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Cerebral oxygenation and haemodynamics in the foetus and newborn infant

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SUMMARY

Quantitative techniques have been derived for the measurement of global cerebral blood flow, cerebral blood volume, its response to changing arterial carbon dioxide tension and mixed cerebral venous saturation in the human newborn undergoing intensive care. Normal ranges have been established and significant disturbances of cerebral oxygenation and perfusion have been demonstrated in a variety of pathological conditions. Recently, absolute cerebral deoxyhaemoglobin concentration has been obtained in the newborn using second differential spectroscopy. When combined with the measurement of total cerebral haemoglobin concentration, the mean saturation of cerebral blood ($SmcO_2$) may be obtained, allowing global cerebral oxygenation to be determined continuously in the intensive care unit.

Marked changes in the concentrations of cerebral oxy- and deoxyhaemoglobin have been observed in foetuses undergoing labour. Measurements of $SmcO_2$ from the foetal brain prior to delivery have shown the expected close correlation with acid–base status at birth. Although movement artefact remains a theoretical risk during uterine contractions, preliminary measurements of optical path length by intensity-modulated spectroscopy have demonstrated only small fluctuations. In future the clinical application of time, phase and spatially resolved spectroscopy is likely to improve both the quantitative accuracy and the regional specificity of physiological measurements in the foetal and neonatal brain.

1. INTRODUCTION

Despite improvements in perinatal care, hypoxic-ischaemic injury to the brain remains an important cause of death and permanent neurodevelopmental impairment in both term and preterm infants. Near-infrared spectroscopy (NIRS) has the potential to provide quantitative indices of cerebral oxygenation and perfusion in the sick infant undergoing intensive care and in the foetus undergoing labour. The aim of this article is to review the progress that has been made in establishing quantitative methodologies for investigating the newborn brain, discuss the unsolved problems that remain and briefly to assess the likely clinical implications of future technical developments in this rapidly changing area.

2. PRINCIPLES OF QUANTITATIVE SPECTROSCOPY

The total attenuation of near-infrared light that has traversed biological tissue is a complex function of absorption due to mobile and fixed chromophores and scattering. However, if it is assumed that background attenuation is constant during the course of an experiment, changes in attenuation from an arbitrary baseline must arise only from changes in the concentration of a small number of mobile chromophores, oxyhaemoglobin (HbO_2), deoxyhaemoglobin (Hb) and the Cooper A moeity of cytochrome oxidase. If the mean optical path length is known or can be estimated, changes in tissue chromophore concentrations from baseline (in mM) can be obtained from a modification of the Beer–Lambert relationship (Delpy *et al.* 1988; Wray *et al.* 1988).

By viewing HbO_2 and Hb as endogenous intravascular tracer molecules it is possible to derive methods to obtain global cerebral blood flow (CBF), cerebral blood volume (CBV), its response to changing arterial carbon dioxide tension (CBVR) and mixed cerebral venous saturation (SvO_2) in the human newborn undergoing intensive care (Edwards *et al.* 1988; Wyatt *et al.* 1990*a*, 1991; Skov *et al.* 1993; Yoxall *et al.* 1995). In each case the method involves the establishment of a stable haemodynamic baseline, the induction of a small and quantitative physiological disturbance, the measurement of changes in [HbO_2] and [Hb] from the previously established baseline and the application of a standard formula.

In the majority of neonatal studies performed to date, optical path length was estimated from the use of a differential path length factor obtained from previous time-of-flight measurements in postmortem infants (Wyatt *et al.* 1990*b*; Van der Zee *et al.* 1991). An estimate of path length is obtained by multiplying the distance between the transmitting and receiving optical fibre bundles by this constant.

The fundamental assumptions behind this methodological approach to quantitation must be examined to assess the possible sources of systematic errors. The tissue is assumed to be optically homogeneous with no regional variations in chromophore concentration or scattering characteristics. It is assumed that there are only three chromophores present in variable con-

centrations, and the spatial distribution of the chromophores, in particular [HbO_2] and [Hb], is assumed to remain constant despite the induced changes in physiological variables. There must be no contribution to the NIRS signal from extracerebral haemoglobin, no change must occur in the physical geometry of the transmitting and receiving fibre bundles during each experiment, and tissue scattering characteristics must remain constant. It is clear that real-world deviations from these assumptions are likely to lead to significant errors in the quantification of haemodynamic variables, and the analysis of systematic errors will be an important area for ongoing research.

3. NIRS STUDIES IN NEWBORN INFANTS

A number of groups have obtained quantitative measurements from the brain in newborn infants undergoing mechanical ventilation and intensive care. Measurement of global CBF depends on the induction of a rapid increase in arterial oxygen saturation, induced by a rapid change in the inspired oxygen concentration. The small additional bolus of HbO_2 acts as an intravascular tracer and using the Fick principle, CBF is obtained from the immediate rise in cerebral [HbO_2] (Edwards *et al*. 1988; Elwell *et al*. 1992).

Measurements of CBF in very preterm infants undergoing intensive care have shown a remarkably wide range of values, from 5 to 30 ml 100 g^{-1} min^{-1}. Appropriately grown very preterm infants demonstrated a consistent rise in CBF over the first three days of life, probably representing a normal adaptive response of the cerebral circulation to delivery (Meek *et al*. 1995). By contrast, there was no evidence of a similar consistent pattern in a group of infants with objective evidence of intrauterine growth failure. Some of these growth-retarded infants had an elevated CBF on the first day of life, possibly indicating cerebral vasodilatation secondary to prolonged intrauterine hypoxia.

In one recent study no relationship between CBF and mean arterial blood pressure was found, suggesting that autoregulation of cerebral perfusion may remain intact at very low arterial blood pressures between 24 and 30 mm Hg (Tyszczuk *et al*. 1995). Although it seems highly likely that there is a critical lower limit of CBF required for substrate delivery to maintain cellular integrity, this has not yet been defined.

The measurement of CBF involves additional assumptions, which have been discussed elsewhere (Elwell *et al*. 1992). It is assumed that the small additional bolus of intravascular oxyhaemoglobin acts as a biologically inert tracer molecule and that there is no alteration in CBF, CBV or cerebral oxygen extraction during the experiment. Although these assumptions appear to be accurate in many infants, some individuals demonstrate marked changes in total cerebral haemoglobin concentration with small variations in arterial saturation (Livera *et al*. 1991; Wolf *et al*. 1996). Measurements must also be made within the cerebral transit time. An additional limitation is that in some infants with severe lung disease a satisfactory step-change in arterial saturation cannot be achieved. Conversely, in infants with normal lungs, saturation may approach 100% while breathing room air.

Despite these methodological limitations, two validation studies comparing NIRS measurements of CBF with the intravenous ^{133}Xenon technique have indicated reasonable accuracy (Skov *et al*. 1991; Bucher *et al*. 1993), although higher CBF values were underestimated by NIRS, probably due to shortening of the cerebral transit time. The use of indocyanine green as an exogenous intravascular tracer for CBF measurements has recently been described (Roberts *et al*. 1993; Patel *et al*. 1996).

Cerebral blood volume is measured using the indicator dilution principle by observing the effect on cerebral [HbO_2] of a small and slowly induced change in arterial saturation (Wyatt *et al*. 1990*a*). The absence of an acceptable comparison method for use in newborn infants has meant that no direct validation of this method in the neonate has yet been published. However, NIRS measurement of changes in CBV, induced by jugular venous occlusion, showed a reasonable correlation with strain gauge plethysmography (Wickramasinghe *et al*. 1992).

Changes in cerebral blood volume may be determined from alterations in the total cerebral haemoglobin concentration (obtained from the sum of the HbO_2 and Hb signals). This method has been used to measure the response of the cerebral circulation to changes in arterial carbon dioxide tension (Pryds *et al*. 1990; Wyatt *et al*. 1991). Discrepancies have been observed between the change in CBV calculated by this method and CBV derived by the indicator dilution technique (Brun *et al*. 1994). This discrepancy is unexplained, but it is likely to be due to deviation from the underlying assumptions of optical homogeneity as a result of a change in carbon dioxide tension.

Cerebral venous saturation may be estimated from an induced manoeuvre that causes a change in the size of the venous compartment without a significant effect on the remainder of the cerebral circulation. This may be produced by tilting of the body (Skov *et al*. 1993) or by partial jugular venous occlusion (Yoxall *et al*. 1995). This latter method has been validated in infants undergoing cardiac catheterization by comparison with measurements of SvO_2 obtained from blood samples from the jugular bulb.

The use of these quantitative methodologies enables conventional NIRS spectrometers to be employed as a research tool to investigate cerebral haemodynamics in infants undergoing intensive care. However, a major limitation of this technology is the inability to determine optical path length directly at the bedside, raising the possibility of significant errors from the use of a fixed differential path length factor (see below).

4. NIRS STUDIES IN THE FOETUS

A number of preliminary studies have demonstrated the feasibility of obtaining quantitative information about cerebral oxygenation in human foetuses undergoing labour (Peebles *et al*. 1992; Faris *et al*. 1994). Using a specially designed flexible probe that may be

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inserted through the dilated cervix following rupture of the amniotic membranes, continuous measurements of oxy- and deoxyhaemoglobin may be obtained throughout labour. The probe is maintained in position on the foetal scalp by suction.

Large changes in cerebral haemoglobin concentration are observed during uterine contractions, due to the effect of the mechanical forces of labour on the foetal cranium (Peebles *et al*. 1994). Mean cerebral saturation ($SmcO_2$) may be estimated from the ratio of oxy- and deoxyhaemoglobin in the blood entering and leaving the field of illumination. In a study of 31 infants undergoing uncomplicated labour $SmcO_2$ measured within 30 min of delivery had a wide range of 22–73 % (Aldrich *et al*. 1994). However, a close correlation with umbilical cord acid–base measurements at delivery was observed. These preliminary observations suggest that measurement of $SmcO_2$ during labour may be of value for intrapartum foetal surveillance, provided the reliability of these observations is validated in large-scale clinical trials. However, anxieties about the possibility that NIRS measurements during labour may be influenced by movement artefact have been expressed (Hamilton *et al*. 1995). To investigate this issue we have employed intensity-modulated optical spectroscopy using apparatus designed and built at University College London (Duncan *et al*. 1993). Preliminary observations in three foetuses have indicated that path length changes during uterine contractions are small (unpublished observations). Although these results need to be verified in larger studies, they suggest that it is unlikely that major errors will result from movement of the optical probe or from path length changes during uterine contractions.

5. SECOND DIFFERENTIAL SPECTROSCOPY

The use of a white light source and a wideband spectrometer coupled to a sensitive light detector for investigation of the infant brain has recently been described (Cooper *et al*. 1996). This technique has several advantages. First, because data are obtained simultaneously at a large number of discrete wavelengths, curve-fitting techniques can be used to improve the accuracy of chromophore measurements. This is particularly useful in determining changes in the redox state of cytochrome oxidase. Second, by employing second differential spectroscopy, the optical path length can be measured continuously using the absorption peak due to tissue water (Matcher *et al*. 1993), and absolute cerebral [Hb] is estimated from the unique spectral features of the deoxyhaemoglobin spectrum (Matcher & Cooper 1994). Preliminary results in 19 newborn infants gave a mean differential path length factor of 3.91 ± 0.75 and a mean deoxyhaemoglobin concentration of $14.6 \pm 4.0\ \mu M$ (Cooper *et al*. 1996).

By combining these measurements with the calculation of total haemoglobin concentration, the mean saturation of blood within the brain can be obtained, providing a continuous and potentially useful index of the adequacy of cerebral oxygen delivery. Thus this technique enables both cerebral oxygen saturation and blood volume to be measured continuously at the bedside, allowing the effects on the brain of clinical interventions, such as changes in ventilator settings or inotrope infusions, to be assessed in real time.

A similar technique has recently been applied to an experimental newborn animal model of delayed energy failure following transient hypoxia-ischaemia (Springett *et al*. 1996). Marked cerebral vasodilation with a rise in mean cerebral saturation was seen during the development of delayed cerebral energy failure. A progressive decline in the redox state of cytochrome oxidase correlated very closely with simultaneous measurements of adenosine triphosphate concentrations made by phosphorus magnetic resonance spectroscopy. These data suggest that wideband NIRS may be capable of providing quantitative information on cerebral energetics as well as oxygenation.

6. NIRS IMAGING OF THE NEONATAL BRAIN

Development of NIRS apparatus designed to generate two-dimensional images of cerebral absorption and scattering is taking place very rapidly. Van Houten *et al*. recently described the first use of an imaging spectrometer capable of providing a two-dimensional image of the neonatal brain, although the collection of a single image took several hours (Van Houten *et al*. 1996). Within the next few years it is likely that multichannel imaging spectrometers will become widely available, enabling detailed spatial information on cerebral oxygenation and perfusion to be obtained rapidly and conveniently at the bedside.

7. CONCLUSIONS

NIRS has obvious potential as a practical tool for the investigation of cerebral haemodynamics. Although conventional spectrometers are capable of providing valuable quantitative information, further work is required to gain an improved understanding of the origin of observed discrepancies in NIRS data. In future the clinical application of time, phase and spatially resolved spectroscopy is likely to improve both the quantitative accuracy and the regional specificity of physiological measurements in the foetal and neonatal brain.

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