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

Kazuya Akaki[1], Cristel X. Baiu[2], Matt Bruce[3], Paul L. Carson[4], H. M. Cho[5], David O. Cosgrove[6], Vadivel Devaraju[7], Dave Dubberstein[8], Todd Erpelding[1], **J. Brian Fowlkes[4] (co-chair)**, Jing Gao[9], Anne Hall, Timothy Hall[10], Mauro Hanaoka[11], **James Jago[12] (co-chair)**, **Oliver D. Kripfgans[4] (co-chair)**, Ron Leichner[12], Mark Lockhart[13], Ted Lynch[14], Ravi Managuli[15], Andy Milkowski[16], Stephen Z. Pinter[4], Michelle Robbin[13], Jonathan M. Rubin[4], Anthony Samir[17], Chen Shigao[18], Randall Sung[4], Rimon Tadross[8], Kai Thomenius, Marijean Trew[2], Theresa Tuthill[19], Keith Wear[20], Yi Hong Chou[21], James A. Zagzebski[3] - Affiliations shown below
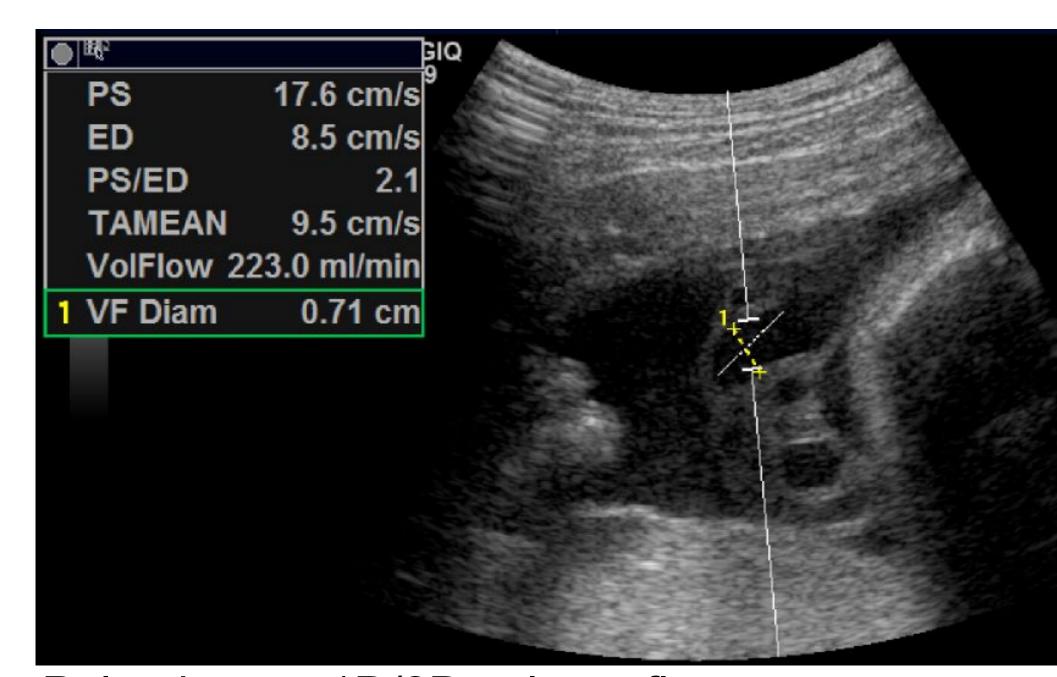
Significance

Clinical Need for Flow Quantification

- In many clinical practices, ultrasound scans commonly include a blood flow imaging component (*i.e.*, pulsed wave, color- or power mode Doppler) that is typically used to 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 exist approximately 200,000 ultrasound machines (2014 Klein Report), that yield 136 million exams (2013 Klein Report), and thus annually 27 million ultrasound scans, where true flow measurements are potentially of interest.
- Most flow measures are heuristic and qualitative, semi-quantitative or just inaccurate, which indicates a need for a robust quantitative 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

Anatomically configured flow phantom

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

Performance Sites

Mayo Clinic • MIT • University of Alabama at Birmingham • University of Michigan • University of Washington • University of Wisconsin • Hitachi Healthcare Americas • Canon Medical Systems USA

Participating Laboratories and Vendors

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

Approach
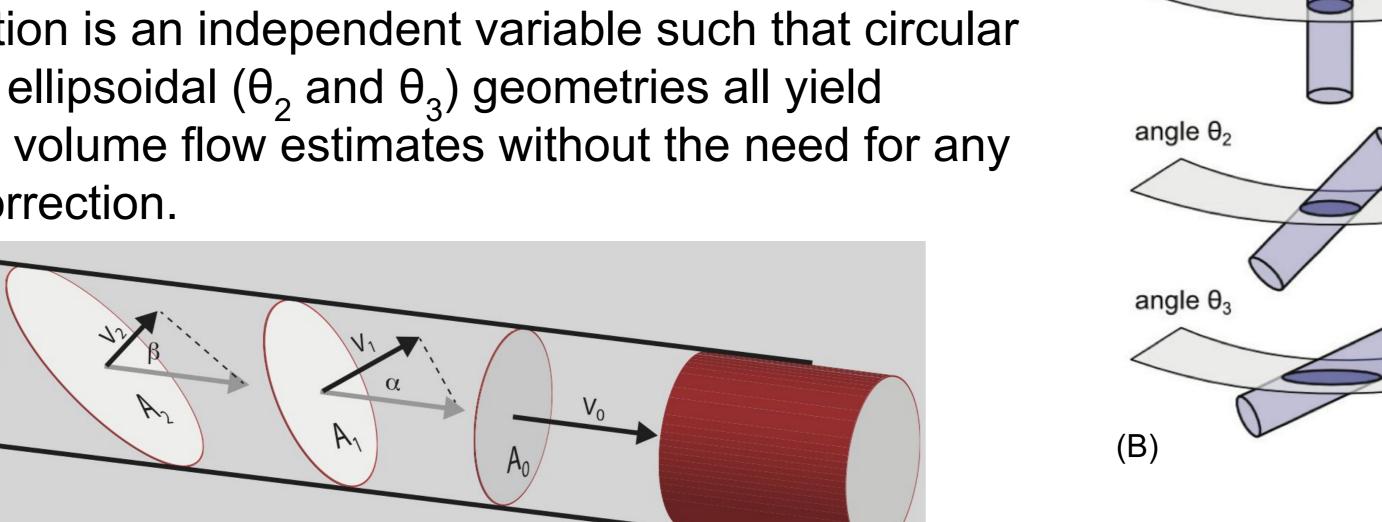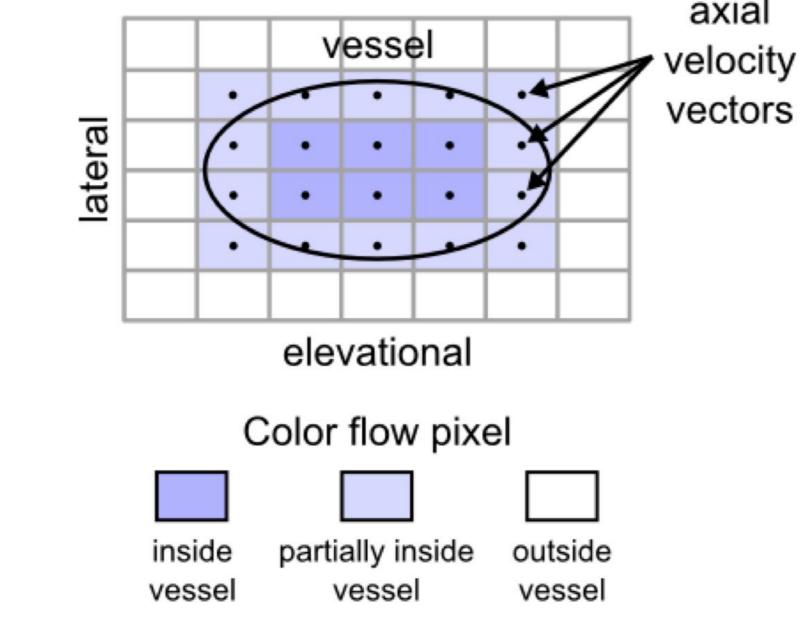
3D Volume Flow Technique

- The volume flow biomarker measures blood volume flow rate (mL/min), in vessels with no need to make assumptions about the vessel cross sectional shape.
- The general principle of the technique is that the flow can be computed by multiplying blood velocity components along all US beams by local increments of the vessel cross-sectional area as "seen" from the transducer surface. These values are summed over a surface intersecting the vessel.
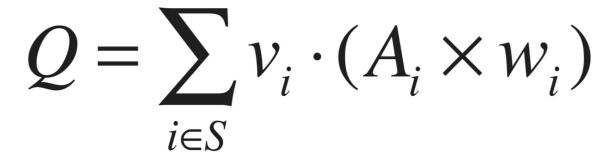
Illustration of (A) imaging geometry required for 3D volume flow measurement. Probe is oriented such that the lumen intersects the c-surface (lateral-elevational surface) in cross section. (B) Angle of c-surface intersection is an independent variable such that circular (θ_1) and ellipsoidal (θ_2 and 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.

Color flow pixel
inside vessel | partially inside vessel | outside vessel

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

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.

Protocol and Data

- Provide sites with minimal and uniform guidelines for system setup and allow for adequate user vessel positioning and parameter selection (gain, PRF, WF).
- Collect data for the identification and assessment of bias and inter- and intra-observer variability (reproducibility and repeatability) across operators, systems, and centers.

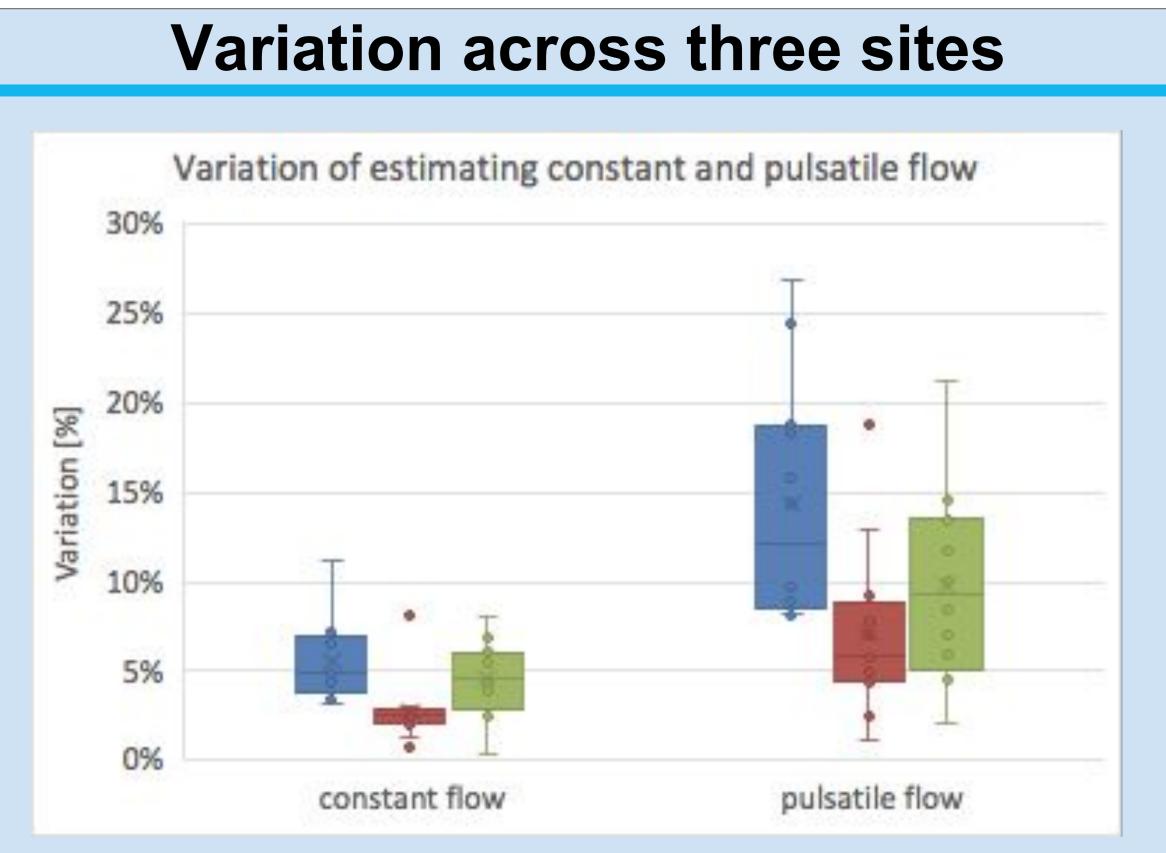## Update on Multi-Site Testing Results and Discussion
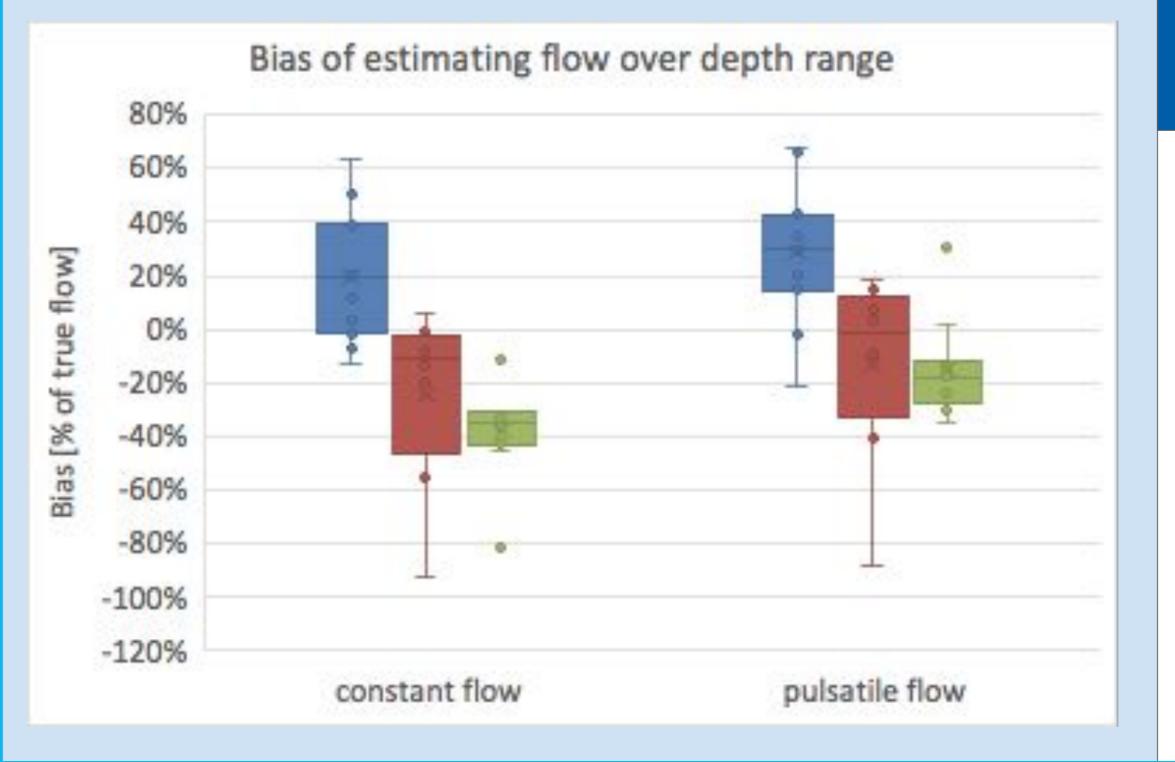
Multi-Site Flow Phantom Evaluation

A prototype phantom was used for 3D volume flow assessment in realistic *in situ* conditions, with curved, stenotic and non-circular tubing sections (see photo of phantom in first figure). Nominal lumen diameter is 5 mm, flow rates range from 30 to 750 mL/min (12 steps), depth range 2.5 to 7.5 cm (11 steps) and flow condition (constant and pulsatile, 60 bpm). The phantom was tested at three sites for each of the three enrolled systems.

Bias across three sites

Variation across three sites
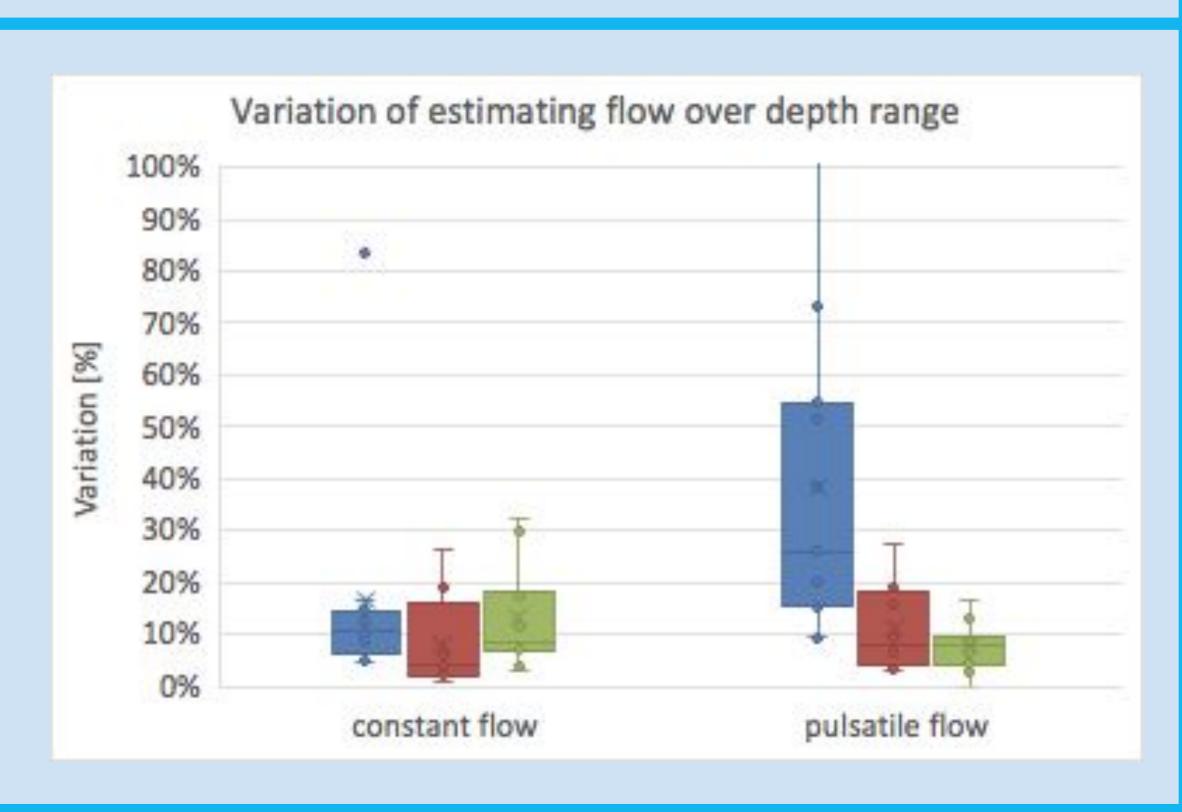
Flow Dependence

Underline: Left: Bias in the measurement of a flow range between sites. Each color represents one system. Pulsatile flow covers a larger range in bias than constant flow, which is likely due to algorithmic instabilities during diastole, which we seek to address in the future. For each system and flow condition a box plot is shown with error bars, mean ('x') and 25-75% range (boxes). Right: Variation between sites for each of the 12 flow rates.
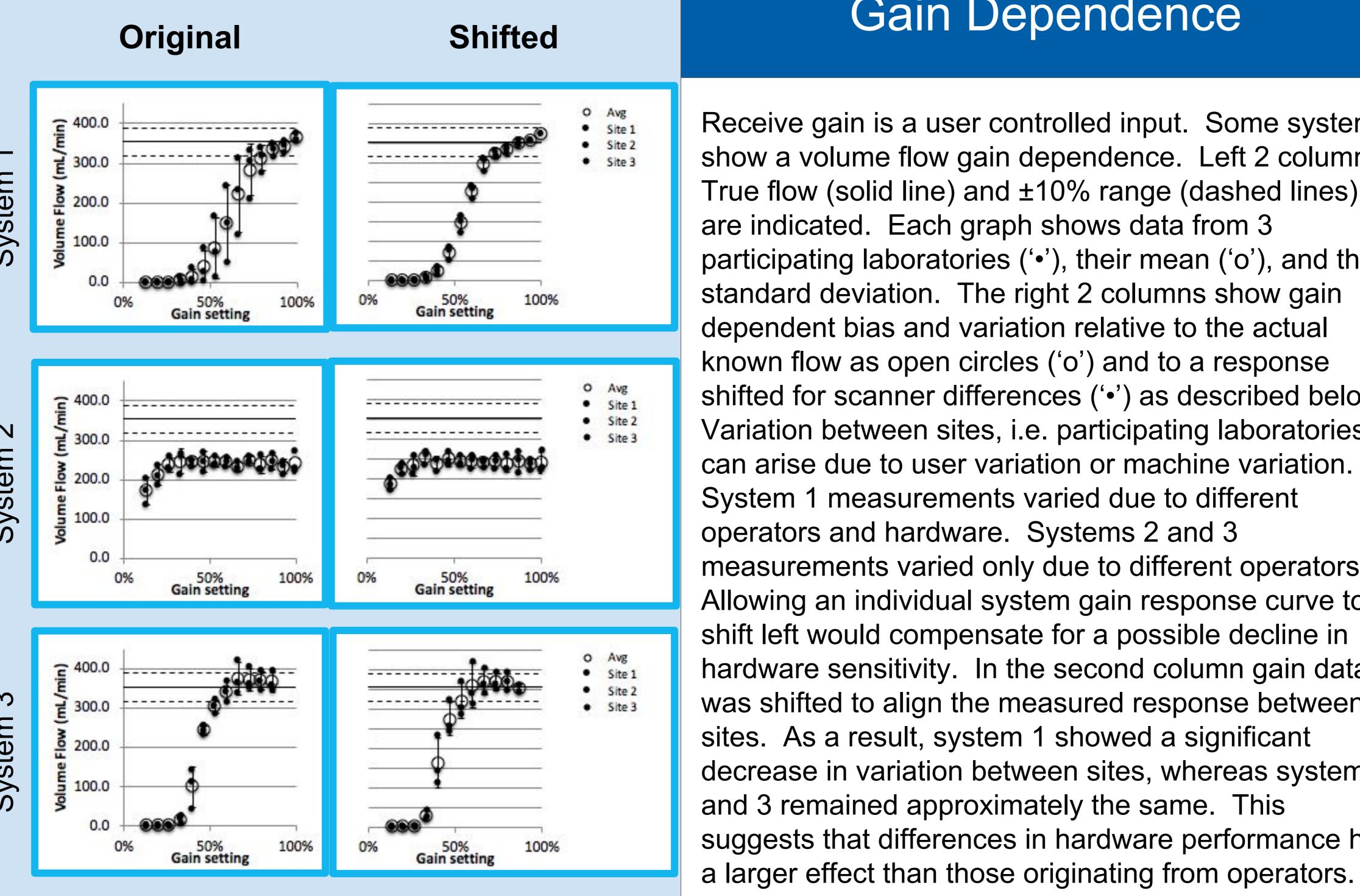
Depth Dependence

Left: Bias in the measurement of volume flow as a function of depth (range 2.5 to 7.5 cm). Each color represents one system. Constant and pulsatile flow cover similar ranges in bias. Although the green system has a comparatively tighter spread over depth, it shows a larger overall bias. Right: Variation is mostly between 10 and 20% except for outliers which may be subsequently removed as outside the operating range for a given imaging probe, i.e. large depth for a high frequency array.

Gain Dependence

Receive gain is a user controlled input. Some systems show a volume flow gain dependence. Left 2 columns: True flow (solid line) and ±10% range (dashed lines) are indicated. Each graph shows data from 3 participating laboratories ('•'), their mean ('o'), and their standard deviation. The right 2 columns show gain dependent bias and variation relative to the actual known flow as open circles ('o') and to a response shifted for scanner differences ('•') as described below. Variation between sites, i.e. participating laboratories, can arise due to user variation or machine variation. System 1 measurements varied due to different operators and hardware. Systems 2 and 3 measurements varied only due to different operators. Allowing an individual system gain response curve to shift left would compensate for a possible decline in hardware sensitivity. In the second column gain data was shifted to align the measured response between sites. As a result, system 1 showed a significant decrease in variation between sites, whereas systems 2 and 3 remained approximately the same. This suggests that differences in hardware performance had a larger effect than those originating from operators.

Original | Shifted
System 1 | System 2 | System 3

Bias | Variation