

[Adv Exp Med Biol.](#) 2005;566:195-201.

Validation of the CAS neonatal NIRS system by monitoring vv-ECMO patients: preliminary results.

[Benni PB](#), [Chen B](#), [Dykes FD](#), [Wagoner SF](#), [Heard M](#), [Tanner AJ](#), [Young TL](#), [Rais-Bahrami K](#), [Rivera O](#), [Short BL](#).

The CAS neonatal NIRS system determines absolute regional brain tissue oxygen saturation (SnO₂) and brain true venous oxygen saturation (S_{nv}O₂) non-invasively. Since NIRS-interrogated tissue contains both arterial and venous blood from arterioles, venules, and capillaries, SnO₂ is a mixed oxygen saturation parameter, having values between arterial oxygen saturation (SaO₂) and cerebral venous oxygen saturation (SvO₂). To determine a reference for SnO₂, the relative contribution of SvO₂ to SaO₂ drawn from a brain venous site vs. systemic SaO₂ is approximately 70:30 (SvO₂:SaO₂). If the relationship of the relative average contribution of SvO₂ and SaO₂ is known and does not change to a large degree, then NIRS true venous oxygen saturation, S_{nv}O₂, can be determined non-invasively using SnO₂ along with SaO₂ from a pulse oximeter.

PMID: 16594153 [PubMed - indexed for MEDLINE]

VALIDATION OF THE CAS NEONATAL NIRS SYSTEM BY MONITORING VV-ECMO PATIENTS: PRELIMINARY RESULTS

Paul B. Benni¹, Bo Chen¹, Francine D. Dykes², Scott F. Wagoner², Micheal Heard², April J. Tanner², Teresa L. Young², Khodayar Rais-Bahrani³, Oswaldo Rivera³, Billie L. Short³

1. INTRODUCTION

The CAS neonatal NIRS system determines absolute regional brain tissue oxygen saturation (SnO₂) and brain true venous oxygen saturation (SvO₂) non-invasively. Since NIRS interrogated tissue contains both arterial and venous blood from arterioles, venules, and capillaries, SnO₂ is a mixed oxygen saturation parameter, having values between arterial oxygen saturation (SaO₂) and cerebral venous oxygen saturation (SvO₂). To determine a reference for SnO₂, the relative contribution of SvO₂ to SaO₂ drawn from a brain venous site vs. systemic SaO₂ is approximately 70:30 (SvO₂:SaO₂). If the relationship of the relative average contribution of SvO₂ and SaO₂ is known and does not change to a large degree, then NIRS true venous oxygen saturation SvO₂ can be determined non-invasively using SnO₂ along with SaO₂ from a pulse oximeter.

2. METHODS

NIRS Methodology: The CAS NIRS system is a continuous wave (CW), three wavelength (775, 800, 850 nm), low power laser system that uses a specially designed sensor for neonates. The sensor's light source to detector separation distance is 25 mm to allow for sufficient brain tissue interrogation of neonatal subjects. The sensor is usually attached to the subject at a hairless site on the forehead to monitor forebrain regional oxygenation. The CAS NIRS algorithm¹ is based on an expanded version of the Modified Beer-Lambert Law to determine SnO₂:

$$A_{\lambda} = -\log(I/I_0)_{\lambda} = \alpha_{\lambda} * C * d * B + G_{\lambda} + F_{\lambda} + N_{\lambda} \quad \text{Eq. (1)}$$

A is the optical attenuation in tissue at wavelength λ (units: optical density OD); I_0 is the incident light intensity (W/cm²); I is the detected light intensity (W/cm²); α_{λ} is the wavelength-dependent absorption coefficient of the chromophore (OD * cm⁻¹ * μ M⁻¹); C is the concentration of chromophore (μ M); L is the light source to detector distance (cm); B is the light scattering differential pathlength factor (unit-less); G_{λ} is the light scattering loss (OD); F_{λ} is the "fixed" background absorption (OD); and N_{λ} accounts for any instrumentation related errors. $E_{\lambda} = G_{\lambda} + F_{\lambda} + N_{\lambda}$ for non-hemoglobin losses (OD).

¹ CAS Medical Systems, Branford, CT USA 06405; www.casmed.com

² Dept. of Pediatrics, Emory University and Children's Healthcare of Atlanta at Egleston, Atlanta, GA, USA.

³ Dept. of Neonatology, Children's National Medical Center, Washington, DC. USA.

The differential wavelength form of Eq. (1) minimizes the effects of E_{λ} as shown in Eq. (2). The three-wavelength form of Eq. (2) to solve for Hb (deoxyhemoglobin) and HbO₂ (oxyhemoglobin) are shown in Eqs. (3)-(4). Then $SnO_2 = HbO_2 / (HbO_2 + Hb)$ as shown in Eq. (5), where Ψ_{Hb} and Ψ_{HbO_2} are empirical NIRS calibration coefficients which are set once by experimental data or by optical phantoms. NIRS tissue SnO_2 is then related to the calibration reference $SmvO_2$, determined from the weighted venous and arterial oxygen saturations from venous (Kv) and arterial (Ka) compartment contributions shown in Eq. (6). NIRS true venous $SnvO_2$ is determined from Eq. (7):

$$A_{\lambda 1} - A_{\lambda 2} = \Delta A_{\lambda 12} = (\Delta\alpha_{Hb\lambda 12} * Hb + \Delta\alpha_{HbO_2\lambda 12} * HbO_2) * d * B + \Delta E_{\lambda 12} \quad \text{Eq. (2)}$$

$$\frac{|\Delta A_{\lambda 12}|}{|\Delta A_{\lambda 13}|} \frac{|\Delta\alpha'_{\lambda 12}|}{|\Delta\alpha'_{\lambda 13}|} (d*B)^{-1} - \frac{|\Delta E_{\lambda 12}|}{|\Delta E_{\lambda 13}|} \frac{|\Delta\alpha'_{\lambda 12}|}{|\Delta\alpha'_{\lambda 13}|} (d*B)^{-1} = \frac{|Hb|}{|HbO_2|} \quad \text{Eq. (3)}$$

$$\frac{|A_{Hb}|}{|A_{HbO_2}|} (d*B)^{-1} - \frac{|\Psi_{Hb}|}{|\Psi_{HbO_2}|} (d*B)^{-1} = \frac{|Hb|}{|HbO_2|} \quad \text{Eq. (4)}$$

$$SnO_2\% = (A_{HbO_2} - \Psi_{HbO_2}) / (A_{HbO_2} - \Psi_{HbO_2} + A_{Hb} - \Psi_{Hb}) * 100\% \quad \text{Eq. (5)}$$

$$SnO_2 \approx SmvO_2 = [Ka * SaO_2 + Kv * SvO_2], \text{ where } Ka + Kv = 1 \quad \text{Eq. (6)}$$

$$\text{NIRS true venous } SnvO_2 = [SnO_2 - Ka * SaO_2] / Kv \quad \text{Eq. (7)}$$

Clinical Setting: Extracorporeal membrane oxygenation (ECMO) is a procedure to treat infants and children with life-threatening cardiorespiratory failure that is unresponsive to conventional therapy². Venous jugular bulb or cephalad catheters, are sometimes used during veno-venous ECMO to increase cerebral venous drainage and provide a means to monitor internal jugular oxygen saturation ($SjvO_2$)², a gold-standard to validate NIRS cerebral monitors. ECMO centers using the cephalad catheter often have an in-line monitor (Statsat, Gish Biomedical, Rancho Santa Margarita CA, USA) to measure $SjvO_2$ continuously, which allows for high temporal resolution comparison of $SjvO_2$ to NIRS.

Experimental Setup: The prototype CAS NIRS monitor used a laptop computer to collect and process NIRS data as well as to record data from a pulse oximeter (Radical, Masimo Corp., Irvine CA, USA) attached to the neonate's foot and from the Statsat $SjvO_2$ monitor, if available. Data was sampled every three seconds and displayed on the laptop computer. Periodic drawing of $SjvO_2$ blood samples were analyzed by a co-oximeter to verify the Statsat values, as well as to provide further data for NIRS validation. NIRS monitoring sessions of ECMO patients were 2 to 10 days long, so a large quantity of high temporal resolution data was collected. This allowed for detection of brain oxygenation changes that may occur naturally without disturbing the subject or altering the ECMO procedure. During the weaning phase of ECMO, inspired oxygen (FiO_2) was sometimes increased to assess the viability of the neonate's lungs, which increased $SjvO_2$ by about 20%.

Data Analysis: Calibration of the CAS NIRS system and determination of the optimum tissue small-vessel venous to arterial blood volume (Kv:Ka) ratio is an iterative process using linear and non-linear regression techniques, as well as by trial and error, to best fit

Eq. (5) to Eq. (6). Since the Kv:Ka ratio has never been thoroughly studied in humans, especially neonates, we empirically estimated the Kv:Ka ratio during different brain oxygenation transitions. To do this, segments of data from each subject was analyzed to identify the best candidates for determination of the Ka:Kv ratio. Data segments that show changes of $SjvO_2 \geq 10\%$ with trend changes of SnO_2 that track well with SaO_2 and $SjvO_2$ over several hour periods were selected for analysis. Multivariate linear regression techniques following that of Brun, et al.³ and Watzman, et al.⁴, were utilized to resolve Kv:Ka. Once the optimum NIRS calibration was found, Bland-Altman analysis was applied to compare NIRS SnO_2 to $SmvO_2$ reference of Eq (6) and NIRS $SnvO_2$ to $SjvO_2$.

3. RESULTS

Figure 1 and Figure 2 show the linear regression results for NIRS SnO_2 and $SnvO_2$, respectively, from the combination of different data segments from three subjects that show brain oxygenation changes over several hour periods. Figures 1 and 2 included a total of 50.7 hours (~60,000 samples) of data, consisting of 20.4 hours from Subject N1, 5.9 hours from Subject N2, and 24.4 hours from Subject N3. The range of SaO_2 , as determined by a pulse oximeter was 86-100%. The range of $SjvO_2$ as determined by the Statsat cephalad venous monitor was 41.2-88.3%. NIRS SnO_2 ranged from 55.3 to 99.7% and $SnvO_2$ ranged from 38.7 to 99.6%. The NIRS interrogated brain venous to arterial compartment ratio Kv:Ka was estimated to be 70:30 from analysis of candidate transitional brain oxygenation data segments for each subject as shown in Table 1. Bland-Altman analysis results (bias \pm 2*standard deviation) of SnO_2 was 1.01 ± 5.19 , and $SnvO_2$ was 1.46 ± 7.36 . A representative 10-hour recording of NIRS SnO_2 and $SnvO_2$ along with SaO_2 and $SjvO_2$ are shown in Figures 3 and 4. NIRS and $SjvO_2$ monitoring appeared more sensitive to brain oxygenation changes compared to pulse oximetry.

It was found that prior methods^{3,4} to determine Kv:Ka ratio with confidence were insufficient, because different results were found using the two methods. To elaborate, Brun, et al.³ related relative oxygenation changes (i.e. ΔSnO_2) = $B_1 * SvO_2 + B_2 * SaO_2 + B_3$, whereas $Kv = B_1 / (B_1 + B_2)$, $Ka = B_2 / (B_1 + B_2)$, and B_3 is the Y-intercept of the multivariate liner regression equation. This technique was used to calculate the ‘‘Relative Method’’ results in Table 1. The Relative Method was also useful to obtain an initial Kv:Ka ratio estimate for an uncalibrated NIRS monitor using ΔSnO_2 , provided that the Kv:Ka ratio was consistent. Watzman, et al.⁴ related absolute oxygen saturation (i.e. SnO_2) = $Kv * SvO_2 + Ka * SaO_2$, where $Ka + Kv = 1$, without a Y-intercept (Table 1 ‘‘Absolute Method’’). We found that only in some data segments the determined Kv:Ka ratios from the two methods were similar, provided that the Y-intercept was close to zero. We concluded that a data segment with a near zero Y-intercept indicated that the Kv:Ka ratio was either relatively constant or a good estimation of the ratio average, accounting for some variations.

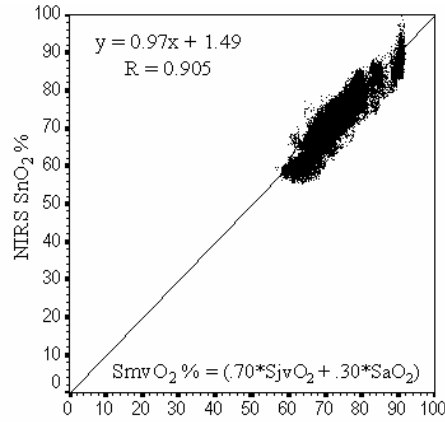


Figure 1. Correlation of NIRS SnO₂ vs. SmvO₂.

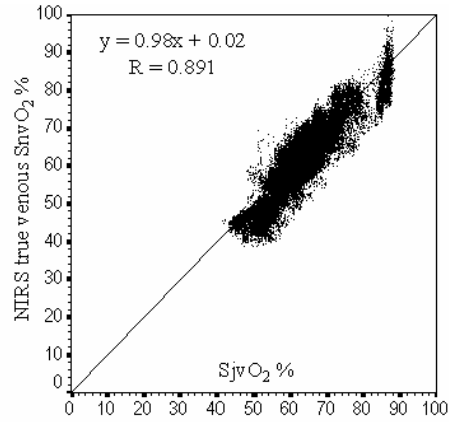


Figure 2. Correlation of NIRS SnvO₂ vs. SjvO₂.

Table 1. Analysis of NIRS interrogated venous to arterial compartment (Kv:Ka) ratio.

Subject ID	Data file ID	Data length hours	Brain oxygen change	Kv from Absolute Method	Kv from Relative Method	Relative Method: intercept	Regression correlation R ²	Estimated Ave. Kv (range)
N1	N1-cal1	10.0	^FiO ₂	.730	.676	-5.24	.852	.67 -.73
N1	N1-cal2	10.4	^SjvO ₂	.703	.722	2.09	.831	.70 -.73
N2	N2-cal	5.9	random	.743	.713	-5.76	.708	.71 -.75
N3	N3-cal1	5.4	^FiO ₂	.601	.546	-6.28	.876	.54 -.60
N3	N3-cal2	6.1	various	.502	.804	23.5	.826/.837	unknown
N3	N3-cal2a	3.2	^FiO ₂	.545	.548	0.32	.897	.54 -.55
N3	N3-cal2b	2.9	random	.644	.682	3.78	.642	.64 -.69

To interpret the values in Table 1, the estimated average venous compartment contribution, Kv, was somewhere between the values obtained from the Relative Method and Absolute Method, whereas the closer the Kv values were to each other, the higher confidence we had in the results. The average Kv for Subject N1 was found to be .67 to .73 (mean Kv:Ka ratio 70:30), and the average Kv for Subject N2 was .71 to .75 (mean Kv:Ka ratio 73:27). However for Subject N3, the Y-intercepts for some data segments were high, and the Kv values determined by the two methods were far apart. For example, one data segment “N3-cal2” (see Table 1) had a high Y-intercept and well-separated Kv values from the two methods. Interestingly, when this data segment was partitioned at a time where the brain oxygenation appeared to be affected by different causes to form two smaller data segments called “N3-cal2a” (^FiO₂ hyperoxia event) and “N3-cal2b” (random oxygenation changes), two different Kv values were found with near zero Y-intercepts. Along with the results from data “N3-cal1”, the Kv:Ka ratio for subject N3 was interpreted to vary from 54:46 to 69:31 with a high degree of certainty.

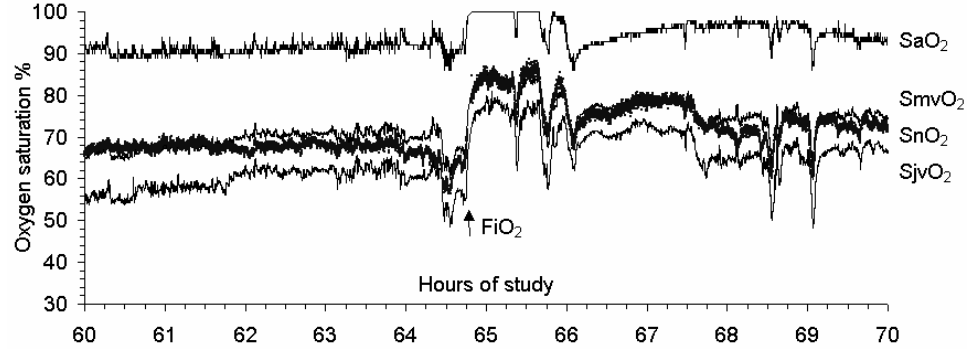


Figure 3. Representative result from Subject N1 during brief increase of FiO_2 showing relationship of NIRS SnO_2 to $SmvO_2 = [.70 * S_{jv}O_2 + .30 * SaO_2]$. (From data ID “N1-cal1”). SaO_2 : upper solid thin line, $S_{jv}O_2$: lowest solid thin line, $SmvO_2$: middle solid thin line, and NIRS SnO_2 : thick dotted line.

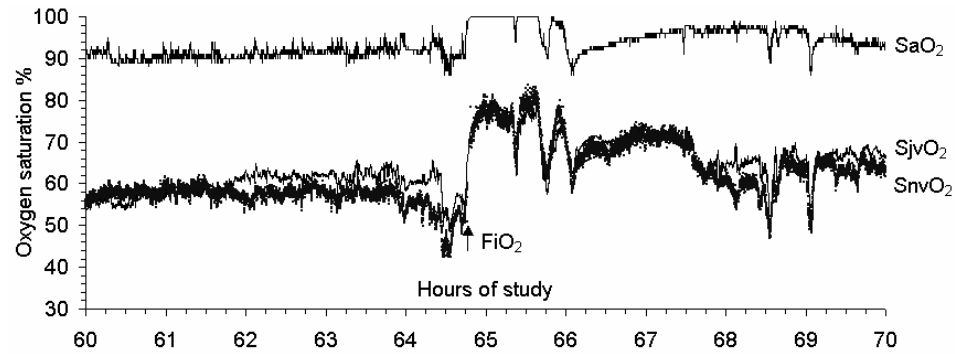


Figure 4. NIRS true venous $S_{nv}O_2$ result from Subject N1 during brief increase of FiO_2 . (From data ID “N1-cal1”). SaO_2 : upper solid thin line, $S_{jv}O_2$: lower solid thin line, and NIRS $S_{nv}O_2$: thick dotted line.

If we took the mean $K_v:K_a$ ratio of all three subjects (N1: 70:30; N2: 73:27; and N3: 61.5:38.5), the overall mean $K_v:K_a$ result was 68:32. Since $n = 3$ subjects was a small sample size, we used a value of 70:30 to correlate NIRS to $S_{jv}O_2$ and SaO_2 to generate Figures 1 and 2 for our preliminary results. The analyzed data segments tabulated in Table 1 was included in the NIRS correlation results, including 12.9 hours of other data from Subject N3 where the $K_v:K_a$ ratio could not be determined. If the $K_v:K_a$ ratio varies, the possible error in determination of SnO_2 , assuming that the regional NIRS value tracks well with the global O_2 saturation values, can be evaluated by the expression:

$$\text{Error } (SnO_2) = \Delta SmvO_2 = \Delta K_v * (SaO_2 - S_{jv}O_2) \quad \text{Eq. (8)}$$

Notice that the higher the $SaO_2 - S_{jv}O_2$ difference, the higher the possible error in SnO_2 . Under normal conditions ($SaO_2 = 100$, $S_{jv}O_2 = 70$), if ΔK_v changed 0.1, the error in SnO_2 would be 3%. The $SaO_2 - S_{jv}O_2$ difference included in the NIRS correlation results shown in Figures 1 and 2 ranged from 11.6 to 52.2%.

4. DISCUSSION

Internal jugular venous $SjvO_2$ is a global brain oxygenation parameter, while NIRS parameters, depending on the placement of the sensor, represent regional brain oxygenation. Our preliminary results show that NIRS measured oxygen saturation generally tracks well with global brain measurements, which suggest that a regional measurement can approximate global brain oxygenation. We demonstrated that NIRS determined true venous oxygen saturation $SnvO_2$ is possible by combining NIRS with a pulse oximeter, provided that the venous to arterial compartment Kv:Ka ratio does not vary to a large degree within a subject or between subjects. However, some brain pathologies, such as stroke, regional brain death, and carotid artery stenosis, may decouple the relationship between regional and global oxygenation parameters, as well as alter the Kv:Ka ratio to a large degree. Cerebral hemodynamic changes such as hypercapnia and hypocapnia may also influence the Kv:Ka ratio⁴. Inhomogeneous systemic arterial oxygen saturation could occur in neonates with ductus arteriosus or septal defects since arterial and venous blood may not be fully mixed in the brain compared to the lower extremities. Therefore, knowledge of the patient's condition is important in interpreting NIRS measurements. Also surgical procedures that briefly occlude the carotid artery for insertion of a shunt or cannulae, as done for veno-arterial ECMO, could disrupt the Kv:Ka ratio, especially if brain hemisphere collateral perfusion is poor.

An accurate estimate of the Kv:Ka ratio depends on how well NIRS regional measurements track global measurements. High temporal resolution monitoring of brain oxygenation changes aid in the assessment compared to discrete blood sampling alone. Good Kv:Ka ratio estimates emerge from data analyzed by multivariate linear regression that show a near zero Y-intercept, backed by comparable results from linear regression analysis with a forced zero Y-intercept. High Y-intercepts and lack of agreement between the regression methods indicate that the Kv:Ka ratio may have changed during the study. Extracerebral tissue interference may hinder accurate Kv:Ka ratio estimation due to increased scattering of NIRS data to reference brain oxygenation measurements. In conclusion, the preliminary results of the CAS neonate NIRS monitor are encouraging. Analysis of data from more neonate patients may reveal the general mean and range of the Kv:Ka ratio, and its impact on NIRS interpretation.

REFERENCES

- ¹ P. B. Benni, Method for non-invasive spectrophotometric blood oxygenation monitoring, U.S. Patent No. 6,456,862, USPTO, (2002).
- ² R. Pettignano, M. Labuz, T. Gauthier, J. Huckaby, and R. Clark, The use of cephalad cannulae to monitor jugular venous oxygen content during extracorporeal membrane oxygenation, *Crit. Care.* 1(3), 95-99 (1997).
- ³ N. C. Brun, A. Moen, K. Borch, O. D. Saugstad, and G. Greisen, Near-infrared monitoring of cerebral tissue oxygen saturation and blood volume in newborn piglets, *Am. J. Physiol.* 273(2 Pt. 2), H682-H686 (1997).
- ⁴ H. M. Watzman, C. D. Kurth, L. M. Montenegro, J. Rome, J. M. Steven, and S. C. Nicolson, Arterial and venous contributions to near-infrared cerebral oximetry, *Anesthesiology*, 93(4), 947-953 (2000).