QIBA CEUS BIOMARKER COMMITTEE

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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 and it is used for liver tumors
- 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

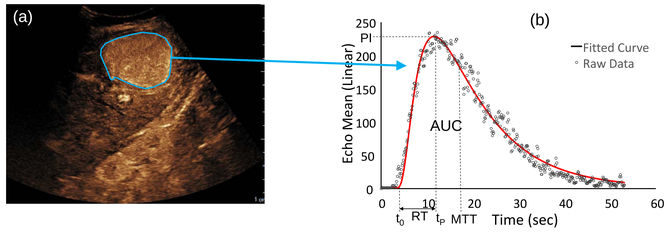


Figure 1. (a) Liver lesion imaged with CEUS. (b) Extracted time-intensity curve (image intensity as a function of time) from the lesion. Bolus dynamics quantification parameters are indicated, namely, peak intensity (*PI*), time-to-peak intensity (t_p), rise time (*RT*), mean transit time (*MTT*), and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

Organizational structure updates

A group of over 50+ experts in the field (clinicians, academics, engineers, basic scientists) have been broken into 5 task force teams to better address the issues and fully develop the QIBA Profile.

1. Clinical focus
   Liver lesions (primary and secondary) will be 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

Profile development status

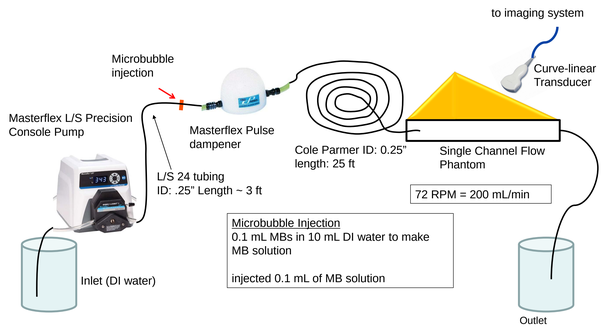
At the present stage, a draft project description and an outline of the group's planned work have been compiled. The goal of this committee is to standardize quantitative CEUS to use as a biomarker of perfusion and thus of tumor response to therapy for liver tumors initially and other clinical applications next.

At first, standardization procedures will be developed on a tissue flow phantom and at a later stage the Profile will be validated with clinical data (existing and new).

Discussions have been initiated with equipment and software suppliers in order to keep the procedures relevant and implementable. Two of the task force teams formed (imaging systems requirements and quantification analysis software) include experts and representatives/engineers from imaging equipment and quantification software industries.

Groundwork project status/results

The primary objectives are geared to the standardization of quantitative CEUS methods and approaches necessary to quantify tumor perfusion characteristics. The initial phase includes the development of a simple phantom set up for generating TICs that are similar to those of liver lesions. Despite this being very different from tumor perfusion it is nevertheless a "standard" first milestone in order to establish that all imaging systems, contrast agents, labs, produce the same TICs and bolus kinetics parameters when measuring the same flow.
The phantom and its main parts are shown below in Fig. 2.



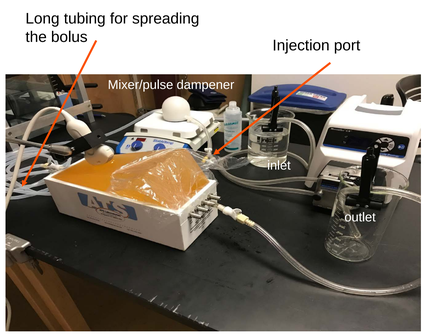


Figure 2. Phantom set-up for producing TICs. Main parts: peristaltic pump, pulse dampeners, tissue flow phantom, injection port, tubing.

Groundwork project status/results (continued)

TICs are collected from the phantom. The user is able to control the bolus parameters (PI, AUC, RT, and MTT) by changing the setting in the pulse dampeners and the length of the tube that allows the bolus spreading. Figure 3 shows TICs collected from this phantom.

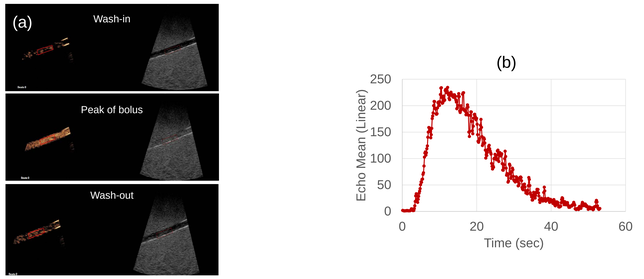


Figure 3. (a) CEUS images during the wash-in, peak, and washout of the bolus. (b) Time intensity curve from the phantom.

Description of experiments that will follow:

1. Form intensity versus concentration curves and confirm linear range. This will help identify optimal contrast concentration to avoid shadowing, and systems settings to avoid signal saturation.
2. Select all phantom parameters (tubing size and length, pump settings, contrast dose, etc.)
3. Evaluate reproducibility between 2 (or more) sites

Example of possible issues:
When plotting the same data with different analysis software packages, the extracted TICs may not be identical, possibly due to issues with the linearization procedure as shown in the figure below. Another issue, is the fact that different analysis software packages will produce different linearized amplitudes. In the example shown below we normalized all data with respect to the respective maximum value. This will have to be further addressed in the future.

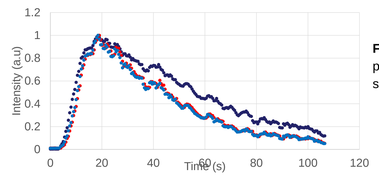


Figure 4. 3 TICs from the same data set processed with 3 different quantification software packages demonstrating differences

Profile impact/implications for clinical trials and patient care

Even though this committee is at a very early stage, potential impact the standardization can bring will be really significant. No field tests or revisions to existing Profiles have been performed. The initial activities will concentrate on the basics using a tissue-mimicking flow phantom to evaluate the Lumason CEUS contrast agent and 2-3 scanners with CEUS software.