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● *Original Contribution*

QUANTIFICATION OF LIVER VISCOELASTICITY WITH ACOUSTIC RADIATION FORCE: A STUDY OF HEPATIC FIBROSIS IN A RAT MODEL

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Abstract—Ultrasound elastography, based on shear wave propagation, enables the quantitative and non-invasive assessment of liver mechanical properties such as stiffness and has been found to be feasible for and useful in the diagnosis of hepatic fibrosis. Most ultrasound elastographic methods use a purely elastic model to describe liver mechanical properties. However, to describe tissue that is dispersive and to obtain an accurate measure of tissue elasticity, the viscoelasticity of the tissue should be examined. The objective of this study was to investigate the shear viscoelastic characteristics, as measured by ultrasound elastography, of liver fibrosis in a rat model and to evaluate the diagnostic accuracy of viscoelasticity for staging liver fibrosis. Liver fibrosis was induced in 37 rats using carbon tetrachloride (CCl_4); 6 rats served as controls. Liver viscoelasticity was measured *in vitro* using shear waves induced by acoustic radiation force. The measured mean values of liver elasticity and viscosity ranged from 0.84 to 3.45 kPa and from 1.12 to 2.06 Pa·s for fibrosis stages F0–F4, respectively. Spearman correlation coefficients indicated that stage of fibrosis was well correlated with elasticity (0.88) and moderately correlated with viscosity (0.66). The areas under receiver operating characteristic curves were 0.97 (≥F2), 0.91 (≥F3) and 1.00 (F4) for elasticity and 0.91 (≥F2), 0.79 (≥F3) and 0.74 (F4) for viscosity, respectively. The results confirmed that shear wave velocity was dispersive in frequency, suggesting a viscoelastic model to describe liver fibrosis. The study finds that although viscosity is not as good as elasticity for staging fibrosis, it is important to consider viscosity to make an accurate estimation of elasticity; it may also provide other mechanical insights into liver tissues. (E-mail: tfwang@szu.edu.cn or chensiping@szu.edu.cn)

Key Words: **Viscoelasticity, Liver fibrosis, Acoustic radiation force, Shear wave.**

INTRODUCTION

Liver fibrosis is the excessive accumulation of extracellular matrix proteins, including collagen, which disturb the normal architecture of the liver. Liver fibrosis may ultimately lead to cirrhosis, liver failure and portal hypertension and often requires liver transplantation (Bataller and Brenner 2005). Liver biopsy is currently considered the gold standard for diagnosis and staging of liver fibrosis. However, liver biopsy is an invasive procedure with several disadvantages. One disadvantage is that it is a disconcerting process with certain unavoidable risks and complications, such as pain, bleeding and bile peritonitis, which may lead to mortality (McGill et al. 1990; Piccinino et al. 1986). More significantly, the accuracy of fibrosis staging is compromised because only a small volume of liver tissue is sampled and liver fibrosis is heterogeneously distributed (Ratziu et al. 2005; Regev et al. 2002). Therefore, reliable, simple and non-invasive methods for assessing liver fibrosis are needed.

Recently, the potential for diagnosing hepatic fibrosis by measurement of the mechanical properties of liver has been investigated (Martinez et al. 2011). Several imaging-based techniques, often called elastography, have been developed for non-invasively quantifying liver elasticity (Sarvazyan et al. 2011). These elastographic methods are based primarily on either magnetic resonance imaging (MRI) or ultrasound imaging. Magnetic

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resonance elastography (MRE) is a dynamic technique that allows assessment of the shear moduli of tissues by application of an external vibration to induce a shear wave in the tissue and detection of the shear wave propagation using motion-sensitive MR sequences (Muthupillai et al. 1995). MRE has been used to measure liver fibrosis in both animal models and clinical applications (Faria et al. 2009; Huwart et al. 2007; Rouviere et al. 2006; Salameh et al. 2007; Yin et al. 2007). These studies found that liver stiffness increases significantly with the degree of fibrosis and that MRE is able to distinguish between different stages of fibrosis. Although MRE has exhibited potential as a non-invasive method for grading hepatic fibrosis, it is relatively expensive and complex, making it less likely to be widely used in clinical practice, compared with less expensive, ultrasound-based techniques.

In contrast, ultrasound elastography involves mechanical excitation of the tissue and detection of the tissue displacement using either Doppler or simple displacement measurements based on ultrasound pulse-echo methods (Greenleaf et al. 2003). The mechanical excitation for ultrasound elastography has been provided by external quasi-static compression, external dynamic vibration or acoustic radiation force (Sarvazyan et al. 2011). Research over the past two decades has led to significant developments in ultrasound elastographic methods, including quasi-static elastography (Ophir et al. 1991), transient elastography (TE) (Sandrin et al. 2003), sonoelastography (Hoyt et al. 2007), acoustic radiation force impulse (ARFI) imaging (Nightingale et al. 2002), shear wave elasticity imaging (SWEI) (Sarvazyan et al. 1998), supersonic shear imaging (SSI) (Bercoff et al. 2004) and shear wave dispersion ultrasound vibrometry (SDUV) (Chen et al. 2009).

The TE technique has been developed into a commercial ultrasound device called Fibroscan (EchoSens, Paris, France), which has been widely used in liver diagnosis in clinical situations (Castera et al. 2005; Marcellin et al. 2009; Pinzani et al. 2008). This device uses an external actuator to transmit a low-frequency shear wave into the liver. A single-element transducer is applied to track the shear wave and measure its velocity, which is directly related to liver stiffness. Clinical trials of Fibroscan have indicated that its stiffness measurements are significantly correlated with the stage of fibrosis, and the areas under the receiver operating characteristic curves (AUROCs) were close to those achieved by biopsy (Marcellin et al. 2009; Martinez et al. 2011).

Ultrasound elastographic methods that use acoustic radiation force can also be useful for interrogating the mechanical properties of liver. In contrast to the TE technique, which uses external mechanical vibrators, acoustic radiation force uses a focused ultrasound beam to mechanically excite a focal region directly in deep tissue to induce a shear wave. In this way, the energy can be transmitted through fat layers or ascites, overcoming the limitations of the Fibroscan system (Foucher et al. 2006). Two ultrasound elastographic methods based on acoustic radiation force, ARFI and SSI, have been integrated into ultrasound systems (Acuson S2000, Siemens Medical Solutions, Erlangen, Germany, and Aixplorer, Supersonic Imagine, Aix-en-Provence, France, respectively). The clinical trials of these two methods reported diagnostic accuracies similar to those of the TE trials (Bavu et al. 2011; Friedrich-Rust et al. 2009).

Most of the ultrasound methods use a linear elastic model to describe tissue mechanical properties, and only tissue elasticity is quantified. Therefore, liver viscosity is neglected in these methods, and this omission may cause bias in the estimation of tissue elasticity. Some MRE studies have explored the relationships between the viscoelastic properties of liver tissue and fibrosis (Huwart et al. 2007; Salameh et al. 2007). These studies found a correlation between shear viscosity and the amount of fibrosis in the liver, suggesting that viscosity may provide useful information about liver fibrosis. One way to characterize the viscoelastic properties of liver is to measure the dispersion property of a shear wave using multiple frequencies. This multi-frequency approach has previously been implemented in MRE studies (Asbach et al. 2008, 2010; Klatt et al. 2007) in which multiple wave images corresponding to different driving frequencies were collected by different scans to deduce the dispersion of the complex shear modulus in the frequency range 25−62.5 Hz. Recently, some studies using ultrasound elastography also applied the multi-frequency approach to measure the mechanical properties of liver. Barry et al. (2012) used sonoelastography to measure the crawling wave over 100−400 Hz in a mouse liver model and found that the dispersion patterns were strongly correlated with the degree of steatosis. Deffieux et al. (2009) used the SSI technique to acquire the dispersion curve (75−450 Hz) for the livers of three healthy volunteers. Their findings indicated that liver tissue is highly dispersive over this frequency range. Furthermore, in a preliminary study, they explored the feasibility of staging liver fibrosis using the dispersion pattern (Muller et al. 2009). Chen et al. (2009) conducted an *in vivo* experiment in swine liver using the SDUV technique, which resulted in viscoelastic values similar to those measured by MRE. However, insofar as we know, few studies have investigated changes in viscoelastic properties, as measured by ultrasound elastography, during various stages of fibrosis. Recently, Chen et al. (2013) reported a study of human patients with liver fibrosis using shear waves induced by ultrasound