Considerations for Evaluating the Accuracy of Hemoglobin Monitoring

To the Editor:

Masimo manufactures the Radical-7®, a multi-wavelength Pulse CO-Oximeter that continuously measures noninvasive hemoglobin concentration (SpHb®). This technology was the subject of a study by Applegate *et al.*, evaluating the accuracy of revision "E" SpHb sensors and software during abdominal and pelvic surgery.[1] Masimo appreciates the work of Applegate *et al.*, and we are grateful for the opportunity to comment.

Applegate *et al.* reported wider SpHb variation from laboratory hemoglobin than some other investigators have seen, and also reported that in some cases, SpHb did not trend in a consistent direction with the laboratory device they used in the study. The authors stated that the laboratory device, an operating room CO-Oximeter, has documented accuracy of ±0 to ±0.2 g/dl based on quality checks performed during the study. These quality checks do not actually assess accuracy but rather device precision (variation) in measurement based on running multiple reference samples. Quality analyses can be misleading because they do not use consecutive clinical blood samples run on the same or multiple laboratory devices. Significant variation in laboratory measurement is introduced by the blood sampling, storage, and mixing technique. For example, without careful attention, withdrawing blood through an arterial or venous line can allow fluid in the line to mix with the blood. Likewise, insufficient or inconsistent mixing allows blood to coagulate and renders hemoglobin measurements inaccurate.

The true accuracy of any laboratory hemoglobin device can only be assessed by comparing it with the international standard for hemoglobin, the hemiglobincyanide method,[2] as described by the International Council for Standardization in Hematology and required by the Food and Drug Administration for laboratory device submissions. Because the hemiglobincyanide method is challenging to perform in clinical settings because of complexity and time requirements, the hematology analyzer (*e.g.*, Beckman Coulter or Sysmex) is often used as the best available clinical standard.[3] Bland and Altman pointed out that both reference devices and test devices produce and contain inherent errors.[4] Therefore, a complete picture of SpHb accuracy must be relative, with SpHb and other laboratory devices used clinically today at the point of care, such as operating room CO-Oximeters and portable devices such as i-Stat (Abbott Laboratories, Abbott Park, IL) and Hemocue (HemoCue, Inc., Cypress, CA), compared with the international hemoglobin reference standard, cynanmethemoglobin, or at least to the best-known clinical standard, a hematology analyzer.[5] In such studies, it is critical that only one laboratory device of each type be used, as variation exists even within the same device model of different serial numbers – shown to be as high as 0.9 g/dl SD.[6]

Reporting the bias and SD of invasive but commonly available laboratory devices along with SpHb in the same subjects provides an objective evaluation of SpHb accuracy, provided proper and consistent blood sampling, storage, and mixing techniques are followed, as well as running the reference sample on a single, appropriate laboratory device, as previously described. Frasca *et al.* used a study design like this to evaluate the accuracy of revision E SpHb sensors in 471 comparisons made in the intensive care unit. SpHb, a satellite laboratory CO-Oximeter (RapidPoint 405; Siemens Healthcare Diagnostics Inc., Tarrytown, NY), and a point-of-care device (Hemocue 301) were compared with reference hemoglobin from the central laboratory hematology analyzer (Sysmex XT2000i; Sysmex, Kobe, Japan).[7] The bias ± precision of SpHb was 0.0 ± 1.0 g/dl, the CO-Oximeter was 0.9 ± 0.6 g/dl, and the point-of-care device was 0.3 ± 1.3 g/dl. In the same study, changes in SpHb compared with changes in the reference hemoglobin showed the same correlation as the laboratory CO-Oximeter and better correlation than the point-of-care device.

In addition to laboratory device and blood sampling, storage, and mixing, other factors can affect the accuracy of SpHb technology, including initial sensor placement, monitoring of the sensor placement during use for potential misalignment, and use of light shielding. We would also like to point out that SpHb was configured to a long averaging time of approximately 3 min in the study by Applegate *et al.* During periods of rapidly changing hemoglobin concentration, the blood sample representing blood over several seconds was compared with SpHb values averaged during approximately 3 min. When hemoglobin concentration is dropping rapidly, this can lead to an overestimation by SpHb. When hemoglobin concentration is rising rapidly, this can lead to an underestimation by SpHb. Lastly, the investigators chose to record SpHb values manually, rather than using an automated data collection method, which can introduce error into the study results, especially if hemoglobin is changing rapidly. Masimo makes available data collection software that allows for time stamping of blood draws and other events during SpHb data collection.

In the analysis technique used by Applegate *et al.* in their figure 3 scatterplot, the change in SpHb is plotted *versus* the change in laboratory hemoglobin. Because of variability in laboratory hemoglobin from the aforementioned factors, small changes in hemoglobin, such as those under 2.0 g/dl, should not be compared with SpHb changes. Other investigators have performed similar analyses in which reference data points with small magnitude changes were removed.[8] Critchley *et al.* have proposed a "polar plot" technique that may provide the optimal method to evaluate trending ability by taking into account both bias and the magnitude of the changes.[9]

Masimo is proud of the innovations we have brought to monitoring, as well as our ability to rapidly improve technologies. The absolute accuracy reported by Applegate *et al.* is similar to that reported by Miller *et al.* in complex spine

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surgery, but significantly different than at least two other published studies in surgery evaluating SpHb revision E technology.[10] Berkow *et al.* also evaluated revision E SpHb sensors in complex spine surgery and reported a 1.0 g/dl SD and clinically acceptable trend accuracy.[8] Lamhaut *et al.* evaluated revision E in major urologic surgery and showed a similar 1.1 g/dl SD, whereas a point of care device showed a 0.7 g/dl SD.[11]

We are confident that SpHb will reduce inappropriate blood transfusions during periods of visible blood loss but with stable hemoglobin status, and will enable earlier detection of occult bleeding. We believe these evaluations have greater clinical relevance than point-to-point accuracy comparisons. A randomized controlled trial has already been presented in abstract form that showed decrease in blood transfusion frequency (from 4.5 to 0.6%) in orthopedic surgery patients monitored with SpHb compared with a group managed by standard care, with no negative impact on patient safety.[12] We expect this to be the first of many studies showing SpHb's impact on patient care.

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In Reply:

We thank Dr. O'Reilly for his interest in our study and we appreciate the opportunity to respond. We would like to address several points that he raised related to our methods. We compared hemoglobin reported by the Radical-7® Pulse Co-Oximeter (SpHb®; Masimo Corporation, Irvine, CA) to hemoglobin determined by cooximetry from an arterial blood gas analyzer.[1] Although mentioned as a limitation, this use reflects the care of many patients undergoing surgery during which blood loss is likely in surgery suites that have arterial blood gas analysis immediately available. Although comparison to the hemiglobincyanide method would be the best standard, as Dr. O'Reilly points out this is not practical in the clinical setting. Data collection and specimen handling were the responsibility of a research team member who had no other clinical responsibility. This controlled errors in specimen handling and data entry. The blood sample handling methods used during a previous volunteer study[2] were also used for this study, and the arterial hemoglobin measurements were all performed on one device. Further, the research staff had been involved in the previous volunteer study and received training from Masimo for that study. The research staff received device-specific clinical training along with retraining from Masimo in correct methods of sensor application and shielding for this study. We believe this attention to training eliminated errors related to sensor placement.

Dr. O'Reilly also raises questions regarding interpretation of our data. It is clear that hemoglobin changes rapidly during rapid bleeding, and that use of the 3-min averaging time could lead to differences between hemoglobin measures. In 192 of 269 paired sequential hemoglobin measurements we found the value changed in the same direction, which may support the concept that 3-min averaging still allows detection of a trend in hemoglobin concentration. However, in 42 sequential measurement pairs the direction of change was not the same, including some in which the amount of difference was large. The suggestion that we not compare hemoglobin changes within 2.0 g/dl to pulse cooximetry hemoglobin changes deserves comment. At measured hemoglobin of 7, this range would imply that SpHb between 5 and 9 should be accepted as equivalent. We