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# • Original Contribution

## ATTENUATION OF SHEAR WAVES IN NORMAL AND STEATOTIC LIVERS

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Abstract—Shear wave propagation in the liver has been a robust subject of research, with shear wave speed receiving the most attention. The correlation between increased shear wave speed and increased fibrosis in the liver has been established as a useful diagnostic tool. In comparison, the precise mechanisms of shear wave attenuation, and its relation to diseased states of the liver, are less well-established. This study focused on the hypothesis that steatosis adds a viscous (lossy) component to the liver, which increases shear wave attenuation. Twenty patients' livers were scanned with ultrasound and with induced shear wave propagation, and the resulting displacement profiles were analyzed using recently developed estimators to derive both the speed and attenuation of the shear waves within 6-cm<sup>2</sup> regions of interest. The results were compared with pathology scores obtained from liver biopsies taken under ultrasound guidance. Across these cases, increases in shear wave attenuation were linked to increased steatosis score. This preliminary study supports the hypothesis and indicates the possible utility of the measurements for non-invasive and quantitative assessment of steatosis. (E-mail: kevin.parker@rochester.edu) © 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Shear wave attenuation, Liver, Steatosis, Fibrosis.

#### **INTRODUCTION**

Elastography of the liver has provided an important means of assessing fibrosis in the liver (Barr et al. 2015; Cosgrove et al. 2013). However, the question of steatosis (the accumulation of macrovesicular and microvesicular fat in the liver), particularly in early stages of the progression of liver disease, is largely unresolved. There are conflicting opinions as to the effect of steatosis on shear wave speed (SWS) in the liver. Although SWS has received the most attention in elastography (Barr et al. 2015; Guo et al. 2017; Wang and Jiang 2018), some attention has been given to the attenuation of shear waves in tissues (Clayton et al. 2012; Gennisson et al. 2006; Nenadic et al. 2014) as a specific parameter related to tissue viscoelastic loss.

Recently, a theoretical examination of the rheology of steatosis was proposed (Parker et al. 2018a), and one of the predictions is that the attenuation of shear waves should increase with increasing fat content. The theory is based on classic treatments of composite media composed of spherical inclusions; in this case, the spherical inclusions are the fat vacuoles with their predominantly viscous contribution. Furthermore, other recent theoretical work has provided analytical models for shear waves produced by radiation force push pulses from scanning transducers (Parker et al. 2018c) and estimators for SWS and shear wave attenuation (SWA). We applied these estimators to a clinical population of 20 individuals who were scheduled for liver biopsy.

#### **METHODS**

The Samsung RS85 ultrasound scanner (Samsung Medison, Seoul, South Korea) was used for B-scan imaging of the liver, biopsy guidance and elastographic shear wave measurements. The CA1-7A (Samsung Medison) abdominal probe was used. Custom beam sequences were implemented on the scanner to perform the imaging. All beam sequences used *in vivo* underwent water-tank measurements to ensure compliance with

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U.S. Food and Drug Administration output limitations, in particular a  $I_{\text{spta.3}}$  <720 mW and mechanical index <1.9, using a calibrated hydrophone (Model HMA-0200, Onda Corp., Sunnyvale, CA, USA). Transmit frequencies in the abdominal setting are broadband around 3 MHz and push pulse near 2 MHz, with an f-number >2 for a 5-cm depth.

#### Patient enrollment

The Samsung RS85 system was used on patients under the requirements of informed consent and approval from the University of Rochester Research Subjects Review Board. Adult males and females aged 21 y or older with abnormal liver function tests who were referred for liver biopsy and assessment of nonalcoholic fatty liver disease, steatohepatitis and chronic hepatitis were considered for enrollment. Children were excluded as liver disease is very rare in this age group. There were no enrollment exclusions based on economic status, race, or ethnicity. The average age was 55.1 y, and the average body mass index was 30.5.

#### Ultrasound

Each patient was placed in a supine position with the right arm overhead if possible. The transducer was placed perpendicular to the skin with adequate compression over the mid-axillary line. The sonographer avoided the diaphragm, vessels and liver capsule. The middle of the elastography region of interest (ROI) was placed between 3 and 6 cm deep and at least 1-2 cm below the capsule. The ROI box was positioned away from the edge of the image. The patient was asked to suspend breathing at mid-inspiration (not deep inspiration). Ten repeat scans and elastography ROIs were obtained near or in the sample plane as the biopsy.

#### Signal processing

Raw ultrasound (radiofrequency echoes) data were digitized at 20 MHz and stored for analysis of artifacts (tissue motion problems, noise problems) and the use of signal processing filters to lower the noise and artifacts. Data were stripped of patient information and stored on a 10G external hard drive. Displacement waveforms were tracked over time to estimate SWS. The decay of the waveforms' frequency content was analyzed to estimate SWA as a linear (first-power) function of frequency, with the value at 150 Hz selected for reporting. Further details on the estimators of attenuation are found in Parker et al. (2018c).

### Histology/pathology and statistics

The liver biopsy samples were sent to the University of Rochester's Department of Pathology for analysis ordered by the referring physician. Each specimen was scored as follows (Angulo et al. 2015; Kleiner et al. 2005):

- steatosis less than 5% of hepatocytes affected = S0
- steatosis between 5% and 33% = S1
- steatosis between 34% and 66% = S2
- severe steatosis greater than 67% = S3

In addition, a conventional fibrosis score was assessed on a scale of F0–F4 (severe/cirrhosis). Because the fibrosis and steatosis scores are semiquantitative, Spearman's rank correlation coefficient was used as a non-parametric measure of rank correlation, implemented on MATLAB (The MathWorks, Inc., Natick, MA, USA).

#### RESULTS

The combined B-scan and elastography ROI images were obtained at the beginning of the ultrasound-guided biopsy procedure, and examples of these are provided in Figure 1. After each induced shear wave, shear wave velocity waveforms were obtained, as illustrated in Figure 2.

From these, the estimates of SWS and SWA were obtained. Across the population studied, SWS varied from 1.2 to 2.5 m/s, as illustrated in Figure 3. In each case, the hidden variable is encoded by symbols, as illustrated in the insets. Furthermore, SWA estimated at a shear wave frequency of 150 Hz varied from 5 to 20 dB/cm, with the lower values associated with non-steatotic livers, as illustrated in Figure 4.

The Spearman rank correlation values are summarized in Table 1 and suggest that SWS increases with fibrosis score, whereas SWA increases with steatosis score.

#### DISCUSSION

The relationship between simple steatosis and SWA described herein supports an earlier hypothesis that the viscous triglycerides and fat contained in macro- and microvesicles would increase the loss mechanisms and. therefore, the attenuation of shear waves in the liver (Barry et al. 2015; Parker et al. 2018a). Quantitatively, the theory and phantom studies reported previously reveal a subtle increase in attenuation for low concentrations (<20% by weight) and with increasing rates of change thereafter, suggesting that the measurement of attenuation will be most useful for the higher steatotic grades, but more difficult to distinguish in the very early low grades. This appears to be consistent with the results illustrated in Figure 4. We chose 150-Hz shear wave frequency as it is in the mid-band of the spectrum of the shear wave pulse used in this study. Because attenuation



Fig. 1. B-Mode and elastography images indicating average shear wave speed and shear wave attenuation results in two different patients. (a) Patient with cirrhosis = F4 and S0. (b) Patient with F2 and macro- and microvesicular steatosis (>90%) with steatohepatitis (S3).

is a function of frequency in viscoelastic tissues, the precise value of attenuation measured in a tissue will depend on the shear wave frequency chosen.

At this early time we do not know how many cofactors (besides steatosis) may increase or decrease attenuation in the liver. For example, Nenadic et al. (2017), using a spatial frequency broadening measure of attenuation, concluded that liver transplant rejection cases had a lower SWA than normal livers. In addition, Bernard et al. (2017) employed a frequency downshift



Fig. 2. Shear wave propagation measured in the (a) S0 score patient and (b) S2 score patient.

estimator to assess SWA in phantoms and tissue samples. They found a doubling of attenuation in 20% oil-in-gelatin phantoms compared with the baseline case of 0% oil. Further study is required to establish the mechanisms of any co-factors.

The focus of this study has been on SWA as a function of steatosis. In many previous studies of elastography of the liver, SWS was the primary parameter and attenuation was not directly measured. However, the dispersion of SWS versus frequency is linked by physics to attenuation *via* the Kramers–Kronig relations (Chen and Holm 2003; Parker 2014; Szabo 1995). Thus, dispersion of phase velocity in an individual liver is linked to the lossy, viscoelastic nature of the tissue (Parker et al. 2015). However, when simply examining group velocity of shear wave packets generated from push pulses, the particular frequency band chosen to take measurements can have a strong influence on the experimental results



Fig. 3. Shear wave speed group velocity as a function of fibrosis score (a) and as a function of steatosis score (b). These indicate trends that are in opposition: increasing speed with increasing fibrosis score and decreasing speed with steatosis score.



Fig. 4. Shear wave attenuation estimated at 150 Hz as a function of fibrosis scores (a) and as a function of steatosis scores (b), where Spearman's rank statistical analysis revealed a correlation rho of 0.69 (p < 0.001), confirming the trend of increasing attenuation with increased steatosis. Symbols also encode for the hidden variable: steatosis score (a) and fibrosis score (b).

(Parker et al. 2018a, 2018b). In other words, experimental confusion concerning the effects of simple steatosis on liver SWS can be caused by the choice of experimental conditions: frequency range and measurement type; group velocity versus phase velocity. The situation is more straightforward in the case of SWA; according to models, it should increase monotonically with increasing volume concentrations of viscous fats and oils in dispersion (Parker et al. 2018a), and the attenuation will also increase with increasing frequency.

Table 1. Trends for shear wave speed and attenuation as afunction of pathology grade

|                       |                      | Steatosis        |                           | Fibrosis                  |                  |
|-----------------------|----------------------|------------------|---------------------------|---------------------------|------------------|
|                       |                      | SWS              | SWA                       | SWS                       | SWA              |
| Rho<br><i>p</i> Value | Spearman<br>Spearman | $-0.55 \\ 0.013$ | 0.69<br>7.00 <i>E</i> -04 | 0.76<br>1.19 <i>E</i> -04 | $-0.58 \\ 0.007$ |

SWS = shear wave speed; SWA = shear wave attenuation.

#### CONCLUSIONS

Shear wave attenuation was found to increase with high grades of steatosis in this preliminary study, from approximately 5 dB/cm estimated at 150 Hz to nearly 20 dB/cm in the cases with the highest grade of steatosis. This supports the hypothesis that viscous oil in macrovesicular and microvesicular spaces within the hepatocytes will increase the loss mechanisms within the liver (Parker et al. 2018a). Some major unknowns remain, including the role of any possible co-factors (other than steatosis) that may increase or decrease attenuation, and further studies on larger numbers of livers are required to determine these factors.

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