The Accuracy of Pulse Spectroscopy for Detecting Hypoxemia and Coexisting Methemoglobin or Carboxyhemoglobin

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BACKGROUND: Pulse spectroscopy is a new noninvasive technology involving hundreds of wavelengths of visible and infrared light, enabling the simultaneous quantitation of multiple types of normal and dysfunctional hemoglobin. We evaluated the accuracy of a first-generation pulse spectroscopy system (V-Spec™ Monitoring System, Senspec, Germany) in measuring oxygen saturation (Spo_2) and detecting carboxyhemoglobin (COHb) or methemoglobin (MetHb), alone or simultaneously, with hypoxemia.

METHODS: Nineteen volunteers were fitted with V-Spec probes on the forehead and fingers. A radial arterial catheter was placed for blood sampling during (1) hypoxemia with arterial oxygen saturations (Sao_2) of 100% to 58.5%; (2) normoxia with MetHb and COHb increased to approximately 10%; (3) 10% COHb or MetHb combined with hypoxemia with Sao_2 of 100% to 80%. Standard measures of pulse-oximetry performance were calculated: bias (pulse spectroscopy measured value − arterial measured value) mean ± SD and root-mean-square error (A_{rms}).

RESULTS: The Spo_2 bias for Sao_2 approximately 60% to 100% was 0.06% ± 1.30% and A_{rms} of 1.30%. COHb bias was 0.45 ± 1.63, with an A_{rms} of 1.69% overall, and did not degrade substantially during moderate hypoxemia. MetHb bias was 0.36 ± 0.80 overall and stayed small with hypoxemia. A_{rms} was 0.88 and was <3% at all levels of Sao_2 and MetHb. Hypoxemia was also accurately detected by pulse spectroscopy at elevated levels of COHb. At elevated MetHb levels, a substantial negative bias developed, −10.3 at MetHb >10%.

CONCLUSIONS: Pulse spectroscopy accurately detects hypoxemia, MetHb, and COHb. The technology also accurately detects these dysfunctional hemoglobins during hypoxemia. Future releases of this device may have an improved Spo_2 algorithm that is more robust with methemoglobinemia. (Anesth Analg 2016;XXX:00–00)

Two-wavelength (red and infrared) pulse oximetry is a mature technology that determines the functional saturation of hemoglobin with oxygen. Over the past decade, the addition of more wavelengths of light has enabled oximetry systems to detect dysfunctional hemoglobins (carboxyhemoglobin [COHb] and methemoglobin [MetHb]) and total hemoglobin (e.g., Masimo Pulse Co-Oximetry™; Masimo Corp., Irvine, CA)[1–3] as well as tissue oxygenation (e.g., near-infrared spectroscopy, various manufacturers.)[4]

Five to 12 wavelengths of light are used in the Masimo rainbow® Pulse CO-Oximeters, that is, the Radical-7® (Masimo Corp.).[5] The measured parameter for COHb concentration is named SpCO® and for MetHb, SpMet® by Masimo. Early studies on healthy volunteers for COHb concentrations demonstrated acceptable accuracy of the Masimo Pulse CO-Oximeter for detecting COHb during normoxia.[1,2] Studies with patients with elevated COHb levels (>10% COHb)[5,6] suggested limitations in accuracy.[7,8] More recent studies showed an improved accuracy in volunteer studies and a more robust tolerance for hypoxic oxygen levels,[9,10] but detecting COHb when Sao_2 is approximately <87% is still not possible.

Other multispectral (up to 8 wavelengths) approaches to measuring hemoglobin species have also been developed.[3,11–15] Multiwavelength spectroscopy systems were initially developed for postmortem measurements in forensic medicine applications.[16–18]

Theoretically, the spectroscopic approach can reduce cross talk between the detection of multiple hemoglobin species, especially when the absorbances are in the same region of the spectrum.[19–21] In the region of 600 to 700 nm, deoxyhemoglobin and MetHb are spectrally similar,[20] and a photometer with only few discrete wavelengths (such as current light-emitting diode [LED]–based systems) could fail to discriminate multiple hemoglobin species.[22,23] With the high spectral resolution, the separation of relevant absorption band signals from distortions such as painted fingernails, melanin, water, or subcutaneous fat is also possible by applying a derivative transform to the data of the original spectrum (derivative spectroscopy). Such capabilities are clinically important when mixed intoxications are present or when toxic exposures have secondarily caused hypoxemia from respiratory dysfunction.

In this article, we document and describe the first results with the pulse spectroscopic method in volunteer

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studies for hypoxemia, COHb, and MetHb concentration measurements.

METHODS

The University of California at San Francisco (UCSF) Committee on Human Research approved the study, and all subjects gave informed written consent. The pool of subjects comprised healthy, nonsmoking men and women, from 21 to 38 years of age, willing to volunteer for the study for a nominal payment. The selected group of subjects was gender and ethnically balanced, following the Food and Drug Administration (FDA) requirements for standard studies of pulse oximeter accuracy. The final group included 19 healthy adult subjects, 10 men and 9 women, with a range of skin pigmentation (Table 1). Ten subjects participated in a standard hypoxemia study with normal (low) levels of COHb and MetHb, 6 subjects were studied with elevated COHb levels, and 3 subjects were studied with elevated MetHb levels. The study size was based on prior studies and the size of standard studies of pulse oximeter accuracy for FDA 510(k) approval.

V-Spec Monitoring System

Pulse-spectrometer probes (V-Spec™ Sensors, Germany) and instruments were supplied by Senspec. V-Spec Sensor probes (reusable with soft finger clip or attachment tape) were used to measure oxygen saturation (Spo_2), COHb levels (SpHbCO), and MetHb levels (SpHbMet). The software versions of V-Spec Sensors and V-Spec monitors used in the hypoxemia study were 1.01 and 1.2.4, respectively. During the COHb Study and the MetHb Study, V-Spec Sensors and V-Spec monitors with software versions 2.05 and 03.03.01 were used, respectively.

The V-Spec Sensor is a miniaturized and very fast two-dimensional pulsatile spectroscopy unit. The sensor integrates an LED-based lighting unit, a spectrometer unit, and a microelectronic system to transform the optical signals into digital electronic signals and to transfer the information with high speed to a clinical monitor (V-Spec Monitor). The actual size of the integrated sensor is about 44 mm × 16 mm × 24 mm. The sensor is applied to the patient with a sensor-specific medical attachment tape. In another setup (V-Spec Soft Sensor), the sensor is integrated in a soft finger clip to position the sensor at the patient's fingertip.

The V-Spec Sensor uses a transflectance measurement, also called the remission measuring setup. The light enters the tissue at 1 point, gets scattered and absorbed during the path through the tissue, and then leaves the tissue at a second point, where it enters into the spectrometer unit. The spectrometric sensor splits the light in 350 wavelength points in the range from 500 to 850 nm, instead of 2 points for conventional pulse oximeter and 5 to 10 points for multispectral photometers (Fig. 1). The calculation of hemoglobin species is based on about 15-million, single, 12-bit photo sensor values generated from the sensor in each second. The spectra are preprocessed and white calibrated and then transferred to 40 averaged absorption spectra per second. These spectra are used to extract physiological parameters (e.g., MetHb, Sao_2, etc.) by different mathematical and chemometric procedures.

The integrated lighting unit is LED based. The LED emission spectrum is broadband and specially designed for use with patient skin and human tissue containing typical amounts of hemoglobin. The LED emission efficiency is optimized for the low electrical input power of the light unit.

Two pulse-spectrometer probes (V-Spec sensors) were placed at the forehead and were fixed with the sensor-specific attachment tape. Two to 4 pulse-spectrometer probes (V-Spec Soft Sensor) were placed on different fingers. The probe locations were randomized for each subject and were connected to V-Spec monitors. The monitors were equipped with additional memory and with a special software version to store the original spectral data online during the study. The original spectral data, the extracted pulsatile part of the spectra (representing the pulsing, arterial blood), and the continuous part of the spectra (representing the tissue) were recorded continuously during the study.

Study Protocol

A 22-gauge radial arterial cannula was placed in either the left or the right wrist of each subject. Arterial blood was analyzed with a multiwavelength optical blood gas analyzer (ABL90 FLEX; Radiometer Medical A/S, Copenhagen, Denmark, or OSM3, Radiometer Medical A/S) to determine arterial oxygen saturation (Sao_2), COHb concentration (%COHb), and MetHb concentration (%MetHb).

Studies on each subject began with 1 arterial blood sample drawn as a baseline value while patients were

Table 1. Demographic Summary for the Different Study Types

	Hypoxemia (*n* = 10)	Carboxyhemoglobin (*n* = 6)	Methemoglobin (*n* = 3)
Age (y)	26 ± 4	28 ± 5	25 ± 3
Gender			
Female	7 (70%)	2 (33%)	0 (0%)
Male	3 (30%)	4 (67%)	3 (100%)
Ethnicity			
Asian	1 (10%)	1 (17%)	0 (0%)
African American	2 (20%)	0 (0%)	0 (0%)
Caucasian	6 (60%)	5 (83%)	2 (67%)
Hispanic	1 (10%)	0 (0%)	1 (33%)
Skin color			
Light	3 (30%)	4 (67%)	3 (100%)
Intermediate	5 (50%)	2 (33%)	0 (0%)
Dark	2 (20%)	0 (0%)	0 (0%)

Data are mean ± SD or *n* (%).

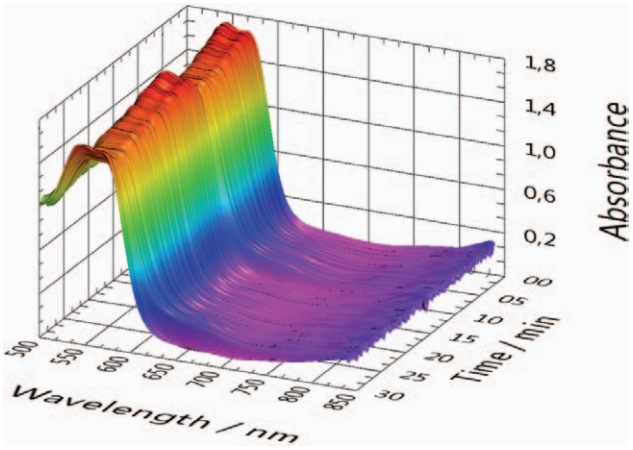

Figure 1. Data obtained with a V-Spec Sensor on the left thumb of a subject undergoing 2 different desaturation episodes over a 30-minute period. The sequence includes 1800 arterial blood spectra (1 spectrum per second). The spectra span the 500–850-nm wavelength range, and absorbance is shown in a color scale (inset). The double-peak absorption visible between 525 and 600 nm for oxygen saturation levels exceeding 90% gradually fades and a lower-wavelength peak shifts toward higher wavelengths with decreasing oxygen saturation. Furthermore, absorbance increases with decreasing oxygen saturation over the wavelength range from 600 to 700 nm.

breathing room air. Hypoxemia was then induced to 5 to 6 different targeted plateaus from 100% to 60% by having subjects breathe mixtures of nitrogen, air, and carbon dioxide according to a protocol previously detailed.[24] Oxygen saturation is calculated from end-tidal Po_2 and Pco_2 breath-by-breath, which guides the gas mixtures. Each saturation plateau level was maintained for at least 60 seconds. When pulse oximeter values had stabilized, 2 arterial blood samples were obtained approximately 30 seconds apart. After the final Sao_2 plateau, subjects breathed 100% O_2 and then returned to breathing room air.

Elevated COHb was induced by having subjects breath carbon monoxide (CO) gas to produce a target COHb level of approximately 10% to 12% based on the volunteer study by Barker et al.[1] and accumulated experience in volunteers in UCSF laboratory.[7] CO (15–30 mL) was added to a 1-L bag prefilled with approximately 200 mL of oxygen. Subjects then briefly rebreathed this mixture from a mouthpiece, allowing us to produce approximately 2% stepwise changes in COHb. Blood samples were obtained 5 minutes after each administration of CO. When COHb reached target levels (10%–12%), hypoxemia was induced in steps from 100% to 80%, and blood samples were taken using the prior protocol.

In a different group of subjects, elevated MetHb levels were induced by slow IV administration of approximately 300 mg sodium nitrite to produce a target MetHb level of 10%. During sodium nitrite infusion, blood samples were obtained every 5 minutes to confirm elevated MetHb levels. Hypoxemia was then induced to in steps from 100% to 80% after reaching the target level of MetHb, and blood samples were taken using the prior protocol.

For the COHb and the MetHb part of the study, the analysis of pulse spectroscopy was performed separately and blinded to the results of blood gas analysis. In Figures 2 and 3, typical sequences for COHb and MetHb studies are shown.

Data Analysis and Statistics

Accuracy of measuring hypoxemia (Spo_2) is specified by an international guideline (DIN EN ISO 80601-2-61:2011).[25] For the measurement of tissue hypoxia by near-infrared spectroscopy, no standard is established.

There is also no current FDA standard for accurately determining noninvasively measured COHb and MetHb concentrations. For Spo_2, root-mean-square error (A_{rms}) <3% is the acceptable accuracy standard established by the FDA. We considered that the Spo_2 accuracy would be degraded if elevated %COHb or %MetHb reached A_{rms} >3%. A_{rms} <3% would certainly represent acceptably accurate performance for determining COHb and MetHb concentration noninvasively although it may not be reasonable to expect the same accuracy and precision as for determining Spo_2.

Pulse spectrometer performance was analyzed by calculating mean bias (Spo_2 – Sao_2; SpHbCO – COHb; or SpHbMet – MetHb), precision (SD of the bias), and A_{rms} over different ranges of $\%Sao_2$, %COHb, and %MetHb. The distribution of bias was plotted and tested for normality with the Shapiro-Wilk test. Results ranged from $P < 0.0001$ to $P = 0.27$. Where data were not normally distributed, this was predominantly due to high and low outliers, so no data transformation was performed. Bias, precision, and A_{rms} were determined and analyzed separately for Spo_2, SpHbCO, and SpHbMet. Bias within different ranges of Sao_2 was compared with a repeated-measures analysis of variance, and Tukey-Kramer honest significant difference was used for multiple comparison testing. Levene F test was used to compare SDs within various ranges specified in the tables. Limits of agreement were calculated according to Bland and Altman,[26] with adjustments for multiple measurements for each individual according to the "Method Where The True Value Varies". The 95% confidence intervals (CIs) of the limits of agreement were calculated by bootstrapping.

Bias was plotted against arterial blood percent COHb, percent MetHb, or Sao_2. Arterial values were treated as a gold standard. For bias plots, linear regression was performed accounting for repeated measures. Slopes are reported with 95% confidence limits.

Receiver operating characteristics (ROC) were analyzed by setting percent COHb ≥10% and ≥5% as positive carboxyhemoglobinemia. Data from the 6 devices were combined for the analysis. Area under the curve (AUC) with 95% confidence limits was calculated.

Data are reported as mean ± SD or mean (95% CI) as indicated. All statistical tests were 2 sided, and P value <0.05 was considered significant. Data were analyzed with JMP 11.0 (SAS Institute, Cary, NC) and Stata 14.0 (StataCorp, College Station, TX).

RESULTS

Demographics

Table 1 summarizes the demographic information separately for each study type. Ten subjects of different gender, ethnicity, and skin color participated in the hypoxemia study. The COHb study was performed with 6 subjects and 3 subjects participated in the MetHb study.

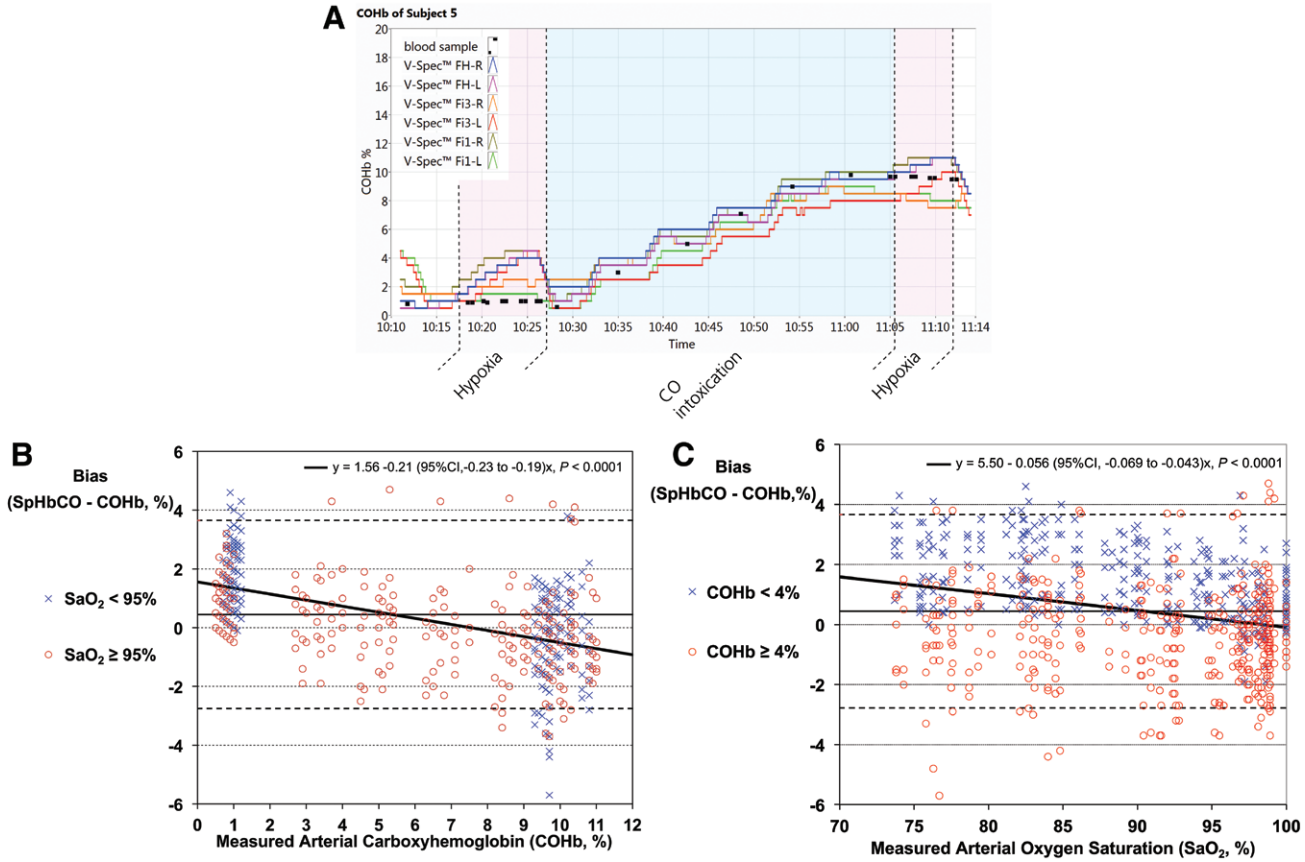

Figure 2. A, Typical carboxyhemoglobin study protocol. B, Pulse spectroscopy carboxyhemoglobin (SpHbCO) bias (SpHbCO − percentage of carboxyhemoglobin in arterial blood [%COHb]) as a function of %COHb. Data in normoxia (arterial oxygen saturation [Sao_2] ≥95%) are shown by open red circles and for hypoxemia (Sao_2 <95%) by blue Xs. Mean bias is shown by a solid horizontal line and the upper and lower limits of agreement (mean bias ± 1.96·SD [adjusted for repeated measures]) by dashed horizontal lines. The regression equation is shown on the figure as solid black line. The relation was statistically significant ($P < 0.0001$). C, SpHbCO bias as a function of Sao_2. Data at low COHb (<4%) are shown by blue Xs, whereas data at high COHb (≥4%) are shown by red open circles. The regression equation is shown on the figure as solid black line. The relation was statistically significant ($P < 0.0001$).

Accuracy of Detecting Hypoxemia

For 4 different probes placed randomly on the forehead and fingers, 902 data points for 250 blood draws were obtained from the 10 subjects participating in the hypoxemia portion of the study. The Sao_2 values ranged from 58.5% to 100.0%.

Table 2 shows a summary of pulse spectroscopy oxygen saturation bias (Spo_2 – Sao_2) within different Sao_2 ranges. Although bias did differ significantly with Sao_2 level, the overall mean bias, precision, and root-mean-square error (A_{rms}) were all low. Mean bias on the finger was 0.5% ($P < 0.0001$) higher than the mean bias on the forehead; however, data are clinically so similar that the combined data are shown in the table. Missing data occurred from 2 causes. One was a combination of sweating and movement during the study so that the sensor was not positioned. The second case was the skin-detection algorithm in combination with very dark skin. In 1 subject, the forehead sensors detected only weak signals.

In Figure 4A, bias is plotted versus Sao_2. While bias increases significantly at lower Sao_2 ($P < 0.0001$), the effect is small, only 1.5% over the range of Sao_2 from 100% to 50%. Figure 4B shows a standard scatterplot of Spo_2 versus Sao_2.

Accuracy of Detecting Elevated COHb During Normoxia and Hypoxemia

During the COHb study, 152 blood draws and 888 corresponding pulse spectroscopy readings with 6 devices were obtained. Observations spanned Sao_2 from 73.7% to 100% and COHb from 0.5% to 11.0%. The MetHb was not varied and stayed low during this part of the study.

Table 3 summarizes the COHb bias (%SpHbCO – %COHb) statistics. While the bias was statistically different in different ranges of both Sao_2 and COHb, the differences were small. Overall bias, precision, and A_{rms} were low in all ranges of Sao_2 and COHb. The overall A_{rms} was 1.69%, and it was <3% even with hypoxemia.

An example of step changes in COHb induced by intermittently breathing small quantities of carbon monoxide is shown in Figure 2A. Figure 2B shows the percent COHb bias versus percent COHb. In Figure 2C, the bias is shown versus Sao_2. While statistically significant ($P < 0001$), the effects of both percent COHb and percent Sao_2 on the bias were small: a difference in bias of 2.5% over the range of COHb of 0 to 12% and 1.7% over the range of Sao_2 from 70% to 100%.

ROC curves showed very good sensitivity and specificity for detecting carboxyhemoglobinemia. Figure 5A shows the

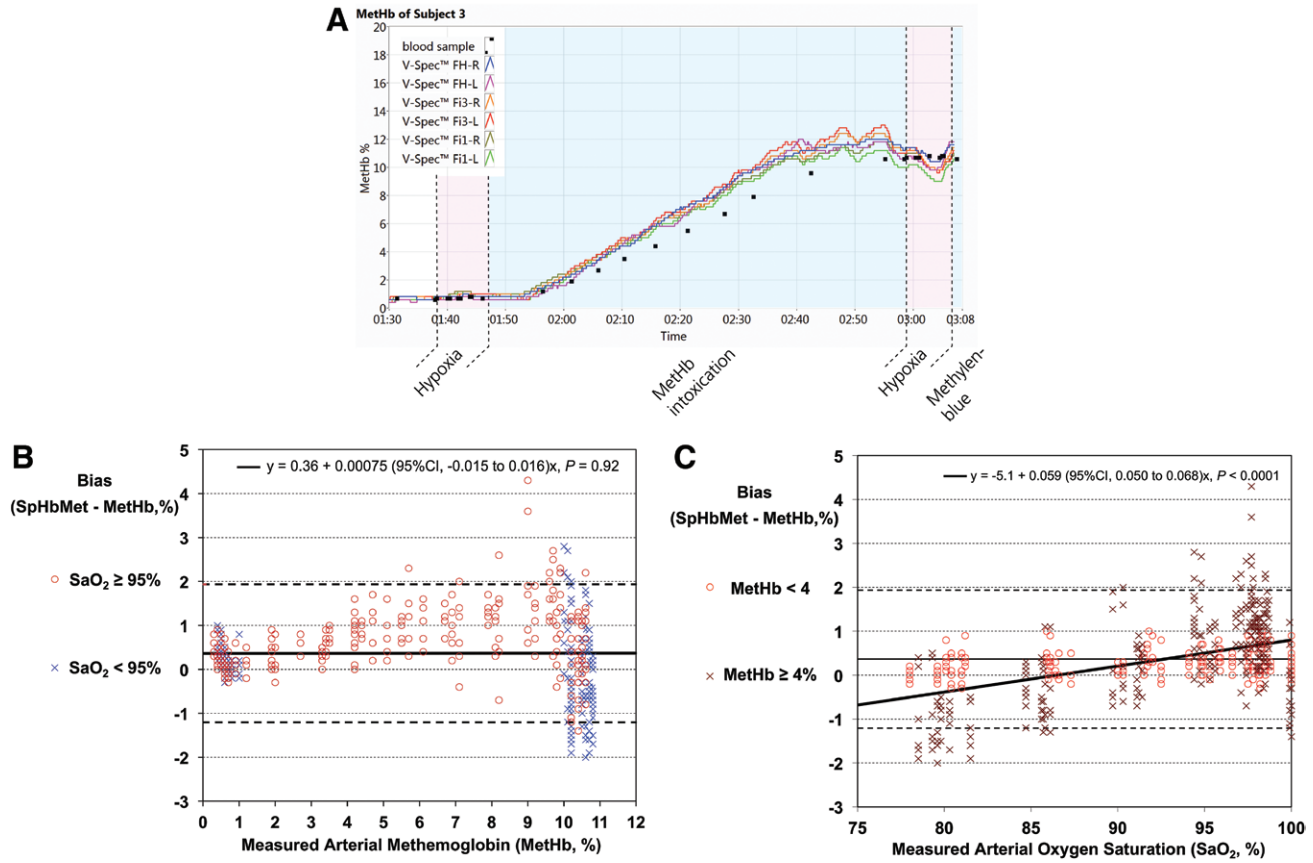

Figure 3. A, Typical methemoglobin study protocol. B, Methemoglobin bias (SpMet – percentage of methemoglobin in arterial blood [%MetHb]) as a function of measured arterial %MetHb. Data for normoxia (Sao_2 ≥95%) are shown by open red circles and for hypoxemia (Sao_2 <95%) by blue Xs. Mean bias is shown by a horizontal solid line and the upper and lower limits of agreement (mean bias ± 1.96 · SD [adjusted for repeated measures]) by dashed horizontal lines. The regression equation with 95% confidence intervals for slope is shown on the figure, and the line is overlapping with the mean bias. The relation was not statistically significant ($P = 0.92$). C, SpMet bias as a function of Sao_2. Data at low MetHb (<4%) are shown by red open circles, whereas data at high MetHb (≥4%) are shown by brown crosses. The regression equation is shown on the figure as solid black line. The relation was statistically significant ($P < 0.0001$).

Table 2. Spo_2 Bias (Spo_2 – Sao_2) Summary

Sao_2 range	<70%	70%–80%	80%–90%	90%–100%	All	*P* value
Paired observations, *n*	70	234	319	279	902	
Mean bias (%)	1.29[a]	0.17	−0.06	−0.20[b]	0.06	<0.0001
Precision (%)	1.63	1.40	1.19	1.04	1.30	<0.0001
A_{rms} (%)	2.06	1.40	1.19	1.06	1.30	
Lower limit of agreement (%)	−1.92	−2.59	−2.40	−2.24	−2.49	
	(−2.56 to −1.28)	(−2.95 to −2.23)	(−2.73 to −2.08)	(−2.88 to −1.59)	(−2.73 to −2.24)	
Upper limit of agreement (%)	4.49	2.93	2.28	1.84	2.61	
	(3.40 to 5.58)	(2.48 to 3.38)	(2.01 to 2.56)	(1.35 to 2.33)	(2.36 to 2.86)	

A_{rms} = root-mean-square error; Bias = Spo_2 – Sao_2; limits of agreement (with 95% confidence intervals) = mean bias ± 1.96 · SD (adjusted for repeated measures), which represents 95% of expected data; precision = SD of bias; Spo_2 = oxygen saturation read by pulse spectroscopy; Sao_2 = functional oxygen saturation from arterial blood samples.

[a]Different from all other groups by multiple comparisons.

[b]Different from groups <70% and 70%–80%.

ROC curve for carboxyhemoglobinemia defined as COHb ≥5%. The AUC was 0.99 (95% CI, 0.99–1.0). Figure 5B shows the ROC curve for a positive COHb of ≥10%. The AUC was 0.91 (95% CI, 0.89–0.92).

Accuracy of Detecting Elevated MetHb During Normoxia and Hypoxemia

During the MetHb study, 98 blood draws and 539 corresponding pulse spectroscopy readings were obtained. Observations spanned Sao_2 from 78% to 100% Sao_2 and MetHb from 0.3% to 10.8%. The COHb remained low (<1%) during this part of the study.

Table 4 summarizes the MetHb bias (percent SpHbMet – percent MetHb) statistics. While mean bias did differ significantly between different ranges of percent Sao_2 and percent MetHb, the differences were small. A_{rms} was <3% in all ranges.

Figure 3A shows an example of changes in MetHb levels during and after the infusion of sodium nitrite. Figure 3B

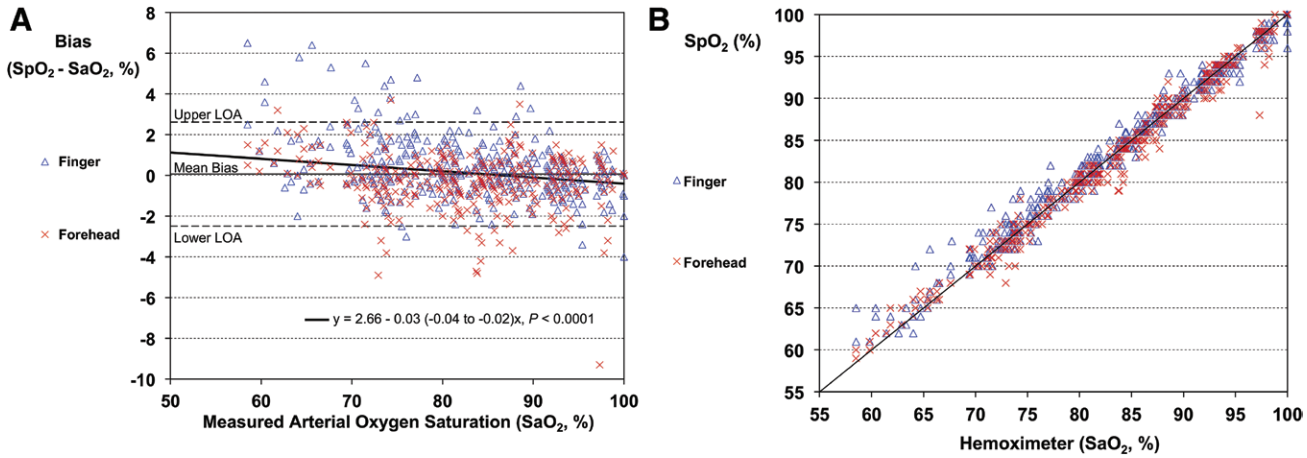

Figure 4. A, The pulse spectroscopy (Spo_2) reading bias (Spo_2 – measured arterial oxygen saturation [Sao_2]) as a function of Sao_2. Open triangles indicate the 2 V-Spec devices placed simultaneously on different fingers, and Xs indicate the 2 simultaneous forehead sensors. Mean bias is displayed as a solid horizontal line. The upper and lower limits of agreement (mean bias ± 1.96 · SD [adjusted for repeated measures]) are shown by dashed horizontal lines. The regression line and equation are shown on the figure with 95% confidence limits for the slope. Bias increased at lower saturation ($P < 0.0001$), but only by 1.5% over the Sao_2 range of 100% to 50%. B, Sao_2 versus Spo_2. The diagonal line of identity is shown by the solid black line.

Table 3. Carboxyhemoglobin Bias (SpHbCO – COHb) Summary

COHb range	0%–5%	5%–10%	10%–15%	All	*P* value
Paired observations, *n*	438	300	150	888	
Mean bias (%)	1.31[a]	−0.53	−0.17	0.44	<0.0001
Precision (%)	1.22	1.51	1.59	1.64	0.001
A_{rms} (%)	1.79	1.60	1.60	1.69	
Lower limit of agreement (%)	−1.08 (−1.26 to −0.91)	−3.51 (−3.87 to −3.15)	−3.41 (−3.81 to −3.01)	−2.78 (−2.98 to −2.58)	
Upper limit of agreement (%)	3.71 (3.51 to 3.91)	2.46 (2.13 to 2.80)	3.06 (2.48 to 3.65)	3.66 (3.48 to 3.84)	
Sao_2 range	**70%–80%**	**80%–90%**	**90%–100%**	**All**	***P* value**
Paired observations, *n*	138	210	540	888	
Mean bias (%)	0.95	1.08	0.06[a]	0.44	<0.0001
Precision (%)	1.83	1.62	1.48	1.64	0.005
A_{rms} (%)	2.05	1.94	1.48	1.69	
Lower limit of agreement (%)	−2.64 (−3.32 to −1.96)	−2.10 (−2.56 to −1.64)	−2.84 (−3.07 to −2.61)	−2.78 (−2.98 to −2.58)	
Upper limit of agreement (%)	4.54 (4.06 to 5.02)	4.26 (3.93 to 4.60)	2.97 (2.74 to 3.19)	3.66 (3.48 to 3.84)	

A_{rms} = root-mean-square error; Bias = SpHbCO − COHb; COHb = carboxyhemoglobin level from arterial blood samples; limits of agreement (with 95% confidence intervals) = mean bias ± 1.96 · SD (adjusted for repeated measures), which represents 95% of expected data; Sao_2 = functional oxygen saturation from arterial blood samples; SpHbCO = carboxyhemoglobin level read by pulse spectroscopy; Precision = SD of bias.
[a]Different from other groups by multiple comparisons.

shows the MetHb bias versus percent MetHb from arterial blood samples. In Figure 3C, the MetHb bias is shown versus percent Sao_2. Hypoxemia had a statistically significant effect on the MetHb bias ($P < 0.0001$), but this amounted to a difference in bias of only 1.5% over the range of Sao_2 from 100% to 75%.

Accuracy of Detecting Hypoxemia During Carboxyhemoglobinemia and Methemoglobinemia

Table 5 shows a summary of Spo_2 bias statistics during carboxyhemoglobinemia. Higher levels of COHb caused slightly negative bias. A_{rms} was still <3% except at lower Sao_2 level. Figure 6 shows the Spo_2 bias as a function of COHb in panel A and Sao_2 in panel B.

Table 6 shows summarized Spo_2 bias during methemoglobinemia. Mean bias was dramatically negative at higher levels of MetHb. Figure 7 shows Spo_2 bias as a function of MetHb in panel A and Sao_2 in panel B.

DISCUSSION

The primary purpose of this study was to assess the in vivo accuracy of a new pulse spectroscopy sensor system. The main findings were that the V-Spec Monitoring System accurately detects hypoxemia in normal levels of COHb and MetHb, that COHb and MetHb are detected accurately at normoxia, and, finally, that even in the presence of substantial arterial hypoxemia, the V-Spec Monitoring System is able to accurately measure both MetHb and COHb. The simultaneous and accurate detection of both COHb and MetHb during significant degrees of hypoxia could be of clinical utility in situations where simultaneous hypoxemia and dyshemoglobinemia coexist.

The clinical importance for noninvasive measurement of COHb and MetHb has been reviewed in numerous case reports.[27–31] The ability to diagnose suspected cases of CO exposure or elevated MetHb levels in a timely manner and to avoid unnecessary invasive testing requires good sensitivity and specificity. Detecting elevated COHb and MetHb

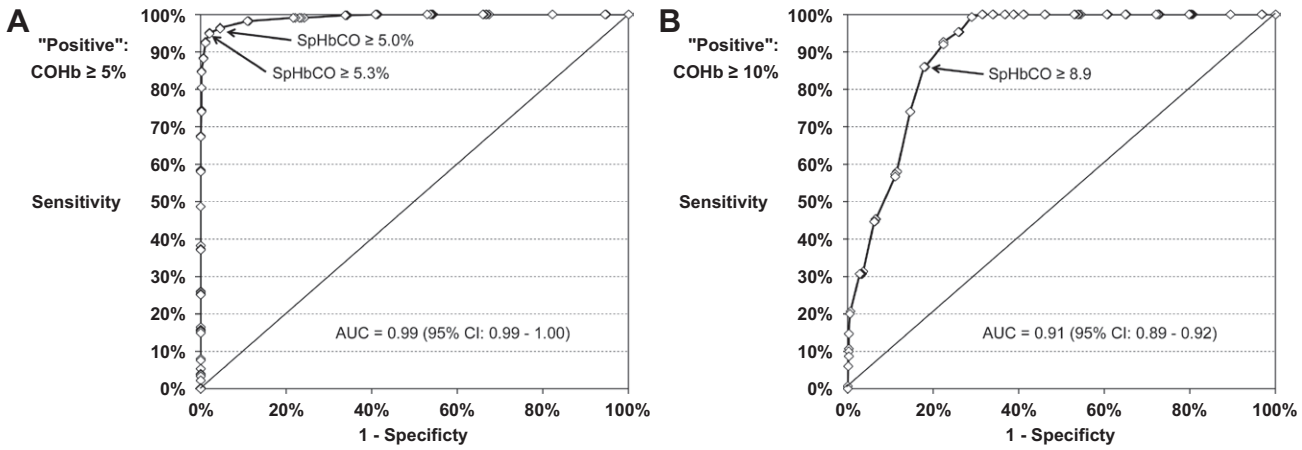

Figure 5. Receiver operating characteristic curves for determination of carboxyhemoglobinemia, defined for (A) as COHb ≥ 5% and for (B) as ≥10%. Area under the curve (AUC) with 95% confidence limits is shown on the figures. Key cutoff points are indicated by arrows.

Table 4. Methemoglobin Bias (SpHbMet – MetHb) Summary

MetHb range	0–4%	4%–8%	8%–12%	All	*P* value
Paired observations, *n*	239	72	227	538	
Mean bias (%)	0.26	0.96[a]	0.29	0.36	<0.0001
Precision (%)	0.29	0.48	1.11	0.80	<0.0001
A_{rms} (%)	0.38	1.07	1.14	0.88	
Lower limit of agreement (%)	−0.31 (−0.37 to −0.26)	0.01 (−0.20 to 0.23)	−1.89 (−2.12 to −1.67)	−1.21 (−1.35 to −1.07)	
Upper limit of agreement (%)	−0.37 (−0.26 to 0.83)	−0.20 (0.23 to 1.90)	−2.12 (−1.67 to 2.47)	−1.35 (−1.07 to 1.94)	
Sao_2 range	**70%–80%**	**80%–90%**	**90%–100%**	**All**	***P* value**
Paired observations, *n*	36	114	388	538	
Mean bias (%)[b]	−0.65	−0.09	0.59	0.36	<0.0001
Precision (%)	0.76	0.68	0.70	0.80	0.27
A_{rms} (%)	0.99	0.68	0.92	0.88	
Lower limit of agreement (%)	−2.22 (−2.62 to −1.82)	−1.45 (−1.69 to −1.20)	−0.79 (−0.93 to −0.66)	−1.21 (−1.35 to −1.07)	
Upper limit of agreement (%)	0.92 (0.62 to 1.22)	1.28 (1.04 to 1.51)	1.97 (1.78 to 2.17)	1.94 (1.77 to 2.10)	

A_{rms} = root-mean-square error; Bias = SpHbCO − COHb; limits of agreement (with 95% confidence intervals) = mean bias ± 1.96·SD (adjusted for repeated measures), which represents 95% of expected data; MetHb = methemoglobin level from arterial blood samples; Precision = SD of bias ; Sao_2 = functional oxygen saturation from arterial blood samples; SpHbMet = methemoglobin level read by pulse spectroscopy.

[a]Different from other groups by multiple comparisons.

[b]All different from each other by multiple comparisons.

levels to enable rapid initiation of appropriate treatment may improve outcomes and increases patient safety. The measurement of elevated COHb levels, in particular, can lead to different treatment procedures, such as normal or hyperbaric oxygen administration. ROC curves for detecting abnormal level of COHb indicate very good sensitivity and specificity.

Detecting elevated COHb levels, even at levels that may not be clinically deleterious, may identify sources of CO exposure at home or at work that could cause serious harm. This, in turn, could lead to testing of others exposed to an event that might otherwise go unrecognized. Determining whether COHb levels are improving in patients requires more frequent measurements. In this case, noninvasive and continuous point-of-care technologies are preferable. Simultaneous hypoxemia would be likely in cases of smoke inhalation and loss of consciousness.

Limitations of our study included the small number of subjects for the COHb and MetHb portions of the study. Gender and ethnicity balance is harder to achieve with smaller numbers. However, repeated-measures data are so robust that we are able to detect highly significant effects that are actually not clinically significant. For example, the difference in Spo_2 bias with a decrease in Sao_2 to 70% amounts to <1%. This is also the first human testing of a pulse spectrometer device, which has not yet undergone multiple iterations, correcting the algorithms for multiple different simultaneous hemoglobin species, such as MetHb and deoxyhemoglobin. Initial versions of multiple-wavelength oximeters had some difficulty with separation of multiple different hemoglobin species before correction with further human testing.[32,33] This is because only real recorded in vivo data for the calibration of the device can be used. The extreme bias of Spo_2 under the influence of MetHb is an example of the need to include real absorbance information in the algorithm, as the first release was developed without considering any MetHb spectra. The in vivo data recorded during this study can be used to increase the algorithm's performance, and further releases of the device could have a revised Spo_2 algorithm that is more robust to MetHb.

In conclusion, pulse spectroscopy, involving the spectral analysis of hundreds of wavelengths of light, demonstrates

Table 5. Spo_2 Bias (Spo_2 – Sao_2) Summary with Carboxyhemoglobinemia

COHb range	0–5%	5%–10%	10%–15%	All	*P* value
Paired observations, *n*	433	322	149	904	
Mean bias (%)	0.55[a]	−0.83	−1.48	−0.28	<0.0001
Precision (%)	2.79	2.99	2.64	2.96	0.75
A_{rms} (%)	2.84	3.10	3.01	2.97	
Lower limit of agreement (%)	−4.98 (−5.45 to −4.52)	−6.74 (−7.30 to −6.18)	−6.71 (−7.32 to −6.10)	−6.11 (−6.44 to −5.79)	
Upper limit of agreement (%)	6.08 (5.41 to 6.75)	5.07 (4.14 to 6.01)	3.76 (3.02 to 4.50)	5.56 (5.08 to 6.04)	
Sao_2 range, COHb ≥4%	**70%–80%**	**80%–90%**	**90%–100%**	**All**	***P* value**
Paired observations, *n*	66	89	334	489	
Mean bias (%)	0.90	0.22	−1.75[a]	−1.03	<0.0001
Precision (%)	4.03	2.87	2.22	2.86	<0.0001
A_{rms} (%)	4.09	2.86	2.82	3.03	
Lower limit of agreement (%)	−7.16 (−8.38 to −5.94)	−5.51 to 5.95	−6.13 to 2.63	−6.67 to 4.60	
Upper limit of agreement (%)	8.96 (6.67 to 11.25)	5.95 (4.56 to 7.34)	2.63 (2.14 to 3.13)	5.56 (5.08 to 6.04)	

A_{rms} = root-mean-square error; Bias = Spo_2 – Sao_2; COHb = carboxyhemoglobin level from arterial blood samples; limits of agreement (with 95% confidence intervals) = mean bias ± 1.96 · SD (adjusted for repeated measures), which represents 95% of expected data; Precision = SD of bias; Sao_2 = functional oxygen saturation from arterial blood samples; Spo_2 = oxygen saturation read by pulse spectroscopy.

[a]Different from other groups by multiple comparisons.

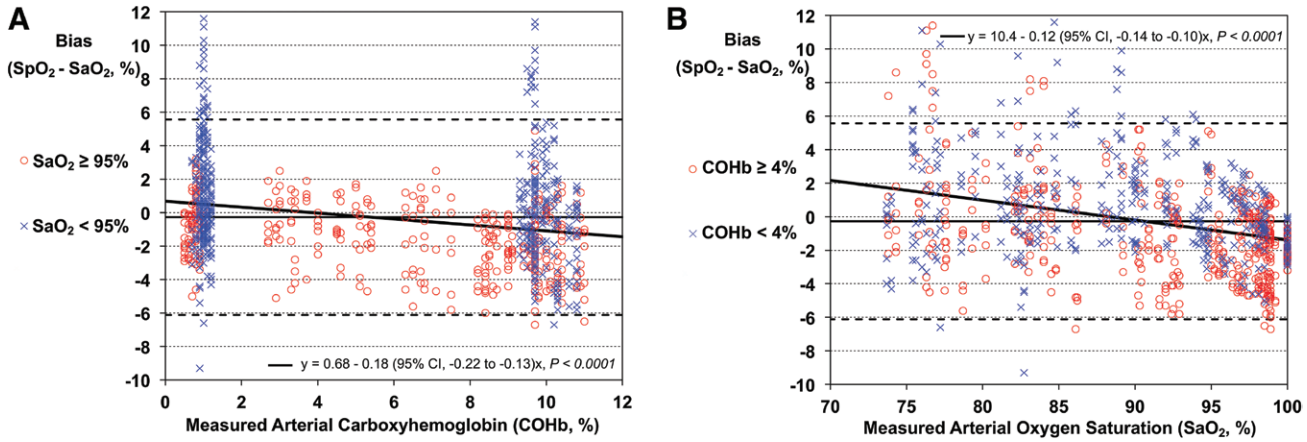

Figure 6. Pulse spectroscopy oxygen saturation (Spo_2) reading bias (Spo_2 – measured arterial oxygen saturation [%Sao_2]) during carboxyhemoglobinemia. Data represent 4 V-Spec devices placed simultaneously on different fingers and 2 V-Spec forehead sensors. A, Bias as a function of carboxyhemoglobin level (COHb). Open red circles indicate data obtained with Sao_2 ≥95%, while blue Xs show data for Sao_2 <95%. B, Spo_2 bias as a function of Sao_2. Open red circles indicate data for COHb ≥4%, while blue X's show data for COHb <4%. Mean bias is displayed as a solid horizontal line, and the upper and lower limits of agreement (mean bias ± 1.96 · SD [adjusted for repeated measures]) are shown by dashed horizontal lines. The regression lines and equations are shown on the figures with 95% confidence limits for the slope. Bias increased at both lower Sao_2 and lower COHb ($P < 0.0001$).

Table 6. Spo_2 Bias (Spo_2 – Sao_2) Summary with Methemoglobinemia

MetHb range	0–5%	5%–10%	10%–15%	All	*P* value
Paired observations, *n*	251	123	168	542	
Mean bias (%)[a]	−1.13	−12.88	−10.26	−6.62	<0.0001
Precision (%)	3.56	4.38	5.03	6.71	<0.0001
A_{rms} (%)	3.73	13.60	11.42	9.42	
Lower limit of agreement (%)	−8.11 (−8.99 to −7.23)	−21.48 (−23.19 to −19.77)	−20.21 (−21.29 to −19.13)	−19.82 (−20.70 to −18.95)	
Upper limit of agreement (%)	5.86 (5.19 to 6.52)	−4.28 (−5.56 to −3.00)	−0.30 (−1.80 to 1.19)	6.57 (5.82 to 7.32)	
Sao_2 range, MetHb ≥4%	**70%–80%**	**80%–90%**	**90%–100%**	**All**	***P* value**
Paired observations, *n*	23	48	244	315	
Mean bias (%)[a]	−3.24	−7.51	−12.46	−11.03	<0.0001
Precision (%)	3.18	3.57	4.18	4.90	0.092
A_{rms} (%)	4.49	8.30	13.14	12.07	
Lower limit of agreement (%)	−9.60 (−11.91 to −7.28)	−14.88 (−17.11 to −12.66)	−20.72 (−21.76 to −19.67)	−20.61 (−21.56 to −19.65)	
Upper limit of agreement (%)	3.12 (1.31 to 4.92)	−0.13 (−2.62 to 2.35)	−4.19 (−5.07 to −3.32)	−1.45 (−2.47 to −0.42)	

A_{rms} = root-mean-square error; Bias = Spo_2 – Sao_2; limits of agreement (with 95% confidence intervals) = mean bias ± 1.96 · SD (adjusted for repeated measures), which represents 95% of expected data; MetHb = methemoglobin level from arterial blood samples; Precision = SD of bias; Sao_2 =functional oxygen saturation from arterial blood samples; Spo_2 = oxygen saturation read by pulse spectroscopy.

[a]All different from each other by multiple comparisons.

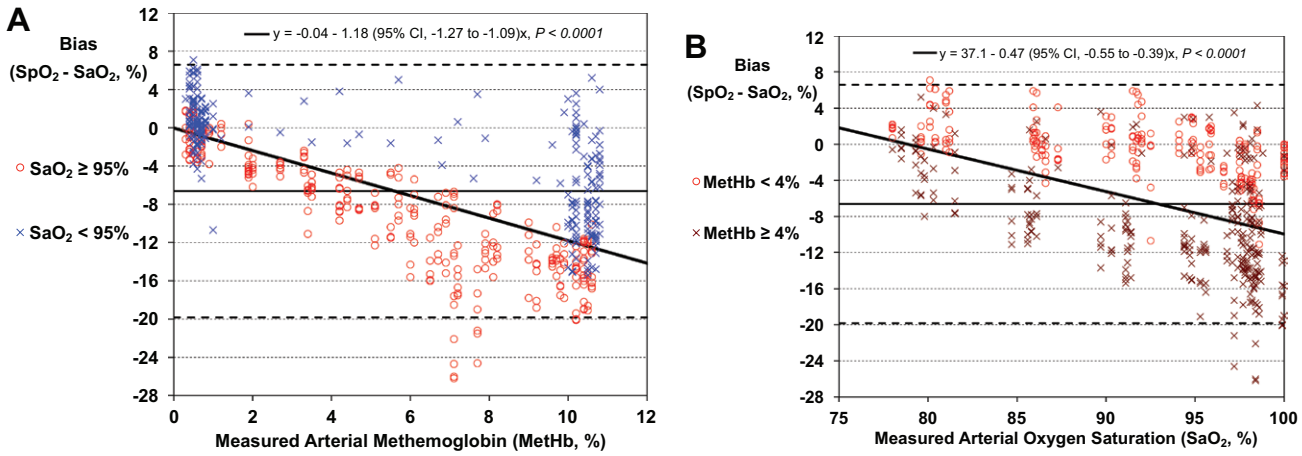

Figure 7. Pulse spectroscopy oxygen saturation (Spo_2) reading bias (Spo_2 – measured arterial oxygen saturation [Sao_2]) during methemoglobinemia. Data represent 4 V-Spec devices placed simultaneously on different fingers and 2 V-Spec forehead sensors. A, Bias as a function of methemoglobin level (MetHb). Open red circles indicate data for Sao_2 ≥95%, while blue Xs show data for Sao_2 <95%. B, Bias as a function of Sao_2. Open red circles indicate data for MetHb <4%, while brown Xs show data for MetHb ≥4%. Mean bias is displayed as a solid horizontal line, and the upper and lower limits of agreement (mean bias ± 1.96 · SD [adjusted for repeated measures]) are shown by dashed horizontal lines. The regression lines and equations are shown on the figures with 95% confidence limits for the slope. Bias increased at both lower Sao_2 and lower MetHb ($P < 0.0001$).

a high level of accuracy for measuring hypoxemia, COHb, and MetHb up to 11%, which did not degrade strongly during hypoxemia.

DISCLOSURES

Name: Axel Kulcke, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Axel Kulcke has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Axel Kulcke worked for Senspec.
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: John Feiner has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
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Conflicts of Interest: Amadeus Holmer worked for Senspec.
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Attestation: Josef Hayoz has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Josef Hayoz works for Sentec.
Name: Philip Bickler, MD, PhD.
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Attestation: Philip Bickler has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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This manuscript was handled by: Maxime Cannesson, MD, PhD.

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