

Arterial and Venous Contributions to Near-infrared Cerebral Oximetry

H. Marc Watzman, M.D., C. Dean Kurth, M.D.,† Lisa M. Montenegro, M.D.,‡ Jonathan Rome, M.D.,§ James M. Steven, M.D.,† Susan C. Nicolson, M.D.‖*

Background: **Cerebral oximetry is a noninvasive bedside technology using near-infrared light to monitor cerebral oxygen saturation (Sco_2) in an uncertain mixture of arteries, capillaries, and veins. The present study used frequency domain near-infrared spectroscopy to determine the ratio of arterial and venous blood monitored by cerebral oximetry during normoxia, hypoxia, and hypocapnia.**

Methods: **Twenty anesthetized children aged < 8 yr with congenital heart disease of varying arterial oxygen saturation (Sao_2) were studied during cardiac catheterization. Sco_2, Sao_2, and jugular bulb oxygen saturation (Sjo_2) were measured by frequency domain near-infrared spectroscopy and blood oximetry at normocapnia room air, normocapnia 100% inspired O_2, and hypocapnia room air.**

Results: **Among subject conditions, Sao_2 ranged from 68% to 100%, Sjo_2 from 27% to 96%, and Sco_2 from 29% to 92%. Sco_2 was significantly related to Sao_2 ($y = 0.85 \times -17$, $r = 0.47$), Sjo_2 ($y = 0.77 \times +13$, $r = 0.70$), and the combination ($Sco_2 = 0.46\ Sao_2 + 0.56\ Sjo_2 - 17$, $R = 0.71$). The arterial and venous contribution to cerebral oximetry was 16 ± 21% and 84 ± 21%, respectively (where $Sco_2 = \alpha\ Sao_2 + \beta\ Sjo_2$ with α and β being arterial and venous contributions). The contribution was similar among conditions but differed significantly among subjects (range, ≈ 40:60 to ≈ 0:100, arterial:venous).**

Conclusions: **Cerebral oximetry monitors an arterial/venous ratio of 16:84, similar in normoxia, hypoxia, and hypocapnia. Because of biologic variation in cerebral arterial/venous ratios, use of a fixed ratio is not a good method to validate the technology. (Key words: Brain; congenital heart disease; hypoxia; monitor; near-infrared spectroscopy; oxygenation.)**

NEAR-infrared spectroscopy (NIRS) is a noninvasive optical technique to monitor cerebral oxygenation. It relies on the relative transparency of tissue to near-infrared light (700–900 nm), where oxygen-carrying chromophores, hemoglobin, and cytochrome aa_3 absorb light. By measuring near-infrared light absorption by these chromophores, it is possible to monitor cerebral oxygen saturation (Sco_2), oxyhemoglobin and deoxyhemoglobin concentration, and cytochrome aa_3 redox state.[1–4] NIRS has been used to describe the cerebral oxygen supply–demand relation in critically ill neonates, infants, children, and adults.[5–8] Despite its applicability and availability, NIRS is used infrequently to guide clinical care because of quantitation problems related to the biophysics of measurement and lack of a standard to validate the measurement. Like pulse oximetry, NIRS is based on the principle of the Beer law relating light absorption (measured by the instrument) to oxyhemoglobin and deoxyhemoglobin concentration. However, this approach requires constancy of optical path length and light scattering in the tissue field, neither of which is strictly constant in adults or children.[9,10] It also requires no contamination by extracranial tissues, which holds true in neonates and infants but not in adults.[11–13] As a result, absolute quantitation has been subject to an uncertain error in a given patient, limiting the technology to relative quantitation (monitoring changes over time). It has been difficult to establish the exact error in the measurement because NIRS lacks a standard to compare it against. Unlike pulse oximetry, NIRS monitors saturation within an uncertain mix of arteries, capillaries, and veins. No other method exists to measure saturation in this mixed circulation. Previous studies[2,3,14] used a weighted average of arterial oxygen saturation (Sao_2) and jugular bulb oxygen saturation (Sjo_2) in a fixed ratio (25:75, Sao_2:Sjo_2). However, this ratio has not been validated and may itself introduce error in study to evaluate the technology.

In the last few years, advances in technology and biophysics now permit absolute Sco_2 quantitation. Time- and frequency-domain instruments were invented to determine light absorption, light scattering, and optical path length and thereby calculate oxyhemoglobin and deoxyhemoglobin concentrations and Sco_2.[12,15] Blood perfused *in vitro* brain models have validated frequency-domain NIRS (fdNIRS) against blood oximetry.[16] In the present study, we used fdNIRS to examine the relation between NIRS Sco_2 and the arterial and venous ratio (*e.g.*, Sao_2 and Sjo_2) in children with congenital heart disease during normoxia, hypoxia, and hypocapnia. We tested the hypothesis that the cerebral arterial/venous ratio is 25:75 (Sao_2: Sjo_2).

* Fellow, Brain Research Laboratory, Departments of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, † Associate Professor, Brain Research Laboratory, Departments of Anesthesiology and Critical Care Medicine and Pediatrics, The Children's Hospital of Philadelphia, and the Departments of Anesthesia and Pediatrics, University of Pennsylvania School of Medicine, ‡ Assistant Professor, ‖ Professor, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, and the Department of Anesthesia, University of Pennsylvania School of Medicine, § Associate Professor, Department of Pediatrics, The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine.

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Address reprint requests to Dr. Kurth: Department of Anesthesiology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, Pennsylvania 19104. Address electronic mail to: kurth@email.chop.edu.

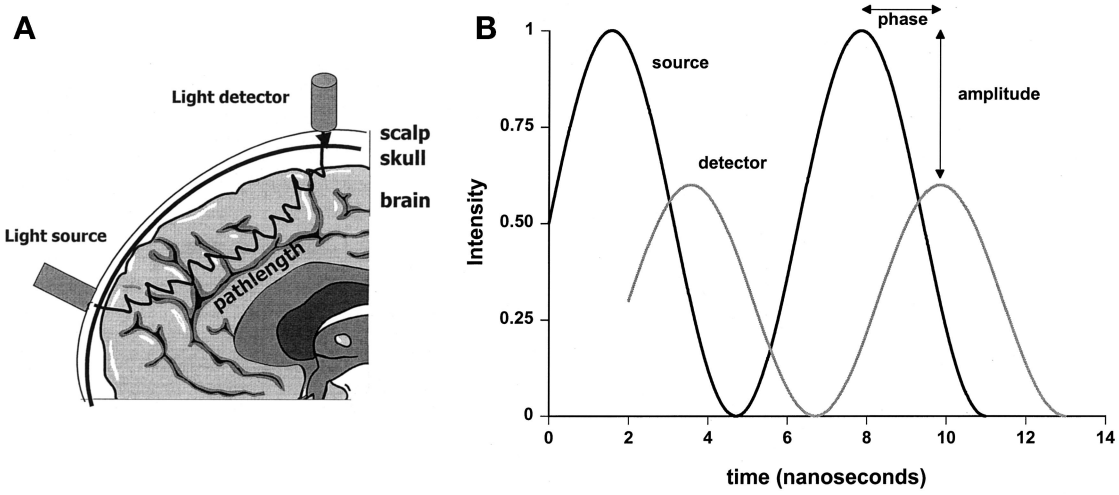

Fig. 1. Principles of cerebral oximetry. (*A*) Cerebral oximeter probe contains a light source and detector. Cerebral O_2 saturation is related to light intensity at the source (I_o), detector (I), and light pathlength (L) through the tissue according to the Beer Law (equation 1). (*B*) In frequency domain cerebral oximetry, the intensity of the light source (I_o) is oscillated at high frequency. After the light passes through the tissue, the detected intensity (I) is amplitude demodulated and phase shifted. Cerebral O_2 saturation is related to amplitude and phase, corresponding to intensity and pathlength in the Beer Law.

Methods

Subjects

After obtaining approval from the Institutional Review Board at the Children's Hospital of Philadelphia and informed parental consent, we studied 20 children undergoing cardiac catheterization for diagnostic or therapeutic purposes. Inclusion criteria included age less than 8 yr and a diagnosis of congenital heart disease requiring cardiac catheterization with general anesthesia and mechanical ventilation. Exclusion criteria included known structural neurologic or craniofacial disease and anemia (hemoglobin < 8 g/dl). Children were enrolled from the Day Medicine Clinic or inpatient care units and were studied from August 1997 to March 1999.

Anesthetic management was conducted according to our institutional practice. Premedication included pentobarbital (4 mg/kg orally) for age 6 months to 1 yr and pentobarbital and meperidine (3 mg/kg orally) for age 1–8 yr. The anesthetic was either (1) propofol (3 mg/kg then 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$), (2) propofol–fentanyl (propofol 2 mg/kg then 125 $\mu g \cdot kg^{-} \cdot min^{-}$, fentanyl 5 μg/kg then 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$), (3) fentanyl–midazolam (fentanyl as before, midazolam 0.2 mg/kg then 0.2 mg $\cdot kg^{-1} \cdot h^{-1}$), or (4) isoflurane (1% expired)–fentanyl (1 $\mu g \cdot kg^{-1} \cdot h^{-1}$). All children received mechanical ventilation through an endotracheal tube. Tracheal intubation was facilitated by intravenous pancuronium (0.1 mg/kg). Lidocaine 1% was infiltrated into the catheterization site. End-expired carbon dioxide, pulse oximetry (N-200; Nellcor Puritan Bennet, Pleasanton, CA), electrocardiogram (Hewlett-Packard, Andover, MA), arterial pressure (Dinamap; Critikon, Tampa, FL), and rectal temperature were monitored. No blood products, vasodilators, or vasoconstrictors were administered during the study.

Measurements

At present, cerebral oximetry instrumentation is based on continuous-wave, time-domain, or frequency-domain technologies. In continuous-wave technology, the instrument emits light at constant intensity (I_o) and detects this light whose intensity is attenuated (I) after passing through the head (fig. 1A). Sco_2 is determined from the intensity changes through an expression based on the principles of the Beer Law:

$$\sum_{1}^{n} \log(I_o/I) = \sum_{1}^{n} (\varepsilon LC) \qquad (1)$$

where L represents the path length of light through the tissue, C the concentration of the compounds (usually oxyhemoglobin, deoxyhemoglobin, and water), ϵ the extinction coefficient of the compounds, and n the number of compounds and wavelengths of the light being used. Because path length through the tissue is uncertain, continuous-wave instruments are semiquantitative, limited to monitoring changes in Sco_2 over time (baseline Sco_2 cannot be determined). In frequency-domain technology (fig. 1B), the instrument emits light whose intensity is oscillated at high frequency. The light passing through the tissue is amplitude demodulated and phase shifted relative to the emitted light. Sco_2 is determined from amplitude and phase, which correspond to intensity changes and path length, respectively. Time-domain instruments use a pulse light source, require expensive hardware, and are not commercially viable in the foreseeable future. Continuous-wave and frequency-

domain instruments are viable, although only frequency-domain instruments are absolutely quantitative.

In our study, Sco_2 was measured with a prototype fdNIRS (PMD, NIM Incorporated, Philadelphia, PA).[12] Briefly, the instrument uses laser diodes at measuring wavelengths of 754 nm, 780 nm, and 816 nm, with a reference wavelength at 780 nm that is not directed through the sample. The laser light intensities are oscillated at 200 MHz. The instrument uses heterodyne frequency-domain technology to monitor phase shifts at the three measuring wavelengths relative to the internal reference. The instrument is calibrated before use against an external standard. Fiberoptic bundles mounted in soft rubber housing (optical probe) deliver the laser light to and from the subject's head. The distance separating the emitter and detector fiberoptic is 3 or 4 cm. A computer captures the phase signals at 2/s and signal averages them over 15 s. Sco_2 is calculated from amplitude and phase signals according to an algorithm.[12] Instrument precision and bias relative to blood oximetry is 6% and −2%, respectively, from 0% to 100% saturation.[12]

Cerebral oximetry views a banana-shaped tissue volume between the emitter and detector located approximately 2 cm deep to the surface.[9,10] In young children, the thin extracerebral tissues do not contaminate the measurement of Sco_2 from the surface of the head.[10,12,13] With the probe on the forehead, the cerebral oximeter appears to monitor both gray and white matter in the frontal neocortex.

Protocol

After completion of the catheterization, the cardiologist advanced the catheter located in the systemic venous circulation into the left or right jugular vein until the tip was at the level of the jugular bulb, confirmed by fluoroscopy. The catheter located in the systemic arterial circulation was positioned with its tip in the aorta. The cerebral oximeter optical probe was applied to the forehead at midline below the hairline.

Subjects experienced three conditions selected in random order: baseline, 100% inspired oxygen, and hyperventilation. Baseline was normocapnia with inspired oxygen at the preoperative concentration (usually room air). One hundred percent inspired oxygen was also at normocapnia. Hyperventilation was achieved by increasing tidal volume or ventilatory rate to decrease end-tidal carbon dioxide by 10–15 mmHg, while returning inspired oxygen to the baseline concentration. The protocol required approximately 40 min, with each condition achieved in approximately 3 min, followed by 10-min steady state ventilation. Sco_2 at the condition was taken as the average value over the last minute, during which arterial and jugular bulb samples were drawn. Jugular bulb samples were drawn slowly.[17]

Demographic and physiologic data were recorded. Mean arterial and systemic venous pressure, Sao_2, Sjo_2, Sco_2, and arterial blood gases were recorded during each condition. A subject was defined as *normoxic* if baseline Sao_2 was > 95%.

Analysis

Data are presented as mean ± SD. Comparisons between conditions or groups were made by analysis of variance. When a significant overall F was found, pairwise multiple comparisons were made using Tukey's test. Linear regression was used to determine the relation between Sco_2 and Sjo_2, Sao_2, and Swo_2, where Swo_2 was defined as $Swo_2=(0.25)Sao_2+(0.75)Sjo_2$ Swo_2 was used in other studies and was included in the current study for historical comparisons.[2,3,14] The contribution of Sjo_2 and Sao_2 to Sco_2 for each subject–condition was determined by solving paired equations for α and β: $Sco_2 = \alpha\ Sao_2 + \beta\ Sjo_2$ $1 = \alpha + \beta$ where α and β represent the fraction of arterial and venous blood in tissue and Sjo_2, Sao_2, and Sco_2 were the measured values for the subject–condition. Equations 3 and 4 assume all blood in tissue exists in either arterial or venous compartments. Arterial/venous ratios that were negative were not included in the analysis but were noted as "undeterminable." A one sample *t* test was used to validate the hypothesis that the α/β ratio is different from the 25/75 ratio. Pearson's correlation coefficients were calculated between Sco_2 and demographic, physiologic, and arterial and jugular venous blood ratio variables. Multivariable regression was explored between Sco_2 and the variables having correlation coefficients with 0.01 level of significance to adjust for the multiple correlation tests. Bias and precision of fdNIRS Sco_2 relative to Sjo_2, Sao_2, and Swo_2 were calculated.[3]

Results

Table 1 lists the study subjects. The subjects' age ranged from newborn to 6 yr, with 12 males and 8 females, 16 being white and 4 black. Fifteen subjects had complex congenital heart disease, among which 13 had single-ventricle disease. Ten subjects received medications for heart failure and 2 received prostaglandin infusions for ductus arteriosus-dependent lesions. Of the 20 subjects, 14 successfully completed the protocol, while 4 completed two conditions and 2 completed one condition. Reasons for incomplete data on all conditions included inadequate hyperventilation (n = 4) or malfunction of the jugular bulb catheter (n = 3) or cerebral oximeter (n = 3). Arterial/venous ratios were undeterminable in four instances (three subjects) because Sjo_2 was greater than Sco_2 (Sjo_2 *vs.* Sco_2: 85% *vs.* 73%, 84% *vs.* 58%, 96% *vs.* 88%, and 60% *vs.* 45%).

Figure 1 displays a representative Sco_2 tracing (subject 9) during the study protocol. Table 2 presents the physiologic data in all subjects and in the normoxic subjects.

Table 1. Subject Demographics

Patient	Disease	Medications	Age (mo)	Weight (kg)	Race	Gender	Hemoglobin (g/dl)	CVP
1	TOF, PA	1, PGE	0	2.9	W	F	12.1	3
2	HLHS, hemifontan	1, digoxin, captopril, coumadin	19	11.8	W	M	16	6
3	TOF, PA	1, PGE	0	3.6	W	M	12.3	4
4	TGA, PS, VSD, Rastelli	3, dopamine, milrinone, furosemide	8	7.8	B	M	10.7	15
5	ASD	4	72	23.0	W	F	10.1	3
6	TOF, AVC	4	7	5.1	B	M	14	10
7	DILV, TGA, PS	4, digoxin, furosemide, captopril	4	4.9	W	F	17	10
8	HLHS, hemifontan	1	20	10.5	W	M	15.3	16
9	TOF, PA, BTS	2	9	7.0	B	M	14.5	3
10	Epstein, BTS	1	24	11.8	W	M	12	8
11	PA	2	8	6.9	W	F	10.3	8
12	VSD	1, digoxin, furosemide, captopril, aldactone	2.5	2.0	W	F	9.8	4
13	TOF/PA	3, milrinone, O_2 dobutamine, furosemide	8	7.4	W	F	14.5	10
14	DORV, PS, CAVC, BTS	1, digoxin, furosemide, aspirin	3	4.8	W	F	10.4	3
15	DORV, PS, Rastelli	4, digoxin, furosemide	19	9.4	B	M	10	13
16	D-TGA, VSD, CoAo	4, digoxin, furosemide, captopril, aldactone	40	12.5	W	M	9.8	9
17	HTXY, DORV, PS, AVC	2, digoxin, furosemide	3	4.8	W	F	14.6	1
18	TOF/PA	2, digoxin, furosemide	17	8.5	W	M	10.8	3
19	HLHS, BDG	1, captopril	30	15.3	W	M	14.9	5
20	Cardiomyopathy, PS	1	11	7.1	W	M	10.2	14

1–4 denote the anesthetic: 1 = propofol; 2 = propofol, fentanyl; 3 = fentanyl, midazolam; 4 = isoflurane, nitrous oxide, fentanyl; B = black; BDG = bi-directional Glenn; BTS = Blalock-Taussig shunt; CAVC = complete atrioventricular canal; CoAo = coarctation of aorta; CVP = systemic venous pressure; DILV = double inlet left ventricle; HLHS = hypoplastic left heart syndrome; HTXY = heterotaxy; PA = pulmonary atresia; PS = pulmonary stenosis; TGA = transposition of great arteries; TOF = tetralogy of Fallot; W = white.

In all subjects, Sco_2, Sao_2, and Sjo_2 increased significantly from baseline to 100% O_2, whereas from baseline to hyperventilation, Sao_2 increased and Sjo_2 decreased, whereas Sco_2 did not change significantly. In normoxic subjects, Sco_2 decreased significantly with hyperventilation, whereas Sjo_2 tended to decrease ($P = 0.15$).

Of the demographic and physiologic variables in all subjects, only Sao_2 and Sjo_2 correlated significantly with Sco_2 ($r = 0.61$, $P < 0.01$; $r = 0.76$, $P < 0.001$, respectively). Multivariable regression found a significant relation: $Sco_2 = 0.46\ Sao_2 + 0.56\ Sjo_2 - 17$ ($R = 0.71$, $P < 0.03$). Other variables, including age, hemoglobin, type of cardiac lesion and anesthetic, and mean arterial and systemic venous pressure, did not significantly correlate with Sco_2 ($r = 0.1$–0.3, all $P > 0.2$).

Accordingly, we focused on the relation of Sco_2 to Sao_2, Sjo_2, and Swo_2. Sco_2 was linearly related to Sao_2 (fig. 3), Sjo_2 (fig. 4), and Swo_2 (fig. 5). Sao_2 ranged from 68% to 100%, Sjo_2 from 27% to 96%, Swo_2 from 37% to 98%, and Sco_2 29% to 92%. Cerebral oximetry bias and

Table 2. Physiologic Data during the Study

	All Subjects (n = 20)			Normoxic Subjects (n = 6)		
	Baseline	Hyperventilation	100% O_2	Baseline	Hyperventilation	100% O_2
pH	7.42 ± 0.1	7.51 ± 0.08*	7.39 ± 0.04	7.40 ± 0.10	7.52 ± 0.10	7.40 ± 0.04
Pco_2 (torr)	36 ± 3	26 ± 3*	37 ± 3	36 ± 3	26 ± 2*	36 ± 4
Po_2 (torr)	50 ± 14	51 ± 21	251 ± 146*	84 ± 15	71 ± 13	250 ± 95
MAP (mmHg)	72 ± 20	69 ± 15	70 ± 14	70 ± 18	66 ± 15	68 ± 15
Sao_2 (%)	84 ± 4	87 ± 5*	94 ± 3*	98 ± 1	97 ± 1	99 ± 1
Sjo_2 (%)	54 ± 4	49 ± 8*	64 ± 6*	69 ± 9	56 ± 15	75 ± 12
Sco_2 (%)	53 ± 8	55 ± 8	62 ± 7*	73 ± 10	56 ± 14*	70 ± 16

Data are mean ± SD.

*$P < 0.05$ *vs.* corresponding baseline.

MAP = mean arterial pressure; Pco_2 = partial pressure of carbon dioxide; Po_2 = partial pressure of oxygen; Sao_2 = arterial oxyhemoglobin saturation; Sco_2 = cerebral oxyhemoglobin saturation; Sjo_2 = jugular bulb oxyhemoglobin saturation.

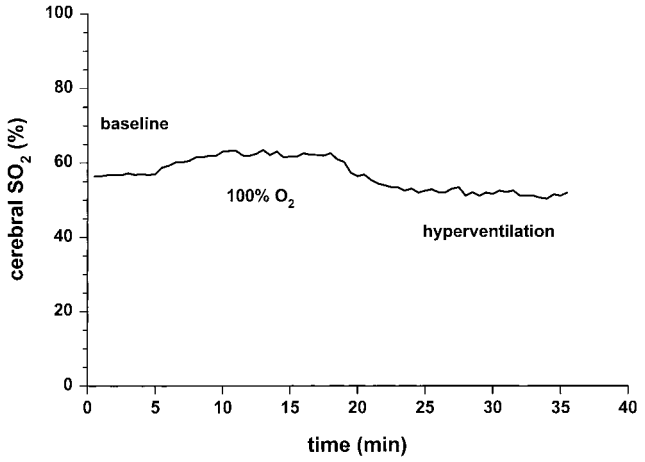

Fig. 2. Representative recording of cerebral O_2 saturation (Sco_2) by frequency domain cerebral oximetry in a subject during the study protocol in which ventilation and inspired O_2 concentration were manipulated.

precision were, respectively, 1.4 and 11.4 relative to Sjo_2, −30 and 14.2 relative to Sao_2, and −3.2 and 5.4 relative to Swo_2. As noted by the biases and intercepts of the lines, Sco_2 was less than Sao_2, greater than Sjo_2, and close to Swo_2.

Because NIRS Sco_2 was closest to Swo_2, we examined in greater detail the arterial and venous contribution to cerebral oximetry (table 3). Cerebral venous blood (Sjo_2) accounted for the majority (≈ 85%) of NIRS-monitored blood. Although the arterial/venous ratio did not vary significantly in individual subjects with changing conditions (all comparisons, $P > 0.2$), significant variability existed between subjects ($P < 0.001$). For example, in 10 subjects (4 were normoxic), NIRS monitored essentially cerebral venous blood (arterial/venous ratio ≈ 0/100), whereas in 2 subjects (1 was normoxic), it monitored a more equal mixture (arterial/venous ratio ≈ 40/60). In the remaining 8 subjects, the ratio fell between these values. No demographic or physiologic factor (*e.g.*, age, hemoglobin, arterial or systemic venous pressure, or Sao_2) significantly correlated with the arterial/venous ratio (r = 0.05–0.3, all $P > 0.2$). The cerebral arterial/venous ratio in all subjects at baseline was significantly different from the 25:75 ratio ($P = 0.03$).

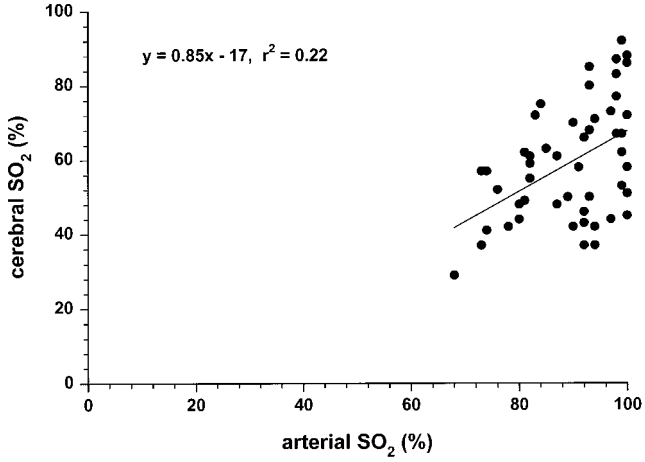

Fig. 3. Relation between arterial O_2 saturation (Sao_2) and cerebral O_2 saturation (Sco_2) in the subjects during the study conditions.

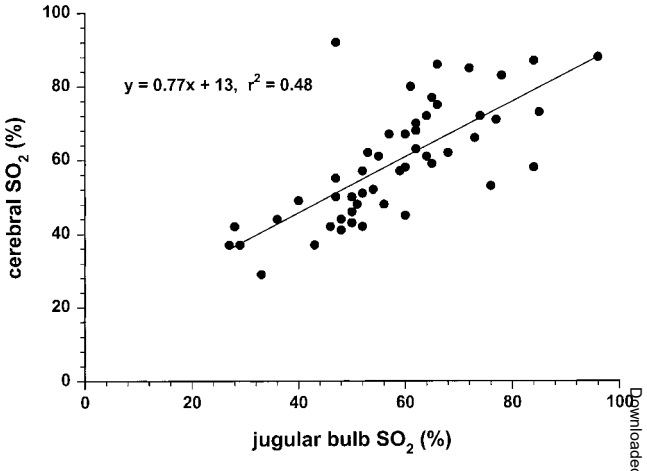

Fig. 4. Relation between jugular venous O_2 saturation (Sjo_2) and cerebral O_2 saturation (Sco_2) in the subjects during the study conditions.

Discussion

More than 20 yr ago, Jobsis[18] demonstrated the feasibility of monitoring cerebral oxygenation noninvasively with near-infrared light. The method, which became known as NIRS, was qualitative because light scattering by tissue precluded knowledge of optical path length necessary to solve the Beer Law equation. Current commercially available NIRS monitors have the same problem, although they use empirical calibration or a differential path length factor to make them "semiquantitative," describing relative changes in cerebral oxygenation from an

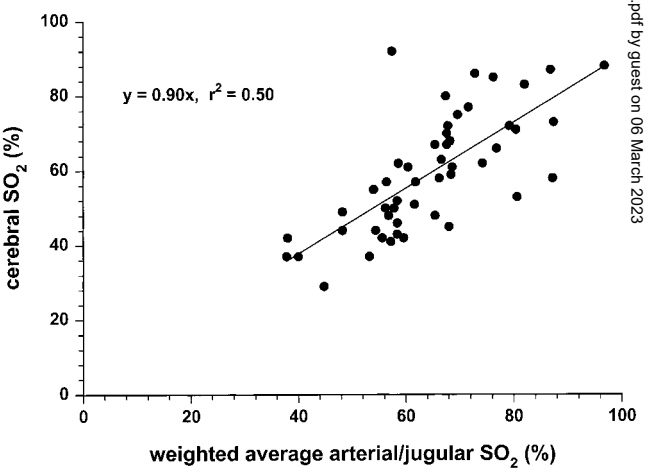

Fig. 5. Relation between cerebral O_2 saturation (Sc_{O2}) and a weighted average O_2 saturation (Swo_2) of arterial and jugular bulb blood in the subjects during the study conditions. Swo_2 = 0.25 Sao_2 + 0.75 Sjo_2, where Sao_2 and Sjo_2 are arterial and jugular bulb O_2 saturation, respectively.

Table 3. Contribution of Arterial and Venous Blood to Cerebral Oximetry

	Arterial (%)	Venous (%)
All subjects (n = 20)		
Baseline	12 ± 15	88 ± 15
100% O_2	9 ± 16	91 ± 16
Hyperventilation	20 ± 25	80 ± 25
Average	16 ± 21	84 ± 21
Normoxic subjects (n = 6)		
Baseline	15 ± 16	85 ± 16
100% O_2	15 ± 25	85 ± 25
Hyperventilation	18 ± 22	82 ± 22
Average	15 ± 19	85 ± 19

Mean ± SD. n is number of subjects. Average originates from baseline, 100% O_2, and hyperventilation values.

unknown baseline.[1–8,14] fdNIRS, a new class of instrumentation, uses frequency-domain technology to determine optical path length to make it absolutely quantitative.[13,15] In a validated *in vitro* brain model, fdNIRS was found accurate against blood oximetry.[13,16] A validated *in vivo* model to test NIRS accuracy does not exist. Previous human and animal studies[2,3,14] used a weighted average of Sa_{O_2} and Sj_{O_2} in a fixed ratio of 25:75 (Sa_{O_2}:Sj_{O_2}) for comparison with NIRS Sc_{O_2}. However, this weighted average has not been validated for the cerebral circulation *in vivo*.

In the present study, we investigated the relation of fdNIRS Sc_{O_2} to a number of physiologic variables in infants and young children, including Sa_{O_2} and Sj_{O_2}, to test the weighted average *in vivo* model. Of the variables examined, only Sa_{O_2} and Sj_{O_2} significantly correlated with Sc_{O_2}. NIRS Sc_{O_2} fell between Sa_{O_2} and Sj_{O_2}, closer to Sj_{O_2} than Sa_{O_2}. The arterial/venous contribution to NIRS Sc_{O_2} averaged 85% venous and 15% arterial, not differing differ significantly between normoxia, hypoxia, and hypocapnia. However, this arterial:venous ratio differed significantly among subjects and from the 25:75 arterial:venous ratio. Thus, our results do not validate this fixed, weighted average *in vivo* model to test cerebral oximetry.

Data on the arterial/venous ratio for the cerebral circulation is limited.[19–21] The circulation is anatomically divided into five groups. The first group comprises large conducting arteries, which for the brain include the Circle of Willis and middle cerebral artery. The second group includes distal arterial branches and arterioles that function to regulate blood flow. The third group, consisting of end arterioles, capillaries, and postcapillary venules, serves gas exchange. The fourth and fifth groups include venules and large collecting veins, respectively. Each group's volume contribution has been calculated from *in situ* measurements of number, length, and radius of the vessels in one adult dog brain and one bat wing.[19,20] In adult dog brain, the first through the fifth groups contain 10%, 17%, 28%, 20%, and 25% of the blood volume, respectively.[19] In bat wing, the corresponding figures are 10%, 5%, 39%, 25%, and 21%, with group 3 being 1% end arteriole/capillary and 38% venular.[20] From this data, we calculate the arterial/venous ratio to be 14/86 in bat wing and 28/72 in dog brain, assuming the end arteriole/capillary to venous percentage in group 3 is the same for dog brain as for bat wing. The commonly used 25/75 ratio,[2,3,14] originates from Mchedlishvili's[21] calculations based on cerebrovascular resistance measured by another investigator (Tkachenko BI: Venous blood circulation. Meditsina, Leningrad, 1979, undocumented). To our knowledge, no published data exist about variance in the ratio among subjects or physiologic conditions. However, in our studies of the pial circulation in piglets using intravital microscopy, we have observed considerable variation in the relative numbers of arterioles and venules among animals (unpublished observations). Other investigators have reported vessel groups 1–4 to dilate and constrict during hypoxia and hypocapnia.[22,23] Thus, it is likely biologic variation exists in arterial/venous ratios and that the ratio does not change substantially during hypoxia or hypocapnia.

Several biologic and instrument-related factors might have influenced our calculation of the cerebral arterial/venous ratio. Biologic factors relate to the assumptions of negligible extracerebral blood in the jugular bulb and of negligible capillary blood volume. If extracerebral blood in the jugular bulb were not negligible, it would increase Sj_{O_2} because oxygen extraction by extracranial tissue is minimal,[24] with the result that our calculation of the ratio would be falsely high. Although extracerebral contamination of the jugular bulb is negligible in normal adult humans,[25] it may not have been so in some of our subjects, given the vascular malformations present in complex congenital heart disease. Perhaps the four instances of Sj_{O_2} exceeding Sc_{O_2} represented an example of this extracerebral contamination. If capillary blood volume were not negligible, it would make our calculation of the ratio falsely high or low, depending on the net change in the arterial and venous coefficients (equations 3 and 4). Because chronic hypoxia increases brain microvessel density,[26] it is possible that capillary blood volume may not have been negligible in some of our subjects. However, similar cerebral arterial/venous ratios in the normoxic subjects, in whom these assumptions are likely valid, argue against these biologic factors biasing our calculation of the ratio, although they could increase its variance.

Instrument-related factors include measurement precision and the field of view. Our optical probe monitors the frontal neocortex.[12,27] Ideally, the cerebral arterial/venous ratio is calculated from venous saturation in this tissue field rather than Sj_{O_2}. Variations in regional cerebral oxygen extraction have been measured and may have contributed to the variance in arterial/venous ratios among our subjects.[24,28] Measurement precision of the cerebral oximeter (6%) and blood oximeter (3%) could contribute to the variance in our calculation of the arte-

rial/venous ratio.[12] A carry-through error analysis of equation 2 using these precision values reveals that approximately one half of the variance could arise from this instrument factor. The other one half of the variance in the cerebral arterial/venous ratio would have to originate from true biologic variability among subjects. This biologic variability did not seem to originate from physiologic differences among subject because factors that regulate cerebral blood volume, such as central venous and arterial pressure, hemoglobin concentration, and arterial saturation,[23] were not associated with the cerebral arterial/venous ratio.

There has been some question about the circulation monitored by cerebral oximetry. NIRS signal changes with Trendelenberg positioning clearly demonstrate a component of the venous circulation.[29] Our findings and those of Brun *et al.*[30] also show an arterial contribution to NIRS. *In vitro* work illustrates the NIRS signal to originate mainly from small blood vessels.[31] The NIRS signal changes during complete ischemia clearly demonstrate that it monitors gas-exchanging vessels.[5] Gas exchange has been found to take place in arterioles and venules as well as in capillaries.[32] These gas-exchanging vessels contain the majority of blood in the circulation (*e.g.*, vessel groups 3 and 4).[19–21] Together, the body of evidence points to cerebral oximetry monitoring a mixed vascular bed dominated by gas-exchanging vessels, especially venules.

Our findings have implications in the evaluation of cerebral oximetry for use in clinical medicine. Because of biologic variation, use of a fixed arterial/venous ratio is not a good method to validate cerebral oximetry. This requires a direct evaluation of its measurement with a clinical outcome. Cerebral oximetry might be evaluated as a diagnostic or management device for cerebral hypoxia–ischemia in infants and children.[5–7,33,34]

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