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● *Original Contribution*

ULTRASOUND SHEAR WAVE ELASTOGRAPHY: VARIATIONS OF LIVER FIBROSIS ASSESSMENT AS A FUNCTION OF DEPTH, FORCE AND DISTANCE FROM CENTRAL AXIS OF THE TRANSDUCER WITH A COMPARISON OF DIFFERENT SYSTEMS

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Abstract——We evaluated variation in fibrosis staging caused by depth, pre-load force and measurement off-axis distance on different ultrasound shear wave elastography (SWE) systems prospectively in 20 patients with diffuse liver disease. Shear wave speed (SWS) was measured with transient elastography, acoustic radiation force impulse (ARFI) and 2-D shear wave elastography (SWE). ARFI and 2-D-SWE measurements were obtained at different depths (3, 5 and 7 cm), with different pre-load forces (4, 7 and 10 N and variable) and at 0, 2 and 4 cm off the central axis of the transducer. A single, blinded pathologist staged fibrosis using the METAVIR system (F0–F4). Area under the receiver operating characteristic curve was charted to differentiate significant fibrosis ($F \geq 2$). Depth was the only factor found to influence ARFI-derived values; no acquisition factors were found to affect 2-D-SWE SWS values. ARFI and 2-D-SWE for diagnosis of significant fibrosis at a depth of 7 cm along the central axis had good diagnostic performance (areas under the receiver operating characteristic curve: 0.92 and 0.82, respectively), comparable to that of transient elastography. Further investigation of this finding will likely be of interest. (E-mail: xiangfx@hotmail.com)

Key Words: **Ultrasound elastography, Shear wave, Variation, Liver fibrosis, Depth, Pre-load force, Off-axis.**

INTRODUCTION

Chronic liver disease (CLD) has an estimated overall prevalence of 14.78% in the United States (Younossi et al. 2011) and comprises a number of different illnesses, all characterized by chronic hepatocyte damage. Irrespective of etiology, CLD follows a common pathophysiologic pathway along which repeated episodes of liver injury are followed by healing, regeneration and fibrosis. In a significant minority of patients, this ultimately culminates in an irreversible state of fibrosis-induced hepatic dysfunction termed *cirrhosis* (Pellicoro et al. 2014). Cirrhosis causes an estimated 49,500 deaths in the United States annually and more than one million deaths worldwide, accounting for 1.95% of all global deaths (Mokdad et al. 2014; Murray et al. 2013). Hepatic fibrosis, the progenitor state of cirrhosis, was originally thought to be irreversible, but is now recognized as a dynamic process with potential for resolution (Friedman and Bansal 2006). It is therefore clinically important to identify and accurately measure liver fibrosis in CLD patients, both to identify those at risk of cirrhosis and to evaluate for fibrosis progression or resolution.

Histopathologic examination of liver biopsy tissue remains the reference standard for staging hepatic fibrosis. However, liver biopsy has a number of limitations, including invasiveness (Actis et al. 2007; Ravindran

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et al. 2016) high cost, inter-pathologist variation (Burt et al. 2015; Kaswala et al. 2016) and sampling error (Brunt 2016; Parikh et al. 2017; Shiha et al. 2017). As a result, alternative non-invasive staging methods have been proposed including blood tests (Chin et al. 2016; Rosenberg et al. 2004), magnetic resonance elastography (MRE) (Dulai et al. 2016; Petitclerc et al. 2017) and ultrasound elastography (UE) (Crespo et al. 2012; Dhyani et al. 2015; Sigrist et al. 2017). UE approaches that employ acoustic or mechanical force to generate tissue shear waves have been reported to correlate with liver fibrosis stage (Dhyani et al. 2017; Ferraioli et al. 2012; Li et al. 2016; Samir et al. 2015).

In clinical practice, UE measurements exhibit variability that limits their capability to precisely quantify liver fibrosis. We cite two of the reasons for this:

1 *Technology heterogeneity*: Proprietary technologies differ among manufacturers, resulting in measurement output heterogeneity (Barr et al. 2015) and manufacturer-dependent liver stiffness measurement correlations with different liver fibrosis stages (Ferraioli et al. 2015).
2 *Technique heterogeneity:* Elastography measurements obtained using different techniques on the same system and patient may vary. Many technique factors may affect UE measurements, including region of interest (ROI) depth (D'Onofrio et al. 2010; Kaminuma et al. 2011), pre-load force (Mantsopoulos et al. 2015) and phase of inspiration (Yun et al. 2011). Data regarding the magnitude and meaning of these effects for liver fibrosis staging in clinical practice are limited.

The objective of this study was to evaluate the influence of variation in acquisition technique factors on fibrosis staging. We evaluated depth of measurement, operator pre-load force and the distance of the ROI from the central axis of the transducer on different ultrasound shear wave elastography (SWE) systems.

METHODS

Patients

This prospective single-institution study was performed at the Department of Radiology of Massachusetts General Hospital and approved by the institutional review board. Twenty participants meeting the following criteria were enrolled between June 1, 2015 and September 30, 2015: (i) age ≥18, (ii) suspected diffuse liver disease, (iii) non-focal liver biopsy in the past 6 y or scheduled to have liver biopsy in the next 3 y as part of routine clinical care. Exclusion criteria were (i) pregnancy and (ii) acute illness/cognitive impairment resulting in the inability to cooperate with ultrasound. Participants were asked to fast for a minimum of 4 h before the SWE examinations. Informed consent was obtained from all participants.

Elastography

Each participant underwent same-day elastography using three different elastography methods: transient elastography (TE, Echosens, Fibroscan), acoustic radiation force imaging (ARFI, Siemens, S3000) and 2-D-SWE (SuperSonic Imagine, Aixplorer). All elastography was performed by a single sonologist (L.C.) with more than 10 y of experience who was not aware of the biopsy results.

Scanning protocol

Participants were scanned with three systems. All measurements were performed in the right lobe of the liver through an intercostal approach while the patients were lying in a supine decubitus position with the right arm in maximal abduction. Scanning was performed at almost the same location in the liver for the three systems. Shear wave speed (SWS) was used for statistical analyses in our study. The relationship between Young's modulus and SWS is $E = 3\rho c_s^2$ (E is Young's modulus, c_s is the speed of the shear wave and ρ is the density of tissue). This equation assumes an elastic, linear, isotropic and homogeneous material that is nearly incompressible.

With the FibroScan device (EchoSens, Paris, France), TE shear wave propagation was measured in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 and 65 mm below the skin surface. All acquisitions were made as per standard protocol recommended by the vendor and by a single investigator (L.C.) who had been trained and certified as competent by the vendor's U.S. representative (Sandhill Scientific) and who had completed TE on 10 practice participants prior to study initiation.

Acoustic radiation force impulse imaging was performed with a Siemens Acuson S3000 ultrasound system (Siemens AG, Erlangen, Germany) using a 4 C1 transducer. Ultrasound examinations, along with elastography measurements, were performed at varying depths (3, 5 and 7 cm from the skin), pre-load forces (variable [unmonitored, "conventional" technique] and fixed at 4, 7 and 10 N) and distances from the ROI to the central axis of the transducer (0, 2 and 4 cm). Two parameters were fixed while one was varied. When depth was varied, distance from the ROI to the central axis was fixed at 0 cm and pre-load forces were unmonitored. When pre-load forces varied, the depth was fixed at 5 cm and distance from the central axis was fixed at 0 cm. When distance from the central