

# Effects of Changes in Arterial Carbon Dioxide and Oxygen Partial Pressures on Cerebral Oximeter Performance

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## ABSTRACT

**Background:** Cerebral oximetry (cerebral oxygen saturation;  $\text{ScO}_2$ ) is used to noninvasively monitor cerebral oxygenation.  $\text{ScO}_2$  readings are based on the fraction of reduced and oxidized hemoglobin as an indirect estimate of brain tissue oxygenation and assume a static ratio of arterial to venous intracranial blood. Conditions that alter cerebral blood flow, such as acute changes in  $\text{Paco}_2$ , may decrease accuracy. We assessed the performance of two commercial cerebral oximeters across a range of oxygen concentrations during normocapnia and hypocapnia.

**Methods:** Cased FORE-SIGHT Elite (CAS Medical Systems, Inc., USA) and Covidien INVOS 5100C (Covidien, USA) oximeter sensors were placed on 12 healthy volunteers. The fractional inspired oxygen tension was varied to achieve seven steady-state levels including hypoxic and hyperoxic  $\text{Pao}_2$  values.  $\text{ScO}_2$  and simultaneous arterial and jugular venous blood gas measurements were obtained with both normocapnia and hypocapnia. Oximeter bias was calculated as the difference between the  $\text{ScO}_2$  and reference saturation using manufacturer-specified weighting ratios from the arterial and venous samples.

**Results:** FORE-SIGHT Elite bias was greater during hypocapnia as compared with normocapnia ( $4 \pm 9\%$  vs.  $0 \pm 6\%$ ;  $P < 0.001$ ). The INVOS 5100C bias was also lower during normocapnia ( $5 \pm 15\%$  vs.  $3 \pm 12\%$ ;  $P = 0.01$ ). Hypocapnia resulted in a significant decrease in mixed venous oxygen saturation and mixed venous oxygen tension, as well as increased oxygen extraction across fractional inspired oxygen tension levels ( $P < 0.0001$ ). Bias increased significantly with increasing oxygen extraction ( $P < 0.0001$ ).

**Conclusions:** Changes in  $\text{Paco}_2$  affect cerebral oximeter accuracy, and increased bias occurs with hypocapnia. Decreased accuracy may represent an incorrect assumption of a static arterial–venous blood fraction. Understanding cerebral oximetry limitations is especially important in patients at risk for hypoxia-induced brain injury, where  $\text{Paco}_2$  may be purposefully altered. (ANESTHESIOLOGY 2018; 128:97-108)

CEREBRAL oximetry is a noninvasive optical monitor of brain oxygenation that integrates arterial and venous oxyhemoglobin saturation in cortical tissue using near-infrared spectroscopy.<sup>1,2</sup> The volumetric contribution of cerebral capillary blood is minimal (less than 2%).<sup>3</sup> Clinical studies have examined the use of cerebral oximetry for goal-directed care of patients requiring cardiopulmonary bypass,<sup>4</sup> with decreased oximeter readings correlating with an increased incidence of neuropsychiatric impairment,<sup>5</sup> stroke,<sup>6</sup> organ dysfunction, and mortality.<sup>7,8</sup> Other studies have examined cerebral oximetry for detection of cerebral hypoperfusion during carotid endarterectomy,<sup>9</sup> adequacy of advanced cardiac life support,<sup>10</sup> and directing care of patients with traumatic brain injury.<sup>11</sup> However, case reports describe ischemic events occurring without changes in cerebral oximeter signals<sup>12</sup> and potential for false-positive cerebral oximeter desaturation events not correlated with adverse neurologic sequelae in beach chair position.<sup>13,14</sup> In addition, there is currently poor correlation between cerebral oximeter desaturation events and the incidence of adverse neurologic outcomes in cardiac surgery patients and traumatic brain injury.<sup>15,16</sup>

### What We Already Know about This Topic

- In the indirect assessment of brain tissue oxygenation (cerebral oxygen saturation;  $\text{ScO}_2$ ) by cerebral oximetry, a key assumption is that the ratio of arterial to venous blood remains constant. Physiologic variables that can affect the arterial to venous blood ratio, such as oxygenation and arterial carbon dioxide tension, may introduce bias into the oximeter readings.
- Using commercially available devices,  $\text{ScO}_2$  measurements during both normocapnia and hypocapnia were compared directly with arterial and jugular venous hemoglobin saturations across both a hypoxic and hyperoxic range of arterial oxygenation.

### What This Article Tells Us That Is New

- Induction of hypocapnia decreased cerebral oxygen saturation ( $\text{ScO}_2$ ); of significant interest is the observation that with hypocapnia the oximeters increased bias and overestimated brain tissue oxygenation.
- The data indicate that caution and thoughtful clinical interpretation should be exercised in the assessment of cerebral oximeter readings, especially in patients with decreased arterial carbon dioxide levels and those at risk of cerebral hypoxia-induced injury.

Cerebral oximetry relies on assumptions requiring additional study to determine the degree of measurement limitation. Cerebral oximetry measures the ratio of

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oxyhemoglobin to total hemoglobin (oxy- plus deoxy-) within cortical tissue as an indirect estimate of regional brain tissue oxygenation (cerebral oxygen saturation;  $\text{ScO}_2$ ). Near-infrared light is transmitted through the forehead with two sets of photodetectors used to capture light from different tissue depths. Although it is assumed that this allows discrimination of signal from shallow tissues (*i.e.*, scalp, galea, or bone sinuses) in favor of deeper brain tissue measurement, the actual degree of extracranial contamination is unclear and likely varies significantly between devices and associated algorithms.<sup>17</sup> Additional assumptions of cerebral oximetry include uniform patient tissue geometry, metabolic rate, and a constant ratio of venous to arterial blood volume (*e.g.*, 70% venous/30% arterial) in the sensor field using values derived from previous cerebral positron emission tomography volumetric imaging studies.<sup>18</sup>

Although previous human studies evaluated the performance of cerebral oximetry in relation to hypoxia,<sup>2,19,20</sup> possible error in measurement from varying  $\text{Paco}_2$  has not been examined. Changes in  $\text{Paco}_2$  alter the relative volumes of arterial and venous blood in the brain<sup>21</sup> and may create significant error with the assumption of a fixed venous/arterial volume ratio, because a 10-mmHg decrease in  $\text{Paco}_2$  can decrease the intracranial arterial blood volume by 50%.<sup>3</sup> Compared with normoxemia, hypoxemia (80% arterial saturation) with isocapnia results in a significant increase in middle cerebral artery flow velocity (approximately 25%) that is attenuated with hypocapnia.<sup>22</sup> Various degrees of hypocapnia combined with hypoxia may individually alter cerebral blood flow (CBF),<sup>23</sup> highlighting the need to examine changes in both simultaneously. Although studies have noted a direct relationship between  $\text{ScO}_2$  and  $\text{Paco}_2$ ,<sup>24–27</sup> we are unaware of studies in which oximeter accuracy and bias were examined in relation to an acute change in  $\text{Paco}_2$  during concurrent changes in  $\text{Pao}_2$ . This has clinical significance because patients at risk for cerebral ischemia, those with brain injury, or those undergoing neurosurgical procedures are often purposefully held in a hypocapnic state with mechanical ventilation. Hyperoxia is relevant because patients routinely receive ventilation with high inspired oxygen levels in the operating room or intensive care unit (ICU), which often results in a high  $\text{Pao}_2$  unless there is underlying pulmonary dysfunction.

Clinical trials with cerebral oximetry often include interventions that manipulate inspired oxygen and minute ventilation. This may significantly alter total and regional CBF patterns with unclear effects on the underlying theoretical measurement assumptions.<sup>28,29</sup> Accurate interpretation of cerebral oximetry values relies on knowing whether these interventions result in a true increase in brain oxygen levels or are an artifact from extracranial signal contamination or changes in the ratio of arterial and venous cerebral volume. Accordingly, the purpose of this healthy volunteer investigation was to assess the accuracy and limitations of cerebral oximetry under simulated clinical conditions with changes in both  $\text{Paco}_2$  and  $\text{Pao}_2$ . We hypothesized that hypocapnia

in combination with extremes of inspired oxygen would decrease both the accuracy and precision of cerebral oximetry.

## Materials and Methods

All of the protocols were approved by the University of California at San Francisco Committee on Human Research (San Francisco, California) and written informed consent obtained before any intervention. Methods were similar to previous evaluation of cerebral oximeter accuracy by Bickler *et al.*<sup>2</sup> Thirteen subjects were enrolled in this study. One subject completed less than half of the breathing protocol due to nausea and was eliminated from analysis. Of the 12 subjects completing the study, there were eight men and four women of various ethnicities (nine white, one Asian, and two black) and a range of skin tones (half lighter and half darker). Subjects were between the ages of 23 and 30 yr of age (mean  $\pm$  SD,  $26 \pm 2$  yr) with average body mass index ( $24.8 \pm 3.9 \text{ kg/m}^2$ ). Preenrollment screening with a history and physical examination excluded cardiopulmonary conditions that could affect measurements and safety. Pregnancy was excluded by history. Data were collected between October 2013 and February 2014.

A 22-gauge radial arterial catheter was placed to monitor blood pressure and sample arterial blood. A right internal jugular venous catheter was inserted under ultrasound visualization using a Seldinger technique with the wire directed cranially. A 5-cm, 20-gauge catheter was threaded over the wire and advanced toward the jugular bulb. The intravascular location of the catheter and position of the catheter tip within the internal jugular bulb was confirmed by ultrasound and adjusted if necessary.

The accuracy of two commercial cerebral oximeters (FORE-SIGHT Elite; CAS Medical Systems, Inc., USA; and INVOS 5100C; Covidien, USA) was evaluated under two  $\text{Paco}_2$  levels and a range of fractional inspired oxygen ( $\text{FIO}_2$ ). An oximeter from each manufacturer was placed on the forehead symmetrically to either side of midline with maximal separation as allowed by the subject's anatomy. Right or left position was determined by previous subject randomization. Sensors were covered with a dark opaque cloth to minimize signal contamination by ambient light.

Arterial and venous blood were withdrawn simultaneously. A 1-ml jugular venous sample was obtained over a period of 30 s to prevent nonjugular bulb reflux into the catheter from the distal circulation.<sup>2,30</sup> Arterial and venous gases were analyzed using either the ABL 800 or ABL 90 multiwavelength blood gas analyzers (Radiometer Medical, Denmark), because the device available changed during the study period. Daily calibrations were performed to ensure accuracy. Consistency between the devices was ensured by concurrent analysis of a subset of arterial and venous blood samples before use in our protocol, and only one device was used on any particular subject.

Blood samples were analyzed to determine arterial and venous oxygen saturations,  $\text{Pao}_2$  and  $\text{Paco}_2$ . A weighted reference saturation was calculated for each pair of samples

using the fixed ratio of arterial to venous intracranial blood described previously by the device manufacturers. Weighting ratios are 25%/75% arterial/venous for the INVOS and 30%/70% for the FORE-SIGHT. Heart rate, arterial blood pressure, peripheral capillary oxygen saturation,  $\text{FIO}_2$ , and end-tidal carbon dioxide were also continuously monitored throughout the study and recorded at each point of blood gas analysis. All of the data were collected and stored using a LabVIEW (National Instruments, USA) interface, which allowed temporal resolution from the various continuous monitoring devices. Continuous data values used in the analysis (e.g.,  $\text{ScO}_2$ ) were averaged over a 10-s period spanning the timestamp that marked the initiation of each arterial blood draw.

Baseline data were obtained with subjects breathing room air. The volunteers were then exposed to set levels of  $\text{FIO}_2$ , including 1.0, 0.8, 0.6, 0.4, 0.21 (room air), 0.085, and 0.06, using a semiopen breathing system that allowed each  $\text{FIO}_2$  to be held constant for the necessary period of equilibration. The two hypoxic levels ( $\text{FIO}_2$  approximately 0.085 and 0.06) were titrated to target an arterial oxygen saturation ( $\text{Sao}_2$ ) of 90% and 80%, respectively. To evaluate the effect of varying  $\text{Paco}_2$ , the same set of  $\text{FIO}_2$  measurements was performed under conditions of both normocapnia and hypocapnia. We targeted a  $\text{Paco}_2$  of 40 and 30 mmHg, respectively, with an analysis cutoff of 35 mmHg. Any sample outside the intended  $\text{Paco}_2$  range was reclassified for analysis. Hypocapnia was induced by coached subject hyperventilation, and normocapnia required the addition of carbon dioxide in the inspired gas flow.  $\text{Paco}_2$  levels were maintained constant at the desired target level by continuously monitoring end-tidal carbon dioxide, which was then compared with the  $\text{Paco}_2$  blood gas samples to determine a relative difference and allow small corrections in subject breathing or exogenous inspired carbon dioxide as needed. To negate any sequential effects, subjects were randomly assigned to both the order of  $\text{Paco}_2$  studied (normocapnia first or hypocapnia first) and the order in which the  $\text{FIO}_2$  was varied (increasing  $\text{FIO}_2$  vs. decreasing  $\text{FIO}_2$ ).

### Statistical Analysis

The study was powered based on previous experience with similar repeated-measures analyses for cerebral oximeters.<sup>2</sup> A  $P$  value less than 0.05 was considered significant. An *a priori* power calculation based on previous data<sup>2</sup> and pilot studies of paired differences in  $\text{ScO}_2$  between step changes in  $\text{Sao}_2$  or  $\text{Paco}_2$  determined that we would need seven subjects to detect an average difference of 3%  $\text{ScO}_2$ , based on the SD of differences determined to be less than 2%. Stated another way, the use of repeated measures is very robust and powerful for these data because measured changes in  $\text{ScO}_2$  within subjects is very consistent. Based on previous experience, we used 12 subjects to increase our sensitivity to detect smaller differences. The repeated-measures regression used for our primary analysis is more robust because it combines all data, using a continuous

measurement scale. Statistical analyses were performed with JMP 11.0 (SAS Institute, USA) and Stata 14 (StataCorp, USA).

Oximeter bias from each paired arterial and venous blood sample was computed as the difference between the displayed oximeter reading and the weighted reference saturation described above. Bland–Altman plots were constructed displaying the bias as a function of the weighted reference saturation under both normocapnic and hypocapnic conditions. In addition, the following standard statistics associated with device performance were calculated across the range of  $\text{FIO}_2$  examined: mean bias, SD, 95% limits of agreement (LOA) adjusted for repeated measures,<sup>31</sup> and average root mean square error ( $A_{\text{RMS}}$ ). The 95% CIs for  $A_{\text{RMS}}$  and LOA were calculated using bootstrapping (random resampling with replacement) with 50,000 repetitions. These measures were calculated for each instrument under both normocapnic and hypocapnic conditions, as well as a composite.

Comparison of bias for a given carbon dioxide level within  $\text{FIO}_2$  targets or within reference saturation ranges was determined using repeated-measures ANOVA. Tukey–Kramer honestly significant difference was used for multiple comparisons of values between the different reference saturation ranges. Because multiple comparisons would be excessive for seven different  $\text{FIO}_2$  levels and the primary analysis was a linear regression, these were not performed for the  $\text{FIO}_2$  groups. A paired  $t$  test was used for comparison of values between high and low  $\text{Paco}_2$ .

Linear regression lines were constructed for the bias plots using a repeated-measures analysis. The repeated-measures analysis was performed as a linear mixed-effects analysis using the subject identification as a random effect. Regression of  $\text{ScO}_2$  versus the reciprocal of  $\text{Pao}_2$  using the mixed-effects model fit the data well, with additional variables not significantly improving fit. This regression was analyzed separately for normocapnic or hypocapnic groups with respect to repeated measures. Separate analysis of values near full  $\text{Sao}_2$  ( $\text{FIO}_2 \geq 0.21$ ) used a simple repeated-measures linear regression for  $\text{ScO}_2$  and  $\text{Svo}_2$ . Linearity was examined by testing the statistical significance of a chi-squared term.

### Results

Arterial and venous samples were drawn simultaneously at each inspired oxygen level under both normocapnic and hypocapnic conditions for all 12 subjects. A total of 168 paired samples were analyzed.

Table 1 displays a summary of the oximeter and blood gas data for each of the target  $\text{Paco}_2$  levels and range of specific  $\text{FIO}_2$ .  $\text{Paco}_2$  was controlled within a narrow range, clearly separating the normocapnia and hypocapnia groups, with only 3 of the 168 paired samples requiring reclassification for not meeting the intended  $\text{Paco}_2$ . Mean  $\text{Pao}_2$  for each of the target  $\text{FIO}_2$  levels was similar when comparing analogous samples from the normocapnia and hypocapnia groups.

Although arterial blood pressure showed a statistically significant decrease with hypoxia, this change represented

less than 4-mmHg difference in mean arterial pressure over the range of  $\text{PaO}_2$  and  $\text{PaCO}_2$ . However, we did observe a clinically relevant increase in heart rate at lower  $\text{PaO}_2$  levels (not shown) consistent with previous studies addressing the hemodynamic effects of hypoxia.<sup>22</sup>

### Cerebral Oxygenation

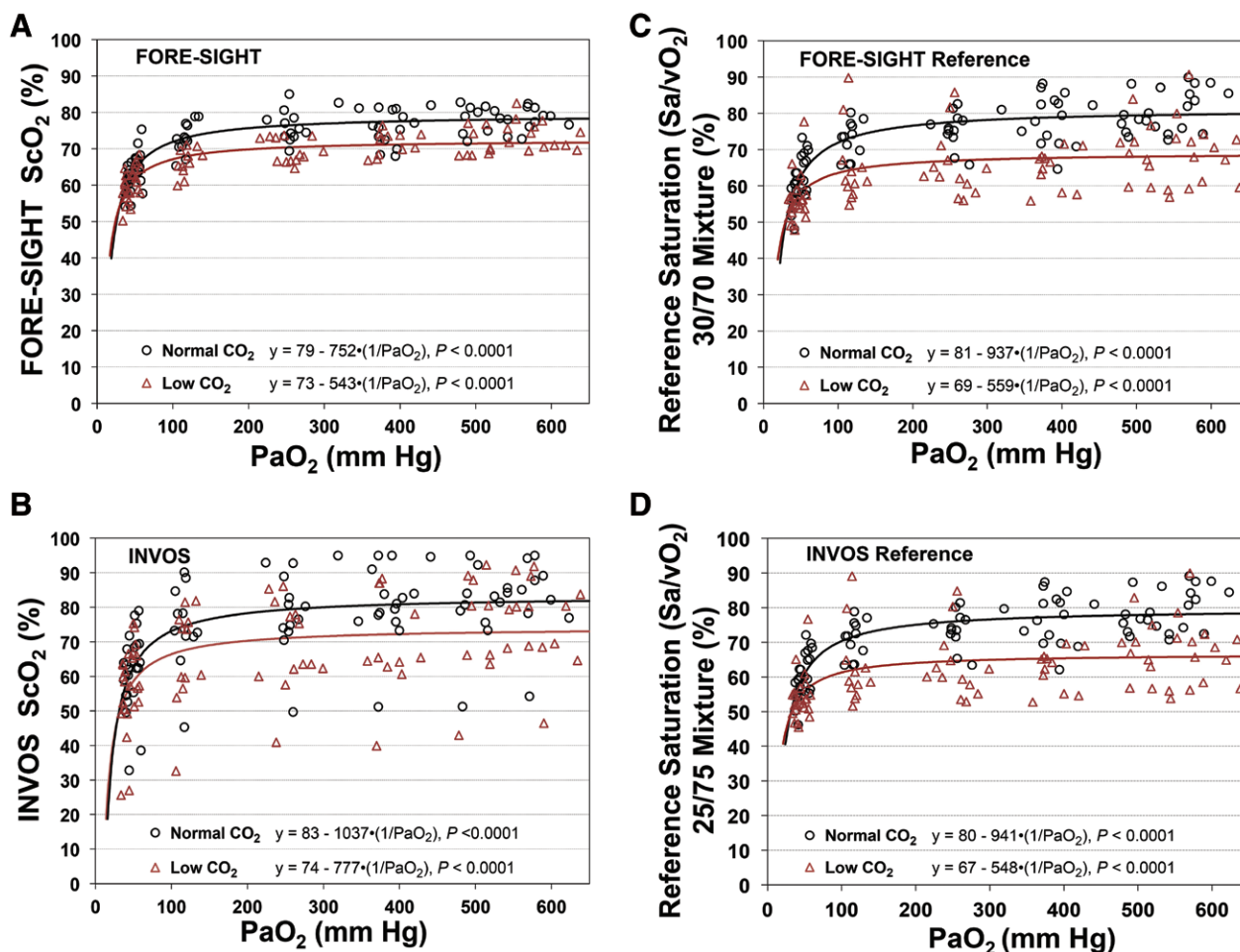
To examine the effect of  $\text{PaCO}_2$  and  $\text{PaO}_2$  on  $\text{ScO}_2$ , displayed values from both the FORE-SIGHT and INVOS measurement systems were plotted as a function of  $\text{PaO}_2$  over the range of  $\text{FIO}_2$  for both normocapnia and hypocapnia (fig. 1, A and B,

**Table 1.** Summary of Cerebral Saturation, Bias, and Blood Gas Data

Data	SaO <sub>2</sub> 80%	SaO <sub>2</sub> 90%	Room Air	FIO <sub>2</sub> 0.4	FIO <sub>2</sub> 0.6	FIO <sub>2</sub> 0.8	FIO <sub>2</sub> 1.0	P Value
<b>Low Carbon Dioxide</b>								
n	12	12	12	12	10	12	13	
PaCO <sub>2</sub> , mmHg	28.6±1.7	28.2±1.9	29.0±1.9	30.1±1.6	29.3±1.8	30.7±2.5	31.7±2.2	< 0.0001
FORE-SIGHT bias, %	4±7	4±9	2±12	4±11	7±5	4±9	3±10	0.38
FORE-SIGHT ScO <sub>2</sub> , %	58±4	62±4	67±4	69±3	71±3	72±3	74±4	< 0.0001
Weighted ref sat, 30%/70%	54.0±4.9	58.3±6.9	65.0±10.3	65.8±9.5	63.9±5.2	67.3±8.1	70.7±8.5	< 0.0001
INVOS bias, %	1±11	4±13	3±18	6±18	8±16	8±16	7±16	0.001
INVOS ScO <sub>2</sub> , %	54±11	60±13	65±14	69±14	70±15	73±14	75±13	< 0.0001
Weighted ref sat, 25%/75%	52.1±5.3	55.9±7.4	62.5±11.1	63.4±10.1	61.4±5.6	65.0±8.6	68.7±9.2	< 0.0001
PaO <sub>2</sub> , mmHg	37.9±3.1	51.4±4.2	118±10	252±20	375±33	499±42	577±53	< 0.0001
SaO <sub>2</sub> , %	80.8±3.6	91.3±2.0	99.2±0.5	99.8±0.2	100.0±0.1	100.0±0.1	100.0±0.0	< 0.0001
PvO <sub>2</sub> , mmHg	21.9±3.1	22.8±4.1	26.4±7.1	27.2±6.3	25.1±3.0	27.5±4.3	31.4±7.2	< 0.0001
SvO <sub>2</sub> , %	42.5±7.5	44.1±9.8	50.3±14.8	51.2±13.5	48.5±7.4	53.4±11.5	58.2±12.2	< 0.0001
Arterial oxygen content, ml oxygen/dl	15.7±2.0	17.8±2.1	19.5±2.1	20.0±2.1	20.3±2.2	20.9±2.0	21.3±2.1	< 0.0001
Venous oxygen content, ml oxygen/dl	8.3±1.8	8.6±2.2	9.7±2.9	9.9±2.6	9.3±1.6	10.4±2.4	11.5±2.8	< 0.0001
Oxygen extraction, ml oxygen/dl	7.4±2.0	9.2±2.3	9.8±3.2	10.1±2.9	11.0±2.0	10.5±2.6	9.8±2.6	< 0.0001
Fractional extraction	0.47±0.10	0.52±0.11	0.50±0.15	0.50±0.13	0.54±0.07	0.50±0.11	0.46±0.11	0.11
<b>Normal Carbon Dioxide</b>								
n	12	12	12	12	14	12	11	
PaCO <sub>2</sub> , mmHg	40.2±2.6	40.5±2.5	40.5±2.7	40.7±2.4	40.5±3.1	40.8±2.7	42.5±3.1	0.04
FORE-SIGHT bias, %	3±5	1±6	±5	1±5	-2±7	-1±5	-4±5	0.0004
FORE-SIGHT ScO <sub>2</sub> , %	61±4	66±5	73±4	76±4	76±5	78±4	79±3	< 0.0001
Weighted ref sat, 30%/70%	58.1±4.6	65.2±5.4	72.7±5.0	75.5±4.9	78.0±7.0	79.0±5.1	82.9±5.4	< 0.0001
INVOS bias, %	1±11	2±12	4±13	4±13	4±13	4±12	2±14	0.14
INVOS ScO <sub>2</sub> , %	58±10	65±11	74±12	78±12	80±11	81±12	84±12	< 0.0001
Weighted ref sat, 25%/75%	56.6±4.8	63.5±5.8	70.9±5.4	73.7±5.3	76.5±7.5	77.5±5.5	81.7±5.8	< 0.0001
PaO <sub>2</sub> , mmHg	41.3±2.5	54.6±3.3	116±9	254±13	379±26	497±41	564±47	< 0.0001
SaO <sub>2</sub> , %	78.8±3.2	89.5±1.5	98.8±0.4	99.7±0.2	99.8±0.2	99.9±0.1	99.9±0.1	< 0.0001
PvO <sub>2</sub> , mmHg	26.7±2.4	29.6±3.7	33.4±3.8	35.6±4.1	37.8±6.0	39.2±5.4	44.0±5.9	< 0.0001
SvO <sub>2</sub> , %	49.2±5.8	54.8±7.8	61.6±7.2	65.1±7.1	68.7±10.0	70.0±7.3	75.6±7.7	< 0.0001
Arterial oxygen content, ml oxygen/dl	15.3±1.9	17.5±2.0	19.4±2.1	20.0±2.0	20.6±1.9	20.8±2.0	20.8±1.9	< 0.0001
Venous oxygen content, ml oxygen/dl	9.6±1.6	10.7±2.0	12.0±2.0	12.7±2.1	13.5±2.3	13.6±1.9	14.6±2.2	< 0.0001
Oxygen extraction, ml oxygen/dl	5.7±1.1	6.8±1.7	7.4±1.5	7.3±1.5	7.1±2.2	7.2±1.7	6.2±1.5	0.0001
Fractional extraction	0.38±0.07	0.39±0.09	0.38±0.07	0.37±0.07	0.35±0.10	0.35±0.07	0.30±0.07	< 0.0001

Data are mean ± SD. Bias was calculated as the difference between cerebral oxygen saturation ( $\text{ScO}_2$ ) and the manufacturer-specified weighted arterial ( $\text{SaO}_2$ ) and jugular bulb ( $\text{SvO}_2$ ) saturation. For weighted  $\text{SaO}_2/\text{SvO}_2$ , weighting for jugular venous blood to arterial blood mixture is 70%/30% for the FORE-SIGHT and 75%/25% for the INVOS. *P* values are from repeated-measures ANOVA.

Fractional extraction = oxygen extraction/arterial oxygen content; Oxygen extraction = arterial oxygen content minus venous oxygen content;  $\text{PaO}_2$  = arterial oxygen partial pressure;  $\text{PvO}_2$  = jugular venous oxygen partial pressure; Ref sat = reference saturation.



**Fig. 1.** The relationship of raw cerebral oxygen saturation (ScO<sub>2</sub>) output from the FORE-SIGHT (A) and INVOS (B) measurement systems were plotted as a function of PaO<sub>2</sub> over the range of inspired oxygen concentrations for both normocapnia and hypocapnia. C and D plot the weighted reference saturation against the PaO<sub>2</sub>. The reference saturation was derived from the same hemoximeter values for both plots, but using the 30%/70% arterial-venous weighting ratio for the FORE-SIGHT (C) and the 25%/75% ratio for the INVOS (D). The data were fitted to the inverse of PaO<sub>2</sub>. All of the relationships were statistically significant,  $P < 0.0001$ . Equations are shown on the figures.

respectively). Both the INVOS and FORE-SIGHT ScO<sub>2</sub> plots were fit by the same nonlinear inverse function (see figures for equations). ScO<sub>2</sub> increased in a curvilinear manner with increasing PaO<sub>2</sub>, with modest but significant increases in the ScO<sub>2</sub> above a PaO<sub>2</sub> of approximately 100 mmHg.

For FIO<sub>2</sub> of room air and higher, data were analyzed by linear regression, because the chi-squared term was not statistically significant. From room air to the hyperoxic PaO<sub>2</sub> range, the ScO<sub>2</sub> continued rising at higher FIO<sub>2</sub> for both FORE-SIGHT and INVOS ( $P < 0.0001$ ). Hypocapnia resulted in decreased ScO<sub>2</sub> values as compared with normocapnia across the range of inspired oxygen concentrations for both the FORE-SIGHT ( $P < 0.0001$ ) and INVOS ( $P = 0.0061$ ) monitors. However, the slopes were not statistically different between normal and low PaCO<sub>2</sub>.

Figure 1, C and D, plot the weighted reference saturation against the PaO<sub>2</sub>. The reference saturation was derived from the same blood gas values for both plots but using the 30%/70% arterial-venous weighting ratio for the FORE-SIGHT (fig. 1C) and the 25%/75% ratio for the INVOS (fig. 1D). Similar to

the raw ScO<sub>2</sub> plots for each oximeter, both the FORE-SIGHT and INVOS weighted reference saturations increased in a curvilinear manner with increasing PaO<sub>2</sub> and were well fit with a simple inverse function. Hypocapnia resulted in a decrease in the weighted reference saturation over the range of PaO<sub>2</sub> for both the FORE-SIGHT and INVOS ( $P < 0.0001$ ).

### Accuracy of ScO<sub>2</sub> Measurement

Accuracy was assessed using bias calculated by comparing the ScO<sub>2</sub> with a weighted saturation determined from the blood gas samples, as described previously. Table 2 displays oximeter accuracy data broken down by corresponding weighted saturation ranges for both normocapnic and hypocapnic conditions. Mean bias, precision, LOA, and A<sub>RMS</sub> with corresponding CIs are shown for designated ranges of weighted reference saturations. Over the entire range of experimental conditions, the mean bias  $\pm$  precision and A<sub>RMS</sub> error were  $2 \pm 8\%$  and  $8\%$  (95% CI, 7 to 9%) for the FORE-SIGHT and  $4 \pm 14\%$  and  $14\%$  (95% CI, 13 to 16%) for the INVOS.

**Table 2.** Summary of Bias Statistics for Two Cerebral Oximeters

	Weighted Reference Saturation, %				
Bias Statistic	45–60	60–75	75–95	All	P Value
FORE-SIGHT					
Low carbon dioxide					
n, paired observations	36	38	9	83	
Mean bias, %	9	4	–15*	4	< 0.0001
Precision, %	5	6	8	9	0.45
A <sub>RMS</sub> , %	10 (9 to 11)	7 (6 to 8)	17 (13 to 21)	10 (9 to 11)	
Lower limit of agreement, %	–3 (–7 to 2)	–7 (–11 to –3)	–35 (–45 to –24)	–10 (–14 to –6)	
Upper limit of agreement, %	20 (17 to 22)	15 (13 to 18)	5 (–11 to 20)	18 (16 to 20)	
Normal carbon dioxide					
n, paired observations	10	36	39	85	
Mean bias, %†	5	1	–4	0	< 0.0001
Precision, %	4	5	5	6	0.95
A <sub>RMS</sub> , %	7 (4 to 9)	5 (4 to 6)	6 (5 to 8)	6 (5 to 7)	
Lower limit of agreement, %	–4 (–8 to 1)	–8 (–12 to –5)	–14 (–18 to –10)	–10 (–12 to –8)	
Upper limit of agreement, %	14 (10 to 18)	11 (9 to 14)	7 (4 to 10)	9 (7 to 11)	
INVOS					
Low carbon dioxide					
n, paired observations	44	30	9	83	
Mean bias, %	8	6	–12*	5	< 0.0001
Precision, %	11	19	9	15	0.0001
A <sub>RMS</sub> , %	14 (11 to 16)	19 (17 to 22)	14 (9 to 20)	16 (14 to 18)	
Lower limit of agreement, %	–14 (–25 to –4)	–33 (–47 to –19)	–31 (–43 to –20)	–18 (–24 to –12)	
Upper limit of agreement, %	31 (24 to 38)	45 (38 to 51)	8 (–1 to 18)	28 (25 to 32)	
Normal carbon dioxide					
n, paired observations	13	40	32	85	
Mean bias, %	5	6	–2	3	0.13
Precision, %	6	10	15	12	0.01
A <sub>RMS</sub> , %	8 (6 to 10)	12 (10 to 14)	14 (11 to 18)	12 (11 to 14)	
Lower limit of agreement, %	–7 (–15 to 0)	–15 (–26 to –5)	–32 (–42 to –21)	–15 (–21 to –9)	
Upper limit of agreement, %	18 (14 to 22)	27 (21 to 33)	28 (22 to 34)	21 (19 to 24)	

Bias was calculated as the difference between cerebral oxygen saturation (ScO<sub>2</sub>) and the manufacturer-specified weighted arterial (SaO<sub>2</sub>) and jugular bulb (SvO<sub>2</sub>) saturation. In weighted SaO<sub>2</sub>/SvO<sub>2</sub>, weighting for jugular venous blood to arterial blood mixture is 70%/30% for the FORE-SIGHT and 75%/25% for the INVOS; precision is the SD of the bias; A<sub>RMS</sub> are average root mean square error (with 95% CI); limits of agreement (with 95% CI); mean bias ± 1.96 SD (adjusted for repeated measures). Mean bias was compared by repeated-measures ANOVA and precision compared by Levene's test.

\*Data are different from other groups.

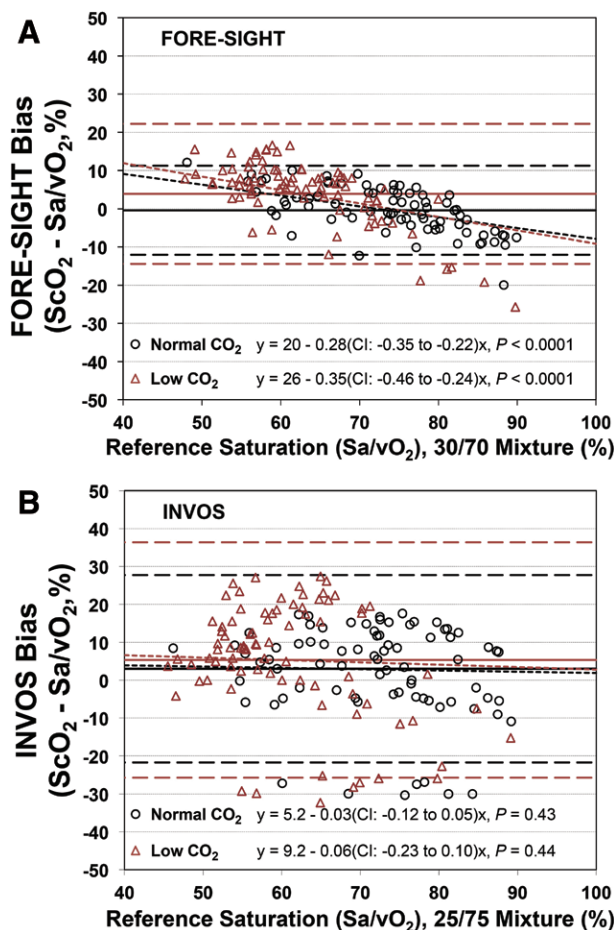
†Data are all different by multiple comparisons (Tukey–Kramer honestly significant difference).

Figure 2 displays Bland–Altman plots of oximeter bias *versus* weighted reference saturation for both devices. As in previous studies, bias for the FORE-SIGHT monitor under conditions of normocapnia (fig. 2A) was greater at lower weighted reference saturations, indicated by the negative bias plot slope (slope –0.28;  $P < 0.0001$ ). Stated differently, the FORE-SIGHT tended to overestimate the ScO<sub>2</sub> at lower saturations while underestimating it at higher saturations. Bias was also more positive during hypocapnia as compared with normocapnia ( $4 \pm 9\%$  *vs.*  $0 \pm 6\%$ ;  $P < 0.001$ ). Hypocapnia altered the bias plot slope, –0.35 *versus* –0.28 for normocapnia ( $P = 0.010$ ). The LOA and A<sub>RMS</sub> were greater for hypocapnia than normocapnia, suggesting greater variability at low carbon dioxide.

The plot of bias as a function of weighted reference saturation for the INVOS monitor (fig. 2B) showed marginally negative slopes for both normocapnia (–0.03) and hypocapnia (–0.06) that were not significant. Bias was more positive during hypocapnia than normocapnia ( $5 \pm 15\%$  *vs.*  $3 \pm 12\%$ ;  $P = 0.010$ ).

Hypocapnia did not appreciably alter the relationship of bias to the weighted reference saturation with similar slopes between the two PaCO<sub>2</sub> conditions. The LOA and A<sub>RMS</sub> errors were larger for hypocapnia as compared with normocapnia. Both values were larger for the INVOS than for the FORE-SIGHT.

Figure 3 plots the effect of PaO<sub>2</sub> on bias to determine whether the oximeter accuracy varied as a function of increasing PaO<sub>2</sub>. For the FORE-SIGHT (fig. 3A), bias decreased with increasing PaO<sub>2</sub> under normocapnic conditions ( $P < 0.001$ ) but was relatively constant under hypocapnic conditions. As in the Bland–Altman plots, bias was more positive for hypocapnia as compared with normocapnia across the range of PaO<sub>2</sub> ( $P < 0.0001$ ). The slope of the relationship of bias to PaO<sub>2</sub> was significantly more negative for normocapnia as compared with hypocapnia ( $P = 0.03$ ). For the INVOS monitor (fig. 3B), bias remained relatively constant with increasing PaO<sub>2</sub> for normocapnia, whereas bias increased with increasing PaO<sub>2</sub> during hypocapnia.



**Fig. 2.** Bland-Altman plots of bias as a function of the weighted reference saturation based arterial oxygen saturation ( $\text{SaO}_2$ )/mixed venous oxygen saturation ( $\text{SvO}_2$ ) measured by hemoximeter for the FORE-SIGHT (A) and INVOS (B) cerebral oximeters for normal and low carbon dioxide conditions. Solid horizontal lines represent mean bias, whereas coarse dashed horizontal lines indicate the 95% limits of agreement for each data group. Fine dashed lines show linear regressions for normal and low carbon dioxide conditions. The regressions were statistically significant for FORE-SIGHT ( $P < 0.0001$ ) but not for the INVOS. Equations are shown on the figures with the 95% CI for the slopes.

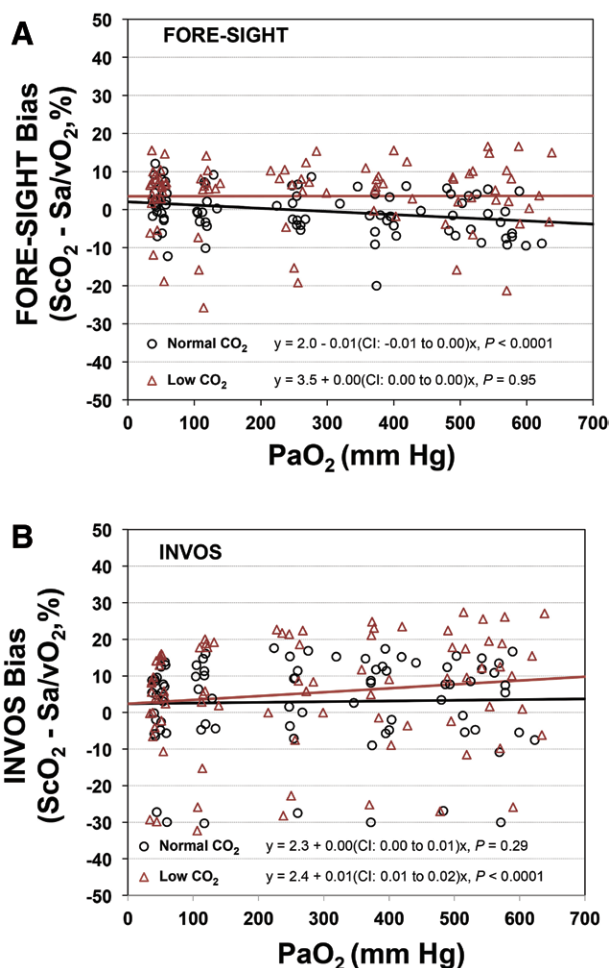
( $P < 0.0001$ ). Again, bias was greater and more positive for hypocapnia than normocapnia ( $P = 0.004$ ). The slope of the relationship between bias and  $\text{PaO}_2$  was increased for hypocapnia as compared with normocapnia ( $P = 0.04$ ).

### Relationship of Arterial and Venous Cerebral Oxygen Levels

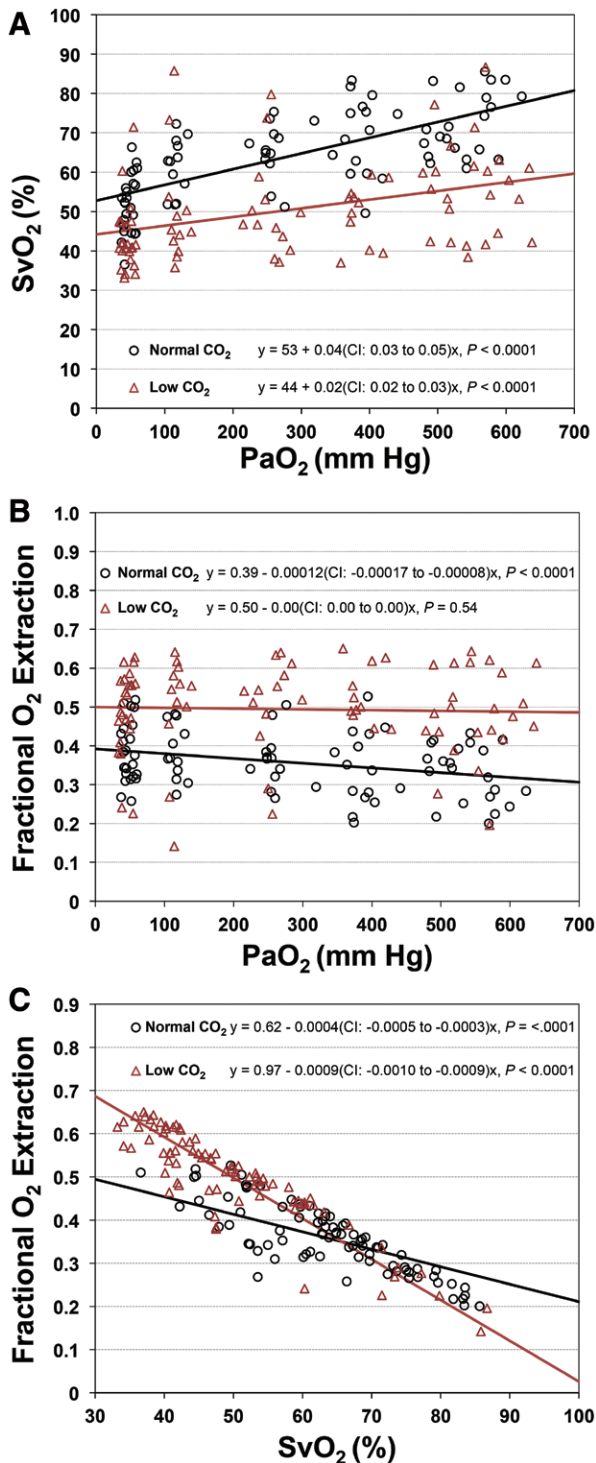
Given the known effects of  $\text{PaCO}_2$  on  $\text{CBF}$ ,<sup>21</sup> we plotted jugular bulb oxygen saturation ( $\text{SvO}_2$ ) as a function of  $\text{PaO}_2$  under both normocapnic and hypocapnic conditions (fig. 4A).  $\text{SvO}_2$  increased linearly with  $\text{PaO}_2$  under conditions of both normocapnia (slope = 0.04;  $P < 0.0001$ ) and hypocapnia (slope = 0.02;  $P < 0.0001$ ). Hypocapnia caused a decrease in  $\text{SvO}_2$  and flattening of the slope ( $P < 0.0001$ ), suggesting

greater oxygen extraction. Jugular venous oxygen content similarly increased linearly with  $\text{PaO}_2$  under both normocapnic and hypocapnic conditions (not shown). Again, hypocapnia caused a decrease in jugular venous oxygen content over the range of  $\text{PaO}_2$  and flattened the slope of the plot (not shown).

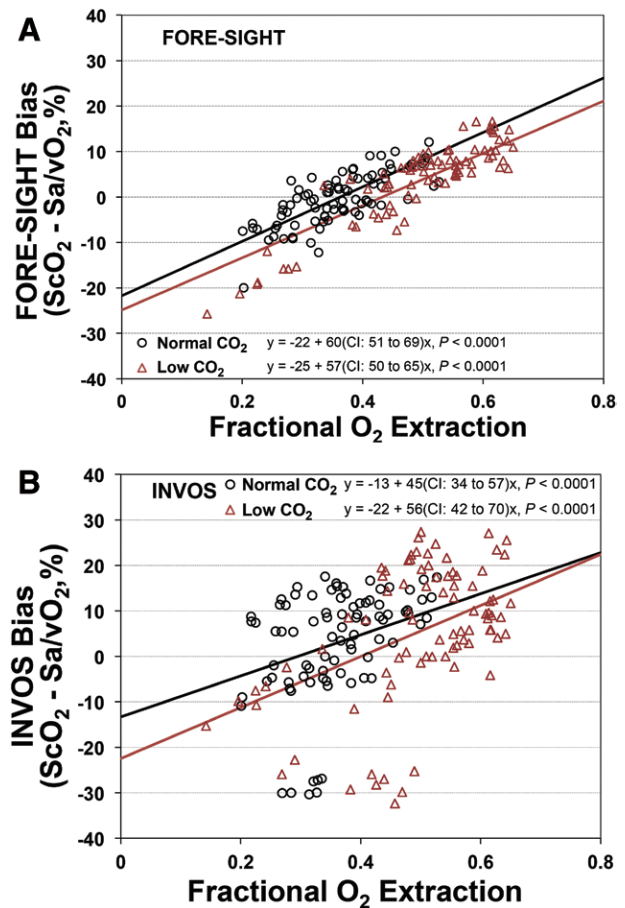
Overall oxygen extraction remained relatively constant with increasing  $\text{PaO}_2$  (plot not shown). However, extraction was greater during hypocapnia ( $9.7 \pm 2.7 \text{ ml/dl}$ ) as compared with normocapnia ( $6.9 \pm 1.7 \text{ ml/dl}$ ;  $P < 0.0001$ ). Oxygen extraction was normalized to arterial oxygen content to produce a fractional oxygen extraction (FOE) and eliminate the effect of baseline differences in oxygen content (fig. 4B). When FOE was plotted against  $\text{PaO}_2$ , the FOE decreased with increasing  $\text{PaO}_2$  for normocapnia ( $P < 0.0001$ ). Hypocapnia



**Fig. 3.** Cerebral oximeter reading bias (instrument reading minus weighted saturation value from blood gas analysis) versus arterial  $\text{Po}_2$  for FORE-SIGHT (A) and INVOS (B) instruments. Lines show linear regressions for normal and low  $\text{PaCO}_2$  conditions. For the FORE-SIGHT, the regression was significant for the high carbon dioxide ( $P < 0.0001$ ) but not for the low carbon dioxide ( $P = 0.95$ ). For the INVOS, the regression was not significant for the high carbon dioxide ( $P = 0.28$ ) but was for the low carbon dioxide ( $P < 0.0001$ ). Equations are shown on the figures with the 95% CI for the slopes.



**Fig. 4.** Physiologic data based on hemoximeter measurements of arterial and jugular venous blood sampling. (A) Jugular venous saturation ( $SvO_2$ ) plotted against  $PaO_2$ . The regressions were significant for both high and low carbon dioxide ( $P < 0.0001$ ). (B) Fractional oxygen extraction versus  $PaO_2$ , which was statistically significant for high carbon dioxide ( $P < 0.0001$ ) but not for low carbon dioxide ( $P = 0.54$ ). (C) Fractional oxygen extraction versus  $SvO_2$ . The relationships for both high and low carbon dioxide were statistically significant ( $P < 0.0001$ ). Equations are shown on the figures with the 95% CI for the slopes.



**Fig. 5.** Relationship between cerebral oximeter reading bias and cerebral fractional oxygen extraction for the FORE-SIGHT (A) and INVOS (B) monitors. The relationships were statistically significant for both devices ( $P < 0.0001$ ). Equations are shown on the figures with the 95% CI for the slopes.

not only caused an increase in FOE over the entire range of  $PaO_2$  but also negated the decrease in FOE noted at higher  $PaO_2$  under normocapnic conditions. This increase in the slope for hypocapnia compared with normocapnia was significant ( $P < 0.0001$ ).

Because many studies used  $SvO_2$  as a surrogate for CBF and extraction, we plotted FOE as a function of  $SvO_2$  (fig. 4C). FOE was negatively correlated with  $SvO_2$  and increased as  $SvO_2$  decreased ( $P < 0.0001$ ). Hypocapnia magnified this relationship with a more negative slope ( $P = 0.005$ ).

We next plotted oximeter bias as a function of FOE to assess for a relationship. For normocapnia, FORE-SIGHT bias (fig. 5A) increased with FOE ( $P < 0.0001$ ). Hypocapnia resulted in a uniform decrease in the bias across the range of FOE ( $P < 0.0001$ ) without changing the slope of the relationship.

For the INVOS oximeter (fig. 5B) under conditions of normocapnia, bias increased with increasing FOE ( $P < 0.0001$ ). With hypocapnia, bias decreased as compared with normocapnia. The difference in the slopes between normocapnia and hypercapnia was not significant.

## Discussion

Our study shows that cerebral oximetry reflects changes in brain tissue oxygenation with increasing  $\text{PaO}_2$ , but coexisting hypocapnia causes a clinically significant decrease in  $\text{ScO}_2$  with a moderate positive bias in the readings. This suggests that assumptions of a constant arterial–venous blood volume may be incorrect under certain conditions and that  $\text{PaCO}_2$  levels should be taken into account when interpreting  $\text{ScO}_2$ .

### Relationship of Cerebral Oximeter Performance with $\text{PaO}_2$

The relationship between  $\text{PaO}_2$  level and cerebral oxygenation was curvilinear, similar to previous studies<sup>32</sup> (fig. 1).  $\text{FIO}_2$  greater than 0.3 is common during surgery and ICU care. In the corresponding hyperoxic range, increases in cerebral saturation occurred with increasing  $\text{PaO}_2$  despite arterial hemoglobin saturations remaining constant near 100%. This increase was likely driven by increased dissolved oxygen and greater cerebral venous saturation. Previous studies note a positive correlation between  $\text{ScO}_2$  and cerebral venous saturation.<sup>19</sup>

The accuracy of  $\text{ScO}_2$  estimates of cerebral oxygenation varied with the  $\text{PaO}_2$ . For the FORE-SIGHT, bias was positive at low saturations but progressively decreased as the saturation increased, becoming negative in the hyperoxic range (fig. 2A), thus overestimating the state of cerebral oxygenation with hypoxia while underestimating it with hyperoxia. This relationship did not exist for the INVOS monitor, possibly related to greater variability in the readings.

The relationship of bias to  $\text{PaO}_2$  under conditions of normocapnia depended on the oximeter. For the FORE-SIGHT, bias decreased with increasing  $\text{PaO}_2$ , whereas for the INVOS there was no change as  $\text{PaO}_2$  increased. However, the data variability for this INVOS relationship was large. In contrast, bias was closely correlated with FOE, likely from the higher weighting of the venous compartment in the oximeter output. This suggests that  $\text{ScO}_2$  accuracy is perhaps more affected by hypocapnic changes in CBF rather than the  $\text{PaO}_2$ .

### Relationship of Cerebral Oximeter Performance with $\text{PaCO}_2$

A shift from normocapnia to hypocapnia caused a decrease in  $\text{ScO}_2$  across the range of measured  $\text{PaO}_2$  for both oximeters (fig. 1). This is consistent with previous research demonstrating that  $\text{ScO}_2$  increased in a linear fashion with increasing carbon dioxide during conditions of constant  $\text{PaO}_2$ ,<sup>24–27,32</sup> although  $\text{ScO}_2$  accuracy and bias were not systematically examined.

With hypocapnia, one would expect lower CBF and a decreased cerebral blood volume due to constriction of the cerebral vasculature.<sup>28</sup> In our study, hypocapnia resulted in increased FOE and a decreased cerebral venous oxygen content. These values correspond with physiologic changes expected from a decrease in CBF during hypocapnia. Both the  $\text{ScO}_2$  and weighted reference saturation decreased during hypocapnia (fig. 1). However,  $\text{ScO}_2$  decreased less than the reference saturation, resulting in a more positive bias for

hypocapnia (compared with normocapnia) for both oximeters. When analyzing bias as a function of  $\text{PaO}_2$  (fig. 3), hypocapnia increased both mean bias and the bias across all of the measured  $\text{PaO}_2$  levels. However, when examining bias as a function of weighted reference saturation (fig. 2), part of this difference in mean bias appears to be driven by a clustering of the hypocapnic values at the lower reference saturations where bias is greater. This is consistent with previous accuracy studies under normocapnic hypoxia.<sup>2</sup> Presumably the leftward clustering of hypocapnic values is due to increased FOE and the anchoring effect of the greater weighting of the venous fraction, resulting in a lower weighted reference saturation for any given  $\text{PaO}_2$  with hypocapnia. This results in a significantly greater bias with hypocapnia.

Commercially available cerebral oximeters assume a fixed ratio of arterial to venous intracranial blood volumes. However, the specific fixed arterial–venous weighting ratio varies modestly between oximeter models as a result of differences in the signal processing algorithm and original device calibration studies (*e.g.*, a 25%/75% fixed ratio is used for the INVOS, whereas a 30%/70% is used for the FORE-SIGHT). However, based on imaging studies, changes in CBF seen with altered  $\text{PaCO}_2$  levels manifest as changes in intracranial arterial blood volume without a significant change in venous blood volume.<sup>29</sup> This change in arterial blood volume is linear in relation to  $\text{PaCO}_2$ , and a  $\text{PaCO}_2$  decrease of similar magnitude (40 to 30 mmHg) is demonstrated to create a twofold decrease in both the intracranial arterial blood volume and the fraction of arterial blood (46 to 23%) based on a study by Ito *et al.*<sup>3</sup> Because the arterial–venous weighting ratio of the oximeter is fixed, we would expect decreases in arterial flow during hypocapnia to create significant error. Our data demonstrate that, with acute hypocapnia (which decreases brain oxygen levels), the oximeters tend to overestimate the state of cerebral oxygenation, a bias that is even greater at lower states of oxygenation.

A study of patients with traumatic brain injury with positron emission tomography imaging noted that hyperventilation reduced CBF, increased FOE, and increased ischemic brain volume.<sup>33</sup> Our study found substantially increased variability in the  $\text{ScO}_2$  between subjects under conditions of hypocapnia. It may be that hypocapnia has significantly different effects on vascular tone between individuals. In addition, a complex interplay of CBF, oxygen extraction, and contamination from other signal sources may also be at work.<sup>23</sup> Hypocapnia resulted in a rightward shift and flattened slope of the plot of cerebral venous saturation *versus*  $\text{PaO}_2$  (fig. 4A), suggesting greater FOE during the lower flow state. Our results (fig. 4B) also noted that, under normocapnic conditions, FOE decreased with increasing  $\text{PaO}_2$ , yet with hypocapnia this relationship no longer remained. This suggests that, under the lower flow hypocapnic state, oxygen extraction may have reached its limit. Approaching an extraction limit may also increase the  $\text{ScO}_2$  measurement variability between individuals.

Finally, the contribution of extracranial tissue perfusion to the signal is unknown, particularly under conditions of hypocapnia and hypoxia. Although previously assumed to be small, recent studies have demonstrated a 7 to 17% decrease in  $\text{ScO}_2$  readings when scalp cutaneous blood flow was manipulated by inflating a circumferential cranial pneumatic cuff.<sup>34</sup> The magnitude of this decrease varied depending on the oximeter used and was only partially attenuated by using a four-wavelength measurement present in newer-generation devices.<sup>17</sup> Although cutaneous blood flow appears relatively unaffected by  $\text{PaCO}_2$ ,<sup>35</sup> blood flow may also be affected by the increases in heart rate and cardiac output seen with hypoxemia. Any extracranial flow differences may contribute a larger error, because hypocapnia decreases the overall CBF and individual differences may account for some of the between-subject variability.

### Limitations

We studied healthy volunteers rather than patients at risk for cerebral ischemia. Patients often have structural central nervous system abnormalities and perturbations in autoregulation of CBF that may alter cerebral oximetry in a manner distinct from healthy individuals. Patient studies remain important, because use of vasoactive medications, rapidly changing hemodynamics, hematomas of skull and extracranial tissues, and pulmonary dysfunction can all affect global and regional cerebral oxygenation. Therefore, it is important to exercise caution in translating our volunteer findings to patients. Our results reflect acute changes in  $\text{PaCO}_2$ , which might change if the level is maintained for an extended period.

For this study, we focused on normocapnia and hypocapnia, and our results do not cover hypercapnic conditions often encountered in the ICU and operating room due to pulmonary insufficiency. Based on unpublished experience with targeted hypercapnia, we found that reliably maintaining a  $\text{PaCO}_2$  in the range of 50 mmHg with the addition of hypoxia was technically difficult due to issues with minute ventilation stability. In addition, the protocol necessary to encompass this third condition would be significantly longer. Therefore, we chose to focus on normocapnia and hypocapnia in this initial study. Elucidating the accuracy of cerebral oximeters under conditions of hypercapnia with varying  $\text{FIO}_2$  remains an important question for future investigation.

In attempting to explain the variation observed in  $\text{ScO}_2$  and oximeter bias, we used venous saturation and FOE as surrogates for CBF. As such, we made a number of assumptions about the expected changes in CBF and volume based on previous studies addressing the complex interplay of  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , and cardiac output on cerebral hemodynamics. Because we did not measure CBF or blood volume directly using either transcranial Doppler or imaging techniques, it is impossible to quantitate to what degree our various experimental conditions altered these parameters. Future efforts

combining measurement of CBF or cerebral blood volume with assessments of cerebral oximeter accuracy could provide insight into the basis of the observed changes.

Although the number of subjects was sufficient based on U.S. Food and Drug Administration recommendations for validation of oximetric devices, cerebral oximeter readings varied considerably between individuals, which increased with hypocapnia, leading to corresponding variability in the bias. This was especially true for the INVOS monitor, because the mean error of the measurements was higher than for the FORE-SIGHT. This variability may have prevented the resolution of trends in the bias by failing to reach significance under certain conditions.

Finally, different patient positioning may have an effect on accuracy. Although the 30° of head elevation in our study is similar to ICU positioning, a supine position is more common in the operating room. Although intracranial blood flow appears to be minimally affected by position changes based on transcranial Doppler<sup>36</sup> and thermodilution,<sup>37</sup> there is early evidence that  $\text{ScO}_2$  signals may decrease with a change from supine to standing in stroke patients in the distribution of the stroke<sup>38</sup> and with head-up tilt in anesthetized patients,<sup>39</sup> although 20° changes in head position did not significantly affect cerebral oximetry in awake volunteers.<sup>26</sup> Unfortunately, the accuracy of cerebral oximeters has not been studied with varying position, and so it is unclear whether our study results reflect other positions.

### Clinical Implications

The decreased CBF induced by hypocapnia results in a decreased  $\text{ScO}_2$ , with an increased bias. The oximeter is in effect overestimating the  $\text{ScO}_2$  under this condition. This is relevant during measurement in patients undergoing induced hyperventilation. Understanding this increased bias is especially important for patients at risk for hypoxia-induced injury, such as in the setting of increased intracranial pressure.

Normalizing  $\text{PaCO}_2$  by eliminating hyperventilation and raising  $\text{PaO}_2$  by increasing  $\text{FIO}_2$  both increased cerebral oxygen saturation in our study. With hyperoxia, the  $\text{ScO}_2$  reflected an increase in cerebral oxygenation but underestimated the actual amount. Future clinical studies verifying changes in cerebral oxygenation are essential to understanding whether recommended interventions of recent clinical trials using cerebral oximetry truly augment brain oxygenation. Our results demonstrate that changes in cerebral oximeter readings may not accurately reflect changes in cerebral oxygenation under hypocapnic conditions secondary to altered CBF.

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## Competing Interests

The authors declare no competing interests.

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