QIBA CEUS BIOMARKER COMMITTEE

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QIBA MISSION: ***Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, sites, patients, and time***

Need for standardization

- The Contrast Enhanced Ultrasound Biomarker Committee (CEUS BC) is actively developing a draft Profile for quantitative CEUS measurements in the liver
- CEUS liver use is approved in many countries including USA
- Quantitative tumor flow and perfusion is needed for better diagnosis and therapy monitoring
- Time-intensity curve (TIC) analysis from video loops acquired from different imaging systems, following different protocols, and analyzed with different software packages, are producing non-reproducible and sometimes conflicting results
- There is a need for a Profile standardizing CEUS liver quantification
- A tissue flow phantom that is capable of producing TICs similar to those in liver will be used to study bolus kinetics (wash-in/washout analysis) in an effort to standardize the imaging protocol, type of image data, software analysis, curve fit model, and important parameters
- The ultimate objective is to produce the same TIC and extract the same important parameters from all imaging systems and analysis software packages, at least those claiming conformance with QIBA CEUS Profile.

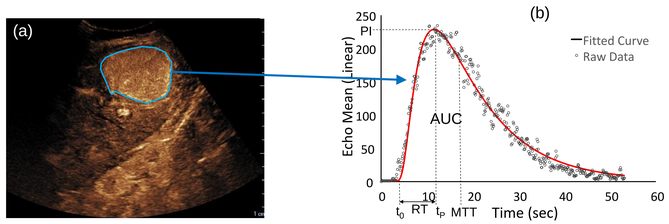
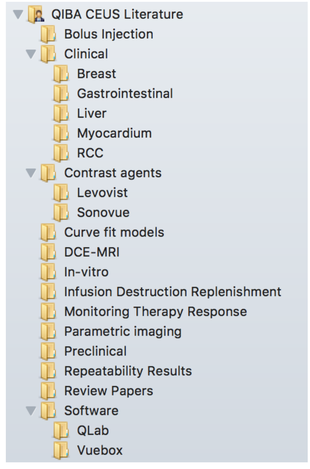


Figure 1. (a) Liver lesion imaged with CEUS. (b) Extracted time-intensity curve (image intensity as a function of time) from the lesion. Bolus dynamics quantification parameters are indicated, namely, peak intensity (*PI*), time-to-peak intensity (t_p), rise time (*RT*), mean transit time (*MTT*), and area under the curve (AUC).

Organizational structure updates

A group of over 50+ experts in the field (clinicians, academics, engineers, basic scientists) are meeting with monthly T-cons. 5 task force teams were formed to better address the issues and fully develop the QIBA Profile, namely:

1. Clinical focus
   Liver lesions (primary and secondary) are the initial focus. Other clinical applications (kidney, inflammatory bowel disease, prostate, breast) will be considered next
2. Literature review: Mendeley library created https://www.mendeley.com/community/qiba/.
   Articles organized into groups and subgroups (see insert)
3. System requirements
   Dual display, tissue cancellation, 2 decimal digit MI, vendors to define minimum s/w version
4. Quantification analysis software
   Operate only on linear/linearized data, online or offline software, use common curve fit model
5. Basic science



Decisions made by QIBA CEUS BC so far

- The bolus kinetics (wash-in/washout) protocol is considered first. At a later stage we will evaluate infusion delivery of ultrasound contrast agent (UCA) with a destruction-replenishment protocol.
- The initial clinical application is liver tumor perfusion. Other clinical applications will follow in the future.
- We are starting with a phantom study before moving to a clinical study.
- For an analysis software to be used it must be able to extract and use linear or linearized data.
- The lognormal distribution model is an acceptable curve fit model (reference PMID: 20529706)
- The following are the primary QIBA quantification parameters: Rise Time, Mean Transit Time, Peak Intensity, Area under the Curve (RT, MTT, PI, AUC)

QIBA CEUS Phantom

The initial QIBA CEUS phantom is shown below. The carrier fluid is deionized water at room temperature. It will be saline at 36C in later studies It was designed such that it produces TICs that resemble clinical liver TICs. Average parameters from 17 patient liver loops (HCC, metastases, FNH, and normal parenchyma) were used. The selected curve characteristics are such that RT=15-20 s, MTT=30-40 s.

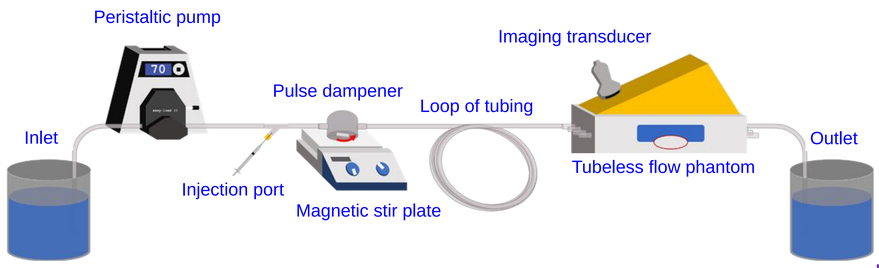


Figure 2. Phantom set-up for producing TICs. Main parts: peristaltic pump, pulse dampener (bubble trap), tissue flow phantom, injection port, tubing for spreading the bolus.

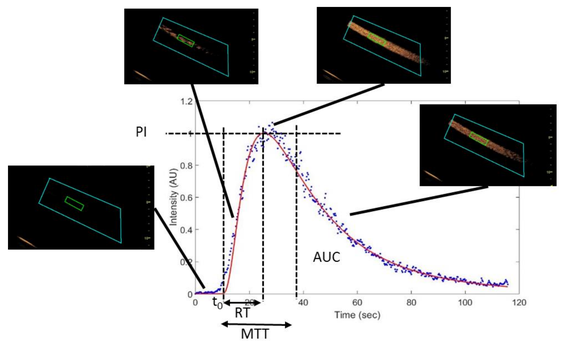


Figure 3. Example TIC curve formed from the QIBA phantom and representative images at different times. Blue dots are data from images, and the red line is the fitted lognormal distribution curve.

Phantom Variability Study

- Use 3 different premium ultrasound systems (names not revealed per QIBA policy)
- Use an FDA-approved ultrasound contrast agent (name not revealed per QIBA policy)
- Collect 5 TICs per system on a single day. Repeat procedure on 3 different days for a total of N=15 (TICs) per system
- Keep system parameters constant between trials. Image tube in exact same location (depth) every time
- Use 3 different analysis software packages (2 commercial,1 custom based on Matlab code). Produce and evaluate 45 parameter sets.
- Extract linear or linearized data using the commercial systems and software packages
- Calculate QIBA quantification parameters (RT, MTT, PI, AUC) and evaluate variability

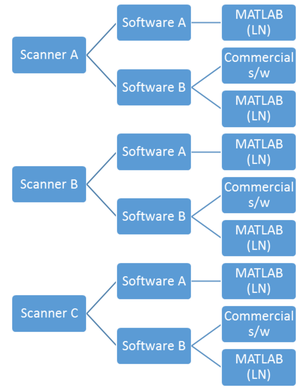


Figure 4. Flowchart of data collection and analysis. Collect video loops from 3 imaging systems, convert to linear or linearized data with 2 different software packages, and curve-fit with 2 different fitting algorithms

Results

Parameter variability (coefficient of variability) derived from the 15 trials (45 curve fits per system)

RT	MTT	PI	AUC	
3-16%	2-19%	22-54%	16-56%	All scanners
4-13%	3-11%	23-37%	16-37%	Scanner A
3-10%	3-19%	53-54%	52-56%	Scanner B
6-16%	2-19%	43-54%	34-54%	Scanner C

Profile impact/implications for clinical trials and patient care

Even though this committee is at a very early stage, the potential impact the standardization can bring will be very large. No field tests or revisions to existing Profiles have been performed. The reported variability study is the first milestone of this BC.
Ongoing and future activities include:

1. Imaging system amplitude standardization
2. Source of variability analysis, and
3. Initial evaluation of destruction-replenishment protocol