

# PREDICTING OSCILLATION IN ARTERIAL SATURATION FROM CARDIORESPIRATORY VARIABLES

## Implications for the Measurement of Cerebral Blood Flow with NIRS during Anaesthesia

A. T. Lovell,<sup>1</sup> H. Owen-Reece,<sup>1</sup> C. E. Elwell,<sup>2</sup> M. Smith,<sup>1</sup> and J. C. Goldstone<sup>1</sup>

<sup>1</sup>Division of Academic Anaesthesia  
Department of Surgery  
University College London Medical School  
The Middlesex Hospital  
Mortimer St., London, W1N 8AA, United Kingdom

<sup>2</sup>Department of Medical Physics and Bioengineering  
University College London  
Shropshire House, 11-20 Capper St.  
London, WC1E 6JA, United Kingdom

### 1. INTRODUCTION

The potential of near infrared spectroscopy (NIRS) as a non invasive tissue oxygenation monitor was first outlined by Jöbsis (Jöbsis, 1977). Extension of the basic technique to measure tissue blood flow using a Fick technique was developed by Edwards and Reynolds (Edwards et al., 1988; Edwards et al., 1993). This uses a rapid change in arterial oxyhaemoglobin concentration to act as an intravascular tracer, avoiding the problem of recirculation of indicator.

$$\text{Blood Flow}(\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}) = \frac{\Delta \text{HbO}_2 - \Delta \text{Hb}}{2 \cdot [\text{tHb} \cdot 10^{-2}] \cdot \int \Delta \text{SpO}_2 dt} \cdot \frac{[MW_{\text{Hb}} \cdot 10^{-6}]}{[D_t \cdot 10]} \quad (1)$$

This technique has been successfully validated against <sup>133</sup>Xenon clearance for the measurement of cerebral blood flow (CBF) at flows upto 40 ml 100 g<sup>-1</sup> min<sup>-1</sup> in neonates

(Skov *et al.*, 1991; Bucher *et al.*, 1993), and against venous occlusion plethysmography in the adult forearm (Edwards *et al.*, 1993).

In the last few years there has been increasing interest in the use of NIRS to monitor adult cerebral haemodynamics (Kirkpatrick *et al.*, 1995; Mason *et al.*, 1994; Villringer *et al.*, 1993); Elwell *et al.*, 1992; Owen-Reece *et al.*, 1996). A major problem with the CBF technique is that with the induction of mild hypoxia, oscillation in arterial saturation and  $\text{HbO}_2$  have been reported (Elwell *et al.*, 1992). The finding that the dominant frequency of a fast fourier transform of both arterial saturation and  $\text{HbO}_2$  were very strongly correlated with the breathing rate strongly suggested that these oscillations were of a respiratory nature (Elwell *et al.*, 1994a).

The most likely explanation for the respiratory "artifact" was that the intrathoracic pressure changes during respiration were causing cyclical changes in cardiac output and that these were responsible for the oscillations in  $\text{HbO}_2$ . Elwell and colleagues have demonstrated that oscillations in  $\text{HbO}_2$  occur whilst breathing room air, and that the magnitude of these oscillations increases with expiratory loading (Elwell *et al.*, 1994b; Elwell *et al.*, 1996). It was hypothesized that expiratory loading decreases the venous return and hence cardiac output during the respiratory cycle. However, the magnitude of the changes in cardiac output would be very unlikely to be sufficient to explain the changes in arterial saturation. Oscillations of the arterial partial pressure were first observed 50 years ago by Bjurstead. Consideration of the composition of gas within an alveolus would suggest that it should oscillate at the same frequency as respiration, due to the intermittent nature of gas flow, and this has been amply confirmed by studies of Yokota, Kreuzer and others during the 1970's (Yokota *et al.*, 1973; (Yokota & Kreuzer, 1973; Folgering *et al.*, 1978).

The measurement of CBF varies if the rise of  $\text{HbO}_2$  and  $\text{SpO}_2$  do not begin at the same time (Elwell *et al.*, 1992). For example, a one second offset between  $\text{HbO}_2$  and  $\text{SpO}_2$  can change the measured CBF by 70%. Clearly if  $\text{SpO}_2$  is oscillating determining the correct temporal relationship to  $\text{HbO}_2$  can be difficult, and this may partially explain the previously high reported coefficient of variation of this technique.

Our model was developed to test the hypothesis that changes in ventilatory parameters might play a major role in the oscillations seen in arterial saturation.

## 2. THE MODEL

We have derived a two compartmental model. One compartment representing the dead space of the respiratory tract, in which gas mixing but no uptake of oxygen to the blood occurs, and the other representing the alveoli in which gas mixing and oxygen uptake occurs. The model assumes complete, and immediate, mixing of gas within each compartment.

The alveolar volume oscillates in a sinusoidal manner around the mean alveolar volume. During expiration, the volume of the alveolar compartment ( $V_A$ ) is given by

$$V_A(t) = FRC + \frac{V_T}{2} + \cos\left(\frac{t}{k_1}\right) \cdot \frac{V_T}{2} = FRC + \frac{V_T}{2} \cdot \left\{1 + \cos\left(\frac{t}{k_1}\right)\right\} \quad (2)$$

where  $k_1$  is a term used to set the inspiratory to expiratory ratio and respiratory rate, defined in Eq. 8 and 9 below. If a short time ( $\delta t$ ) passes then the change in volume of the alveolar compartment ( $\delta V$ ) is given by

$$\delta V = V_A(t) - V_A(t + \delta t) \quad (3)$$

substituting Eq. 2 in Eq. 3 yields

$$\delta V = \frac{V_T}{2} \cdot \left\{ \cos\left(\frac{t}{k_1}\right) - \cos\left(\frac{t + \delta t}{k_1}\right) \right\} \quad (4)$$

The fractional concentration of oxygen in the alveoli ( $F_A O_2(t)$ ) will vary with time. Since no oxygen is added but oxygen consumption continues during expiration.

$$F_A O_2(t + \delta t) = \frac{F_A O_2(t) \cdot V_A(t) - \dot{v} O_2}{V_A(t)} \quad (5)$$

During expiration gas leaves the alveoli and enter the dead space, and an equal volume of gas is lost to the atmosphere from the dead space. If complete mixing of gas occurs then the fractional concentration of oxygen in the dead space ( $F_D O_2(t)$ ) is given by

$$F_D O_2(t + \delta t) = \frac{F_D O_2(t) \cdot V_D - \{F_I O_2 - F_D O_2(t)\} \cdot \delta V}{V_D} \quad (6)$$

During inspiration the volume of the alveolar compartment ( $V_A$ ) is given by

$$\begin{aligned} V_A(t) &= FRC + \frac{V_T}{2} + \cos\left(\frac{\pi(k_2 - 1) - \pi(k_1 - 1) + t}{k_2}\right) \cdot \frac{V_T}{2} \\ &= FRC + \frac{V_T}{2} \cdot \left\{ 1 + \cos\left(\frac{\pi(k_2 - k_1) + t}{k_2}\right) \right\} \end{aligned} \quad (7)$$

where  $k_1$  and  $k_2$  are terms used to set the inspiratory to expiratory ratio and respiratory rate such that the duration of one breath is  $2\pi(k_1 + k_2)$  seconds and the inspiratory to expiratory ratio is given by

$$\text{inspiratory to expiratory ratio} = \frac{k_2}{k_1} \quad (8)$$

and

$$k_1 + k_2 = \frac{30}{\pi(\text{breaths per minute})} \quad (9)$$

If a short time ( $\delta t$ ) passes then during inspiration the change in volume of the alveolar compartment ( $\delta V$ ) is given by substituting Eq. 7 in Eq. 3

$$\delta V = \frac{V_T}{2} \cdot \left\{ \cos\left(\frac{\pi(k_2 - k_1) + t}{k_2}\right) - \cos\left(\frac{\pi(k_2 - k_1) + t + \delta t}{k_2}\right) \right\} \quad (10)$$

During inspiration gas passes from the dead space into the alveoli and an equal volume of gas enter the dead space with a fractional concentration of oxygen of  $F_I O_2$ . If the gas entering the alveoli from the dead space and that entering the dead space is immediately mixed then

$$F_A O_2(t + \delta t) = \frac{F_A O_2(t) \cdot V_A(t) + F_D O_2(t) \cdot \delta V - \dot{v} O_2}{V_A(t)} \quad (11)$$

$$F_D O_2(t + \delta t) = \frac{F_D O_2(t) \cdot V_D + \{F_I O_2 - F_D O_2(t)\} \cdot \delta V}{V_D} \quad (12)$$

The model first solves Eq. 8 and 9 to yield  $k_1$  and  $k_2$ . If the transition from inspiration to expiration is taken as  $t=0$  then  $F_A O_2(0)$  can be calculated using the alveolar gas equation and  $F_D O_2(0)$  can be approximated by  $F_I O_2$ .

Because of the need to be able to produce an asymmetrical "sine" wave the use of two separate waves was chosen. However, implicit with this technique is the fact that in order to synthesize a repeating waveform the value of  $t$  used in Eq. 2 and 7 must be set to zero on each transition from inspiration to expiration.

Conversion from alveolar oxygen concentration to arterial saturation is performed using the method of Farmery and Roe (Farmery & Roe, 1996) assuming complete equilibration of the mixed pulmonary venous blood with the alveoli and no diffusion barrier to oxygenation.

### 3. RESULTS

The results of a typical desaturation - resaturation run, for a 70 kg male, are shown in Figure 1. It is very clear that the magnitude of the oscillation increases as the arterial saturation falls, and that the magnitude of the oscillation is influenced by the tidal volume. The link between respiratory frequency and oscillatory frequency is clear. The shape of the saturation-time curve appears identical to that seen in clinical practice. Formal comparison with experimental measurements is in progress. The influence of the patient's oxygen consumption ( $\dot{V}O_2$ ) and alveolar volume ( $V_A$ ) are shown in Figure 2. The importance of minimizing the reduction in FRC during anaesthesia is clearly shown. The effects of prolongation of the inspiratory to expiratory (I:E) time at differing values for  $\dot{V}O_2$  are shown in Table 1. The effects of even relatively small changes of the I:E ratio is quite marked at high  $\dot{V}O_2$ . This effect is magnified by the use of larger tidal volumes. However, if small tidal volumes are used and the patient has a lower than normal  $\dot{V}O_2$ , the effect of changes in I:E ratio can probably be ignored.

The effects of signal averaging upon the peak to peak magnitude of the oscillations in arterial saturation is shown in Table 2. It is clear that applying a moving average smoothing function can reduce the magnitude of these oscillations, but this also introduces a phase delay between the oscillation in the arterial signal and that actually measured.

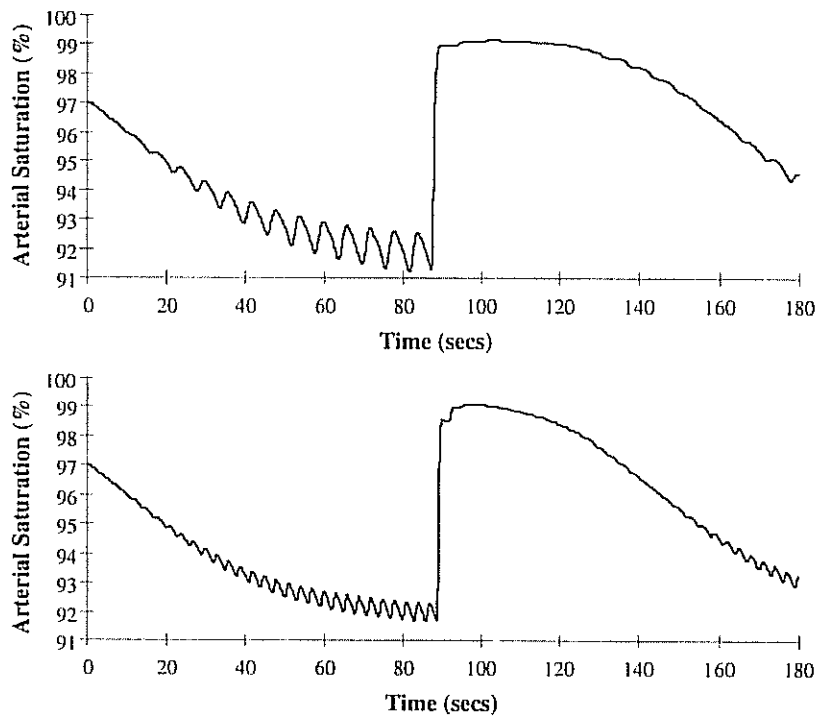


Figure 1. Computer predicted SpO<sub>2</sub> against time. V<sub>A</sub> 2500 ml. VO<sub>2</sub> 250 ml min<sup>-1</sup>. F<sub>I</sub>O<sub>2</sub> 0.12. At 90 seconds 3 breaths of 100% O<sub>2</sub> were delivered. Top panel V<sub>T</sub> 1000. 10 breaths min<sup>-1</sup>. Bottom Panel V<sub>T</sub> 500. 20 breaths min<sup>-1</sup>.

This time offset must be taken account of when performing measurements of CBF. In practice the effects of signal averaging will be to dramatically reduce the number of time points as well. This may further reduce the magnitude of the oscillations since the peaks and troughs would be unlikely to fall precisely at either end of one of the time periods. Given that the current generation of commercially available NIRS instruments have a maximum sampling rate of 2 Hz it is not surprising that these oscillations have not been consistently observed.

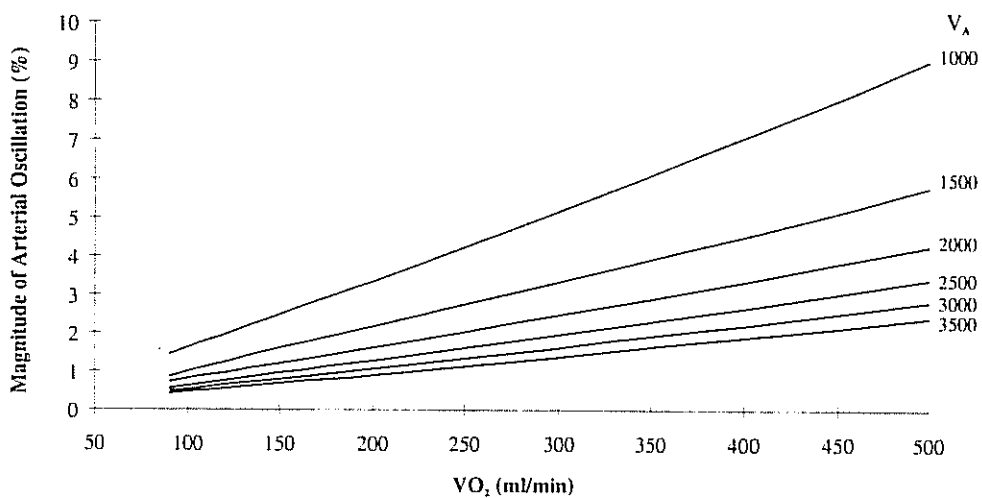


Figure 2. Effects of changes in alveolar volume (V<sub>A</sub>) and minute oxygen consumption (VO<sub>2</sub>) on the peak to peak magnitude of oscillation of the computer predicted arterial saturation when desaturated to a mean arterial saturation of 90%. V<sub>T</sub> 500 ml 14 breaths min<sup>-1</sup> V<sub>D</sub>/V<sub>T</sub> 0.3.

**Table 1.** Effects of changes in inspiratory:expiratory (I:E) ratio and minute oxygen consumption ( $\text{VO}_2$ ) on the peak to peak magnitude of oscillation of the computer predicted arterial saturation. Mean predicted arterial saturation 90%.  $V_T$  500 ml 14 breaths  $\text{min}^{-1}$   $V_D/V_T$  0.3

I : E Ratio	$\text{VO}_2$ (ml $\text{min}^{-1}$ )					
	100	150	200	250	300	400
4 : 1	.35	.53	.72	.91	1.10	1.50
3 : 1	.38	.57	.77	.99	1.18	1.61
2 : 1	.42	.64	.86	1.09	1.32	1.80
1 : 1	.52	.78	1.06	1.34	1.63	2.21
1 : 2	.63	.95	1.28	1.61	1.96	2.62
1 : 3	.69	1.04	1.39	1.76	2.14	2.90
1 : 4	.72	1.09	1.47	1.85	2.25	3.06

#### 4. DISCUSSION

Oscillations in arterial saturation are likely to be a universal finding in adults subjected to a desaturation manoeuvre. The magnitude of these oscillations increases dramatically as the saturation falls. At first sight this seems to be a contradiction with the work of Kreuzer and his colleagues (Folgering *et al.*, 1978) who reported a much larger value for  $\Delta\text{PaO}_2$  at high values for  $\text{PaO}_2$  than at low values. However, once it is realized that at the high values for  $\text{PaO}_2$  used in their study the oxygen dissociation curve is flat, then it is clear that the saturation change would be very small. Previous studies (Nye, 1970) using a two compartment model under normoxic conditions have observed oscillations in alveolar  $\text{PO}_2$  which changes with changes in the respiratory pattern. Because these studies were only conducted under normoxic conditions where the oxygen dissociation curve is essentially flat the equivalent change in arterial saturation was only 0.5% despite a 10 mmHg change in  $\text{PO}_2$ .

It is possible to dramatically reduce the magnitude of these oscillations by minimizing the tidal volume ( $V_T$ ) used. However, reductions in the  $V_T$  limit the rate of rise of alveolar oxygen concentration and hence arterial saturation following exposure to 100%

**Table 2.** Effects of applying moving average smoothing to the peak to peak magnitude of the oscillations in the predicted arterial saturation. Mean predicted arterial saturation 90%. Simulations performed for a typical 70 kg person. Minute ventilation 7 l  $\text{min}^{-1}$ .  $V_A$  2500 ml  $\text{VO}_2$  250 ml  $\text{min}^{-1}$   $V_D/V_T$  0.3

Duration of moving average (sec)	Tidal volume (ml)		
	500	750	1000
Raw data	1.61	2.27	3.29
0.25	1.59	2.25	3.28
0.50	1.52	2.20	3.24
0.75	1.44	2.12	3.18
1.00	1.35	2.04	3.10
1.50	1.15	1.86	2.93
2.00	0.95	1.65	2.73

oxygen. It is important that this rate of rise is as fast as possible in order to maximize the input of tracer, oxyhaemoglobin, to the brain. An alternative strategy to minimize these oscillations is to maximize the alveolar volume ( $V_A$ ), or minimize the  $VO_2$ . Under anaesthesia  $V_A$  generally falls by 20–30% from the awake value, although there are methods, such as the addition of PEEP, that can be applied to reduce this. The  $VO_2$  generally falls under anaesthesia since active movement, the prime consumer of oxygen, generally ceases. It is possible to further reduce the  $VO_2$  by the use of mechanical ventilation. The most likely explanation for the effects of changes in  $V_T$  and  $V_A$  is that the smaller the  $V_T:V_A$  ratio the smaller the proportion of alveolar gas that is exchanged each breath, and therefore the greater the ability for the alveolar gas to act as a buffer.

The other strategy for minimizing oscillation in arterial saturation is prolongation of the duration of active inspiration. With mechanical ventilation of patients this is fairly simple to achieve, but is all but impossible in conscious volunteers. The explanation behind the changes in oscillation with changes in the I:E ratio and  $VO_2$  is that during expiration oxygen is being consumed from the alveolar gas, but is not being replaced. The cyclical nadir in  $P_AO_2$  will be reached early in inspiration when gas that had resided in the dead space at the end of expiration reenters the alveoli. Thus the greater the proportion of the respiratory cycle spent in expiration, or the higher the  $VO_2$ , the greater the difference in oxygen concentration in the alveolar gas at the nadir compared to the end of inspiration. In this context, the addition of an inspiratory pause will lead to an increase in oscillation assuming complete and uniform equilibration of gas in the alveoli. This is because no further oxygen is delivered to the alveoli during this pause, but consumption is already proceeding.

The effects of the signal averaging built into many pulse oximeters is to markedly reduce the magnitude of these oscillations and to cause a considerable change in their phase angle compared to the true saturation of arterial blood. The averaging built in to the current generation of NIRS instruments when operated at their maximum capture rates causes only a very small reduction in magnitude of the oscillation.

Under anaesthesia it is often possible to select ventilatory parameters which minimize the introduction of respiratory "artifacts" on NIRS signals and thus facilitate the use of dynamic NIRS techniques. Furthermore this model suggests that there maybe categories of patients, such as those with a high  $VO_2$  and low  $V_A$  where the oxygen CBF technique may be impractical due to respiratory artifacts.

It is possible to criticize the assumptions of our model on several grounds. The use of a two compartmental model is an oversimplification. Although there are millions of alveoli, in health they should all exchange oxygen in a relatively similar manner. It is possible to expand the dead space compartment into multiple smaller compartments, but if this approach is taken then very careful consideration has to be given to the partitioning of gas between these sub-compartments.

The assumption of continuous pulmonary blood flow was made to facilitate simplification of the model. In reality the pulmonary blood flow is pulsatile and will thus apply a convolution function to the arterial saturation signal. The currently commercially available NIRS instruments have a maximum sampling rate of 2 Hz. From Nyquist's theorem the maximum observed frequency of any convolution function is thus 1 Hz, which equates to a heart rate of 60  $\text{min}^{-1}$ . Thus in clinical practice with the currently available devices the effect of the convolution will generally not be directly observable as an oscillating signal. Yokota and Kreuzer have shown that the effect of pulsatile blood flow is to cause a damping of the arterial oscillations (Yokota & Kreuzer, 1973). This is predominantly due to mixing within the left ventricle, with very little difference from aorta to the carotid (Fol-

gering *et al.*, 1978), or more distally in the arterial tree (Yokota & Kreuzer, 1973). Typically this damping leads to a reduction by approximately 50% of the oscillation seen in the left atrium, and predicted by our model. Furthermore, as the ratio of ventilation rate to heart rate decreases the attenuation of the oscillation decreases.

The idea that perfect equilibrium of end capillary blood with alveolar gas may seem at first sight extremely optimistic. However, in health blood traveling through the pulmonary capillaries is fully saturated by the time it has spent a third of its residence time. Thus there is a very considerable reserve before diffusion limitation for oxygenation will occur. In pathological states or circumstances with a very rapid pulmonary blood flow, such as exercise, this may not be true. The finding of a very strong correlation between fluctuations in end capillary and arterial saturations, although at reduced magnitude, supports this (Yokota & Kreuzer, 1973).

Gas flow, even in health, is usually turbulent which should produce near perfect mixing. However, if there are regions of the lungs with unequal time constants, such as in asthma, or very low gas flow rates are used, then this may not be true. Thus assuming complete and immediate mixing of gas in both compartments is probably reasonable. However, if the dead space compartment was further partitioned the exact location of the sub-compartments would have to determine whether this assumption could remain, or whether laminar flow considerations should be introduced.

We have assumed that the induction of hypoxia does not lead to an increase in total oxygen consumption ( $\text{VO}_2$ ). If the  $\text{VO}_2$  changes as hypoxia is induced then the rate that the alveolar oxygen reservoir is depleted during the expiratory and early inspiratory phase of each respiratory cycle will change. Over the range of saturations that the model has been designed to cope with this should be a reasonable approximation. The hypoxia chemoreceptors usually remain relatively silent until an arterial saturation well below 90%.

It is known that the dead space changes with lung volume. However, whether  $V_D/V_T$  remains constant throughout the respiratory cycle is less clear. In the extreme circumstance when the deflating lung approaches its residual volume (RV) during expiration this is clearly untrue. However, even allowing for the reductions in FRC that are known to occur during anaesthesia, alveolar volume is usually maintained well above RV.

## 5. CONCLUSIONS

In order to minimize the induction of respiratory "artifacts" when performing CBF NIRS studies using the oxygen method, care should be taken to use as high a baseline arterial saturation as possible. It is however inevitable that this limits the magnitude of the "tracer" input, and may lead to a rise in the signal to noise ratio. Attempts at minimizing the arterial oscillations by manipulation of either  $V_T$  or  $V_A$  involve an inevitable compromise if the oxygen CBF method is used. This is because of the fundamental requirement of the oxygen CBF technique for a rapid rise in arterial saturation which necessitates a high  $V_T:V_A$  ratio and directly conflicts with the requirements to minimize baseline arterial oscillations, namely a low  $V_T:V_A$  ratio. Prolongation of the duration of active inspiration, although effective is currently only possible with a small number of anaesthetic ventilators, and is impossible in the spontaneously breathing patient. Minimization of the patient's oxygen consumption, in order to minimize the oxygen consumption during the expiratory phase whilst making perfect logical sense, is only rarely amenable to manipulation.

Minimization of the induction of these respiratory "artifacts" in order to facilitate the measurement of CBF thus requires a carefully weighted compromise over the choice of respiratory parameters. Some clinical circumstances may preclude manipulation of some of the respiratory variables, and the resultant oscillation in the baseline arterial saturation may be such as to preclude the use of the oxygen CBF technique. For these patients other methods of measuring CBF will have to be applied.

## ACKNOWLEDGMENT

This work has been supported by a grant from the Wellcome Trust.

## REFERENCES

- Bucher, HU; Edwards, AD; Lipp, AE; Duc, G (1993): Comparison between Near Infrared Spectroscopy and  $^{133}\text{Xe}$  Clearance for Estimation of Cerebral Blood Flow in Critically Ill Preterm Infants. *Pediatr Res* 33, 56–60.
- Edwards, AD; Richardson, C; van der Zee, P; Elwell, C; Wyatt, JS; Cope, M; Delpy, DT; Reynolds, EOR (1993): Measurement of hemoglobin flow and blood flow by near-infrared spectroscopy. *J Appl Physiol* 75, 1884–1889.
- Edwards, AD; Wyatt, JS; Richardson, C; Delpy, DT; Cope, M; Reynolds, EOR (1988): Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet* 2, 770–771.
- Elwell, CE; Cope, M; Edwards, AD; Wyatt, JS; Reynolds, EOR; Delpy, DT (1992): Measurement of cerebral blood flow in adult humans using near infrared spectroscopy - methodology and possible errors. *Adv Exp Med Biol* 317, 235–245.
- Elwell, CE; Cope, M; Edwards, AD; Wyatt, JS; Delpy, DT; Reynolds, EOR (1994a): Quantification of adult cerebral hemodynamics by near-infrared spectroscopy. *J Appl Physiol* 77, 2753–2760.
- Elwell, CE; Owen-Reece, H; Cope, M; Edwards, AD; Wyatt, JS; Reynolds, EOR; Delpy, DT (1994b): Measurement of changes in cerebral haemodynamics during inspiration and expiration using near infrared spectroscopy. *Adv Exp Med Biol* 345, 619–626.
- Elwell, CE; Owen-Reece, H; Wyatt, JS; Cope, M; Reynolds, EOR; Delpy, DT (1996): Influence of Respiration and Changes in Expiratory Pressure on Cerebral Haemoglobin Concentration Measured by Near Infrared Spectroscopy. *J Cereb Blood Flow Metab* 16, 353–357.
- Farmery, AD; Roe, PG (1996): A model to describe the rate of oxyhaemoglobin desaturation during apnoea. *Br J Anaesth* 76, 284–291.
- Folgering, H; Smolders, FDJ; Kreuzer, F (1978): Respiratory oscillations of the arterial  $\text{PO}_2$  and their effects on the ventilatory controlling system of the cat. *Pflügers Arch* 375, 1–7.
- Jöbsis, FF (1977): Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 198, 1264–1267.
- Kirkpatrick, PJ; Smielewski, P; Whitfield, PC; Czosnyka, M; Menon, D; Pickard, JD (1995): An observational study of near-infrared spectroscopy during carotid endarterectomy. *J Neurosurg* 82, 756–763.
- Mason, PF; Dyson, EH; Sellars, V; Beard, JD (1994): The assessment of cerebral oxygenation during carotid endarterectomy utilising near infrared spectroscopy. *Eur J Vasc Surg* 8, 590–594.
- Nye Jr, RE (1970): Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange. *Respir Physiol* 10, 321–337.
- Owen-Reece, H; Elwell, CE; Harkness, W; Goldstone, J; Delpy, DT; Wyatt, JS; Smith, M (1996): Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anesthetized adult subjects. *Br J Anaesth* 76, 43–48.
- Skov, L; Pryds, O; Greisen, G (1991): Estimating Cerebral Blood Flow in Newborn Infants: Comparison of Near Infrared Spectroscopy and  $^{133}\text{Xe}$  Clearance. *Pediatr Res* 30, 570–573.
- Villringer, A; Planck, J; Hock, C; Schleinkofer, L; Dirnagl, U (1993): Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci Lett* 154, 101–104.
- Yokota, H; Hoofd, LIC; Kreuzer, F (1973): Alveolar oxygen tension in anesthetized, artificially ventilated dogs. *Pflügers Arch* 340, 273–290.
- Yokota, H; Kreuzer, F (1973): Alveolar to arterial transmission of oxygen fluctuations due to respiration in anesthetized dogs. *Pflügers Arch* 340, 291–306.

**Appendix.** Definition of variables and their units

Variable	Definition	Units
CBF	Cerebral blood flow	ml 100g <sup>-1</sup> min <sup>-1</sup>
D <sub>i</sub>	Cerebral tissue density	g ml <sup>-1</sup>
F <sub>A</sub> O <sub>2</sub>	Fractional alveolar oxygen concentration	—
F <sub>D</sub> O <sub>2</sub>	Fractional dead space oxygen concentration	—
F <sub>I</sub> O <sub>2</sub>	Fractional inspired oxygen concentration	—
FRC	Functional residual capacity of the lungs	litres
ΔHb	Change in cerebral deoxyhaemoglobin concentration	μmol litre <sup>-1</sup>
ΔHbO <sub>2</sub>	Change in cerebral oxyhaemoglobin concentration	μmol litre <sup>-1</sup>
I:E	Inspiratory to expiratory ratio	—
k <sub>1</sub>	Expiratory time factor	—
k <sub>2</sub>	Inspiratory time factor	—
MW <sub>Hb</sub>	Molecular weight of haemoglobin	g
SpO <sub>2</sub>	Arterial saturation	%
t	Time	sec
tHb	Tissue haemoglobin concentration	g dl <sup>-1</sup>
V <sub>A</sub>	Alveolar volume	litres
V <sub>D</sub>	Dead space volume	litres
V <sub>T</sub>	Tidal volume	litres
iO <sub>2</sub>	Minute oxygen consumption	litres sec <sup>-1</sup>