CEREBRAL BLOOD FLOW IN MECHANICALLY VENTILATED, PRETERM NEONATES

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5. Greisen G, Trojaborg W. Cerebral blood flow, $PaCO_2$ changes, and visual evoked potentials in mechanically ventilated preterm infants. Acta Paediatr Scand 1987; 76: 394-400.
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1. TABLE OF CONTENTS

2. INTRODUCTION

The perinatal brain is comparatively resistant to acute hypoxia-ischaemia (*Fazekas et al* 1941). This is related to low energy metabolism (*Thurston & McDougal* 1969). Notwithstanding this, preterm infants run a high risk of perinatal brain damage, the principal types of which are haemorrhagic and hypoxic-ischaemic (*Pape & Wigglesworth* 1979). Such damage accounts for a major part of subsequent neurodevelopmental deficit (*Stewart et al* 1983).

Observing proportionality between arterial blood pressure and cerebral blood flow (CBF) in stressed infants shortly after birth, it was proposed that asphyxia leading to abolishment of the normal pressure-flow autoregulation would allow moderate hypotension to cause ischaemia (*Lou et al* 1977), and moderate hypertension to be transmitted to the capillary bed and cause rupture and cerebral haemorrhage (*Lou et al* 1979a). Indeed, in fetal lamb lesser degree of hypertension was followed by cerebral haemorrhage if preceded by asphyxia (*Reynolds et al* 1979).

Excessive mechanical ventilation, causing severe hypocarbia and thereby presumably cerebral vasoconstriction, in preterm neonates may be associated with hypoxic-ischaemic brain damage (*Calvert et al* 1987), and neurodevelopmental deficit (*Greisen et al* 1987b). Several other risk factors for the development of structural brain damage have been identified (*Trounce et al* 1988), but most often it occurs without a clearly defined precipitating event, and prevention has largely been unsuccessful. Therefore, a more thorough understanding of the physiology, and pathophysiology of the perfusion of the preterm brain appears necessary.

3. ESTIMATION OF CBF IN NEWBORN INFANTS

Cerebral blood flow is a complex variable varying in time and distribution. Venous outflow may change within seconds in hypoxia, epileptic seizures, or when blood pressure changes abruptly. Such events are frequent in the neonatal period. Autoradiography in newborn puppies has shown different rates of blood flow to different parts of grey as well as white matter, with the flow distributions overlapping (*Kennedy et al* 1972); this is likely to be the case in newborn infants as well. During hypoxia or asphyxia in lambs and puppies, CBF may increase in the brainstem, cerebellum and central ganglia, while remaining constant or even decreasing in the cerebral hemispheres (*Blomstrand et al* 1978, *Hernandez et al* 1982). The methods available for estimation of CBF in human newborns provide only crude measures of those complexities – and up to now there is no generally accepted method.

3.1. ^{133}Xe CLEARANCE

^{133}Xe clearance has yielded unexpectedly low values of CBF in preterm infants, therefore the following discussion is focused on methodological errors, which may result in falsely low flow values.

3.1.1. *Theory*

^{133}Xe clearance is commonly used for CBF estimation in adults. The method is a development of the Kety-Schmidt method and is based on the Fick principle of indicator exchange in tissue

$$1)\quad dC_t/dt = f \cdot (C_a - C_v)$$

i.e. the concentration change of a metabolically inactive indicator, C_t equals the flow rate, f multiplied by the difference between the arterial and venous indicator concentrations, C_a and C_v. To circumvent the need for sampling of venous blood, external scintillation detection may be used to measure tissue indicator concentration. The relation of tissue indicator concentration to venous blood concentration was analysed by *Kety* (1951) who made the assumption of diffusion across the capillary membrane, into a fully stirred tissue chamber ('with the advantage of simplicity if not of verisimilitude'). The result may be expressed (*Tomita & Gotoh* 1981) as

$$2)\quad dC_t/dt = m \cdot f/\lambda \cdot (\lambda \cdot C_a - C_t)$$

where $m = 1-e^{-p\cdot s/f}$ is called the extraction, $p \cdot s$ is the permeability-surface product of the indicator, and λ is the solubility of indicator in brain tissue relative to that in blood, the so-called brain-blood partition coefficient. For boundary condition $C_t=0$ at time zero, equation 2 may be solved

$$3)\quad C_t(t) = \lambda \cdot k \cdot \int_0^t C_a(u) \cdot e^{-k\cdot(t-u)}du$$

where $k = m \cdot f/\lambda$. Therefore, the rate constant, k calculated from external scintillation curves includes the partition coefficient and a measure of diffusion as well as the blood flow rate.

If the tissue is composed of two separate, non-communicating compartments (e.g. grey and white matter) recorded tissue concentrations, $C_t(t)$ represents the weighted sum of two equations. Estimates of the two respective rate constants and compartment weights may be obtained.

3.1.2. *Partition coefficient*

The solubility of Xenon in blood depends on the haemoglobin concentration, and is similar for adult and preterm human blood (*Greisen* 1986a). The brain-blood partition coefficient depends mainly on brain lipid content and blood haemoglobin concentration. Brain lipid content increases significantly during development. In newborn puppies the brain-blood partition coefficient *in vivo* was about two-thirds of adult values (*Hernandez et al* 1978). The partition coefficient of human newborn brain tissue was found *in vitro* to be independent of gestational age and to be similar for grey and white matter (*Greisen* 1986a). For grey matter this is similar to adult values, for white matter it is only slightly more than half.

3.1.3. *Extraction*

Diffusion may be expected to constrain the clearance of indicator from the brain when the capillary permeability-surface product is low, in particular at high blood flow rates. The capillary density, and hence capillary surface, may be relatively low during early stages of brain development and further capillary collapse may happen in ischaemia (*Tomita & Gotoh* 1981). Therefore it is not certain that the underestimation of flow rate by ^{133}Xe clearance will be negligeable even at the low levels observed in preterm human brain. A more important error may be counter-current exchange, which during wash-out will cause Xenon to diffuse from vein to artery. The result will be a slower clearance, and hence underestimation of flow rate. This error will be greater the lower the flow rate. Unfortunately, there is only little experimental data on which to base a quantification of the possible errors. In newborn lambs, ^{133}Xe clearance with external detection yielded 'fast compartment' flow rates comparable to the hemispheric flow rates obtained by the radioactive microsphere technique (*Blomstrand et al* 1978). In newborn puppies, values of 25-40 ml/100 g/min have been obtained by the Kety-Schmidt method using ^{133}Xe (*Hernandez et al* 1978, *Gregoire et al* 1978) as well as by radioactive microspheres (*Goddard-Finegold et al* 1984, *Ment et al* 1985)

3.1.4. *Intravenous bolus injection technique*

Noninvasive ^{133}Xe clearance after inhalation (*Obrist et al* 1975) is well established in adults. When ^{133}Xe in 0.9% saline is injected intravenously as a bolus, the arterial concentration of ^{133}Xe, $C_a(t)$ gradually increases, peaks, gradually decreases, and continues at a low level throughout the period of analysis. The brain tissue concentration as a function of time then represents $C_a(t)$ convolved with the clearance function. Cranial ^{133}Xe clearance curves after intravenous administration in healthy human adults may be analysed to yield flow rates similar to those obtained by intra-arterial ^{133}Xe injection technique (*Thomas et al* 1979).

3.1.4.1. *Determination of the arterial input function*

In adults external scintillation detection over the chest, allows $C_a(t)$ to be estimated by correcting for the contribution of counts from

^{133}Xe in the chestwall (*Jaggi & Obrist* 1982). ^{133}Xe recirculation is increased, however, in case of alveolar hypoventilation, ventilation/perfusion imbalance, or shunting of blood past the lungs (right-to-left) through the foramen ovale, all of which is frequent in newborns. Then the standard correction for the chest wall contribution underestimates the arterial input during the last part of the analysis period and hence underestimates cerebral blood flow rates (*Greisen & Pryds* 1988). Perivenous uptake of part of the bolus of Xenon followed by slow release may also result in increased late ^{133}Xe input. A modified correction compares well with estimations of $C_a(t)$ from ^{133}Xe concentrations in exhaled air, and from right radial artery blood samples (*Greisen* 1986a, *Greisen & Pryds* 1988). These two latter methods account fully for increased late input of ^{133}Xe, but are unsuitable for routine use.

3.1.4.2. *Global CBF in neonates*

Intravenous ^{133}Xe clearance yields unreliable separate estimates of the flow rates to grey and white matter in ill, newborn infants (*Greisen et al* 1984a). Even in 'healthy' preterm infants the estimates of grey matter flow were surprisingly high (*Younkin et al* 1982). The weighted mean of the flows to the two compartments, CBF_∞, conceptually similar to the result of non-compartmental analysis of clearance curves extrapolated to infinity, remains well defined (*Obrist & Wilkinson* 1980) and fairly resistant to various sources of error, even when the clearance period is shortened to 8 min (*Greisen* 1984). The test-retest variation is 10-15% (*Greisen & Trojaborg* 1987). The advantage of shortening the clearance period to 8 min is paid for by somewhat lower accuracy compared with 15 min clearance period, and the results are 15-20% higher (*Greisen & Pryds* 1988).

Due to the small size of the brain in preterm infants and the high proportion of scattered radiation in the detected counts (window 55-105 KeV, 17mm×17 mm NaI crystal with a 20 mm long cylindrical collimation) the 'sample volume' of 100-200 ml may be considered to represent the entire brain, and CBF_∞ to represent global rather than regional cerebral blood flow. The slightly faster clearance curves recorded over the temporal and occipital regions compared to the parietal and frontal regions in preterm infants (*Younkin et al* 1988) may reflect an aspect of brain immaturity, but may also simply be due to airway artefacts. The time scale of the clearance means that the CBF value respresents an average over 4-6 min.

Patient radiation dose is higher compared to adults: when 1 mCi/kg (37 MBq) ^{133}Xe is injected intravenously, the dose to the lungs is 1.3 mGy (130 mRem), 0.07 mGy to the gonads, and average 0.23 mGy to other tissues, depending on fat content, thereby being higher in term compared to preterm infants (*Greisen et al* 1984a). This corresponds to the yearly excess background radiation on the island of Bornholm compared to the area of Copenhagen.

In conclusion, estimates of global CBF from ^{133}Xe clearance after intravenous bolus injection are unlikely to be grossly erroneous. The patient radiation allows a few measurements in each infant making intra-individual comparisons possible.

3.2. ***Doppler ultrasound***

The Doppler effect on ultrasound in the MegaHertz range is used to estimate blood flow velocity

$$V = \cos\Theta \cdot \Delta f/2 \cdot f \cdot V_s$$

where V is the estimated blood flow velocity, V_s is the velocity of sound in tissue, $\Delta f/2 \cdot f$ is half of the relative frequency shift, and Θ is the angle between the sound beam and the vessel under study.

Determination of cerebral blood flow (in terms of volume flow per 100 g brain weight) by Doppler ultrasound faces a number of difficulties: 1) to obtain a signal from a single straight, non-dividing artery, 2) to get an equal representation of the flow profile in the recorded frequency spectrum, 3) to remove frequency shifts due to the slowly moving vessel wall, 4) to determine the weighted mean frequency shift, 5) to determine the time averaged mean frequency shift, 6) to determine the angle between the vessel and the sound beam, and 7) to determine the arterial cross-sectional area in relation to the mass of brain tissue supplied by the artery. Comparison of time-averaged frequency shifts (space-average or maximum) with measures of volume flow have showed fairly encouraging results. *In vitro*, using fine rubber tubing, the coefficient of variation around the regression line ('accuracy') is in the order of ±5% (*Lundell et al* 1984), in human adults ±10% (*Risberg & Smith* 1980), in experimental newborn animals ±30% (*Batton et al* 1983; *Hansen et al* 1983, *Rosenberg et al* 1985); in newborn infants the accuracy was ±35% (*Greisen et al* 1984b). This moderate level of accuracy in perinatal animal and clinical research gives room for significant systematic errors. Even in the best of situations, in shortterm studies of trends within individual infants, with constant transducer position, dynamic changes in arterial diameter may give rise to errors (*Busija et al* 1981) and factors affecting arterial diameter such as adrenosympathetic tone (*Busija et al* 1985), blood pressure (*Kontos et al* 1978), P_aCO_2 (*Wei et al* 1980), and P_aO_2 (*Rosenberg et al* 1985) must be considered. In addition to these 'classical' factors influencing arterial diameter, it has recently been realized that increased flow velocity in itself, through increased endothelial shear stress, results in local vasodilation (*Anonymous* 1988). Thus, in principle, flow velocity in distributary arteries is actively regulated and may therefore be relatively independent on volume flow.

A pulsatility index ((systolic flow – diastolic flow)/systolic flow) has often been used in neonates as proposed by *Bada et al* (1979). This index is expected to reflect cerebrovascular resistance, but also to vary with cerebrovascular compliance and changes in aortic blood pressure wave form. It correlates poorly with CBF (*Greisen et al* 1984b, *Batton et al* 1983, *Hansen et al* 1983, *Rosenberg et al* 1985) and the index has not been validated against a standard calculation of cerebrovascular resistance. Its use will not be further discussed here.

4. NORMAL VALUES OF CBF IN PRETERM INFANTS

Premature infants are basically in an abnormal situation, and normality can only be considered apparent. The question is what values of CBF are compatible with optimal brain function, growth and development. Unfortunately, methods for the characterisation of brain optimality are not available. Only few studies of cerebral blood flow rates in 'healthy', preterm infants have been published (Table 1). The data suggest that CBF increases with gestational age and postnatal age. The latter was already hinted at by *Garfunkel et al* (1954), who did the very first measurements of CBF in infants and children with various neurological disorders. In animal species such as rats and dogs, equally immature at birth as man, neonatal CBF is low compared to adults (*Moore et al* 1971, *Kennedy et al* 1972).

Flow provides substrate for three kinds of processes; growth, synaptic transmission, and 'structurumsatz' (*Astrup* 1982). Whereas little is known of the energy metabolism of brain growth which may not be well studied in acute animal experiments, the low CBF in such studies is matched by a low metabolic rate (*Thurston & McDougal* 1969, *Hernandez et al* 1978). In the adult brain, more than half of the metabolic rate is associated with synaptic transmission. The spontaneous electrical activity of premature infants is characterised by periods of quiescence becoming shorter and fewer with increasing gestational and postnatal age. It is possible that the periodic absence of background activity represents a change of the organisation of electrical activity rather than an absolute decrease since no difference in CBF was found in preterm infants between quiet sleep with discontinuous EEG activity and active sleep with continuous EEG activity (*Greisen et al* 1985). Low energy expenditure, however, is also suggested by the paucity of neuronal synapses of preterm human brain (*Huttenlocher et al* 1982), as well as the fragility of behavioral control. Finally, it has been

Author	Method	N	Gest.age	Age	CBF (ml/100 g/min)
Greisen et al 1986	^{133}Xe clearance	11	31	0-5d	19.8+5.3
Younkin et al 1982	^{133}Xe clearance	15	31	3-57d	27.7+8.2
Leahy et al 1980	venous occl plethys	24	34	2-24d	32.5 (16-50)
Cooke et al 1979	venous occl plethys	13	term	3-24h	31.3 (23-48)
Cross et al 1979	venous occl plethys	16	40	2-8d	40 (20-59)
Settergren et al 1976	N_2O	12	–	1-12m	69±27
Kennedy et al 1957	N_2O	9	–	3-11y	106 (96-120)
Lou et al 1984	^{133}Xe clearance	9	–	7-15y	71±10
Meyer et al 1978	^{133}Xe clearance	15	–	23-62y	45±8

note: the data of *Younkin et al* have been recalculated using the neonatal brain-blood partition coefficient of 0.8 ml/g for grey and white matter.

Table 1. *Normal values of 'global' CBF.*

suggested that immature neurones may be less permeable to K^+ (*Hansen* 1977), which would decrease basic energy requirements for the maintenance of membrane potentials.

It can therefore be concluded that cerebral blood flow rate is low in healthy preterm infants compared with adult reference values, and is likely to increase with increasing gestational age and/or increasing postnatal age.

5. CBF IN MECHANICALLY VENTILATED PRETERM INFANTS

Mechanical ventilation is used in preterm infants primarily to treat respiratory distress syndrome (surfactant deficiency), other forms of respiratory distress, and apnea of prematurity. Although these are pathophysiologically different in principle, in practice, the distinction is rarely clear, especially in the first few days of life. The most important distinction may be some measure of the intensity of ventilator support, but it should be remembered that the vigour of treatment may differ greatly among institutions. Mechanical ventilation was the factor most closely associated with CBF in 42 infants, 26 to 33 weeks of gestation, in the first week of life (*Greisen* 1986a). In the mechanically ventilated infants the average CBF_∞ was 11.8 ml 100 g/min ±3.2 SD, reduced by 40% compared with the spontaneously breathing infants. Recently, this finding was corrobated by others, also using ^{133}Xe clearance (*Duc et al* 1987). It does not agree with venous occlusion plethysmography studies (*Milligan* 1980), in which the CBF-index exceeded that reported for healthy term infants (*Cross et al* 1979). Doppler ultrasound studies, however, also have suggested that CBF may be decreased in ventilated infants (*Ellison et al* 1986). The low CBF in mechanically ventilated infants was not related to lower P_aCO_2 (*Greisen* 1986a, *Ellison et al* 1986, *Duc et al* 1987) or to the use of phenobarbitone (*Greisen* 1986a).

Respiratory distress syndrome is strongly associated with germinal layer haemorrhage (*Allan & Volpe* 1986), and in some studies mechanical ventilation has been associated with neurodevelopmental deficit (*Ruiz et al* 1981, *Greisen et al* 1986). Consequently, the capacity of mechanically ventilated infants to regulate CBF is of great interest to evaluate the role of CBF in the development of structural brain damage.

6. REGULATION OF CBF IN PRETERM INFANTS

Regulation of CBF is usually classified as metabolic, chemical (CO_2, O_2), autoregulatory, or neurogenic (*Lassen* 1974). Studies of the physiologic mechanisms of the CBF regulation has not changed this desciption.

6.1. FLOW-METABOLISM COUPLING

In normal brain, flow is coupled to metabolic rate. In human adults, the metabolic rate is lower in all areas of the brain during deep sleep compared to the waking state (*Kennedy et al* 1982). Rapid eye movement sleep has been associated with the highest blood flow rates (*Sakai et al* 1980). CBF is increased during rapid eye movement sleep in healthy, term infants compared with deep sleep (*Milligan* 1979, *Rahilly* 1980a, *Muhktar et al* 1982). CBF was lower in deep sleep compared to the waking state in preterm infants, 29 to 34 weeks of gestation, 5 to 17 days after birth (*Greisen et al* 1985); this is evidence of the flow-metabolism coupling which thus may be assumed to be developed in humans at 32 weeks of gestation if not earlier.

Doppler estimated flow velocity was normalised after normalisation of the haematocrit by plasmanate exchange transfusion in infants with polycytaemia (*Rosenkrantz et al* 1982). In a group of 'healthy', preterm infants haematocrit was related to CBF estimated by ^{133}Xe clearance (*Younkin et al* 1987). This can be interpreted as evidence of 'flow-metabolism' coupling (a coupling of flow to substrate delivery in relation to requirements) or as a relation of CBF to blood viscosity. In newborn lambs, arterial oxygen content was reduced by sodium nitrite or methaemoglobin leaving haematocrit constant; the CBF increase suggests that flow-metabolism coupling is the dominating factor (*Rosenkrantz et al* 1984, *Hudak et al* 1986).

Recently, hypoglycaemia a few hours after birth was found to be associated with a 2.5 fold increase in CBF (*Pryds et al* 1988a). Most of the infants were spontaneously breathing, but two hypoglycaemic, mechanically ventilated infants presented CBF_∞ of 29 and 32 ml/100 g/min, demonstrating the ability of cerebral vasodilation in response to decreased substrate availability.

6.2. CBF-O_2 REACTIVITY

Hyperoxia decreases CBF as estimated by jugular venous occlusion plethysmography (*Leahy et al* 1980, *Rahilly* 1980b) or Doppler ultrasound (*Nijima et al* 1988). Apparently the decrease (15-30%) exceedes the increase in artrial oxygen content.

6.3. CBF-CO_2 REACTIVITY

Reactivity of cerebral blood flow to acute changes in CO_2 is about 30%/kPa in human adults; blood flow normalises over 24-36 h following a persistent change of P_aCO_2 (*Lassen,* 1974). The reactivity depends on the metabolic state of the brain and on the perfusion pressure; at the lower threshold of pressure-flow autoregulation, or below, the CO_2 response is decreased or absent (*Häggendal & Johansson* 1965, *Harper & Glass* 1965).

In healthy term newborn infants, studies with CO_2 inhalation have shown 18-34%/kPa increases in cranial blood flow estimated by venous occlusion plethysmography or electrical impedance plethysmography (*Rahilly* 1980b, *Costeloe et al* 1984). In healthy preterm infants, a similar study showed CBF-CO_2 reactivity of 59%/kPa (*Leahy et al* 1980). Similar CBF-CO_2 reactivity was found in clinically stable, mechanically ventilated preterm infants studied in the second day of life (*Greisen & Trojaborg* 1987). This finding indicates a normal vasodilatory reserve in such infants and in particular suggests that the perfusion pressure was above the lower threshold of pressure-flow autoregulation; ie that the low flow condition may be well regulated in respiratory distress, at least once the immediate postnatal period is over. Recently, the CBF-CO_2 reactivity as estimated by Doppler ultrasound in similar infants was found to 44%/kPa in the first 24 h of life and 53%/kPa thereafter (*Levene et al* 1988).

The association of hypocarbia with brain damage (*Calvert et al* 1987, *Greisen et al* 1987b) is surprising. Such damage has not been reported in adult humans or in animals. In newborn dogs CBF decreased by two thirds at P_aCO_2 of 1.8 kPa, but cerebral oxygen consumption decreased by 20% only, and there was no increase in base deficit (*Reuter & Disney* 1986). Cerebral phosphocreatinine and ATP were unchanged after 90 min of hyperventilation to P_aCO_2 of 2.3 kPa (*Young & Yagel* 1984). Furthermore, in newborn lambs hypoxia abolishes CBF-CO_2 reactivity (*Kjellmer et al* 1974), providing an efficient escape mechanism from excessive vasoconstriction. Therefore significant ischaemia seems unlikely.

6.4. PRESSURE-FLOW AUTOREGULATION

Normal brain maintain constant flow rates over a fairly wide range of perfusion pressures. The observation of *Lou et al* (1977,1979a) of proportionality of CBF and arterial blood pressure in distressed newborn infants a few hours after birth, suggested that the pressure-flow autoregulation was abolished. Experimental studies have confirmed the presence of pressure-flow autoregulation in the newborn puppy (*Hernandez et al* 1980) and the preterm fetal lamb (*Papile et al* 1985). Moderate hypoxia ($SO_2 < 50\%$ for 20 min) resulted in disruption of the pressure-flow autoregulation lasting for 4-7 h in newborn lambs (*Tweed et al* 1986).

Milligan (1980) found proportional rises in arterial blood pressure and CBF after transfusion in 5 mechanically ventilated preterm infants. Several recent studies of mechanically ventilated preterm infants using Doppler ultrasound have demonstrated increasing mean flow velocity with increasing blood pressure, either spontaneous (*Ahman et al* 1983), following transfusion (*Greisen et al* 1988), or following transfusion and/or dopaminergic drugs (*Jorch & Jorch* 1987). It is important, however, to realise that these changes may be caused by diameter change of the artery studied, rather than by change of flow rate (*Greisen* 1986b).

Parallel increases in arterial blood pressure and CBF are not necessarily an expression of impaired autoregulation. If blood pressure goes above or below the limits of the autoregulatory plateau, CBF will follow; this is a normal phenomenon. Moreover, if blood pressure falls with cardiac output, this in itself may affect CBF by sympatho-adrenergic reflex mechanisms (may be blocked by α-blocking drugs in newborn puppies, *Hernandez et al* 1982). In such case CBF-pressure reactivity is increased, but 'autoregulation' can hardly be said to be impaired.

Particular interest has been paid to the significance of persistant arterial ductus for the cerebral circulation. An open arterial ductus often complicates respiratory distress in preterm infants. Unfortunately all studies have used Doppler ultrasound and most report the pulsatility index. It is obvious that the diastolic flow velocity decreases with diastolic blood pressure as the left-to-right shunt becomes more severe. A direct effect of the increased pulsatility on cerebroarterial tone – and hence on blood flow rate – was suggested by more marked increase in carotid blood flow velocity than in arterial blood pressure immediately following surgical closure (*Sonesson et al* 1986). Preterm infants with severe respiratory distress were found not to increase their cardiac output in response to haemodynamically significant patent arterial ductus, as did infants with less severe respiratory distress; arterial blood pressure and cerebral blood flow velocity were decreased in the former infants (*Mellander & Larsson* 1988). Apart from the ambiguity due to the possibility of arterial constriction at the point of measurement when the duct closes, the interrelation between cardiac output, arterial blood pressure, and the arterial ductus in itself, and cerebral blood flow is unclear.

Using ^{133}Xe, no relation of CBF to arterial blood pressure was found among preterm infants several days or weeks of age (*Greisen 1986a, Younkin et al* 1987); neither were changes in CBF related to (small and spontaneous) changes in arterial blood pressure in mechanically ventilated, preterm infants in the second day of life (*Greisen & Trojaborg* 1987).

Unfortunately, it is difficult to manipulate blood pressure in newborn infants and no study has as yet demonstrated directly or quantified the pressure-flow autoregulation in newborn infants. Meanwhile, it may be reasonably assumed that pressure-flow autoregulation is present in normocapnic newborn infants unless interrupted by recent hypoxic or asphyxic insult. The ranges of perfusion pressures covered and the gestational age when it develops can only be guessed at.

6.5. NEUROGENIC REGULATION OF CBF

From animal studies it appear that the sympathetic system may play a more marked role in the perinatal period compared to later life (*Hernandez et al* 1982, *Hayashi et al* 1984, *Wagerle et al* 1986). No studies of neurogenic regulation of CBF in newborn infants have been reported, although the observation of a 30-40% decrease in CBF as estimated by jugular venous occlusion plethysmography lasting 60 min after feeding (*Dear* 1980, *Rahilly* 1980a) may suggest a neurogenic mechanism.

7. GERMINAL LAYER HAEMORRHAGE AND CBF

Germinal layer haemorrhage (GLH) is typical of preterm infants, 26 to 32 weeks of gestation, occurring in nearly 50% of such infants. Few haemorrhages are present at birth, about half appear before 24 h of age, and few after the first week. Often a small GLH may later enlarge and/or give rise to intraventricular clots, which may completely fill or even distend the ventricular system. In some cases cerebral parenchyma (periventricular white matter) may become involved.

The neurodevelopmental consequences of GLH not complicated by ventricular dilation or parenchymal involvement have at present not been documented; in any case cerebral palsy is very unlikely. In contrast, death or major neurodevelopmental deficit follow the majority of parenchymatous haemorrhages.

7.1. PATHOPHYSIOLOGY

The current evidence is patchy, partly conflicting, and a certain multiplicity of types of haemorrhages and etiologies is possible. In view of the clinical importance a brief outline is attempted.

Apart from the strong relation to prematurity, GLH is strongly related to respiratory distress syndrome. Furthermore, hypoxia, hypercarbia, acidosis, treatment with sodium bicarbonate, mechanical ventilation, pneumothorax, arterial hypotension, intravascular volume expansion, hypertensive peaks, patent arterial ductus, and coagulopathy have all been found associated with GLH (*Allan & Volpe* 1986). These factors, however, are all interrelated, and their individual significances are unclear.

Germinal layer haemorrhage may be produced in the preterm sheep fetus (*Reynolds et al* 1979) and in the newborn, term beagle puppy (*Goddard et al* 1980a, 1980b, *Goddard-Finegold et al* 1982). Asphyxia followed by arterial hypertension, rapidly induced hypercarbia (with secondary arterial hypertension), or phenylephrine induced hypertension produce GLH in some cases, whereas asphyxia followed by venous hypertension or haemorrhagic hypotension followed by reinfusion-induced hypertension result in GLH in nearly 100% of experiments.

The primary insult (asphyxia or hypotension) may induce vascular damage so the secondary increase of transmural pressure may cause rupture. This interpretation is supported by finding that in the beagle puppy model, GLH may be prevented by pretreatment with superoxide dismutase, without interfering with neither the acute blood pressure changes, nor with the relative hyperperfusion of the germinal matrix following reinfusion (*Ment et al* 1985). Surprisingly, however, CBF was *increased* during haemorrhagic hypotension (*Goddard-Finegold & Michael* 1984), suggesting absence of an ischaemic/hypoxic primary insult. The microsphere technique used to demonstrate these sequential changes in CBF did not, however, allow estimation of flow to the germinal matrix itself, and it is still possible that this 'low-flow' structure (*Pasternak et al* 1982) is

selectively vulnerable, being a vascular watershed area (*Takashima & Tanaka* 1978).

In a significant proportion of infants dying with parenchymatous haemorrhage as a complication to GLH there are only subtle histologic signs of ischaemia, and the ependyma is intact, whereas the haemorrhage is wedge-shaped corresponding to the drainage zone of the terminal vein, and perivenous rupture and/or perivenous haemorrhages may be demonstrated. It is suggested that this represents venous infarction due to terminal vein obstruction by the primary GLH (*Gould et al* 1987).

7.2. CLINICAL STUDIES

No method for estimation of flow to the germinal layer in the human infant is available, and to the extent to which the flow to this area is particular, the clinical studies are irrelevant for the pathogenesis.

The most direct evidence of a relation between changes in CBF and GLH is provided in the study by *Milligan* (1980). Clinical signs of major cerebral haemorrhage developed shortly after increases in arterial blood pressure and CBF induced by transfusion. In a prospective study *Ment et al* (1981) used ^{133}Xe inhalation and antero-posterior projection on a portable gamma-camera. The CBF-index was slightly lower in the infants who later were shown to have GLH by CT-scanning compared to those who did not bleed. The CBF to the two hemispheres at 24 h of age differed considerably from each other in the infants with GLH, about half of which would be expected not yet to have bled at the time of the CBF study. In a later study (*Ment et al* 1984) GLH was timed by cranial ultrasonography. Seven of the 19 haemorrhages were major. The CBF-index at 6 h of age was lowest in the infants who already had GLH at that time, and was lower in those who bled later compared to those not bleeding at all. These differences in CBF persisted at 5 d of age. Using positron emission tomography with a spatial resolution of 1-2 cm, *Volpe et al* (1983) could demonstrate wide areas of very low CBF surrounding established parenchymatous haemorrhages. In contrast, *Greisen* (1986a) found global CBF higher in infants with GLH, when the effect on CBF of mechanical ventilation was accounted for. Seven of nine haemorrhages were present at the time of study, whereas none of the haemorrhages were major.

Thus, hyperperfusion may be present in relatively healthy infants who only develop small haemorrhages, whereas low CBF may signal a cerebrovascular abnormality with risk of major haemorrhage. Low CBF may in turn be the consequence of large amounts of extravascular blood. Depression of cortical EEG activity, indicating a global neurophysiologic disturbance, is associated with major haemorrhage but not with minor haemorrhage (*Greisen et al* 1987b).

8. ISCHAEMIA OF THE PRETERM BRAIN

The typical structural lesion to the preterm brain (apart from parenchymatous haemorrhage) is periventricular leucomalacia. It is located supero-laterally to the lateral ventricles, a watershed area between centrifugal and centripetal arterial blood supply during this period. The severity ranges from mild gliosis to multiple, large cysts all along the margins of the ventricles. It is often bilateral, but may be markedly asymmetric.

Periventricular leucomalacia shares many clinical risk factors with GLH (*Trounce et al* 1988) and may often be found in the same infants, but notably the risk does not increase with extreme prematurity and the lesion may occur at any time during the neonatal period, e.g with septic shock.

The acute stages can not be diagnosed with certainty, cysts develop over several weeks, and may be demonstrated by cranial ultrasound in about 5% of survivors with birthweight less than 1500 g. The majority develop cerebral palsy.

No animal model of periventricular leucomalacia has been developed. In the newborn puppy, flow to periventricular white matter decreased markedly during haemorrhagic or endotoxin induced hypotension (*Young et al* 1982), whereas flow to grey matter was unaffected. During arterial hypoxaemia flow to subcortical white matter only doubled whereas glucose utilization increased 4 to 5 fold (*Cavazutti & Duffy* 1982), indicating that the flow increase was insufficient for the maintenance of aerobic glycolysis, in contrast to the findings in grey matter structures. These findings point to a selective vulnerability of periventricular white matter to hypoxic-ischaemic injury.

8.1. ELECTROPHYSIOLOGICAL SIGNS OF ISCHAEMIA

In acute, localised brain ischaemia the concept of a grey zone of 'penumbra' has been proposed (*Astrup* 1982), a state where the flow rate is low enough to cause electrical failure but not to cause membrane failure and tissue damage. In adult human cortex electrical failure occurs when the flow rate falls below 20 ml/100 g/min (*Trojaborg & Boysen* 1973), in adult baboon cortex the threshold was 12-16 ml/100 g/min, for baboon subcortical grey matter 10-15 ml/100 g/mins (*Branston et al* 1984).

Flash evoked visual potentials can easily be recorded from preterm infants shortly after birth and may be acutely, reversibly affected by hypoxia (*Hrbek et al* 1978, *Pryds et al* 1988b). Flash evoked potentials could be recorded in clinically stable, mechanically ventilated infants with the lowest levels of global CBF (down to 7 ml/100 g/min, *Greisen & Trojaborg* 1987). Although in one third of the infants the recorded potentials showed prolonged latencies compared to similar spontaneously breathing infants (*Pryds et al* 1988b), this was not related to the level of CBF. Furthermore, latency did not change when CBF changed as a result of acute P_aCO_2 change. As the visual pathways pass the periventricular white matter, these findings would suggest that such low flow is adequate, for function, and therefore for structural integrity, if not for growth and development.

In mechanically ventilated, preterm infants, who were hypotensive with low cerebral blood flow velocities during the first hours of life, spontaneous cortical electrical activity was present in all cases although nearly always reduced, compared to circulatorily stable infants (*Greisen et al* 1988). There was only partial improvement of the electrical dysfunction when circulation was improved by transfusion. It is not clear if the concept of ischaemic penumbra is relevant to global ischaemia, to white matter ischaemia, or to ischaemia lasting several hours or even days (*Jones et al* 1981) and it is likely that the electrical dysfunction demonstrated in these two studies was more related to primary (asphyxial?) insult than to current ischaemia.

8.2. LOW CBF AND OUTCOME

Lou et al (1979b) demonstrated brain atrophy in six of the ten infants, who had 'cortical' flow rates of less than 20 ml/100 g/min a few hours after birth. *Ment et al* (1983) found neurodevelopmental deficit associated with high or low CBF-index in the first days of life. In contrast, normal neurodevelopmental outcome was recently demonstrated in two preterm infants with mean CBF of 5 ml/100 g/min at 6 and 11 days of age as estimated by ^{15}O positron emission tomography (*Altman et al* 1988).

In conclusion, the threshold of electical failure for global CBF is likely to be considerably less than 10 ml/100 g/min, and the threshold of membrane failure still lower, at a level at which the methods of measurement are too inaccurate for conlusions about individual infants. The thresholds will be higher if arterial hypoxaemia, hypoglycaemia, or seizures are present. Such factors may explain the omnious prognostic significance of low CBF shortly after birth.

9. SUMMARY AND PERSPECTIVES

Studies of cerebral blood flow (CBF) in preterm infants were reviewed. CBF is low in healthy infants, 30 to 35 weeks of gestation, compared with older infants, children, and adults. Normal CBF-CO_2 reactivity and normal flow-metabolism coupling have been demonstrated at this early stage of human brain development. CBF

is reduced during neonatal illness treated with mechanical ventilation to levels similar to those associated with electrical failure in adult man and adult animals. The presence of normal CBF-CO_2 reactivity in clinically stable, mechanically ventilated infants, however, suggests that the low flow state is regulated, and in particular that the low flow is not a result of low perfusion pressure. Furthermore, the low levels of CBF are not associated with evidence of electrical failure, nor could electrical failure be demonstrated in the low flow condition preceding treatment of arterial hypotension in preterm infants during the first hours of life. Improved methods for the measurement of blood flow to white matter combined with the search for more subtle signs of neurophysiological disturbance may allow description of the contribution of ischaemia to the development of periventricular leucomalacia. The role of disrupted CBF-regulation in the pathogenesis of cerebral haemorrhage in preterm infants still remains to be elucidated, and may have to await methods for measurement of blood flow to the germinal matrix itself.

10. SUMMARY IN DANISH

En intravenøs ^{133}Xe udvaskningsmetode blev tilpasset nyfødte børn. Efter datamatsimulation og sammenligning af ^{133}Xe aktiviteten i arterielt blod og udåndingsluft med resultaterne af ekstern skintillation over thorax kunne det konkluderes at den intravenøse metode giver samme værdier for den globale hjernegennemblødning (CBF_∞) som ville kunne opnås med den arterielle metode. CBF_∞ sammenlignedes med Doppler ultralydbestemmelse af strømningshastigheden i arteria carotis interna hos nyfødte børn; der fandtes rimelig overensstemmelse. CBF_∞ er lav hos raske, for tidligt fødte børn, ca. 20 ml/100 g/min, sammenlignet med 45 ml/100 g/min for raske voksne. Hjernegennemblødningen faldt under dyb søvn som tegn på normal kobling til hjernens stofskifte. Hos respiratorbehandlede, for tidligt fødte børn var CBF_∞ endnu lavere, 10-14 ml/100 g/min. Årsagen til dette lave niveau kunne ikke identificeres. Under respiratorbehandling kunne påvises spontan EEG aktivitet, flash-udløste EEG potentialer og normal CBF-CO_2 reaktivitet. Den spontane EEG aktivitet ændredes ikke sikkert i forbindelse med øgning af CBF ved blodtransfusion i de første levetimer. De udløste EEG potentialer ændredes heller ikke i forbindelse med ændring af CBF ved ændring af P_aCO_2 i 2. levedøgn. Det vil sige at der trods det lave CBF niveau ikke var funktionelle tegn på cerebral iskæmi og dermed ingen sandsynlig direkte betydning for udvikling af hypoksisk-iskæmisk hjerneskade. Derfor kan måling af hjernens globale gennemblødning endnu ikke anbefales til klinisk brug.

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