QIBA CEUS BIOMARKER COMMITTEE

Kenneth Hoyt, PhD; Mike Averkiou, PhD; Richard Barr, MD; David Cosgrove, MD; Stephanie Wilson, MD; Paul Carson, PhD; Beth McCarville, MD; Nathalie Lassau, MD; Wayne Monsky, MD; Christina Kalli, MS; Alex Jackson, PhD; Peter Frinking, PhD; Thierry Bettinger, PhD; Christian Greis, PhD; John McQuarrie, PhD; Andy Milkowski, PhD; Ravi Managuli, PhD; Edward Grant, MD; Vinay Duddalwar, MD; Eric Perlman, MD; Michelle Robbin, MD; Todd Erpelding, PhD; Theresa Tuthill, PhD; Nikolay Tzaribachev, MD; Abhay Patil, PhD; Andrej Lyshchik, MD

Quantitative Imaging Biomarkers Alliance® RSNA®

Project Description

Tissue perfusion is affected in a wide range of pathologies including neoplasms, inflammation, and ischemia. Therefore, a quantitative biomarker related to tissue perfusion based on contrast-enhanced ultrasound (CEUS) imaging would be of tremendous use clinically. Although Doppler ultrasound (US) can evaluate blood flow, it is not useful in the assessment of tissue perfusion as it does not detect blood flow at the microvascular level.

As a noninvasive technique with no renal or hepatic toxicity, CEUS has the advantages of real-time imaging, easy repeatability, and wide availability. Further, microbubble (MB) contrast agents are a pure blood pool agent (intravascular tracer), thus providing blood flow information at the capillary level. Many potential patients for CEUS imaging have chronic disease, especially neoplastic or inflammatory, often necessitating multiple scans over a long time interval. Thus, this US technique would limit the radiation exposure from multiple computed tomography (CT) scans and possible toxicity or alergenicity from multiple injections of contrast agents used for CT or magnetic resonance imaging (MRI).

Quantitative CEUS has been evaluated by several groups and demonstrated to be clinically useful. However, these groups standardized their US imaging to a single system configuration and MB contrast agent. For the clinical benefits to be applied widely and for specific contrast agent kinetic measures to become biomarkers, CEUS measurement standardization across different imaging systems and MB contrast agent types is required. To that end, **the ultimate goal of this QIBA Biomarker Committee is to standardize the quantification of tissue perfusion based on CEUS images**.

Primary Goals & Objectives

The primary objective is the standardization of measures related to tissue perfusion and based on CEUS imaging across various US systems and MB contrast agent types for the diagnosis and monitoring in a wide range of clinical conditions. Our initial approach will be to use two US systems (Logiq E9, GE Healthcare; Epiq 7, Philips Healthcare) and a single MB contrast agent (Lumason, Bracco Diagnostics) to develop a profile that other MB contrast agents and US systems can then be tested against. Note Lumason was selected as it is approved for use in more countries including the USA. Once a profile has been technically validated, a clinical study of CEUS imaging for the characterization of focal liver lesions can be pursued. Such a study will yield an understanding of patient influences on quantitative tissue perfusion measurements including physical body differences, US propagation and attenuation through tissue and tissue motion. Notwithstanding, the short-term goal of Phase 1 of our proposed study is to evaluate the impact of both CEUS imaging system settings and image processing software used for quantification of tissue perfusion. Using a tissue-mimicking flow phantom (containing a 2 mm diameter vessel) and a precision flow pump setup, we propose to use indicator-dilution methods and a bolus injection for wash-in/wash-out analysis from time-intensity curve data, Figure 1. This multi-site study will help determine the sources of measurement variance, such as, US system transmission power, transmission focal depth, dynamic range, signal gain and transmission frequency. Phase 2 of our multisite study will then evaluate the impact of MB-related factors on bolus dynamics quantification, such as MB injection and dosage. Using data collected during Phase 1 and 2, we will evaluate what parametric tissue perfusion dynamics measure (i.e., peak intensity, I_P; time-to-peak intensity, t_p; wash-in time, *WIT*; mean transit time, *MTT*; and area under the curve, *AUC*) exhibits the least intra-site and inter-site statistical variance while accurately reflecting true blood flow conditions. Collectively, our experimental results will be used to guide development of a CEUS protocol for obtaining reproducible tissue perfusion measurements and help engage industry partners on engineering strategies to standardize image acquisition across different platforms.

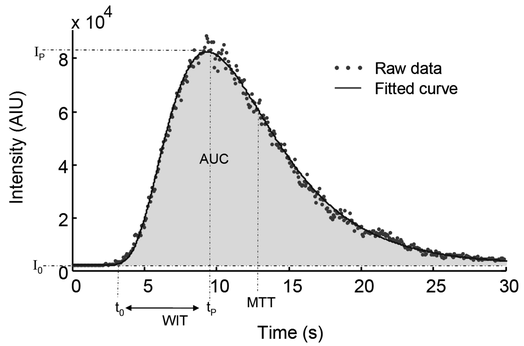

Figure 1 Representative time-intensity curve (image intensity as a function of time in a region of interest). Bolus dynamics quantification parameters are indicated, namely, peak intensity (I_P), time-to-peak intensity (t_p), wash-in time (*WIT*), mean transit time (*MTT*), and area under the curve (AUC).

Table 2. Detailed timeline for the First Year QIBA project.

Duration	Activity
Months 1 – 2	Construct and test tissue-mimicking flow phantom at different sites.
Months 1 – 4	Evaluate and further develop quantification software (linearization, cine size, and time-intensity curve fitting and tissue perfusion parametric estimation.
Months 2 – 6	Evaluate and optimize clinical US systems for quantification of flow dynamics (MB signal detection sensitivity, tissue signal suppression, minimize MB destruction during DCE-US imaging, and standardization of US scanner settings).
Months 4 – 10	Confirm linear range for US image intensity vs MB concentration relationship (per US system).
Months 8 – 12	Perform and validate measurements of tissue flow dynamics. Perform intra-site and inter-site statistical analyses.
Month 12	Compile and deliver final report with all experimental results.

Table 1. Objectives, motivations, and deliverables for the Phase 1 QIBA project.

Objective	Motivation	Deliverable
1. Establish settings for all US scanners participating in the QIBA initiative. This includes: minimize MB destruction, maximize detection of MB signal and suppression of tissue signal.	US equipment standardization so clinical measures made on different systems will provide matched results.	Provide a profile for effective clinical use of CEUS, including reliable scanner settings.
2. Establish and validate US data linearization scheme (native/raw vs compressed/linearized data).	Select one of several schemes presently being evaluated for standardization.	Provide recommended, or agreed upon, linearization scheme to partnering vendors.
3. Select appropriate indicator-dilution model for curve fitting to CEUS-derived time-intensity curve data.	Improve time-intensity curve analysis and noise suppression.	Provide recommended indicator-dilution model for quantification software adoption.
4. Select appropriate CEUS software for quantification of flow dynamics.	Select one (or more) of the several programs presently available for standardization (or develop our own).	Provide list with recommended CEUS image quantification software.
5. Measure flow dynamics in a 2 mm vessel-mimicking phantom using flow rates of 10 to 500 mL/min.	Determine range of flows over which measurements can be accurately made with CEUS imaging and what clinical situations are appropriate.	Establish range of blood flow rates whereby CEUS image measurements are accurate.
6. Measure flow dynamics in a 2 mm vessel-mimicking phantom using MB doses of 10 to 1000 µL/L.	Determine range of MB dose concentrations that avoid US image saturation and shadowing artifacts.	Establish range of MB dose concentrations whereby CEUS image measurements are accurate.

Participating Sites	
BK Ultrasound	Siemens
Bracco Suisse	Sunnybrook Health Sciences Centre
Cleveland Clinic Foundation	Supersonic Imagine
Gammex Inc	Thomas Jefferson Univ Hospital
GE Healthcare	Toshiba Medical Systems
Hitachi Medical Corp	US FDA
Imperial College	Univ of Alabama at Birmingham
King's College London	Univ of Michigan
Laboratoire IR4M	Univ of Mississippi
Lantheus Medical Imaging	Univ of Southern California
Northeastern Ohio Medical Univ	Univ of Texas at Dallas
Pfizer	Univ of Washington
Philips Healthcare	Univ of Wisconsin