Published in final edited form as:

Crit Care Med. 2011 October ; 39(10): 2369–2371. doi:10.1097/CCM.0b013e3182266013.

CONTINUOUS NONINVASIVE HEMOGLOBIN MONITORING: THE STANDARD OF CARE AND FUTURE IMPACT

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Keywords

Analytical measurement range; critical care; bleeding; confounders; Food and Drug Administration (FDA); pulse oximetry; and transfusion practice

EDITORIAL

Frasca et al. (1) report that continuous noninvasive hemoglobin monitoring (CNHM) "...has absolute accuracy and trending accuracy similar to widely used, invasive methods of hemoglobin measurement at bedside". While the population was small (N=62), the prospective observational study was conducted in a surgical ICU and representative of the performance of Rainbow® adult "resposable" (reusable) sensors (R2-25, Revision E) connected to a Radical-7 Pulse CO-Oximeter (software version 7.6.0.1, Masimo®, Irvine, CA, USA) used with critically ill (SAPS II 46±23, SOFA 6±3) medical and emergency-elective surgery patients. However, "...none of the included patients had active major bleeding".

While the authors present analysis of trends, observations reflect more *static*, than *dynamic* hematological conditions, and they suggest that CNHM "...may be a feasible alternative to invasive hemoglobin monitoring". However, they do not present decision-making or outcomes results, per se, and wisely, stop short of implying CNHM should replace discrete *in vitro* diagnostic hemoglobin testing when the article ends with the somewhat circuitous caveat, "A laboratory hemoglobin determination could be limited to situations where a blood transfusion is considered".

Oxygen saturation measured noninvasively by traditional pulse oximetry using red (~660 nm) and infrared (~905 nm) light emitting diodes (LEDs) differentiates oxy- versus deoxyhemoglobin, respectively (2). The ratio of red versus infrared light is correlated with a calibration curve empirically derived from clinical studies to calculate oxygen saturation over a limited range (2, 3), while pulse rate is determined from the plethysmogram. Newer devices incorporate robust treatment of the red/infrared ratio, multiple wavelengths, advanced algorithms, and proprietary sensor calibrations integrated (3). These principles extend to pulse co-oximetry, where up to twelve wavelengths and sophisticated signal reduction enable measurement of carboxyhemoglobin, methemoglobin, total hemoglobin,

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The authors have not disclosed any potential conflicts of interest.

and total oxygen content (4) with real-time tracking. Table 1 (4–11) presents CNHM systems, characteristics, and intended uses.

Devices may be limited to adults and children weighing more than 30 kilograms (7)—pediatric intensivists should proceed with caution. Notable is the limited range of hemoglobin measurements. Lower bounds of 7 to 8 g/dL could compromise transfusion decisions in critically ill trauma, emergency, and burn surgery patients (12), for whom it would be wise to use CNHM strictly according to FDA-approved intended uses and only as trend monitors. In fact, Frasca et al. (1) present convincing analysis of trend data that serves to validate this purpose for patients who are not actively bleeding.

Other investigators have mixed recent findings. In an ED study, Gayat et al. (13) concluded, “Results from this widely available noninvasive point-of-care hemoglobin monitoring device were systematically biased and too unreliable to guide transfusion decisions.” and “...use of the Masimo Radical-7 Pulse CO-Oximeter would lead to 13% error in terms of transfusion decisions.” Miller et al. (14) found, “...SpHb [CNHM] may not be as accurate as clinically necessary in some patients.” and “When perfusion diminishes, SpHb underestimates true Hb, so it should not be used to determine the need for blood transfusions without validation using a direct measurement methodology.” Causey et al. (15) observed a correlation of the Masimo Radical-7 SpHb Station versus laboratory hemoglobin measurements of 0.77 ($P < 0.001$) with a mean difference of 0.29 g/dL (95% CI, 0.08–0.49) and reasoned “...the device SpHb to have clinically acceptable accuracy during most types of surgery including those with significant blood loss—...44% of patients in the study sustained significant intraoperative blood loss, the patient population for which the device would prove to be most useful.”

Frasca et al. (1) recommend additional study to evaluate the merits of CNHM in hemorrhaging patients, early detection of bleeding, and monitoring of blood management. We recommend also validation of performance in patients with anemia, hemodilution, severe hypotension, low tissue perfusion, and restrictive blood transfusion thresholds (hemoglobin ≤ 7 g/dL). Noting limitations, the authors (1) state, “...less than 10% of measures were performed in patients with hemoglobin concentration below 8 g/dL.” In fact, data sets presented to the FDA typically lack these low range observations (6–8).

The litany of confounders plaguing pulse (co)-oximetry is extensive [e.g., ambient light, bilirubin, hemoglobin variants, intravascular dyes, patient motion, pressure necrosis, sensor malpositioning and type, skin temperature readings (see recall: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=97029>), and venous congestion]. Investigators point to potential technical issues with hemoglobin monitoring, such as edema and multiple physiological changes that render optical spectroscopic tissue parameters inaccurate or impossible to track (16), inconsistent inter-individual path length and high tissue lipid content that challenge calibration assumptions (17), and blood volume depletion that alters optical scattering and absorption characteristics (18).

Clearly, the use of CNHM in critically ill patients shows strong merit. Trend monitoring may be a useful alternative to serial *in vitro* testing, especially when reducing iatrogenic blood loss, conserving patient blood volume, enhancing the timeliness of decision-making, and improving the cost-effectiveness of transfusions. Thus, Frasca et al. (1) imply a disruptive shift toward continuous measurement at the point of need (19) and a subtle, but interesting drift in the standard of care for hemoglobin determinations.

The concept of standard of care is based on *Vaughn v. Menlove* (1837), wherein the judge instructed the jury to reason whether the defendant “proceed[ed] with such reasonable caution as a prudent man would have exercised under such circumstances.” Before declaring

that CNHM has changed the standard of *critical* care, reasonable caution dictates a) the technology be improved and validated better in the low range (< 8 g/dL); b) continuous validation occurs during *dynamic*, rather than static, hematological conditions; and c) multicenter investigators provide evidence of improved decision-making and outcomes related to early detection of bleeding episodes and transfusion practices.

Whether or not these challenges are fully met, CNHM has the potential to reduce the medical-financial burden of repeated or unnecessary *in vitro* laboratory hemoglobin measurements, help conserve patient blood volume by reducing iatrogenic losses, avoid the risks of anemia, optimize intraoperative transfusions, and even enhance care in low-resource settings, such as epidemic Dengue hemorrhagic fever outbreaks where erythrocyte repletion based on hourly spun hematocrits can be partially or completely supplanted by following trends in hemoglobin. Therefore, future impact is high.

Acknowledgments

This editorial was supported by the Point-of-Care Testing Center for Teaching and Research (POCT CTR) and by a National Institute for Biomedical Imaging and Bioengineering (NIBIB) Point-of-Care Technologies Center grant (Dr. Kost, PI, NIH U54 EB007959). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIBIB or the National Institutes of Health. The table was provided with permission and courtesy of Knowledge Optimization®, Davis, CA.

Funding

This editorial was supported by the Point-of-Care Testing Center for Teaching and Research (POCT•CTR) and by a National Institute for Biomedical Imaging and Bioengineering (NIBIB) Point-of-Care Technologies Center grant (Dr. Kost, PI, NIH U54 EB007959). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIBIB or the National Institutes of Health.

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Table 1
Clinical Utility of Non-Invasive Continuous Hemoglobin Monitoring Technology in Critically Ill Patients

Manufacturer	Device Name (Format)	Continuous Measurements	Methodology	Hb Analytical Measurement Range	Manufacturer's Product Claims	FDA Approved Intended Use
Biosense www.biosense.in	ToucHb ^a (Portable)	THb	In development	In development	In development	Not applicable
Hutchison Technologies www.hthc.com	InSpectra Model 325	Tissue Hb ^a , SiO ₂	3 wavelengths spectrophotometry (5)	Tissue Hb sensor In development	In development	Not applicable
Masimo www.masimo.com	Pronto ^b (Handheld)	THb, SpO ₂ , pulse	8-wavelength spectrophotometry	8 – 17 g/dL, ±1 g/dL c.d (adults and pediatrics) (6)	THb spot checking	THb spot checking in clinical and non-clinical settings (6)
	Pronto-7 ^b (Handheld)	THb, SpO ₂ , pulse, P _{if}	“	6 – 18 g/dL, ±1 g/dL c.d (adults and pediatrics >30 kg) (7)	“	THb spot checking in clinical and non-clinical settings (7)
	Rad-57 (Portable)	THb, SpO ₂ , COHb, MetHb, pulse, P _{if} ^{e-g}	≤8 wavelengths spectrophotometry (4)	7 – 17 g/dL, ±1 g/dL c.d (adults and pediatrics) (8)	Continuous monitoring of THb	Continuous THb monitoring (8)
	Rad-87 (Handheld)	THb, SpO ₂ , COHb, MetHb, pulse, P _{if} ^{e-g} , RR	“	“	Continuous THb monitoring with wire-less connectivity	“
	Radical-7 (Portable)	THb, SpO ₂ , COHb, MetHb, P _{if} , P _{if} ^{e-g} , total O ₂	≤12 wavelengths spectrophotometry	“	Continuous and trend monitoring of THb	“
MBR Optical Systems www.mbr-optical-system.com	Mediscan 2000 (portable)	^a THb	Wavelength ranging from 350 – 1020 nm ^{h,i} (9,10)	In development	In development	Not applicable
OrSense www.orsense.com	NBM-200MP ^a (Portable)	THb, SpO ₂ , pulse, pleth,	4-wavelength spectrophotometry	THb sensor in development	In development	Not applicable
Sysmex www.sysmex.com	Astrim ^a (Portable)	THb	In development	Evaluated with Hb from 6.7 – 18.4 g/dL (11)	In development	Not applicable

Footnote:

^aNot FDA-approved;

^bCLIA-waived;

^caccuracy claim from 510k FDA-approval;

^d determined during conditions of non-motion and good perfusion;

^e calculated parameter,

^f $PI = (\text{constant amount of absorbed light/variable amount of absorbed light}) \times 100\%$;

^g $pVI = [(PI_{\text{max}} - PI_{\text{min}})/(PI_{\text{max}})] \times 100\%$;

^h infants; and

ⁱ neonates.

Abbreviations: COHb, carboxyhemoglobin; Hb, hemoglobin; MetHb, methemoglobin; PI, perfusion index; pleth, plethymographic waveform; PVI, plethymographic waveform variability index; RR, respiratory rate; SpO₂, oxygen saturation; StO₂, tissue oxygen saturation and THb, total hemoglobin.