Achievements, challenges, and present status of QIBA’s Contrast-Enhanced Ultrasound committee

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What are ultrasound contrast agents?

- encapsulated microbubbles
- diameter 1-10 μm
- surfactant or polymeric shell
- PFC gas
- resonant scatterers
- delivered intravenously
- true “blood pool” agent
- diffuse in blood stream
- filtered by liver

SonoVue, Bracco
Approved ultrasound contrast agents around the world

<table>
<thead>
<tr>
<th>Agent/Manufacturer</th>
<th>Approved indications</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>SonoVue/Lumason/Bracco</td>
<td>LVO – Cardiology Macro and micro vascular imaging – Radiol.</td>
<td>EU, ASIA, <strong>USA!</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU, ASIA, <strong>USA!</strong></td>
</tr>
<tr>
<td>Optison/GE Healthcare</td>
<td>LVO – Cardiology</td>
<td>USA, EU, ASIA</td>
</tr>
<tr>
<td>Definitiy/Lantheus Medical Imaging</td>
<td>LVO – Cardiology Liver, kidney – Radiol.</td>
<td>USA, EU, ASIA A few countries, not EU or USA</td>
</tr>
<tr>
<td>Sonazoid/Daiichi Pharma Co.</td>
<td>Liver, Breast – Radiol.</td>
<td>Japan</td>
</tr>
</tbody>
</table>
Cancer therapy monitoring and evaluation

• Current tumor therapy evaluation relies on RECIST criteria (strictly tumor size)

• New anti-vascular therapies are mainly cytostatic and thus current therapy evaluation criteria are inadequate
  • Tumors responding to therapy may not shrink at first
  • Tumors shrinking in size may not be responding

• CT and MRI may be used for therapy assessment but certain disadvantages exist: ionizing radiation, cost, availability, clinical validation

• CEUS offers an attractive alternative method for tumor response evaluation
  • Blood pool contrast agent (macro- and micro-circulation, perfusion)
  • Harmless, easily available, bedside, quantifiable
Limitations with RECIST* criteria

*Response Evaluation Criteria In Solid Tumors

Pre Avastin (antiangiogenic drug)  
Post Avastin- 3 months

Apparent lesion growth despite other information suggesting tumor response

*Adapted from JAMA (Vauthey, Chun et al. 2009)
Why we need CEUS quantification

Colorectal metastasis before any chemotherapy

**Quantification objective:** Extract important physiologic information from the time evolution of the tumor image intensity during the bolus transit (wash-in/washout)

*Outlined lesion is colorectal metastasis in the liver*
Why we need CEUS quantification

Colorectal metastasis after 3 months of chemotherapy

Quantification objective: Extract important physiologic information from the time evolution of the tumor image intensity during the bolus transit (wash-in/washout)

*Lesion had a dramatic shape change
Description of CEUS quantification technique

- Administer microbubble contrast agent
- Collect a 60 sec video
- Draw ROI on tumor and normal liver and form time-intensity curve
- Curve fit data to perfusion model
- Extract important flow parameters
QIBA: Quantitative Imaging Biomarker Alliance (RSNA)

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

• QIBA Profiles standardize methods to create biomarkers that meet a claimed performance (accurate and reproducible)

• QIBA advances quantitative imaging in clinical trials and clinical practice

• QIBA engages researchers, healthcare professionals and industry
QIBA CEUS (since 2015)

- **Objective**: Standardize vascularity and perfusion-related quantification with CEUS for clinical use and to create an accurate and reproducible imaging biomarker

- CEUS biomarker committee consists of 50+ experts in the field (clinicians, academics, engineers, basic scientists)

- Task forces: Literature review, clinical focus, imaging systems requirements, quantification analysis software, basic science

- **Completed phantom variability study**

How do we analyze and measure a perfusion-related parameter from a CEUS loop with different scanners, different analysis software, at different hospitals, and get the same answer and be able to compare our results?
QIBA CEUS: Decisions so far

• **Bolus kinetics** (wash in--wash out). Infusion with destruction replenishment may be considered at a later stage.

• Clinical application: liver lesions. Other applications to follow, e.g., IBD, kidney, prostate, etc.

• Start with **phantom study** first before moving to clinical study

• Must use **linear** or **linearized data**

• Curve fit **lognormal distribution** model (or LDRW*). Do not consider recirculation.

• Extract the following parameters: **RT, MTT, AUC, PI**

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*Local density random walk*
Evaluation of the Reproducibility of Bolus Transit Quantification With Contrast-Enhanced Ultrasound Across Multiple Scanners and Analysis Software Packages—A QIBA Study

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QIBA-CEUS manuscript in press:
Methods—the QIBA CEUS phantom

- Sonovue/Lumason: 0.2 ml in 19.8 ml saline, inject 2 ml of diluted solution into flow phantom (effort to mimic clinical dose and to be in middle of intensity-concentration linearity range)
- Collect 5 TICs per scanner on a single day (4 scanners used)
- Repeat above procedure on 3 different days (total of N=15 per scanner)
- Keep system parameters constant between trials. Image tube in same orientation and depth every time
Methods—extract TICs from video

Collect 2 minutes image loops of bolus transit

Form time-intensity (TIC) curves from linearized data
Methods—scanner/software combinations

Linearization scheme

Scanner
- Philips iU22
- Philips EPIQ
- GE LOGIQ E9
- Siemens Sequoia

Native linearization:
- QLAB (Philips)
- TIC Analysis (GE)
- CDx (Siemens)

VueBox® (Bracco)

Curve fitting
- Matlab Lognormal
- VueBOX® Lognormal
- Matlab Lognormal

Imaging settings for all the scanners

<table>
<thead>
<tr>
<th></th>
<th>Philips iU22</th>
<th>Philips EPIQ</th>
<th>GE LOGIQ E9</th>
<th>Siemens Acuson Sequoia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical index</td>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>Gain</td>
<td>71%</td>
<td>51%</td>
<td>14</td>
<td>“Low”</td>
</tr>
<tr>
<td>Image depth, cm</td>
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<td>16</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Focal depth, cm</td>
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<td>12.5</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Dynamic range, dB</td>
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<td>62</td>
<td>96 (max)</td>
<td>70 (max)</td>
</tr>
<tr>
<td>Persistence</td>
<td>Off</td>
<td>Off</td>
<td>Frame avg: 0</td>
<td>1 (lowest)</td>
</tr>
<tr>
<td>Frame rate, Hz</td>
<td>9</td>
<td>12</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Imaging mode</td>
<td>CPen</td>
<td>Gen</td>
<td>Res</td>
<td>Not available</td>
</tr>
</tbody>
</table>

5 scans x 3 days=15 scans
Produce 3 fitted curves per scan
Total: 45 samples per scanner
Results (sample TIC’s)

- Substantially similar curves are produced from all scanners.
- Arbitrary amplitude calibration among vendors produces different intensity values—current challenge.
- Lognormal distribution produces curves well fitted to the data.
- We use fitted curves to extract the important perfusion-related parameters.
Results (variability single system)

Use a single scanner and different analysis software to extract parameters

- Low variability for time parameters (RT and MTT)
- Amplitude parameters are more variable (higher COV)
- We cannot compare amplitude parameters across different analysis software

Scanner: Philips EPIQ
Results (variability across systems)

Use a multiple scanners and a single analysis software to extract parameters

- We can only compare time parameters when using multiple scanners
- Low variability for time parameters (RT and MTT)

Analysis s/w and curve fitting: VueBox
Results (overall summary)

RT and MTT: 10-20% variability
PI and AUC: 50% variability
Conclusion (QIBA CEUS phantom study)

• An imaging and quantification protocol was established for the accurate measurement of bolus transit parameters

• We have identified RT, MTT, PI, and AUC as the primary bolus transit parameters and the lognormal distribution as the standard model for fitting the TIC

• From repeated trials and while using a single scanner and analysis software, the variability (COV) for RT was less than 8%, for MTT less than 12%, for PI less than 49%, and for AUC less than 50%

• The variability of the time parameters (RT and MTT) slightly increases when comparing values calculated from 4 different scanners and 3 analysis software

• At the present time, it is not possible to compare amplitude values from different scanners and analysis software packages because of the arbitrary linearization algorithm used among vendors

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