

Abnormal cerebral haemodynamics in perinatally asphyxiated neonates related to outcome

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Abstract

Aim—To measure changes in cerebral haemodynamics during the first 24 hours of life following perinatal asphyxia, and relate them to outcome.

Methods—Cerebral blood volume (CBV), its response (CBVR) to changes in arterial carbon dioxide tension (PaCO₂), and cerebral blood flow (CBF) were measured using near infrared spectroscopy (NIRS) in 27 term newborn infants with clinical and/or biochemical evidence consistent with perinatal asphyxia.

Results—Both CBF and CBV were higher on the first day of life in the infants with adverse outcomes, and a CBV outside the normal range had a sensitivity of 86% for predicting death or disability. The mean (SD) CBVR on the first day of life was 0.13 (0.12) ml/100 g/1/kPa, which, in 71% of infants, was below the lower 95% confidence limit for normal subjects.

Conclusion—An increase in CBV on the first day of life is a sensitive predictor of adverse outcome. A reduction in CBVR is almost universally seen following asphyxia, but is not significantly correlated with severity of adverse outcome.

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Keywords: perinatal asphyxia; cerebral haemodynamics

Despite advances in obstetric and neonatal care, perinatal asphyxia as a result of critical impairment of intrapartum gas exchange is still a significant cause of hypoxic-ischaemic brain injury in term newborn infants. Early assessment of the degree of resulting hypoxic-ischaemic encephalopathy (HIE) can provide prognostic information for both clinical management and the potential use of cerebroprotective strategies.¹⁻³ However, clinical assessment is often difficult because the neurological state of the infant may be altered by pharmacological interventions such as sedation, muscle relaxation, or anticonvulsant treatment. Moreover, clinical signs of HIE may not develop until at least 12 hours after birth. Conventional perinatal variables such as Apgar score and cord pH (originally intended as measures of condition at birth) are not specific predictors of adverse outcome.^{4 5}

Several techniques are now available for use at the cotside in the first few hours of life, to assess the extent of HIE and provide prognostic information. These include electrophysiological methods such as electroencephalography (EEG), cerebral function monitoring

(CFM), and visual evoked potentials (VEP)^{6 7}; or ultrasound techniques, including Doppler flow velocity measurements and two dimensional imaging.⁸ Magnetic resonance spectroscopy also yields accurate prognostic information,⁹ but cannot be applied at the cotside outside specialised centres.

Measurements using cranial Doppler ultrasonography suggest that increased cerebral blood flow velocity and a low cerebral artery pulsatility index are present after asphyxia,^{10 11} but these are predictive of a poor outcome only in some studies. The loss of response of CBF measured by the Xenon clearance technique to changes in PaCO₂ is a useful marker of outcome.¹² These studies have also shown increased global CBF, with the loss of autoregulation of CBF with changing blood pressure, but the technique involves ionising radiation and is not widely available.

Near infrared spectroscopy (NIRS) permits cotside measurement of cerebral haemodynamics in babies undergoing intensive care.¹³ Absolute values of CBV, CBVR, and CBF can be measured directly and quickly without interrupting the routine care of the infant. Increased CBV after perinatal asphyxia has been shown before, using NIRS.¹³ Van Bel *et al*¹⁴ followed trends in cerebral haemodynamics and oxygenation in the first 24 hours after birth asphyxia, but few data have been published on the relation between haemodynamic variables and outcome. In this study CBV, CBVR, and CBF were measured in a group of asphyxiated infants in the first three days of life and related to outcome at 1 year of age.

Methods

Approval for NIRS studies of asphyxiated infants was granted by the University College London Faculty of Clinical Sciences Committee on the Ethics of Clinical Investigation, and parental consent was obtained before the study.

Twenty seven neonates born at 36 to 44 weeks of gestation were studied. They were admitted to the neonatal unit at University College London Hospital and studied within 24 hours of birth. To be eligible for study, each infant had to have a clinical history consistent with perinatal asphyxia, and either clinical signs of moderate or severe HIE (Sarnat grade II or III), or biochemical evidence of perinatal asphyxia (base excess ≤ 15 mmol/l on umbilical vessel blood gas sampling or on the first arterial blood gas sample acquired after admission). The study did not include every eligible infant, as it was not always possible to include

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Table 1 Clinical details of infants studied

	GA	pH	BE	Sarnat	Ventilation	Cranial ultrasound	Outcome	PaCO ₂ (kPa)	NIRS studies
1	37	6.8	-30	II	IPPV	Oedema	Early death	4.4	CBVR
2	41	6.9	-25	III	IPPV	Oedema	Early death	4.5	CBV, CBVR
3	39	6.9	-29	III	IPPV	Oedema	Early death	4.5	CBVR
4	36	7.0	-24	III	IPPV	Oedema	Early death	5.2	CBV, CBVR, CBF
5	43	N/K	-26	III	IPPV	Oedema	Early death	4.1	CBVR
6	39	6.5	-32	III	IPPV	Oedema	Early death	5.3	CBV, CBVR, CBF
7	36	7.0	-23	III	IPPV	Oedema	Early death	4.1	CBV, CBVR
8	42	6.8	-22	II	Spontaneous	Normal	Late death	4.0	CBV, CBF
9	40	7.2	-16	II	IPPV	Normal	Late death	4.0	CBV, CBVR
10	42	7.0	-18	III	IPPV	Oedema	Late death	3.0	CBV, CBVR, CBF
11	38	6.7	-30	III	IPPV	Normal	Late death	4.3	CBV, CBVR
12	39	6.8	-18	III	IPPV	Oedema	Late death	4.8	CBV, CBVR
13	40	6.9	N/K	II	CPAP	Bright caudate nucleus	Impairment with disability	5.3	CBVR
14	38	6.8	-26	III	IPPV	Oedema	Impairment with disability	9.1	CBV, CBVR
15	44	7.1	-9	II	IPPV	Oedema	Impairment with disability	5.5	CBV, CBVR, CBF
16	41	7.1	-18	II	IPPV	Oedema	Impairment with disability	4.3	CBV, CBVR
17	40	7.2	-22	II	IPPV	Oedema	Impairment with disability	3.2	CBV, CBVR
18	36	7.1	-17	II	IPPV	Normal	Impairment, no disability	4.5	CBV, CBVR, CBF
19	38	6.7	-23	II	IPPV	Normal	Impairment, no disability	4.8	CBV, CBVR
20	40	7.0	-14	N/K	IPPV	Normal	Impairment, no disability	3.6	CBV, CBVR
21	39	6.7	-29	II	IPPV	Normal	Impairment, no disability	5.3	CBV, CBVR
22	42	7.1	-19	I	Spontaneous	Normal	Impairment, no disability	4.8	CBV, CBF
23	43	7.1	-14	II	Spontaneous	Normal	Normal	4.0	CBVR
24	42	7.2	-18	I	Spontaneous	Normal	Normal	6.0	CBV, CBF
25	40	7.1	-15	II	Spontaneous	Oedema	Normal	4.2	CBV, CBVR
26	38	7.2	-20	II	IPPV	Normal	Normal	6.1	CBV, CBVR
27	36	6.8	-16	N/K	IPPV	Normal	Normal	5.2	CBVR, CBF

GA gestational age (weeks); BE base excess mmol/l; N/K not known.

those in both MRS and NIRS studies during the first 24 hours of life.

The theory of NIRS has been described in detail elsewhere.¹⁵ The application of the technique to the measurement of CBV, CBVR,¹⁶ and CBF¹⁷ is described in the Appendix. In this study either an NIR1000 or NIRO500 spectrophotometer (Hamamatsu Photonics KK, Japan) was used, with a differential path length factor (DPF) of 5.13.¹⁸ Data were accepted for analysis for CBV, CBVR, and CBF according to previously established criteria.¹⁹

Infants were studied while undergoing intensive care, with simultaneous monitoring of SaO₂ (Novamatrix 505 or Nellcor N200) and mean arterial blood pressure via a transducer in an indwelling umbilical or peripheral arterial line or by an oscillometric technique, using an inflatable cuff (Dinamap 1846SX, Critikon). Continuous measurement of PaO₂ and PaCO₂ using a transcutaneous monitor (Novamatrix model 850 or Hewlett Packard 78834A) calibrated with arterial blood gas samples was also carried out. The arterial haemoglobin concentration of each infant was measured on the day of each study. Cranial ultrasound scans (Ultramark 4, Advanced Technical Laboratories, Letchworth, UK) were performed daily. Surviving infants underwent detailed neurodevelopmental assessment at the age of 1 year, according to the protocol described by Roth *et al.*²⁰ They were assessed by a paediatrician and a psychologist who were blind to the NIRS data, using a structured neurological examination,²¹ and the Griffiths Developmental Scale. Throughout the assessment particu-

lar attention was paid to vision and hearing. Neurodevelopmental status was assigned according to the presence of impairments. Impairments with disability included those of neuromotor function, sensorineural hearing loss requiring amplification, blindness or partial sightedness in one or both eyes, and a Griffiths General Quotient of less than 70. Impairments without disability were usually identified on neurological examination and included abnormalities of tone and reflexes. Children with no detectable neurodevelopmental impairment were designated normal.

Infants who died within one week of birth were described as early deaths, to distinguish them from those who died after one week.

Results

Of the 27 study infants, 10 had severe (Sarnat III), 13 moderate (Sarnat II), and two mild encephalopathy (Sarnat I) (table 1). In two infants the grade of encephalopathy could not be assessed because they were mechanically ventilated with muscle relaxation from an early stage. The median gestational age of the group was 40 (range 36–44) weeks and the median birthweight 3.23 (range 1.88–4.23) kg. Fourteen infants had evidence of cerebral oedema on cranial ultrasound examination during the neonatal period, and one had a region of increased echodensity in the right caudate nucleus. Infants were studied on 1–4 (median 2) occasions between 2 and 72 hours of age. Every infant was studied within the first 24 hours.

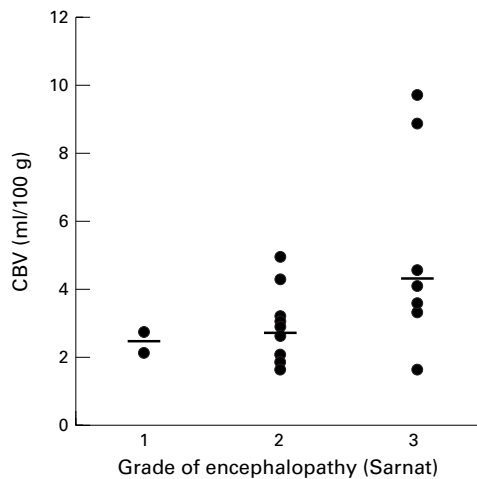


Figure 1 CBV on the first day of life as a function of grade of encephalopathy. Median values of CBV for each grade of encephalopathy are shown by horizontal bars.

Twelve infants died—seven within the first week. Of the 15 surviving infants, five were making normal progress at 1 year of age and five had impairments without disability. Five children had multiple disabling impairments, including those of neuromotor and overall developmental delay (Griffiths GQ < 70). Two of these disabled infants died after the first year of life. Table 1 summarises the clinical details of the infants in the study, including the mean PaCO₂ of each infant.

CBV was measured during the first 24 hours of life in 21 infants. The median (range) CBV in the infants with severe encephalopathy was 4.4 (1.7–9.7) which was significantly higher ($p=0.003$ Mann Whitney U test) than in infants with moderate encephalopathy, 2.8 (1.7–4.9) ml/100 g. The variation of CBV with grade of encephalopathy is shown in fig 1. Figure 2 shows the relation between CBV and outcome. Although there was a trend towards increased CBV in the poor outcome groups, the differences did not achieve significance. However, considering a cutoff for CBV of greater than 2.6 ml/100 g (2 SD above the CBV

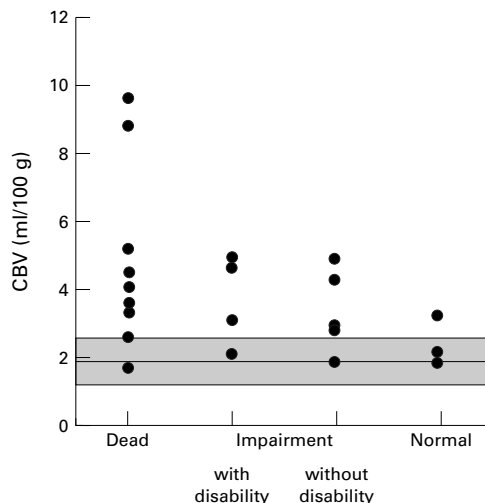


Figure 2 CBV on the first day of life for different outcomes at 1 year of age. Shaded area represents mean (2 SD) CBV measured previously in normal infants.¹³

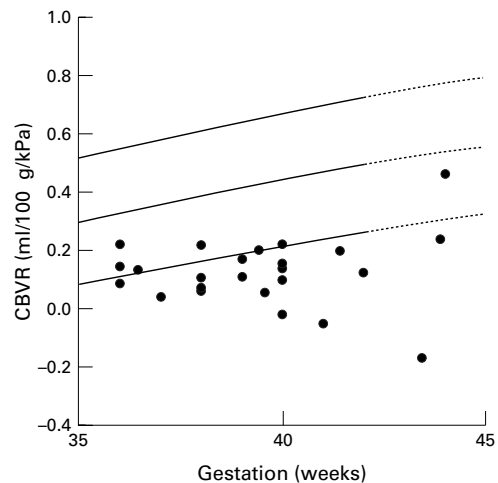


Figure 3 Variation of CBVR with gestational age. Comparison of data from perinatally asphyxiated infants on the first day of life (circles) with previously published normal data¹⁶ (lines denote best fit and 95% confidence limits).

measured in healthy neonates¹³ corrected for a DPF of 5.13), the sensitivity for an outcome of death or disability at one year was 85%, the specificity 38%, and the positive predictive value 69%.

Satisfactory measurements for CBVR were obtained in 24 of the infants studied on day 1, and in 12 infants on days 2 or 3. The mean CBVR for the group on the first day was 0.13 (0.12) ml/100 g/kPa. This is lower than previously published values for normal infants which ranged from 0.37 (0.19) ml/100 g/kPa at 36 weeks to 0.51 (0.21) ml/100 g/kPa at 42 weeks. Figure 3 compares the CBVR measured in the 24 asphyxiated infants in the present study on the first day of life with previously published normal data,¹⁶ corrected for a path length factor of 5.13. In 17 out of the 24 asphyxiated infants the CBVR was below the lower 95% confidence limit for the normal subjects. When compared with the expected distribution of the normal data this gives a χ^2 value of 57.6 ($p < 0.001$).

The mean CBVR on the second or third day of life was 0.33 (0.26) ml/100 g/kPa. This was significantly higher than on the first day for the whole group ($p=0.012$, Mann-Whitney U test), so that the attenuation of CBVR was seen most clearly during the first 24 hours of age. The median (range) CBVR for each outcome group on the first day compared with that of subsequent days is shown in table 2. There was no significant correlation between CBVR and either grade of encephalopathy or severity of outcome.

Satisfactory measurements of CBF on the first day of life were obtained in only nine infants, because of the difficulty in achieving a rapid increase in arterial saturation in many infants. The relation between CBF and outcome is shown in table 3. There is a clear trend towards increasing CBF in infants with the most adverse outcome, but the results did not reach significance.

Table 2 Relation of CBVR to outcome

Outcome	CBVR on day 1 median (range) ml/100 g/kPa	N =	CBVR day 2 or 3 median (range) ml/100 g/kPa	N =
Normal	0.12 (0.13)	4	0.38 (0.48)	2
Impairment without disability	0.14 (0.05)	4	0.17	1
Impairment with disability	0.10 (0.49)	5	0.19 (0.16)	3
Late death	0.13 (0.13)	4	0.16 (0.55)	3
Early death	0.17 (0.15)	7	0.44 (0.88)	3
Mean (SD) for all infants	0.13 (0.12)		0.33 (0.26) (p=0.012)	

No significant differences between outcome groups on day 1
No statistical analysis for individual groups on days 2 or 3 because of small numbers.

Table 3 Relation of CBV and CBF on day 1 to outcome

Outcome	CBV median (range) ml/100 g	N =	CBF median (range) ml/100 g/min	N =
Normal	2.2 (1.9–3.2)	3	21.2 (19.6–22.8)	2
Impairment without disability	2.9 (1.9–4.9)	5	15.5 (11.4–19.6)	2
Impairment with disability	3.9 (2.1–4.9)	4	33.2	1
Late death	3.4 (1.7–5.3)	5	20.5 (20.4–20.6)	2
Early death	6.7 (4.1–9.7)	4	59.7 (57.2–62.1)	2

Discussion

The haemodynamics in term infants with acute encephalopathy are deranged during the first 24 hours after presumed perinatal asphyxia. These consist of an increase in CBV and a significant reduction in CBVR compared with previously established control data. CBVR tended to return to normal values after the first 24 hours of age. CBV and CBF were frequently increased in the first 24 hours after birth, and there was a trend for this increase to be associated with greater severity of acute encephalopathic signs and an increased risk of adverse outcome. These results are consistent with observations that following an acute hypoxic-ischaemic insult there is abnormal control of cerebral haemodynamics with a combination of vasodilatation and vasoparalysis.¹⁵

The assumptions underlying the use of NIRS to measure CBV and CBF have been discussed elsewhere.¹⁹ The use of a constant value for the DPF assumes that there is no change in cerebral optical path length as a result of a hypoxic-ischaemic insult. Although small changes in scattering properties of brain tissue may occur following asphyxia, they would be very unlikely to account for the observed increases in CBV and CBF. An average reduction in DPF of over 50% in the asphyxiated infants would be needed to produce changes of this magnitude. Although the extent of cerebral oedema associated with asphyxia is variable,²² data from 7 day old rats suggest that the maximum change of cerebral water content after asphyxia is of the order of 3%.²³ Measurements using NIRS on asphyxiated newborn piglets suggest that significant changes in optical path length do not occur until late into secondary energy failure, rather than during the first 24 hours.²⁴

Brun and Greisen²⁵ have reported discrepancies in the measurement of CBV obtained from changes in Hb_{sum} compared with an alternative method involving comparison of CBV measurements at different values of PaCO₂. The reason for these discrepancies is not clear, but they do not affect the validity of the results reported here, as we used identical methods for measurement of CBV and CBVR in both the

asphyxiated infants and the normal infants on whom data have been published before.

The measurement of CBV and CBF was restricted to those infants in whom small changes in SaO₂ could be induced by adjusting the FIO₂. This excluded infants who were well saturated in air, or who were ventilated with 100% oxygen. As a result, CBF measurements were obtained in only nine out of 26 subjects. The CBF technique has been adapted using cardio-green as an NIR absorbing tracer,²⁶ and this might allow measurements to be obtained from a wider group of subjects.

Our data indicate that the most severely affected infants tended to have the greatest degree of cerebral hyperaemia. Acute hypoxia-ischaemia releases several vasoactive agents. These include extracellular hydrogen and potassium ions, adenosine, prostaglandins and nitric oxide (NO). Possible mechanisms for the coupled response of vasodilatation and abolished CBVR include a disturbance in prostanoid metabolism following brain injury and an increased production of nitric oxide. Vasodilatory prostaglandins, especially PGE₂ are increased after asphyxia²⁷ and prostanoids may have a role in the regulation of endothelial CO₂ reactivity.²⁸

The role of NO in postasphyxial hyperaemia is not clear. Evidence from animal work suggests that NO is implicated in vasodilatation due to both hypercapnia and ischaemia. Rats treated with nitric oxide synthase (NOS) inhibitors display decreased CBF response to changes in PaCO₂.²⁹ Models using carotid artery occlusion in rats have shown that NO radicals are formed during ischaemia.³⁰ Marks *et al*^{31,32} have shown two phases of vasodilatation after carotid artery occlusion in fetal lambs, with analogous biphasic alterations in the EEG and cerebral impedance (which reflects impaired energy metabolism). In this model NOS inhibitors attenuated only the delayed phase of vasodilatation, and resulted in a worse histological outcome. However, experiments in healthy newborn piglets have failed to show significant suppression of CBVR by an NOS inhibitor,³³ or of the CBF response to changing PaCO₂.³⁴ Thus it is not clear that the role of NO as a regulator of cerebral haemodynamics is identical in the adult rat and newborn animals or babies.

When the neonatal brain is subjected to hypoxia, hypotension, and ischaemia, other vasodilators are produced, adenosine being the most potent.³⁵ It can regulate CBF in the healthy neonatal piglet,³⁶ and is probably a factor in the vasodilatation observed in asphyxiated infants.

Although most of the severely asphyxiated infants had increased CBV in this study, CBV values ranged widely from 1.7 to 9.7 ml/100 g in the infants who died. This variability was not related to the timing of the measurements after birth. A subgroup of severely asphyxiated infants had low CBV values, either because of a failure to reperfuse the brain on resuscitation, or a fall in CBV after the initial rise caused by increasing intravascular pressure related to cerebral oedema. Poor contractility of the injured

myocardium may have led to decreased cerebral perfusion and hence attenuated the increase in CBV in some infants.

Eleven infants had clinical seizure activity during the first three days of life, which is associated with increased cerebral blood flow velocity.³⁷ Cerebral function monitoring was not routinely performed during the NIRS studies, but seizures were unlikely to have been a major confounding factor, as the infants with the most severe encephalopathies (who were more likely to have grossly reduced electrical activity) had the highest values of CBV.

An association between deranged cerebral haemodynamics and cellular energy failure following asphyxia is implied in this study by the correlation of CBV both with grade of encephalopathy and with outcome. Metabolic data have been obtained from both animals and human infants using magnetic resonance spectroscopy (MRS), where both phosphorus and hydrogen spectroscopy were used to measure markers of cerebral energy failure which correlate with neurodevelopmental outcome.^{9,38} Simultaneous NIRS and MRS studies in newborn piglets subjected to hypoxic-ischaemic insults have shown a close correlation between the rise in [HbO₂] and MRS markers of cerebral energy failure.³⁹

NIRS has also been used to measure concentration changes in cytochrome oxidation (CuA),⁴⁰ and a reduction in CuA has been suggested as a marker of abnormal cellular energetics. Studies in piglets have shown a close association between changes in [CuA] and MRS measures of energy failure,^{40,41} and a fetal lamb model has been used to relate the decrease in cytochrome signal to the degree of histological cell damage resulting from cerebral ischaemia.³¹ The time course of the [CuA] change mirrors the onset of secondary energy failure. In a clinical setting the measurement of cellular damage by this method would involve prolonged periods of spectroscopy, preferably from the time of the asphyxial insult. This was not attempted during the present study.

The clinical use of CBV measurements as an early marker of the severity of perinatal asphyxia is of limited value. Although the sensitivity of a raised CBV for a poor outcome is 85%, specificity is low. The positive predictive value of a raised CBV for death or disability at 1 year is 69%. Recent technical advances have expanded the use of NIRS to measure changes in cerebral venous HbO₂ saturation,⁴² oxidised cytochrome concentration, optical path length and absolute haemoglobin concentration,^{18,43} so that it may be possible in the future to combine measurements, to improve the accuracy of prediction in asphyxia.

We conclude that abnormalities of cerebrovascular control mechanisms are present after perinatal asphyxia, and that these may be prognostically important. In particular, an increase in CBV is a sensitive, although not highly specific, predictor of adverse outcome. A reduction in CBV is almost universal in encephalopathic infants following perinatal asphyxia, although it is not related to the severity of adverse outcome. The non-invasive measure-

ment of early hyperaemia at the cotside may be a useful adjunct to other modalities in the assessment of perinatally asphyxiated neonates.

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Appendix

MEASUREMENT OF CBV

Total CBV was measured by inducing a slow small change in arterial oxygen saturation within the range

92% to 98% by manipulation of the inspired oxygen concentration and determining the resulting change in [HbO₂] concentration. CBV was then obtained from the following formula:

$$CBV = k_1 \Delta([HbO_2] - [Hb]) / (2 \times \Delta SaO_2 \times H) \quad (13)$$

where H is the large vessel haemoglobin concentration in g/dl and k₁ is a constant which includes brain tissue density, the molecular weight of haemoglobin, and the cerebral:large vessel haematocrit ratio. No measurements were possible in those infants who maintained normal SaO₂ values while breathing room air, or for those who were ventilated with 100% oxygen.

MEASUREMENT OF CBVR

CBVR was assessed by inducing small changes in PaCO₂ of about 1-2 kPa and measuring the resulting changes in total haemoglobin concentration ($\Delta[Hb_{sum}] = \Delta[HbO_2] + \Delta[Hb]$). The induced change in PaCO₂ was in the direction of normality, so that PaCO₂ was maintained within the clinically accepted range (4-7 kPa). If the infant was receiving intermittent mandatory ventilation either the ventilation rate or the deadspace was changed, while manipulating the inspired oxygen fraction (FIO₂) to maintain a constant SaO₂. With spontaneously breathing infants, a mixture of air with 5% CO₂ (BOC Gases, Surrey Research Park, Guildford, UK) was supplied into a headbox via a funnel placed a few centimetres from the face. The change in PaCO₂ was determined using a transcutaneous sensor calibrated with a prior arterial blood gas sample. Changes in CBV in ml/100 g were calculated from changes in [Hb_{sum}] in $\mu\text{mol/l}$ from the formula:

$$\Delta CBV = k_1 \Delta [Hb_{sum}] / H$$

The CBVR (change in CBV per kPa change in PaCO₂) in ml/100 g/kPa was then obtained by plotting changes in [Hb_{sum}] against PaCO₂ for each study and performing a least squares regression.

MEASUREMENT OF CBF

CBF was measured using a modified Fick principle, with [HbO₂] as an intravascular tracer.¹⁷ A rapid rise in SaO₂ was induced by a step increase in FIO₂. CBF in ml/100 g/1/min was then calculated from the integral of the saturation rise and the rate of the rise of tracer using the equation:

$$CBF = k_2 \Delta [HbO_2] / (H \times \int \Delta SaO_2 \cdot dt)$$

where k₂ is a constant incorporating brain tissue density and the molecular weight of haemoglobin. This technique was only used for infants who were oxygen dependent.