

METHODS OF QUANTITATING CEREBRAL NEAR INFRARED

SPECTROSCOPY DATA

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INTRODUCTION

Non invasive infrared spectroscopy is a well established technique for monitoring changes in the oxygenation status of tissues (1). The technique has in particular been successfully employed to monitor changes in cerebral blood and tissue oxygenation by observing the absorption of haemoglobin and cytochrome aa3 respectively. Because of the highly light scattering nature of the tissues studied, it has normally not been possible to quantitate the observed changes.

We have been applying near infrared spectroscopy (nirs) clinically to study the oxygenation of the brain of newborn infants in the neonatal intensive care unit at UCH (2). These studies have been performed in the transillumination mode with purpose built equipment (3). By operating in transillumination mode we are able to define a minimum path length for the light traversing the tissues. This permits upper limits to be placed on any calculated values of nir derived data. We propose that in certain circumstances, absolute quantitation of nir data is possible. This is achieved by correlating measured variations in the nir absorption with data from other physiological sensors during a small known disturbance from a previous baseline.

EXPERIMENTAL BACKGROUND

The instrument used to monitor NIR absorption changes in the neonate employs four semiconductor laser diodes as light sources (wavelengths 775, 813, 847 and 904 nm). Light from the diodes is guided to the head by a fibre optic bundle, and attached to a site equidistant from the anterior fontanelle and the external auditory meatus. Light emerging at the other side of the head is collected in a similar optode, and lead to a photomultiplier tube detector. Changes in light absorption at three of the wavelengths are converted to equivalent changes in oxygenated haemoglobin (HbO₂), deoxygenated haemoglobin (HbR) and oxygenated cytochrome aa3 (cytaa3). Total Haemoglobin (HbT) is obtained

from the sum of HbO₂ and HbR. This calculation is performed by a linear summation of absorption changes (in optical densities) multiplied by the following factors at each wavelength:

Multiplying Factors

	<u>775 nm</u>	<u>847 nm</u>	<u>904 nm</u>
HbO ₂	-927	-618	+1831
HbR	+1433	-1744	+709
cytaa3	-84	+1339	-1107

The resulting concentration changes are expressed in $\mu\text{mol/l}$ multiplied by optical path length in centimetres. The multiplying factors for haemoglobin were derived from measured absorption spectra for haemoglobin solutions. Those for cytochrome aa3 were obtained from in vivo spectra of (oxygenated-reduced) cytochrome aa3 (4). The assumption made in these calculations is that changes in concentration of the chromophores in the tissues produce a logarithmic change in transmitted light intensity. This relationship applies in clear (ie non scattering) absorbing media, but experimental data showing that it can be applied in the case of tissue is limited. Experimental studies of the attenuation of transmitted light in brain tissue (5,6) do however indicate a logarithmic fall in intensity with distance when measured through considerable thickness of tissue. A Monte Carlo simulation of light transport in brain tissue (7) also predicts that for transmitted light, a logarithmic relationship is obtained over a considerable range of absorption coefficient, and that this applies also for tissues having a large range of scattering coefficient. (It is interesting to note that the model predicts a non logarithmic response for the reflected light intensity over the equivalent range of absorption and scattering coefficients. If these predictions are correct, then a simple linear addition cannot be employed when performing reflection mode nir spectroscopy).

To verify the predictions, a simple experiment has been performed using the nir instrument. The optodes were attached to opposite faces of a square transparent plastic container (5 cm side length), and the container filled with physiological saline. Aluminium Oxide particles (7 μm diameter) were then added to produce a scattering medium. A magnetic stirrer was used to prevent particle settling. Sufficient scatterer was

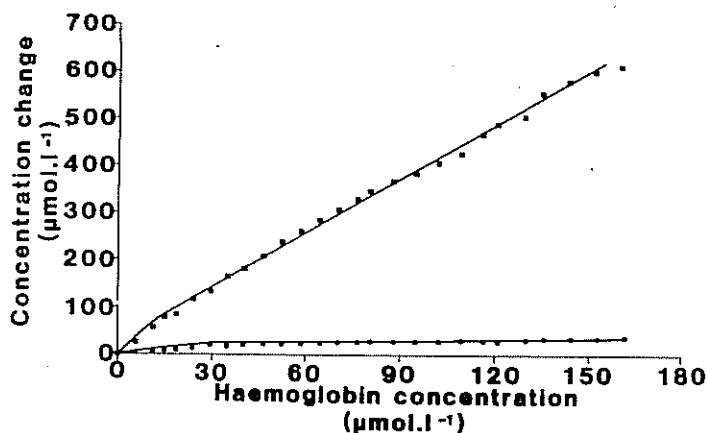


Fig. 1. Changes in calculated HbT and cytaa3 concentration in a scattering phantom as a function of added haemoglobin concentration.

added to produce an attenuation in transmitted intensity of approximately 5 OD (the attenuation of neonatal brain is approximately 1 OD/cm). Known aliquots of washed human red blood cells were then sequentially added to the container, and the resulting absorption changes recorded. These absorption variations were then converted to equivalent changes in total haemoglobin and cytochrome aa3 using the previously mentioned relationship. The results of this experiment are shown in Figure 1. It can be seen that the resulting relationship between HbT and true haematocrit, is in fact slightly non linear over this large range of haemoglobin concentration. This range is however greater than that observed in the human neonate. Over the physiological range of tissue haemoglobin concentration, the assumption of linear addition of absorbencies is justifiable within experimental error. The calculated cytochrome signal in this experiment should have remained constant, since there was no cytochrome present in the solution. It can be seen however that this signal did change slightly with haemoglobin concentration. The derived cytochrome signal was particularly sensitive to the initial rise in haemoglobin concentration, and virtually unaffected by later increases. This probably reflects the initial change in "effective" optical path length with wavelength, as the added absorber selectively attenuates the more highly scattered components of transmitted light.

This effect is again predicted by the Monte Carlo simulation (7) where maximum deviation from linearity is observed in circumstances of high scattering and low absorption. In practice, brain tissue always contains some absorber (haemoglobin or cytochrome), and therefore this initial part of the experimental curve does not represent a practical physiological situation. It is therefore justifiable to say that over the normal range of physiological variation, changes in blood volume will not affect the derived cytochrome signal. By repeating this experiment using a scattering medium which more closely mimics brain tissue, we hope to quantitate the overall non linearity of this response, and incorporate these results in the algorithm.

QUANTITATION OF CEREBRAL MIXED VENOUS SATURATION

Changes in HbO₂, HbR and HbT can be observed by tilting of an infant so that the head is raised or lowered with respect to the heart. Such a manoeuvre alters by a small amount, the hydrostatic pressure in both the cerebral arterial and venous compartments. Since the pressure change is small in comparison with mean arterial pressure, and the compliance of the blood vessels in the arterial system is low, it may reasonably be assumed that the blood volume change has occurred in the cerebral venous compartment. If this is so, then the mixed cerebral venous saturation (SvO₂) can be derived from the formula:

$$\% SvO_2 = \frac{\Delta HbO_2}{\Delta(HbO_2 + HbR)} \times 100$$

This calculation requires no assumption to be made regarding the mean optical path length through the tissues. The calculation is only valid if the cerebral blood flow and oxygen consumption remain constant during the manoeuvre. This is likely to be so if PaCO₂ and SaO₂ are stable during the tilting procedure. These conditions can be met by monitoring PaCO₂ with a transcutaneous electrode and SaO₂ with a pulse oximeter.

In practice, we have found the small tilt involved in the procedure (approximately 10°) does not disturb the infant, who will often sleep throughout the test. Figure 2 is a recording made during a head tilt on a full term infant with cystic encephalomalacia. In this infant

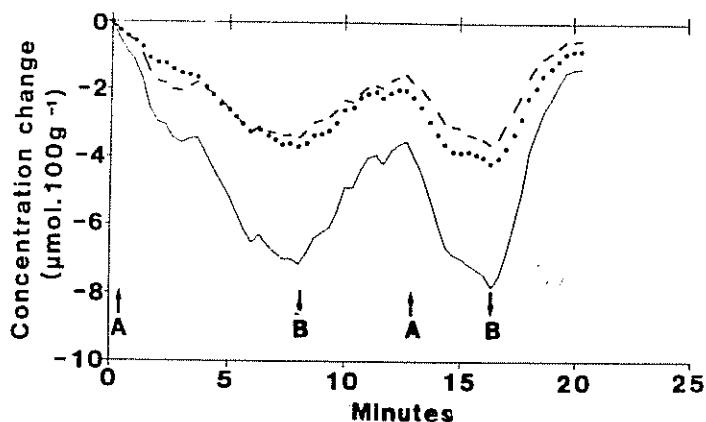


Fig. 2. Changes in HbO₂, HbR and HbT during tilting of an infant 10° head up at A, back to level at B and repeated. The infant was 9 weeks old having been born at term and had developed encephalomalacia following severe birth asphyxia.

the mean saturation was 66%. In a normal preterm infant, of 28 weeks gestation, studied at five weeks of age, the average SvO₂ was 38%.

QUANTITATION OF CEREBRAL BLOOD FLOW CHANGES

If arterial oxygen saturation is maintained at approximately 100%, then changes in HbR can be related to changes in cerebral blood flow. This assumes that cerebral oxygen consumption remains constant, which is likely to be true in normal preterm infants. In one infant studied in this way, cerebral blood flow was seen to increase linearly in response to changes in PaCO₂. If SaO₂ equals 100%, and SvO₂ is assumed to be 50%, then assuming arterial and venous compartments to be of equal volume, HbR constitutes 25% of HbT. Under these circumstances, the blood flow increases by approximately 9% per kPa. Figure 3 illustrates such a change in blood flow.

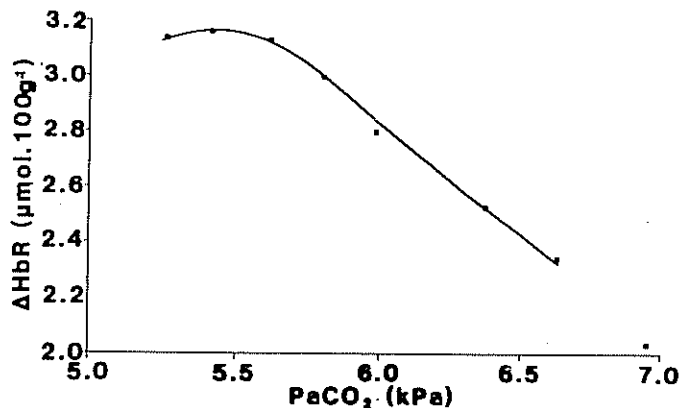


Fig. 3. Change in HbR in response to variation of PaCO₂ in a 2 day old infant born at 36 weeks of gestation with congenital myopathy. The SaO₂ was in the range 98-99% during the manoeuvre.

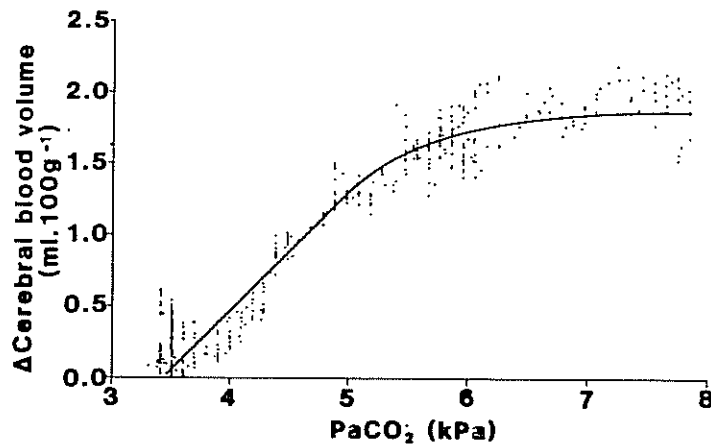


Fig. 4. Changes in cerebral blood volume with increasing PaCO₂ in a 3 day old infant showing a linear increase up to 5.5 kPa but no increase thereafter. He had been born at 39 weeks of gestation with *Listeria septicaemia* but had no evidence of cerebral abnormality.

QUANTITATION OF CEREBRAL BLOOD VOLUME

The sum of the HbO₂ and HbR signals will provide information on the instantaneous changes in cerebral blood volume. The cerebral blood volume changes significantly in normal infants in response to changes in PaCO₂. However in several infants with cerebral oedema, we have observed a very limited response to changes in PaCO₂. Figure 4 shows the changes in blood volume in an infant with *Listeria Septicaemia*, but no evidence of cerebral abnormality.

It is possible to quantitate cerebral volume in some circumstances by using additional information available on arterial saturation. If the cerebral blood flow, blood volume and oxygen consumption remain constant, then if SaO₂ is varied slightly, the same change in SaO₂ will occur in all blood compartments in the brain. A linear relationship will then be obtained between (HbO₂-HbR) and percentage SaO₂ (Figure 5). The cerebral blood volume (CBV) can be calculated from the slope of this relationship using the formula:

$$CBV = \frac{\Delta(HbO_2 - HbR)}{\Delta \% SaO_2} \times 50$$

Applying this relationship to clinical data on neonates results in volume estimates in the range of 3.0 to 17.0 ml/100g. (Brain tissue specific gravity is assumed to be 1.05 g/ml).

DISCUSSION

The algorithm used to convert nir absorption changes to concentration changes of HbO₂, HbR, etc, produces results expressed in terms of $\mu\text{mol/l}$ tissue multiplied by optical path length. When applying the quantitation techniques mentioned in this paper to clinical data, it is necessary to choose a value for this path length (the exception to this is the quantitation of cerebral mixed venous saturation, where no path length estimate is required). By operating in transmission mode, we

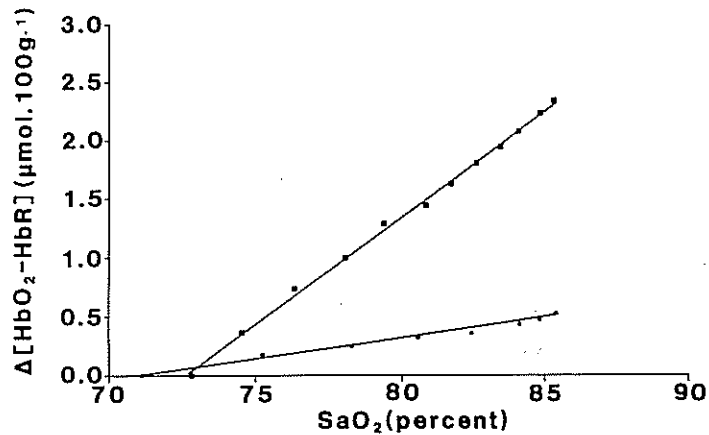


Fig. 5. Relationship between SaO₂ and [HbO₂ - HbR] at two different values of PaCO₂ ■ = 7.8 kPa, ● = 3.5 kPa. Same infant as Figure 4.

are able to place a lower limit on the optical path, (ie the optode spacing), and in this paper, that lower limit has been used. There is however some measured data on which to base an estimate of the upper limit for the path length, although as previously mentioned, it could also be calculated from the Monte Carlo model (7). We can estimate an upper limit by comparing the results obtained above for cerebral blood volume with normal data for human volunteers measured by alternative techniques. Although no data on baseline cerebral blood volume in human neonates has been published, values in adult volunteers obtained by various techniques have been within the range of 3 to 6 ml/100g (8,9). The values derived from nir data on normal neonates, assuming a path length equal to the optode spacing are in the range of 3.0-17.0 ml/100g. This implies an average optical path of 1.5 to 5 times the optode spacing, with a value of approximately 2.0 being most likely. If this is true, then one could apply this path length to the quantitation of data on cytochrome aa3.

CONCLUSION

Quantitation of near infrared spectroscopy data is normally not possible due to uncertainties over the optical path length through the tissues. We have shown that in some circumstances, quantitation is possible by comparing nir signal changes with those obtained from separate independent monitors of physiological variables. By comparing the results obtained in this way on normal patients with the expected normal values, it is possible to estimate the average optical path length through brain tissue.

ACKNOWLEDGMENTS

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