Estimated Cerebral Blood Flow in Term Infants with Hypoxic-Ischemic Encephalopathy

K. SANKARAN,⁽³⁵⁾ K. PETERS, AND N. FINER

Department of Neonatology, Royal Alexandra Hospital, and Department of Pediatrics, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Summary

Estimated cerebral blood flow (eCBF) was measured sequentially in seven term infants with evidence of hypoxic-ischemic encephalopathy (HIE) and compared with that of normal-term infants. The eCBF was determined by a noninvasive method involving brief bilateral jugular venous occlusion with simultaneous measurement of occipitofrontal circumference. There was a significant decrease in eCBF on day 2 (30 ± 4 ml/min/100 g brain weight) and on day 4 (36 ± 5 ml/min/100 g brain weight) compared with control values (56 ± 4 ml/min/100 g brain weight; 54 ± 4 ml/min/100 g brain weight) ($P < 0.01$). The alveolar CO_2 was significantly lower on days 2 and 4 in the HIE group ($P < 0.001$), and these values increased to control values by day 6. There was no significant correlation between estimated cerebral blood flow and alveolar CO_2 in infants with HIE. We conclude that term infants with evidence of hypoxic-ischemic encephalopathy demonstrate lowered eCBF in the first 4 days of life.

Speculation

Some of the treatment schedules used for infants with hypoxic-ischemic encephalopathy may, in fact, alter brain blood flow. Therefore, consideration of low cerebral blood flow in these infants becomes very important when such therapy is contemplated.

Perinatal asphyxia or hypoxic-ischemic encephalopathy (HIE) is a significant cause of neonatal mortality and morbidity (1, 2, 6, 15, 30). The majority of infants who demonstrate neurologic and developmental sequelae after significant perinatal injury are generally of low birth weight and short gestational age (9, 14). Recently, however, there has been an increased awareness that the term infant can also sustain hypoxic-ischemic injury with clear evidence of neurodevelopmental sequelae related to a different underlying pathophysiology (26, 27, 30). It has been shown that severe partial fetal asphyxia in an animal model can lead to damage in the white matter of the hemispheres and in the substance of the cerebral cortex with evidence of neuronal necrosis and parasagittal cerebral necrosis similar to that seen in asphyxiated term infants (29, 32). A knowledge of the sequence of events that follow hypoxic-ischemic brain injury is necessary for appropriate therapeutic intervention. Volpe (31) has pointed out the central role of cerebral blood flow in the understanding of hypoxic-ischemic brain injury.

The information on cerebral blood flow in term infants suffering from HIE is scant and incomplete (12, 18). Using the technique of brief jugular venous occlusion and simultaneous measurement of head circumference, cerebral blood flow (CBF) was estimated sequentially in seven term infants with documented HIE. The results demonstrate significantly decreased eCBF in asphyxiated term infants with an impaired response to CO_2 compared with normal term infants.

MATERIALS AND METHODS

Seven asphyxiated infants showing evidence of HIE and seven normal-term infants were studied. All infants in the control group were selected from the normal newborn nurseries of the Royal Alexandra Hospital and were found to be completely normal upon general physical and detailed neurological examinations (21). All infants in the asphyxia group were cared for in the Newborn Intensive Care Nursery of the same hospital. Infants with evidence of infection, congenital heart disease, congenital abnormalities of the nervous system, or respiratory distress unrelated to asphyxia were not included in this study. Only those infants who fulfilled the following criteria during an initial 24 hr period of observation in the Newborn Intensive Care Nursery were selected:

1. Gestation >37 wk, both by maternal dates and clinical assessment, with a birth weight appropriate for gestational age.
2. A history suggestive of fetal distress including meconium staining, fetal heart rate abnormalities, severe antepartum hemorrhage, or a complicated delivery including breech extraction, difficult forceps extraction, failed forceps, and/or cesarean section for prolonged labor or fetal distress.
3. Immediate neonatal asphyxia as evidenced by the need for immediate intubation and resuscitation or Apgar scores of 3 or less at 1 min or 5 or less at 5 min.
4. Neurologic dysfunction as evidenced by seizures, marked abnormalities of behavioral state, posture, tone, motility, and reflexes (3, 25). Some infants had other system abnormalities related to asphyxia, *i.e.*, renal, hepatic, and metabolic dysfunction.
5. Electroencephalograms and computerized tomographic scans were done on all infants with HIE and showed abnormalities compatible with HIE.

Both groups of infants were quiet before and during the study, breathing spontaneously without any respiratory assistance. Normal-term infants were studied before feeding. Asphyxiated babies were not fed orally but were on intravenous fluids. Fluids were restricted initially (from 55 to 110 cc/kg/day by the fourth day).

The protocol was reviewed and approved by the Clinical Investigation Committee of the Royal Alexandra Hospital. Informed consent was obtained from the parents of all children studied.

Estimation of eCBF was based on the principle originally described by Cross *et al.* (8) and modified for quantitative purposes as described previously (5-7, 12, 13, 23). A gentle brief (2 to 3 sec) compression of the jugular veins bilaterally at the neck without exerting traction of the skin induced a change in the head circumference which was proportional to cerebral blood flow. The relation of skull volume to occipitofrontal circumference (OFC) in normoccephalic infants has been well established. (4, 13, 17).

The change in head circumference was measured using a sensitive strain gauge around the infant's head. Duplicate measurements were taken from each infant in each study. The reproducibility of the estimation of cerebral blood flow by this technique

was also tested and found to be within 3%. We observed that after multiple occlusions (>3) the changes in OFC decreased considerably, possibly due to opening of collateral venous circulation. This was overcome by measuring the first two occlusions.

Mean arterial blood pressure (MAP) was determined using a venous mode of the ultrasonic Doppler (model 810; Parks Electronic, Beaverton, Oregon). The diastolic pressure was recorded at the onset of venous flow through the brachial vein. The MAP was calculated by using the formula:

$$\text{MAP} = \frac{(\text{systolic pressure} - \text{diastolic pressure}) \times 2}{3} + \text{diastolic pressure}$$

The intracranial pressure (ICP) was monitored through the anterior fontanelle by a noninvasive pressure monitor (model 1702; Ladd Intracranial Pressure Monitor, Roche Medical, Cranbury, NY) (28). The fiberoptic sensor was applied on the anterior fontanelle after shaving the hair and was secured in position by an infant electrocardiogram electrode (01-0115; NNDM Corp., Dayton, OH). The calibration was obtained by submerging the sensor in 0 to 20 cm of water. The pressure changes during venous occlusions were tested and showed consistent changes in the ICP rise in each infant at the time of the study. It was also noted that when the jugular vein on one side was occluded, the initial rate of rise in pressure was lower than when occluded bilaterally. The pressure volume relationship between the skulls of the control and HIE infants was examined by simultaneous recording of ICP and OFC. Cranial compliance was calculated as $\Delta V/\Delta P$ (ΔV = volume change (ml) as calculated during a venous occlusion. ΔP = a pressure change (cmH₂O) as recorded from the ICP monitor during an occlusion). In addition, inspiratory and expiratory air flow was monitored by using a nose piece and screen flow meter (22, 24). An infrared CO₂ analyzer (model LB2; Beckman, Schiller Park, IL) was used to monitor alveolar CO₂ (Paco₂). The electrocardiogram was continuously recorded from a biomedical amplifier (model 8811D; Hewlett Packard, Waltham, MA). All the signals were appropriately amplified and recorded on an eight-channel recorder (Hewlett Packard model 7758).

RESULTS

The values for eCBF in the control and asphyxiated infants are shown in Table 1. Infants with HIE had an eCBF which was 54% of the control infants on day 2 and 67% on day 5. Although the mean value was still lower on day 6, this was not statistically different from that of the control infants (Fig. 1). Alveolar CO₂ was significantly lower ($P < 0.001$) in the first two studies, days 2 and 4, in the HIE group than in the control group. Alveolar CO₂ tended to rise by day 4 and approached the value of the

Fig. 1. Estimated cerebral blood flow on days 2, 4, and 6 after birth in normal and HIE groups is shown. There is a significant decrease in eCBF in the HIE group on days 2 and 4.

Fig. 2. ET CO₂ (Paco₂) is plotted against time in days. Paco₂ is significantly lower in HIE group on days 2 and day 4 but not on day 6.

Table 1. Measurements in term infants with and without HIE

	Asphyxia	Control	P
No.	7	7	
Gestation (Wk)	40 ± 0.5 ¹	39 ± 1	NS ²
Birth wt (g)	3424 ± 126	2981 ± 131	NS
APGAR			
1 min	3 ± 0.5	7 ± 1	<0.05
5 min	7 ± 0.5	8 ± 1	NS
Cerebral blood flow (ml/min/100 g brain wt.)			
Day 2	30 ± 4	56 ± 4	<0.01
Day 4	36 ± 5	54 ± 4	<0.01
Day 6	40 ± 8	50 ± 5	NS
Paco ₂ (mm Hg)			
Day 2	23 ± 3	31 ± 2	<0.001
Day 4	30 ± 1	32 ± 1	<0.01
day 6	38 ± 3	34 ± 2	NS

¹ Mean ± S.E.

² NS, not significant.

control infants in spite of the fact that cerebral blood flow remained low (Fig. 2). MAP was no different in the asphyxiated group than the control group ($P > 0.05$). There was no correlation between the MAP and eCBF in either group. No significant relationship was seen in the asphyxiated infants between Paco₂ level and eCBF. However, in the control infants, there was a linear relationship between CO₂ and eCBF with a correlation coefficient of 0.66 ($P < 0.01$).

The resting ICP in the HIE group was 15 ± 2.5 cm of H₂O compared with the control value of 8 ± 2 cm H₂O ($P < 0.05$). The pressure-volume relationship was tested in both groups and found to be linear throughout the range of this study. As others, we have also observed that spontaneous crying produced much higher ICP changes (mean, 25 cm H₂O; range, 20 to 28 cm H₂O) than that produced by occlusion. The Student *t* test was used for statistical analysis.

DISCUSSION

The mean estimated cerebral blood flow we obtained in normal-term infants ranged from 50 to 56 ml/min/100 g brain weight and

was in the range described by other investigators using invasive methods (5, 6, 11, 15). Lou *et al.* (15) used an invasive ^{133}Xe technique and demonstrated pressure passive cerebral blood flow with a lack of autoregulation in stressed infants. The majority of their patients were low birth weight with only four infants weighing greater than 2500 g. Only two of the group were 37 wk gestation or greater, both of whom were not asphyxiated and had cerebral blood flows, comparable with our control values.

Cooke *et al.* (5), using a technique similar to the present study, estimated cerebral blood flow in 14 term infants at frequent intervals over the first 24 hr of life and demonstrated a significant decrease in estimated cerebral blood flow over the first 3 hr to a level at 24 hr of 30.7 ± 2.2 ml/min/100 g brain weight which was significantly lower than our value for control groups. Cross *et al.* (7), using a noninvasive method, also reported values in the term infant which ranged from 22 to 59 ml/min/100 g brain weight. The methodology in these studies did not include the monitoring of arterial and venous flows and interference with either of these by the occlusion may produce lower values for eCBF.

In addition to the expansibility of the skull, the overall brain and cranial compliance must be considered when using this technique. A lowered compliance, secondary to increased intracellular water or other fluids shifts within the brain, may be expected to result in underestimation of blood flow. In an effort to examine this relationship, compliance was calculated during jugular venous occlusions. The volume-pressure relationship was similar in both the control infants and the HIE group, in spite of the fact that resting ICP was significantly higher in the HIE infants and suggests that the volume-pressure relationship is still linear throughout the range of our study.

After a global ischemic insult in both animals and humans, there is a decrease in blood flow similar to that seen in our study (19, 23). Lou *et al.* (16) have shown that low cerebral blood flow less than 20 ml/min/100 g brain weight in the first few hours of life has a significant relationship to later sequelae. Preliminary follow-up results from our study also indicate a highly significant correlation with outcome. The depression in the blood flow seen after an hypoxic-ischemic insult is thought to be secondary to brain swelling, intracellular fluid shifts, and neuronal damage as well as capillary obstruction secondary to edema of the endothelial cells and astrocyte foot processes (10, 20). Cerebral blood flow measured in animal models after 16 to 37 hr of asphyxia was decreased in proportion to the severity of the asphyxia and was more depressed in the cerebrum than in the brain stem (20). This decrease in flow was felt to be secondary to brain edema with a predelection for the paracentral and posterior parietal areas of the cerebral cortex.

We were unable to demonstrate the linear relationship between blood pressure and flow in this, and this may suggest an autoregulatory phenomenon (11, 15). There was no attempt in this study to manipulate blood pressure or blood volumes and thus we do not have sequential data relating eCBF to alterations in MAP in any given infant. It would appear that flow limitation postischemia is, at the capillary level, similar to that of larger vessels when in a state of vasoparalysis secondary to cerebral lactic acidosis. Six hr after global ischemic insult, cerebrospinal fluid is still acidotic with maximally dilated brain arteries (10). Lou *et al.* (15) were able to demonstrate a relationship between blood pressure and flow in their preterm infants studied within the first 12 hr of life; our infants were term infants studied at 2 days of age or older. This may account for the discrepant results.

The effect of arterial CO_2 tension on cerebral blood flow is well established (11, 18). In this present study, we did not test CO_2 reactivity of cerebral vasculature by raising arterial or alveolar CO_2 levels. However, we were unable to show any significant relationship of alveolar CO_2 and eCBF in HIE group, whereas in control infants there was a linear relationship between Paco_2 and eCBF. This may mean attenuated cerebrovascular CO_2 reactivity in the affected areas of the brain in asphyxiated infants. Because both physiologic variables rise concomitantly in infants with HIE,

one may speculate that the low Pco_2 contributes to their low cerebral blood flow. However, we believe that this is unlikely.

Noninvasive eCBF by the venous occlusion plethysmography is significantly decreased in term asphyxiated infants.

Infants suffering from HIE show no correlation between eCBF and alveolar CO_2 . The eCBF appeared to improve by the end of the first wk and was similar to those of the control group.

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35. Requests for reprints should be addressed to: Dr. K. Sankaran, Division of Neonatology, University Hospital, Saskatoon, Saskatchewan, Canada.
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