Vasoactivity of the major intracranial arteries in newborn infants

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SUMMARY Blood flow to the head and arms was measured by a new volumetric Doppler technique in 30 preterm infants and 10 full term infants. At least 80% of this blood flow is considered to perfuse the brain. At the same time mean blood velocity in the middle and anterior cerebral arteries was measured by Duplex Doppler scanning. While blood flow to the head and arms remained substantially constant in both groups over the first 48 hours of life (60 ml/100 g brain weight/min), blood velocity doubled in both cerebral arteries in the preterm group. The term infants had higher blood velocities in both arteries at all times, but the velocities also increased over 48 hours, although to a lesser extent than in the preterm group. These findings imply that the major intracranial arteries are themselves vasoactive, being dilated at birth and subsequently constricting, possibly as an autoregulatory response to rising arterial blood pressure. While vasodilated, the cerebral arteries will be less efficient at damping pressure transients, placing preterm infants at particular risk of periventricular haemorrhage during the early hours of life. The implications for possible approaches to the prevention of cerebral haemorrhage are discussed.

Despite extensive investigation, the physiological and pathological mechanisms underlying both cerebral haemorrhage and ischaemia in the preterm newborn infant remain controversial. The common observation of a high incidence of periventricular haemorrhage during the first 48 to 72 hours of life^{1 2} and the relative rarity thereafter, irrespective of the severity of later illness, has led to the hypothesis that susceptibility to haemorrhage and possibly cerebral ischaemia is related to the process of cardiovascular adaptation to extrauterine life. In this study we investigated the dynamics of the cerebral circulation in both full term and preterm infants during the first 48 hours of life.

Doppler techniques may be used to measure the velocity of blood within the anterior and middle cerebral arteries through either the anterior fontanelle or the thin bone of the newborn infant's skull.^{3 4} Although under experimental conditions and in animal models mean velocity in the anterior cerebral arteries has been shown to correlate with cerebral blood flow, the use of measurements of cerebral artery velocity to predict cerebral perfusion presupposes that these arteries do not themselves change in calibre. Physiological studies in mature

animals have suggested that the arteries as proximal as the circle of Willis have a capability to dilate and constrict, particularly in response to changes in perfusion pressure.^{5–8} A new volumetric Doppler technique has therefore been devised that makes no assumptions about the vasomotor properties of the arteries supplying the brain.

Patients and methods

Study populations. We studied two groups of infants.

The preterm group comprised 30 infants born at the Bristol Maternity Hospital between June 1985 and January 1986 with a gestation of 33 weeks or less (range 24–32 weeks, median 30 weeks), excluding those with congenital malformation. Their birth weights ranged from 760 to 2140 g, with a median of 1430 g. Their clinical characteristics are summarised in Table 1.

The term group comprised 10 infants with a gestation of 37 weeks or more (range 38–41 weeks, median 40 weeks) born during the same period and who had no perinatal problems. Their birth weights ranged from 2730 to 3960 g, with a median of 3275 g.

Table 1 Clinical characteristics of preterm study group (n=30)

Sex (M:F)	13:17
Reason for delivery:	
Spontaneous preterm labour	18
Antepartum haemorrhage	5
Prolonged rupture of membranes (complicated)	6
Hypertension	1
Delivery (vaginal/caesarean section)	18:12
Singletons/twins	22:8
Respiratory distress syndrome	16
Outcome:	
Periventricular haemorrhage (real time ultrasound)	4
'Flares' and/or periventricular leucomalacia (real time ultrasound)	5
Survival to discharge from hospital	29

Principles and instrumentation. In the newborn infant blood leaving the left ventricle is distributed by way of the aortic arch to three major vascular territories—the head and arms, the pulmonary circulation through the patent ductus arteriosus, and subdiaphragmatic structures. Blood velocity within the aorta may be calculated from the Doppler shift in ultrasound frequency returned by moving blood cells according to the formula:

$$\text{Velocity} = \text{frequency shift} \times c / 2f \cos A$$

where c is the speed of ultrasound in tissue (1500 cm/sec), f is the frequency of ultrasound (5 MHz in this study), and A is the Doppler angle.

The vessel cross-sectional area may be calculated from M mode measurement of its diameter, assuming a circular section, and the volume flow obtained by multiplication of area and mean velocity. The technique has been widely described in both adult and paediatric publications for the measurement of cardiac output.^{9 10} If flow is measured before and after the origin of the great vessels leaving the aortic arch subtraction will leave that portion of blood flow that supplies the head and arms. In the adult about 77% of this blood perfuses the brain. (Skidmore R. Unpublished observations. See appendix.) In the newborn infant, particularly the preterm infant, where the brain is large compared with the body, this proportion will be even higher (at least 80%) and so this measurement is likely to be a good indicator of cerebral perfusion. Brain weight may be estimated from the head circumference according to the method of Dobbing and Sands,¹² which allows blood flow to be standardised between patients.

Doppler signals from the ascending aorta were obtained in the substernal four chamber view where an oblique Doppler angle allows more even sampling across the vessel diameter than is possible using the suprasternal approach. Signals from the preductal descending aorta were obtained in the

long axis view from the suprasternal or left supraclavicular window.

The instrumentation used was a Duplex scanner (ATL Mk 600, ATL, Bellevue, Washington State) with 5 MHz Doppler flowmeter directly interfaced to a microcomputer (Apple IIe). The Duplex system uses the real time image for identification of the vessel, precise placement of the discrete Doppler sample volume, and measurement of the Doppler angle. The digitally encoded Doppler spectrum is stored in computer memory. Here noise is removed by thresholding before computing mean and maximum frequency shift contours, which are stored on disc and used for calculation of flow variables. The system allows about 3.5 seconds of Doppler signal to be collected, corresponding to four to eight cardiac cycles.

Errors in Doppler assessment of volume flow may be both random and systematic. The random errors resulting from inaccuracy in determination of the vessel size and Doppler angle may be reduced by taking the mean of several measurements at each site. In most cases a minimum of four observations were made. Systematic errors largely arise from preferential sampling of the central stream velocity in larger arteries and have been minimised by laboratory calibration of the system over a range of vessel diameters using a pulsatile flow rig.

Measurements of the *velocities* in the anterior and middle cerebral arteries were made with a similar technique, using a transfontanelle approach in the former case and a temporal approach for the latter, a near zero Doppler angle being achieved in each case. Arterial blood pressure in the preterm group was measured non-invasively using the oscillometric method (Sentry Automated Blood Pressure Monitor, Automated Screening Devices Inc, California), with the cuff placed whenever possible on the right arm. Doppler and blood pressure measurements were made at fixed intervals after birth—between 1 and 2 hours and at 12, 24, and 48 hours. Infants in the preterm group also had measurements made at 6 hours.

The results were analysed using paired and unpaired t tests (two tailed) for velocity and blood pressure data and Wilcoxon signed ranks, matched pairs, or Mann-Whitney U tests as appropriate for volumetric data (also two tailed).

Informed parental consent was obtained for this study.

Results

Velocity. In both the middle and anterior cerebral arteries of the preterm infants there was a progressive increase in velocity over the first 48 hours of life

(Figures 1 and 2); at 48 hours the velocities were about double those shortly after birth ($p<0.001$ for each artery). A similar but less pronounced change was seen in the term infants (significantly only for the anterior cerebral artery, $p<0.01$). At each age studied the velocities in the term infants were significantly higher than in the preterm infants.

Blood flow to head and arms. In contrast there were no significant differences in blood flow to head and arms per 100 g brain weight over this period in either the preterm or term groups (Table 2), but flow per unit mass was similar in the two groups. On subtracting an estimated 20% from these values to compensate for blood perfusing tissues other than the brain, our mean estimate of cerebral blood flow for both groups was 46 ml/100 g brain weight /min

Fig. 1 Mean (SD) velocities in the anterior cerebral artery in the two groups. There were significant differences between term and preterm infants at all ages and significant increases in velocity from initial recordings in both term and preterm infants by 24 hours of age.

* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Fig. 2 Mean (SD) velocities in the middle cerebral artery in the two groups. There were significant differences between term and preterm infants at all ages and significant increases in velocity from initial recordings in the preterm infants by 24 hours of age.

* $p<0.05$; ** $p<0.001$.

for the full term group and 51 ml/100 g brain weight/min for the preterm group.

Arterial blood pressure. Mean arterial blood pressure increased progressively in the preterm infants (Table 2). The differences were significant at 24 and 48 hours ($p<0.01$).

Discussion

The values of 46–51 ml/100 g brain weight/min were well within the wide range of values for cerebral blood flow measured using other techniques,¹³ and the similar values obtained in both term and preterm infants lends credence to this Doppler method. The

Table 2 Blood flow to head and arms (ml/100 g brain weight) and arterial blood pressure (mm Hg) over the first 48 hours of life (insufficient blood pressure data on term infants)

Age (hours)	Full term infants				Preterm infants					
	Flow to head and arms (n=)				Flow to head and arms				Mean blood pressure (n=)	
	Mean	(SD)	95% Confidence limits		Mean	(SD)	95% Confidence limits	Mean	(SD)	95% Confidence limits
1-5	57.0	(21.5)	41-73	(10)	62.0	(37.2)	48-76	40.4	(8.0)	37-44
6-0	—	—	—	—	63.4	(36.4)	50-77	43.4	(9.1)	40-47
12-0	59.1	(12.5)	50-68	(10)	60.7	(32.2)	49-72	43.6	(8.6)	40-47
24-0	59.5	(13.6)	49-70	(10)	69.6	(34.1)	57-83	45.9	(7.2)	43-49
48-0	55.6	(16.6)	43-68	(10)	62.6	(28.1)	52-73	49.4	(11.0)	45-54

constancy of cerebral blood flow in both groups of infants over a period during which arterial blood pressure and presumably also cerebral perfusion pressure is rising (Table 2)¹¹ suggests that autoregulation was intact at least for most of the infants studied.

The anterior and middle cerebral arteries between them supply blood to a large proportion of the brain and so velocities in these two arteries may be assumed to be representative of the velocities in all major cerebral arteries. As blood flow is the product of velocity and cross-sectional area the likely explanation of the constant cerebral blood flow with increasing velocities is that the major arteries have altered calibre, being dilated at birth but progressively constricting over the next 48 hours. The ratio between flow and mean cerebral artery velocity provides a measure of cerebral artery area, which may be seen to decrease over time (Fig. 3).

Physiological studies of the cerebral circulation in mature animals may provide an explanation for these findings. By measuring pressure gradients across various segments of the cerebral arterial system during hypo- and hypertension, several workers have shown that the major cerebral arteries are responsible for a large part of cerebral autoregulation, while 'chemical' control of cerebral perfusion

operates more peripherally.⁵⁻⁸ Arterial blood pressure is low at birth and progressively increased in both preterm (Table 2) and term infants.¹¹ We may postulate that the progressive reduction in arterial calibre may be part of the autoregulatory response to these perfusion pressure changes. Histological examination of the cerebral arteries show that they have an ample muscle layer to accomplish the calibre change that we have described, but whether the mechanism of the change is humoral, neurologic, or myogenic remains speculative.

Cerebral artery velocities were higher in the term infants, while apparent cerebral blood flow was similar in both groups. The ratio between flow and velocity—that is, cerebral vessel area—shows not only a progressive reduction in calibre with time but also a markedly increased vessel calibre per unit brain weight in the preterm infants (Fig. 3). This is to be expected as arterial blood pressure is higher in term than in preterm infants, while perfusion per unit brain mass is similar.

Volpe and his group have advanced the hypothesis that periventricular haemorrhage occurs with transient surges in blood pressure and have shown that an unstable pattern of blood pressure is characteristic of infants with respiratory disease, particularly those who do not synchronise with their ventilators.^{14 15} These surges are more likely to be transmitted to the delicate capillary beds as the degree of dilatation of the large cerebral arteries becomes greater. In other words, the risk is greater the more preterm and the younger the infant. This is in accord with observed fact.¹ Thus the susceptibility of these infants to haemorrhage may be not so much due to a *failure* of autoregulation, as has been widely suggested, but rather a consequence of the mechanism by which autoregulation is achieved. Similarly, the very preterm and the very young infant with maximal cerebral vasodilatation might be at or to the left of the autoregulatory portion of the preterm pressure/cerebral blood flow curve and thus be simultaneously at high risk of cerebral ischaemia as well as haemorrhage.

These observations may also have therapeutic implications. If the cause of cerebral arterial vasodilatation is hypotension then methods of supporting the circulation during the early hours of life may be effective in lowering the risk not only of cerebral ischaemia but also of haemorrhage. The ready improvement in peripheral perfusion and arterial blood pressure attendant on colloid infusion in many sick preterm infants suggests that their relative hypotension is secondary to hypovolaemia. The report of a reduced incidence of periventricular haemorrhage after routine administration of plasma to preterm infants¹⁶ is of interest in this respect.

Fig. 3 Mean (SD) standardised flow:velocity ratios in the two groups, showing that preterm infants were significantly more cerebrally vasodilated than term infants at all ages but that they became more vasoconstricted with age (significant from 24 hours of age).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

More work is required to determine the effects of circulatory support on both cardiac function and on the cerebral vasculature. Doppler ultrasound offers an apparently safe and convenient method for continuing the investigation of the neonatal circulation.

Appendix

Doppler ultrasound flow measurements in the adult neck (ml/min)

Brachiocephalic trunc 700	} leaving aortic arch	
Left common carotid artery 500		
Left subclavian trunc 200		
		700+500+200
		=1400

Internal carotid arteries	} to brain 2(380+
380 each	
Vertebral arteries 160 each	160)=1080

Approximate percentage flow to brain = $1080/1400 \times 100 = 77\%$.

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