RSNA/QIBA: Variability Sources and Potential Mitigation Strategies in Shear Wave Elastography for the Staging of Liver Fibrosis

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OVERVIEW

The Quantitative Imaging and Biomarkers Alliance (QIBA), comprising researchers, clinicians, imaging system manufacturers and representatives from the federal government (FDA, NIH, NIST) was established in 2008. QIBA's mission is to "Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time." The QIBA Ultrasound Technical Committee has focused on mitigating variability in shear wave elastography for liver fibrosis staging.

Shear wave elastography has shown promise for the evaluation of intermediate stages of liver fibrosis (Samir 2012, Ferraioli 2012, Palmeri 2011). There are, however, multiple potential sources of variability; disease factors, operator dependency, and imaging system variation. Measurement variability is evident in differing shear wave speed values observed in different studies for similar stages of liver fibrosis.

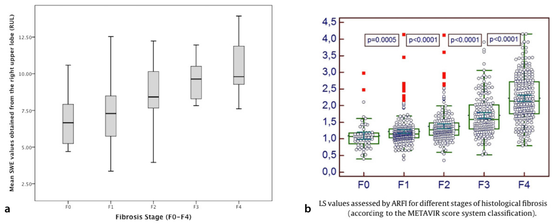


Figure 1: Box and whisker plot demonstrates the range of SWE values for each fibrosis stage.
(a) Taken from Samir et al (Samir 2014) (b) Taken From Sporea et al (Sporea 2012)

LS values assessed by ARFI for different stages of histological fibrosis (accorcing to the METAVIR score system classification).

This poster summarizes potential sources of SWS measurement variability in SWS, some results of related QIBA studies, and discusses potential variability mitigation strategies.

SOURCES OF VARIABILITY

A. TECHNICAL SOURCES OF VARIABILITY

Technical Variability Sources
Variability as a function of technology
Variability as a function of measurement depth
Variability as a function of probe type
Variability as a function of shear wave frequency

Imaging Technique and Patient Related
Fasting state
Body mass index (BMI)
Patient position
Patient breathing
Liver lobe

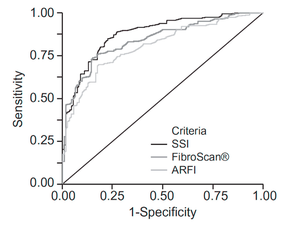
Clinical Confounders
Steatosis
Inflammation
Acute hepatitis
Right heart insufficiency
Cholestasis

Variability in Technology

Several studies comparing different technologies on the same patient cohort have demonstrated inter-system variation for SWS estimation in liver fibrosis. This variability is higher for higher fibrosis grades as described by Kircheis et al (Kircheis 2012). Ferraioli et al also described the different area under the ROC curve for differentiating higher grades of fibrosis using SWE and TE (Ferraioli 2012) and Cassinotto et al have demonstrated the variation amongst three systems (Cassinotto 2014).

Figure 2. Variable area under the ROC curve to differentiate higher grades of fibrosis from lower grades as assessed by TE, ARFI and SWE. (Image provided by Dr. Christophe Cassinotto – Cassinotto 2014)

F2 ROC curves for the diagnosis of significant fibrosis



Depth and Drequency Dependence

Chang et al have demonstrated that best measurements are obtained superficially with a high frequency probe, while measurements at greater depth are best performed with a low frequency (Chang 2013). Similarly, Potthoff et al (Potthoff 2013) showed that measurements are best made away from the liver capsule but within a depth of 5-6cm.

B. IMAGING TECHNIQUE AND PATIENT-RELATED

Fasting/Meals

Arena et al and Mederacke et al demonstrated that food intake increases estimated liver stiffness using Fibroscan (Mederacke 2009). Similarly, Goertz et al and Popescu et al demonstrated that food intake increases ARFI-derived shear wave velocity estimates (Goertz 2012, Popescu 2013). By contrast, Kaminuma et al (Kaminuma 2011) showed no effect of food intake on stiffness measurements using ARFI on 20 healthy volunteers. The weight of the evidence presently suggests recent food intake increases ARFI or FibroScan-derived estimates of liver stiffness.

BMI

High BMI has shown to be a limiting factor for acquisition of SWE values in several studies. Palmeri et al (Palmeri 2011) have demonstrated the rate of successful SWS acquisitions decreases with increasing BMI. Similarly, lower measurement interquartile range (IQR) has been reported in patients with lower BMI (Bota 2011). Subcutaneous fat thickness has similarly been shown to correlate negatively with measurement acquisition quality by Cournane et al in a phantom study using FibroScan (Cournane 2011).

C. CLINICAL CONFOUNDERS

Steatosis

Several authors have reported that steatosis grade does not influence liver fibrosis staging with shear wave elastography (Yoneda 2008, Friedrich-Rust 2009, Lupsor 2009, Fierbinteanu-Braticevici 2009, Bota 2011, Rifai 2011). In two studies SWS was shown to decrease with increasing steatosis (Yoneda 2010, Fierbinteanu-Braticevici 2013).
Similar to BMI, steatosis within the liver may not have a direct effect on stiffness measurement but could cause attenuation that can indirectly impact liver stiffness measurements and hence decrease correlation with fibrosis stage. Hence, larger studies with detailed analysis are required for accurate assessment of the impact of steatosis grade in the liver in comparison to the effect of subcutaneous adipose tissue.

Inflammation/Acute Hepatitis

There is overwhelming evidence that inflammation and/or acute hepatitis increase SWE estimation of liver stiffness (Bota 2013, Chen 2012, Ebinuma 2011, Fierbinteanu-Braticevici, 2013, Friedrich-Rust 2009, Guzmán-Aroca 2012, Lupsor 2009, Potthoff 2013, Rifai 2011, Sporea 2012, Takahashi 2010, Takaki 2014, Yoon 2012). However, to what extent this effect manifests, and how to correct for it – remains yet to be determined.

Right Heart Insufficiency

Goertz et al (Goertz 2012) demonstrated that right heart insufficiency can cause significant increase in estimated shear wave velocity.

Cholestasis

Millonig et al (Millonig 2008) and Harata et al (Harata 2011) reported that cholestasis resulted in increased liver stiffness as measured with FibroScan. Similarly Attia et al (Attia 2014) and Pfeifer et al (Pfeifer 2014) reported the same results with SWS measured by an ARFI method.

SUMMARY OF CLINICAL STUDY (PHASE 2 OF QIBA)

- For a period of 1 year (September 2013-September 2014) 252 subjects were enrolled in a clinical study at the Massachusetts General Hospital
- All patients underwent 10 SWE measurements prior to liver biopsy
- All liver biopsy specimens are reviewed by a single sub-specialist pathologist with greater than 20 years of experience in reviewing liver biopsy specimens
- Currently pathology is available for 125 of these cases
- A detailed data analysis will be completed in the coming few months

Goal

- On completion: analyze the effect of steatosis and inflammation

Secondary Analyses

- SWE acquisition quality as a function of disease, depth, and adiposity

TECHNICAL SOURCES OF VARIABILITY

- Shear wave frequency content (center frequency and bandwidth) can be variable (~50-500 Hz) and is dependent on ARFI focal configuration and excitation duration
- Soft tissue viscoelasticity makes the reconstructed shear wave speed dependent on the shear wave frequency content
- Assumptions in wave propagation direction to perform time-of-flight estimates can be violated:
  - Depth dependencies due to off-axis excitation sources (Zhao 2011)

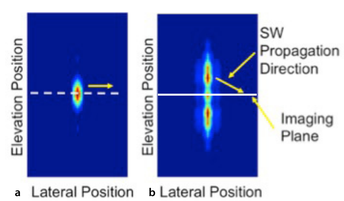


Figure 3 (a) and (b). Significant sources of acoustic radiation force that are spatially-offset from the imaging plane can generate shear waves that violate shear wave propagation assumptions used in time-of-flight algorithms, leading to shear wave speed biases. LEFT: Acoustic radiation force distribution at the focal depth. RIGHT: Acoustic radiation force distribution shallow to the focal depth (30 mm), with significant sources that are offset in the elevation dimension.

- Different shear wave propagation paths
- Reflection artifacts from tissue structures (e.g., capsules, vessels, ducts)

TISSUE MIMICKING PHANTOM STUDY

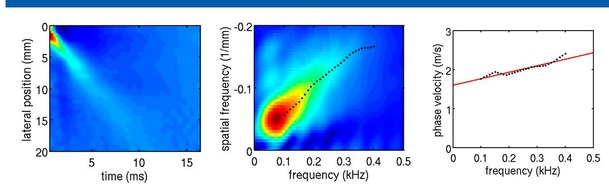


Figure 4 LEFT: Shear wave displacement field at the focal depth propagating across lateral positions through time. CENTER: The corresponding 2D power spectrum of the shear wave particle velocity profile. The line shows the maximum projection of energy. RIGHT: Calculated phase velocities at individual temporal frequency components. This linear dispersion can be quantified and reported (1) as the phase velocity at 200 Hz (c(200 Hz)) and the linear slope in phase velocity (dc/df).

- Take 2D FFT of SW particle velocity
- Estimate phase velocity using a linear model
- Use -12 dB upper bandwidth
- Determine c0, dc/df from max sum
- Report c(200Hz), dc/df

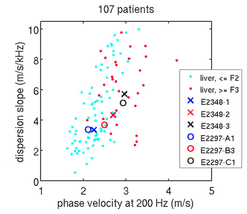


Figure 5. Comparison of tissue-mimicking phantoms developed by CIRS, Inc. compared to human data (Palmeri 2011) of difference fibrosis stages as a function of phase velocity and linear dispersion slope.

DIGITAL PHANTOMS

Finite element simulation code of elastic and viscoelastic materials has been posted on GitHub: https://github.com/RSNA-QIBA-US-SWS/fem

Digital phantom datasets corresponding to Phase I & II studies are hosted on the RSNA Quantitative Imaging Data Warehouse: http://qidw.rsna.org

MITIGATION STRATEGIES

Technical Factors

- QIBA effort to reduce inter-vendor variability
- Phantom Study
- Clinical study using different systems on the same patients to understand sources of bias

Imaging Techniques and Patient Related Factors

- UPICT Guidelines for clinical trials

Clinical Confounders

- Clinical trial to assess effects of steatosis and inflammation and potentially provide a correction mechanism
- Develop a Case Report Form, to simplify data aggregation and reporting of clinical confounders

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