Advanced Assessment of Liver Diseases with Magnetic Resonance Elastography in Animal Models

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Introduction: To reduce biopsy-related complications and sampling errors, hepatic MR Elastography (MRE) has been shown to be a safer, more comfortable, and less expensive noninvasive alternative to liver biopsy for diagnosing hepatic fibrosis (1-3). Recently, many studies have shown that the mechanical parameters have potential value for differentiating between several different pathologic processes (4-7). For instance, liver stiffness can have a static component that is mainly determined by extracellular matrix composites and structure (e.g., hepatic fibrosis), and a dynamic component that is affected by intrahepatic transudative and hemodynamic changes (e.g., inflammation and portal hypertension) (8,9). It is likely that independent mechanical properties other than "shear stiffness", such as the frequency dispersion of mechanical properties, will improve the identification of specific pathophysiologic changes of the liver. A comprehensive assessment of hepatic tissue mechanical parameters that are sensitive to specific microstructure changes and pathophysiological states would further increase the value of MRE as a primary tool for assessing liver disease.

Methods and Materials: All experiments were implemented on a 1.5-T (pig study) or a 3.0-T (mouse study) whole-body GE imager (HDx, GE Healthcare, Milwaukee, WI), using custom multi-channel coils. Fig.1(A) demonstrates the experimental setup for mouse studies. A silver needle is used to generate shear waves within the liver. Fig.1(B) demonstrates the experimental setup for pig studies. Two passive drivers are used to generate shear waves throughout the abdomen. As shown in Fig.1(C), MRE wave images were acquired with a multislice, spin-echo EPI MRE sequence with three motion-encoding directions using multiple harmonic vibrations (60-100 Hz for pigs, 80-200Hz for mice). With reference measurements obtained using dynamic mechanical analysis (DMA; RheoSpectris C500+, QC, Canada), a reliability study was performed to validate the agreement between 3D MRE measurements of tofu and liver tissue samples of various size like those in these large and small animal models. The dispersion of mechanical properties was reported as the slope of the least-squares linear regression of each property over the multiple frequencies of motion. Using the validated methodology, all mechanical quantities were reported as means and standard deviations of ROIs drawn to encompass as much of the liver as possible that had significant wave propagation. Statistical analysis was performed with a two-sided paired t-test and 5% significance. CCl_4 induced liver injury was used for the mouse studies: *1) short-term response of one dosage of CCl4 injection*: MRE exams were performed 24, 48, and 72 hours after one dosage of IP injection of 1ul/g CCl_4 in 9 mice; *2) long-term response of CCl4 injection:* MRE exams were performed 2, 4 and 6 weeks after IP injection of 1ul/g CCl_4 twice a week in 9 mice; *3) control groups:* 6 control mice with IP injections of pure olive oil at the same time as models 1&2. An FAH-deficient pig model with chronic liver disease under treatment was used for the pig study. MRE exams were performed every month to assess the severity of liver disease. Both animal studies are still ongoing. Serum and histologic analyses of the liver will be obtained by the time this work is presented.

Fig.1

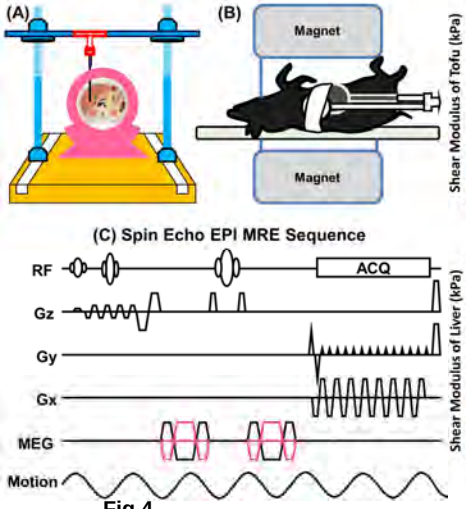


Fig.2

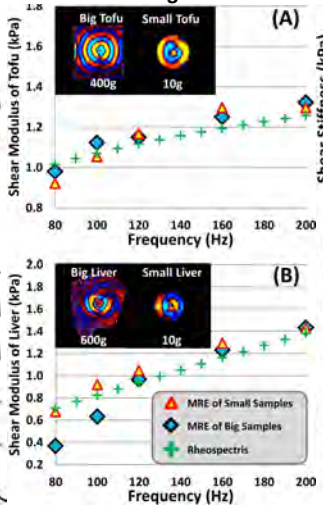


Fig.3

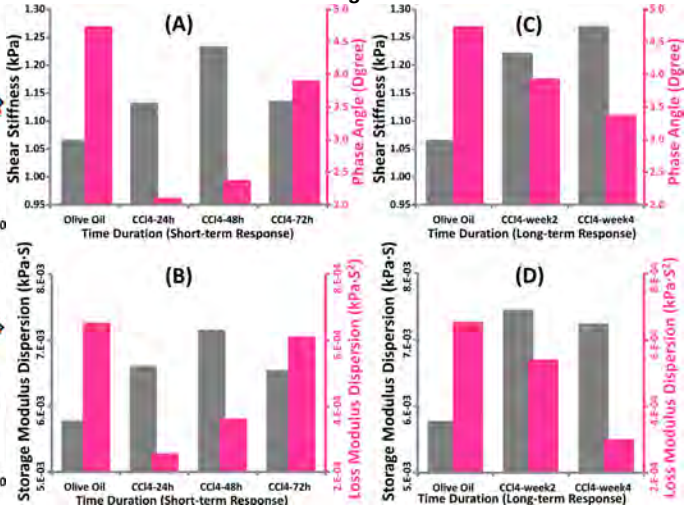
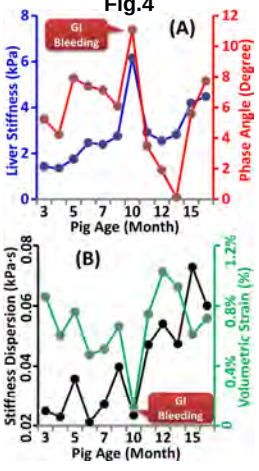


Fig.4



Results: 3D MRE measurements at multiple frequencies (less than 200 Hz) is highly reliable and reproducible in both large and small samples (Fig.2AB). For CCl_4 mouse model, compared with the control groups, liver stiffness (200 Hz) and storage modulus frequency dispersion (80-200Hz) were significantly elevated at 24-, 48-, and 72-hour after a single dose injection, with the highest peak observed at 48 hours (Fig.3AB, gray bars). In contrast, phase angle and loss modulus frequency dispersion were significantly decreased after 24 and 48 hours, with the lowest value observed at 24 hours, which then returned to near normal after 72 hours (Fig.3AB, pink bars). In the long-term response, liver stiffness consistently increased with time (Fig.3C, gray bars), shear modulus dispersion increased at 2 weeks then slightly decreased at 4 weeks (Fig.3D, gray bars), while phase angle and loss modulus dispersion decreased systematically with time (Fig.3CD, pink bars). Fig.4AB shows four mechanical quantities measured in an FAH-deficient pig under treatment. This pig had severe gastrointestinal bleeding (indication of portal hypertension) at 10 months. Both liver stiffness and phase angle reached their peak value, while volumetric strain reached its lowest value at this time point. Liver stiffness and its dispersion increased systematically with age. No significant correlations were found between these quantities and AST values.

Discussion and Conclusion: Results indicate that 3D MRE measurements in both large and small animal models are reliable, equivalent and thus interchangeable. It has been well established that a single dose of CCl_4 leads to centrizonal necrosis and steatosis, while prolonged administration leads to liver fibrosis and cirrhosis. The short-term response of a single dose is mainly associated with the severity of necroinflammation, while the long-term response of a prolonged dose is associated with the severity of fibrosis. The phase angle of the complex shear modulus may be useful to discriminate between inflammation and fibrosis alone in early-stage disease. It may also detect portal hypertension associated with GI bleeding in advanced liver disease. However, the change is bidirectional with different pathophysiology. The storage and loss modulus frequency dispersions may also be useful for differentiating inflammation and fibrosis because they had unique performance comparing with liver stiffness and phase angle in our animal models. Considering the rich experience from human studies in detecting hepatic fibrosis with MRE, it is likely that the use of more sophisticated mechanical models of the liver will provide important insight into the identification of hepatic inflammation and fibrosis. Much of this information can be evaluated using *in vivo* animal models only, which allow measurements that are usually unavailable with human studies.

References: 1. Yin CGH 2007; 2. Asbach MRM 2008; 3. Huwart Gastroenterology 2008; 4. Yin TMRI 2009; 5. Barry UMB 2012; 6. Tapper CGH 2012; 7. Ding JHUST 2012; Yin ISMRM 2009, 110; 9. Yin ISMRM 2010, 256.