RSNA/QIBA: Shear wave speed as a biomarker for liver fibrosis staging

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Overview

In 2008, the Radiological Society of North America (RSNA) created the Quantitative Imaging Biomarker Alliance (QIBA) with pharmaceutical companies, imaging system manufacturers, academics, clinicians and representatives from the federal government (e.g., FDA, NIH, NIST) to advance the concept of converting "imaging systems" to "measurement systems". The Alliance is organized by Modality Committees and within these committees are Technical Committees whose efforts involve specific classes of biomarkers. The Ultrasound Technical Committee was formed in 2012.

Our initial efforts are toward improving the measurement and analysis of shear wave speeds (SWS) as a surrogate measure of liver fibrosis. There is a relatively large body of literature reporting these methods, commercial systems are available, there are numerous reports for clinical trials, and there is evidence of systematic bias among different commercial systems and numerous reports of sources of estimate variance. Results (shown in the table below) from a recent international multicenter study† of SWS in patients with chronic hepatitis C involving 914 patients illustrates the challenge. Understanding these sources of bias and variance, and minimizing them, is consistent with the goals of QIBA.

Fibrosis Stage (METAVIR score)	Siemens S2000 Mean SWS	Siemens S2000 Optimal Cutoff	Fibroscan Optimal Cutoff
F0	**1.09±0.42 m/s**		
F1	**1.22±0.41 m/s**	≥1.19 m/s	≥2.15 m/s (5.2 kPa)
F2	**1.37±0.48 m/s**	≥1.36 m/s	≥2.44 m/s (6.7 kPa)
F3	**1.70±0.59 m/s**	≥1.47 m/s	≥2.92 m/s (9.6 kPa)
F4	**2.23±0.71 m/s**	≥1.69 m/s	≥3.25 m/s (11.9 kPa)

Methods

To begin investigating the difference is SWS estimates among systems, a "simple" phantom study was performed. Eleven pairs of phantoms, one 'soft' and one 'stiff' in each pair, was constructed. Each phantom was a right circular cylinder about 10cm diameter and 10cm deep. The phantom materials were (nominally) elastically lossless so they would exhibit minimal dispersion. The intent was to make comparisons between SWS estimation systems under the simplest conditions.

Test samples of the phantom materials were constructed in the appropriate geometry for each system and sent to the University of Wisconsin and Rheolution, Inc. for independent dynamic mechanical assessment (DMA).

All phantoms were shipped to Duke University where the SWS was systematically estimated throughout the phantoms using a custom acoustic radiation force impulse (ARFI) implementation on a Verasonics system. The Duke study found small, but important, differences in SWS estimates among the phantoms. Lacking a one-to-one correspondence between the test samples and the phantoms, the Duke SWS estimates were used and reference values and all analysis that follows uses SWS values adjusted to account for the differences in mean SWS shown in Figure 1.

These results are consistent with those from DMA, but the materials showed much higher loss than expected (at 300Hz, tan-δ = 0.75 and 0.3 for the soft and stiff materials, respectively). This requires further investigation.

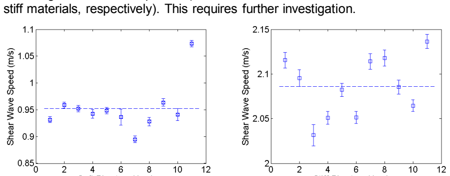

Figure 1. Plots of SWS estimates performed on all phantoms by Duke using a Verasonics implementation.

Results

Figure 2. Combined SWS estimates (adjusted for phantom differences).

Each site had at least three participants measure each phantom at three previously specified depths. The order in which data were acquired was randomized for participant, phantom and depth. Each participant acquired 10 SWS estimates at particular trial and there were three trials for each condition. With 12 sites, at least 3 participants at each site, and in some cases multiple systems were used, there are over 3000 SWS estimates for each set of phantoms. Figure 2 shows the combined results from each site. There are several confounding factors to consider in these results. For example, Siemens and Southwoods used the same phantom pair. Southwoods and UW used multiple systems, and that could induce a systematic error among SWS estimates.

Regardless of these confounding sources of error, there is remarkably good agreement among the mean values of measurements for both the soft and stiff phantoms. There is, however, relatively large variance in several cases. With many randomized measurements, we can dig deeper to begin to understand some of the sources of variance.

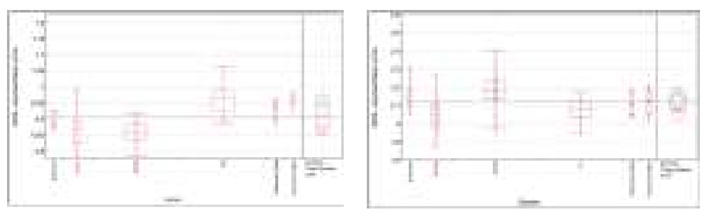

Figure 3 shows plots of combined SWS estimates grouped by the system used. There appears to be a bias among the various shear wave implementations.

Figure 4 shows that data obtained among 'identical' systems is equivalent (minimal differences in mean SWS estimates among systems and participants).

Figure 3. SWS estimates grouped according to the system used for data acquisition. The Philips and Siemens system provided slower than average SWS in the soft, lossy medium while the Philips and SSI systems provided slower than average SWS estimates in the stiffer medium.

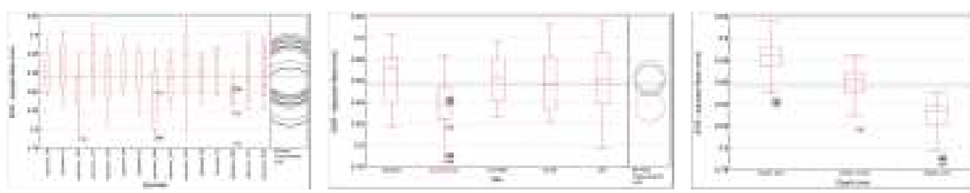

Figure 4. SWS estimates for the soft phantoms acquired with the Siemens S2000. All data at the same depth are nominally equivalent with the exception of data acquired at Southwoods where a different transducer was used.

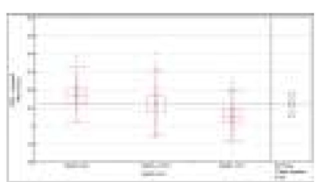

Figure 5 demonstrates a depth dependence in SWS estimates in the stiff phantoms too. There are several possible sources for the observed depth dependence. For example, the focal properties of the pushing pulses likely changes with depth. That would change the frequency content of the shear wave and its group velocity. It is also possible that there is a gradient in material properties in the phantoms (data from Duke support this notion).

This Phase 1 phantom study has been highly informative. It is clear that there are biases among SWS estimates from different implementations of shear wave elasticity systems. It is also clear that there is little difference in SWS estimates among equivalent systems or replicate participants. These observations will lead to a more efficient Phase 2 phantom study that is now being planned.

Conclusions

- **The 'simple' Phase 1 phantom study was not simple**
- **Fewer phantoms with test samples from those exact materials are needed to independently assess phantom material properties**
- **It is very difficult to measure the complex shear modulus of materials softer than 1kPa**
- **The bias and variance in SWS estimates is currently large compared to the difference in mean SWS estimates for early stage liver fibrosis**
- **There are many potential sources to improve both bias and variance in SWS estimates among implementations**

Literature cited

†Sporea, et al. "Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study", European Journal of Radiology 81 (2012) 4112– 4118.

Acknowledgments

This work was supported by a generous donation of phantoms by CIRS, funding from the RSNA, and donated effort.by many.

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