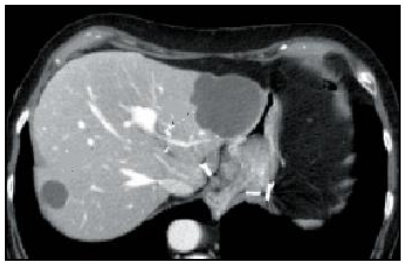
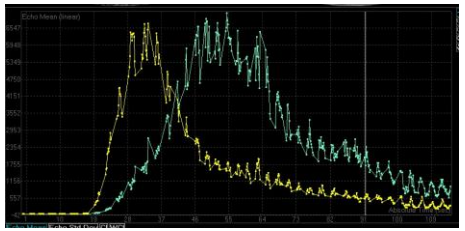
Achievements, challenges, and present status of QIBA's Contrast-Enhanced Ultrasound committee

Mike Averkiou, PhD

University of Washington, Bioengineering

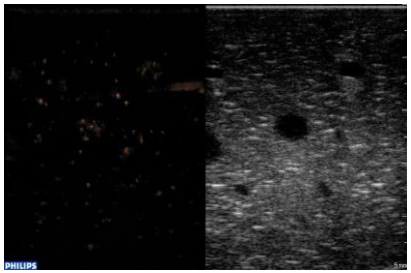
Seattle, WA





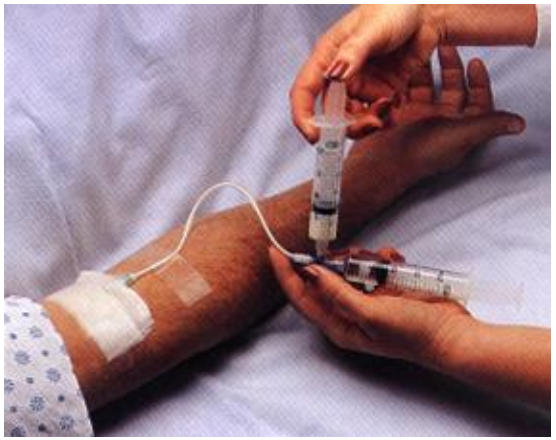
AAPM/COMP Meeting

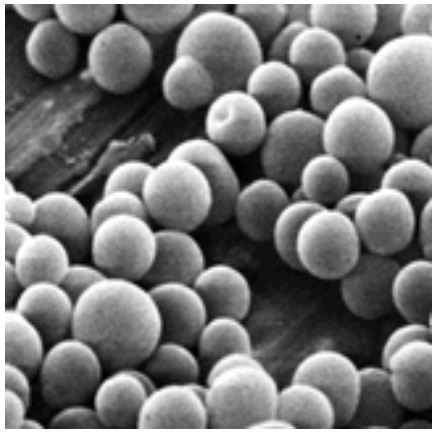
July 14, 2020

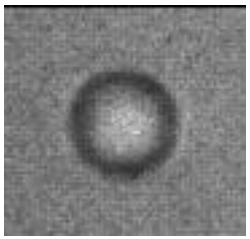


What are ultrasound contrast agents?

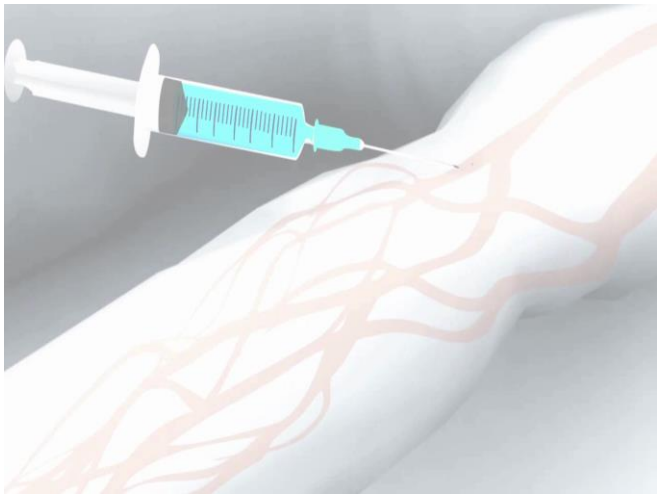
SonoVue, Bracco







- 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



Approved ultrasound contrast agents around the world

Agent/ Manufacturer	Approved indications	Countries
SonoVue/Lumason/ Bracco	LVO – Cardiology Macro and micro vascular imaging – Radiol.	EU, ASIA, **USA!** EU, ASIA, **USA!**
Optison/ GE Healthcare	LVO – Cardiology	USA, EU, ASIA
Definitiy/ Lantheus Medical Imaging	LVO – Cardiology Liver, kidney – Radiol.	USA, EU, ASIA A few countries, not EU or USA
Sonazoid/ Daiichi Pharma Co.	Liver, Breast – Radiol.	Japan

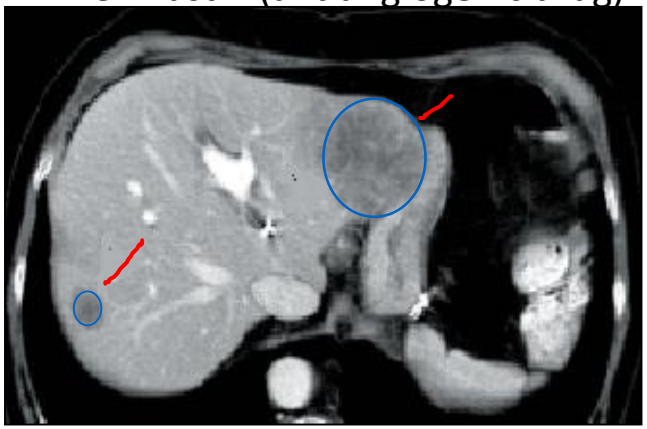
Cancer therapy monitoring and evaluation

- 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

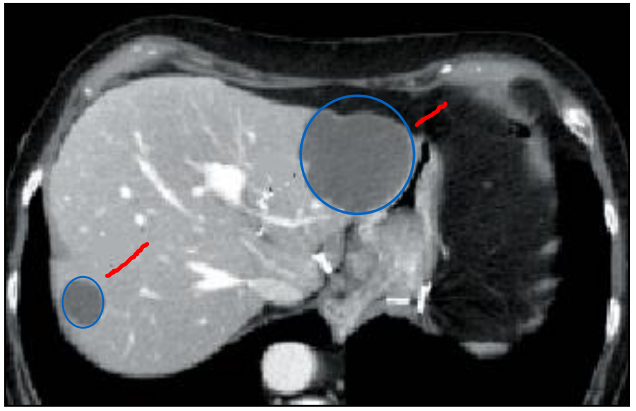
Limitations with RECIST* criteria

*Response Evaluation Criteria In Solid Tumors

Pre Avastin (antiangiogenic drug)



Post Avastin- 3 months

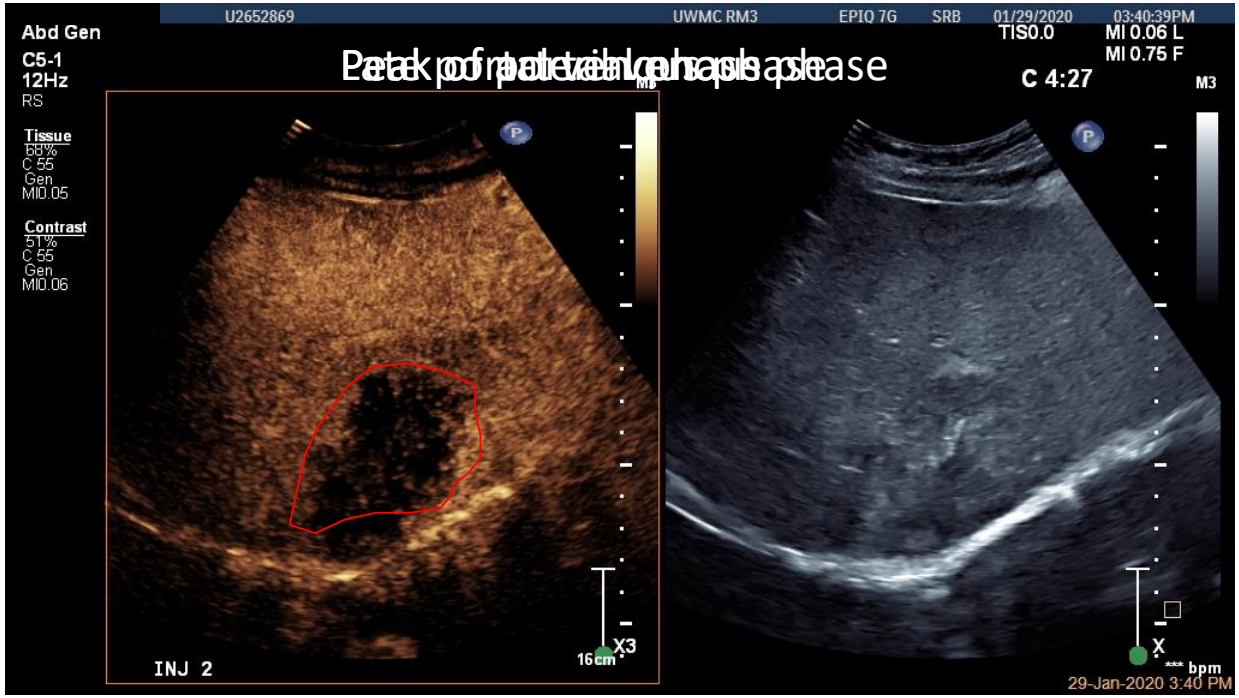


Apparent lesion growth despite other information suggestion tumor response

*Adapted from JAMA (Vauthey, Chun et al. 2009)

Why we need CEUS quantification

Colorectal metastasis before any chemotherapy

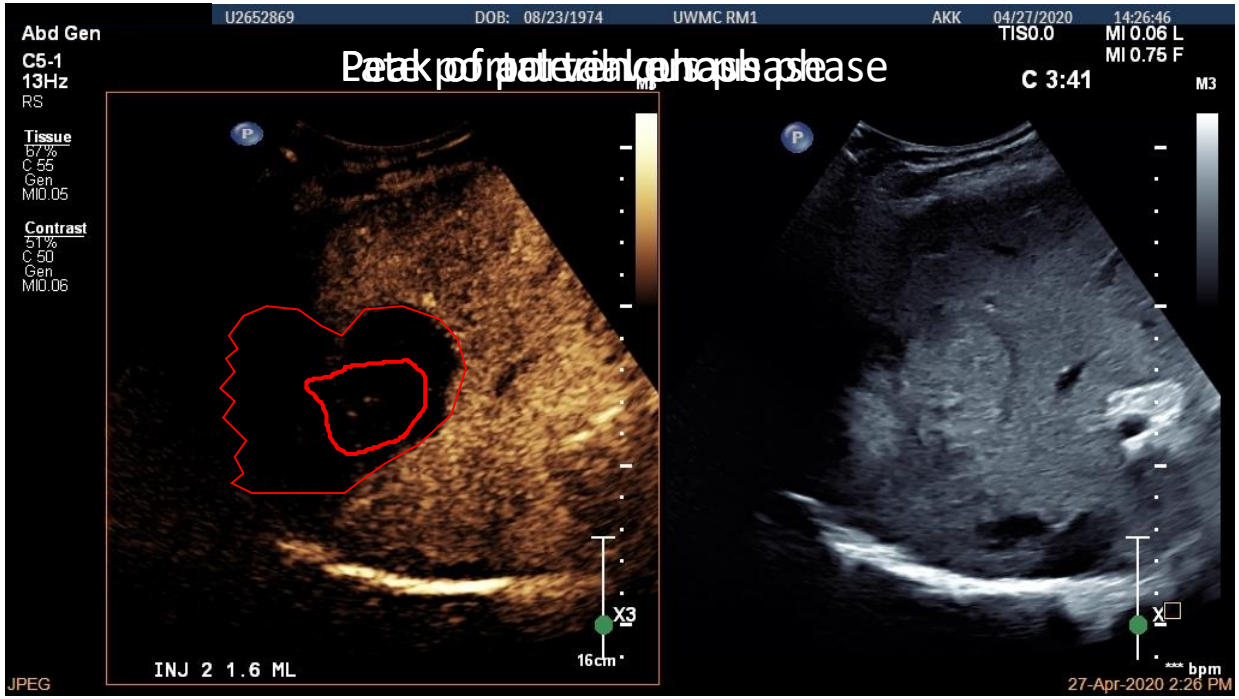


Quantification objective: Extract important physiologic information from the time evolution of the tumor image intensity during the bolus transit (wash-in/washout)

*Outlined lesion is colorectal metastasis in the liver

Why we need CEUS quantification

Colorectal metastasis after 3 months of chemotherapy

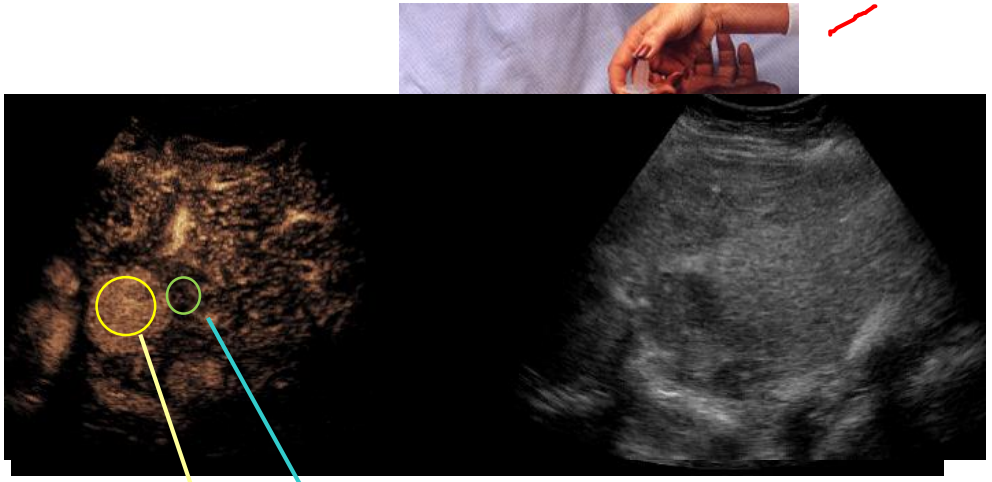


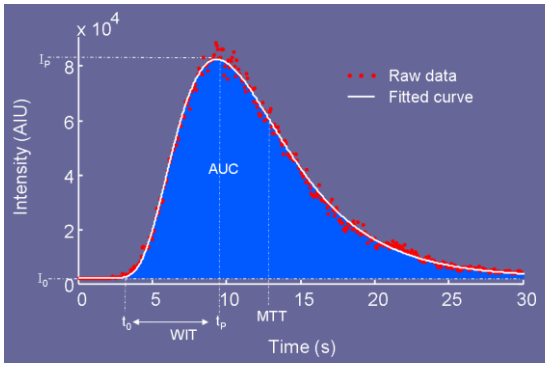
Quantification objective: Extract important physiologic information from the time evolution of the tumor image intensity during the bolus transit (wash-in/washout)

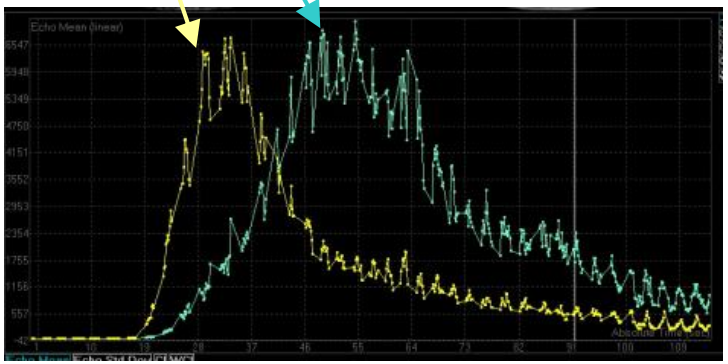
*Lesion had a dramatic shape change

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







Dietrich CF, Averkiou MA, et al., *Ultraschall Med.*, 33(4), 2012

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
- https://qibawiki.rsna.org/index.php/Ultrasound_CEUS_BC

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

*Local density random walk

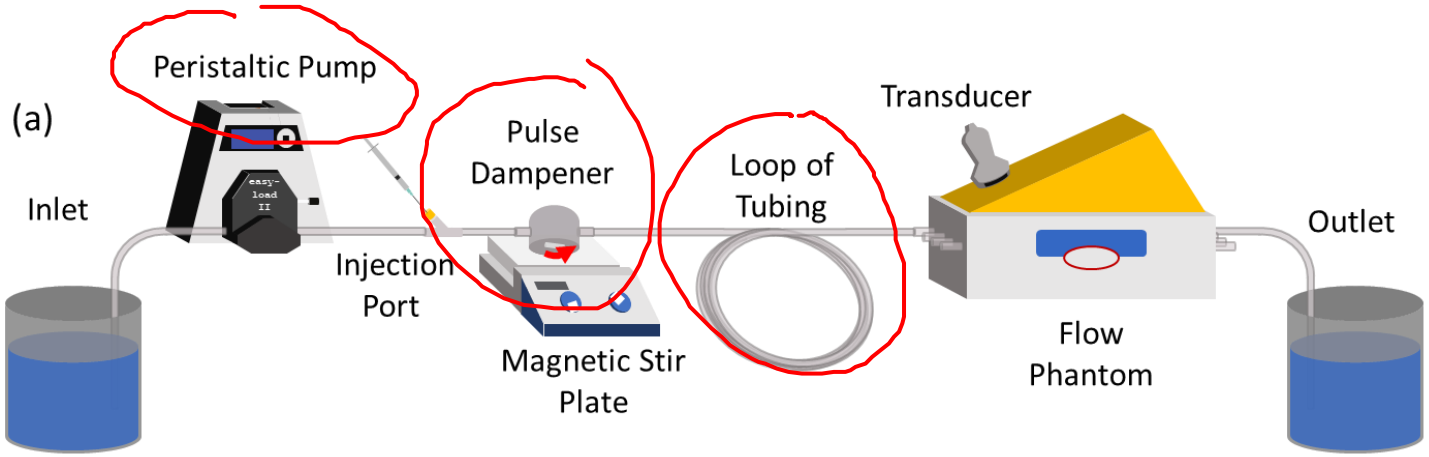
QIBA-CEUS manuscript in press:

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

Michalakis A. Averkiou, PhD,* Eric K. Juang, MSc,* Madison K. Gallagher, BS,* Maria Alejandra Cuevas, BS,* Stephanie R. Wilson, MD,† Richard Barr, MD,‡ and Paul L. Carson, PhD§

Investigative Radiology • Volume 55, Number 10, October 2020

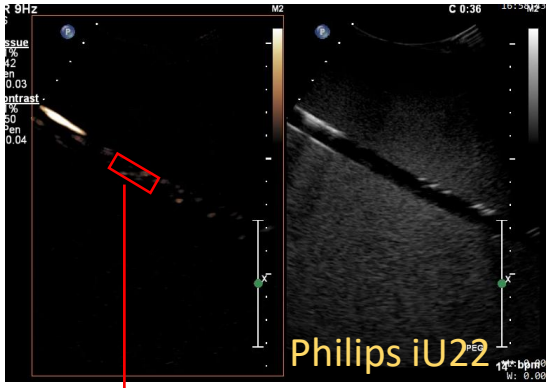
Methods—the QIBA CEUS phantom

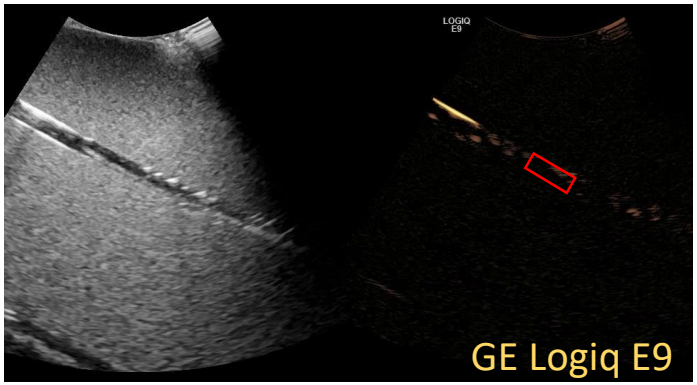


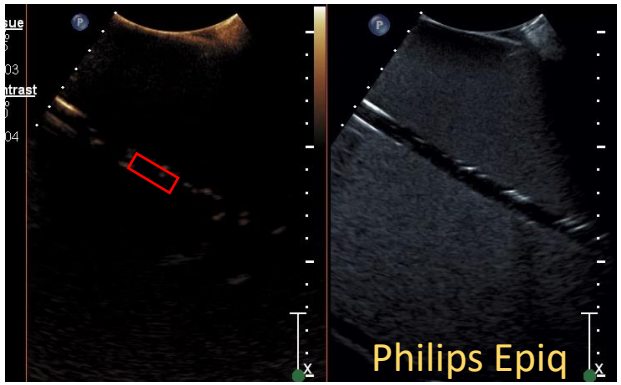
- Sonovue/Lumason: 0.2 ml in 19.8 ml saline, inject 2 ml of diluted solution into flow phantom (effort to mimic clinical dose and to be in middle of intensity-concentration linearity range)
- Collect 5 TICs per scanner on a single day (4 scanners used)
- Repeat above procedure on 3 different days (total 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

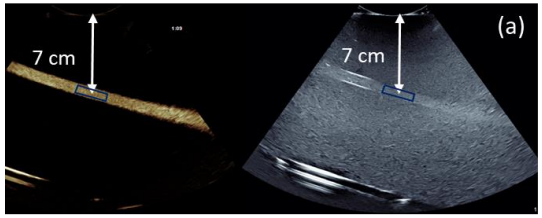
Collect 2 minutes image loops of bolus transit

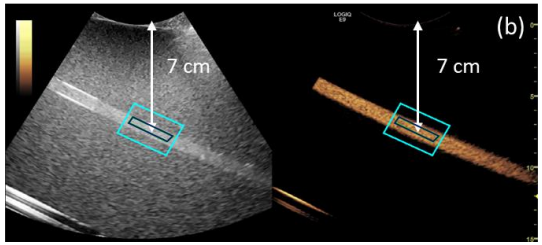


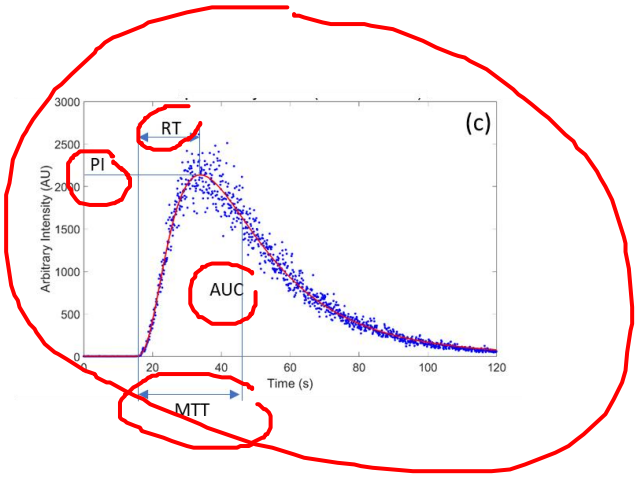




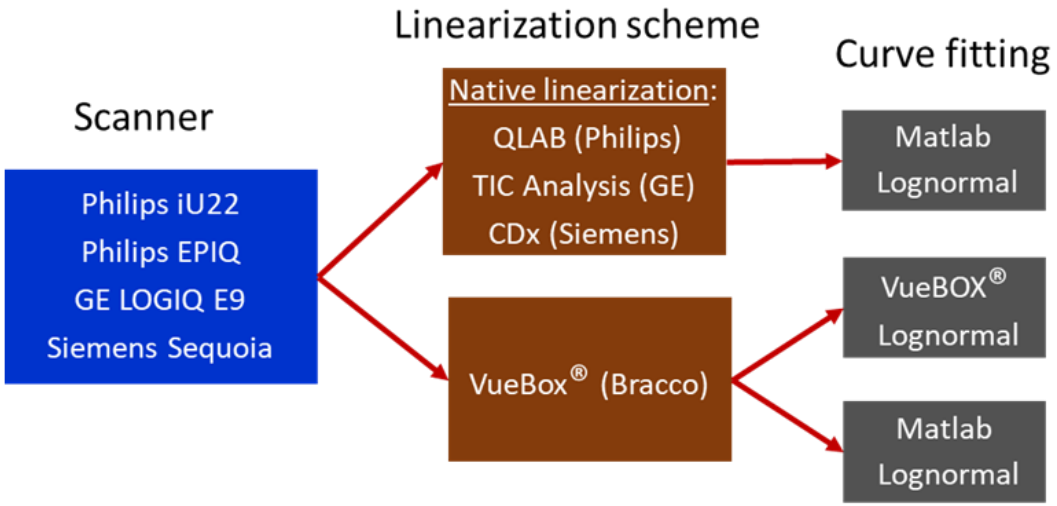
Form time-intensity (TIC) curves from linearized data







Methods– scanner/software combinations

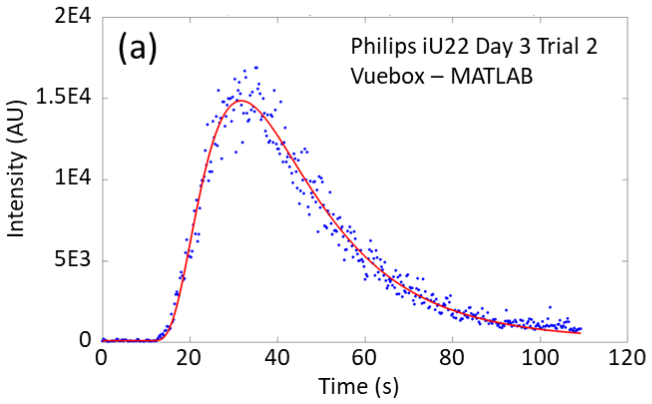


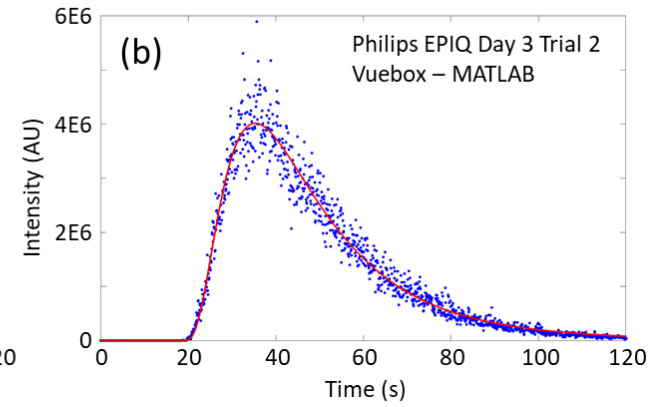
5 scans x 3 days=15 scans
Produce 3 fitted curves per scan
Total: 45 samples per scanner

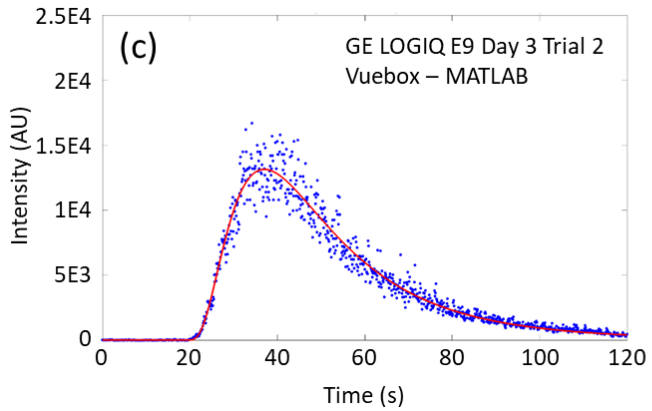
Imaging settings for all the scanners

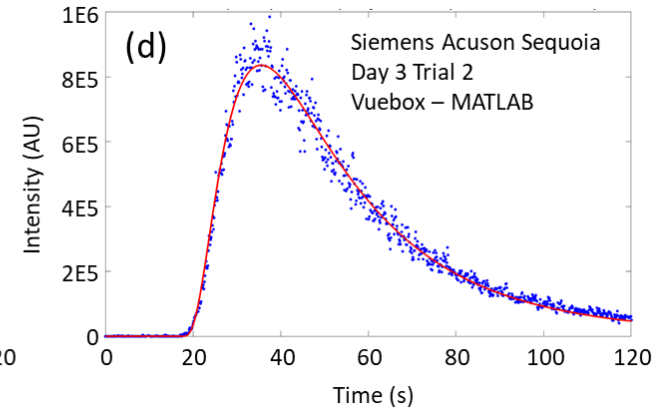
	Philips iU22	Philips EPIQ	GE LOGIQ E9	Siemens Acuson Sequoia
Mechanical index	0.04	0.05	0.06	0.08
Gain	71%	51%	14	"Low"
Image depth, cm	14	16	15	16
Focal depth, cm	10.5	12.5	12	12
Dynamic range, dB	50	62	96 (max)	70 (max)
Persistence	Off	Off	Frame avg: 0	1 (lowest)
Frame rate, Hz	9	12	9	8
Imaging mode	CPen	Gen	Res	Not available

Results (sample TIC's)





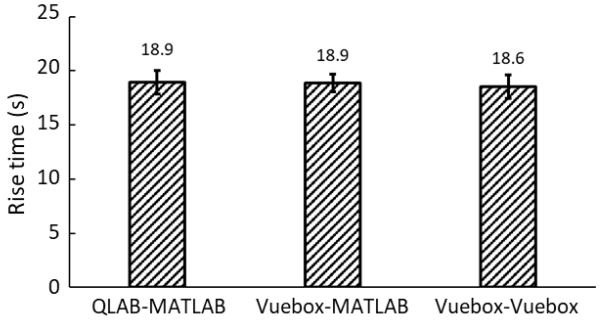


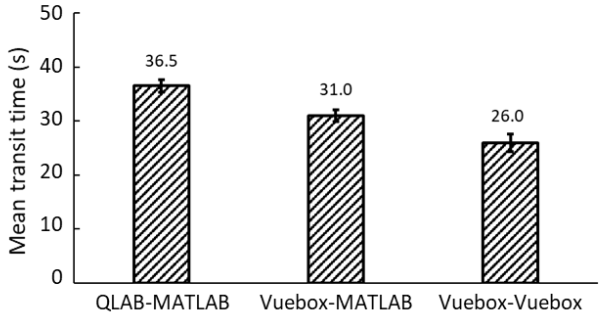


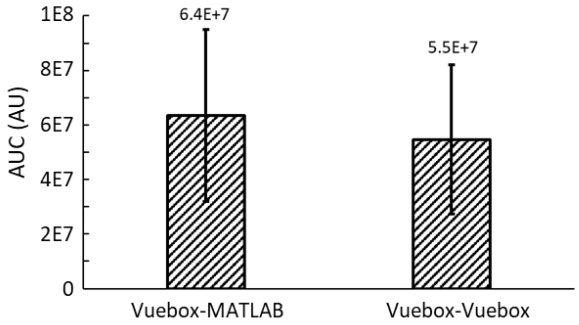
- Substantially similar curves are produced from all scanners
- Arbitrary amplitude calibration among vendors produces different intensity values—current challenge
- Lognormal distribution produces curves well fitted to the data
- We use fitted curves to extract the important perfusion-related parameters

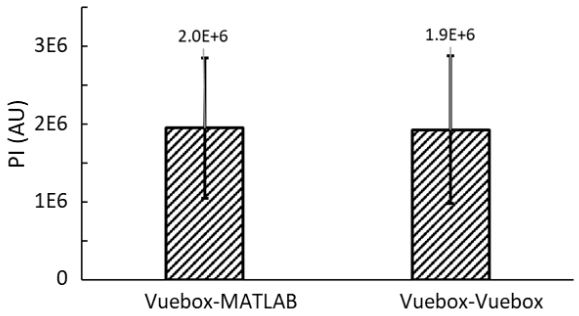
Results (variability single system)

Use a single scanner and different analysis software to extract parameters







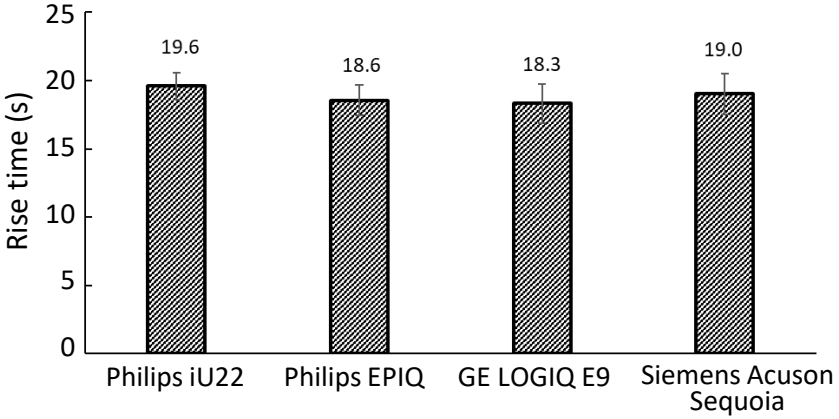


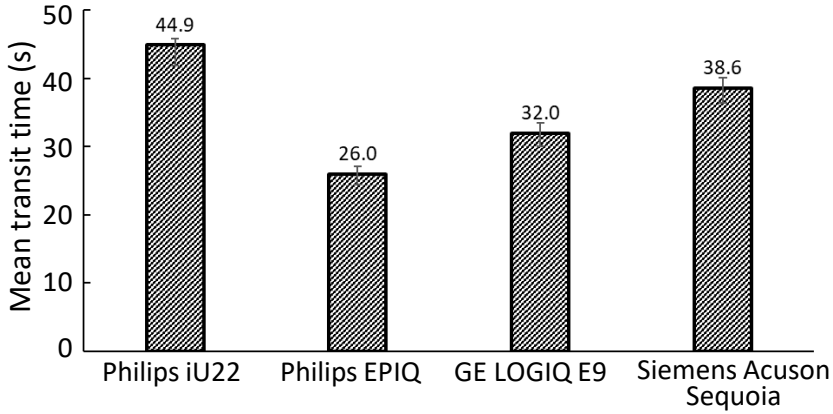
- Low variability for time parameters (RT and MTT)
- Amplitude parameters are more variable (higher COV)
- We cannot compare amplitude parameters across different analysis software

Scanner: Philips EPIQ

Results (variability across systems)

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

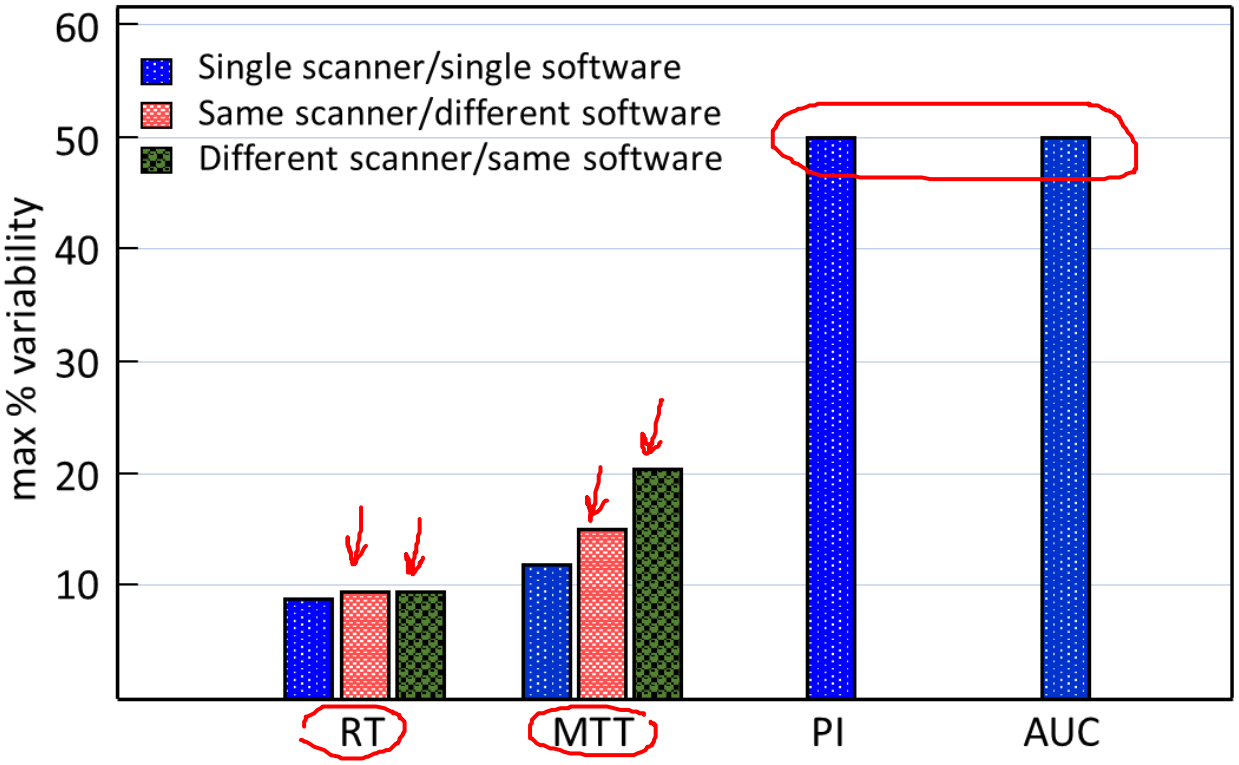




- We can only compare time parameters when using multiple scanners
- Low variability for time parameters (RT and MTT)

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

Acknowledgements: RSNA/QIBA, all QIBA CEUS committee members, Bracco, GE, Philips, Siemens, Canon