

## MEASUREMENT OF CMRO<sub>2</sub> IN NEONATES UNDERGOING INTENSIVE CARE USING NEAR INFRARED SPECTROSCOPY

Clare E. Elwell, Julian R. Henty, Terence S. Leung, Topun Austin, Judith H. Meek, David T. Delpy, and John S. Wyatt

**Abstract:** Greater understanding of the rate of oxygen delivery and uptake in sick preterm and term infants undergoing intensive care is an important aim of brain-orientated neonatal medicine. Near infrared spectroscopy (NIRS) is a continuous, non-invasive and portable technique which can be used to measure cerebral blood flow (CBF) in infants. It is also possible to use spatially resolved spectroscopy to measure absolute mean cerebral oxygen saturation (SmcO<sub>2</sub>). The aim of this study was to investigate the derivation of cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) from these two measurements. Nine preterm infants were studied, of median (range) gestational age 25 (23-37) weeks. A NIRO300 was used to measure CBF and SmcO<sub>2</sub> simultaneously over the right and left hemisphere. Median (range) left and right cerebral hemisphere values for CMRO<sub>2</sub> were 0.95 (0.79-1.53) ml 100g<sup>-1</sup>.min<sup>-1</sup> and 0.88 (0.69-1.46) ml 100g<sup>-1</sup>.min<sup>-1</sup>, respectively. No significant difference was seen between the left- and right-sided values. These values are similar to median (range) values previously reported in infants using positron emission tomography or more invasive NIRS methods. Further work is necessary to define limits on the use of this technique, particularly in the assumption of the venous:arterial compartment volume ratio across different infants.

### 1. INTRODUCTION

Advances in neonatal medicine, leading to increased survival rates among extremely preterm and sick term infants, have led to a focus on the causes of long-term neurological deficit in babies who have undergone neonatal intensive care. Central to the premise of

brain-orientated neonatal medicine is the development of reliable, non-invasive, and outside techniques for the assessment of cerebral circulation and metabolism. Cerebral hypoxia and ischemia are important causes of neurodisability, but most current techniques only provide information about the level of oxygen delivery to the cerebral tissue. Measurements of cerebral tissue metabolism, which would provide information about the balance of cerebral oxygen delivery and demand, may prove to be of much greater clinical relevance. In adults, measurements of cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) have been used to relate the severity of cerebral ischaemia to long-term cerebral deficit.<sup>1</sup> No such correlation has yet been definitively described in the neonate.

The key to any measurement which will influence clinical decision making is its reliability, ease of use, and, specifically in neonates, its non-invasive nature. CMRO<sub>2</sub> has previously been measured in neonates using positron emission tomography (PET),<sup>2</sup> <sup>133</sup>Xe clearance,<sup>3</sup> and near infrared spectroscopy (NIRS) methods.<sup>4</sup> To varying degrees, each of the manoeuvres or interventions in these studies has ethical implications which may limit the number of infants in which measurements can be performed. In this paper, we describe a new method for the minimally invasive measurement of regional CMRO<sub>2</sub> in neonates undergoing intensive care using a combination of conventional NIRS and spatially resolved spectroscopy methods.

## 2. BACKGROUND

### 2.1. Measurement of CMRO<sub>2</sub>

A generic expression for CMRO<sub>2</sub> can be given by:

$$CMRO_2 (ml O_2 \cdot 100g^{-1} \cdot min^{-1}) = CBF \cdot OEF \cdot O_2^{art} \quad (1)$$

where CBF is cerebral blood flow (ml of blood. 100g<sup>-1</sup> tissue.min<sup>-1</sup>), OEF is the oxygen extraction fraction, and O<sub>2</sub><sup>art</sup> is the arterial oxygen content (ml of O<sub>2</sub>.ml blood<sup>-1</sup>). This expression is central to the measurement of CMRO<sub>2</sub> by PET, where CBF can be measured using the injection of <sup>15</sup>O labelled H<sub>2</sub>O, and OEF is measured using inhalation of <sup>15</sup>O labelled O<sub>2</sub>, as performed on neonates in a study by Altman et al.<sup>2</sup> Arterial blood sampling is also required for the measurement of O<sub>2</sub><sup>art</sup>.

Where direct measurement of OEF is not possible, the expression for CMRO<sub>2</sub> can be expanded to:

$$CMRO_2 (ml.O_2 \cdot 100g^{-1} \cdot min^{-1}) = CBF \cdot (SaO_2 - SvO_2) \cdot K \cdot tHb \quad (2)$$

where SaO<sub>2</sub> is the arterial oxygen saturation (fractional value); SvO<sub>2</sub> is the venous oxygen saturation (fractional value); K is the oxygen combining power of haemoglobin (Hb) (1.306 ml.g<sup>-1</sup>)<sup>5</sup>; tHb is the haemoglobin concentration in blood (g.ml<sup>-1</sup>). This expression does not incorporate dissolved oxygen, which is a reasonable omission given that within the range of haemoglobin concentrations seen in neonates this would only account for less than 1% of the blood oxygen content. In 1993, Skov et al.<sup>3</sup> measured absolute CMRO<sub>2</sub> by measuring CBF using <sup>133</sup>Xe clearance and SvO<sub>2</sub> using NIRS and a

head down tilt manoeuvre, Yoxall et al.<sup>4</sup> used entirely NIRS-based methods and measured CBF using the oxygen bolus technique<sup>6</sup> and SvO<sub>2</sub> by employing partial jugular venous occlusion. Recent technical developments (described below) have led to the advent of systems which provide an online continuous measurement of absolute mean cerebral tissue oxygen saturation, SmcO<sub>2</sub>, which is a mean tissue saturation across all vascular compartments in the tissue of interest. The relative contributions to this measurement of the venous and arterial oxygen saturations can be estimated with the venous volume fraction ( $V_{ven} \approx 0.75$ ) using the equation:

$$SmcO_2 = V_{ven} \cdot SvO_2 + (1 - V_{ven}) \cdot SaO_2 \quad (3)$$

Using this relationship, a new expression for CMRO<sub>2</sub> can be derived that is independent of SvO<sub>2</sub>:

$$CMRO_2 \text{ (ml.100g}^{-1} \cdot \text{min}^{-1}\text{)} = CBF \cdot \frac{(SaO_2 - SmcO_2)}{V_{ven}} \cdot K \cdot tHb \quad (4)$$

## 2.2. Near Infrared Spectroscopy Techniques

Conventional NIRS or differential spectroscopy provides a continuous measurement of the quantified changes in concentration of oxy (HbO<sub>2</sub>) and deoxyhaemoglobin (HHb). Skov et al.<sup>3</sup> and Yoxall et al.<sup>4</sup> measured the changes in HbO<sub>2</sub> and total haemoglobin concentration (Hbtot) (HbO<sub>2</sub> + HHb) during manoeuvres designed to alter venous blood volume only (i.e. head down tilt and partial jugular venous occlusion). SvO<sub>2</sub> is then easily computed from the ratio of the change in HbO<sub>2</sub> to the change in tHb. Spatially resolved spectroscopy (SRS) depends upon measuring light attenuation as a function of spacing across a series of detectors. This attenuation slope is then fitted to a modified diffusion equation, and assuming a wavelength dependence of scattering, scaled absorption coefficients for HbO<sub>2</sub> and HHb can be derived. From this, the tissue oxygenation index (TOI) can be computed.<sup>7</sup> For measurements in the neonatal brain, this parameter provides a continuous, absolute, non-invasive measurement of the mean cerebral tissue saturation (SmcO<sub>2</sub>), without the need for any physiological manipulation.

CBF can be measured using NIRS by employing a small change in oxyhaemoglobin concentration as an intravascular tracer.<sup>8</sup> The arterial input of this bolus into the brain is measured using pulse oximetry and the cerebral response function is measured using NIRS via the change in cerebral HbO<sub>2</sub> concentration. A modified Fick principle is then used to calculate CBF in absolute units of ml.100g<sup>-1</sup>.min<sup>-1</sup>. The aim of this study is to use the measurement of SmcO<sub>2</sub> and CBF to investigate the derivation of CMRO<sub>2</sub> using Eq. (4).

## 3. METHODS

Nine infants were studied, all of whom were receiving ventilatory support. The median (range) gestational age was 25 weeks (23-37) and their median (range) birth

weight was 800 g (512-2676). The median age (range) at study was 3 days (1-43) post-delivery. Ethical permission for the study was obtained from the local ethics committee, and informed consent was obtained from one or both parents of each infant prior to the study. A NIRO300 spectrometer (Hamamatsu Photonics K.K.) was used to measure CBF and  $\text{SmcO}_2$  simultaneously over the right and left hemisphere. The optodes were placed over each parietal region with an interoptode spacing of 4 cm. Optical density data were collected at 6 Hz. Arterial oxygen saturation ( $\text{SaO}_2$ ), mean arterial blood pressure, partial pressure of carbon dioxide, and heart rate were simultaneously recorded. For each infant, between 2 and 5 successful measurements of CBF were made.  $\text{SmcO}_2$  was measured continuously throughout each study and CBF measurements were made after collecting stable  $\text{SmcO}_2$  data. tHb was measured for each baby from a venous blood sample and a differential pathlength factor of 5.13 was assumed.<sup>9</sup>  $\text{CMRO}_2$  was calculated using Eq. (4), assuming a venous volume fraction of 0.75 (see Discussion).

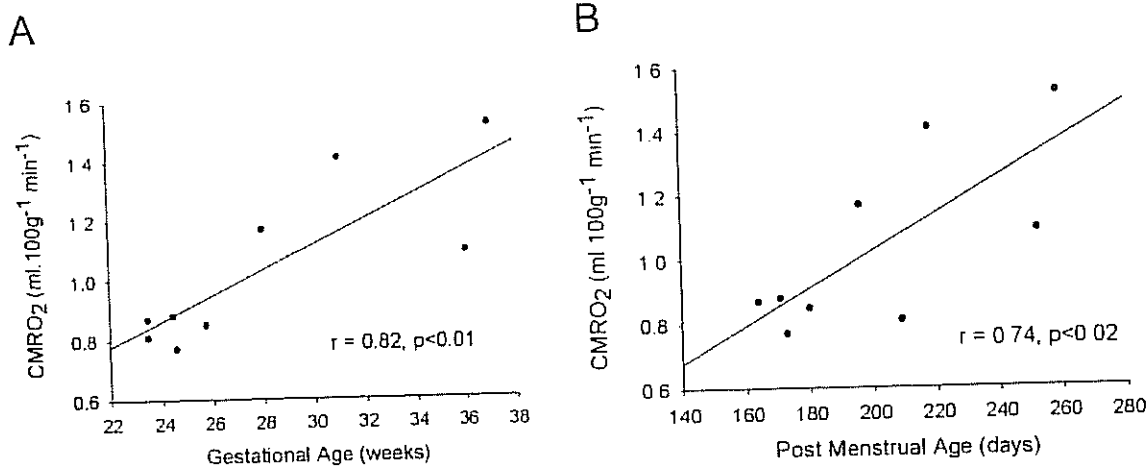
#### 4. RESULTS

Table 1 lists the results of the mean  $\text{CMRO}_2$  measurements for each infant and includes a clinical summary. Median (range) right and left cerebral hemisphere values for  $\text{CMRO}_2$  were found to be 0.95 (0.74 – 1.52)  $\text{ml } 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  and 0.90 (0.66 – 1.52)  $\text{ml } 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ , respectively. Using a paired *t* test, no significant difference was seen between the left and right sided values. Figure 1 shows the relationship between the average of the left and right sided  $\text{CMRO}_2$  values for each infant and (a) gestational age (in completed weeks) at birth and (b) post-menstrual age (in days) at the time of study. Using linear regression analysis, a positive correlation was found between  $\text{CMRO}_2$  and gestational age ( $P < .01$ ) and postmenstrual age ( $P < .02$ ).

**Table 1.** Summary of the  $\text{CMRO}_2$  results and clinical details of the infants studied.

Gestational Age at Birth (completed weeks)	Age at Study (Days)	$\text{CMRO}_2$ ( $\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$ )		Clinical Summary
		Right	Left	
23	1	0.86	0.88	HMD
23	43	0.76	0.88	PDA
24	1	0.87	0.89	HMD
24	2	0.80	0.74	HMD
25	8	0.98	0.69	HMD
28	16	1.23	1.17	HMD
31	2	1.46	1.46	Asphyxia
36	5	0.95	1.31	Asphyxia
37	1	1.53	-	Asphyxia

HMD: hyaline membrane disease, PDA: patent ductus arteriosus.



**Figure 1.** Relationship of CMRO<sub>2</sub> with (a) gestational age at birth in completed weeks and (b) post-menstrual age at the time of study in days. The mean of the left and right sided CMRO<sub>2</sub> values for each infant was used in the regression analysis.

### 5. DISCUSSION

We describe a minimally invasive technique for the measurement of regional CMRO<sub>2</sub> in neonates undergoing intensive care. The median (range) values we report of 1.03 (0.72 – 1.52) ml.100g<sup>-1</sup>.min<sup>-1</sup> are within the range of those quoted by other studies using more invasive methods. Altman et al.<sup>2</sup> used PET to measure CMRO<sub>2</sub> in a group of 11 infants and reported values of median 0.4 ml.100g<sup>-1</sup>.min<sup>-1</sup> (range 0 – 1.3). Skov et al.<sup>3</sup> reported values of 1.4 ml.100g<sup>-1</sup>.min<sup>-1</sup> in 10 asphyxiated term babies and a lower value of 1.0 ml.100g<sup>-1</sup>.min<sup>-1</sup> in nine preterm infants with hyaline membrane disease. An NIRS based study by Yoxall et al.<sup>4</sup> reported median values of 0.47 ml.100g<sup>-1</sup>.min<sup>-1</sup> (range 0.17 – 1.60) from a group of 20 neonates of median gestational age 27 weeks (range 24 – 41) (values corrected to a DPF of 5.13 and K of 1.304 ml.g<sup>-1</sup> to allow direct comparison with those reported in the current study) and an increase of CMRO<sub>2</sub> with gestational age. The data from all of these studies show that the vast majority of reported values for CMRO<sub>2</sub> in neonates are below the value of 1.3 ml.100g<sup>-1</sup>.min<sup>-1</sup> assumed to be the lower limit of viability of the adult brain. This lowered level of cerebral metabolism has been attributed to reduced energetic demand in the neonatal brain and decreased levels of functional activation.

The use of continuous, online S<sub>mc</sub>O<sub>2</sub> measurements for the estimate of CMRO<sub>2</sub> reported in this paper negates the need for any physiological manoeuvre such as a head down tilt or partial jugular venous occlusion. Central to our method, however, is the assumption of venous volume fraction, V<sub>ven</sub>, which, in the absence of any published neonatal values, we have assumed to be 0.75 (the value generally employed for studies in adults<sup>10</sup>). However, a number of partial venous jugular occlusion measurements was performed on one of the infants in our study, which allowed the estimation of S<sub>v</sub>O<sub>2</sub>. Combining these data with simultaneous S<sub>a</sub>O<sub>2</sub> and S<sub>mc</sub>O<sub>2</sub> measurements allowed the calculation of V<sub>ven</sub> in this infant from the following equation:

$$V_{ven} = \frac{SaO_2 - S_{mc}O_2}{SaO_2 - SvO_2} \quad (5)$$

The mean value of  $V_{ven}$  calculated in this single infant was 0.70. Further work is obviously required to determine the range of  $V_{ven}$  values to be expected in neonates of different ages and with varying pathology.

To date, the number of infants in which  $CMRO_2$  has been measured has been limited by the use of physiological manoeuvres which may not always be appropriate to perform repeatedly on infants undergoing intensive care. When CBF is measured using a NIRS system capable of delivering an absolute measure of mean tissue saturation, the method described in this paper allows the automatic calculation of  $CMRO_2$ . It is therefore hoped that a large database of  $CMRO_2$  values can be acquired in a wide range of infants to allow normal ranges to be defined and the clinical and prognostic significance of such measurements to be assessed.

## 6. ACKNOWLEDGEMENTS

We thank the parents and staff of the Neonatal Unit, University College Hospitals, London. This work was supported by the Wellcome Trust, Hamamatsu Photonics KK, and the United Kingdom Engineering and Physical Sciences Research Council.

## REFERENCES

1. W. J. Powers, R. L. Grubb, D. Darriet, and M. E. Raichle, Cerebral blood flow and cerebral metabolic rate of oxygen for cerebral function in humans, *J. Cereb. Blood Flow Metab.* **5**, 600-608 (1985).
2. D. I. Altman, J. M. Perlman, J. J. Volpe, and W. J. Powers, Cerebral oxygen metabolism in newborns, *Pediatrics* **92**, 99-104 (1993).
3. L. Skov, O. Pryds, G. Griesen, and H. Lou, Estimation of cerebral venous saturation in newborn infants by near infrared spectroscopy, *Pediatr. Res.* **33**, 52-55 (1993).
4. C. W. Yoxall, and M. Weindling, Measurement of cerebral oxygen consumption in the human neonate using near infrared spectroscopy: cerebral oxygen consumption increases with advancing gestational age, *Pediatr. Res.* **44**(3), 283-290 (1998).
5. I. C. Gregory, The oxygen and carbon monoxide capacities of foetal and adult blood, *J. Physiol.* **236**, 625 (1974).
6. A. D. Edwards, J. S. Wyatt, C. E. Richardson, D. T. Delpy, M. Cope, and E. O. Reynolds, Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy, *Lancet* **2**(8614), 770-771 (1988).
7. S. J. Matcher, P. Kirkpatrick, K. Nahid, M. Cope, and D. T. Delpy, Absolute quantification methods in tissue near-infrared spectroscopy, *Proc. SPIE* **2389**, 486-495 (1995).
8. C. E. Elwell, M. Cope, A. D. Edwards, J. S. Wyatt, D. T. Delpy, and E. O. R Reynolds, Quantification of adult cerebral haemodynamics by near infrared spectroscopy, *J. Applied Physiol.* **77**, 2753-2760 (1994).
9. A. Duncan, J. Meek, M. Clemence, C. E. Elwell, L. Tyszczuk, M. Cope, and D. T. Delpy, Optical pathlength measurements on adult head, calf and forearm and the head of the newborn infant using phase resolved optical spectroscopy, *Phys. Med. Biol.* **40**, 295-304 (1995).
10. G. McHedlishvili, *Arterial behaviour and blood circulation in brain* (Plenum Press, New York, 1986).