QIBA US Biomarker Committee: Overview and Status Update - *Ultrasound Volume Blood Flow Biomarker*

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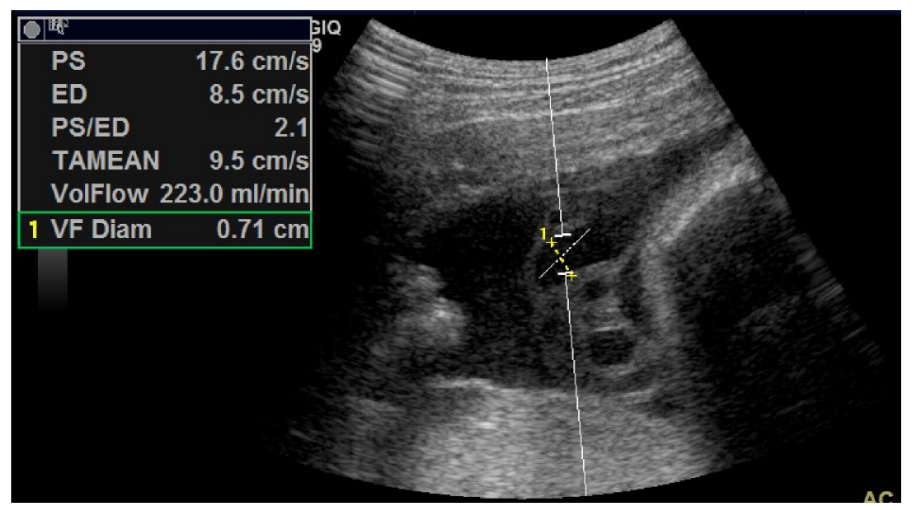
Significance

Clinical Need for Flow Quantification

- In many clinical practices, ultrasound scans commonly consist of some blood flow imaging component (i.e., pulsed wave, color flow, or power mode) that is typically used to simply indicate the presence or absence of flow
- Approximately 20% of ultrasound scans employ some degree of blood flow measurement and quantification
- In the United States, there are about 200,000 ultrasound machines (2014 Klein Report), that yield a total of approximately 136 million exams (2013 Klein Report), and thus about **27 million** ultrasound scans per year where true flow measurement is potentially of interest
- Most flow measures are heuristic and qualitative, semi-quantitative or just inaccurate, which indicates a need for a **robust quantitative volume flow biomarker**

1D/2D Volume Flow Technique

- 1D flow velocity measurement based on range gate position in a 2D image
- Current volume flow is computed based on **several assumptions**
  a. accurate user knowledge and selection of beam-to-flow angle
  b. accurate user knowledge and measurement of vessel diameter
  c. cylindrically symmetric flow velocity profile
  d. circular vessel cross section



Pulsed wave 1D/2D volume flow measurement in the umbilical vein

Clinical Limitations

- Current 1D/2D volume flow technique is user dependent and is associated with poor accuracy and a time-consuming acquisition
- Time-dependent volume flow is not measured
- Turbulence or curved vessels prohibit meaningful volume flow estimation
- Dynamic changes in cross-sectional area influence volume flow estimation

Profile and Protocol Committee

Objective: Create profile and protocol standard for 3D volume flow biomarker
Members: P. L. Carson, V. Devaraju, J. B. Fowlkes, M. Lockhart, R. Managuli, J. M. Rubin

Phantom Committee

Objective: Design and produce prototype phantom for round-robin study
Members: C. X. Baiu, V. Devaraju, D. Dubberstein, J. B. Fowlkes, O. D. Kripfgans, T. Lynch, S. Z. Pinter, J. M. Rubin, R. Tadross, M. Trew

Approach

3D Volume Flow Technique

- The volume flow biomarker measures blood volume per unit time (milliliters per minute), commonly confused with blood flow velocity (centimeters per second)
- The general principle of the technique is measurement of blood volume flowing through a surface intersecting the vessel

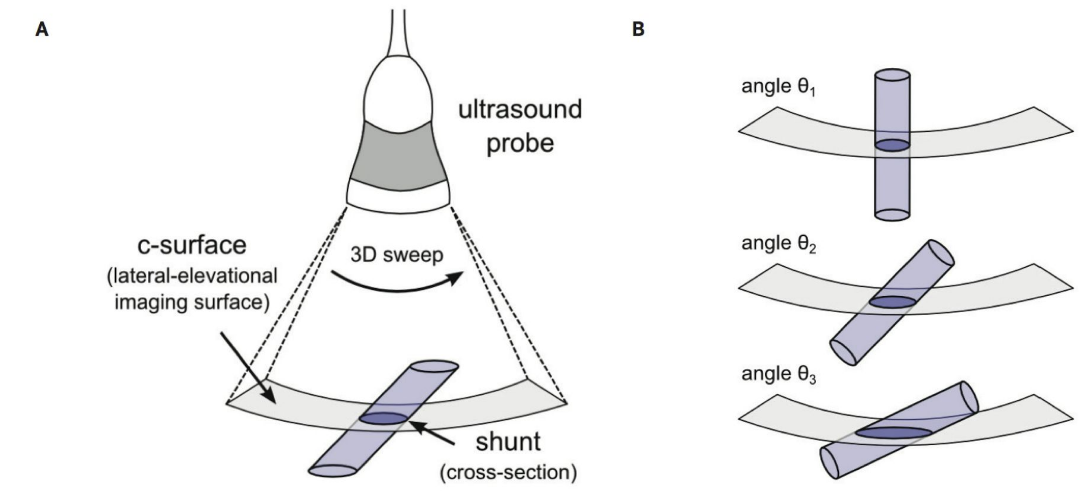
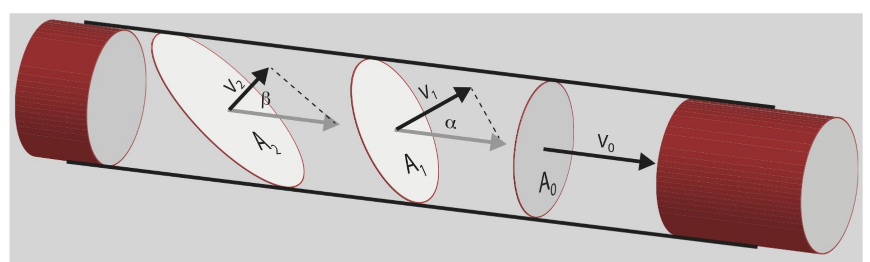
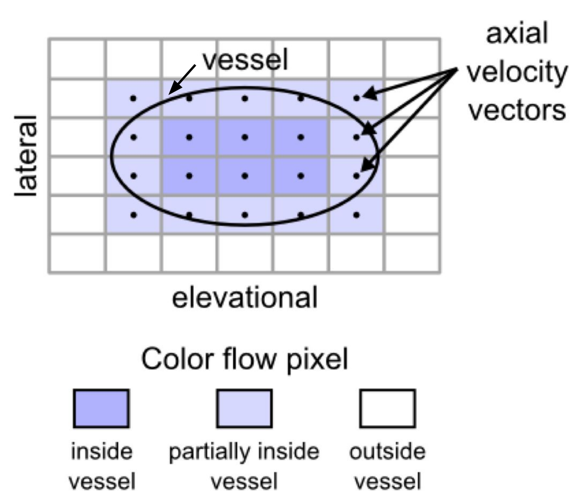


Illustration of (A) imaging geometry required for 3D volume flow measurement. Probe is oriented such that the lumen intersects the c-surface (lateral-elevational surface) in cross section. (B) Angle of c-surface intersection is an independent variable such that circular (θ_1) and ellipsoidal (θ_2 and θ_3) geometries all yield identical volume flow estimates without the need for any angle correction.



3D volume flow (Q) is computed by multiplying blood flow velocity (v_n), as measured by color flow, by the surface area of the intersected lumen (A_n). Given that $Q = A_0 \times v_0 = A_1 \times v_1 = A_2 \times v_2$, 3D volume flow is independent of angle. Specifically, $A_n = A_0 / \cos(\alpha_n)$ and $v_n = v_0 \times \cos(\alpha_n)$, therefore, the cosine factor cancels when A is multiplied by v.



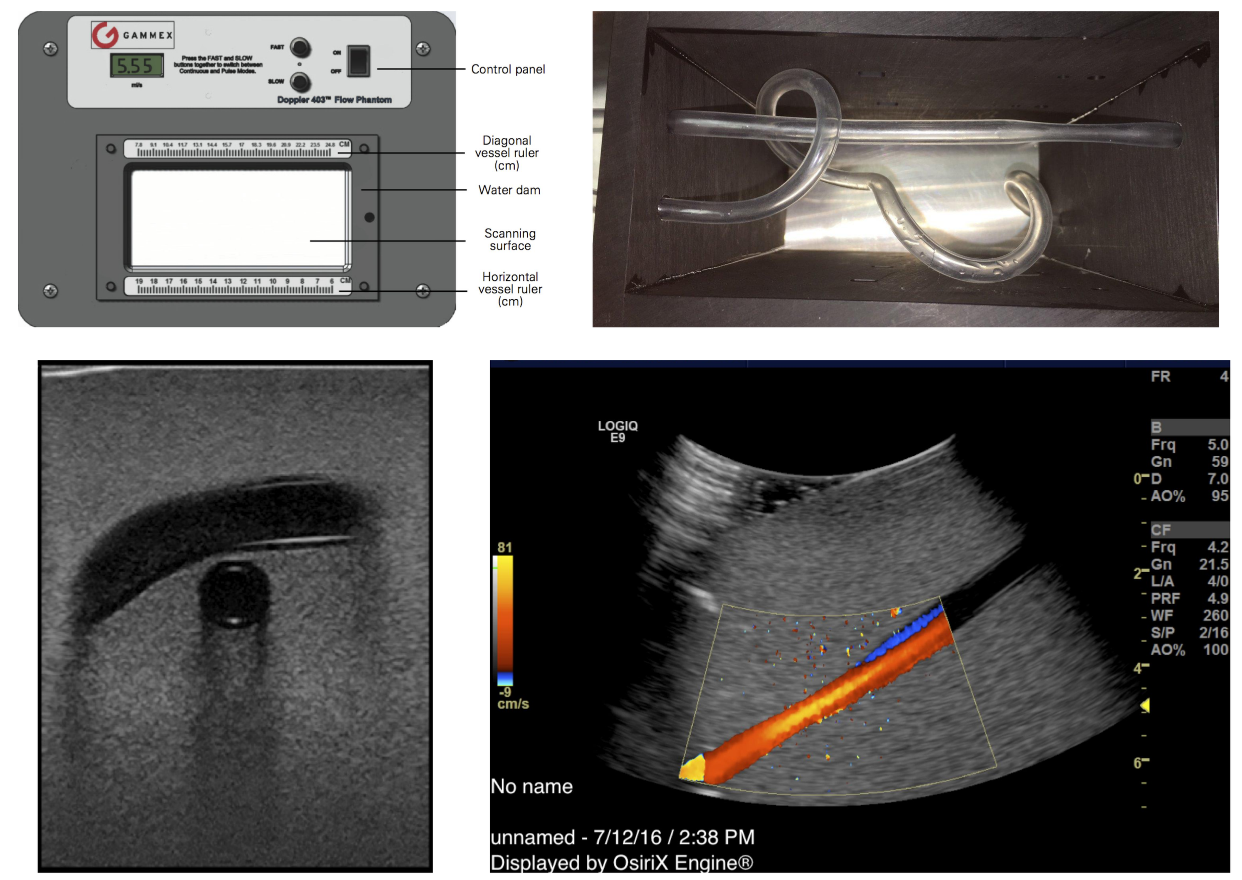
Partial volume effect in 3D volume flow measurement. Three types of color flow pixels exist. Color flow pixels inside the vessel correspond to 100% blood, those outside the vessel correspond to 0% blood, and those partially inside the vessel correspond to values between 0% and 100% blood. Color flow power is directly proportional to the amount of blood in each voxel and can therefore be used to correct the partial volume effect.

$$Q = \sum_{i \in S} v_i \cdot (A_i \times w_i)$$

Gauss' Theorem states that volume flow (Q) can be obtained by integrating the product $A_i \times v_i$ over the surface area (S), i.e., the c-surface. Power mode data is used to weight each area (A_i) in order to correct for partial volume effects.

Current and Planned Efforts

Flow Phantom Design and Prototype



Prototype phantom for 3D volume flow assessment in realistic *in situ* conditions, i.e., curved and stenotic tubing sections. Nominal lumen diameter is 5 mm, flow rates can range from 1.0 to 12.5 mL/s, and the stenotic section consists of a 40% reduction (5 to 3 mm). The final phantom design will enable imaging both pre and post stenosis. Sections of tortuous tubing will extend from 0.7 mm below the scanning surface to as deep as 10 cm. Some sections of curved tubing are intentionally designed with a non-circular cross-section. Phantom produced by Gammex.

Flow Phantom Round-Robin Evaluation

Performance Sites and Ultrasound Systems

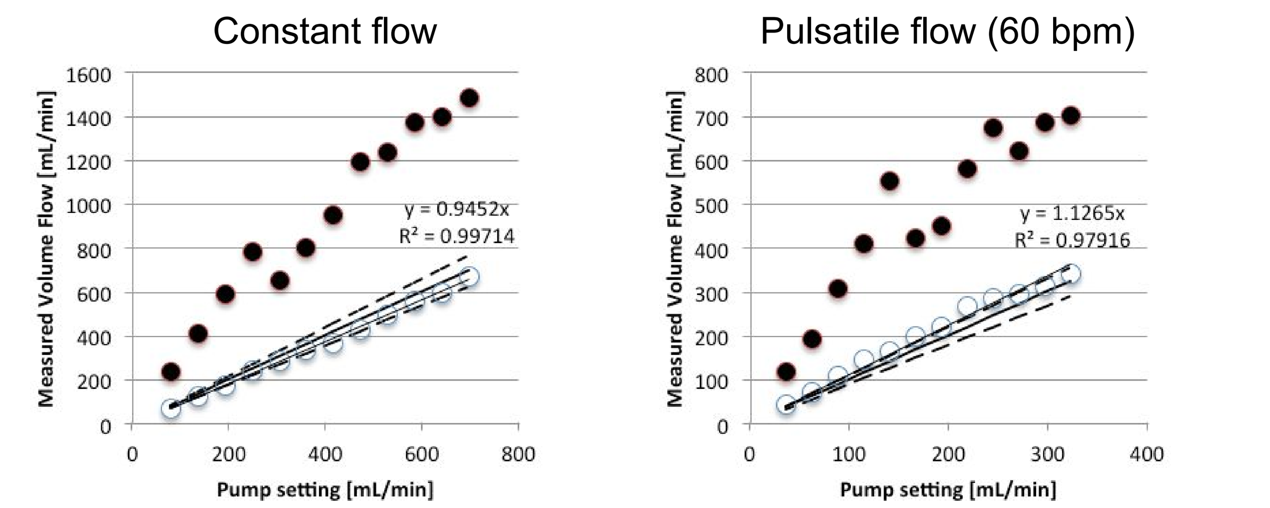
Cornell University (Siemens) • Harvard Medical School (Siemens) • Mayo Clinic (GE) • MIT (GE) • University of Alabama at Birmingham (Philips) • University of Michigan (GE, Philips, and Siemens) • University of Washington (Philips) • University of Wisconsin (Siemens) • Hitachi Aloka Medical America (Hitachi) • Toshiba America Medical Systems (Toshiba)

Protocol and Data

- Provide sites with minimal and uniform guidelines for baseline system setup, but allow adequate user discovery for vessel positioning and for setting parameters such as color/power gain, pulse repetition frequency, and wall filter
- Collect data for the identification and assessment of bias and inter- and intra-observer variability (reproducibility and repeatability) across operators, systems, and centers

Studies

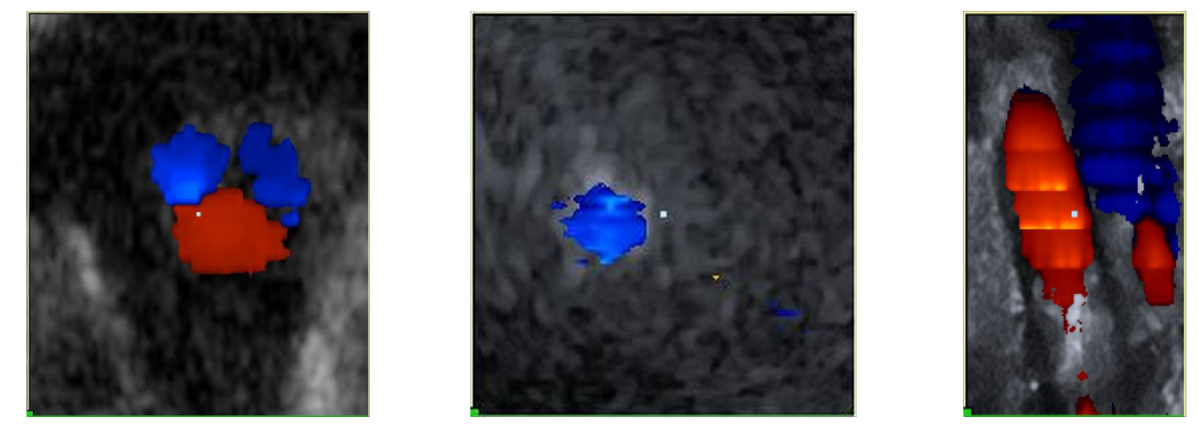
Phantom Studies with 3D Volume Flow



Phantom study results for 78 to 696 mL/min (left) and 43 to 341 mL/min (right) show partial volume corrected (○) and not partial volume corrected (●) data. The thin solid line is the linear regression fit and the thick solid line represents true flow with ±10% intervals (dashed lines). Nominal lumen diameter is 5 mm.

Clinical Studies with 3D Volume Flow

- Several clinical studies have demonstrated the feasibility and widespread applicability of the approach (see figures below)
- A straightforward reference standard is unavailable, except for MRI, which is costly, impractical (pregnancy), or presents artifacts (TIPS)



Umbilical cord (c surface) | TIPS (c surface) | CCA (c surface)

Clinical Verification of QIBA Study

- Volume flow biomarker will be assessed in renal transplant cases, with the intention of rapid extension to several applications that involve large vessels
- Renal transplant cases enable the direct validation of blood volume flow measurements during transplant surgery using a cuff-type flow probe

Participating Laboratories

[3]University of Washington, [4]University of Michigan, [5]Korea Research Institute of Standards and Science, [6]Hammersmith Hospital, [7]University of Mississippi, [9]Weill Cornell University, [10]University of Wisconsin, [11]University of São Paulo, [13]University of Alabama at Birmingham, [17]Harvard Medical School, [18]Mayo Clinic, [20]Food and Drug Administration, [21]Taipei Veterans General

Participating Vendors

[1]Toshiba America Medical Systems, [2]Gammex, [8]GE Healthcare, [12]Philips Healthcare, [14]CIRS, [15]Hitachi Aloka Medical America, [16]Siemens Healthcare, [19]Pfizer Inc.