Journal of Perinatology (2006), 1–8

www.nature.com/jp

ORIGINAL ARTICLE

Validation of a noninvasive neonatal optical cerebral oximeter in veno-venous ECMO patients with a cephalad catheter

K Rais-Bahrami[1,2], O Rivera[2,3] and BL Short[1,2]

[1]Department of Neonatology, Children's National Medical Center, Washington, DC, USA; [2]The George Washington University School of Medicine, Washington, DC, USA and [3]Department of Biomedical Engineering, Children's National Medical Center, Washington, DC, USA

Introduction: Cerebral Oximetry is an optical technique that allows for noninvasive and continuous monitoring of brain oxygenation by determining tissue oxygen saturation ($SctO_2$). In conjunction with pulse oximetry, cerebral oximetry offers a promising method to estimate cerebral venous oxygen saturation (SvO_2).

Objective: The aim of this study was to validate the cerebral oximetry measurements with the cerebral oxygen saturation measured from blood drawn in neonates on veno-venous ECMO with existing cephalad catheter with a prototype neonatal cerebral oximeter developed by CAS Medical Systems (Branford, CT, USA).

Study design: After obtaining informed consent, neonates undergoing VV-ECMO with cephalad catheterization were monitored by the CAS cerebral oximeter. Cephalad blood samples were periodically obtained to validate the monitor's accuracy.

Results: Seventeen neonates were studied with 1718 h of cerebral oximetry data collected. Compared to the reference values, the bias ± precision for cerebral oximetry $SctO_2$ was 0.4 ± 5.1% and derived SvO_2 was 0.6 ± 7.3%

Conclusion: We recommend the use of this noninvasive method as an alternative to blood draws for cerebral venous saturation measurements in neonates requiring extracorporeal life support.
Journal of Perinatology advance online publication, 10 August 2006; doi:10.1038/sj.jp.7211573

Keywords: ECMO; NIRS; Brain; Cerebral Oximetry

Introduction

Cerebral Oximetry, which is based on near-infrared spectroscopy (NIRS) technology, is an optical technique that allows for noninvasive and continuous monitoring of brain oxygenation by determining cerebral tissue blood oxygen saturation ($SctO_2$). Many research and observational studies were performed with neonates using various types of NIRS/cerebral oximetry monitors.[1–15] However, no food and drug administration (FDA) approved cerebral oximeter is available for neonates. Successful validation of cerebral oximetry for the FDA has been done in human adult volunteer studies under protocols were jugular bulb and arterial blood samples were obtained under different levels of fractional inspired oxygen (FiO_2) levels.[16–19] However, this type of cerebral oximetry validation study for neonates would be too high of risk and unethical. Finding the appropriate neonatal clinical study that allows access to brain venous blood without altering clinical care procedures is difficult. As a result, validating a cerebral oximeter monitor for neonate applications is a major challenge.

The aim of this study was to validate the noninvasive cerebral oximetry measurements. Cerebral venous oxygen saturation (SvO_2) measured from blood drawn from the cephalad catheter in neonates undergoing veno-venous (VV) extracorporeal membrane oxygenation (ECMO) was compared to the saturations measured using a prototype neonatal cerebral oximeter developed by CAS Medical Systems (FORE-SIGHT™, Branford, CT, USA, www.casmed.com). This study follows a protocol similar to a preliminary validation study of the CAS neonatal cerebral oximeter.[20] Neonatal patients undergoing VV-ECMO with cephalad catheterization offer a unique opportunity to validate cerebral oximetry by allowing access to cerebral venous blood via catheterization of proximal internal jugular vein.

ECMO background

Extracorporeal membrane oxygenation (ECMO) is defined as the use of a modified heart-lung machine combined with a membrane oxygenator to provide cardiopulmonary support for patients with reversible pulmonary and/or cardiac failure in whom maximal conventional therapies have failed. Most causes of neonatal respiratory failure are self-limited and ECMO allows time for the lung to recover from the underlying disease process and for reversal of pulmonary hypertension, which frequently accompanies respiratory failure in the newborn.

Correspondence: Dr K Rais-Bahrami, Department of Neonatology, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010, USA.
E-mail: kraisbah@cnmc.org
Received 13 April 2006; revised 26 June 2006; accepted 29 June 2006

At the initiation of extracorporeal life support, a decision is first made as to whether the infant would best be served with VV or venoarterial (VA) support. More than 60% of neonatal ECMO patients reported in the Extracorporeal Life Support Organization (ELSO) registry have received treatment with VA bypass.[21] In neonates with respiratory failure, VA ECMO is gradually being replaced by a VV technique, which uses a single double-lumen catheter. The catheter is placed in the right atrium, where blood is drained and reinfused into the same chamber, thus requiring cannulation of only the right jugular vein, sparing the carotid artery. Other advantages of VV ECMO include maintenance of normal pulsatile blood flow and the theoretical advantage that particles entering the ECMO circuit enter by way of the pulmonary rather than the systemic circulation. The design of the original VV catheter resulted in significant recirculation, limiting its use when ECMO flows >350 ml/min were required. Research by Rais-Bahrami *et al*. resulted in development of a new catheter design which significantly lowers the degree of recirculation.[22] This catheter design in 12, 15, and 18 Fr. sizes allows the use of VV ECMO in a greater number of infants.[23]

In VV-ECMO the proximal end of internal jugular vein is also cannulated for cephalad drainage. This catheter is placed at the jugular bulb to augment cerebral venous outflow. The jugular bulb catheter is connected to the venous tubing of the ECMO circuit via a luer connector with a three-way stopcock to facilitate blood sampling for cephalic venous saturation measurement.[24] This catheter allows access for brain venous blood needed to validate neonatal cerebral oximetry in a routine clinical setting.

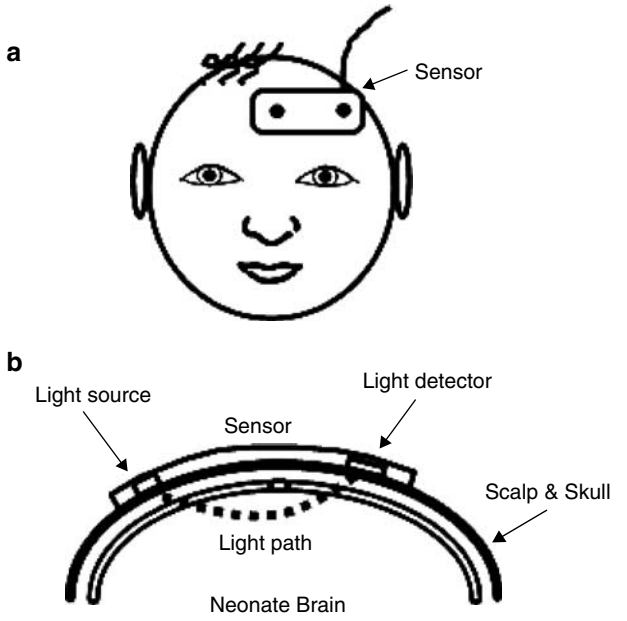

Figure 1 Neonatal cerebral oximeter sensor detail. (**a**) Placement of sensor on neonate's forehead. The two black circles inside the sensor represent the positioning of the light source and detector. (**b**) Side view of the sensor on neonate forehead is shown with estimated light path from light source to detector to demonstrate brain tissue interrogation after passage through scalp and skull.

Cerebral oximetry background

Cerebral oximetry is based on NIRS techniques where light is emitted at one point and sensed by a detector at a second point after passage through a medium such as biological tissue.[25] A cerebral oximetry sensor is placed on the forehead, and if there is adequate space, off to one side of the forehead to monitor one brain hemisphere as shown in Figure 1a. Bilateral left and right forehead sensors could also be used if collateral flow in the brain hemispheres is a concern.[8] In healthy subjects, bilateral sensor measurements are similar.[18,19] Light from the sensor passes through the scalp and skull to interrogate primarily the gray matter of brain tissue as shown in Figure 1b. As a result of the high light scattering properties of biological tissue, a small amount of light reaches the sensor detector and can be used for spectroscopic analysis. Interrogation depth of the sensor is estimated to be ½ of light source to detector separation distance.[26] Interrogation depth into the brain also depends on scalp and skull thickness which must be subtracted from the sensor's overall interrogation depth. The sensor of the prototype CAS cerebral oximeter used in this study has a light source to detector separation of 25 mm. For example, for a 1-month-old infant that has an estimated scalp thickness of 3 mm[27] and a skull thickness of 4 mm,[28–30] the resultant estimated brain tissue interrogation depth for the CAS sensor is about 6 mm.

Like pulse oximetry, cerebral oximetry uses near-infrared light at different wavelengths to distinguish oxy-hemoglobin (HbO_2) and deoxy-hemoglobin (Hb) to quantify blood oxygenation in tissue based on spectroscopy techniques. This is possible because Hb and HbO_2 greatly absorb near-infrared light compared to other biological components and that Hb and HbO_2 have different light absorption spectras. The prototype CAS neonatal cerebral oximeter used in this study is a continuous wave NIRS system that uses a three wavelength laser light source (780, 804 and 850 nm) to resolve HbO_2 and Hb. $SctO_2$ is determined from the ratio of $HbO_2/(HbO_2 + Hb)$. Light from the sensor interrogates blood in the microvasculature (i.e., arterioles, venules and capillaries),[31] with the contribution of venous to arterial blood volume at approximately 70–30% ratio.[20,32] Therefore cerebral tissue blood oxygen saturation values are usually below arterial oxygen saturation (i.e. (SaO_2) or pulse oximeter arterial oxygen saturation (SpO_2)) values and above brain venous oxygen saturation (i.e., cephalad catheter internal jugular oxygen saturation ($SjvO_2$)) values. Unlike pulse oximetry, cerebral oximetry does not need pulsatile flow to make a measurement. Therefore cerebral oximetry offers a means to monitor brain blood oxygenation during

circulatory arrest or cardiopulmonary bypass utilizing non pulsatile flow, whereas a pulse oximeter is non functional. When used as a standalone monitor, the cerebral oximeter displays $SctO_2$. When used in conjunction with pulse oximetry, cerebral oximetry offers a promising method to determine noninvasively SvO_2 representative of cephalad or jugular bulb oxygen saturation under many physiological states when peripheral pulse oximetry SpO_2 is representative of brain SaO_2 and the venous to arterial blood volume ratio of 70% to 30% as described previously holds true.[18,20] Other features of the CAS cerebral monitor include automatic shutdown of the sensor light source in case the sensor becomes dislodged from the patient, with an alarm to alert the user. Besides being a noninvasive monitor, cerebral oximetry does not need to be periodically recalibrated with cerebral venous blood samples, unlike the on-line catheter monitoring systems and jugular bulb oximetry monitors.[33–35]

Methods

Validation procedure

This study was approved by the Institutional Review Board (IRB) at Children's National Medical Center (CNMC). After obtaining parental informed consent, neonates routinely undergoing VV-ECMO with cephalad catheterization were enrolled in this study. The cerebral oximeter sensor was affixed on the neonate's forehead (Figure 1a) with a custom made adhesive pad and further secured by a Hypafix tape (BSN Medical GmbH & Co. Hamburg, Germany). A laptop computer displayed and stored data every 3 s from the cerebral oximeter along with pulse oximetry SpO_2 data (N595 Tyco/Nellcor, Pleasanton, CA, USA). Cephalad blood samples were periodically obtained and analyzed by the i-STAT (Abbott Point of Care, East Windsor, NJ, USA) and the IL-682 Co-oximeter (Instrumentation Laboratory, Lexington, MA, USA) to obtain $SjvO_2$ used to validate the monitor's accuracy. The IL-682 co-oximeter is used as a blood oximetry gold standard based on it's high accuracy of measuring oxygen saturation ($\%O_2Hb$ accuracy: bias and precision $1 \pm 0.5\%$, IL-682 Product Specification). The time of each cephalad blood sample draw was recorded from the cerebral oximeter monitor clock for synchronization and matched to the corresponding cerebral oximetry $SctO_2$, SvO_2 and pulse oximetry SpO_2 values for statistical analysis. The first objective of this study was to validate cerebral tissue saturation ($SctO_2$) measured by the CAS monitor with weighted values of $SjvO_2$ obtained from the cephalad catheter and pulse oximetry SpO_2 to calculate a co-oximetry Reference $SctO_2$ based on the following relationship using a venous to arterial blood volume ratio of 70–30%:[18–20]

$$\text{Reference } SctO_2 = (0.7 \times SjvO_2 + 0.3 \times SpO_2) \quad (1)$$

The second objective was to validate the derived noninvasive cerebral venous saturation (SvO_2) from combining cerebral oximetry $SctO_2$ with pulse oximetry SpO_2 of Equation (2) to internal jugular oxygen saturation ($SjvO_2$):[18,20]

$$\text{Noninvasive } SvO_2 = (\text{cerebral oximetry } SctO_2 - 0.3 \times SctO_2)/0.7 \quad (2)$$

The data are presented in scatter plot form for linear regression analysis with determined Bias and Precision (1 s.d.) comparing cerebral oximetry $SctO_2$ to the Reference $SctO_2$ (from Equation (1)), and cerebral oximetry SvO_2 (from Equation (2)) to cephalad $SjvO_2$ to determine the accuracy of the monitor for $SctO_2$ and SvO_2. As it is expected that unequal number of data value pairs would be obtained from each subject, correlated data linear regression techniques were used to determine the linear regression relationship and correlation coefficient.[36]

Results

Our results from 17 neonates studied over a three year period demonstrated that $SctO_2$ and SvO_2 measured by the prototype cerebral oximeter showed a high level of agreement with the measured cephalad SvO_2 values. For subjects 1–7, the i-STAT was used to obtain $SjvO_2$ values and for subjects 8–17, the IL-682 co-oximeter was used to obtain $SjvO_2$ values. An example of data collected during this study is presented as tracing of raw data in Figure 2. This figure shows two IL-682 co-oximetry measurements of $SjvO_2$ and the calculated Reference $SctO_2$ represented by the triangle and square data points respectively, along with the cerebral oximetry $SctO_2$ and derived SvO_2 measurements. Cerebral oximetry and pulse oximetry values were temporally matched to the co-oximetry data at the time the blood samples were drawn to form the respective $SctO_2$ and SvO_2 data sets to generate the scatter plots shown in Figures 3 and 4. Scatter plots of $SctO_2$ vs reference $SctO_2$ (from Equation (1)) are shown in Figure 3(a) (i-STAT $SjvO_2$ measurements) and Figure 3(b) (IL-682 $SjvO_2$ measurements). The bias and precision (1 s.d.) of the cerebral oximetry $SctO_2$ to the reference $SctO_2$ was $0.26 \pm 5.09\%$ using the i-STAT measured $SjvO_2$ and $0.40 \pm 5.08\%$ using the IL-682 measured $SjvO_2$. Scatter plots of cerebral oximetry SvO_2 vs cephalad $SjvO_2$ are shown in Figure 4(a) (i-STAT $SjvO_2$ measurements) and Figure 4(b) (IL-682 $SjvO_2$ measurements). The bias and precision of the derived cerebral oximetry SvO_2 to the $SjvO_2$ was $0.37 \pm 7.27\%$ using the i-STAT measured $SjvO_2$ and $0.57 \pm 7.25\%$ using the IL-682 measured $SjvO_2$.

Regression equations were shown in Figures 3 and 4, but do not provide overly meaningful information due to the limited range of oxygen saturation values measured from the subjects. The limited range of oxygen saturation values are inherent in a study like this because care of the patient is paramount, with blood samples randomly drawn during times when the subject was clinically stable. To show how the cerebral oximeter responds to drops in arterial oxygenation, an anecdotal desaturation event is shown in Figure 5 where $SctO_2$ and SvO_2 along with pulse oximetry SpO_2 decreased about 25–30%.

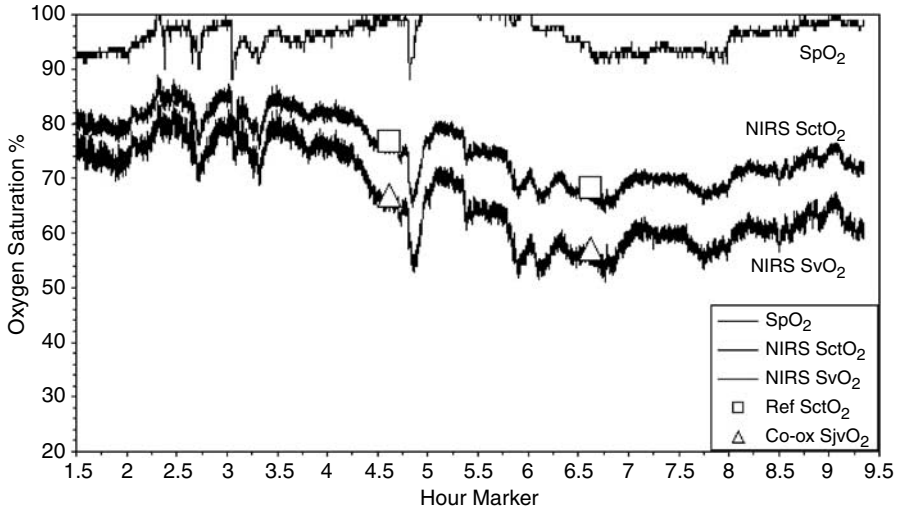

Figure 2 A representative recording of pulse oximetry SpO_2 (top trace), cerebral oximetry $SctO_2$ (middle trace) and cerebral oximetry SvO_2 (lower trace) over an 8 h period. Two co-oximetry measurements for the reference $SctO_2$ and $SjvO_2$ indicated by squares and triangles, respectively, are also shown.

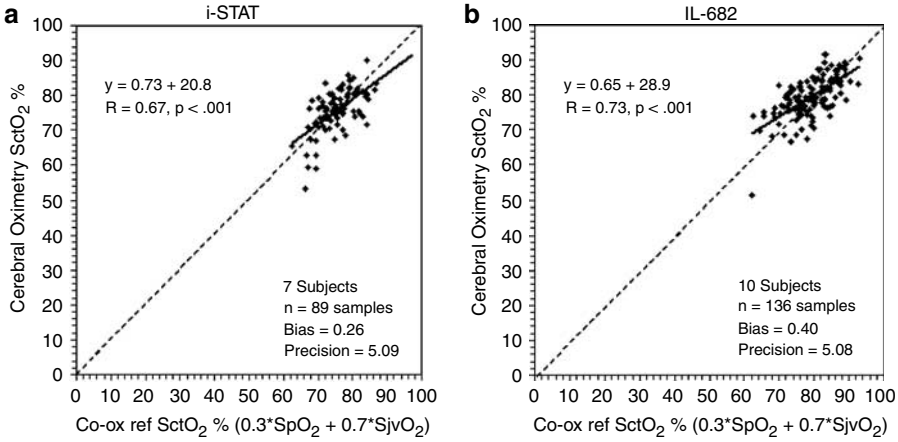

Figure 3 Scatter plots of cerebral oximetry $SctO_2$ vs the reference $SctO_2$ derived from co-oximetry $SjvO_2$ and pulse oximetry SpO_2: (**a**) i-STAT as reference; and (**b**) IL-682 as reference.

Direct comparison of the cerebral blood saturations measured by i-Stat method vs the IL-682 co-oximeter, revealed that the correlation between the two commonly used blood analyzers were poor for 10 blood sample pairs (Figure 6) where the bias and precision was 9.5 ± 6.0%. Therefore, for subjects 8-17, cephald blood samples were analyzed by the IL-682 to obtain $SjvO_2$.

Demographic information: 17 neonate subjects were studied, nine males and eight females, with weights ranging from 2.5 to 4.7 kg. Race breakdown: five subjects were Caucasian, six subjects were Hispanic and 6 subjects were African American. Diagnosis: nine subjects had meconium aspiration syndrome, seven subjects had primary pulmonary hypertension, and one subject had total anomalus pulmonary venous return. For the 17 subjects, the prototype CAS cerebral oximeter collected 1718 h (i.e. 71.6 days) of data, ranging from 24 to 218 h per subject. Two hundred and twenty-five blood samples were drawn from the cephalad catheter for co-oximetry analysis, ranging from five to 28 samples per subject.

Discussion

While NIRS technology based monitors have become a useful research tool for monitoring the brain, their clinical application has been hampered by accuracy, reliability and clinical interpretation of the measurements. One concern regarding accuracy of adult cerebral oximetry is the issue of signal contamination by the extracranial tissue layers. Compared to adults, neonates have a much thinner skull and scalp thickness,

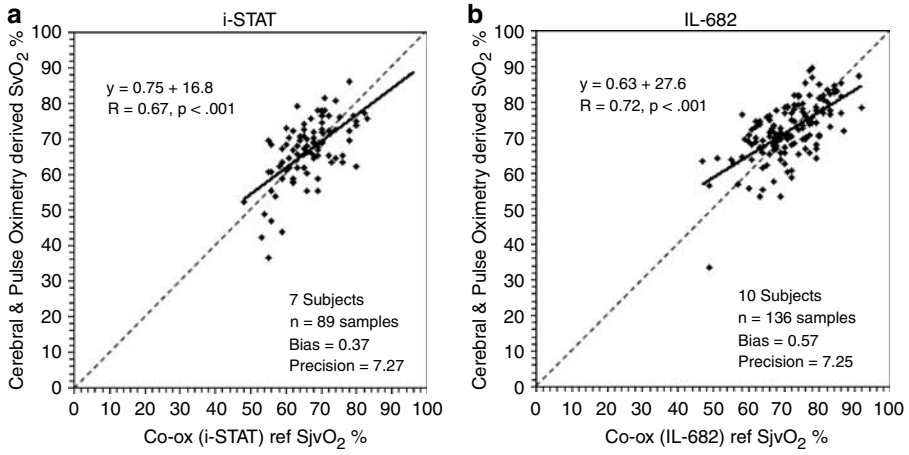

Figure 4 Scatter plots of cerebral oximetry SvO_2 vs $SjvO_2$ from co-oximetry: (**a**) i-STAT as reference; and (**b**) IL-682 as reference.

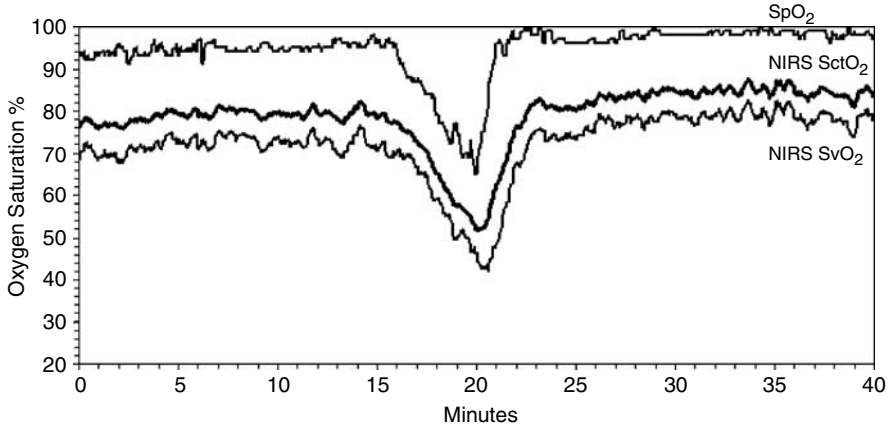

Figure 5 A representative recording of pulse oximetry SpO_2 (top trace), cerebral oximetry $SctO_2$ (middle trace) and cerebral oximetry SvO_2 (lower trace) over a 40 min period during an oxygen desaturation event.

which theoretically results in less extracranial interference. Another concern regarding accuracy is comparison of cerebral oximetry parameters to a gold standard. For cerebral oximetry validation in adults, $SctO_2$ is compared to the weighted global measures of 70% SvO_2 from jugular bulb oximetry and 30% arterial oxygen saturation under controlled conditions based on relative venous to arterial blood volume in the microvasculature.[18,19,32] The relative 70:30 venous to arterial blood volume ratio (V:A) to validate $SctO_2$ is meant to be an average since the V:A ratio can vary under different physiological conditions, especially in the neonatal cerebral circulation. High temporal resolution studies using the CAS neonate cerebral oximeter demonstrated that V:A varied from 54:46 to 75:25, with an average about 70:30 for three neonates.[20]

Like pulse oximetry, the accuracy of cerebral oximetry determined from adult and neonatal validation studies seems to decrease for neonatal applications. For example, pulse oximeter SpO_2 precision (1 s.d.) is ±2% (i.e., two digits) for adults, ±3% for neonates over a 70–100% range (from Masimo Radical® Product Specification, Masimo Corp., Irvine, CA, USA). Validation studies of the adult version of the prototype CAS cerebral oximeter demonstrate a precision (1 s.d.) of ±3.7% for $SctO_2$ and ±5.5 for SvO_2.[18,19] The neonate version of the CAS cerebral oximeter used in this study demonstrated a precision (1 s.d.) of ±5.1% (i.e., five digits) for $SctO_2$, and ±7.3% for SvO_2. The accuracy of noninvasive SvO_2 is lower than the accuracy of $SctO_2$ because potential errors from both $SctO_2$ and SpO_2 affect the measurements. The lower accuracy of cerebral oximetry in neonate applications could be attributable to an immature neonatal cerebral circulatory system, resulting in a more variable venous to arterial blood volume ratio from the average 70:30 used to validate cerebral oximetry. Other possibilities include increased contamination of cephalad brain venous blood with extracerebral tissues, possibly due to the small vessel diameters in relation to the sampling catheter which could result in non-ideal placement of the catheter. While cerebral

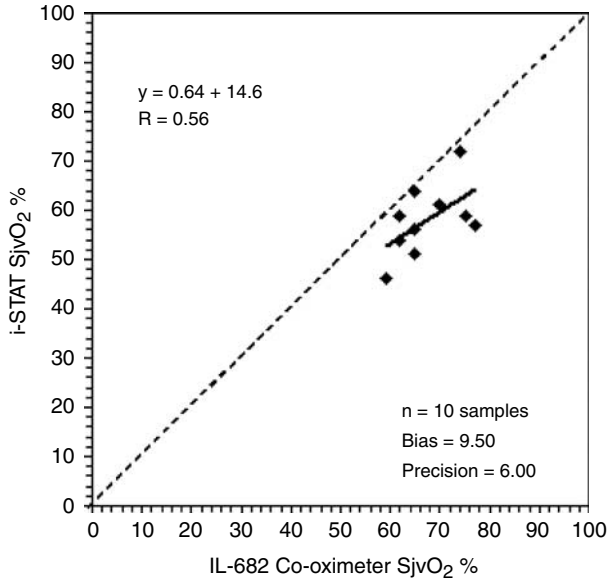

Figure 6 Concurrent i-STAT measurements compared to IL-682 measurements for a small sample of data points: i-STAT and IL-682 do not agree.

oximetry accuracy is poorer than that pulse oximetry, the normal range for cerebral oximetry values is much greater, thus errors in cerebral oximetry accuracy are not clinically significant. For example, adult cerebral oximeter and jugular bulb measurements of SvO_2 was found to vary 15% for healthy subjects breathing room air,[18,19] while pulse oximetry SpO_2 typically range from 95–100%.

Validation of cerebral oximetry on neonates cannot ethically be done in similar controlled conditions as adults, so the next best clinical scenario is to validate the monitor during clinical procedures where brain venous blood is accessible, such as in VV-ECMO. A disadvantage of validation under noncontrolled conditions is that brain tissue oxygenation cannot be altered to obtain a full range of oxygenation changes. Therefore, for VV-ECMO subjects, reference co-oximetry measurements from blood samples were done at intervals of several hours based on clinical protocols during long term cerebral oximetry monitoring sessions. Several high temporal resolution desaturation events were observed where the prototype cerebral oximeter and pulse oximeter trended together. An example is presented in Figure 5. This cohesive trending pattern further confirms the cerebral oximeter's performance during changes in brain oxygenation.

$SctO_2$ is a relativity new parameter. Lack of experience in the use of the parameter can therefore confuse the clinical interpretation of the measurements. $SctO_2$ values are below SaO_2 and above venous oxygen saturation values because of the mixed arterial–venous blood in the microvasculature. Clinicians are familiar with measuring the arterial to venous oxygen saturation difference to infer oxygen consumption in tissue. However, obtaining cerebral venous blood oxygen saturation is difficult because of its invasive nature. Therefore, cephalad or jugular bulb catheters for co-oximetry analysis is often utilized only in critically ill patients. Cerebral oxygenation status is then evaluated indirectly for most patients by peripheral blood oxygenation measurements from arterial blood co-oximetry and pulse oximetry monitoring. However, peripheral blood oxygenation monitoring does not guarantee that the brain is adequately oxygenated.

$SctO_2$ offers the capability to monitor direct brain tissue blood oxygen saturation noninvasively. One major advantage of cerebral oximetry is that $SctO_2$ measurements are not affected by impeded cerebral circulation, circulatory arrest or nonpulsatile flow. As blood flow is stagnant, circulatory arrest disrupts reliable pulse oximetry monitoring, as well as cephalad, jugular bulb oximety and arterial blood gas measurements. During circulatory arrest, cerebral oximetry $SctO_2$ will decrease as oxygen is being metabolized by brain tissue (our unpublished observations).[8,9] $SctO_2$ is much more sensitive to brain oxygenation compared to pulse oximetry. For neonates, pulse oximetry SpO_2 readings typically vary from 85 to 100%. Even when SpO_2 is high (95–100%), $SctO_2$ can vary from 30 to 100%. This fluctuation is dependant on oxygen supply and demand, which can be affected by cerebral metabolism, hypercapnia, hypocapnia, hypothermia or other physiological conditions.

SvO_2 is a cerebral oximetry parameter derived from $SctO_2$ and pulse oximetry SpO_2 by reversing the 70:30 venous to SaO_2 relationship (Equations (1 and 2)) used to verify $SctO_2$. Cerebral oximetry SvO_2 measurements are valid provided that the cerebral circulation is intact and that pulse oximetry SpO_2 represents the SaO_2 input to the brain. Cerebral circulatory arrest or impediment by carotid artery blockage disrupts this relationship, making cerebral oximetry SvO_2 measurements not possible. Also, poor pulse oximetry measurements, impeded by poor peripheral circulation, can also disrupt SvO_2 measurements. For ECMO patients, cerebral circulation is intact, so cerebral oximetry SvO_2 monitoring can be done when cephalad catheters are not used, especially in the case of VA-ECMO.

To our knowledge, this is the first clinical trial in neonates to evaluate and validate the noninvasive optical cerebral oximeter in VV ECMO patients with direct access to a cephalad catheter for measurement of SvO_2. In our clinical practice, our goal is to maintain a cephalad $SjvO_2 \geqslant 60\%$ for our VV-ECMO patients. Using the CAS neonatal cerebral oximeter, our goal is to also maintain $SvO_2 \geqslant 60\%$. If the cephalad $SjvO_2$ is 60% and SpO_2 from pulse oximetry is 93%, the target cerebral oximetry $SctO_2$ would be $\geqslant 70\%$ by use of Equation (1). Our institution is one of the few ECMO centers that use the cephalad catheter to monitor brain oxygenation. Since most VV-ECMO and VA-ECMO procedures do not use cephalad catheters, cerebral oximetry offers an alternative, noninvasive means to monitor brain oxygenation.

There has been renewed interest in NIRS type monitors, such as cerebral oximetry, as an easy to use, noninvasive technique for

measuring tissue oxygenation in the brain. Recent technical advances have led to the development of compact, portable instruments that detect changes in optical attenuation of several wavelengths of light. NIRS is an evolving technology that holds significant potential for technical advancement. In particular, NIRS shows future promise as a clinical tool for bedside cerebral blood flow measurements and as a cerebral imaging modality for mapping structure and function.

Conclusion

The cerebral oximeter measurements agree well with the measured cerebral venous saturation. This noninvasive method of measuring cerebral tissue and venous saturation could easily be recommended as a substitute for drawing venous blood samples in order to measure cerebral venous saturations in neonates requiring extracorporeal life support. The blood sample measurements to verify and/or validate cerebral oximeters should preferably be done by standard co-oximeter such as the IL-682 and not by the i-Stat method.

Abbreviations

ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal life support organization; VV, veno-venous; VA, veno-arterial; NIRS, near infrared spectroscopy; SvO_2, cerebral venous oxygen saturation; $SctO_2$, cerebral tissue oxygen saturation; SpO_2, pulse oximeter arterial oxygen saturation; SaO_2, arterial oxygen saturation; $SjvO_2$, cephalad catheter internal jugular oxygen saturation

Acknowledgments

Presented in part at the American Pediatric Society, Society of Pediatrics Research, San Francisco, CA. May 2004 and the American Academy of Pediatrics National Conference & Exhibition, San Francisco, CA. October 2004. The Study was supported by NIH NINDS Grant # R44NS39723 and sponsored by CAS Medical Systems.

References

1 Edwards AD, Wyatt JS, Richardson C, Delpy DT, Cope M, Reynolds EO. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet* 1988; **2**(8614): 770–771.

2 Brazy JE. Cerebral oxygen monitoring with near infrared spectroscopy: clinical application to neonates. *J Clin Monit* 1991; **7**(4): 325–334. Review.

3 Rolfe P, Wickramasinghe YA, Thorniley MS, Faris F, Houston R, Kai Z *et al.* Fetal and neonatal cerebral oxygen monitoring with NIRS: theory and practice. *Early Hum Dev* 1992; **29**(1–3): 269–273.

4 Toet MC, Flinterman A, Laar I, Vries JW, Bennink GB, Uiterwaal CS *et al.* Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 h after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome. *Exp Brain Res* 2005; **165**(3): 343–350.

5 Toet MC, Lemmers PM, van Schelven LJ, van Bel F. Cerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. *Pediatrics* 2006; **117**(2): 333–339.

6 Weiss M, Dullenkopf A, Kolarova A, Schulz G, Frey B, Baenziger O. Near-infrared spectroscopic cerebral oxygenation reading in neonates and infants is associated with central venous oxygen saturation. *Paediatr Anaesth* 2005; **15**(2): 102–109.

7 Nicklin SE, Hassan IA, Wickramasinghe YA, Spencer SA. Related articles, the light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**(4): F263–F268. Review.

8 Andropoulos DB, Diaz LK, Fraser Jr CD, McKenzie ED, Stayer SA. Is bilateral monitoring of cerebral oxygen saturation necessary during neonatal aortic arch reconstruction? *Anesth Analg* 2004; **98**(5): 1267–1272.

9 Andropoulos DB, Stayer SA, Diaz LK, Ramamoorthy C. Neurological monitoring for congenital heart surgery. *Anesth Analg* 2004; **99**(5): 1365–1375.

10 Tsuji M, Saul JP, du Plessis A, Eichenwald E, Sobh J, Crocker R *et al.* Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000; **106**(4): 625–632.

11 Naulaers G, Morren G, Van Huffel S, Casaer P, Devlieger H. Measurement of tissue oxygenation index during the first three days in premature born infants. *Adv Exp Med Biol* 2003; **510**: 379–383.

12 Naulaers G, Cossey V, Morren G, Van Huffel S, Casaer P, Devlieger H. Continuous measurement of cerebral blood volume and oxygenation during rewarming of neonates. *Acta Paediatr* 2004; **93**(11): 1540–1542.

13 Huang L, Ding H, Hou X, Zhou C, Wang G, Tian F. Assessment of the hypoxic-ischemic encephalopathy in neonates using noninvasive near-infrared spectroscopy. *Physiol Measure* 2004; **25**: 749–761.

14 Sakamoto T, Duebener LF, Laussen PC, Jonas RA. Cerebral ischemia caused by obstructed superior vena cava cannula is detected by near-infrared spectroscopy. *J Cardiothoracic Vascular Anesthesia* 2004; **18**: 293–303.

15 Yamamoto A, Yokoyama N, Yonetani M, Uetani Y, Nakamura H, Nakao H. Evaluation of change of cerebral circulation by SpO_2 in preterm infants with apneic episodes using near infrared spectroscopy. *Pediatr Int* 2003; **45**: 661–664.

16 Shah N, Trivedi NK, Clack SL, Shah M, Shah PP, Barker S. Impact of hypoxemia on the performance of cerebral oximeter in volunteer subjects. *J Neurosurg Anesthesiol* 2000; **12**(3): 201–209.

17 Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Stoddart HF. Validation in volunteers of a near-infrared spectroscope for monitoring brain oxygenation *in vivo*. *Anesth Analg* 1996; **82**(2): 269–277.

18 MacLeod DB, Ikeda K, Moretti E, Keifer JC, Grocott H. Using the CAS cerebral oximeter to estimate cerebral venous oxygen saturation. *Anesthesiology* 2005, asaabstracts.com; A16.

19 MacLeod DB, Ikeda K, Keifer JC, Moretti E, Ames W. Validation of the CAS adult cerebral oximeter during hypoxia in healthy volunteers. IARS 80th Clinical and Scientific Congress. *Anesth Analg* 2006; **102**, S-162.

20 Benni PB, Chen B, Dykes FD, Wagoner SF, Heard M, Tanner AJ *et al.* Validation of the CAS neonatal NIRS system by monitoring VV-ECMO patients: preliminary results. *Adv Exp Med Biol* 2005; **566**: 195–201.

21 Neonatal ECMO Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor, MI, July 2005.
22 Rais-Bahrami K, Rivera O, Mikesell GT *et al.* Improved oxygenation with reduced recirculation during venovenous extracorporeal membrane oxygenation: evaluation of a test catheter. *Crit Care Med* 1995; **23**: 1722–1723.
23 Rais-Bahrami K, Walton DM, Sell JE *et al.* Improved oxygenation with reduced recirculation during venovenous ECMO: comparison of two catheters. *Perfusion* 2002; **17**: 415–419.
24 Rais-Bahrami K, Hartman GE, Short BL. Extracorporeal membrane oxygenation cannulation and decannulation. In: MG MacDonald, J Ramasethu (3rd eds). *Atlas of Procedures in Neonatology*. Lippincott Williams & Wilkins, 2002, pp 232–242.
25 Owen-Reece H, Smith M, Elwell CE, Goldstone JC. Near infrared spectroscopy. *Br J Anaesth* 1999; **82**(3): 418–426. Review.
26 Strangman G, Boas DA, Sutton JP. Noninvasive neuroimaging using near-infrared light. *Biol Psychiatry* 2002; **52**(7): 679–693. Review.
27 Young RW. Age changes in the thickness of the scalp in white males. *Hum Biol* 1959; **31**(1): 74–79.
28 Adeloye A, Kattan KR, Silverman FN. Thickness of the normal Skull in the American blacks and whites. *Am J Phys Anthrop* 1975; **43**(1): 23–30.
29 Hwang K, Kim JH, Baik SH. The thickness of the skull in Korean adults. *J Craniofac Surg* 1999; **10**(5): 395–399.
30 Margulies SS, Thibault KL. Infant skull and suture properties: measurements and implications for mechanisms of pediatric brain injury. *J Biomech Eng* 2000; **122**(4): 364–371.
31 Kurth CD, Steven JL, Montenegro LM, Watzman HM, Gaynor JW, Spray TL *et al.* Cerebral oxygen saturation before congenital heart surgery. *Ann Thorac Surg* 2001; **72**(1): 187–192.
32 Ito H, Kanno I, Iida H, Hatazawa J, Shimosegawa E, Tamura H *et al.* Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Ann Nucl Med* 2001; **15**(2): 111–116.
33 Gupta AK. Monitoring the injured brain in the intensive care unit. *J Postgrad Med* 2002; **48**: 218–225.
34 Millar SA, Alston RP, Souter MJ, Andrews PJ. Continuous monitoring of jugular bulb oxyhaemoglobin saturation using the Edslab dual lumen oximetry catheter during and after cardiac surgery. *Br J Anaesth* 1999; **82**(4): 521–524.
35 Anastasiou E, Gerolioliou K, Karakoulas K, Peftoulidou M, Giala M. Reliability of continuous jugular venous bulb hemoglobin oxygen saturation during cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; **13**(3): 276–279.
36 Mitchell K. *Multivariable Analysis: A Practical Guide for Clinicians*, 2nd edn, Cambridge University Press: New York, 2006.