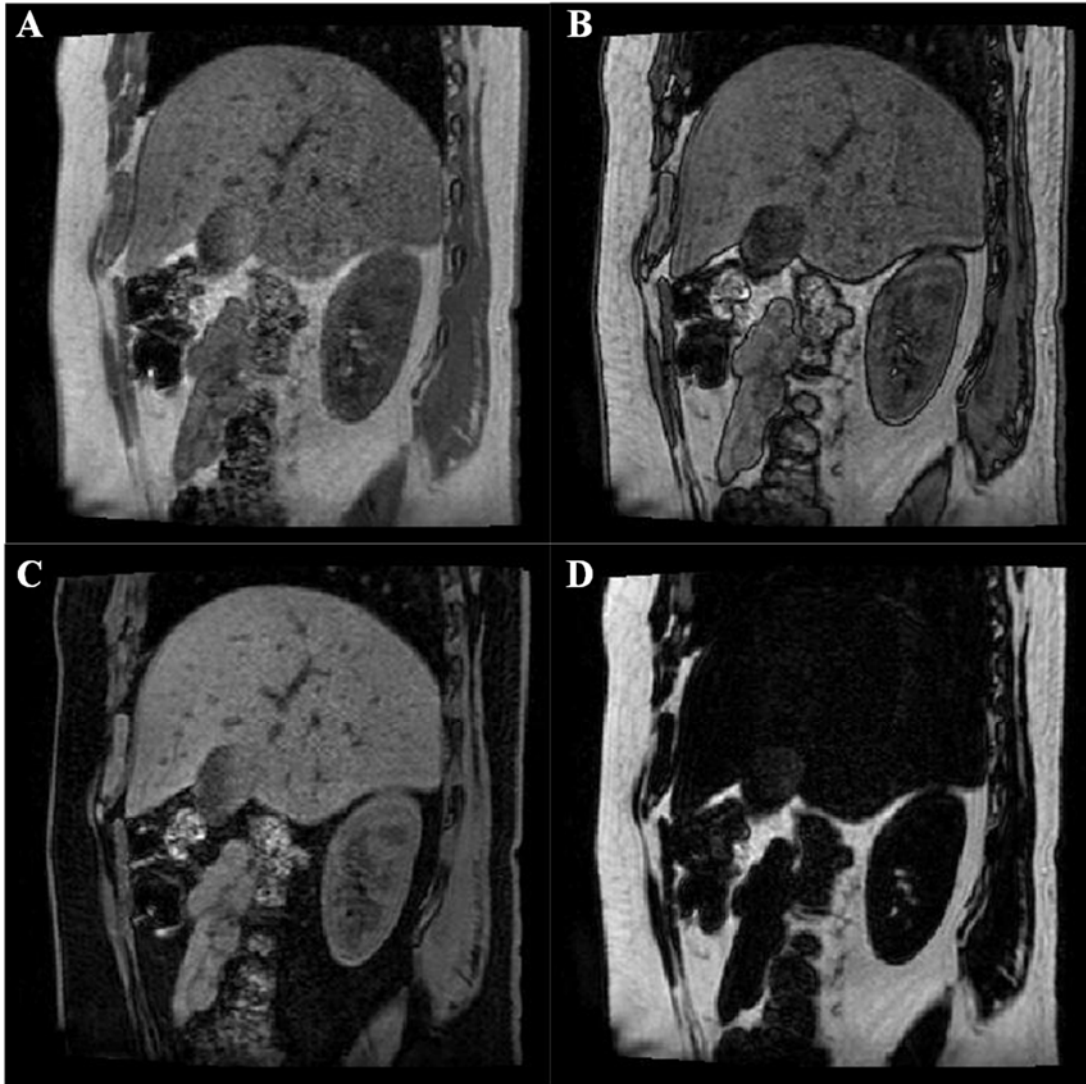
Figure 2. MR imaging using mDIXON sequence to acquire (A) in phase, (B) out of phase, (C) water-only, and (D) fat-only images aids image segmentation and tissue classification within the model.

3. RESULTS

As shown in Figure 3, breath-hold image volumes from both end-inspiration and end-expiration are used in conjunction with the MIE methodology to generate a volumetric map of the spatial distribution of relative stiffness within the liver, kidney, and surrounding visceral adipose tissue. Natural diaphragmatic respiratory motion is used to induce deformation, providing sufficient information for liver elasticity reconstruction. Here, the kidney is shown to be stiffer than liver, a qualitative confirmation from literature experience. Also notice, a generally elevated stiffness value for kidney cortex versus calyces regions, cortex is generally more turgid *in vivo*. The cirrhotic patient exhibited significant focal heterogeneity of liver stiffness with areas approximately 2-fold greater than background liver stiffness values. Assessment at the liver ROI level yielded mean stiffness of the cirrhotic liver, normalized to fat, as 1.64 times greater than mean liver stiffness of a normal volunteer.
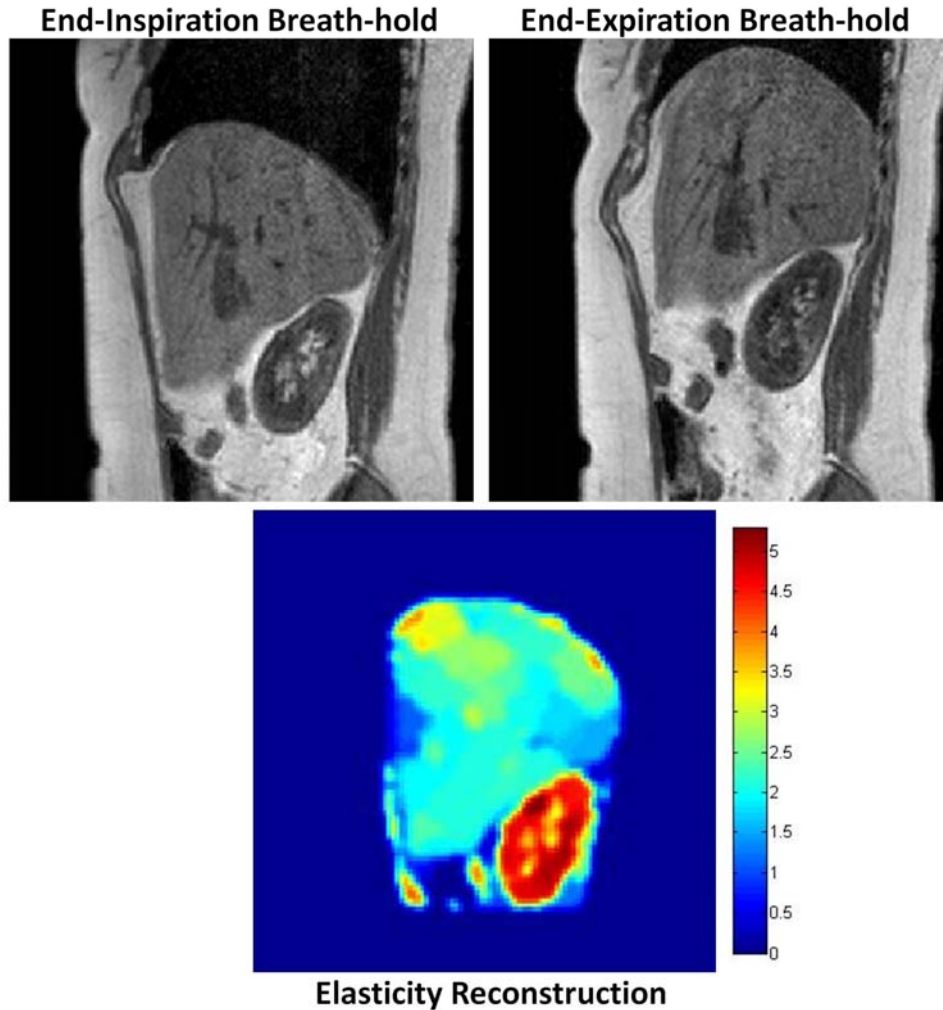
Figure 3. Preliminary assessment of liver elasticity in a cirrhotic patient using diaphragmatic motion-based elastography. End-inspiration and end-expiration breath-hold image volumes are used in conjunction with a biomechanical model-based reconstruction algorithm to generate an estimate of the spatial distribution of relative elasticity within the liver and surrounding tissue structures.

4. CONCLUSIONS

In this work, we present preliminary results towards the development of an elasticity imaging framework that harnesses natural diaphragmatic respiratory motion to generate estimates of stiffness for the liver and surrounding tissue structures, for the purpose of monitoring fibrosis, using clinically available (and standard of care) volumetric MR imaging and computer biomechanical models. Using a quasi-static model-based elasticity imaging methodology, we demonstrate the feasibility of diaphragmatic respiratory motion to induce deformation between end-inspiration and end-expiration breath hold image acquisitions that is sufficient for volumetric elasticity reconstruction. While preliminary, results indicate that our approach is capable of non-invasive image-based assessment of liver stiffness using natural diaphragmatic respiratory motion, and may provide valuable non-invasive image-based assessment of liver stiffness. As an offline image processing methodology, this approach is eminently amenable to routine clinical imaging workflow and eliminates the need for specialized motion sensitive pulse sequences and/or external excitation hardware to induce tissue displacement. Given the method's workflow simplicity, further studies with additional patients is warranted in order to assess the diagnostic impact and performance. Our results provides considerable enthusiasm for extension of our

approach towards monitoring liver stiffness in cirrhotic patients with limited impact to standard-of-care clinical imaging acquisition workflow.

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