QIBA Newsletter

Quantitative Imaging Biomarkers Alliance RSNA

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QIBA MISSION

Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.

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IN MY OPINION

Challenges in Staging Liver Fibrosis

By TIMOTHY J. HALL, PhD

Chronic fibrosis can disrupt liver function and progress to cirrhosis, the final phase of chronic liver disease—one of the major causes of death in the U.S. Staging fibrosis is a key to determining liver health. Although core biopsy is the current clinical standard for staging fibrosis, its accuracy is limited by the heterogeneity of the disease and the small sample size. Further, liver biopsy is painful and is associated with several potential complications.

Noninvasive quantitative measures of liver stiffness have been proposed as surrogate measures of liver fibrosis since the excess collagen increases the elastic modulus of tissue. Typical sound waves (including ultrasound) are "longitudinal" or "compressional", meaning wave propagation moves in the direction of the disturbance of the wave action. A "shear" or "transverse" wave, commonly associated with earthquakes, can be created in tissue using a relatively long duration and relatively high-intensity compressional wave to push the tissue—in a very localized area—a few microns. That action causes movement in the tissue next to it, creating a wave traveling perpendicular to the direction of the compressional wave propagation. In simple media (homogeneous, isotropic, large compared to the wavelength) the speed of shear waves (c_s) is directly related to the shear modulus (μ) of the medium ($\mu = \rho\, c_s^2$ where ρ is mass density). New ultrasound techniques, found on some of the most advanced imaging systems, can create and track shear waves to estimate their speed and thus, noninvasively provide quantitative estimates of liver stiffness and liver fibrosis.

Studies found in the MR imaging and ultrasound literature have compared shear wave speed (SWS) and fibrosis stage from core biopsy. The research demonstrated excellent correlation, especially considering the uncertainties in the staging. Using the nonalcoholic steatohepatitis Clinical Research Network scoring system to grade the biopsy specimens, SWS can differentiate bridging fibrosis (stage 3) and cirrhosis (stage 4) from normal tissue and the more mild stages of fibrosis (stages 0-2; see figure 1). Unfortunately, the threshold SWS for classifying fibrosis varies among different imaging systems. The QIBA Ultrasound Shear Wave Speed Technical Committee is challenged to understand the sources of bias and variance in these

measurements and to develop methods for direct comparison of results obtained with different imaging systems and system configurations.

Ultrasound methods for generating shear waves in tissues create individual pulse packets of shear waves that propagate only a few millimeters before the energy is absorbed by the tissue. The SWS of these packets (the "group velocity" of the shear wave) is the quantity currently estimated by ultrasound imaging systems. A wave packet is the superposition of waves from a range of frequencies (each having their own "phase velocity"). One difficulty in direct comparison of shear wave speeds (group velocities) among different imaging systems and configurations is that different system configurations produce shear waves with different frequency content (superposition of different phase velocities over different frequency ranges).

One approach the Committee is considering is the direct comparison of a single-phase velocity that is common among each of the different systems and system configurations for the specific task of staging liver fibrosis. As simple as it might seem, it is essential to get the details right for direct comparisons. An alternative, model-based approach might be to use a constitutive model (relating stresses to strains in fibrotic liver tissue) to map the group velocity measured with one system to the group velocity measured with another system.

Although the QIBA Ultrasound Sheer Wave Speed Technical Committee is very new, and the task is quite challenging, this is a broadly representative, outstanding group of scientists, clinicians and industry representatives who are committed to the goal and actively involved in defining and addressing this important clinical need. Application of the approach to many other SWS biomarkers could follow rapidly.

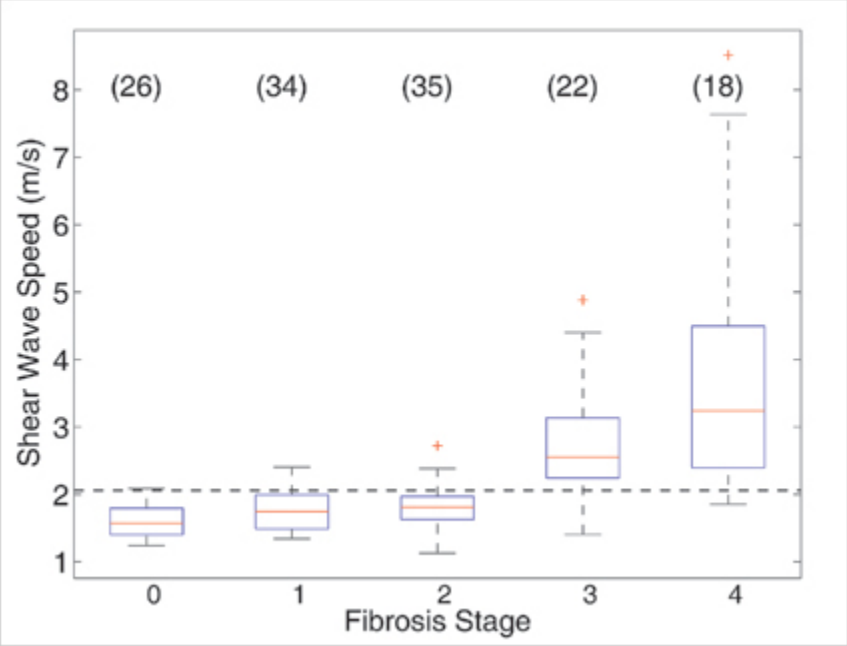

Figure 1. A box plot of ultrasound - measured shear wave speed for various stages of liver fibrosis. The numbers of subjects in each group are shown in parentheses. (Data replotted from Palmeri, et al, *J Hepatology* 55(3): 666-672, 2011, with permission from the lead author).

Timothy J Hall, PhD, is a professor in the Medical Physics Department at the University of Wisconsin, Madison. He is co-chair of the QIBA Ultrasound Shear Wave Speed Technical Committee and co-chair of the Phantoms Subcommittee. His research group has been developing, implementing and testing quantitative ultrasound techniques for 25 years.

PubMed Search on: "Challenges in Staging Liver Fibrosis"

Each issue of *QIBA Newsletter* features a link to a dynamic search in PubMed, the National Library of Medicine's interface to its MEDLINE database. Link to articles on: "Challenges in Staging Liver Fibrosis" here.

ANALYSIS: TOOLS & TECHNIQUES

Digital Reference Objects for Dynamic Contrast-enhanced MRI

By DANIEL BARBORIAK, MD, and RICHARD PRICE

Dynamic contrast-enhanced MRI (DCE-MRI) has generated considerable interest as a technique that may aid drug development by providing insight into the mechanism of action for therapies believed to have anti-angiogenic or anti-vascular effects, and by helping determine optimal dosing and scheduling of drug administration for further clinical trials [1]. As noted in a previous issue of the QIBA Newsletter [2], one of the challenges to the more widespread use of DCE-MRI in clinical trials and drug development research is the high variability of the technique.

Some of the sources of this variability—for example, errors in calculation of baseline T1 rates before gadolinium-based contrast agent injection, or inaccuracies in the assessment of the vascular input function needed for the calculation of parameter maps [3]—are related to the technical factors in the MR image acquisition. Another somewhat less recognized source of variability is that the software used to extract parameter maps is not standardized and differences in the implementation of the image analysis could affect the quantitative results. If the experience gained in analyzing the results of CT perfusion analysis software is any guide [3], the choice of which software package is used to analyze DCE-MRI could have substantial impact on the results.

One approach to exploring this question further that has been taken by the QIBA Perfusion/Diffusion/Flow MRI (PDF-MRI) Technical Committee and our lab has been to create synthetic images called digital reference objects (DROs) using known parameter values to test the performance of software. The DROs can be used as standard input to be analyzed by a variety of software packages, and the results of these analyses can be objectively compared with expected values. DROs provide the additional advantage of being amenable to deliberate, controlled modification by the researcher. For example, the noise level can be altered to document the effect of noise on the bias and variability of extracted parameter values and to determine if these vary across software packages.

Several variations of test DROs have been generated and are available for download at: https://sites.duke.edu/dblab/. Links to the open source software used to generate the DROs are also provided.

We have begun a formal evaluation of a variety of academic, open source and commercial software packages used to create T1 maps from variable flip angle MR imaging [Fig. 1]. This evaluation is a preliminary step toward QIBA's goal of developing acceptance criteria for software packages suitable for use in clinical trials of DCE-MRI.

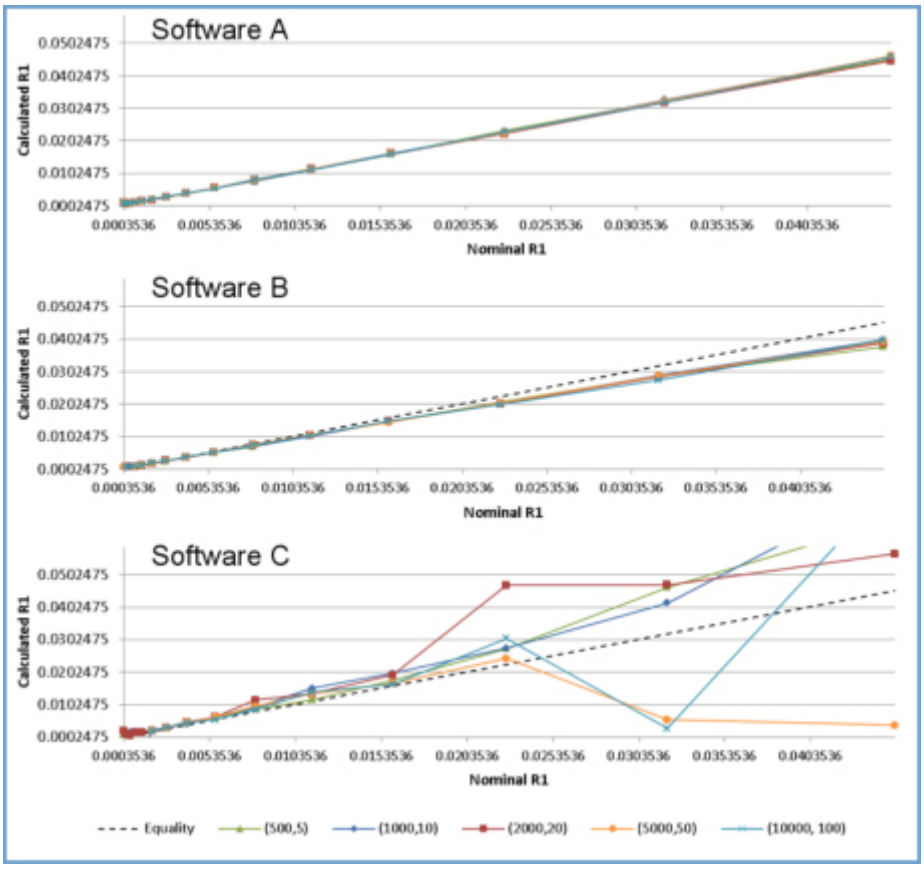

Fig. 1: *Effects of applied noise on bias of R1 (1/T1) estimation demonstrated on graphs of nominal vs. calculated R1 for three software packages A, B, and C. Results were obtained from identical DROs with Rician noise added to simulate signal-to-noise ratio (equilibrium magnetization signal intensity, noise standard deviation) of 100. Software A shows small underestimates of R1 at high R1. Software B shows larger underestimates of R1 at high R1. Software C shows overestimates of R1 at low R1 and high variability depending on equilibrium magnetization at high R1.*

REFERENCES:

[1] O'Connor JPB, Jackson A, Parker GJM, Roberts C, Jayson GC. Dynamic contrast-enhanced MRI in Clinical Trials of Antivascular Therapies. Nat Rev Clin Oncol 2012 Mar;9(3):167-177.

[2] Guimaraes AR. Challenges in Tackling Quantitative DCE-MRI. QIBA Newsletter 2012 Mar; 4(1).

[3] Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H, Ogasawara K. Differences in CT Perfusion Maps Generated by Different Commercial Software: Quantitative Analysis by Using Identical Source Data of Acute Stroke Patients. Radiology 2010 Jan;254(1):200-209.

Daniel Barboriak, MD, is a professor of radiology in the Neuroradiology Division at Duke University Medical Center. His research interests include use of advanced imaging for treatment assessment in patients with brain tumors. He is a member of the QIBA PDF-MRI Technical Committee and chairman of the ECOG-ACRIN Brain/Head and Neck subcommittee.

Richard Price is currently in his senior year at Princeton University, earning a bachelor's degree in computer science and a Certificate in Global Health and Health Policy. His research interests include medical imaging and the proliferation of mobile technologies in low-resource settings.

Daniel Barboriak, MD

Richard Price

QIBA AND QI/ IMAGING BIOMARKERS IN THE LITERATURE

This list of references showcases articles that mention QIBA, quantitative imaging, or quantitative imaging biomarkers.

QIBA in the Literature

In most cases, these are articles published by QIBA members, or relate to a research project undertaken by QIBA members that may have received special recognition. New submissions are welcome and may be directed to QIBA@rsna.org