CBF Reactivity in Hypotensive and Normotensive Preterm Infants

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ABSTRACT

Perinatal distress in the preterm neonate, and the consequent loss of cerebrovascular autoregulation, has been implicated in the pathogenesis of neonatal cerebral lesions. A component of this distress is thought to be hypotension. We examined the autoregulatory capacity of hypotensive and normotensive infants using the ^{133}Xe technique to measure cerebral blood flow. Global CBF was measured during only normotension in 5 infants, and during both hypotension and normotension in 11 infants. All the infants were ventilated and blood pressure was measured using an intra-arterial catheter. Fourteen CBF measurements were made on the normotensive infants. Forty-seven CBF measurements were made on the hypotensive infants, 34 measurements during hypotension and 13 during normotension. The global CBF of the normotensive and hypotensive infants were 13.3 and 13.6 mL/100 g/min, respectively. The mean arterial blood pressure (MABP)-CBF reactivity (95% CI) of the normotensive and hypotensive infants were 1.9% (-0.8% to 4.7%)/mm Hg and 1.9% (0.8% to 3.0%)/mm Hg, respectively. The CO_2-CBF reactivity (95%CI) of the normotensive and hypotensive infants was

11.1% (6.8% to 15.5%)/KPa $\Delta PaCO_2$ and 4.1% (-5.0% to 14.1%)/KPa $\Delta PaCO_2$. The implications of these calculated CBF reactivities is that normotensive infants may have intact autoregulation but with a diminished response to fluctuations in $PaCO_2$. The hypotensive infants appear to have attenuated or absent autoregulation with little or no response in CBF to changes in $PaCO_2$. (*Pediatr Res* **54: 848–853, 2003**)

Abbreviations
CBF, global cerebral blood flow
CBFv, cerebral blood flow velocity
MABP, mean arterial blood pressure
MAP$_{15}$, MABP averaged over 15 min
PaCO$_2$, partial pressure of carbon dioxide
PDA, patent ductus arteriosus
VLBW, very low birthweight
95%, CI 95% confidence interval
^{133}Xe, ^{133}Xenon radionuclide

Hypotension in the sick preterm infant has been implicated as one causative factor in the pathogenesis of a number of serious conditions including intraventricular hemorrhage (IVH) (1), periventricular leukomalacia (PVL) (2), necrotizing enterocolitis (3), and developmental delay in preterm infants (4).

It is thought that perinatal asphyxia combined with hypotension leads to a loss of cerebrovascular autoregulation, which may lead to a pressure passive cerebral circulation (5). In this state, abrupt elevations in systemic blood pressure may be transmitted to the fragile vessels of the germinal matrix, possibly resulting in intraventricular hemorrhage. Historically, systemic hypotension was thought to lead to under perfusion of watershed areas, which then underwent infarction and cystic

necrosis, resulting in PVL (6). Thus, absent autoregulation may be central to many causes of perinatal CNS pathology.

The work of Tyszczuk *et al.* among others, has led to the re-evaluation of the absent autoregulation hypothesis (7). They found no significant difference between the cerebral blood flow (CBF) of normotensive infants and that of hypotensive infants. Furthermore, a number of studies have found no association between hypotension and PVL (2, 8, 9). More recently, it was found that 53% of ventilated preterm infants had evidence of impaired autoregulation (10) and Boylan *et al.* have identified abnormalities in the autoregulatory capacity of preterm infants (11). Only in the work of Tyszczuk was the influence of hypotension analyzed in the etiology of impaired autoregulation.

Changes in arterial carbon dioxide are a major mediator of CBF variation in the normal preterm infant (12, 13). It has been suggested that blunting of this normal variation in vessel caliber is associated with cerebral lesions (13).

CBF may be measured using different modalities. If a gold standard for measurement could be said to exist, it might be radioactive microsphere method (14). The i.v. ^{133}Xe technique

method is a good compromise, in which global CBF may be measured accurately over 15 min, and compares with both the radioactive microsphere method (in animals) (15) and other modalities (16, 17).

The aim of this study was to test the hypothesis that CBF reactivity to changes in MABP or $PaCO_2$ is lost in hypotensive, ventilated, preterm infants.

METHOD

Infants were eligible to enter the study if they were mechanically ventilated and had an intra-arterial catheter, either umbilical or peripheral. The indwelling arterial lines were calibrated before each measurement of CBF. All infants were sedated with a diamorphine infusion and, if clinically indicated, some received muscle paralysis with pancuronium bromide. Written informed consent was obtained from one or both parents and the hospital research ethics committee approved the study. Radiation dosage was kept well within accepted national guidelines.

The infant's physiologic parameters were displayed on a Hewlett Packard physiologic monitoring system, Merlin 66S (Hewlett Packard, Palo Alto, CA, U.S.A.). This was connected to a continuous monitoring system (MARY system, Meadowbank Medical Systems Ltd, Loughborough, U.K.) that recorded second-to-second data.

The infants were enrolled in a study investigating the effect of treating hypotension on CBF. The sequence of events for measuring CBF and MAP_{15} are outlined in Fig. 1. During the period of this study it was the policy of this unit to maintain MABP above the 10th centile (BPmin) for birthweight and postnatal age (18). Hypotension was treated in a stepwise manner, and following initiation of treatment, thirty minutes was allowed for stabilization of MABP. The initial intervention was the use of 4.5% human albumin solution infused over 30 min, which may have been repeated once. If volume expansion was ineffective, a dopamine infusion was started at a dose of 5 $\mu g/kg/min$. After stabilization, and if still hypotensive, the infant was randomized to either increase of dopamine to 10 $\mu g/kg/min$ or the addition of dobutamine at a dose of 10 $\mu g/kg/min$. If still hypotensive, either the dopamine dose was increased to 10 $\mu g/kg/min$ or dobutamine was added at 10 $\mu g/kg/min$, the cross over treatment. If an infant had resistant hypotension, then by the end of the treatment protocol, it should be receiving both dopamine and dobutamine at doses of 10 $\mu g/kg/min$.

Before and 30 min after intervention, the CBF was measured using the i.v. ^{133}Xe technique. This has been described before (16) but is outlined briefly here. 30 MBq/kg of the radionuclide ^{133}Xe was injected as a peripheral, 1 mL i.v. bolus. Collimated Sodium-Iodide gamma-detectors were used to measure activity over the upper right chest wall and the temporofrontal region of the infant's skull for 15 min. Data from detectors were converted by an analogue to digital converter and stored on a laptop computer (Cortexplorer, Vertec Scientific Limited, U.K.). Background activity was measured for between 2 and 5 min before injecting the Xe radioisotope. The intra-individual variation of CBF using the ^{133}Xe technique is between 10% and 15% (19). One investigator (DJ) recorded the CBF measurements. The maximum radiation dosage of Xenon per measurement administered to each infant is shown in Table 1. No baby received more than 3.5 μSv, in contrast to one chest x-ray that delivers a dose of 20 μSv.

The CBF was calculated over a 15-min period from the point that the chest count fell to 20% of the maximum. This value was used to minimize contamination of the cranial counter from activity in the upper airway. At the end of a CBF measurement arterial blood was withdrawn to measure $PaCO_2$. The MABP during the CBF measurement was averaged to yield a mean over 15 min (MAP_{15}).

If the MAP_{15} was less than or equal to the BPmin during any of the CBF recordings then the infant was deemed to be hypotensive. Alternatively, the infant is designated normotensive if the MAP_{15} was above BPmin before and after treatment. Table 1 contains clinical details of the infants in the two groups, including the level of sedation, inotrope requirement, total number of CBF measures and the maximum dosage of radiation given.

Statistics. The Mann-Whitney U test was applied for comparisons between groups, since the data were not normally distributed. A *p* value of less than 0.05 was deemed to represent significance.

Multiple regression was used to assess CBF reactivity because it allowed modeling of the simultaneous effects of predictor variables. To ensure a homogeneous variance the natural logarithm of the CBF was used as the dependent variable and the MAP_{15} and $PaCO_2$ as the independent variables. The study made use of repeated measures on each infant. To allow for this, dummy variables were used, one for each of n infants in each group (D1-Dn) (20). This produces a regression equation of the form :

The anti-logarithm of the regression coefficients β_1 and β_2 provide the percentage values of MAP_{15} and CO_2-CBF reac-
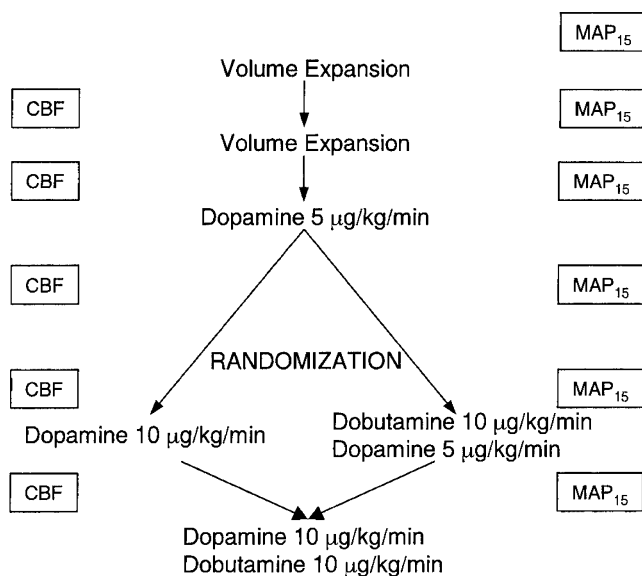

Figure 1. The hypotension treatment protocol is illustrated. A maximum of 5 CBF measurements were obtained, before and after initiation or escalation of treatment. The duration of a CBF measurement is 15 min, during which MABP is continuously measured and averaged for the 15-min period (MAP_{15}).

Table 1. *Clinical details of infants enrolled into the study*

Infant	BWt (g)	Hb (g/dL)	Glucose (mmol/L)	Paralysis	CBF (n)	Max dosage MBq (μSv)	Treatment level	Most severe cranial ultrasound	Outcome
1	1260	15.2	1.9,2.3	Yes	5	57.5 (2.9)	DA5, 10	?	Discharged
2	760	13.8	?	Yes	5	28 (1.4)	DA5, 10, Dob10	Bulky choroids	Care withdrawn
3	2100	17.6	?	Yes	3	72 (3.5)	V, DA5,	Normal	Discharged
4	660	13.4	5.0	Yes	5	21 (1.1)	V, DA5, Dob10	Ventricular Infarct	Care withdrawn
5	600	14.9	?	Yes	3	21.5 (1.1)	V, DA5	?	Discharged
6	540	18.1	?	No	4	22.5 (1.2)	V, DA5, Dob10	Grade 2	Care withdrawn
7	720	10.5	2.6,8.1	No	4	30 (1.5)	DA5, 10	Mild ED	Discharged
8	580	18	?	No	5	24 (1.2)	DA5, Dob10	Bilateral grade 2	Discharged
9	620	16.6	5.9,10.3	No	5	26 (1.3)	V, DA5, Dob10	Left grade 2	Discharged
10	1200	17.4	5.9	No	3	53 (2.6)	DA5, Dob10	?	Discharged
11	1100	17.9	4.4	Yes	5	36 (1.8)	DA5, 10, Dob10	Bilateral ED	Discharged
12	1000	12.2	?	No	4	49 (2.5)	V	Bilateral ED	Care withdrawn
13	1040	18.3	?	Yes	2	40 (2.0)	V	Normal	Discharged
14	1355	12.0	?	No	2	57 (2.8)	V	Normal	Discharged
15	1080	?	?	No	3	43.1 (2.2)	V	Bilateral ED	Discharged
16	1060	13.3	2.9	No	3	36 (1.8)	DA5, 10	Left grade 2	Discharged

Clinical details of all patients: BWt, birth weight; Hb, hemoglobin and glucose at the time of CBF measurement; Paralysis with pancuronium bromide; CBF, number of CBF measurements; Maximum dosage given for one CBF measurement in MBq (μSv); Treatment level (V, volume expansion; DA and Dob, dopamine and dobutamine dosage in μg/kg/min.); Most severe cranial ultrasound scan graded by the system of Papille *et al.* (ED echodensity).

tivities, respectively. Confidence limits for MAP_{15}-CBF and $PaCO_2$-CBF reactivity were calculated using the *t* distribution. One degree of freedom was subtracted from the total number of observations for each factor estimated.

CBF reactivity. The calculated CBF-reactivity is the percentage by which CBF varies per unit variation of another factor (*e.g.* MAP_{15} or $PaCO_2$). When the 95% confidence interval encompasses zero there may be no change in CBF for variation in another factor. In the case of MAP_{15}-CBF reactivity, no change in CBF against fluctuating MAP_{15} implies intact autoregulation (21). In contrast 0% $PaCO_2$-CBF reactivity implies absence of the normal change in vessel caliber in response to fluctuating $PaCO_2$ (22).

RESULTS

Sixty-one CBF recordings were obtained from sixteen infants over 23 mo. The infants were divided into two groups based upon their MAP15 at the time of CBF acquisition. None of the infants appear in both groups.

All 14 CBF measurements on the normotensive infants (infants 12–16) were acquired while MAP_{15} was greater than BPmin. Four infants (infants 12–15) were treated with volume for poor peripheral perfusion, low urine output or metabolic acidosis, and the CBF measured before and after. The fifth infant (infant 16) was treated inadvertently for hypotension while normotensive, the MAP_{15} being greater than BPmin.

During 34 of the 47 CBF measurements performed on the hypotensive infants (infants 1–11) MAP_{15} was less than BPmin. During the remaining 13 measurements, the infants were normotensive.

Table 2 contains clinical data about the two groups. The two groups differ significantly in two of the parameters, MAP_{15} and postnatal age. The upper range of the MAP_{15} in the hypotensive infants has values measured after treatment, when some infants were rendered normotensive.

The changes in physiologic parameters between CBF measurements are detailed in Table 3. The interval represents the

Table 2. *Demographic details for the normotensive and hypotensive infants as median (range) values*

	Normotensive (5 infants)	Hypotensive (11 infants)	*p* value*
Birthweight (g)	1060 (1000 to 1355)	720 (540 to 2100)	0.26
Gestation (weeks)	28 (26 to 29)	26 (24 to 32)	0.26
Postnatal age (hours)	43 (5 to 94)	13 (3 to 61)	0.02
MAP_{15} (mmHg)	40 (27 to 44)	24 (19 to 51)	0.0001
$PaCO_2$ (KPa)	5.6 (3.9 to 12.3)	4.9 (2.3 to 6.9)	0.15
CBF (ml/100g/min)	13.3 (8.6 to 23.1)	13.6 (7.0 to 39.7)	0.86

PaCO2 (mmHg) = KPa*0.133).

* Normotensive versus hypotensive groups.

time between serial CBF measurements. The step change in MAP_{15} between CBF measurements is given both as absolute values and the percentage change, relative to the previous value.

Normotensive group. The MAP_{15}-CBF reactivity and 95% confidence limits for the normotensive group were 1.9% (−0.8% to 4.7%)/mm Hg ΔMAP_{15}. The CO_2-CBF reactivity with 95% confidence limits is 11.1% (6.8% to 15.5%)/KPa $\Delta PaCO_2$. The lower confidence interval of the MAP_{15}-CBF encompasses zero and that of the CO_2-CBF reactivity does not (Fig. 2*A* and *B*).

The analysis was repeated excluding the infant who received dopamine (infant 16), the calculated reactivities were similar; MAP_{15}-CBF reactivity 5.0% (−5.6% to 7.0%)/mm Hg ΔMAP_{15}, and CO_2-CBF reactivity 9.5% (3.4% to 15.5%)/KPa $\Delta PaCO_2$.

Hypotensive group. The MAP_{15}-CBF reactivity with 95% confidence limits is 1.9% (0.8% to 3.0%)/mm Hg ΔMAP_{15}. In contrast to the normotensive infants, the lower confidence interval of MAP_{15}-CBF reactivity is greater than zero. The CO_2-CBF reactivity with 95% confidence limits are 4.1% (−5.0% to 14.1%)/KPa $\Delta PaCO_2$ (Fig. 2*A* and *B*).

DISCUSSION

The aim of this study was to assess the influence on CBF of changes in blood pressure in hypotensive, ventilated, preterm

Table 3. *Variation of physiological variables between CBF measurements as the median (range)*

	Normotension	Hypotension	*p* value*
Number of CBF measures	14	47	
(Normotensive/hypotensive)	(14/0)	(13/34)	
Interval between CBF	84 minutes	90 minutes	0.50
Measurements	(20 min to 87 hours)	(24 min to 45 hours)	
Absolute ΔMAP_{15} (mm Hg)	2 (0 to 9)	2 (0 to 29)	0.63
Relative ΔMAP_{15} (%)	6% (0% to 465%)	10% (0% to 109%)	0.29
Absolute $\Delta PaCO_2$ (KPa)	0.0 (-8.1 to 2.1)	0.0 (-2.7 to 2.7)	0.80
Absolute ΔCBF (ml/100g/min)	1.0 (0.6 to 12.6)	2.7 (0.1 to 26.6)	0.99
Relative ΔCBF (%)	12% (4% to 55%)	18% (1% to 99%)	
MAP_{15}-BPmin (mm Hg)	+10 (+1 to +14)	-1 (-10 to +24)	<0.001

* Normotensive versus Hypotensive groups.

infants. The MAP_{15}-CBF reactivity of normotensive and hypotensive infants was 1.9%/mm Hg, but the lower confidence interval of the normotensive infants encompassed 0. The CO_2-CBF reactivities of the normotensive and hypotensive infants were 11.1% and 4.1%/KPa $\Delta PaCO_2$, respectively. We speculated from our results an impairment of MAP_{15}-CBF autoregulation, and attenuation of $PaCO_2$-CBF reactivity in these hypotensive, ventilated preterm infants. The CBF was measured using the i.v. ^{133}Xe technique, which is accepted as a valid tool for measuring the CBF in both term and preterm infants (16, 23, 24). The repeated measures design of this study, combined with the need for incorporating simultaneous changes in two factors (MAP_{15} and $PaCO_2$), necessitates the type of analysis used (25).

Others have used Doppler ultrasound to measure CBFv (26–29). While there is close agreement between ^{133}Xe technique measured global CBF and CBFv (16), Doppler ultrasound is limited by the assumptions of constant vessel caliber, and constant angle of insonation to the artery under scrutiny. When studied in an animal model, the Doppler derived values of CBFv were erroneous under conditions of low flow (30), so it seems that large insonated cerebral vessels take part in autoregulation (31), and that indices derived from CBFv values may underestimate true CBF under extreme physiologic conditions (30). The ^{133}Xe technique permits accurate measurement of global CBF compared with radioactive microsphere technique (14). Additionally, from an ethical perspective, measurement of CBF must not compromise the care of the infant. Each ^{133}Xe derived CBF measurement took 15 min to acquire caused minimal disturbance to the infant and did not materially affect the starting of treatment for the low blood pressure. The technique has limitations; rapid serial CBF measurements over short time intervals, less than 15 min, cannot be measured. Furthermore, there is also a look-through phenomenon, where tissues with a high CBF are measured in preference to tissues with a lower CBF in the same field of interest. Lastly, there is an exposure of radiation to the infant. The dose per measurement is in the order of 5 μSv, and the total dose per infant from a maximum of 5 CBF measurements (Table 1) is approximately less than the equivalent dose from one neonatal chest x-ray (20 μSv); this is well within national safety margins.

The MAP_{15}-CBF reactivities of both normotensive and hypotensive infants were 1.9%/mm Hg change in MAP_{15}. The value of 1.9%/mm Hg is similar to reactivities calculated by others (27, 28) in preterm infants, using different methodologies. The most comparable report is an observational study undertaken by Pryds and colleges, who used the ^{133}Xe technique (13). In a group of ventilated, preterm infants they calculated a mean change in CBF of 0.8% (95% CI -0.6% to 2.0%) per mm Hg MABP. Unlike this study, they did not categorize the infants with regard to blood pressure or induce changes in blood pressure. The MAP_{15}-CBF reactivities calculated by our group and others imply a small change in CBF per unit change in MAP_{15}.

While the MAP_{15}-CBF reactivity of both the hypotensive and normotensive infants is the same, the lower confidence limit of the hypotensive infants, 0.8%/mm Hg, is greater than zero. This is in contrast to the work of others, where the lower confidence interval includes zero (13, 27, 28). Some authors (13) have concluded that autoregulation is preserved when the lower confidence limit encompasses zero. Therefore, one interpretation is that there are significant alterations in CBF with fluctuation in the MAP_{15} of the hypotensive infants, and that their capacity for autoregulation may be disrupted.

The CO_2-CBF reactivities were 11.1% and 4.1%/KPa $PaCO_2$ in the normotensive and hypotensive infants. Assessing the reactivity of the cerebral circulation to alterations in $PaCO_2$ within the physiologic range has fewer technical and ethical difficulties. Consequently, investigators have sought to use CO_2-CBF reactivity, both qualitatively and quantitatively, in the assessment of at risk infants (32, 33). Others have shown that the CO_2-CBF reactivity using the same methodology is 32.8% (95% CI 21.8% to 44.4%)/KPa $PaCO_2$ (13). The infants studied by Pryds and colleagues were of the same postnatal age with persistently normal cranial ultrasound scans. By contrast, others have found values that range from 32.7%/KPa (28) up to 67%/KPa (19, 32). Consequently, a value of 11.1%/KPa $PaCO_2$ in the normotensive infants may be interpreted as an attenuated CO_2-CBF reactivity. While the CBF still accommodates to changes in CO_2, the magnitude of change is less than that seen by others. The infants presented here are of a lower gestational age than those studied previously (12, 13, 19, 28, 32), which may part way explain the low CO_2-CBF reactivity. This discrepancy may be due to maturational differences in the reactivity of the CBF to acute changes in CO_2 (34). In contradistinction to the normotensive infants, the hypotensive infants have a CO_2-CBF reactivity of 4.1% (95% CI -5.0% to 14.1%). This is much lower than expected and encompasses zero within its confidence limits. Thus it would seem that the reactivity of the cerebrovasculature is greatly diminished and
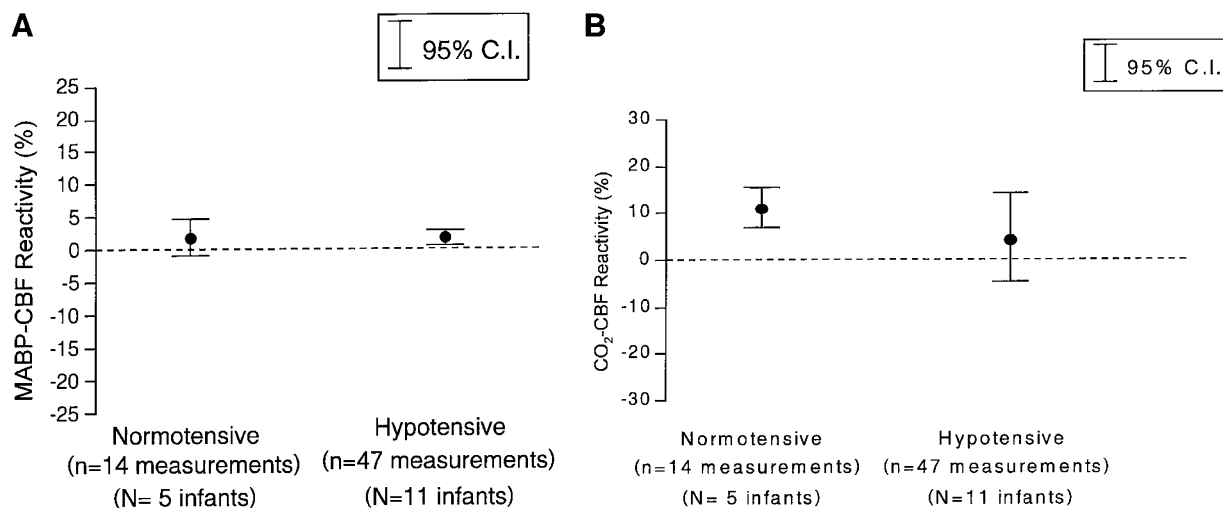
Figure 2. (*A*) The MABP-CBF reactivities for the normotensive and hypotensive infants is illustrated. The vertical bars represent the 95% confidence intervals. (*B*) The CO_2-CBF reactivities for the two groups studied is illustrated. The vertical bars represent the 95% confidence intervals.

possibly absent. This differential loss of autoregulation has been documented in neonatal animal studies (35). It may be that at the level of blood pressure experienced by the hypotensive group, the cerebrovasculature was able to compensate for reduced perfusion pressure by vasoconstriction but unable to accommodate for changes in $PaCO_2$. A teleological argument could be made that it is more important to maintain an adequate CBF in the face of borderline perfusion pressure than to adjust to fluctuations in $PaCO_2$. It must be born in mind however that the hypotensive infants have a lower postnatal age, and that this may contribute to the lower CO_2-CBF reactivity; Pryds and colleges (24) have shown that CO_2-CBF reactivity increases with postnatal age.

We have studied a simple static model of autoregulation (36), in which CBF was measured before and after a step change in another factor, either MAP_{15} or $PaCO_2$. This model dose not incorporate changes in rapidly changing factors such as hematocrit, blood glucose or arterial pH, which may be included in a more dynamic model of autoregulation (11, 26), but for which rapid serial measurements of CBF are necessary. Thus, we have used CBF reactivity as a surrogate measure for autoregulation. We analyzed a 15 minute average of MABP, MAP_{15}, as an independent predictive factor on CBF because it is a routinely measured and reported (18, 37–40) value in neonatal intensive care units, but an alternative may be to examine the effect of systolic blood pressure on CBF; we did not collect the corresponding systolic blood pressure data. Serum glucose has an impact on CBF (41), but where this information was available the infants had near normal glucose values (Table 1) at the time of the CBF measurement. Muscle relaxation was dictated by the clinical judgment of the physician, and it may reduce the variability of CBF (42); there was no systematic bias in the use of muscle relaxation (Table 1) and is unlikely to have biased the CBF data. All the infants in the study were sedated with diamorphine infusion. The effects of opiates on cerebral blood flow in the human newborn has not been studied, but as all the subjects were given the same dosage regimen we do not believe that this influenced our

overall results. Finally, infants with a hemodynamically significant PDA may have reduced CBF (43). There is a suggestion that significant flow through a PDA may reduce systemic blood flow, which may have a causative role in the etiology of intraventricular hemorrhage (44). There are no studies directly examining the effect of ductal flow on CBF autoregulation, but if it does have a significant effect, then the more preterm hypotensive infants are at greater risk of this further complication. There is evidence that even a large PDA does not affect EEG activity (45). Our predictive model of CBF did not include presence or absence of a hemodynamically significant PDA.

The treatment of systemic hypotension aims to improve perfusion of vital organs. A predicament for the clinician is defining hypotension due to the variety of normal values quoted for the MABP of preterm, VLBW, infants (18, 37–39). A widespread clinical guideline is to maintain MABP above 30 mm Hg, since MABP below this is found to be associated with intraventricular hemorrhage (46). This lower limit of 30 mm Hg has been tested and a CBF independent of MABP was found (7), due to presumed intact autoregulation. Another widely used guideline is to assume that the gestational age of the infant as the lowest acceptable MABP in mm Hg (40). Our study defined hypotension using the criteria of Watkins *et al.* (18), whose 10th centiles for MABP are lower than either of the two former recommendations, during the early postnatal period. Watkins' definition of hypotension is supported by their finding that infants who had a MABP persistently lower than the 10th centile were found to have severe intracranial lesions (18). Our findings indicate that hypotensive infants, as defined by Watkins' criteria, have blunted or absent MAP_{15}-CBF reactivity, and possibly absent autoregulation; this suggests that Watkins' values may be acceptable as the normal values. However we are unable to prove this in relation to the development of cerebral lesions in those infants who were hypotensive. This may well reflect the number of infants studied in the respective groups, and the reduction of intraven-

tricular hemorrhage rates seen in the preterm population in the last 10 y.

Neonatologists have recognized for a long time that blood pressure alone is a poor reflector of tissue perfusion. It remains a challenge in neonatology to identify other physiologic measurements that can be used on a continuous basis to give a clearer indication of tissue perfusion before we are able to identify with any degree of precision the lower limit of normal blood pressure in the sick preterm infant. Our study suggests that clinicians managing blood pressure should try and avoid abrupt elevations in MABP in hypotensive infants as this may be transmitted directly to the cerebral circulation.

In conclusion, the normotensive ventilated infants described in this study appear to have near constant CBF in the face of fluctuating MABP. They also display a CBF that is reactive to changes in $PaCO_2$, though to a lesser degree than expected, perhaps due to maturational changes. We speculate from the data that the hypotensive infants may have blunted MABP-CBF autoregulation, and their CBF-reactivity to changes in $PaCO_2$ is very diminished and possibly absent.

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