CEREBRAL BLOOD FLOW IN NEWBORN INFANTS

BY

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ABSTRACT

To determine (1) the effect of arterial CO_2 change on the neonatal cerebral circulation and (2) if 100% O_2 would produce significant decrease in cerebral blood flow to explain the late (5 minutes) hyperventilation observed in these infants during hyperoxia, we studied 24 preterm infants. Of these, 12 were studied before and during inhalation of 2-3% CO_2 and 12 before and during the inhalation of 100% O_2. We measured CBF by a modification of the venous occlusion plethysmography technique and found that CBF increased 7.8% per mmHgP_ACO_2 change and that it decreased 15% with 100% O_2. These findings suggest: (1) CO_2 is an important regulator of CBF in the preterm infant, (2) CBF - CO_2 sensitivity in these infants may be greater than in adult subjects, (3) 100% O_2 reduced CBF significantly, (4) relative brain ischaemia during administration of 100% O_2 may be, at least partially responsible for the increase in ventilation with hyperoxia.

We designed this study to determine the changes in cerebral blood flow (CBF) during inhalation of CO_2 and 100% O_2 in preterm infants. Changes in CBF with CO_2 may be relevant to our understanding of the mechanisms related to asphyxia and intracranial bleeding. Preliminary evidence suggests an association between asphyxia and intraventricular haemorrhage (20,28) which may be mediated by the increase in CBF which occurs in the early phase of asphyxia (10). On the other hand, a pronounced decrease in CBF with central accumulation of CO_2 in response to 100% O_2 may explain why human subjects increase ventilation during hyperoxia (14). Our results suggest that (1) CBF is very sensitive to changes in CO_2 and (2) the decrease in CBF induced by 100% O_2 might explain, at least in part, the late increase in ventilation observed during hyperoxia.

METHODS

We studied 24 preterm infants. Of these 12 inhaled 2 to 3% CO_2 and 12 inhaled 100% O_2 after a control period breathing 21% O_2. In the CO_2 group, mean gestational age was 34 wk±1 S.E., mean birth weight 1820 g±170, mean age 8 days±2. In the O_2 group, mean gestational age was 34 wk±1, mean birth weight was 1960 g ±140, mean age 11 days±2.

The method of measuring CBF was a modification of the technique described by Cross (6,15,16). Briefly, it entails measurements of occipito-frontal circumference (OFC), and skull volume (SV) and monitoring sagittal sinus venous and carotid arterial flow velocities. The only major difference in the present methodology in relation to previous work (15) is the use of our own correlation between SV and OFC. This was achieved by making polystyrene casts of the head and measuring volume of water it contains in a series of 100 infants, whose gestational ages varied from 26 weeks to 40 weeks. The measurements obtained were accurate to within 5% when compared to 35 post mortem brain weights. We found the relationship curvilinear over this period of gestation and could be expressed by $SV=.0117.\ OFC^3$ (Fig 1).

CALCULATION OF CBF

Theoretically, we expect skull volume to be proportional to the cube of head circumference. The relationship should fit

a power curve according to the general equation.

$$Y = aX^{M} \quad (1)$$

where Y - SV, X = OFC, a = constant of proportionality

m = power

For our data a = .0117, if SV is measured in ml and

OFC in cm

Therefore, rearranging (1)

$$SV = .0117.OFC^{3} \quad (2)$$

differentiating with respect to time

$$\frac{dSV}{dt} = .0117.3.OFC^{2}.\frac{dOFC}{dt}$$

during venous occlusion

$$CBF\ ml/min = .0351.OFC^{2}.slope$$

$$CBF\ ml/min/100g = \frac{3.51.OFC^{2}.slope}{SV}$$

We also monitored end tidal gases by a system previously described (22). All studies were performed during sleep. After satisfactory control studies were obtained 2 to 3% CO_2 was added to the system and occlusions performed during steady state hypercapnia. In the O_2 study, 1 to 2% CO_2 was added to compensate for the hyperventilation seen with hyperoxia.

RESULTS

Inhalation of CO_2 produced a mean rise in CBF from 31 ml/min/100g to 44 ml/min/100g (P=0.0013; Table 1; Fig 2). This represented a mean increase in CBF of 7.8% per mmHgP_ACO_2.

Inhalation of O_2 produced a decrease in CBF from 34 ml/min/100g to 30 ml/min/100g; (P=.004; Table 2, Fig 3). This represented a 15% decrease in CBF.

DISCUSSION

We found that CBF increases significantly with inhalation of CO_2 and decreases significantly with inhalation of 100% O_2. The increase in CBF per mmHgP_ACO_2 is approximately twice that observed in adult subjects. Our control mean value for CBF is approximately half (63 ml/min/100g) we reported previously (15). This is explained by the fact that in our previous study, we used the slope of a regression equation for SV and OFC in infants derived by Buda et al (4). This slope was linear and related to an older group of infants. In the present study, using our own data to derive the regression equation between SV and OFC over the period of gestation, 26 weeks to 40 weeks, we found a curvilinear relationship. The mean control value in the present study was comparable to the mean value obtained by Lou et al (40 ml/min/100g) in normotensive neonates (19).

These findings suggest that CO_2 is an important regulator of CBF in preterm infants and that relative brain ischaemia, during inhalation of 100% O_2 may be responsible, at least in part for the late increase in ventilation during hyperoxia.

Most studies in animals suggest that CBF-CO_2 sensitivity in the neonate is less than that in adult man (3,21,22,26). However, in the newborn rat, Barker found that the CBF-CO_2 sensitivity was at least as sensitive as that in the adult (2). No comparative studies in human subjects have so far been reported.

There is obvious variability in the CBF-CO_2 sensitivity in our infants (Fig 2). Factors known to contribute to this variability, apart from the variability inherent to the method itself, include (a) baseline CBF (1,7),(b) reduced mean arterial blood pressure and (c) time lag after the onset of steady state hypercapnia for CBF to reach a steady value (27). In our study, there is no relationship between control CBF and CO_2 sensitivity ($r=-.313$) but there appears to be a trend in that direction. It has been shown that at a reduced mean arterial blood pressure, the responsiveness of the cerebral vessels to acute changes in P_ACO_2 is diminished (9). We did not measure blood pressure in our infants but there may have been differences in mean arterial blood pressures. We also found no relationship between the length of time spent in hypercapnia and the CBF-CO_2 responsiveness. Since our findings suggest an increased CBF-CO_2 sensitivity in

the preterm infant, this may be important to the pathogenesis of intraventricular hemorrhage.

Our results indicate a significant decrease in CBF with 100% O_2. The provocative question is whether a 15% decrease in CBF would cause enough cerebral ischaemia to induce hyperventilation. If one considers that hyperventilation is usually small during inhalation of 100% O_2 and that there is great variability in the vascular reactivity to O_2 in various brain structures, some brain stem structures showing the greatest decrease in CBF in response to 100% (11), it is conceivable that central ischaemia may be the initial step to increase ventilation with 100% O_2. The changes in CBF with 100% O_2 are in general agreement with Kennedy's study on the newborn dog (11). He showed that 100% O_2 lowered CBF by 25% in two day old beagle puppies but at 3 weeks of age, the effect was much less (13%). There is no data available from studies on newborn infants for comparison. In adult man, a decrease of 15% in CBF has been reported (12,14).

In summary, our results suggest that (1) CO_2 is an important regulator of CBF in the preterm infant, (2) CBF-CO_2 sensitivity may be higher in the preterm infant than in adult man, (3) 100% O_2 reduces CBF significantly, (4) relative brain ischaemia during inhalation of 100% O_2 may be responsible for the late ventilatory response to hyperoxia.

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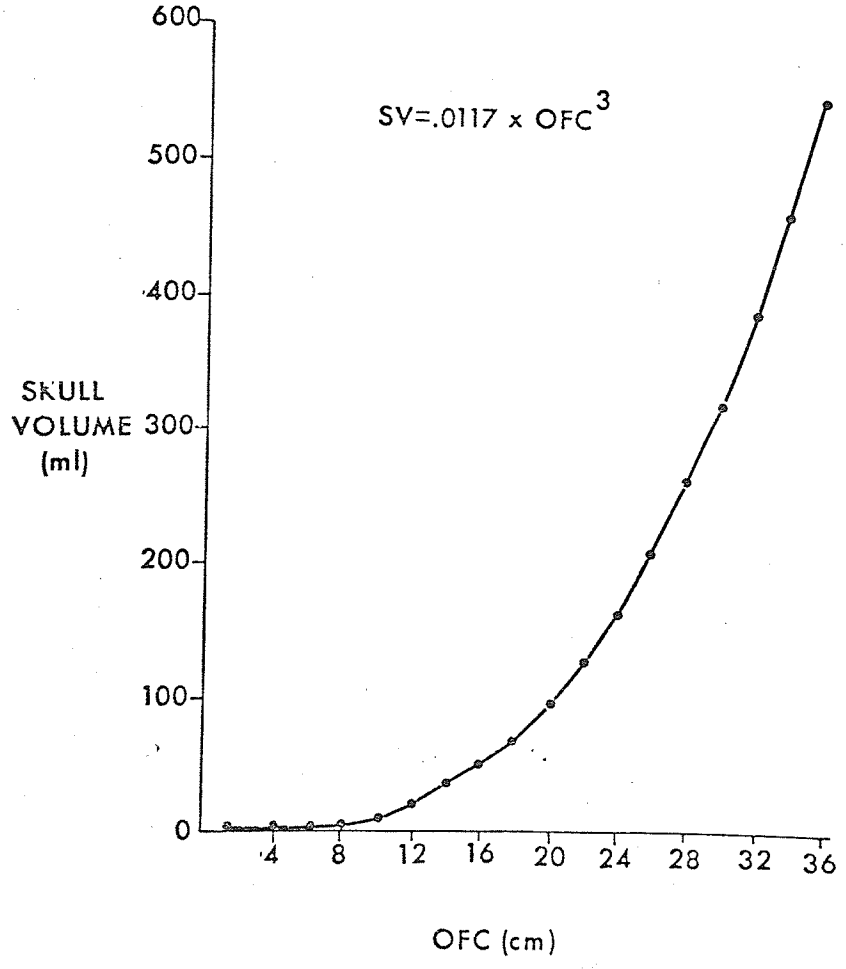
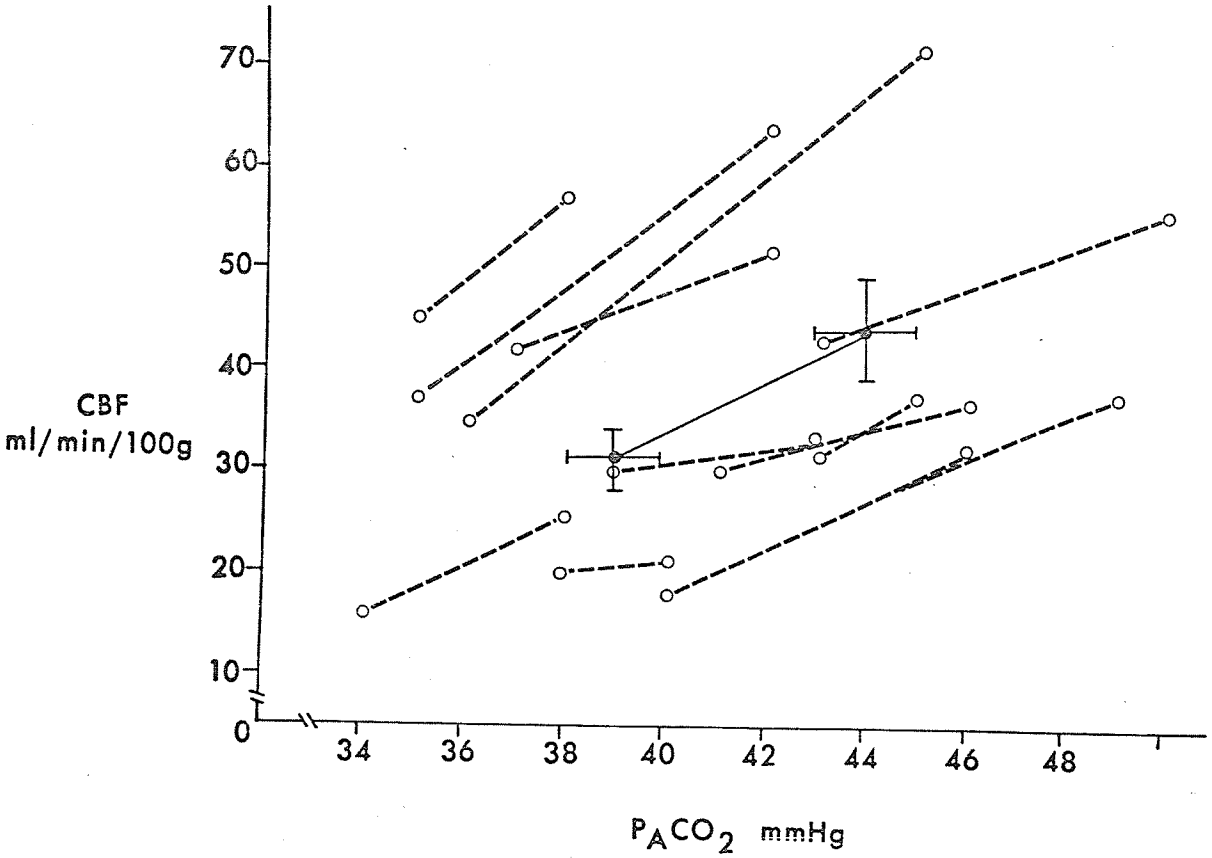

SV=.0117 x OFC^3
SKULL VOLUME (ml)
600
500
400
300
200
100
0
4
8
12
16
20
24
28
32
36
OFC (cm)


70
60
50
40
30
20
10
0
CBF
ml/min/100g
34
36
38
40
42
44
46
48
P_ACO_2 mmHg

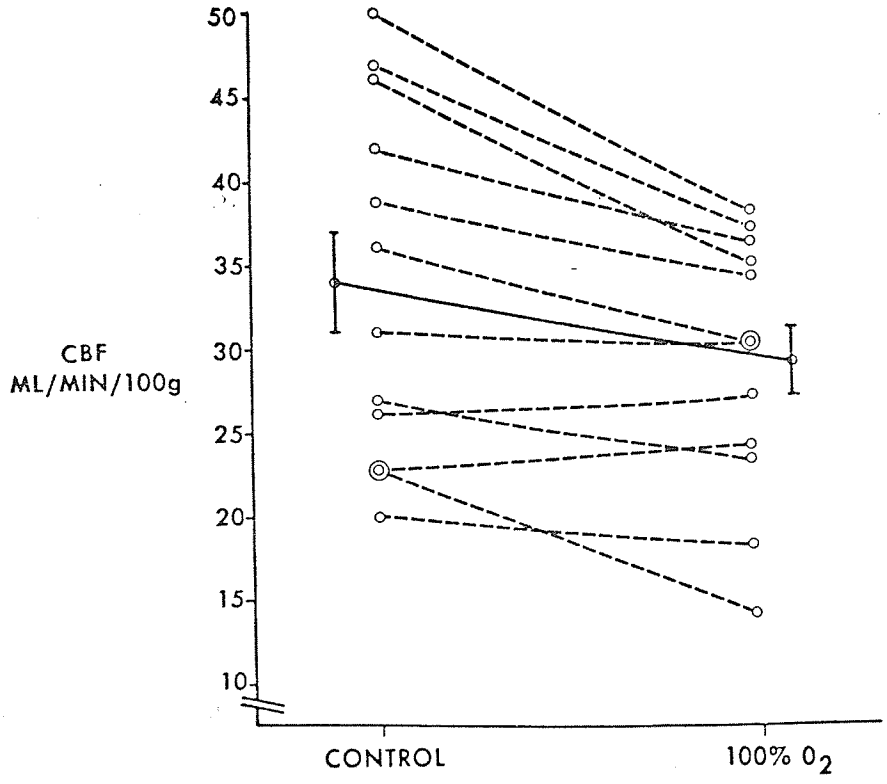

50
45
40
35
30
25
20
15
10
CBF
ML/MIN/100g
CONTROL
100% O_2

TABLE 1. EFFECT OF CO_2 ON CBF

AGE (days)	SEX	GESTATION (wk)	BIRTH WEIGHT (g)	CONTROL		CO_2		CBF % CHANGE PER mmHg P_ACO_2
				P_ACO_2 (mmHg)	CBF (ml/min/100g)	P_ACO_2 (mmHg)	CBF (ml/min/100g)	
3	F	37	2070	37	42	42	52	+ 6
11	F	34	1720	36	35	45	72	+11
1	M	38	2640	34	16	38	25	+13
6	F	37	1760	35	45	38	57	+ 5
2	M	32	1910	35	37	42	64	+ 8
5	F	32	1560	40	18	46	32	+13
9	F	32	980	43	32	45	37	+14
4	M	36	2840	39	30	43	34	+12
6	F	32	1160	38	20	40	21	+ 5
10	F	34	1570	44	27	49	38	+ 8
24	F	33	1130	41	30	46	37	+ 4
18	M	34	2480	43	43	50	56	+ 4
MEAN 8 S.E. ±2		34 ±1	1820 ±170	39 ±1	31 ±3	44 ±1	44* ±5	7.8 ±1

* $P < 0.005$ IN RELATION TO CONTROL

TABLE 2. EFFECT OF 100% O_2 ON CBF

AGE (days)	SEX	GESTATION (wk)	BIRTH WEIGHT (g)	CONTROL		100% O_2		CBF % CHANGE
				P_ACO_2 (mmHg)	CBF (ml/min/100g)	P_ACO_2 (mmHg)	CBF (ml/min/100g)	
10	M	36	2500	34	26	34	14	-33
7	M	36	1700	38	23	37	27	+17
7	F	34	1900	36	36	36	30	-18
9	M	37	2600	36	31	37	30	- 6
26	F	31	2000	35	27	34	23	-15
6	F	32	1200	37	23	37	24	+ 6
13	M	33	2000	41	46	41	36	-16
18	F	29	1300	32	39	32	34	-13
2	F	37	2100	35	20	35	18	-16
6	F	34	1700	36	42	34	36	-15
4	M	36	2800	34	50	34	38	-22
22	F	30	1700	42	47	41	37	-21
MEAN 11 S.E. ±2		34 ±1	1960 ±140	36 ±1	34 ±3	36 ±1	29* ±2	-15 ±4

* $P < 0.005$ IN RELATION TO CONTROL

LEGENDS

FIG 1 Relationship between skull volume and occipito-frontal circumference in a series of 100 infants. Note that the relationship becomes more linear with increasing OFC.

FIG 2 CBF-CO_2 sensitivity. The dotted lines with open circles represent individual values. The solid line represents the mean values±SE.

FIG 3 Represents the effect of 100% O_2 on CBF. The open circles indicate individual values. The solid lines represent the mean values.

TABLE 1 Individual values for control and test CBF and P_ACO_2 in infants breathing CO_2.

TABLE 2 Individual values for control and test CBF and P_ACO_2 in infants breathing 100% O_2.

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A QUANTITATIVE NON-INVASIVE METHOD TO MEASURE CEREBRAL BLOOD FLOW IN NEWBORN INFANTS.

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A METHOD TO MEASURE CEREBRAL BLOOD FLOW IN NEWBORN INFANTS

Running Head: Cerebral Blood Flow in Neonates

Key Words: Cerebral blood flow, neonates
plethysmography, skull volume, occipito-frontal circumference.

ABSTRACT

We measured cerebral blood flow (CBF) in 32 healthy neonates by venous occlusion plethysmography. Mean CBF was 63 ml/min/100 g which compared favourably with invasive methods used in older children and adult subjects. We suggest that this is a useful method to quantitate CBF in neonates. It may be invaluable in assessing sequential changes occurring during asphyxia, intracranial hemorrhage, or during administration of various gas mixtures and drugs such as theophylline.

There are few techniques to measure cerebral blood flow (CBF) in human subjects, but all are invasive requiring blood sampling or administration of radioactive material. [1] Because changes in CBF may play a fundamental role in neonatal asphyxia, [2,3,4] intracranial bleeding, [5] paradoxical response to low O_2 in preterm infants, [6] and in the ventilatory response to theophylline, [7] it is becoming imperative that a non-invasive method to measure CBF be available. We have, therefore, devised a simple, safe and reproducible method of measuring CBF based on the principle of jugular occlusion plethysmography. [8] This paper describes our method, its virtues and its potential limitations, and gives the results of measurements of cerebral blood flow in 32 healthy neonates. Approval for the study was given by the Ethics Committee and informed consent was obtained.

MATERIALS AND METHODS

Our method is based on the principle described by Cross et al, i.e. a gentle short compression of the jugular veins at the neck induces a change in head circumference which is proportional to CBF [8]. The method entails measurement of occipito-frontal circumference (OFC) and skull volume and monitoring of sagittal venous and carotid arterial velocities.

1. Measurements of Head Circumference (OFC) - These were made using a 270 Mercury Strain Gauge Plethysmograph (Parks Electronics Laboratories, Beaverton, Oregon) applied around the OFC and held in position by a small strip of tape at the forehead. As the gauge is stretched its internal resistance increases. This change in resistance was recorded using a D.C. system (Gould Brush Polygraph Recorder, Gould Inc., Cleveland, Ohio). Calibration was obtained by laying the gauge alongside a ruler and changing its length. This could be displayed on the recorder using appropriate sensitivity on the D.C. amplifier. We have compared this calibration measurement to the measurement obtained using an engineer's calipers with a vernier and obtained an identical value. In practice, change in OFC is measured as downward slope (Fig. 1).

2. Measurement of Skull Volume (V) - Buda et al, derived a regression equation for skull volume and OFC in infants from calculations by MacKinnon.[9] Such calculations were made using radiographic tridimensional diameters of the skull. We used the slope of this equation to calculate CBF.

3. Monitoring of Sagittal Venous Flow Velocity - This was done using a doppler probe applied to the scalp above the superior sagittal sinus. Such monitoring was essential in order to assess excellence of jugular compressions. If the veins are properly occluded, sagittal flow should stop for a fraction of time (Fig. 1). The venous occlusion time was also measured. This is defined as the time in seconds from the initial slope of the strain gauge tracing to the point of zero flow on the venous recording. The rationale for using this measurement is that it helps defining the consistency of the occlusion maneuver in tracings of similar technical excellence.

4. Monitoring of Internal Carotid Flow Velocity - A second doppler probe was applied over the supraorbital branch of the opthalmic artery. This was essential to rule out interference with internal carotid flow when the jugular veins were compressed.

5. Estimation of Cerebral Blood Flow - The regression equation for skull volume on head circumference in infants [10] is:

$$V = b\ OFC - c. \quad (1)$$

Where V = skull volume; b = slope of regression line; OFC = occipito-frontal circumference; and c = intercept. Differentiating equation (1) with respect to time:

$$\frac{dV}{dt} = \frac{dOFC}{dt}. \qquad (2)$$

Where $\frac{dV}{dt}$ = CBF and $\frac{dOFC}{dt}$ = rate of change of OFC with time.

$$= 59.1 \frac{dOFC}{dt} \qquad (3)$$

$$= \frac{59.1}{10} \text{ (slope) cc/sec} \qquad (4)$$

$$= 5.91 \text{ (slope) mm/sec}$$

$$\text{Flow cc/mm} = 5.91 \text{ X } 60 \text{ (slope) cc/mm} \qquad (5)$$

$$= 355 \text{ (slope) ml/mm}$$

$$\text{CBF} = \frac{355}{V} \text{ (slope) ml/min/100g} \qquad (6)$$

So, to calculate CBF all we need is the slope of the regression line of skull volume on OFC (b) and the rate of change in OFC with respect to time ($\frac{dOFC}{dt}$).

In addition to measuring variables needed to calculate CBF, we monitored breath-to-breath concentrations of end tidal CO_2 using our system.[11] This was done to define whether there was a close relationship between

resting CO_2 and measured CBF. All measurements were recorded on a Brush polygraph, model 480.

We studied 42 healthy neonates during sleep, an hour after feeding. Satisfactory results were obtained in 32 cases. The criteria for considering the study satisfactory consisted of : a) absence of movement of the infant's head or wrinkling of the forehead during jugular compression, as this would interfere with the strain gauge recording; and b) evidence of complete occlusion and no early interference with carotid flow (Fig. 1) The 32 infants studied were 12±1 (mean ± SE) days old. Birth weight was 1880±80g and gestational age 34±1 week. 18 were female and 14 were male. 12 infants were small for gestational age (SGA) using the Usher intrauterine growth chart [12]. In 20 infants two to four occlusions were performed in order to assess reproducibility of the measurements. We always waited at least 2 minutes in between occlusions.

RESULTS

Table 1 illustrates our findings. In 32 neonates the average CBF was 63±3 (Mean ± SE) ml/min/100g. In 20 infants in which two to four measurements were made over a short period of time at the same P_ACO_2, reproducibility was within 5%. There was no correlation between CBF and gestational age (Fig 2) ($r = -.19$, $p>0.05$). Also, CBF did not correlate with alveolar PCO_2 ($r = -0.09$, $p>0.05$). Venous occlusion time was 3.3±0.2 (mean ± SE) seconds.

DISCUSSION

Methods currently used to quantitate CBF are invasive and thus not suitable for use in neonates. There is a great need for a non-invasive approach which could be used to assess sequential changes in CBF. We took advantage of the known compliant skull of neonates and expanded the technique originally described by Cross et al, in order to quantitate CBF. We found an average CBF of 63 ml/min/100g in neonates; and by using similar venous occlusion times in a particular infant, reproducibility was quite satisfactory (within 5%). See Table 2. Our results indicate large differences in CBF values (range 32-127) between normal neonates. These two extreme values were obtained in only two infants of 32 studied. We cannot at the present time account for this.

Cooke et al using a similar technique in normal neonates found a mean value of 32 ml/min/100g and noted that the apparent CBF decreased 20% following an oral feed and that a mean fall of 50% occurred over the first 3 hours of life [13]. Our mean resting value is approximately twice the above value. The difference may be due to incomplete venous occlusion or that a different relationship was obtained between brain volume and OFC which is used to estimate CBF. Dear et al showed a higher apparent CBF in REM sleep than in non-REM sleep in neonates using the same technique [14]. It is difficult to compare our values obtained using invasive techniques since most studies have been done in sick neonates. Our values are comparable to those of Settergren et al, who found an average CBF of 69 ml/min/100g in healthy infants at 5 months of age [15]. Lou et al measured CBF using intraarterial Xe^{133} in 8 asphyxiated neonates, two of whom were neurologically normal and had normal blood pressures. he found values of 40 and 55 ml/min/100g respectively [16]. Garfunkel et al whose study group included 3 neurologically abnormal neonates found values of approximately 20 ml/min/100g [17]. Values reported in adult subjects are of the order of 50 ml/min/100g [18]. This may suggest that there is no major change in CBF per unit of brain tissue from infancy to adulthood, but sequential or cross-sectional studies using the same method are needed to clarify changes with age.

Our findings suggest a lack of correlation between CBF and gestational age. The number of patients is small to draw a more definite conclusion on this. Behrman et al found that there was no significant change in CBF during the first week of life in the fullterm monkey [19]. However in dogs, Kennedy et al found that CBF increased during the first few weeks of life [20]. Štulcová found in the rat that after 25 days of age the CBF increased sharply [21]. These differences may illustrate the different degrees of cerebral metabolic maturity in the various species during the newborn period. The lack of correlation between CBF and P_ACO_2 between babies suggests that (1) CBF is independent of minor differences in resting P_ACO_2 observed between healthy neonates and (2) That there are other factors which control CBF besides CO_2. Despite the apparent lack of correlation, we have shown that the inhalation of 2 - 3% CO_2 produces an increase in CBF of 8.6% per mmHgP_ACO_2 [22].

The limitations of our new method are not entirely clear and some aspects deserve comment. First, we realize that it would be ideal to compare the method against a standard technique of measuring brain blood flow. We have explored the possibility of making such measurements, but there is no suitable animal model and the chance of performing comparative measurements in sick newborns is remote.

Secondly, during venous occlusion there is a late decrease in arterial blood flow velocity captured at the supraorbital branch of the opthalmic artery. We feel that this is due to back pressure from the venous side being transmitted to the arterial side of the circulation (Fig 1). It could however, be due to compression of the carotid arteries during jugular occlusion. This would underestimate CBF. Because our measurements are made before a change in arterial flow, it is unlikely that we are making such an error.

Thirdly, the change in intracranial pressure during the occlusion maneuver could affect the CBF value. Measured rate of change in OFC with time might then be not only a pure reflection of change in CBF but also of increased intracranial pressure. We have measured the intracranial pressure change during complete venous occlusion using the Model 1702 Ladd Intracranial Pressure Monitor (rate of response 3.5 cm H_2O per second) in ten premature infants. We found that the intracranial pressure rose from a mean of 8 cm H_2O ±4 to a mean of 20 cm H_2O ±3. In monitoring the intracranial pressure during episodes of crying in the same babies we found that the intracranial pressure increased from a baseline of 8 cm H_2O ±4 to 24 cm H_2O ±5. We calculated the intracranial pressure change during the initial second,

the period over which we measure CBF and found a mean pressure increase of 2.5 cm H_2O ±1. Because we used the initial part of the slope (see Fig. 1), the eventual effect of increased intracranial pressure was negligible. However differences in skull compliance between infants may affect the absolute value for CBF. Cross et al has also shown that there is no harm in increasing skull volume by compression of the jugular veins as the infant produces far larger increases by crying or straining [8]. The method, therefore, seems safe and easy to use.

Fourthly, for clinical reasons, we do not have measurements of intracarotid arterial pressure during the occlusion maneuver, but it is unlikely that it would change in any different way from that during crying. Finally, the accuracy of extracranial recording of intracranial blood flow may be questioned. Studies in adult subjects, however suggest the error to be no more than 5% [23].

It would be of interest to know whether cerebral blood flow is more susceptible to change in the neonatal period than later in life. If the pronounced retinal arterial constriction occurring with inhalation of 100% O_2 in preterm infants is a reflection of the capability of immature arteries to constrict with high O_2, then preterm infants may have a more

vulnerable CBF control mechanism than adult subjects, who usually do not develop retrolental fibroplasia. Such sensitivity of cerebral vessels in neonates with a change in diameter to accomodate more or less flow may, for instance, explain why these infants show a unique response to low inhaled O_2, and a paradoxical response to CO_2 with various background concentrations of O_2. Similarly, theophylline may decrease cerebral blood flow in adult subjects by 33% [24]. Is this the case in preterm infants? This is a crucial question considering that this drug is being widely used for the treatment of apnea of prematurity. Finally, preterm infants are unique in their susceptibility to intraventricular hemorrhage, a rather lethal entity. Evidence is now accumulating that this is preceded by profound changes in CBF during asphyxia [2,3,4]. Assessment of changes in CBF occurring during asphyxia may help to unravel the physiopathogenic mechanism underlying intraventricular bleeding. For all these provocative questions measurements of CBF using the non-invasive technique we devised may be invaluable.

ACKNOWLEDGEMENT

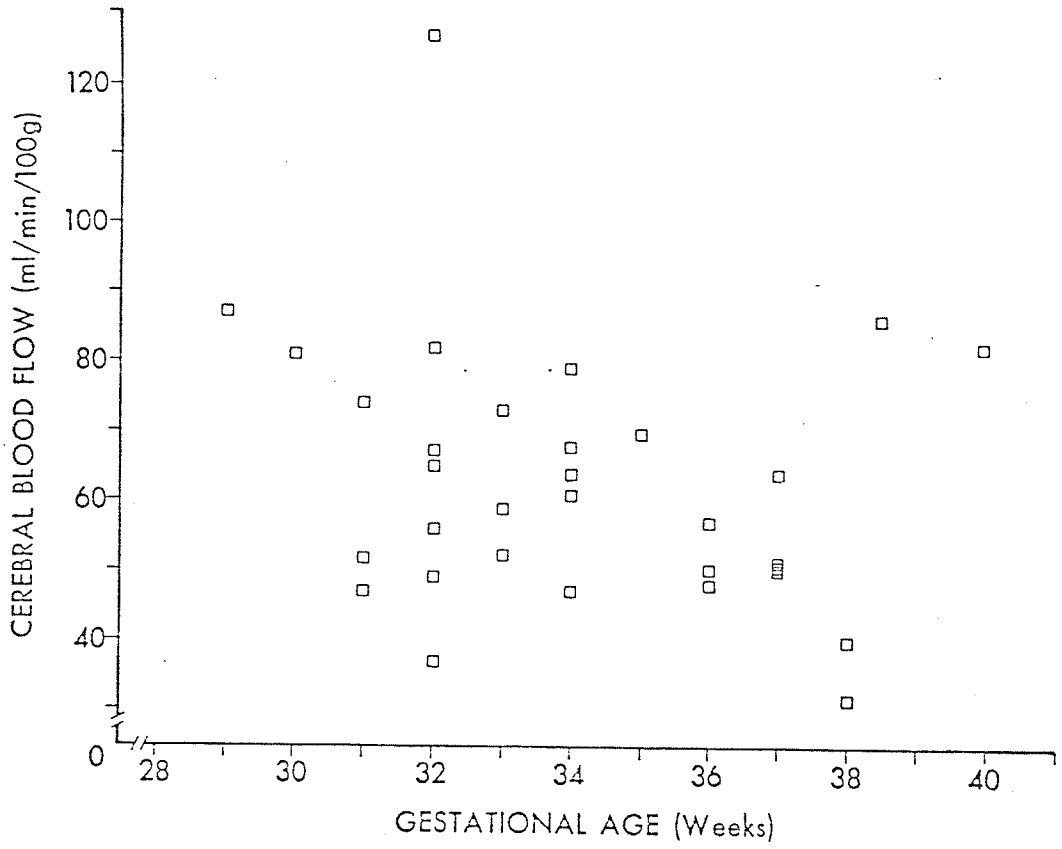
We are grateful to Betty Penney and Johanna Christensen for typing and helping in the preparation of the manuscript.

LEGENDS

Figure 1: Representative tracing on infant number 12. Compression of the jugular veins causes an increase in OFC which is recorded as a downward slope. The initial slope, corresponding to an increase in OFC with time, is used to calculate cerebral blood flow. Note that sagittal venous flow decreases. There is no decrease in arterial flow velocity during the initial slope. The respiratory pause is an occasional occurrence in infants who have periodic breathing.

Figure 2: There is no correlation between measured cerebral blood flow and gestational age.

Table 2: Reproducibility obtained with measurements taken approximately 2 minutes apart.


CEREBRAL BLOOD FLOW (ml/min/100g)
120
100
80
60
40
0
28
30
32
34
36
38
40
GESTATIONAL AGE (Weeks)

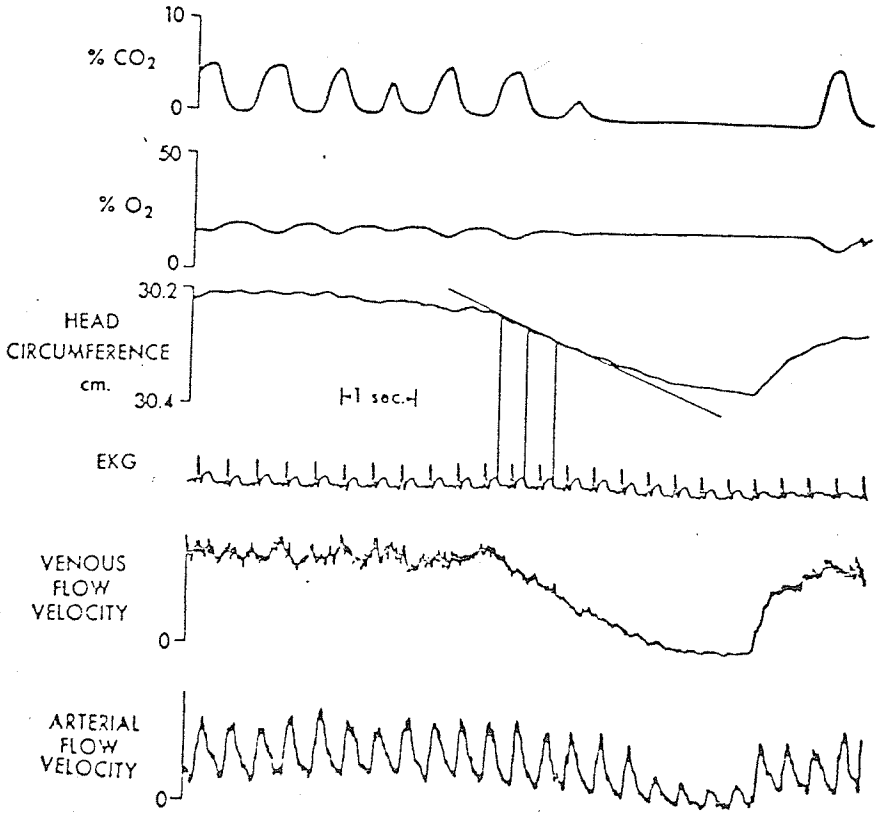

10
% CO_2
0
50
% O_2
0
30.2
HEAD
CIRCUMFERENCE
cm.
30.4
1 sec.
EKG
VENOUS
FLOW
VELOCITY
0
ARTERIAL
FLOW
VELOCITY
0

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TABLE 1. CALCULATED CEREBRAL BLOOD FLOW IN NEONATES

INFANTS	SEX	AGE (DAYS)	GESTATIONAL AGE (WEEKS)	BIRTH WEIGHT (GRAMS)	P_ACO_2	VENOUS OCCLUSION TIME (SECONDS)	CEREBRAL BLOOD FLOW (ml/min/100g)
1	F	27	31	1800	43	2.4	52
2	F	19	31	1700	44	4.4	74
* 3	M	7	36	1700	38	1.2	50
4	M	10	36	2500	36	2.0	57
* 5	F	6	34	1700	36	2.7	79
6	F	11	33	1600	44	4.6	52
7	F	18	29	1300	32	5.0	87
8	F	26	31	2000	36	3.0	47
9	M	9	37	2600	36	4.0	50
10	M	13	33	2000	41	3.2	73
11	F	8	34	1900	36	3.2	61
* 12	F	5	37	2100	35	4.8	50
13	M	4	36	2800	40	2.9	48
14	M	12	38	2500	37	3.0	40
15	M	14	34	2500	33	4.3	47
* 16	F	3	40	2000	34	3.5	82
* 17	F	24	33	1100	45	3.1	59
* 18	M	10	32	1300	35	3.2	127
* 19	F	3	37	2000	35	3.3	51
* 20	F	17	32	980	40	2.4	65
21	F	5	32	1600	39	4.0	37
22	M	2	32	1900	36	4.4	67
* 23	F	6	37	1800	37	4.2	82
24	M	1	38	2600	37	2.7	32
* 25	F	25	34	1700	36	2.4	64
26	M	18	34	2300	43	2.6	68
27	F	22	30	1700	42	3.6	81
* 28	F	20	37	1300	42	4.2	64
29	M	8	38	2300	39	2.4	86
* 30	F	6	32	1200	37	2.0	49
31	M	13	35	2100	37	3.3	70
32	M	17	32	1640	42	2.8	56
MEAN ±S.E.		12 ±1	34 ±1	1880 ±80	38 ±1	3.3 ±.2	63 ±3

* SGA using Usher growth chart [12].

TABLE 2. REPRODUCIBILITY OF THE METHOD

	CBF ml/min/100g	P_ACO_2 mmHg
1.	44	35
	47	36
	47	35
2.	64	35
	64	36
	67	35
3.	60	41
	56	42
	51	42
	55	41
4.	50	44
	52	44
	48	44

1134

SERUM BILIRUBIN: A POOR PREDICTOR OF KERNICTERUS
M.H.Kim, J.J.Yoon, J.Chor, A.K.Brown SUNY Downstate Med. Ctr.,Brooklyn & Bronx-Lebanon Hosp., Bronx

Kernicterus was found in 20 infants autopsied between Jan'72 and June'77 at Kings County Hospital-Downstate Medical Center. Most of the infants were very premature; mean gestational age was 31.5(27-37)wks with mean birth weight of 1430(670-2910)g. Age at death ranged from 41 hrs. to 5 mos. with a median of 130 hrs. Peak serum bilirubin values ranged from 6.5 to 20.6 mg% (mean, 11.5mg%). Only 2 infants had values greater than 15mg%; both of these infants received exchange transfusion and 11 others had phototherapy.

Since the bilirubin levels were so low, we analyzed the clinical and laboratory features which may have contributed to the development of kernicterus. Hypoalbuminemia (<2.5g%) was found in 6/9. In 4 of 5 infants in whom HABA dye binding studies were done, the values were very low (<25%). Anemia was present in all infants with evidence of hemolysis in 9/14. Internal bleeding was found in all, including 15/20 cases of intracranial hemorrhage. Respiratory distress with acidosis and hypoxia was present in all cases. There was evidence of infection in 13/20 infants. A greater proportion of the larger (≥1950g) infants had infection (5/6) than did the smaller infants (8/14). Although most of the infants did not exhibit all the classical signs of kernicterus clinically, they did have evidence of non-specific CNS involvement such as apnea, bradycardia and cardiorespiratory arrest.

On the basis of these findings, it is difficult to define a safe level of serum bilirubin below which kernicterus cannot occur. It would appear that in infants with extreme prematurity, infection, acidosis and hypoxia, we must either find a mean of preventing even modest bilirubin accumulation or a new index to assess the state of bilirubin diffusibility.

1135

EFFECT OF POSITIONING AND HEAD BANDING ON INTRACRANIAL PRESSURE IN THE PREMATURE INFANT. **Niki Kosmetatos and Margaret L. Williams, Dept. of Peds., SUNY, Upstate Medical Center, Syracuse, New York.**

The intracranial pressure of 12 infants, birthweight 720-1800 gms., who had no evidence of intracranial hemorrhage, was measured over the anterior fontanelle by the Ladd ICP monitor. Pressures were determined before and one minute after the release of encircling phototherapy eye patches or nasal cannula apparatus. The measurements were performed twice on each infant in three different positions -- head up 30°, horizontal, and head down 30°. A significant decrease in pressure was noted immediately after release of the encircling band in all three positions in most infants. The average decrease was 3.75 (range 0-14.5), 3.73 (range 0-10), and 3.45 (range 0-9) cm H_2O in the head up, horizontal, and head down position respectively. Three of the four infants who demonstrated the smallest decrease in intracranial pressure had been exposed to constricting apparatus for long periods of time prior to their determinations suggesting possible compensation. The magnitude of the decrease in pressure was not different in the various positions studied, although the pressures tended to increase as the infant was placed in the head down position. The changes noted in intracranial pressure both with positioning and banding raise questions as to the effect of such infant care practices on the brain of infants with compressible skulls. Increases in intracranial pressure induced by head banding may play a role in the high incidence of intracranial hemorrhage in the very small infant.

1136

SERIAL MATURATION OF AUDITORY BRAINSTEM EVOKED POTENTIALS IN PRE-TERM INFANTS. Allan Krumholz, Philip J. Goldstein, Jacob K. Felix, Robert F. Carr, and Dorothy Shannon, (spon. by Evan Charney). Depts. of Ob/Gyn, Peds, and Neuro. Johns Hopkins Medical School, Sinai Hospital of Baltimore

The auditory brainstem evoked response to clicks matures to adult values within the first two years of life. To evaluate this procedure as a measure of nervous system maturation in premature infants, serial testing was done in 20 infants of 35 weeks or less gestational age. The children were tested at weekly intervals. Gestational age was determined by Dubowitz's criteria. Thirty normal fullterm infants served as controls. All subjects were tested with clicks of 80 dBSL at a stimulus rate of 9-12/sec and averaged by computer. Responses were obtainable in all infants over 30 weeks. The earliest waves noted were I, III, and V. Waves II, IV, and VI were unstable in early recordings. However, waves II, IV, and VI were present in over 50% of patients as they approached 40 weeks. The latency of wave V gradually decreased at a rate of about .2msec. per week to fullterm. However, waves I and III approached relatively mature latencies earlier, at 34 to 37 weeks. The standard deviation for the latency of wave V was large. This value, contrary to previous reports, is relatively insensitive measure of gestational age and may be influenced by perinatal factors. The appearance of the auditory brainstem evoked response at 30 weeks and the rapid serial decrease in its latency from 30 to 42 weeks gestational age suggest that this procedure can be useful in monitoring the maturity and serial development of the nervous system in the premature infant.

1137

INTRACEREBRAL HEMORRHAGE IN HIGH RISK PREMATURES
Anthony Lazzara, Peter A. Ahmann, Alfred W. Brann, Jr., George W. Cox, Francine D. Dykes, James C. Hoffman, Jr., John D. Meyer, James F. Schwartz, Emory Univ. School of Medicine.

Subependymal (SEH) and intraventricular hemorrhage (IVH) in infants less than 35 weeks gestation, requiring intensive care for 24 hours or longer, were studied prospectively. Initial computerized tomographic scan (CT scan) was obtained, and, if positive for blood, head circumference, clinical course, and serial scans were followed until ventricular size was normal.

29/58 infants were shown to have SEH and/or IVH, 26 by CT scan, 1 by ventricular tap, 2 on autopsy. 8 infants died. 6 of these had marked IVH, 3 shown by CT scan, 1 by ventricular tap, 2 by autopsy. Acute hydrocephalus of only mild to moderate degree occurred in the 3 fatalities with positive scans. The 23 survivors with positive scans had follow-up scans. 18/23 did not show progressive hydrocephalus, and of these 4 had only SEH. Of the others, 10 had mild, 3 moderate, and 1 marked IVH. 5 survivors with IVH developed severe progressive hydrocephalus. 2/5 had only mild IVH, which resolved spontaneously. 3/5 required treatment. IVH was moderate in 1, marked in 2. Serial head circumference was not predictive of need for treatment.

The incidence of SEH and IVH was 50% in study infants and was not related to gestational age. The quantity of blood may be prognostically significant. No infant with SEH or mild IVH required treatment. Progressive hydrocephalus developed in 2 and resolved spontaneously. 7/10 infants with moderate to marked IVH survived. 3 required treatment.

1138

QUANTITATIVE NON-INVASIVE METHOD OF MEASURING CEREBRAL BLOOD FLOW (CBF) IN THE NEWBORN. F. Leahy, K. Sankaran, D. Cates, M. MacCallum, H. Rigatto, University of Manitoba, Department of Pediatrics, Winnipeg, Canada.

We devised a quantitative method to estimate CBF based on the principle of jugular occlusion. With gentle and short compression of both jugular veins there is an increase in head circumference (OFC) which reflects CBF. To make measurements quantitative we differentiated regression of OFC on skull volume: Y=59.1 (X) - 1,608, where Y = skull volume and X = OFC. The formula obtained was CBF=355/Y·dx/dt in ml/100g/min. Method entails measurement of (1)OFC, using a mercury strain gauge. Change in OFC is measured as a slope when jugular veins are compressed. (2)Skull volume, using polystyrene cast of the infant's skull filled with water, and volume measured. Comparing values to autopsy brain weights it is accurate within ±4%.(3)Monitoring intracranial venous and arterial flow by Dopplers taped over superior sagittal sinus and nearby artery. When veins are completely occluded flow stops. Alveolar CO_2 (P_ACO_2) is simultaneously recorded. When values from complete occlusions and no interference with arterial flow are taken, results are reproducible. In 8 preterm infants (G.A. 34wk ±2 S.D.; B.W. 1.8kg ±.6 S.D.; age 9.4 days ±7.9 S.D.) the mean CBF was 67.1 ±13.6 S.E. ml/100g/min. The values are similar to those reported previously using the N_2O method. During administration of 2% to 3% CO_2, CBF increased to 97 ±24.1 S.E. Mean P_ACO_2 increased from 38.7 ±1.2 to 43.4 ±1.1 S.E., therefore the increase in CBF per mmHg P_ACO_2 was 6.9 ml/100g/min. The 10% increase in CBF is double that reported for adults. We suggest that CBF in preterm infants is more sensitive to changes in P_ACO_2 than adults.

1139

QUALITY OF LIFE AFTER PROLONGED NON-TRAUMATIC COMA IN CHILDREN: A REAPPRAISAL. Lewis A. Margolis, Bennett A Shaywitz, Dept. Ped, Yale U. Sch. of Med. New Haven.

Recent advances in medical technology have resulted in a reduced mortality of critically ill children, but quality of life in these survivors remains ill-defined. Such information is of particular importance in an era when physicians are frequently called upon to decide whether and when to discontinue extraordinary measures of life support. We report the outcome (follow-up 1-7 yrs) in 16 children ages 6 mos-16 yrs in coma of non-traumatic origin for longer than 5 days. The 8 girls and 8 boys remained in coma for periods of 6-180 days (median 17.5 days) and 12 children remained in deep coma 1-35 days (median 10.9 days). Major neurological residua (seizures, developmental retardation, blindness) occurred in 4, minor residua (MBD, minimal motor deficits, personality disorder) in 7, and no deficits were observed in 5 children. After recovery 6 were average or superior in intelligence and 2 additional children exhibited no decrement in I.Q. The liklihood of sequelae appeared related to etiology and occurred in all cases of anoxia (5/5), frequently after encephalitis (5/8) but in none of the children with Reye Syndrome (0/3). Duration of deep coma as well as the presence of increased intracranial pressure for more than 2 days appeared to influence outcome. However seizures, the necessity of assisted ventilation, or the duration of light coma was not of any predictive value. Our results suggest that a significant proportion of children surviving prolonged coma of non-traumatic origin are able to attain a meaningful quality of life.

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CHANGES IN CEREBRAL BLOOD FLOW(CBF) IN PRETERM INFANTS DURING INHALATION OF CO_2 AND 100% O_2. F. Leahy*, K. Sankaran*, D. Cates*, M. MacCallum* and H. Rigatto. Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba.

The purpose of this study was to determine how sensitive CBF is to an increase in inspired CO_2 or O_2 in preterm infants. We thought that changes with 100% O_2 might explain the late hyperventilation observed in these infants during hyperoxia. Twelve newborn infants were studied in each group. Infants breathing CO_2 had a mean gestational age of 34±1 wk (S.E.), mean birth weight of 1820±174 g, mean age of 8±2 days. Those breathing 100% O_2 had a mean gestational age of 34±1 wk (S.E.), mean birth weight of 1958±142 g, mean age 11±2 days. The method for CBF estimation consisted of jugular venous occlusion plethysmography using a mercury-in-rubber strain gauge and two dopplers for recording arterial and venous flow velocities respectively. We also recorded venous occlusion time (VOT), defined as the time in seconds taken for the venous doppler tracing to reach zero point, in order to standardize excellence of the occlusion technique. During inhalation of CO_2, CBF increased from 58±5 ml/min/100g to 82±9 ml/min/100g (p=0.001). Mean P_ACO_2 rose from 39±1 to 44±1. Therefore, CBF increased 8.6% per mmHg P_ACO_2 change. During inhalation of 100% O_2 CBF fell from 60±5 ml/min/100g to 52±4 ml/min/100g (p=0.004). Our results suggest: 1) CO_2 is an important regulator of CBF in preterm infants and their CBF-CO_2 sensitivity is greater than in adult subjects; and 2) 100% O_2 reduces CBF significantly. We conclude that relative brain ischemia during administration of 100% O_2 may be responsible for the late ventilatory response to hyperoxia.

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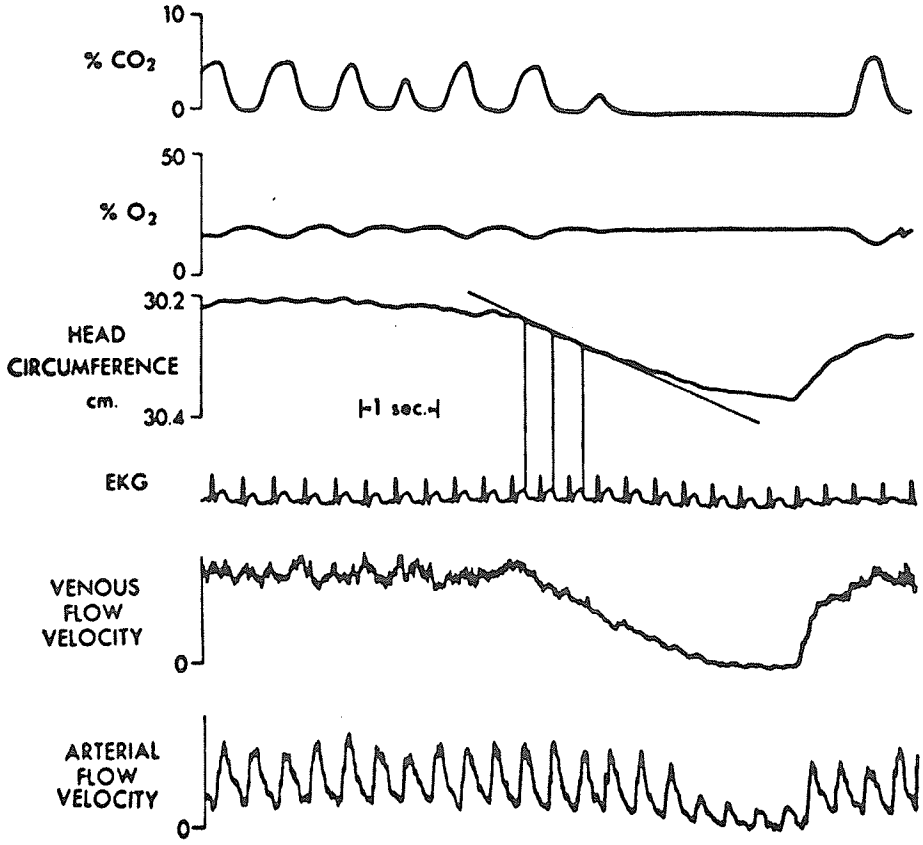

Compression of jugular veins causes increase in OFC. Note that sagittal venous flow(doppler) decreases. There is no decrease in arterial flow velocity during the initial slope. The initial slope corresponding to a change in OFC is used to calculate cerebral blood flow.

TABLE 1. CARBON DIOXIDE AND CEREBRAL BLOOD FLOW

INFANTS	AGE (DAYS)	SEX	GESTATION (WEEKS)	BIRTH WEIGHT (GRAMS)	CONTROL VALUES		VALUES POST CARBON DIOXIDE		
					CEREBRAL BLOOD FLOW (ml/min/100g)	P_ACO_2	CEREBRAL BLOOD FLOW (ml/min/100g)	P_ACO_2	CEREBRAL BLOOD FLOW % CHANGE PER mm Hg P_ACO_2
1	3	F	37	2070	70	37	91	42	+ 6
2	11	F	34	1720	71	36	145	45	+11
3	1	M	38	2640	24	34	37	38	+13
4	6	F	37	1760	90	35	103	38	+ 5
5	2	M	32	1910	67	35	115	42	+ 8
6	5	F	32	1560	36	40	64	46	+13
7	9	F	32	980	76	43	87	45	+14
8	4	M	36	2840	48	39	71	43	+12
9	6	F	32	1160	42	38	46	40	+ 5
10	10	F	34	1570	52	44	72	49	+ 8
11	24	F	33	1130	56	41	67	46	+ 4
12	18	M	34	2480	68	43	89	50	+ 4
MEAN ±S.E.	8 ±2		34 ±1	1820 ±174	58 ±5	39 ±1	82 ±9	44 ±1	8.6 ± 1

TABLE 2. HYPEROXIA AND CEREBRAL BLOOD FLOW

					CONTROL VALUES				VALUES POST HYPEROXIA					
INFANTS	AGE (DAYS)	SEX	GESTATION (WEEKS)	BIRTH WEIGHT (GRAMS)	CEREBRAL BLOOD FLOW (ml/min/100g)	P_ACO_2	P_AO_2	VENOUS OCCLUSION TIME (SECONDS)	CEREBRAL BLOOD FLOW (ml/min/100g)	P_ACO_2	P_AO_2	VENOUS OCCLUSION TIME (SECONDS)	CEREBRAL BLOOD FLOW % CHANGE	VOT ΔZ
1	10	M	36	2500	48	34	123	2.2	32	34	480	2.3	-33	+45
2	7	M	36	1700	46	38	110	3.4	54	37	540	3.2	+17	- 5.9
3	7	F	34	1900	55	36	118	3.3	45	36	600	3.6	-18	+ 9.1
4	9	M	37	2600	50	36	110	4.0	47	37	560	5.2	- 6	+30
5	26	F	31	2000	47	35	-	3.1	40	34	-	5.0	-15	+61
6	6	F	32	1200	49	37	-	2.4	52	37	-	2.2	+ 6	- 8.3
7	13	M	33	2000	73	41	105	3.2	61	41	-	6.4	-16	+100
8	18	F	29	1300	87	32	126	5.0	76	32	560	5.0	-13	0
9	2	F	37	2100	31	35	118	5.2	26	35	580	7.8	-16	+50
10	6	F	34	1700	79	36	95	2.7	67	34	630	4.1	-15	+52
11	4	M	36	2800	77	34	-	2.6	60	34	600	3.1	-22	+19
12	22	F	30	1700	81	42	110	3.6	64	41	576	2.4	-21	-33
MEAN	11		34	1958	60	36	113	3.4	52	36	570	4.2	-13	+27
S.E.	±2		±1	±142	±5	±1	±3	±.3	±4	±1	±14	±.5	±4	±11