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The Accuracy of a Near-Infrared Spectroscopy Cerebral Oximetry Device and Its Potential Value for Estimating Jugular Venous Oxygen Saturation

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Abstract

Background—An intriguing potential clinical use of cerebral oximeter measurements ($S_{ct}O_2$) is the ability to noninvasively estimate jugular bulb venous oxygen saturation ($S_{jv}O_2$). Our purpose in this study was to determine the accuracy of the FORE-SIGHT® (CAS Medical Systems; Branford, CT), which is calibrated to a weighted average of 70% ($S_{jv}O_2$) and 30% arterial saturation, for Food and Drug Administration pre-market approval 510 (k) certification by adapting an industry standard protocol, ISO 9919:2005 [www.ISO.org] (used for pulse oximeters) and to evaluate the use of $S_{ct}O_2$ and S_pO_2 measurements to noninvasively estimate jugular venous oxygen saturation ($S_{nv}O_2$).

Methods—Paired blood gas samples from the radial artery and the jugular venous bulb were collected from 20 healthy volunteers undergoing progressive oxygen desaturation from 100 to 70%. The blood sample pairs were analyzed via co-oximetry and used to calculate the approximate mixed vascular cerebral blood oxygen saturation, or reference $S_{ct}O_2$ values ($refS_{ct}O_2$), during increasing hypoxia. These reference values were compared to bilateral FORE-SIGHT $S_{ct}O_2$ values recorded simultaneously with the blood gas draws to determine its accuracy. Bilateral $S_{ct}O_2$ and S_pO_2 measurements were then used to calculate $S_{nv}O_2$ values which were compared to $S_{jv}O_2$.

Results—Two hundred forty-six arterial and 253 venous samples from 18 subjects were used in the analysis. The ipsilateral FORE-SIGHT $S_{ct}O_2$ values showed a tolerance interval (TI) of $[-10.72 \ 10.90]$ Lin's concordance correlation coefficient (CCC) with standard error (SE) of 0.83 ± 0.073 with the $refS_{ct}O_2$ values calculated using arterial and venous blood gases. The combined data had a CCC of 0.81 ± 0.059 with TI of $[-9.22 \ 9.40]$ with overall bias was 0.09% and amplitude of the root mean square of error after it was corrected with random effects analysis was 2.92%. The bias and variability values between the ipsilateral and the contralateral FORE-SIGHT $S_{ct}O_2$ measurements varied from person to person. The $S_{nv}O_2$ calculated from the ipsilateral $S_{ct}O_2$ and S_pO_2 data showed a CCC + SE of 0.79 ± 0.088 , TI = $[-14.93 \ 15.33]$, slope of 0.98, Y-Intercept of 1.14%) with $S_{jv}O_2$ values with a bias of 0.20% and an Arms of 4.08%. The $S_{nv}O_2$ values calculated independently from contralateral forehead FORE-SIGHT $S_{ct}O_2$ values were not as correlated with the $S_{jv}O_2$ values (contralateral side CCC + SE = 0.72 ± 0.118 , TI = $[-14.86 \ 15.20]$, slope of 0.66 and y-intercept of 20.36%).

Conclusions—The FORE-SIGHT cerebral oximeter was able to estimate oxygen saturation within the tissues of the frontal lobe under conditions of normocapnia and varying degrees of hypoxia (with 95% confidence interval of $[-5.60 \ 5.78]$ with ipsilateral blood ample data). These findings from healthy volunteers also suggest that the use of the calculated $S_{nv}O_2$ derived from $S_{ct}O_2$ and S_pO_2 values may be a reasonable noninvasive method of estimating $S_{jv}O_2$ and therefore global cerebral oxygen consumption in the clinical setting. Further laboratory and clinical research is required to define the clinical utility of near-infrared spectroscopy determination of $S_{ct}O_2$ and $S_{nv}O_2$ in the operating room setting.

Introduction

Cerebral oximetry using near-infrared spectroscopy (NIRS) is a continuous, noninvasive, optical-based method of measurement used to estimate cerebral tissue oxygen saturation ($S_{ct}O_2$). NIRS devices, including both cerebral and conventional pulse oximeters, calculate oxy- and deoxyhemoglobin concentration by measuring the absorbance of light at specific wavelengths.¹ However, cerebral oximeters do not preferentially measure oxygen saturation in pulsatile blood flow. Instead, cerebral NIRS devices estimate $S_{ct}O_2$ by measuring oxy- and deoxyhemoglobin in arterioles, capillaries and venules in intracerebral tissue. The device interrogates a region of cerebral tissue approximately 1.5 cm below the sensor (half the distance between the transmitter and the receiver) and provides a weighted measure of hemoglobin changes in the arterial, capillary, and venous compartments, which makes this a regional cerebral tissue saturation monitor. As opposed to arterial saturation determined from conventional pulse oximetry (a measurement made from the changes in absorbance due to changes in concentration at the apex and the nadir of pulsatile flow between the transmitter and the receiver), cerebral oximetry may allow for more clinically nuanced information about cerebral oxygen supply and demand, which can be gleaned by examining the venous component of the cerebral blood flow (CBF) by mathematically manipulating $S_{ct}O_2$ with S_pO_2 .

The United States Food and Drug Administration requires cerebral oximeters meet parts of the International Organization for Standards (ISO) # 9919:2005 performance standards established for pulse oximeters when requesting pre-market 510(k) clearance. This ISO standard calls for a root-mean-square difference (measure of accuracy) of less than or equal to 4.0 % over a range of 70 to 100 % arterial blood oxygen saturation. While these standards are for pulse oximeters, they are generally adopted for the purpose of evaluating cerebral oximeters. The specifications also recommend stepped reductions in inspired oxygen concentration as a method to assess the accuracy of any type of oximeter used for patient monitoring.

There is no universally agreed upon “gold standard” measurement of $S_{ct}O_2$ in healthy volunteers. However, comparison of NIRS generated $S_{ct}O_2$ -generated values with reference $S_{ct}O_2$ ($refS_{ct}O_2$) values derived from simultaneously sampling and measurement of radial artery oxygen saturation (S_aO_2) and jugular bulb venous oxygen saturation ($S_{jv}O_2$) via co-oximetry as performed by Henson et al² as the standard.

The purpose of this study was to: 1) determine the accuracy of the FORE-SIGHT cerebral oximeter $S_{ct}O_2$ values for Food and Drug Administration 510 (k) pre-market approval by comparing them to $refS_{ct}O_2$ values derived from simultaneous radial artery and jugular bulb venous samples obtained from healthy subjects during room air breathing, mild hypoxemia and hyperoxemia in the presence of normocapnia; and 2) assess the accuracy of noninvasive venous oxygen saturation ($S_{nv}O_2$) derived from S_pO_2 and $S_{ct}O_2$ values.

Methods

After IRB approval (August, 2004), 10 male and 10 female healthy volunteers aged 21 to 35 years with a body mass index of 18–30 kg·m⁻² were enrolled into the study after signing a written consent form. Because of the relatively low systemic saturation targets, the IRB mandated that we report every 3 subjects to the Data Safety and Monitoring Board for review.

An 18G peripheral IV, 20G radial arterial and a 5F venous jugular bulb cannulae were inserted in each of the 20 subjects under 2% lidocaine HCl local anesthesia. The jugular bulb cannula³ was initially inserted under ultrasound guidance (Sonosite Titan, Sonosite, Seattle, WA) and advanced cephalad until the subject reported minor ear discomfort.⁴ A lateral skull radiograph confirmed cannula tip placement cranial to a line extending from the atlanto-occipital joint space and caudal to the lower margin of the orbit, thus insuring the absence of extracranial venous blood contamination.⁵ Bilateral oximeter sensors were applied to the subject's forehead, symmetrically along the midline to avoid the sagittal sinus and as far above the orbital ridge to maximize interrogation of brain as the hairline allowed, and connected to a dual-channel FORE-SIGHT cerebral oximeter. Continuous venous jugular bulb (S_{jb}O₂) and cardiac output in liters per minute were monitored with a Vigilance hemodynamic monitor (Edwards LifeScience, Irvine, CA), and finger arterial oxygen saturations with a Nellcor pulse oximeter (Model N595, Coviden, Boulder CO) respectively. Periodic noninvasive arterial blood pressure, continuous arterial blood pressure, heart rate and electrocardiogram were monitored with a PROPAQ (Model CS, Welch Allyn, Beaverton, OR). Subjects were positioned supine with the head of the bed elevated 35°.

The subject inspired gas mixtures delivered to a facemask from a sequential gas delivery system^{6,7} (Respiract UDB 1000; Thornhill Research, Toronto, Canada) capable of producing and maintaining target end-tidal partial pressure of oxygen (PetO₂) and carbon dioxide (PetCO₂) values independent of one another. The system works by dividing the inspired breath into 2 components, fresh gas and the last end-tidal breath (which has already reached equilibrium with pulmonary venous gas pressures), such that only the small sample of fresh gas contributes to the gas exchange as long as the alveolar ventilation rate exceeds that of the fresh gas flow rate.⁸ End-tidal O₂ and CO₂ values were continuously measured using a Datex Capnomac monitor (Ultima I V90 EN, GE Healthcare, Waukesha, WI) via a sampling port located on the mask, with a sampling line of approximately 2 meters. Each subject initially inspired 21% O₂ followed by 2 sequences of reduced oxygen breathing designed to produce a progressive and then an acute reduction in blood O₂ saturation. After the period of reduced oxygen breathing, the inspired O₂ concentration was returned to 21% and then increased to 50%. The subject was allowed a brief rest period between the 2 hypoxia sequences. The progressive sequence consisted of 10 steps of 4 minutes with inspired oxygen concentrations of 21, 12, 10, 9, 8, 9, 10, 12, 21, and 50%. The acute sequence consisted of 4 steps with inspired oxygen concentrations of 21, 8, 21, and 50%. The target PetCO₂ during each step of the 2 sequences was 40 mmHg (Figure 1).

Each step was maintained for 4 minutes and paired arterial and jugular venous blood samples were obtained during the last 2 minutes of the step. The jugular venous samples

were drawn at a rate of 2 mL/min and the arterial samples were taken at the midpoint of the jugular venous draws (Figure 2).^{9,10}

If the subject did not reach the desired S_pO_2 minimum target value of 70% during either sequence, the O_2 content in the delivered gas mixture was reduced to 5% FiO_2 and additional blood samples were drawn at the new S_pO_2 plateau. Blood draws were omitted if the subject reached the desired S_pO_2 threshold of 70% in fewer steps or became excessively anxious. Blood samples were analyzed immediately by co-oximetry (Model IL282; Instrumentation Laboratories, Lexington, MA).

The NIRS-derived $S_{ct}O_2$ values were calibrated against S_aO_2 and $S_{jv}O_2$ blood samples using a 3-compartment cerebral blood volume (CBV) model ($refS_{ct}O_2$; equation 1):¹¹

$$refS_{ct}O_2 = K_a * S_aO_2 + K_v * S_{jv}O_2 + K_c * S_cO_2 + Error \quad (1)$$

where the distribution coefficients of arterial (K_a), venous (K_v) and capillary blood (K_c) oxygen saturations are set at 0.3, 0.7, and 0.0 for the FORE-SIGHT® (CAS Medical Systems; Branford, CT), respectively. The ratio of the volume of arterial blood (30%) to venous blood (70%) in the cerebral tissue is based on the work of Ito et al.³⁶ The capillary blood compartment volume is considered negligible and so the capillary blood saturation (S_cO_2) contribution to CBV is considered nil ($K_c = 0.0$). The error term is a generic term that sums the various sources of error that may influence the $S_{ct}O_2$ reading. Equation 1 was solved for jugular bulb venous oxygen saturation ($S_{jv}O_2$; equation 2).

$$S_{jv}O_2 = (refS_{ct}O_2 - K_a * S_aO_2 + Error) / K_v \quad (2)$$

Substituting pulse oximetry (S_pO_2) values for co-oximeter determined S_aO_2 and NIRS $S_{ct}O_2$ values for co-oximeter determined $refS_{ct}O_2$ produced a noninvasive estimate of venous oxygen saturation and global cerebral oxygen consumption ($S_{nv}O_2$; equation 3):

$$S_{nv}O_2 = (S_{ct}O_2 - K_a * S_pO_2 + Error) / K_v \quad (3)$$

Furthermore, the relationship between the arterio-jugular oxygen difference ($AVDO_2$), cerebral metabolic rate for O_2 ($CMRO_2$) and CBF as a function of arterial blood oxygen-carrying capacity (C_aO_2) and venous blood oxygen-carrying capacity ($C_{jv}O_2$)¹² can be expressed in terms of $S_{jv}O_2$, S_aO_2 , partial pressure of oxygen in the arteries (P_aO_2), and partial pressure of oxygen in the jugular vein ($P_{jv}O_2$), if the difference between the arterial and venous concentration of hemoglobin is negligible (equations 4 and 5).

$$CMRO_2 / CBF = (C_aO_2 - C_{jv}O_2) \quad (4)$$

$$CMRO_2 / CBF = (S_aO_2 - S_{jv}O_2) \times (1.34 \times [tHb]) + 0.003 \times (P_aO_2 - P_{jv}O_2) \quad (5)$$

Equation 6 shows the noninvasive version of equation 5 where S_pO_2 and $S_{nv}O_2$ have been substituted for S_aO_2 and $S_{jv}O_2$ respectively to determine the relationship between $CMRO_2$ and CBF:

$$\text{CMRO}_2/\text{CBF} = (\text{S}_p\text{O}_2 - \text{S}_{\text{nv}}\text{O}_2) \times (1.34 \times [\text{tHb}]) + 0.003 \times (\text{P}_a\text{O}_2 - \text{P}_{\text{iv}}\text{O}_2) \quad (6)$$

$\text{CMRO}_2 / \text{CBF}$ is approximately proportional to the difference between $\text{S}_{\text{nv}}\text{O}_2$ and S_pO_2 if the effects of dissolved oxygen ($0.003 \times (\text{P}_a\text{O}_2 - \text{P}_{\text{iv}}\text{O}_2)$) are negligible. In the clinical setting, this approximation using noninvasive parameters can be important because the decrease in $\text{S}_{\text{ct}}\text{O}_2$ can indicate either a decrease in CBF, or an increase in CMRO_2 , or both.

Data Analysis

A priori statistical power analysis determined that a minimum of 100 samples would be required to obtain a 99% confidence interval ($(1 - \alpha)$) of a width of $\pm 4\%$ (each side) around the estimate of the mean with a standard deviation of 5. In the present study, we had 18 subjects with 2 sensors each, and each sensor yielded an average of 13 data points per sensor per subject, which netted an average of 27 data points total per subject. The ipsilateral and contralateral forehead $\text{S}_{\text{ct}}\text{O}_2$ values, filtered within the device with a moving average filter with a window of 6 seconds, recorded at each step of the progressive and acute sequences at the midpoint of the predetermined 30 second jugular venous blood draw to avoid extracranial contamination, as reported by Matta and Lam,⁹ were compared to each other, and the $\text{refS}_{\text{ct}}\text{O}_2$ value, and used to compute $\text{S}_{\text{nv}}\text{O}_2$ which was then compared to $\text{S}_{\text{iv}}\text{O}_2$. A paired Student's *t*-test was used to compare the ipsilateral and contralateral sensor $\text{S}_{\text{ct}}\text{O}_2$ measurements for each subject. The correlation and the Lin's concordance correlation coefficient (CCC)^{13,14} (and the 95% confidence interval denoted as standard error (SE)¹⁵) between $\text{S}_{\text{ct}}\text{O}_2$ and $\text{refS}_{\text{ct}}\text{O}_2$ values were examined by constructing linear regression curves for each subject; for each forehead sensor independently and for both sensors combined. The agreement between ipsilateral and contralateral $\text{S}_{\text{ct}}\text{O}_2$ and $\text{refS}_{\text{ct}}\text{O}_2$ values across all subjects and all samples was explored by constructing the Bland and Altman¹⁶ plot and modified for random effect analysis for repeated measures by Myles and Cui.¹⁷ The degree of error, defined as the difference between the $\text{S}_{\text{ct}}\text{O}_2$ and the $\text{refS}_{\text{ct}}\text{O}_2$ values, was assessed in terms of parametric analysis of the errors, including bias (mean of the difference between FORE-SIGHT $\text{S}_{\text{ct}}\text{O}_2$ and $\text{refS}_{\text{ct}}\text{O}_2$), standard deviation (SD), confidence intervals (bias ± 1.95 SD), tolerance intervals (for 99% of future measurements to be within 95% confidence), and first order linear regression,¹⁸ adjusted for random effects analysis as explained by Myles and Cui¹⁷ and adjustments for repeated measures as previously described.¹³ The analysis was repeated for the error between the calculated $\text{S}_{\text{nv}}\text{O}_2$ values and the co-oximeter-determined venous oxygen saturation values ($\text{S}_{\text{iv}}\text{O}_2$). Additional nonparametric analysis was performed in the form of a cumulative distribution function (CDF) because the error is not exactly normally distributed.¹⁹

Results

Of the 20 subjects enrolled in the study 18 were included in the analysis. The prototype FORE-SIGHT was unable to resolve NIRS measurements from 1 subject due to unexpected attenuation of the light through the tissue and blood gas equipment failure prevented blood gas analysis in another. The non-Gaussian distribution of subjects' demographic information is summarized in Tables 1 and 2.

Sixteen paired arterial and venous blood samples were collected during the progressive phase followed by the acute phase of the experiment from 2 subjects, 15 from 7 subjects, 14 from 6 subjects, 13 from 2 subjects and 7 from 1 subject. Variations in the number of samples collected were due to having to reduce or increase the inspired gas exposure duration to achieve the target S_pO_2 of 70% or the necessity to terminate the hypoxia exposure based on subject tolerance. Of the 254 total paired samples drawn, 8 arterial samples and 1 venous sample could not be analyzed due to clotting of the sample. Therefore 246 arterial and 253 venous samples were analyzed and included in the analysis. The lowest recorded S_aO_2 during the course of the study, across all subjects, was 64%. The $P_{et}CO_2$ was independently targeted to 40 mmHg for the entire experiment, which resulted in mean arterial P_aCO_2 during the 2 phase exposure (example in Figure 1) was 38.8 ± 2.2 mmHg (mean $\pm$ SD). The average of the ipsilateral and contralateral $S_{ct}O_2$ values recorded at baseline during room air breathing was $74.6 \pm 3.8\%$ (mean $\pm$ SD) with a range of 66.6 to 83.3%.

The significance of the difference between ipsilateral and contralateral $S_{ct}O_2$ varied from subject to subject, with overall significance of $P = 0.61$ (Table 3). The ipsilateral $S_{ct}O_2$ correlated better with a CCC $\pm$ SE of 0.83 ± 0.073 and a tolerance interval (TI) of $[-10.72 \ 10.90]$ versus the contralateral side of 0.78 ± 0.098 with TI of $[-10.59 \ 10.74]$, with the combined data showing a CCC of 0.81 ± 0.059 with TI of $[-9.22 \ 9.40]$ (Figure 3, Table 4).

The complete parametric analysis of the errors for the ipsilateral, contralateral, and the combined data are in Table 4. The ipsilateral side was on the same side as the jugular bulb catheter, and the data reflect a more accurate measurement from the sensor located on the same side as the catheter.

The calculated proportional error for all ipsilateral and contralateral $S_{ct}O_2$ values is shown on the random effect analysis-corrected Bland-Altman plot (Figure 4). There was a proportional error of less than 0.04% per decade (for every 10 % change in the (FORE-SIGHT $S_{ct}O_2$ + ref $S_{ct}O_2$) / 2 value; X axis) and the error decreased as saturation values decreased.

The relationship between blood gas-determined venous jugular bulb $S_{jb}O_2$ and the $S_{nv}O_2$ values calculated using the combined ipsilateral and contralateral FORESIGHT readings was examined using linear regression analysis (Figure 5) and a Bland-Altman plot (Figure 6)

The ipsilateral, contralateral and combined data for $S_{nv}O_2$ and the data obtained from the jugular bulb catheter ($S_{jb}O_2$) are compared to the $S_{jb}O_2$ values (Table 5). The data show that the $S_{nv}O_2$ calculated from the same side as the jugular bulb catheter (CCC $\pm$ SE = 0.79 ± 0.088 , TI = $[-14.93 \ 15.33]$) was more accurate than the contralateral sensor (CCC $\pm$ SE = 0.72 ± 0.118 , TI = $[-14.86 \ 15.20]$). The jugular bulb catheter (Vigilance) fared only slightly better with CCC + SE = 0.82 ± 0.078 with a TI of $[-12.60 \ 9.66]$.

The CDF plot of the errors in $S_{ct}O_2$ (Figure 7 and Figure 8) clearly shows subject 2 to be an outlier, thus the parametric analysis will be partially biased away from the norm. It also shows that approximately 90% of the error is within 8.5% for the ipsilateral, and 10% for the contralateral. Similarly, the CDF plot of the $S_{nv}O_2$ shows once again that subject 2 is an

outlier. It also shows that 90% of the $S_{ct}O_2$ errors on the ipsilateral are within 12% and 14% on the contralateral.

Discussion

We found a strong positive correlation between the ipsilateral forehead $S_{ct}O_2$ measurements and the $refS_{ct}O_2$ values calculated using arterial and jugular bulb oxygen saturations and the FORE-SIGHT $S_{ct}O_2$ values. The ipsilateral sensor performed better than the contralateral, and the comparison between the 2 sides on a subject-by-subject basis showed that ipsilateral-contralateral dependency varied widely. Differences between the $refS_{ct}O_2$ and FORE-SIGHT $S_{ct}O_2$ values may reflect interindividual variability²⁰ and/or differences in the regional blood flow of the cerebral tissue, as well as contamination from extracranial tissue²¹. Henson et al. sought to use $S_{ct}O_2$ as a predictor of $S_{jv}O_2$, and found that the Somanetics 3100 cerebral oximeter device correlated well with venous oxygen saturation.²

The $\pm 10\%$ tolerance interval of future readings may seem excessively large but given the sigmoid nature of the oxygen-hemoglobin dissociation curve²², this may not be clinically significant. As an example, a reading of 75% $S_{ct}O_2$ may be between 65% or 85%, but a value within this range does not suggest an imminent clinical threat to the patient. An $S_{ct}O_2$ of 55% indicates a venous saturation between 50% and 21%, which is the arbitrary threshold for neurocognitive impairment as set and published by Yao et al²³, given that the arterial saturation is usually near 100%. Several studies have reported neurocognitive deficits and prolonged hospital stay when the INVOS™ (Covidien (formerly Somanetics), Mansfield, MA) rSO_2 decreases below 50% for a prolonged period, 40% for more than 10 minutes, or nadir below 35% where the corresponding cerebral venous saturations decreased below 35%, 20%, and 13% accordingly.^{24,25,26} There is no clear $S_{ct}O_2$ threshold for clinical intervention so the $S_{ct}O_2$ may serve as a graded indicator of risk organized in decades. The normal range is considered 65% and above, elevated risk between 55% and 65%, and high risk at 55% and below (55% $S_{ct}O_2$ corresponds to 35% venous saturation, assuming 100% S_aO_2). Because arterial blood oxygen saturations are very well managed in modern anesthesia practice, estimation of the noninvasive estimate of venous oxygen saturation ($S_{nv}O_2$) as a surrogate of $S_{jv}O_2$ may have some merit and indicate clinically relevant changes in the ratio between $CMRO_2$ and CBF. A crude summary of physiologic conditions and their possible contributors are tabulated in Table 6.

The Bland-Altman plot demonstrated a modest degree of proportional error, which declined as the blood oxygen saturation value decreased; a positive characteristic in the setting of clinical hypoxia. In addition, the data points were equally scattered above and below the zero line suggesting there is no consistent bias of 1 measurement approach (FORE-SIGHT $S_{ct}O_2$) versus the $refS_{ct}O_2$. $S_{nv}O_2$ calculated using the FORE-SIGHT $S_{ct}O_2$ and S_pO_2 values was strongly correlated with blood gas determined $S_{jv}O_2$.

The wide variability of the average FORE-SIGHT $S_{ct}O_2$ values recorded at baseline during room air breathing is generally consistent with what has been reported clinically.^{27,28,29} The significance of the cerebral oximeter can be further demonstrated by substituting equation 3 (assuming blood distribution to be 70% venous ($K_v = 0.7$), 30% arterial ($K_a = 0.3$), and

negligible amount in the capillaries ($K_c = 0$) and ERROR assumed to be zero for the ideal case as suggested by Ito et al.¹¹) into equation 6 and solving the ratio of $CMRO_2$ to CBF as a function of $S_{ct}O_2$ (equation 7).

$$CMRO_2/CBF = (S_pO_2 - S_{ct}O_2) \times K1 + K2 \quad (7)$$

Where $K1 = (1.34 \times [tHb]) / 0.7$

And

$$K2 = 0.003 \times (P_aO_2 - P_{jb}O_2).$$

Solving equation 7 for $S_{ct}O_2$ then becomes (equation 8):

$$S_{ct}O_2 = S_pO_2 + (K2 - CMRO_2/CBF) / K1 \quad (8)$$

From this equation, it can be deduced that the $S_{ct}O_2$ has a proportional relationship to S_pO_2 and $CMRO_2$ and inversely proportional with CBF. Thus, the variation in baseline $S_{ct}O_2$ can either be directly due to interpersonal differences in brain activity and CBF. Any preexisting conditions affecting CBF such as sympathetic activation due to anxiety and reduced CBF due to vasoconstriction (abnormal $PaCO_2$ due to hyperventilation, vasoconstrictors onboard, etc.), or atherosclerosis can affect the baseline $S_{ct}O_2$.

In the current study, the effect of CO_2 on CBF, and therefore oxygen delivery, was controlled by maintaining the $PetCO_2$ at 40 mmHg with a scheme described by Slessarev et al.²⁰ However, inspection of the individual subject's linear regression plots show a slight inflection of the plots at lower saturations, which may indicate that the reference saturation and the NIRS saturation measurements may not be linear at lower saturation levels due to changing $CMRO_2$ and other confounding effects. The end-tidal gas-forcing device software assumes constant oxygen consumption rates that may have introduced an effort-dependent error. Because Seifert and Secher have shown that sympathetic activity can possibly influence CBF and $CMRO_2$ during cycling exercise,³⁰ the increased respiratory effort with the diaphragm muscle during this study could have affected a change in CBF and $CMRO_2$.

The morphology of the Bland-Altman plot [which resembles a "less than" symbol (<), with smaller spread in the 50% range than the 70% range], also suggests an error that is proportional to the magnitude of the $S_{ct}O_2$ reading and corroborates the possibility that the $S_{ct}O_2$ may be slightly nonlinear. In addition, hypoxemia produces changes in CBF³¹ and the full extent of the changes in the venous distribution and mixing of the various tributaries that drain into the jugular venous returns are not entirely known. Due to this uncertain venous mixing, the venous sample taken at the jugular bulb may not have reflected the true venous saturation at the interrogated tissue.

In this study $refS_{ct}O_2$ values were calculated for the purposes of evaluating the accuracy of the FORE-SIGHT device using distribution coefficients ($0.30 \times S_aO_2 + 0.70 \times S_{jv}O_2$) derived from Ito et al.³² However, Pollard et al.³³ have estimated $S_{ct}O_2$ using a slightly different CBV distribution ($0.25 \times S_aO_2 + 0.75 \times S_{jv}O_2$) as has McCormick et al. ($0.18 \times S_aO_2 + 0.82 \times S_{jv}O_2$ and $0.28 \times S_aO_2 + 0.72 \times S_{jv}O_2$).³⁴ Not only does a device manufacturer's choice of

distribution coefficients affect the $S_{ct}O_2$ reported value, but use of a fixed set of distribution coefficients can also be a source of error because the CBV distribution and CBF both change due to various activities and body positions.³³ Functional magnetic resonance imaging studies by Ito et al.³⁵ have shown that an elevated $CMRO_2$ during neural activation causes a decrease in venous blood oxygen saturation. Regional differences in cerebral activity may also cause cerebral blood distribution to change. Ito et al. used controlled visual stimulation to demonstrate significant differences in CBF and CBV during rest and periods of stimulation, which was consistent with positron emission tomography studies estimating CBF and CBV under hypercapnic conditions.³⁶ However, Ito et al. did not precisely control $PaCO_2$ and their findings indicate a wide range of possible distribution of the CBV under these conditions. They also found that CBV changed significantly owing to changes in $PaCO_2$, and arterial compartment volume changed significantly in the direction of CBV changes. However, no significant change was observed in venous or capillary blood volume. This indicates that changes in CBV during hypercapnia and hypocapnia are produced by changes in arterial blood volume and not by changes in venous and capillary blood volume.³⁷ The appropriate distribution coefficients for CBV within arterial and venous compartments remain a somewhat contentious issue but it is generally accepted that any increase in the concentration of CO_2 within the arterial compartment and sympathetic activation due to mental activity can trigger vasodilatation and thus affect changes in the CBV.

Our results were obtained by controlling the $PetCO_2$ in order to achieve a $PaCO_2$ of approximately 40 mmHg (i.e., 38.8 ± 2.2 mmHg), which allowed a more consistent descent down the oxyhemoglobin dissociation curve. The dissociation curve from 20% to 80% is approximately linear and a small shift in the curve to the ipsilateral or contralateral may produce an unacceptable source of error when validating the calibration of a cerebral oximeter. Ito et al. found that the arterial fraction of human CBV during hypercapnia and hypocapnia measured by positron emission tomography changed such that the 25% arterial fraction assumed by the INVOS cerebral oximeter and the 30% arterial fraction assumed by the FORE-SIGHT cerebral oximeter for calculation of $S_{ct}O_2$ were no longer valid under these conditions.^{37,38} The importance of maintaining normocapnia when evaluating the accuracy of a NIRS cerebral oximeter device which uses a fixed arterial to venous blood volume ratio is readily apparent from Ito et al.'s findings. Unfortunately, hypocapnia and hypercapnia in the clinical settings add to the uncertainty and error of these devices that have been calibrated under normocapnic conditions, regardless of whether a device is a "trend" or "absolute" monitor.

The gas delivery system required the gas blender to be calibrated at the beginning of the study to the subject's rate of CO_2 production ($dVCO_2/dt$) and rate of O_2 consumption (dVO_2/dt). Any physical movement³⁹ and / or any changes in the breathing effort alter the $dVCO_2/dt$ and dVO_2/dt .⁴⁰ The increased ventilatory drive at lower S_aO_2 increases respiratory effort thereby increasing both $dVCO_2/dt$ and dVO_2/dt . The nature of the end-tidal-forcing device and technique used in this experiment made it impossible to adjust for these changes during the experiment and the initial set points for $dVCO_2/dt$ and dVO_2/dt were no longer applicable at lower S_aO_2 and therefore resulted in some drift of the end-tidal target gas concentrations. Therefore vasodilatation and vasoconstriction due to hypercapnia

and hypocapnia could have altered the intracranial blood volume distribution, and in turn the $S_{ct}O_2$.

Aside from the sources of error noted, the NIRS device and its interaction with interindividual anatomical differences may also introduce error.⁴¹ The sensors are designed to be placed on the forehead equilaterally. If there is a positional bias towards one side or the other, the sagittal sinus, a prominent anatomical feature, may influence the accuracy of the sensor readings.^{42,43} Because the device is also designed to reject common mode noise, exposure to ambient light should not be an issue. However, an excessive amount of ambient light can saturate the sensors and introduce error in the reading. Individual skull thickness can also affect scattering of the NIRS optical signal and influence device readings.^{44,45} The present study included 2 African-Americans, 3 Asians, and 1 Hispanic male. The varying levels of skin pigmentation may have also manifested as artificially lower readings at lower saturations as Feiner et al. and Bickler et al. have reported.^{46,47}

Conclusions

We found that the FORE-SIGHT NIRS device was able to estimate oxygen saturation (with 95% confidence interval of $[-5.60 \ 5.78]$ with ipsilateral blood sample data) within the tissues of the frontal lobe under conditions of normocapnia and varying degrees of hypoxia as suggested by the ISO 9919:2005 standard. The study findings also suggest that the use of the calculated venous oxygen saturation ($S_{nv}O_2$) may be a reasonable noninvasive method of estimating jugular bulb venous oxygen saturation and therefore global cerebral oxygen consumption in the clinical setting. Further laboratory and clinical research is required to define the value of NIRS determination of $S_{ct}O_2$ and $S_{nv}O_2$ in the operating room and intensive care unit setting.

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Figure 1.
Example of hemodynamic and respiratory data obtained during the progressive hypoxia sequence in a single subject.

Figure 2.

Example of the S_pO_2 , FORE-SIGHT™ $S_{ct}O_2$, Vigilance $S_{jb}O_2$, and co-oximeter determined $S_{jv}O_2$ and S_aO_2 values during the progressive hypoxia sequence in a single subject.

Figure 3.
Plot of FORE-SIGHT™ SctO_2 ipsilateral and contralateral combined sensor values versus calculated refSctO_2 values.

Figure 4.
Bland-Altman plot of the difference between FORE-SIGHT $S_{ct}O_2$ and $refS_{ct}O_2$ values.

Figure 5.

Plot of the calculated noninvasive venous oxygen saturation ($S_{nv}O_2$) versus the blood gas determined jugular bulb venous oxygen saturation ($S_{jv}O_2$) values.

Figure 6.

Bland-Altman plot of the calculated noninvasive venous oxygen saturation ($S_{nv}O_2$) versus the blood gas determined jugular bulb venous oxygen saturation ($S_{jv}O_2$) values.

Figure 7.
Cumulative Density Function Plot of the absolute value of the error between $S_{ct}O_2$ and $refS_{ct}O_2$.

Figure 8.
Cumulative Density Function Plot of the absolute value of the error between ($S_{nv}O_2$) and the blood gas determined jugular bulb venous oxygen saturation ($S_{jv}O_2$) values.

Table 1

Demographics

	Age*	Weight*	BMI*
Female	26.0 [22.0, 33.4]	65.4 [49.8, 75.6]	22.2 [20.1, 26.5]
Male	23.3 [21.4, 35.2]	76.9 [63.4, 99.1]	23.6 [21.8, 29.6]
Overall	25.1 [21.4, 35.16]	70.1 [49.8, 99.1]	22.8 [20.1, 29.6]

* Median and Range

Table 2

Demographics

	African America n	Asian	Caucasia n	Hispanic	Total
Female	0	2	7	0	9
Male	2	1	5	1	9
Total	2	3	12	1	18

Table 3

Paired Student T-Test for the ipsilateral and contralateral values of $S_{ct}O_2$ and $S_{nv}O_2$ per subject. P value below 0.05 is considered significant.

Subject	Student T-Test P Value ($S_{ct}O_2$)	Student T-Test P Value ($S_{nv}O_2$)	($S_{ct}O_2$) Ipsilateral / Contralateral dichotomy significant?	($S_{nv}O_2$) Ipsilateral / Contralateral dichotomy significant?
S02	2.86 e-9	2.86 e-9	Yes	Yes
S03	4.85 e-6	4.85 e-6	Yes	Yes
S04	2.45 e-9	2.45 e-9	Yes	Yes
S05	2.08 e-8	2.08 e-8	Yes	Yes
S06	1.70 e-4	1.70 e-4	Yes	Yes
S07	9.64 e-1	9.00 e-1	No	No
S08	3.67 e-1	3.64 e-1	No	No
S09	6.78 e-2	1.18 e-1	No	No
S10	4.46 e-3	1.88 e-3	Yes	Yes
S11	1.51 e-1	1.99 e-1	No	No
S13	3.42 e-12	3.42 e-12	Yes	Yes
S14	1.69 e-1	2.98 e-1	No	No
S15	8.33 e-3	7.17 e-3	Yes	Yes
S16	1.33 e-2	2.46 e-2	Yes	Yes
S17	3.99 e-5	9.10 e-7	Yes	Yes
S18	1.29 e-2	1.78 e-2	Yes	Yes
S19	1.68 e-1	1.68 e-1	No	No
S20	3.98 e-1	8.98 e-1	No	No
Overall	7.23 e-1	6.93 e-1	No	No

Table 4

Parametric analysis and Random Effects Analysis correction for the ipsilateral, contralateral and combined $S_{ct}O_2$ values compared to $refS_{ct}O_2$ values.

Parametric Analysis with Random Effects Analysis Correction:	$S_{ct}O_2$ Ipsilateral	$S_{ct}O_2$ Contralateral	$S_{ct}O_2$ Combined
Bias	0.09	0.08	0.09
Standard Deviation	2.92	2.88	2.86
95% Confidence Interval	[-5.60 5.78]	[-5.53 5.69]	[-5.48 5.57]
95% Tolerance Interval	[-10.72 10.90]	[-10.59 10.74]	[-9.22 9.40]
Precision	0.20	1.14	0.46
Pearson Correlation	0.85	0.78	0.81
Lin's Concordance Correlation Coefficient $\pm$ Standard Error	0.83 ± 0.073	0.78 ± 0.098	0.81 ± 0.059
Slope	1.05	0.74	0.89
Intercept	-3.08	17.96	7.44

Table 5

Comparison of the calculated $S_{nv}O_2$ values derived from the ipsilateral, contralateral and combined measurements and the Vigilance ($S_{jb}O_2$) measurements to the venous jugular bulb oxygen saturation ($S_{jv}O_2$) values from blood samples.

Parametric Analysis with Random Effects Analysis Correction:	$S_{nv}O_2$ Ipsilateral	$S_{nv}O_2$ Contralateral	$S_{nv}O_2$ Combined	$S_{jb}O_2$ Vigilance
Bias	0.20	0.17	0.19	-1.47
Standard Deviation	4.08	4.06	4.01	3.00
95% Confidence Interval	[-7.80 8.20]	[-7.78 8.12]	[-7.68 8.05]	[-2.88 8.89]
95% Tolerance Interval	[-14.93 15.33]	[-14.86 15.20]	[-12.89 13.26]	[-12.60 9.66]
Precision	0.17	1.92	0.99	0.34
Pearson Correlation	0.81	0.73	0.77	0.85
Lin's Concordance Correlation Coefficient $\pm$ Standard Error	0.79 $\pm$ 0.088	0.72 $\pm$ 0.118	0.76 $\pm$ 0.071	0.82 $\pm$ 0.078
Slope	0.98	0.66	0.82	0.93
Intercept	1.14	20.36	10.75	2.56

All values were compared against jugular bulb venous ($S_{jv}O_2$) blood sample values determined by co-oximetry.

Table 6
Possible causes of inflections in the $S_{nv}O_2$ due to physiological state change in the cerebral tissue.

Indication:	S_aO_2	CMRO ₂	CPP	CBF	Notes
Low $S_{nv}O_2$			Low	Low	Low CPP may be due to Low MAP or high ICP, or both
Low $S_{nv}O_2$		High			Some regions of the brain may be more metabolically active, which may indicate a low $S_{nv}O_2$ relative to systemic S_vO_2
Low $S_{nv}O_2$			High	Low	Possibly vasoconstriction due to low PaCO ₂ and vasopressors
Low $S_{nv}O_2$	Low				Low arterial blood saturation
High $S_{nv}O_2$				High	Possibly vasodilatation due to high PaCO ₂ , drugs that relax smooth muscle, and diuretics
High $S_{nv}O_2$			High	High	Possibly vasodilatation due to high PaCO ₂ , vasopressors, high Cardiac Output, and / or high Mean Arterial Pressure (MAP)
High $S_{nv}O_2$				High	Possibly vasodilatation due to high PaCO ₂ and vasopressors
High $S_{nv}O_2$		Low			Low brain activity

All blank spaces denote normal ranges.