Original Article

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Brain Oximetry

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RESUMEN

Oximetría Cerebral. La espectroscopia infrarroja proporciona una valoración continua no invasiva de la saturación cerebral de hemoglobina midiendo la absorción diferencial de la luz infrarroja. Esta medición recibe contribuciones de los vasos capilares, arteriales y venosos cerebrales, con una predominante contribución venosa. En este estudio se utilizó un prototipo de oximetro cerebral en voluntarios conscientes respirando mezclas hipoxicas para desarrollar un algoritmo que cuantifique la saturación de oxígeno de la hemoglobina cerebral, así como para determinar los efectos de los cambios en posición y el CO_2 sobre la señal del oximetro. Los resultados son comparados con la saturación venosa yugular obtenida por oximetria directa del bulbo de la yugular. La señal del oximetro ($C_{Sf}O_2$), la saturación cerebral de oxígeno estimada ($C_{Scomb}O_2$) y la saturación venosa yugular de oxígeno ($SvjO_2$) fueron significativamente mayores con hipercapnia y significativamente menores con hipocapnia, sin embargo, la influencia de la hiper o hipocapnia sobre la señal del oximetro merece mayores estudios y ajustes al algoritmo antes de su aplicación a pacientes con patología intracraneal (*Rev Mex Anest*, 1997;20:103-109)

Palabras Clave: Espectroscopia infrarroja, oximetro, hipoxia cerebral, oxigenación cerebral, oxihemoglobina, deoxihemoglobina, monitoreo, posición, hipercapnia, hipocapnia

ABSTRACT

Near-infrared spectroscopy provides a continuous, noninvasive assessment of global brain hemoglobin oxygen saturation by measuring the differential absorption of infrared light. The hemoglobin oxygen saturation measured by the cerebral oximeter receives contributions from arterial, venous, and capillary blood vessels, with a predominantly venous contribution. We evaluated a prototype cerebral in conscious volunteers breathing hypoxic gas mixtures, contributing data for the manufacturer to develop an algorithm to quantify brain hemoglobin oxygen saturation. We also performed studies to determine the effects of changes in position and carbon dioxide (CO_2) on the oximeter signal ($C_{Sf}O_2$). In our study, $C_{Sf}O_2$, $C_{Scomb}O_2$, and SjO_2 were significantly higher during hypercapnia and significantly lower during hypocapnia. However, the decrease in $C_{Sf}O_2$ during hypocapnia was much less than the corresponding decrease in $C_{Scomb}O_2$ suggesting that the association between $C_{Sf}O_2$ and $C_{Scomb}O_2$ is less precise during hypocapnia. The influence of hyper- and hypocapnia on the spectroscopic signal merits further investigation, however, and the algorithm may require further adjustment in patients with relevant underlying pathology (*Rev Mex Anest*, 1997;20:103-109).

Key Words: Near infrared spectroscopy, oximeter, cerebral hypoxia, cerebral oxygenation, oxyhemoglobin, deoxyhemoglobin, monitor, position, hypercapnia, hypocapnia

NEAR INFRARED (NIF) spectroscopy provides a continuous, noninvasive assessment of global brain hemoglobin oxygen saturation by measuring the differential absorption of infrared light[1-3]. Milikan, in 1942[4], and Yoshiya et al in 1980[5] , successfully determined that arterial oxygen saturation could be measured using oximetry. Jobsis, in 1977, successfully demonstrated that brain oxygenation could be assessed by measuring the attenuation of infrared light as it passed through the skull[6]. Infrared light at wavelengths between 400 and 1000 nm penetrates skin, subcutaneous tissue, bone, and dura to reach the brain[6-9], where it is absorbed and partially transmitted by oxygenated hemoglobin, deoxygenated hemoglobin, and by cytochrome aa3. Thus, the attenuation of infrared light of specific wavelengths by these chromophores is related to brain oxygenation[1,3,10-13]. The hemoglobin

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oxygen saturation measured by the cerebral oximeter receives contributions from arterial, venous, and capillary blood vessels, with a predominantly venous contribution[13,14]; therefore, like jugular venous bulb oxygen saturation, NIR spectroscopy may reflect the balance between cerebral oxygen consumption and delivery.

NIR spectroscopy has been studied extensively in animals[6,10,15-17] and is widely used as a technique for continuously monitoring brain oxygenation in neonates[18-20]. Cerebral oximetry has also been evaluated in adults under anesthesia[21] and has been used to assess the adequacy of collateral circulation in patients undergoing carotid endarterectomy[22]. The spectroscopic signal changes as quickly in response to progressive cerebral hypoxia as the electroencephalogram[23,24]. It may also aid in the diagnosis and localization of intracranial hematomas[25]. However, NIR spectroscopy has several hurdles to overcome. First, the quantity of transmitted light is small, necessitating a powerful light source if cytochrome aa3, the least abundant of the chromophores mentioned earlier, is to be analyzed. Second, the proportions of arterial and venous blood may vary with changes in cerebral blood flow or venous pressure. Third, validation against a suitable "gold standard" has been difficult.

Clinical validation of the *in vivo* spectroscope has proven difficult, because the saturation measured by the oximeter cannot be directly calibrated, and because global cerebral oxygen saturation, a combination of arterial and venous blood, cannot be measured directly. Many studies have compared the spectroscopic signal to established methods that indirectly assess cerebral perfusion, such as the electroencephalogram[23,24], or that provide partial information, such as nuclear magnetic resonance spectroscopy[17,18], and ^{133}Xenon clearance. The most accessible clinical reference standard, however, remains the estimated global brain oxygen saturation ($C_{Scomb}O_2$), which is calculated from arterial and jugular venous bulb oxygen saturations[23,27].

We evaluated a prototype cerebral oximeter (Invos 3100, Somanetics Corporation, Troy, Michigan) in conscious volunteers breathing hypoxic gas mixtures, contributing data for the manufacturer to develop an algorithm to quantify brain hemoglobin oxygen saturation[28]. We also performed studies to determine the effects of changes in position and carbon dioxide (CO_2) on the oximeter signal ($C_{Sf}O_2$)[29].

METHODS

Description of the Cerebral Oximeter

The prototype cerebral oximeter measures the ratio of the content of oxyhemoglobin to deoxyhemoglobin and thus provides an index of global brain hemoglobin oxygen saturation. Infrared light, generated by an incandescent light source, is focused through a filter that separates the light into two wavelengths of 730 and 810 nm. Fiberoptic cables transmit the light to a miniature light-emitting diode in a self-adhesive sensor that attaches to the subject's forehead. The light then enters the underlying tissues, where it is scattered, causing the photons to travel in random paths through the brain. Computer simulations of the proton paths have shown them to follow an average elliptical path between the emitter and detector[9,30]. The proportion of light returned to the surface is captured by two detectors on the sensor, which are placed at varying distances to sample different light path lengths through the tissue. The more distant detector (D2), placed 4 centimeters (cm) from the sensor in these studies, measures the hemoglobin oxygen saturation of all of the tissues penetrated by the light beam, including skin, muscle tissue, skull, and brain. The closer detector (D1), placed 3 cm from the sensor, measures hemoglobin oxygen saturation primarily from the superficial tissues. By subtracting D1 from D2, an approximate hemoglobin oxygen saturation ($C_{Sf}O_2$) may be estimated in the underlying brain. Monitoring cables deliver the detected light to photodetectors in a microcomputer, which then collects the spectroscopic measurements, averages them, and displays a sliding numerical average of the data on a display screen.

Description of the Cerebral Oximeter Algorithm:

The Beer-Lambert law describes the relationship between incident and received light of suitable wavelength as follows:

$$-I_w / I_{wo} = e^{-awCS}$$

where Iw is the intensity of transmitted light at wavelength w, Iw_o is the intensity of incident light at wavelength w, a is the molar extinction coefficient of the chromophore, C is the concentration of the chromophore molecule in the tissue, and s is the distance of the path length of light in the tissue. The extinction coefficients of oxy- and

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deoxyhemoglobin are known and the transmitted light intensity is a measured parameter.

An algorithm based on the above equation is used to process the incoming intensity data as follows:

$$-\ln(I_w / I_{wo}) = \sum_{j=1} a_{w,j} C_{js}$$

Absorption at a second wavelength, w', is then substracted from the absorption at w to create the expression:

$$-\ln(I_w / I_{wo}) + \ln(I_{w'}/I_{w'o}) = \sum_{j=1} (a(w, j) - a(w', j))\, C_{js}$$

Repeated (N + 1) measurements are made to solve for C_{1s} for oxyhemoglobin and C_{2s} for reduced hemoglobin. Although these expressions do not represent the actual concentration of the molecules, they are proportional to them. The path length, s, which varies with hemoglobin concentration, is assumed constant for all wavelengths over the range of the measurement. Although the path length of photons has been measured with reasonable accuracy[7,20,31], the effects of unknown path lengths can be removed from the equation by calculating the ratio of the expressions:

$$\frac{C2s}{C1s} = \frac{C2}{C1} = \frac{\text{concentration of deoxyhemoglobin}}{\text{concentration of oxyhemoglobin}}$$

Saturation of hemoglobin in the region of measurement is expressed as the ratio of oxyhemoglobin (HbO_2) to total hemoglobin (Hb).

$$C_{Sf}O_2 = \frac{HbO_2}{HbO_2 + Hb} \times 100\%$$

Dividing the numerator and denominator of the fraction by HbO^2 yields the following:

$$C_{Sf}O_2 = \frac{1}{(1 + Hb/HbO_2)} \times 100\% = \frac{1}{(1 + C2/C1)} \times 100\%$$

where C2/C1 is the parameter solved by the processor based on measured intensities.

VOLUNTEER PREPARATION

Hypoxic Gas Mixture Study

In a study approved by the institutional review board, the algorithm for the cerebral oximeter was first optimized for 12 healthy volunteers (age range 23 to 33 years), then validated in an additional 10 volunteers (age range 22 to 35 years). After informed consent was obtained, the volunteers underwent radial arterial and jugular bulb catheterization. A Doppler ultrasonic probe (DYMAX Site Rite, Pittsburgh, PA) was used to localize the internal jugular vein.

Volunteers were continuously monitored using a pulse oximeter (Nellcor Model N 100C, Hayward, CA), an end-tidal carbon dioxide ($ETCO_2$) monitor (DATEX Normocap 200, Helsinki, Finland), an electrocardiogram (Lifescope 6, Tokyo, Japan), and an automated blood pressure monitor (Critikon Vital Signs Monitor 1846-X, Tampa, FL). Volunteers were studied in the supine position.

A double-path, self-adhesive probe containing a near-infrared light source and detectors was also placed on each subject's right frontal forehead to continuously monitor the four optical density signals (one at each wavelength from each detector) and calculate $C_{Sf}O_2$. Subjects breathed randomly ordered hypoxic gas mixtures (FiO_2 = 0.13, 0.125, 0.12, 0.11, 0.1, 0.07, and 0.06) through a tight-fitting mask and a closed circuit using a nitrogen and oxygen gas mixture. Each mixture was breathed until a stable pulse oximeter reading was obtained, at which time simultaneous arterial and jugular venous blood gases were slowly drawn, and heart rate, blood pressure, $ETCO_2$ and pulse oximeter readings were documented. Neurological function was assessed by verbal communication. Subjects breathed the mixtures for at least five minutes before blood sampling, and were allowed a five-minute interval of inhalation of 100% O_2 between challenges.

Hypoxic Gas Mixture/Position Study

We examined the influence of supine, 20° Trendelenburg, and 20° reverse Trendelenburg positions on the bias and precision of $C_{Sf}O_2$. through measurement of the correlation between $C_{Sf}O_2$ and $C_{Scomb}O_2$ during hypoxic challenges. Ten subjects breathed randomized nitrogen and oxygen mixtures (FiO_2 = 0.21, 0.13, 0.12, and 0.1) for at least five minutes through a tight-fitting face mask using a closed circuit. The order of body positions (supine, 20° Trendelenburg or 20° reverse Trendelenburg), and order of hypoxic conditions (baseline, 95%, 85%, or 75%) was randomly assigned for each subject. When the pulse oximeter reading had been stable near the target saturations (baseline, 95%, 85%, or 75%), simultaneous arterial and jugular venous blood gases were slowly drawn.

Table 1. Correlation coefficients, slopes and intercepts

Training Data			
Subject	Correlation Coefficient	Slope	Intercept
1	0.951	0.8949	5.532
2	0.950	0.8138	9.0199
3	0.904	1.3064	-23.114
4	0.967	0.91168	6.9573
5	0.962	1.1409	-6.8769
6	0.798	0.71568	14.79
7	0.962	0.7267	18.543
8	0.967	0.75989	16.435
9	0.953	1.0972	-6.3078
10	0.875	0.78088	11.928
11	0.975	1.0536	4.6783
12	0.987	0.86384	14.008
Validation Data			
Subject	Correlation Coefficient	Slope	Intercept
1	0.915	0.76183	7.8221
2	0.982	1.1075	1.4326
3	0.986	1.0419	-4.2881
4	0.858	0.99429	2.3351
5	0.979	1.0901	-2.6858
6	0.909	1.0619	6.2437
7	0.969	0.48723	30.061
8	0.992	1.0012	4.8264
9	0.927	0.76043	19.399
10	0.794	0.89405	5.6883

Hypocapnia/Hypercapnia/Position Study

We then studied the influence of hypercapnia and hypocapnia on the association between $C_{Sf}O_2$ and $C_{Scomb}O_2$, during position change. Nine subjects were studied supine, and in 20° Trendelenburg and 20° reverse Trendelenberg positions. Nine possible sequences of three body positions and three $ETCO_2$ levels were randomly assigned to each subject. In each position, subjects were asked either to hyperventilate to an end-tidal CO_2 value of less than 15 mm Hg, or to breathe a 7.3% CO_2, O_2, and air mixture through a tight-fitting mask over a five minute period, until the end-tidal CO_2 exceeded 55 mm Hg. Simultaneous arterial and jugular venous blood gases were slowly drawn when end-tidal CO_2 measurements were stable.

Statistical Analysis

All data sets were analyzed separately but in the same manner. Brain oxygen saturation ($C_{Scomb}O_2$) was computed as

$$C_{Scomb}O_2 = 0.25\ SaO_2 + 0.75\ SjO_2$$

where SaO_2 = arterial oxygen saturation and SjO_2 = jugular venous bulb oxygen saturation. Previous publications have indicated that the venous contribution to the cerebral blood content is 70% to 80%[14,32]. The association between brain oxygen saturation and the in vivo spectroscope ($C_{Sf}O_2$) was investigated, assuming a straight-line relationship:

$$C_{Scomb}O_2 = (\text{slope})\ C_{Scomb}O_2 + (\text{intercept})$$

Pearson product-moment correlation coefficients between $C_{Scomb}O_2$ were computed for each subject to measure the intensity of the association. The data sets were also analyzed using the method described by Bland et al, for comparison of two measurements when the actual value is not known[33]. Finally, to determine the influence of position and CO_2, an analysis of variance procedure was performed using Fischer's least-significant procedure to assess the influence of position change on $C_{Scomb}O_2$ and $C_{Sf}O_2$. Effects were assessed at the 0.05 level of significance.

RESULTS

Hypoxic Gas Mixture Study

$C_{Scomb}O_2$ and $C_{Sf}O_2$ were highly associated for each subject in both the training ($r^2 = 0.798$ to 0.987) and validation ($r^2 = 0.794$ to 0.992) sets. The slopes for $C_{Scomb}O_2$ ranged from 0.72 to 1.31 for the training data and 0.49 to 1.11 for the validation data (Table 1). The slopes were not homogeneous for either data set ($p = 0.0001$). Individual Bland-Altman plots demonstrated a close association between $C_{Scomb}O_2$ and $C_{Sf}O_2$.

Hypoxic Gas Mixture/Position Study

There was no statistically significant interaction between position and hypoxia for the four outcome variables, i.e. the effect of position was independent of hypoxic condition. $C_{Sf}O_2$, $C_{Scomb}O_2$, SaO_2, and SjO_2 were significantly lower at 75% and 85% saturation. $C_{Sf}O_2$, $C_{Scomb}O_2$ and SjO_2 were significantly elevated in comparison to the supine position in the 20° Trendelenberg position. There were no significant differences in comparison to the supine position for the four outcome variables studied in the 20° reverse Trendelenburg position.

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$C_{Sf}O_2$ was highly correlated with $C_{Scomb}O_2$; the slopes relating $C_{Sf}O_2$ to $C_{Scomb}O_2$ were homogeneous among the eight subjects for each position and gas mixture studied; and the slopes for SaO_2 and SjO_2 were homogeneous. The intercepts among the eight subjects for $C_{Scomb}O_2$ were statistically significantly different, as were the intercepts for SaO_2 and SjO_2. The effect of body position, adjusted for the covariates $C_{Scomb}O_2$, SaO_2 and SjO_2 was not statistically significant.

Hypocapnia/Hypercapnia/Position Study

There was no statistically significant interaction between position and carbon dioxide levels for the four outcome variables, i.e., the effect of position was independent of hyper-and hypocapnia. Position did not significantly influence $C_{Scomb}O_2$, SaO_2 and SjO_2; however, $C_{Sf}O_2$ was significantly elevated in the 20° Trendelenberg position. As expected, $C_{Sf}O_2$, $C_{Scomb}O_2$, and SjO_2 were significantly higher during hypercapnia and significantly lower during hypocapnia. SaO_2 was significantly higher during hypercapnia and hypocapnia.

$C_{Sf}O_2$ was closely correlated with $C_{Scomb}O_2$ and SjO_2, but correlated weakly with SaO_2 (-0.5 to 0.51). The slopes of $C_{Sf}O_2$ versus $C_{Scomb}O_2$ among individuals were homogenous for each position and carbon dioxide condition. The intercepts among the eight subjects for $C_{Sf}O_2$ versus $C_{Scomb}O_2$ were significantly different. $C_{Sf}O_2$ in the 20° Trendelenberg position, adjusted for the covariates, was also statistically different. The effect of body position, adjusted for the covariates $C_{Scomb}O_2$, SaO_2, and SjO_2, was not statistically significantly different.

The limits of agreement of $C_{Sf}O_2$ and $C_{Scomb}O_2$ were wide under the conditions of this study.

DISCUSSION

The concept of a simple, noninvasive, continuous bedside monitor capable of detecting early cerebral ischemic events is certainly desirable, as irreversible cerebral damage may occur before changes in neurological status become apparent. Continuous monitoring of jugular venous bulb hemoglobin oxygen saturation has become increasingly popular in the management of patients with severe head injury[34,35]. Monitoring SjO_2, however, requires frequent repositioning of the patient, and catheter recalibration, which is technically demanding. Although insertion of a jugular venous bulb catheter is relatively simple, it is nonetheless, an invasive procedure.

Jöbsis et al, first demonstrated that it was possible to assess brain oxygenation by measuring the attenuation of near-infrared light of specific wavelengths passing through the skull and underlying brain[6]. Infrared light readily penetrates the skin and bone[6-8,36], so that measuring the attenuation of light of a particular wavelength passed through the skull permits assessment of cerebral hemoglobin saturation. Contamination of the signal by skin and bone contributions, thought to be minimal, is due mainly to bone contamination, which contributes 5 to 9% to the signal[15,24]. Because direct measurement of optical path length is not possible in the brain, an estimation must be made[7]. The estimated path length, and the resulting estimated hemoglobin saturation must then be validated against an established standard. However, there is no directly measured "gold standard" against which to validate the spectroscopic estimate of saturation in the field beneath the probe ($C_{Sf}O_2$). In the present study, we have attempted to validate the cerebral oximeter by comparing with a calculated brain hemoglobin oxygen saturation ($C_{Scomb}O_2$), based upon assumed weightings of jugular venous bulb and arterial oxygen saturation. While $C_{Scomb}O_2$ may not reflect true brain oxygen saturation, measurement of jugular venous bulb oxygen saturation is well established as an index of global brain oxygenation in the critical care of head-injured patients[37], and by allowing for the arterial contribution[9,38], should closely reflect cerebral oxygen saturation.

Validation of the cerebral oximeter requires a "gold standard" against which $C_{Sf}O_2$ may be calibrated. Because regional saturation underneath the probe cannot be measured directly, estimations of SjO_2 and SaO_2 must be made. We demonstrated a close correlation between $C_{Sf}O_2$ and $C_{Scomb}O_2$. To further reduce the extracerebral contribution to $C_{Sf}O_2$ would require studies using volunteers in whom cerebral venous saturation is varied independently. As such studies are not practical in volunteers, an allowance for extracerebral contamination, based on the conclusions of animal experiments, has instead been incorporated into the algorithm[6,15]. In separate experiments, we have attempted to vary the proportions of the arterial and venous contributions to $C_{Scomb}O_2$ by measuring $C_{Sf}O_2$ in the Trendelenberg and reverse Trendelenberg positions and to alter cerebral venous saturation by changing $PaCO_2$ while holding SaO_2 constant[28,29].

Position changes may influence venous pressure, and may alter the proportion of arterial blood in the cerebral vasculature[39], changing the ration of SaO_2 and SjO_2 used to estimate $C_{Scomb}O_2$, which might be expected to alter the correlation between $C_{Sf}O_2$ and $C_{Scomb}O_2$. Local autoregulatory responses may change brain perfusion in response to changes in body position. Shenkin et al, used the Kety-Schmidt technique to show that cerebral blood flow (CBF) was maintained and cerebral vascular resistance (CVR) was decreased in volunteers studied in the 20° reverse Trendelenberg position[39]. Conversely, CBF was decreased and CVR was elevated in the 20° Trendelenberg position. The authors suggested that this decrease in CBF could in part be explained by extracerebral contamination of the jugular bulb sample in the 20° Trendelenberg position. In our study, $C_{Sf}O_2$, $C_{Scomb}O_2$, and SjO_2 were significantly higher in a 20° Trendelenberg position in the hypoxia study, but were unaltered during position change in the carbon dioxide study. Because arterial and venous contributions can only be estimated, the ratio of SaO_2 and SjO_2 used in our study to estimate $C_{Scomb}O_2$ may not accurately reflect true regional cerebral arterial and venous volumes, which may prevent precise calibration of the in vivo spectroscope.

Local tissue metabolism may also influence cerebral vascular diameter[14,40,41], and thereby change the ratio of arterial to venous volume, which could alter the $C_{Scomb}O_2$ calculation. This change may explain the variability in the correlation coefficients during hypercapnia and hypocapnia, as cerebral arterioles dilate or constrict rapidly in response to local metabolic changes[38, 41-43] and as changes in CBF alter cerebral venous volume. This again limits the use of $C_{Scomb}O_2$ as a calibration standard for the algorithm. In our study, $C_{Sf}O_2$, $C_{Scomb}O_2$, and SjO_2 were significantly higher during hypercapnia and significantly lower during hypocapnia. However, the decrease in $C_{Sf}O_2$ during hypocapnia was much less than the corresponding decrease in $C_{Scomb}O_2$ suggesting that the association between $C_{Sf}O_2$ and $C_{Scomb}O_2$ is less precise during hypocapnia. The cerebral oximeter may thus be less accurate in neurologic and neurosurgical patients, in whom hyperventilation is a common therapeutic intervention.

Another possible variable is probe dioptode distance. Only one group has suggested that this is a problem[44]. The vast majority of the literature suggests that the probe dioptode distances of 1 and 2.7 cm, used in previous studies, are indeed satisfactory[13,15]. Nevertheless, probe dioptode distances of 3 and 4 cm were used in this study, to allow further separation of the superficial and deep tissue contributions.

One final limitation of in vivo spectroscopy is that it measures regional oxygen distribution and may not reflect focal ischemic events. Thus, NIR spectroscopy should not substitute other established techniques, but should be used in conjunction with them, to provide an early warning of a cerebral hypoxic-ischemic event. In conclusion, therefore, cerebral oximetry may prove a useful adjunct in monitoring patients at risk for cerebral ischemia. The influence of hyper- and hypocapnia on the spectroscopic signal merits further investigation, however, and the algorithm may require further adjustment in patients with relevant underlying pathology.

REFERENCIAS

1. McCormick PW, Stewart M, Ray P, Lewis G, Dujovny M, Ausman JI. Measurement of regional cerebrovascular haemoglobin oxygensaturation in cats using optical spectroscopy. *Neur Res* 1991;13:65-70.
2. Chance B, Nioka S, Kent J, McCully K, Fountain M, Greenfeld R, Holtom G. Time-resolved spectroscopy of hemoglobin and myoglobin in resting and ischemic muscles. *Anal Biochem* 1988;174:698-707,.
3. Jöbsis FF, Fox E, Sugioka K. Monitoring of cerebral oxygenation and cytochrome aa3 redox state. *Int Anesthesiol Clin* 1987;25:209-230.
4. Milikan GA. Oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man. *Rev Sci Instrum* 1942;13:343.
5. Yoshiya I, Shimada Y, Tanaka K. Spectrophotometric monitoring of arterial oxygen saturation in the fingertip. *Med Biol Eng Comput* 1980;18:27-32.
6. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977;198:1264-1267.
7. Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt JS. Estimation of optical path length through tissue from direct time of flight measurement. *Phys Med Biol* 1988;33:1433-1442.
8. Chance B, Leigh JS, Miyake II, Smith DS, Nioka S, Greenfeld R, Finander M, Kaufmann K, Levy W. Comparison of time-resolved and -unresolved measurements of deoxyhemoglobin in brain. *Proc Natl Acad Sci* USA 1988;85:4971-4975.
9. McCormick PW, Stewart M, Goetting M, Dujovny M, Lewis G, Ausman JI. Noninvasive cerebral optical spectroscopy for monitoring cerebral oxygen delivery and hemodynamics. *Crit Care Med* 1991;19:89-97.
10. Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EOR. Characterization of the near infrared absorption spectra of cytochrome aa3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. *Biochem Biophys Acta* 1988;933:184-192.
11. Keizer HH, Jöbsis-Vandervliet FF, Lucas SS, Piantadosi CA, Sylvia AL. The near infrared (NIR) absorption band of cytochrome aa3 in purified enzyme, isolated mitochondria and in

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the intact brain in situ. *Adv Exp Med Biol* 1985;191:832-832.
12. Kariman K, Hempel FG, Jöbsis FF, et al.: In vivo comparison of cerebral tissue PO2 and cytochrome aa3 reduction-oxidation state in cats during hemorrhagic shock. J Clin Invest 68:21-27, 1981.
13. McCormick PW, Stewert M, Lewis G, Dujovny M, Ausman JI. Intracerebral penetration of infrared light. Technical note. J Neurosurg 1992;76:315-318.
14. Mchedlishvili GI. Arterial behavior and blood circulation in the brain. New York, Plenum Press, 1986, pp55-60.
15. Kurth CD, Steven JM, Benaron D, Chance B. Near-infrared monitoring of the cerebral circulation. J Clin Monit 1993;9:163-170.
16. Giannini I, Ferrari M, Carpi A, Fasella P. Rat brain monitoring by near-infrared spectroscopy: An assessment of possible clinical significance. *Physiol Chem Phys* 1982;14:295-305.
17. Tamura M, Hazeki O, Nioka S, Chance B, Smith DS. The simultaneous measurements of tissue oxygen concentration and energy state by near-infrared and nuclear magnetic resonance spectroscopy. *Adv Exp Med Biol* 1988;222:359-363.
18. Delpy DT, Cope M, Cady EB, Wyatt JS, Hamilton PA, Hope PL, Wray S, Reynolds EOR. Cerebral monitoring in newborn infants by magnetic resonance and near infrared spectroscopy. *Scand J Clin Lab Invest* 1987;Suppl 1:88:9-17.
19. Brazy JE, Lewis DV, Mitnick MH, Jöbsis-Vandervliet FF: Noninvasive monitoring of cerebral oxygenation in preterm infants: Preliminary observations. *Pediatrics* 1985;75:217-225.
20. Wyatt JS, Cope M, Delpy DT, Wray S, Reynolds EOR. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectroscopy. *Lancet* 1986;2:1063-1066.
21. Fox E, Jöbsis-Vandervliet FF, Mitnick MH. Monitoring cerebral qxygen sufficiency in anesthesia and surgery. *Adv Exp Med Biol* 1985;191:849-854.
22. Ferrari M, Zanette E, Sideri G, Giannini I, Fieschi C, Carpi A. Effects of carotid compression, as assessed by near infrared spectroscopy, upon cerebral blood volume and hemoglobin oxygen saturation. *J R Soc Med* 1987;80:83-87.
23. McCormick PW, Stewart M, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke* 1991;22:596-602.
24. Smith DS, Levy W, Maris M, Chance B. Reperfusion hyperoxia in brain after circulatory arrest in humans. *Anesthesiology* 1990;73:12-19.
25. Gopinath SP, Robertson CS, Grossman RG, Chance B. Near-infrared spectroscopic localization of intracranial hematomas. *J Neurosurg* 1993;79:43-47.
26. Colacino JM, Grubb B, Jöbsis FF. Infra-red technique for cerebral blood flow: Comparison with ^{133}Xenon clearance. *Neurol Res* 1981;3:17-31.
27. Pollard V, DeMelo E, Deyo DJ, Stoddard H, Hoffman DJ, Prough DS. Generation and validation of an algorithm for brain oxygen monitoring. *Anesth Analg* 1994;78:S343, (Abstract).
28. 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;82:269-277.
29. Pollard V, Prough DS, DeMelo AE, Deyo DJ, Ychida T, Widman R. The influence of carbon dioxide and body position on near-infrared spectroscopic assessment of cerebral hemoglobin oxygen saturation. *Anesth Analg* 1996;82:278-287.
30. van der Zee P, Delpy DT. Simulation of the point spread function for light in tissue by a Monte Carlo method. *Adv Exp Med Biol* 1987;215:179-191.
31. van der Zee P, Cope M, Arridge SR, et al. Experimentally measured optical pathlengths for the adult head, calf, and forearm, and the head of the newborn infant as a function of interoptode spacing. *Adv Exp Med Biol* 1992;316:143-153.
32. Portnoy HD, Chopp M, Branch C. Hydraulic model of myogenic autoregulation and the cerebrovascular bed: the effects of altering systemic arterial pressure. *Neurosurgery* 1983;13:482-498.
33. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310.
34. Cruz J. Combined continuous monitoring of systemic and cerebral oxygenation in acute brain injury: preliminary observations. *Crit Care Med* 1993;21:1225-1232.
35. Sheinberg M, Kanter MJ, Robertson CS, et al. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg* 1992;76:212-217.
36. Nossal R, Bonner RF, Weiss GH. The influence of path length on remote optical sensing properties of biological tissue. *Appl Optics* 1989;28:2238-2244.
37. Cruz J, Miner ME: Modulating cerebral oxygen delivery and extraction in acute traumatic coma. *Appl Optics* 1989;28:2238-2244.
38. Mchedlishvili GI. Arterial behavior and blood circulation in the brain. New York, Consultants Bureau, 1986, pp42-95.
39. Shenkin HI, Scheuerman WG, Spitz ED, Groff RA. Effect of change of position upon the cerebral circulation of man. *J Appl Physiol* 1949;2:317.
40. Mueller SM, Heistad DD, Marcus ML. Total and regional cerebral blood flow during hypotension, hypertension and hypocapnia. *Circ Res* 1977;41:350-356.
41. Kontos HA. Regulation of the cerebral circulation. Annu Rev Physiol 1981;43:397-407.
42. Grubb RL Jr, raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in $PaCO_2$ on cerebral blood volume, blood flow, $PaCO_2$ and vascular mean transit time. *Stroke* 1974;5:630-639.
43. Read RC, Johnson JA, Vick JA, Meyer MW. Vascular effects of hypertonic solutions. *Circ Res* 1960;8:538-548.
44. Harris DNF, Bailey SM. Near infrared spectroscopy in adults. Does the Invos 3100 really measure intracerebral oxygenation? *Anesthesia* 1993;48:694-696.