

CURRENT TOPICS

Cerebral blood flow in the newborn infant

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Abnormal cerebral haemodynamics seem to be a significant cause of morbidity and mortality in newborn infants.¹ However, our understanding of cerebral blood flow (CBF) in this age group remains relatively unsophisticated, and still relies heavily on data obtained from studies of animals or adults. This paper examines the merits and difficulties of methods available for measuring CBF in the newborn, and reviews some current concepts concerning perinatal cerebrovascular physiology.

Quantitative estimation of cerebral blood flow

Most methods for CBF measurements in humans are based on the Fick principle, which states that the rate of accumulation of a tracer molecule in an organ (dQ/dt) is equal in the difference between the rate of delivery and the rate of removal of that tracer. The rate of delivery is the product of the blood flow to the organ (F) and the arterial concentration (C_a), and similarly the rate of removal is the product of blood flow and venous concentration (C_v). Thus $dQ/dt = (F \cdot C_a) - (F \cdot C_v)$, and for the brain, by rearrangement:

$$CBF = \frac{dQ}{(C_a - C_v) dt} \quad (1)$$

As well as accumulation of tracer, the clearance of tracer (which is merely negative accumulation) can be used to measure flow. However, use of the Fick principle involves important assumptions: the substance must be neither consumed by, nor be produced in, the organ; the flow must be constant during the measurement period; and tracers must be either fully diffusible or completely non-diffusible.

THE ¹³³Xe CLEARANCE TECHNIQUE

This depends on the rate of clearance of an inert radioactive tracer from the brain. ¹³³Xe is administered via either the carotid artery, the inspiratory gas, or a vein, in sufficient quantity to diffuse into the cells of the brain. As it is not metabolised, it can then only be removed from the brain by diffusing back into the blood, and the rate of clearance is proportional to CBF. The brain clearance ($-dQ$) can be detected by external scintillators placed over the skull and information on global or focal CBF is obtained.

Because the tracer is fully diffusible, C_v equals $Q(t) \cdot \lambda$, where λ is the blood-brain partition coefficient. As 90% of the ¹³³Xe is cleared during each pass through the lungs, C_a is close to zero. Any significant recirculation of the tracer which makes C_a non-zero can be estimated from the activity in the expired air or by placing a detector over the chest, as alveolar gas is in equilibrium with pulmonary venous blood. A typical clearance curve is shown in fig 1.

The ¹³³Xe clearance technique can be performed in the neonatal unit and has allowed a considerable amount of data to be collected, but it involves exposure to β , and β ionising radiation: using intravenous injection the amount of ¹³³Xe in one CBF measurement (20–40 MBq) results in a total body radiation dose of 0.2 mGy (20 mrad) which is similar to one to two chest x-ray examinations. Measurement also requires several minutes, so that rapid changes in CBF cannot be recorded.²

POSITRON EMISSION TOMOGRAPHY

Regional cerebral blood flow, together with glucose and oxygen consumption, can be observed using positron emission tomography (PET). $H_2^{15}O$ is injected and emits positrons which collide with electrons in tissues, leading to annihilation of the particles and the emission of a pair of γ -ray photons at an angle of 180° to each. Suitable detectors can determine the location of the annihilation event, and by comparing the clearance of the positron emitting isotope with the location of the annihilation events, determine regional CBF with a resolution of 3–4 mm.

The ability to measure regional blood flow is a great advantage. Unfortunately PET investigations are limited by the relatively high exposure to ionising radiation of 0.57 mGy (57 mrad),³ and by the need to draw a substantial volume of arterial blood to quantify CBF results. It cannot yet be performed in the neonatal unit, which further constrains its application to studies of sick newborn infants.

XENON COMPUTED TOMOGRAPHY

Regional CBF has been measured using stable xenon computerised tomographic scanning (XeCT).⁴ Non-radioactive Xe is inhaled, resulting in a time-dependent increase in tissue density. CBF is calculated by analysing the

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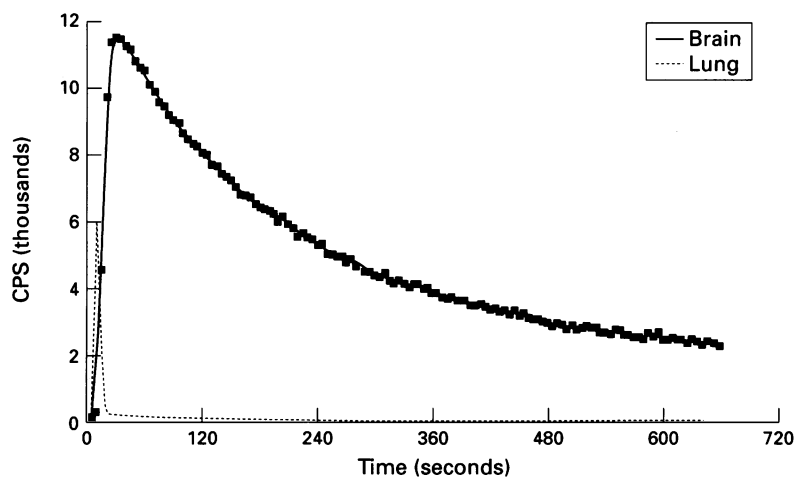


Figure 1 Measurement of cerebral blood flow by intravenous injection of ^{133}Xe . The graph shows the clearance of radioactive tracer from the brain, which is proportional to the rate of cerebral blood flow.

increased absorption of x -rays during the Xe accumulation and C_a obtained from expired gas. XeCT is rapid and safe, although xenon may have an anaesthetic effect at the concentrations used and raised intracranial pressure has been reported. This new technique also requires a special investigation suite and has not been widely used to study newborn infants.

NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy (NIRS) depends on the relative transparency of tissue to light in the near infrared spectrum (700–1000 nm).⁵ Light at several different wavelengths is transmitted from a fibre optic bundle through the infant head where some photons are absorbed by pigmented compounds (chromophores) present in the tissue.

CBF is measured using a modification of the Fick principle. In contrast to previously discussed methods, the technique uses a purely intravascular and non-diffusible tracer. This is introduced rapidly into the arterial supply of the brain and the accumulation in the brain is

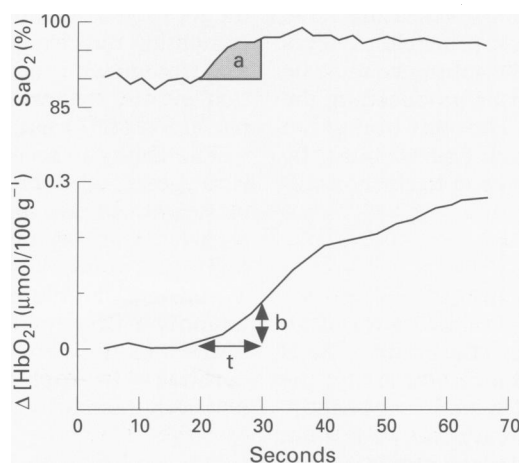


Figure 2 Measurement of cerebral blood flow using near infrared spectroscopy. A sudden change in oxyhaemoglobin concentration is measured in the arterial system by pulse oximeter (SaO_2) and in the brain by near infrared spectroscopy ($\Delta[\text{HbO}_2]$). Cerebral blood flow is quantified by dividing the change in $\Delta[\text{HbO}_2]$ (b) by area (a). (Reproduced with permission from Edwards et al, Lancet 1988; ii: 770–1.)

measured. If it is less than the vascular transit time no tracer will have appeared in the venous system and C_v is zero. Thus:

$$\text{CBF} = \frac{dQ}{\int_0^t (C_a) dt} \quad (2)$$

CBF can be determined from the ratio of the tracer accumulated at time t to the quantity of tracer introduced. Oxyhaemoglobin (HbO_2) absorbs near infrared light, and can be used as an endogenous tracer: a sudden increase in arterial saturation (S_aO_2) over a few seconds is induced by a sharp but transient increase in inspired oxygen concentration. This causes an additional bolus of HbO_2 to enter the arterial supply. C_a is the product of the arterial haemoglobin concentration and the change in S_aO_2 (measured by a pulse oximeter on the face or upper limb). The increase in $[\text{HbO}_2]$ is measured by NIRS. An example of the measurement of CBF measurement by NIRS is given in fig 2.

The technique involves several assumptions: during measurements, CBF cerebral blood volume and cerebral oxygen extraction must remain constant. However, it has been validated by comparison with established methods of blood flow measurement, and permits rapid, repeated measurements in newborn infants without interrupting normal care.^{6,7} It has been used for several studies in newborn infants.⁷ NIRS has the advantage of providing other data on cerebral haemodynamics and oxygenation as well as flow, but there are limitations to the CBF technique, as it is unsuitable for infants with severe lung disease who cannot achieve rapid changes in oxygenation.

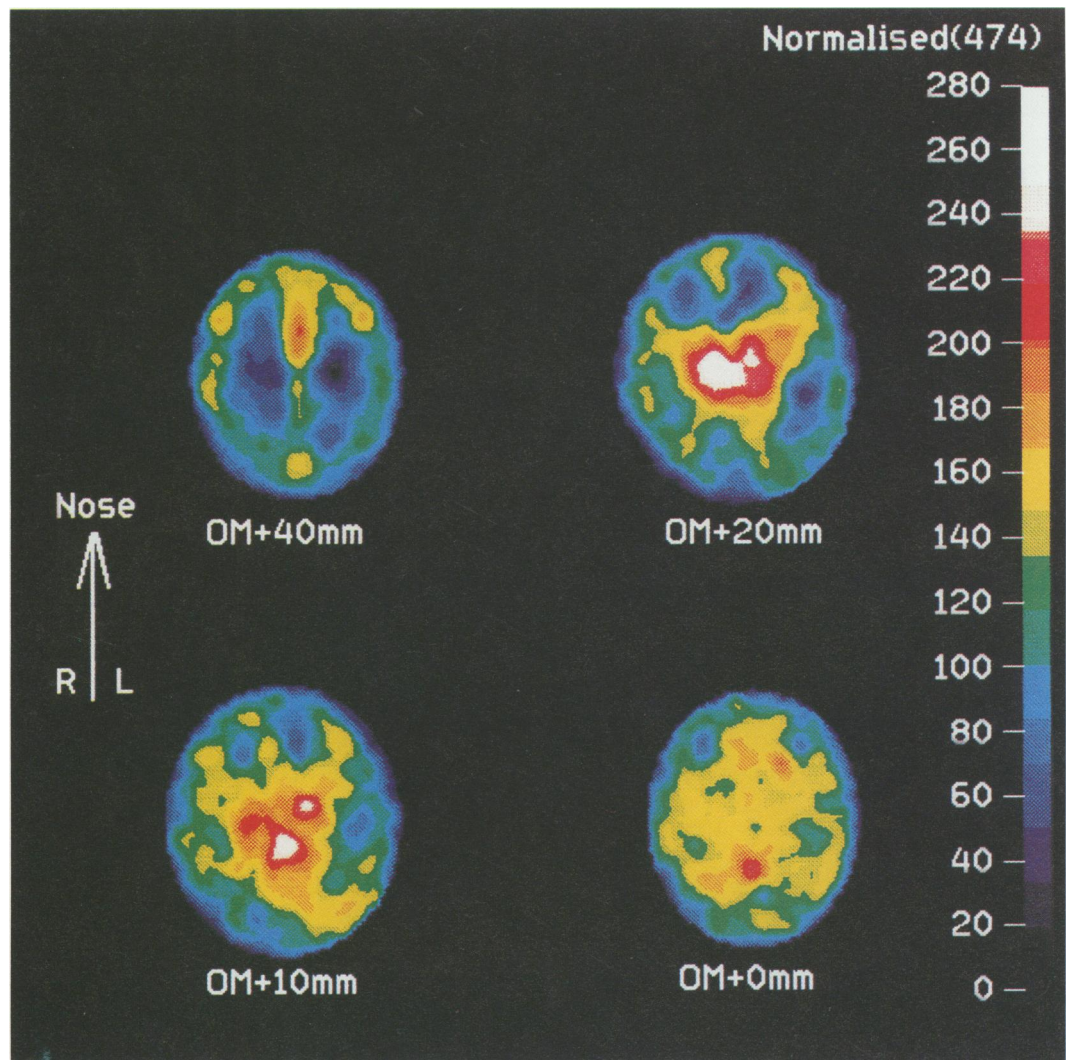
MAGNETIC RESONANCE IMAGING

Several methods have been devised for the manipulation of magnetic resonance imaging data to provide information on cerebral perfusion, although this field is still at an early stage of development.^{8–10} Motion sensitising gradient pulses can be used. These cause attenuation and/or detectable phase shifts in the signals from moving material dependent on the characteristics of the motion concerned. Secondly, 'time of flight effects' which utilise the paradoxical enhancement or attenuation of an image caused by flow during an imaging sequence are used. Thirdly, a paramagnetic contrast agent such as gadolinium-DTPA is used as a tracer for measurements using the Fick principle. This technique is very promising, both because it offers measurement of regional blood flow, and because, like NIRS, it can provide a wide array of additional data. Unfortunately it requires the infant to be transported to an MRI scanner and few data have yet been reported.

NITROUS OXIDE TECHNIQUE

The first quantitative measurement of CBF in humans was performed by Kety and Schmidt using NO_2 as a tracer. When NO_2 is inhaled, and C_a and C_v are monitored by repetitive

Figure 3 Distribution map of relative regional cerebral blood flow in a preterm infant, measured by $^{99m}\text{TcHMPAO}$ single photon emission tomography.



blood samplings, CBF can be derived by substituting dQ with $d(C_v) \cdot \lambda$. Because arterial and cerebral venous catheterisation are required, only a few studies have been performed in neonates.^{11 12}

VENOUS OCCLUSION PLETHYSMOGRAPHY

The skull of the newborn infant is relatively compliant, and will change in size with alterations of cerebral blood volume. The changes in cerebral circumference can be measured by impedance strain gauges and the change in cerebral volume inferred. Gentle occlusion of the jugular veins causes a small increase in cerebral blood volume and CBF can be estimated from the relation of changes in cerebral circumference and time.¹³ Problems in interpretation arise with the calculation of brain volume and with variations in skull compliance between infants, and the method has fallen from favour. However, the technique is remarkably simple and many warrant reassessment now that NIRS can be used to measure changes in cerebral blood volume more accurately.

Non-quantitative observation of cerebral haemodynamics

SINGLE PHOTON COMPUTED TOMOGRAPHY
Relative regional CBF has been observed in

newborn infants using single photon tomography (SPECT) (Greisen *et al*, personal communication). This method requires injection of $^{99m}\text{TcHMPAO}$, which acts as a chemical microsphere: the radioactive ligand becomes trapped in the brain and can be imaged at some later time during its decay. The technique offers the potential for observing CBF during clinical events that would otherwise preclude research activities, such as pneumothorax or severe hypotension. The radioactivity image provides a distribution map of blood flow within the brain at the time of injection, although with less accuracy than PET. Relative regional CBF can be calculated, but unfortunately the values are only relative to each other, and absolute data cannot be obtained. Thus the distribution, but not the quantity of CBF, can be measured. This limits the comparison of data between infants, but it is hoped that the technique may aid understanding of the pathophysiology of periventricular leukomalacia and cerebral infarction. An example of SPECT data is given in fig 3. It shows a centripetal distribution of CBF at 26 weeks of postconceptional age.

DOPPLER ULTRASONOGRAPHY

A shift in frequency occurs when ultrasound is reflected from moving blood cells, and the shift

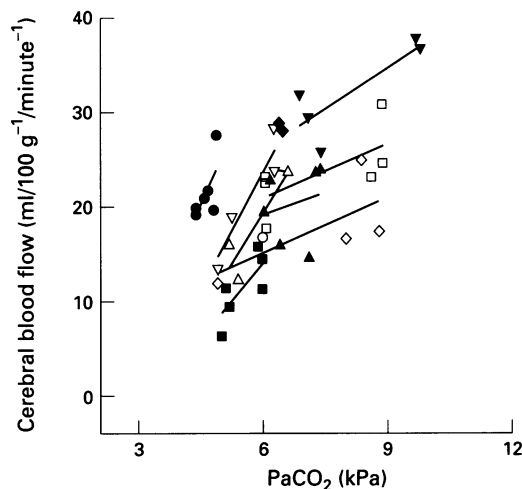


Figure 4 Relation between cerebral blood flow and arterial carbon dioxide tension in eight preterm infants, measured by near infrared spectroscopy. Each infant is denoted by a separate symbol and an individual regression line. (Reproduced with permission from Edwards et al, *Ped Res* 1992; 32: 532-6).

is proportional to the blood cell velocity. It is not possible to derive quantitative data on CBF from velocity as only one artery is insonated and its diameter remains unknown, but in certain circumstances Doppler ultrasonography may indicate trends in CBF.¹⁴

The physiology of cerebral blood flow control

CBF is determined by two factors: the resistance to blood flow in cerebral vascular channels, the cerebrovascular resistance (CVR); and the net pressure gradient across the cerebral vascular bed, the cerebral perfusion pressure (CPP). These are related such that:

$$CBF = \frac{CPP}{CVR} \quad (3)$$

CEREBROVASCULAR RESISTANCE

CVR is mainly determined by arteriolar tone, which is controlled by neuroeffector nerves, paracrine secretion from endothelial cells, circulating hormones and local humoral action. Data on the control of vascular tone in the brain of newborn infants are sparse, and most information has been provided from studies of animals.

Vascular tone is influenced by the balance of the different chemical signals, and a particular stimulus may elicit both vasoconstrictor and vasodilatory effects of great complexity. Important mediators include:

Prostanoids: Intracarotid injection of prostanoids (PGE1, PGE2, PGF2, PGI2) induces cerebral vasodilation in experimental animals, but the physiological roles in the regulation of CBF remains to be defined.¹⁵⁻¹⁷

Angiotensin: Cerebrovascular tone is partially maintained by angiotensin II produced locally in greater cerebral arteries, and in animals higher angiotensin concentrations widen the autoregulatory plateau (see below).¹⁸

Nitric oxide: Endothelial cells respond to physical and chemical stimuli by secreting a series of factors which cause constriction (such as endothelin) or dilation. Nitric oxide (NO) is a vasodilator which is also released from perivascular nerves and neural cells. NO is released constitutively to mediate a constant vasodilator tone, and also in response to stimuli including increased shear stress. Inhibition of endogenous NO synthesis leads to a moderate decline in cerebral blood flow and volume in newborn piglets but the effect seems to be less than that of indomethacin.^{19 20} NO is produced by inflammatory cells and may have a role in the vasodilation caused by sepsis.

Perivascular nerves: Cerebral arteries and arterioles are supplied by sympathetic, cholinergic, and peptidergic nerves. In addition to classic neurotransmitters such as noradrenaline and acetylcholine, many other transmitters have been identified. Nerves usually release two substances together as co-transmitters: ATP and noradrenaline are released together from some sympathetic nerves, where ATP seems to elicit a rapid, shortlived response while noradrenaline has a slower and longer action. The parasympathetic neurons also demonstrate co-transmission in that acetylcholine and vasoactive intestinal peptide are released together and cause vasodilation.²¹

Catecholamines: Infusion of noradrenaline or adrenaline causes noticeable cerebral vasoconstriction in newborn infants, although this effect can be rapidly attenuated (Edwards *et al*, unpublished data). Systemic catecholamines have many actions, including profound effects on cardiac output and systemic blood pressure, and an increase in cerebrovascular tone may protect cerebral capillaries from sudden surges in arterial blood pressure.²²

CEREBRAL PERFUSION PRESSURE

CPP is determined by the difference between arterial pressure and the cerebral venous pressure. In normal circumstances venous pressure is very much lower than arteriolar pressure and contributes little to CVR. However, it has been suggested that pathological situations such as tension pneumothorax, which lead to very high venous pressures, can disrupt CBF sufficiently to cause cerebral infarction in the preterm infant. Raised intracranial pressure may also cause cerebral venous pressure to the point where it contributes significantly to CVR with risk of cerebral hypoperfusion.²³ Unfortunately direct evidence to substantiate these hypotheses is difficult to obtain.

Cerebral blood flow and metabolism

Absolute values of global CBF can be misleading as there is rapid and constant readjustment of regional blood flow to satisfy local metabolic requirements. Relatively low neuronal activity in the newborn brain means that metabolism can be maintained by a global CBF of 10 to 20 ml/100 g/minute, about one third of the value

for the healthy adult brain. CBF is tightly coupled to metabolic demands for oxygen and glucose and is strongly affected by the byproducts of metabolism.

CBF is inversely related to the arterial oxygen content (C_aO_2) which is determined by the haemoglobin concentrations, the oxygen affinity of haemoglobin, and P_aO_2 .²⁴⁻²⁶ The dissociation characteristics of oxygenated haemoglobin mean that changes in C_aO_2 have little effect on CBF until P_aO_2 falls below 5–6 kPa, but further falls occasion significant increases in CBF. One study also suggested that hyperoxia immediately after birth can lead to a prolonged reduction in CBF.²⁷

Hypoglycaemia is accompanied by a two- to threefold increase in CBF.²⁸⁻³⁰ In case of the prolonged glucose restriction associated with placental dysfunction, cerebral hyperperfusion may persist for days after normoglycaemia has been established.³¹

The cerebral vessels are very sensitive to changes in P_aCO_2 as carbon dioxide readily passes the blood-brain barrier and alters the perivascular pH.³² Hypercapnia induces cerebral vasodilatation and a rise in CBF of about 30% per kPa.³³ The response is probably mediated by perivascular bicarbonate concentration,³⁴ and so the CBF- CO_2 reactivity is attenuated during chronic hypercapnia and enhanced during chronic hypocapnia.^{35 36} Studies in adults and animals have suggested that NO mediates CBF- CO_2 reactivity,³⁷ but this does not seem to be the case in the newborn.¹⁹ Reduced responsiveness to CO_2 is also observed after indomethacin,³⁸ when the vessels are maximally dilated because of concomitant hypotension, hypoxia, or hypoglycaemia,^{39 40} or following asphyxia. The relation of CBF to P_aCO_2 in eight newborn infants is shown in fig 4.

Some byproducts of energy metabolism may effect the coupling between metabolic requirements and CBF. Adenosine has a strong vasodilator effect, and adenosine concentration in the brain increases during electrical stimulation or seizure activity. In the immediate vicinity of pial arterioles the potassium ion produces dose-related vasodilatation whereas local application of calcium causes vasoconstriction.⁴¹

Cerebral blood flow and arterial blood pressure

Pressure autoregulation, defined as a constant CBF within a wide range of arterial blood pressures (the 'autoregulatory plateau'), is fully developed in fetal and neonatal animals.^{42 43} Methodological and ethical constraints have prevented it from being appropriately investigated in newborn infants but preliminary results show that CBF remains constant during small and spontaneous changes in blood pressure.³⁴

In animals the autoregulatory plateau is not fixed but depends on the actual diameter of the vessels determined by other factors such as P_aCO_2 and C_aO_2 . Pressure autoregulation becomes impaired when vasodilatation occurs

during hypercapnia, hypoxia, hypoglycaemia or seizures, whereas vasoconstriction widens the autoregulatory plateau.⁴⁴

The effect of blood viscosity on cerebral blood flow

The resistance to blood flow increases with higher haematocrit, and hence CBF tends to decrease. This fall, however, is partially caused by the concomitant rise in oxygen carrying capacity which is highly related to the haematocrit.⁴⁵

This association between increased haematocrit and lower CBF has been well established in adults, and haematocrits greater than 0.7 lead to a significant risk of cerebral ischaemia. In the newborn infant blood viscosity is lower for a given haematocrit than in the adult, due to differences in both plasma components and red cell deformability. Data are not available to decide clearly on the upper limit for a safe haematocrit in the newborn infant, although many clinicians extrapolate from studies in adults for their everyday practice.

Pharmacological agents and cerebral blood flow

Direct measurements of the effects of only a few pharmacological substances have been made in newborn infants:

Indomethacin reduced CBF in newborn infants by 20 to 40% when given intravenously at therapeutic doses of 0.10 or 0.20 mg/kg.^{38 46} In newborn piglets this effect is not observed after administration of Ibuprofen,⁴⁷ and preliminary data suggest that this is also true in newborn infants.⁴⁸

Dopamine administered to treat hypotension leads to a simultaneous increase in arterial blood pressure and cerebral blood flow (Pryds, *et al*, unpublished data).

A small reduction in CBF (10–15%) was shown after intravenous administration of Aminophylline, which is an antagonist of adenosine.⁴⁹

When the metabolic rate is reduced by sedatives or hypothermia, CBF decreases in association with the reduced metabolic demand.^{50 51}

Cerebral blood flow and cerebral injury

LOW CEREBRAL BLOOD FLOW

The lower threshold of CBF to sustain neuronal integrity is unknown in newborn infants as a normal neurological outcome is still possible with CBF as low as 5 ml/100 g/minute.^{3 52 53} Indeed, CBF cannot be used alone as an indicator of the brain's condition as a low flow state may either be normal or pathological. In order to distinguish between normal and abnormal, values for CBF have to be related to oxygen consumption ($CMRO_2$) and oxygen extraction (OER).

When low CBF is coupled to a depressed cerebral function induced, for example, by sedatives or hypothermia, OER may remain normal, implying that CBF and $CMRO_2$ are

properly matched. However, OER will increase when CBF drops without a concomitant change in $CMRO_2$, and this can be most easily observed as increasing desaturation in cerebral venous blood. In newborn dogs maximal OER occurs when the oxygen saturation of cerebral venous blood is about 0.4, and any further decline in oxygen delivery will lead to ischaemia.⁵⁴

HIGH CEREBRAL BLOOD FLOW

Hypoxia, hypercapnia, hypoglycaemia, and anaemia are associated with a rise in CBF which maintains normal $CMRO_2$. However, in the hours following severe perinatal hypoxic-ischaemic injury a significant cerebral hyperperfusion has been observed which seems to be associated with reduced rather than increased $CMRO_2$.^{12 55 56} The mechanism of this 'luxury perfusion' is unclear, although in fetal sheep it is mediated in part by NO production.⁵⁷ The precise relation between delayed hyperperfusion following hypoxia-ischaemia and delayed impairments in cerebral energy metabolism is still unresolved, but in infants with birth asphyxia hyperperfusion is a sign of poor neurodevelopmental prognosis, particularly when accompanied by loss of pressure autoregulation and CO_2 reactivity.⁵⁵

Conclusion

Studies of CBF have provided some insight into cerebrovascular physiology and pharmacology. However, the precise relation between CBF and cerebral damage remains elusive, and there is no definition of a threshold CBF below which ischaemic brain damage always occurs. Measurement of CBF thus does not currently provide a secure guide in the clinical management of sick infants. Further work, particularly using techniques like magnetic resonance imaging and NIRS, which provide data in addition to CBF measurements, may yet disclose strategies which manipulate CBF to reduce cerebral ischaemia. While cerebral injury remains a substantial problem in neonatal intensive care, such research is urgently needed.

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