QIBA Ultrasound Biomarkers: Shearwave Speed Imaging, Contrast Enhanced Ultrasound, Blood Flow Quantification (Part 2)

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Quantitative Imaging Biomarkers Alliance® RSNA®

Contrast Enhanced Ultrasound Quantification

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Liver Cancer Evaluation

The initial application of this Contrast Enhanced UltraSound (CEUS) effort is diagnosis and management of solid Liver Malignant Masses.

CEUS Quantification Current Status

- CEUS, is approved and used extensively worldwide.
- All major ultrasound manufacturers have quantative CEUS.
- Approximately 10% of the 1,600,000 focal liver masses are examined with CEUS per year. That percentage will increase to perhaps 50% as ultrasound becomes more ubiquitous and contrast agents less expensive.
- In Europe, 95% of liver diagnoses are performed with ultrasound. In the USA, CEUS usage for solid liver masses is much smaller, but that usage can be expected to reach perhaps 30% or 13,000/yr. Currently 2.6 million CEUS echocardiograms are performed per year in the USA.
- The cost of a typical exam is $600. http://icus-society.org/2019-coding-and-payment-chart/
- The technical success rate of CEUS liver exams in one study used for FDA approval was 80%.
- There are currently over 500 scientific clinical CEUS quantification publications in this field whose utilization rate is rising at 2-6%/yr.
- > 1/3 of USA pediatric hospitals perform CEUS despite the short time since FDA approval
- Discrimination between malignant and benign focal liver lesions was reported as 98% sensitive and 93% accurate.

https://www.ajronline.org/doi/full/10.2214/AJR.04.1009

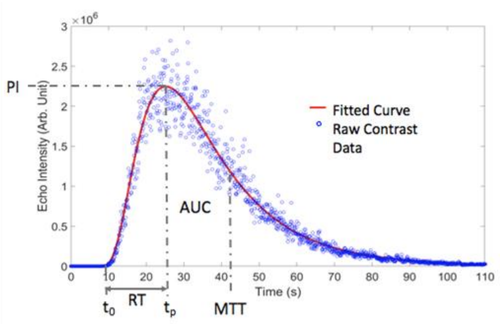

Figure B1. Time Intensity Curves are measured by pulse echo ultrasound sequences tuned to the nonlinear oscillations of stabilized microbubbles injected intravenously. The typical characteristic curve of recorded and displayed log of the US signal is highly nonlinear.

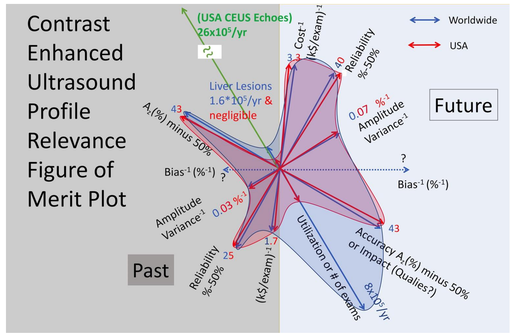

Figure B2. a proposed graphical figure of merit for QIBA Biomarkers. Estimates for "Future" (after profile is well established) are highly speculative as are some preprofile, "Past", estimates.

Time Intensity Curve Measurements

With a phantom study, bolus dynamics parameters were evaluated across 4 scanners and 3 analysis software packages in order to evaluate their reproducibility and to standardize a surrogate for quantification of perfusion in the clinic. As shown in Table B1, after identifying a standardized protocol, variance of time parameters (rise time RT, and mean transit time MTT) were found to range from 2-12%, while parameters (peak intensity and area under the curve AUC) ranged from 15-50% (systems and analysis packages). The variation in the amplitude parameters may be attributed to the inherent noise in microbubble scattering, the polydispersity of microbubbles, signal handling in scanners, and microbubble destruction. The achieved cross vendor consistency of the bolus parameters is an important outcome that enables moving forward to a clinical validation. In future activity, we hope to standardize signal intensity values across systems to enable amplitude comparisons. These and the following other measures of relevance, described above, are illustrated in Figure B2.

RT	MTT	PI	AUC	
3-9	2-12	15-49	17-50	**all scanners**
5-8	3-12	19-33	18-34	**scanner A**
3-6	3-6	40-49	44-50	**scanner B**
6-9	2-6	15-26	17-32	**scanner C**
4	3-6	37-44	37-44	**scanner D**

Table B1 (left): Range of variability (percentage), per scanner and all together, of bolus parameters when 3 different analysis packages are used.

	analysis s/w 1	analysis s/w 2	analysis s/w 3	all
RT	7.5	7.7	3	6.4
MTT	4.4	15.6	23.1	14.7

Table B2: Variability (%) of RT and MTT per analysis software package between the 4 scanners used. (Note: we can only compare RT and MTT across scanners and software packages as amplitude scales are not yet standardized.)

	Scanner			
	A	B	C	D
RT	1.1	3.6	1	6.6
MTT	16.9	10.3	4.1	11.1

Table B3: Variability (percentage) of RT and MTT per analysis software package between the 4 scanners used.

Ultrasound Shear Wave Speed Quantification

Committee Cochairs: T.J. Hall, PhD, B. Garra, MD, Ph.D. and Andy Milkowski, MS

Ultrasound Shear Wave Speed Quantitative Biomarker Committee

Task Force Groups (TFGs) include:

- System Dependencies and Phantom development (Co-chairs M. Palmeri, K.A. Wear)
- Clinical and Applications and Biological Targets (Co-chair A. Samir)
- Profile writing (B. Garra and M. Dhyani)

For detailed information on participating sites and committee members, please scan the code at the corner.

Profile: Ultrasound Measurement of Shear Wave Speed for Estimation of Liver Fibrosis

Shear wave speed (SWS) is a biomarker to identify patients with moderate to significant liver fibrosis, defined as ≥ F2 in the METAVIR system (or equivalent for other scoring systems) of staging liver fibrosis. This profile might be used to monitor progression of fibrosis or to monitor regression of fibrosis during anti-fibrosis therapy. SWS also serves as a biomarker for the evaluation of cirrhosis, defined as F4 stage in the METAVIR system of staging liver fibrosis.

This profile places requirements on ultrasound scanners (acquisition devices), Scanner Manufacturer/Vendor, Technologists/Sonographers, QA (Quality Assurance) Manager, Radiologists, Reconstruction Software and Image Analysis Tools involved in pre-delivery steps, scanner installation, site QA procedures, subject selection and handling, image data acquisition, image data reconstruction, image and other QA and image analysis.

The ultimate clinical performance target is to achieve SWS measurements with a bias of mean value of ≤ 5% and an overall coefficient of variation of 5% (SD/mean).

This profile has been released for public comment.

Claim 1 (technical performance claim)

A shear wave speed measurement has a within-subject coefficient of variation (wCV) depending on the measured SWS and depth of acquisition according to Table 2-1.

Claim 2 (cross-sectional claim)

A 95% confidence interval for the true SWS (in m/sec) is Y ± (1.96 x Y x wCV/100), where Y is the measured SWS and wCV is the within-subject coefficient of variation from Table 2-1. E.g., 95% CI at SWS =2.2 is: 2.2x(1±1.96x.04) = 2.2 ± 0.17 or 2.2 ± 8%.

Claim 3a (longitudinal claim)

A true change in SWS over two time points (Y1 and Y2) has occurred with 95% confidence if the measured %change, defined as 200x|Y2-Y1|/(Y1+Y2) is equal to or greater than the repeatability coefficient (RC) given in Table 2-2 and the same operator performs the exam. Larger CI's are provided in other claims for different operators and different operators and ultrasound systems.

Proposed Clinical interpretation:

According to the consensus standard from the Society of Radiologists in Ultrasound (Oct. 2014)[1]. See the more recent guidelines of the World Federation of Ultrasound in Medicine and Biology[2].

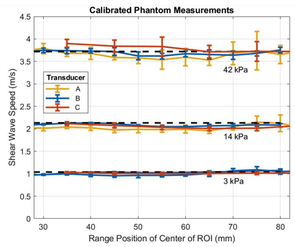

Figure C1. Later measurements on one of the systems with a substantial depth dependence showed the depth dependence had been corrected.

A clinical study at MGH and WDC VAH is designed to test the feasibility of the profile.

Technical Conformation Study

- 30 patients with biopsy proven liver fibrosis
- Profile compliant 10 SWS acquisitions with each machine
- 2 sonographers measure liver stiffness in two visits to assess interrater and intrarater reliability

QIBA effects on SWS Dependencies

Modest differences were found initially between ultrasound systems, between different acquisition depths in a given system and transducer, and between operators. Due to sharing of the QIBA test results with manufacturers, later measurements showed marked improvements in depth dependence, see Figs. C1 and C2. Presumably the data and recommended procedures will have a similar effect on intersystem, operator, and other variance, see Table C3 .

Table C1 Coefficient of Variation (wCV		
Measured SWS (m/s)	**Depth=4.5cm***	**Depth=7.0cm**
0.9 < SWS <= 1.2	**5%**	**8%**
1.2 < SWS <= 2.2	**4%**	**5%**
2.2 < SWS <= 5.0	**10%**	**12%**
* linear interpolation for measurements taken at other depths		

Table C2 Repeatability Coefficient (RC)		
Measured SWS (m/s)	**Depth=4.5cm***	**Depth=7.0cm**
0.9 < SWS <= 1.2	**14%**	**22%**
1.2 < SWS <= 2.2	**11%**	**14%**
2.2 < SWS <= 5.0	**28%**	**33%**
* linear interpolation for measurements taken at other depths		

Table C3 Example Table of Liver Fibrosis Categories and Corresponding Representative Shear Wave Speed Values.*			
Ultrasound System	**No Fibrosis or Minimal Fibrosis (METAVIR F0-F1)**	**Moderate Fibrosis (METAVIR F2 i and F3 ii)**	**Severe Fibrosis/Cirrhosis (METAVIR F3 – F4)**
System A	**SWS < 1.37 m/s (< 5.7kPa) iii**	**1.37 < SWS < 2.2 m/s (> 5.7 kPa, < 15 kPa)**	**SWS > 2.2 m/s (> 15 kPa) iv**
System B	**SWS < 1.66 m/s (<8.29 kPa)**	**1.66 ≤ SWS < 1.88 m/s (≥8.29 kPa, < 10.60 kPa)**	**SWS ≥1.88 m/s (≥ 10.60 kPa)**
*Considerable changes have been adopted by the clinical community since this table was developed.[1,2]			

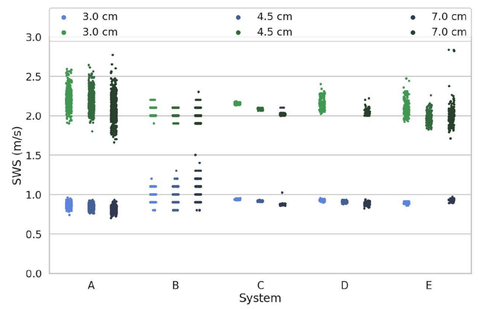

Figure C2. First QIBA tests with multiple systems on elastic phantoms with two stiffnesses (green and blue). There is considerable variation between the three depths (ranges) of data acquisition in ultrasound systems from several of the manufacturers. (Manuscript by M. Palmeri, et al. has been submitted for publication.)

References:

1. Richard G. Barr, Giovanna Ferraioli, Mark L. Palmeri, Zachary D. Goodman, Guadalupe Garcia-Tsao, Jonathan Rubin, Brian Garra, Robert P. Myers, Stephanie R. Wilson, Deborah Rubens, and Deborah Levine. Radiology 2015 276:3, 845-861
2. Ferraioli, Giovanna & Wong, Vincent & Castera, Laurent & Berzigotti, Annalisa & Sporea, Ioan & Dietrich, Christoph & Choi, Byung Ihn & Wilson, Stephanie & Kudo, Masatoshi & Barr, Richard. (2018). Liver Ultrasound Elastography: An Update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. Ultrasound in Medicine & Biology. 10.1016/j.ultrasmedbio.2018.07.008.