Original Paper

Neonatology
formerly Biology of the Neonate

Neonatology 2007;92:120–126
DOI: 10.1159/000101063

Received: July 13, 2006
Accepted after revision: December 7, 2006
Published online: March 23, 2007

Use of Tissue Oxygenation Index and Fractional Tissue Oxygen Extraction as Non-Invasive Parameters for Cerebral Oxygenation

A Validation Study in Piglets

Gunnar Naulaers[a] Bart Meyns[b] Marc Miserez[c] Veerle Leunens[b]
Sabine Van Huffel[d] Paul Casaer[a] Michael Weindling[e] Hugo Devlieger[a]

Departments of [a]Paediatrics, [b]Cardiovascular Surgery and [c]Abdominal Surgery, University Hospital Leuven, [d]ESAT-SCD(SISTA), Department of Electrical Engineering, KU Leuven, Leuven, Belgium, and [e]School of Reproductive and Developmental Medicine, University of Liverpool, Neonatal Unit, Liverpool Women's Hospital, Liverpool, UK

Key Words
Neonates · Near-infrared spectroscopy · Oxygenation · Cerebral tissue oxygenation index

Abstract
Objective: To evaluate the relation between cerebral tissue oxygenation index (TOI), measured with spatially resolved spectroscopy (SRS), and the different oxygenation parameters. To evaluate the relation between a new parameter named fractional tissue oxygen extraction (FTOE) and the cerebral fractional oxygen extraction (FOE). ***Methods:*** Six newborn piglets were measured at 33, 35, and 37°C and in hypocapnia. Mean arterial blood pressure (MABP), haemoglobin (Hb), peripheral oxygen saturation (S_aO_2) and P_aCO_2 were measured at each step. Cerebral blood flow (CBF) was measured by injection of coloured microspheres into the left atrium. Jugular bulb oxygen saturation (JVS), cerebral arterial and venous oxygen content (C_aO_2 and C_vO_2) and FOE were calculated. TOI of the brain was calculated and FTOE was introduced as $(S_aO_2 - TOI)/S_aO_2$. The correlation was calculated with an ANCOVA test. ***Results:*** There was a positive correlation (R = 0.4 and p = 0.011) between TOI and JVS. No correlation was found with CBF, MABP or Hb. There was a positive correlation between P_aCO_2 and cerebral TOI (R = 0.24 and p = 0.03). FTOE correlated well with FOE (R = 0.4 and p = 0.016) and there was a negative correlation between FTOE and P_aCO_2 (R = 0.24, p = 0.03). ***Conclusion:*** The measurement of TOI and FTOE by SRS correlated well with the cerebral venous saturation and FOE, respectively.

Copyright © 2007 S. Karger AG, Basel

Introduction

Measuring cerebral oxygenation continuously is an important step towards understanding and preventing neurological complications in the course of neonatal intensive care. Cerebral complications like periventricular leucomalacia and hypoxic encephalopathy are considered to be the consequence of a period of perinatal cerebral hypoxia. Hypoxia can be classically divided into hypoxic hypoxia (low arterial PO_2), ischaemic hypoxia and anaemic hypoxia [1]. The measurement of peripheral oxygen saturation (S_aO_2), transcutaneous PO_2 and arterial PO_2 (measured with blood gas analyser) are available as

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2007 S. Karger AG, Basel
1661–7800/07/0922–0120$23.50/0

Accessible online at:
www.karger.com/neo

Dr. Gunnar Naulaers
Neonatal Intensive Care Unit, Department of Paediatrics
University Hospital Leuven, Herestraat 49
BE–3000 Leuven (Belgium)
Tel. +32 1634 3211, Fax +32 1634 3209, E-Mail gunnar.naulaers@uz.kuleuven.ac.be

indices of hypoxia in the neonatal intensive care unit. However, these indices can only reflect hypoxic hypoxia, as ischaemic hypoxia can happen with normal S_aO_2 [2]. One approach for the evaluation of oxygenation is to measure the balance between oxygen delivery and oxygen consumption. A useful indicator of this balance is the calculation of the fractional oxygen extraction (FOE) [3]. An increase in FOE is observed when oxygen delivery decreases despite a stable oxygen consumption. Therefore, the continuous and non-invasive measurement of FOE could be a good estimation of this balance.

We used spatially resolved near-infrared spectroscopy (NIRS) to measure tissue oxygenation index (TOI) as an index of cerebral oxygenation. In this study the following questions were tested: (1) Which index of oxygenation corresponds best with cerebral TOI? (2) Can TOI be used to measure FOE?

Methods

Animal Preparation

Newborn piglets (6–36 h of age) were used. The animals were intubated using a 3.5 uncuffed tube after premedication was given. The piglet was fully anaesthetised with halothane and ventilated with an Engstrom ventilator using a frequency of 30 breaths per minute and tidal volume of 3.5 l/min. Ventilation was started with an extra dead space between the endotracheal tube and the ventilator circuit. S_aO_2 was measured with Nellcor 2000 on the right front foot, ECG electrodes were attached and a rectal temperature probe placed. A peripheral venous line was inserted in a vein of the ear. Denudation of the right inguinal region was performed for cannulation of the femoral artery. A NIRS optode, with a fixed distance of 4 cm, was placed on the skin at the left frontoparietal side and fixated with a running suture. Left thoracotomy was done to insert catheters in the left atrium and the pulmonary artery. A left jugular cut down was performed to place a catheter in the jugular bulb.

Experimental Procedure

We used two models to test the effect of changing cerebral blood flow (CBF) on TOI. In the rewarming procedure, normal neurovascular coupling was expected with no change in TOI, while in the hypocapnia procedure a decrease in TOI was expected. Indeed, during an increase in temperature, increased CBF would be expected as a normal response to increased cerebral metabolism, resulting in a constant FOE and stable TOI [4–6]. Thus the method would be useful for detecting an increase in CBF without a change in the relation between CBF and cerebral metabolism. Most hypothermia studies in piglets have used deep hypothermia and in these studies an increase in regional oxygen saturation was described with other instruments [7–9].

The experiment was performed in four steps. Firstly, the piglet was further cooled with cold ice packs to 33°C and in the second and third step warmed up to 35 and 37°C. We used two different ways of rewarming. The classical rewarming mattress was used, but this was not enough to increase the temperature. Therefore a warming lamp was used and placed nearby the thighs and legs of the animal. This is the rewarming procedure. As a fourth step, the extra dead space was removed to achieve hypocapnia without change in minute ventilation (hypocapnia procedure). At each step, blood samples were taken from the femoral artery, pulmonary artery and jugular vein. Each blood sample was analysed for PCO_2, PO_2, pH, Hb and HCO_3. At each step, polystyrene microspheres of different colours (white, eosin, blue, violet and yellow) were injected. The microspheres were injected into the left atrium in a volume of 3 ml over 30 s. Arterial reference blood was withdrawn during 90 s from the aorta at a flow rate of 10 ml/min. The experiment was terminated by the injection of potassium chloride. Afterwards, 1-gram tissue samples were isolated from the brain, the skin under the NIRS patch, the kidney, the liver, the spleen, the stomach and the proximal, mid- and distal part of the jejunum.

Derived Parameters of Oxygenation

The following were calculated:

$$C_aO_2 \text{ (arterial blood oxygen content)} = ([Hb] \times (S_aO_2/100) \times 1.39) + (P_aO_2 \times 0.00003) \quad (1)$$

$$C_{vj}O_2 \text{ (jugular venous blood oxygen content)} = ([Hb] \times (S_{vj}O_2/100) \times 1.39) + (P_{vj}O_2 \times 0.00003) \quad (2)$$

where [Hb] = grams haemoglobin/ml, S_aO_2 and $S_{vj}O_2$ = percentage arterial and jugular venous Hb oxygen saturation, P_aO_2 and $P_{vj}O_2$ = the arterial and jugular venous partial pressure of oxygen (mm Hg), 1.39 = the stoichometric value of oxygen for Hb, and 0.00003 = the coefficient of oxygen solubility (millilitres of O_2/ml of blood).

Because the dissolved fraction ($P_aO_2 \times 0.00003$) is very small, the equation can be simplified as follows:

$$C_aO_2 = [Hb] \times (S_aO_2/100) \times 1.39 \quad (3)$$

CBF was determined by means of the coloured microspheres content by the methods described by Kowallik and co-workers, Rudolph and Heymann, and Wieland et al. [10].

Oxygen delivery (OD) is the product of CBF and C_aO_2.

$$OD \text{ (ml } O_2/100 \text{ g} \cdot \text{min}^{-1}) = CBF \times C_aO_2 \quad (4)$$

Cerebral oxygen consumption ($CMRO_2$) can be described as follows by the Fick principle:

$$CMRO_2 \text{ (ml } O_2/100 \text{ g} \cdot \text{min}^{-1}) = CBF \times (C_aO_2 - C_vO_2) \quad (5)$$

The balance between OD and $CMRO_2$ is shown by the FOE:

$$FOE = OD/CMRO_2 = (C_aO_2 - C_vO_2)/C_aO_2 \quad (6)$$

Near-Infrared Spectroscopy

Changes in oxygenated haemoglobin (ΔHbO_2), reduced haemoglobin (ΔHb) and total haemoglobin (ΔHbT) of the brain were measured with NIRS (NIRO 300, Hamamatsu Photonics, Hamamatsu City, Japan). This NIRS monitor has four different laser diodes with different wavelengths, i.e. 775, 810, 850 and 910 nm to calculate the proportional concentration of the two chromophores Hb and HbO_2.

A cerebral TOI was computed using spatially resolved spectroscopy (SRS). SRS is a new NIRS method that measures cerebral

Hb oxygen saturation. In contrast to differential NIRS, this technique gives absolute values. Measurement of the TOI was by a light detector with three sensors at different distances from the light source. Light passing into tissue is attenuated by scatter and absorption. If the distance between the light source and the sensor is large enough (>3 cm), the isotropy of scatter distribution becomes so homogeneous that the loss due to scatter is the same at the three sensors. TOI was calculated according to the diffusion equation as follows [11, 12]:

$$\frac{kO_2Hb}{kO_2Hb + kHHb} = TOI(\%)$$

where k is the constant scattering contribution, O_2Hb is oxygenated haemoglobin and HHb is reduced haemoglobin.

A new parameter, fractional tissue oxygen extraction (FTOE), was calculated using the following hypothesis.

The FOE is calculated by the following equation:

$$FOE = CMRO_2/COD \quad (1)$$

Cerebral oxygen delivery (COD) and cerebral oxygen consumption ($CMRO_2$) can be calculated using the following equation:

$$COD = CBF \times C_aO_2 \quad (2)$$

(CBF is cerebral blood flow and C_aO_2 is the arterial oxygen content)

$$CMRO_2 = CBF \times (C_aO_2 - C_{vj}O_2) \quad (3)$$

(C_vO_2 is the venous oxygen content)

$$FOE = (CBF \times (C_aO_2 - C_{vj}O_2))/(CBF \times C_aO_2) = (C_aO_2 - C_{vj}O_2)/C_aO_2 \quad (4)$$

C_aO_2 and C_vO_2 are calculated as follows:

$$C_aO_2 = [Hb] \times (S_aO_2/100) \times 1.39$$
$$C_vO_2 = [Hb] \times (S_{vj}O_2/100) \times 1.39$$

This results in the following equation:

$$FOE = \frac{\left([Hb] \times (S_aO_2/100) \times 1.39\right) - \left([Hb] \times (S_{vj}O_2/100) \times 1.39\right)}{\left([Hb] \times (S_aO_2/100) \times 1.39\right)} = \frac{S_aO_2 - S_{vj}O_2}{S_aO_2}$$

Since TOI correlates well with $S_{vj}O_2$ and can be measured continuously, substitution of $S_{vj}O_2$ by TOI yields:

$$\frac{S_aO_2 - TOI}{S_aO_2}$$

which is temptatively called here *fractional tissue oxygenation extraction* – FTOE.

Data Acquisition

The data acquisition system Codas (Dataq Instruments®, USA) was used to record the analogue signals of mean arterial blood pressure (MABP) (measured in the iliac artery), ECG, pulse rate and S_aO_2 (Nellcor 2000) with a sampling frequency of 100 Hz. Since the NIRS measurements are digital with a sampling rate of 6 Hz, they were converted to analogue signals by a sample-and-hold function before their introduction in the CODAS system. For all parameters the data were calculated over a period of 5 min, after reviewing the data to exclude important swings during this period.

Statistics

The relationship between variables was assessed using Pearson's correlation coefficients (mean 95% CI and p value). ANCOVA was used to correct for multiple measurements in different piglets. ANCOVA was also used to describe the effect of temperature on the different parameters (steps 1–3). Paired t-tests were used to describe the effect of hypocapnia on the different parameters. A p value <0.05 was considered significant.

Ethical Committee

The Animal Ethical Committee of the KU Leuven approved the study.

Results

The full procedure (four steps) was performed in 6 piglets. The results of cerebral TOI, CBF and cerebral FOE measurements during temperature rise are presented in table 1. When temperature rose, there was a decrease in CBF and FOE and an increase in jugular venous saturation, although these changes were not significant. There was a significant increase in heart rate.

Jugular venous saturation could only be measured in 3 of the 6 piglets during the hypocapnia procedure. There were non-significant decreases in jugular venous saturation, CBF and cerebral TOI during hypocapnia.

ANCOVA was used to calculate the correlation and significance because four different measurements were performed in 6 different piglets. The results are shown in table 2. There was a positive correlation between jugular venous saturation and cerebral TOI ($R = 0.4$ and $p = 0.011$). This is shown for the different subjects in figure 1. The correlation between cerebral TOI and mixed venous saturation was also significant ($R = 0.27$ and $p = 0.026$). There was no correlation between cerebral TOI and arterial oxygen saturation, CBF, MABP, Hb or temperature. There was a positive correlation between P_aCO_2 and cerebral TOI ($R = 0.24$ and $p = 0.03$).

Since TOI correlated well with $S_{vj}O_2$ and S_vO_2, an equivalent of FOE (which we called FTOE) was computed. The correlations are shown in table 2 and figure 2. A positive correlation was found between FOE and FTOE ($R = 0.4$ and $p = 0.016$).

A negative correlation was found between FOE and P_aCO_2 during the rewarming procedure ($R = -0.23$ and $p = 0.04$). No significant correlation was found between FOE and MABP, Hb or temperature.

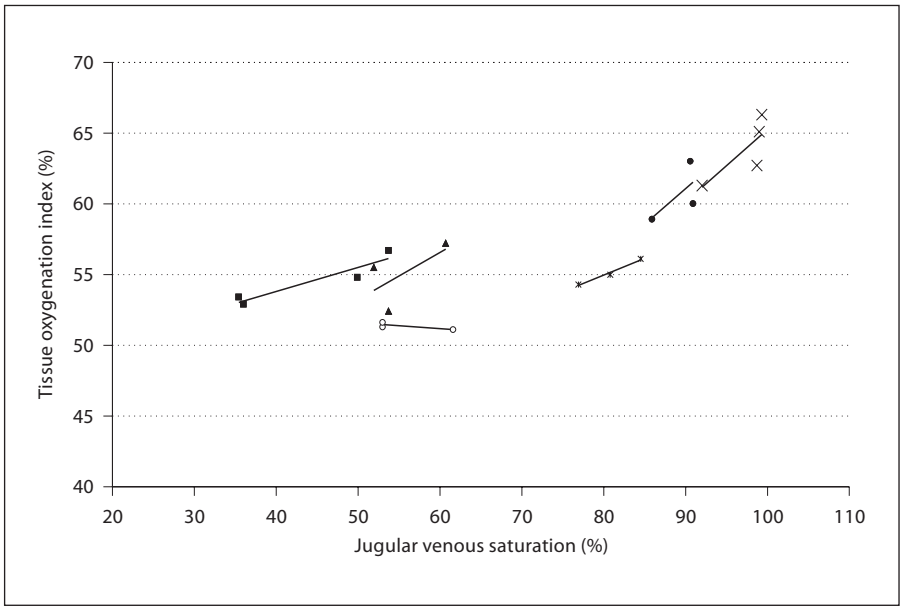


Fig. 1. Jugular venous saturation and tissue oxygenation index (TOI) are shown in the different piglets. Jugular venous saturation correlated significantly with cerebral TOI by the ANCOVA test. The values for the different piglets are shown.

Table 1a. Evolution of the oxygenation parameters during the rewarming procedure

	33°C	35°C	37°C	p value ANCOVA test
Jugular venous oxygen saturation, %	73 (60.7–85.6)	67 (52–90.6)	83.2 (53.7–91)	0.9
CBF, ml/100 g·min^{-1}	89 (36–153)	73 (48–96)	59 (45–72)	0.058
FOE	0.28 (0.15–0.41)	0.34 (0.13–0.49)	0.32 (0.12–0.41)	0.79
TOI	56.5 (53.4–62.7)	55.3 (54.8–63)	55.5 (52.4–60)	0.7
FTOE	0.42 (0.37–0.46)	0.45 (0.37–0.49)	0.44 (0.40–0.48)	0.54
S_aO_2	100 (99.9–100)	100 (99.9–100)	100 (99.9–100)	0.31
Heart rate, beats/min	90 (83–100)	95 (90–112)	103 (98–123)	0.025
P_aCO_2	44.1 (30.8–45.7)	41.9 (33.9–55.5)	48.7 (29.1–62.9)	0.15
MABP, mm Hg	54 (44.6–59.4)	55.4 (52.5–58.3)	57.6 (39.8–63.4)	0.49

Median values and interquartile range are given. A significant change in heart rate was seen during rewarming.

Table 1b. Evolution of the oxygenation parameters during the hypocapnia procedure

	37°C and normocapnia	37°C and hypocapnia	p value (paired t-test) step 4
P_aCO_2, mm Hg	63 ± 13	52.6 ± 12.2	0.0006
Jugular venous saturation, %	73.3 ± 44	66.3 ± 40	NS
CBF, ml/100 g·min^{-1}	54 ± 16	81 ± 50	NS
TOI	61 ± 4.9	57.7 ± 4.3	NS
FTOE	0.44 ± 0.05	0.43 ± 0.05	NS
FOE	0.24 ± 0.14	0.36 ± 0.23	NS

Median values and interquartile range are given. No significant changes could be shown because of the small number (3) of piglets.

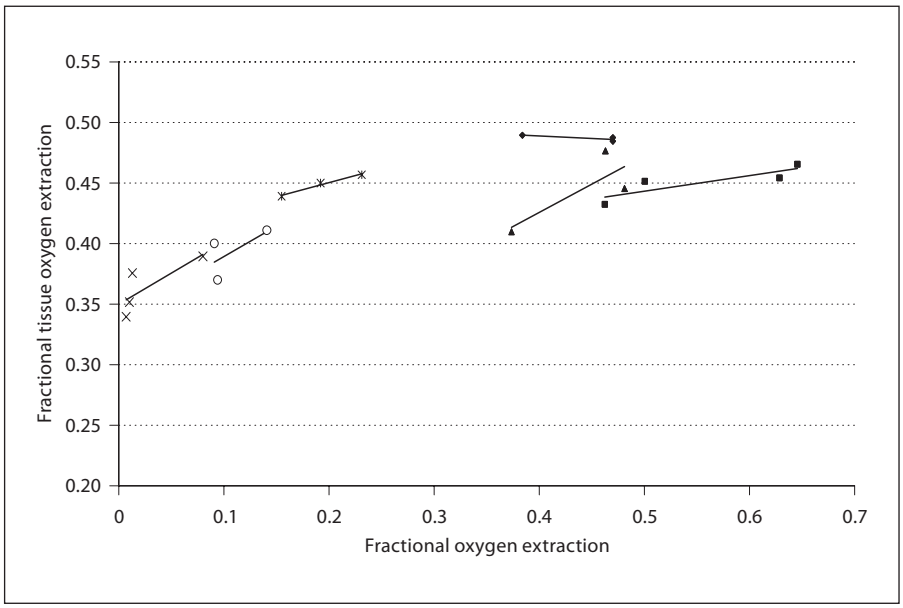


Fig. 2. Fractional oxygen extraction (FOE) and fractional tissue oxygen extraction (FTOE) are shown in the different piglets. There was a significant correlation between FOR and FTOE calculated with the ANCOVA test. The different piglets are shown.

Table 2. Correlations between TOI and several parameters, and between FTOE and these parameters

	Correlation coefficient cerebral TOI	p value
JVSAT	0.4	0.011
MixSAT	0.27	0.026
artSAT	0.005	0.77
Cerebral blood flow	0.08	0.25
P_aCO_2	0.21	0.03
MABP	0.06	0.3
Hb	–0.04	0.8
	Correlation with cerebral FTOE	p value
FOE	0.4	0.016
P_aCO_2	–0.23	0.04
MABP	0.3	0.06
Hb	0.005	0.76
T	0.06	NS

The ANCOVA test was used to calculate the correlation and p values. A significant correlation was found between JVSAT and TOI as well as between FOE and FTOE. P_aCO_2 was the only significant parameter changing TOI and FTOE.

Discussion

Different approaches have been used to measure the cerebral oxygenation using differential NIRS. Brun et al. [13] described the oxygenation index ($\Delta HbO_2 - \Delta Hb$) and found a good correlation with a weighted mean value of S_aO_2 and $S_{ss}O_2$ (venous saturation in the sagittal sinus). Multiple linear regression of the oxygenation index on S_aO_2 and $S_{ss}O_2$ suggested that NIRS detects Hb in tissue in a venous-to-arterial ratio of 2:1. Wardle et al. [14] and Yoxall et al. [3, 15] studied cerebral oxygen consumption by measuring cerebral venous oxyhaemoglobin saturation in neonates with the partial jugular venous occlusion technique. This is a well-validated technique that requires partial venous occlusion for 5–10 s [16]. This method is an accurate non-invasive bedside method to measure cerebral venous oxygenation but it is intermittent and needs manipulation of the patient. The technique described in this paper is for the continuous measurement of cerebral venous oxygenation.

SRS, by using the diffusion law, is another way to measure regional cerebral oxygen saturation [12]. By using SRS with NIRO 300 in this study, we observed a close correlation between cerebral TOI and jugular bulb oxygen saturation (JVS) in both the rewarming and hypocapnia procedures. Shimizu et al. [17] described the cerebral TOI in 5 cardiac patients and found a reasonable agreement by Bland-Altman test between TOI and the jugular venous oxygen saturation 50 and 70%. We can conclude

that TOI mainly reflects the cerebral venous saturation in these piglets and that it could be used as a trend monitor for the JVS. Several studies have been performed in humans [18–23].

We used two models to test the effect of changing CBF on TOI. In the rewarming procedure, normal neurovascular coupling was expected with no change in TOI, while in the hypocapnia procedure a decrease in TOI was expected. In our study, a decrease in CBF was noted. However, a rewarming lamp was used because this method of warming resulted in very hot, even hyperaemic, skin in the region under the lamp. It is therefore likely that there was a redistribution of blood to this area. This was described by Doering et al. [24] who found a decrease in CBF after applications of hot packs to both thighs for 10 min.

Hypocapnia causes a vasoconstriction in the cerebral circulation [25]. This is well described in piglets [26, 27] and has also been found by several investigators using NIRS [28, 29]. Hypocapnia also increases cerebral oxygen demand by increasing neuronal excitability, seizure activity and anaerobic metabolism [30]. The decrease in CBF and concomitant increase in cerebral oxygen demand leads to decreased venous oxygen saturation [23]. This was the main reason why the fourth experimental step was introduced. Only few measurements were made, but there was a trend towards decreased CBF, jugular venous saturation and TOI during hypocapnia. Several other authors have also described a decrease in cerebral TOI during hypocapnia [23, 31]. In this study there was a strongly positive correlation between P_aCO_2 and TOI during both the rewarming and the hypocapnia experiments. This would appear to confirm the importance of taking careful account of P_aCO_2 during ventilation. There was no correlation between MABP and TOI, probably because of autoregulation [32].

Using TOI as a measure of venous oxygen saturation, it is possible to measure the fractional extraction of oxygen continuously. Indeed, by monitoring simultaneously S_aO_2 and TOI, an equivalent measure of FOE, tentatively called here FTOE, can be calculated. This is likely to yield important information about the oxygenation status of the brain because it reflects $CMRO_2/OD$, the balance between oxygen delivery and oxygen consumption. As shown in table 2 and figure 2, cerebral FTOE showed a good correlation with FOE. Therefore, we can conclude that FTOE can be seen as a trend parameter for FOE. There was a negative correlation between cerebral FOE and P_aCO_2 and this fits well with the observations of other authors describing the negative correlation between P_aCO_2 and FOE [14]. A decrease in CBF caused by hypocapnia, without a concomitant decrease in cerebral metabolism, would be expected to lead to a higher FOE. The most likely explanation for FTOE not changing with temperature is because of coupling between cerebral metabolism and CBF. The absence of any correlation between cerebral FOE and MABP confirms autoregulation. Nor was there any correlation between cerebral FOE and the Hb concentration, in line with the observations of a constant cerebral oxygen consumption and cerebral FOE in anaemia [1].

The studies described in this paper have shown that continuous measurement of TOI and FTOE by NIRS is possible using SRS and that measuring FTOE can therefore be used to measure an equivalent of FOE continuously and non-invasively. It must be stressed that these can only be used as trends and not as absolute values of venous oxygen saturation and FOE. However, the ability to observe decreasing TOI and increasing FTOE could be important indicators of developing cerebral hypoxia in a non-invasive way in critically ill neonates. Further studies are needed to validate these findings and to investigate the size of change in these indices that might indicate cerebral hypoxic damage.

Support Grants

Research of G.N. supported by: Fund for Scientific Research, Flanders (Belgium): Clinical Doctoral Grant, Steunfonds Margeurite-Marie Delacroix ter bescherming van het kind en van personen met een mentale handicap. Research of S.V.H. supported by: Research Council KUL: GOA-Mefisto 666, IDO/99/003 (Predictive Computer models for medical classification problems using patient data and expert knowledge, FWO: PhD/postdoc grants, projects, research communities (ICCoS, ANMMM). Belgian Federal Government: DWTC (IUAP IV-02 (1996–2001) and IUAP V-22 (2002–2006): Dynamical Systems and Control: Computation, Identification and Modelling).

References

1 Jones MD Jr, Traystman RJ: Cerebral oxygenation of the fetus, newborn, and adult. Semin Perinatol 1984;8:205–216.

2 Greisen G, Vannuci R: Is periventricular leucomalacia a result of hypoxic-ischaemic injury? Hypocapnia and the preterm brain. Biol Neonate 2001;79:194–200.

3 Yoxall CW, Weindling AM: Measurement of cerebral oxygen consumption in the human neonate using near-infrared spectroscopy: cerebral oxygen consumption increases with advancing gestational age. Pediatr Res 1998; 44:283–290.

4 Okubo K, Itoh S, Isobe K, Kusaka T, Nagano K, Kondo M, et al: Cerebral metabolism and regional cerebral blood flow during moderate systemic cooling in newborn piglets. Pediatr Int 2001;43:496–501.
5 Powel R, Dyess D, Collins J, Roberts W, Tacchi E, Swafford A, et al: Regional blood flow response to hypothermia in premature, newborn and neonatal piglets. J Pediatr Surg 1999;34:193–198.
6 Busija D, Leffler CW: Hypothermia reduces cerebral metabolic rate and cerebral blood flow in newborn pigs. Am J Physiol 1987;253: H869–H873.
7 Abdul-Khaliq H, Schubert S, Troitzsch D, Huebler M, Boettcher W, Baur MO, et al: Dynamic changes in cerebral oxygenation related to deep hypothermia and circulatory arrest evaluated by near-infrared spectroscopy. Acta Anaesthesiol Scand 2001;45:696–701.
8 Baris RR, Israel AL, Amory DW, Benni P: Regional cerebral oxygenation during cardiopulmonary bypass. Perfusion 1995;10: 245–248.
9 Kurth CD, Steven JM, Nicolson SC, Chance B, Delivoria-Papadopoulos M: Kinetics of cerebral deoxygenation during deep hypothermic circulatory arrest in neonates. Anesthesiology 1992;77:656–661.
10 Wieland W, Wouters PF, Van Aken H, Flameng W: Measurement of organ blood flow with coloured microspheres: a first time-saving improvement using automated spectrophotometry. Proceedings of Computers in Cardiology, London, 1993, pp 691–694.
11 Matcher J, Kirkpatrick PJ, Nahid M, Cope M, Delpy DT: Absolute quantification methods in tissue near-infrared spectroscopy. Proc SPIE 1995;2389:486–495.
12 Suzuki S, Takasaki S, Ozaki T, Kobayashi Y: A tissue oxygenation monitor using NIR spatially resolved spectroscopy. Proc SPIE 1999;3597:582–592.
13 Brun NC, Moen A, Borch K, Saugstad OD, Greisen G: Near-infrared monitoring of cerebral tissue oxygen saturation and blood volume in newborn piglets. Am J Physiol 1997;273:H682–H686.
14 Wardle SP, Yoxall CW, Weindling AM: Determinants of cerebral fractional oxygen extraction using near-infrared spectroscopy in preterm neonates. J Cereb Blood Flow Metab 2000;20:272–279.
15 Yoxall CW, Weindling AM, Dawani NH, Peart I: Measurement of cerebral venous oxyhemoglobin saturation in children by near-infrared spectroscopy and partial jugular venous occlusion. Pediatr Res 1995;38: 319–323.
16 Wickramasinghe YA, Livera LN, Spencer SA, Rolfe P, Thorniley MS: Plethysmographic validation of near infrared spectroscopic monitoring of cerebral blood volume. Arch Dis Child 1992;67:407–411.
17 Shimizu N, Gilder F, Bissonnette B, Coles J, Bohn D, Miyasaka K: Brain tissue oxygenation index measured by near infrared spatially resolved spectroscopy agreed with jugular bulb oxygen saturation in normal pediatric brain: a pilot study. Childs Nerv Syst 2005;21:181–184.
18 Ali MS, Harmer M, Vaughan RS, Dunne JA, Latto IP: Spatially resolved spectroscopy (NIRO 300) does not agree with jugular bulb oxygen saturation in patients undergoing warm bypass surgery. Can J Anaesth 2001; 48:497–501.
19 Buunk G, van der Hoeven JG, Meinders AE: A comparison of near-infrared spectroscopy and jugular bulb oximetry in comatose patients resuscitated from a cardiac arrest. Anaesthesia 1998;53:13–19.
20 Daubeney PE, Pilkington SN, Janke E, Charlton GA, Smith DC, Webber SA: Cerebral oxygenation measured by near-infrared spectroscopy: comparison with jugular bulb oximetry. Ann Thorac Surg 1996;61:930–934.
21 Minassian A, Poirier N, Pierrot M, Menei P, Granry JC, Ursino M, et al: Correlation between cerebral oxygen saturation measured by near-infrared spectroscopy and jugular oxygen saturation in patients with severe closed head injury. Anesthesiology 1999;91: 985–990.
22 Quaresima V, Sacco S, Totaro R, Ferrari M: Noninvasive measurement of cerebral hemoglobin oxygen saturation using two near-infrared spectroscopy approaches. J Biomed Opt 2000;5:201–205.
23 Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC: Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology 2000;93: 947–953.
24 Doering TJ, Brix J, Schneider B, Rimpler M: Cerebral hemodynamics and cerebral metabolism during cold and warm stress. Am J Phys Med Rehabil 1996;75:408–415.
25 Kety S, Schmidt CF: The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 1948;27:484–492.
26 Helfaer MA, Kirsch JR, Haun SE, Koehler RC, Traystman RJ: Age-related cerebrovascular reactivity to CO_2 after cerebral ischemia in swine. Am J Physiol 1991;260: H1482–H1488.
27 Whitelaw A, Karlsson BR, Haaland K, Dahlin I, Steen PA, Thoresen M: Hypocapnia and cerebral ischaemia in hypotensive newborn piglets. Arch Dis Child 1991;66:1110–1114.
28 Liem KD, Kollee LA, Hopman JC, de Haan AF, Oeseburg B: The influence of arterial carbon dioxide on cerebral oxygenation and haemodynamics during ECMO in normoxaemic and hypoxaemic piglets. Acta Anaesthesiol Scand Suppl 1995;107:157–164.
29 Owen-Reece H, Elwell CE, Goldstone J, Smith M, Delpy DT, Wyatt JS: Investigation of the effects of hypocapnia upon cerebral haemodynamics in normal volunteers and anaesthetised subjects by near-infrared spectroscopy (NIRS). Adv Exp Med Biol 1994;361:475–482.
30 Laffey JG, Kavanagh MB: Hypocapnia. N Engl J Med 2002;374:43–53.
31 Yoshitani K, Kawaguchi M, Tatsumi K, Kitaguchi K, Furuya H: A comparison of the INVOS 4100 and the NIRO 300 near-infrared spectrophotometers. Anesth Analg 2002;94: 586–590.
32 Tsuji M, duPlessis A, Taylor G, Crocker R, Volpe JJ: Near-infrared spectroscopy detects cerebral ischemia during hypotension in piglets. Pediatr Res 1998;44:591–595.