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Cerebral Blood Flow and O_2 Metabolism after Asphyxia in Neonatal Lambs

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ABSTRACT. A neonatal lamb model has been developed to examine the regulation of cerebral blood flow (CBF) and oxygen metabolism during the critical period after an asphyxial insult. Nine newborn lambs had control measurements and timed measurements after asphyxia of CBF (radioactive microsphere technique), arterial and cerebral venous (sagittal sinus) blood gases and oxygen contents performed. Immediately after resuscitation from asphyxia, there was a marked increase in CBF compared to control (239 ± 22 *versus* 82 ± 7 ml·100 g^{-1}·min^{-1}, mean ± SEM; $p < 0.01$). Cerebral oxygen delivery (CBF × arterial O_2 content) increased from 12.87 ± 1.20 to 37.40 ± 3.40 ml·100 g^{-1}·min^{-1} ($p < 0.01$), while cerebral O_2 consumption was significantly decreased compared to control (4.75 ± 0.42 to 3.42 ± 0.46 ml·100 g^{-1}·min^{-1}, $p < 0.05$). Cerebral fractional O_2 extraction, the relationship between oxygen uptake and delivery fell from 0.38 ± 0.03 to 0.09 ± 0.02; $p < 0.01$. This reactive hyperemia was followed in all animals by a period of hypoperfusion. CBF (52 ± 4 ml·100 g^{-1}·min^{-1}), O_2 delivery (7.94 ± 0.50 ml·100 g^{-1}·min^{-1}), and cerebral O_2 consumption (3.34 ± 0.24 ml·100 g^{-1}·min^{-1}) were all significantly depressed when compared to control. These data demonstrate important changes in CBF and O_2 metabolism after neonatal asphyxia that may be important to the pathogenesis of brain injury. (*Pediatr Res* 20: 778–782, 1986)

Abbreviations

CBF, cerebral blood flow
OD, cerebral oxygen delivery
$CMRO_2$, cerebral oxygen consumption
E, cerebral fractional O_2 extraction

Birth asphyxia with subsequent central nervous system sequelae is a major problem in perinatal medicine with reported incidence ranging from 1–5% of live births (1, 2). The presence of asphyxia is associated with a significant increase in neonatal mortality in infants greater than 27 wk gestation with the most profound increase in the term and near term (greater than 36 wk) population (1). Equally important is the presence of significant neurologic handicap among survivors (18.5–33%) (2, 3).

Clinical and pathologic changes similar to those seen in the human neonate have been nicely illustrated in a fetal/neonatal nonhuman primate model of prolonged partial asphyxia (4). However, these studies did not systematically address specific mechanisms of asphyxial brain injury. Certainly, the initial hypoxic-ischemic insult with cerebral O_2 deprivation is important in this regard. Of potentially equal importance is damage that occurs after the initial insult during the period of cerebral recovery. There are at least four abnormalities of posthypoxic/ischemic CBF and oxygen metabolism regulation described in adult models that may also be pertinent to the neonate.

Failure to reperfuse ischemic regions after restoration of the circulation is one potential mechanism of extended injury during the period after ischemia (5). A second described abnormality of postischemic CBF regulation is late postischemic interference with CBF. In this circumstance, during reperfusion there is a reactive hyperemia followed by a decrease in CBF to below control levels (6, 7). A third potential mechanism of injury is an inability of the cerebral circulation to respond in a normal fashion to maintain cerebral O_2 delivery with subsequent episodes of hypoxia or hypotension during the postasphyxia period. Finally irregularities of cerebral metabolism may be involved in postasphyxial brain injury. However, the effects of transient ischemia on cerebral energy metabolism are complex, and the results obtained with different models of cerebral ischemia have not always demonstrated consistent findings (8, 9).

Currently scant data exist examining the response of CBF and $CMRO_2$ after neonatal asphyxia. The aims of the present study were to: 1) Develop a model for the study of the newborn cerebral circulation specifically during the 4-h time period after asphyxia. 2) To describe changes in CBF, $CMRO_2$, cerebral O_2 delivery, and cerebral fractional O_2 extraction during the period of cerebral recovery.

METHODS

Surgical procedure. Nine newborn lambs were operated upon under pentobarbital anesthesia on days 1–3 of life. Polyvinyl chloride catheters (0.034 in ID × 0.054 in OD; Martech Medical Products, Lansdale, PA) were placed in the left ventricle via an axillary artery, the brachiocephalic artery via an axillary artery, the abdominal aorta via a femoral artery, the inferior vena cava via a femoral vein, and the posterior sagittal sinus proximal to the confluence of the veins. The sagittal sinus catheter was placed through a 1 in in diameter burr hole in the midline proximal to the lambdoidal sutures. The catheters entering through the animal's extremities were protected in a pouch on the abdomen. The sagittal sinus catheter was cut, pinned, and sutured to the lamb's scalp. The animals were returned to their mothers and allowed a 24-h recovery period prior to study. At that time, all lambs were standing and feeding normally. Previous work has demonstrated this is an adequate time interval to eliminate any pentobarbital effect on CBF (10).

Physiologic Measurements. CBF was measured using the reference organ radiolabeled microsphere technique as previously

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described (10–12). Withdrawal of the reference organ through the brachiocephalic artery catheter was into a counting vial by a precalibrated pump (2.47 ml·min^{-1}; Harvard Apparatus, Dover, MA). After completion of the study, animals were sacrificed with T-61 Euthanasia Solution (American Hoechst, Summerville, NJ), position of the catheters checked, and the brain removed. Brains were placed in formalin for 1 wk and then divided into the regions listed in Table 2. The radioactivity in each sample was determined using a three-channel γ-counter (Tracor Analytic, Des Plaines, IL) and regional blood flows calculated as previously described (10). Whole brain blood flow was calculated using the sum of the counts for all regions except brainstem and cerebellum. Adequate central mixing of microspheres using the left ventricular injection site has previously been confirmed in the newborn lamb (11). All reference blood samples and all tissue samples (except white matter) contained over 400 microspheres (13). White matter had 200–400 microspheres.

Blood samples for pH, CO_2 tension (P_{CO_2}), O_2 tension (PO_2), and O_2 content were withdrawan anaerobically into heparinized Natelson glass pipettes from the brachiocephalic artery and sagittal sinus catheters. PO_2, P_{CO_2}, and pH were measured at 39.5° C using the Radiometer BMS3 MK2 (Radiometer, Copenhagen). Blood hemoglobin and O_2 saturation were measured colorimetrically in duplicate by a hemoximeter (Radiometer, Copenhagen, Denmark) and oxygen content was calculated as the product of hemoglobin and O_2 saturation. Blood pressure and heart rate were continuously monitored in the abdominal aorta (Gould Instruments, Oxnard, CA). Blood pressure was referenced to the right atrium.

Experimental Procedure. On the day of study, the animals were paralyzed and sedated lightly with pancuronium (0.1 mg/kg), intubated and ventilated on an infant ventilator (Bird, Co., Palm Springs, CA) with a gas mixture to provide PaO_2 = 80–120 mm Hg and $Paco_2$ 35–40 mm Hg. Pancuronium has been shown to have no effect on CBF and $CMRO_2$ (14). No painful procedures were performed during the course of the study.

One measurement of CBF (radiolabeled microspheres), arterial and venous blood gases, and O_2 contents were made during a control period. The animals were then subjected to a gradual asphyxial insult by altering inspired gas concentrations and ventilator rate (Fig. 1). PaO_2 was lowered to 15–22 mm Hg, CaO_2 to 1.5–2.5 vol%, and $Paco_2$ increased to 60–70 mm Hg. The animals over the final 10–15 min of the insult became bradycardic (heart rate less than 100) and hypotensive with mean arterial blood pressure below the limits of autoregulation for the newborn lamb. The animals were then returned to control ventilator settings and fractional inspired O_2 concentration. CBF (microspheres), arterial and venous blood gases, and O_2 contents were measured at 5 min, 30 min, 1 h, 2 h, and 4 h after the termination of the asphyxial insult. Arterial and venous blood gases and O_2 contents were measured in addition at 1½, 2½, and 3½ h. Blood pressure and heart rate were continuously monitored throughout the entire study period. After completion of the 4-h measurements the animals were sacrificed.

Data Analysis. Comparisons were made among control, 5 min postasphyxia, "late" postasphyxia, and 4 h after asphyxia determinations. The "late" measurement was the time of lowest CBF in a given animal. The data were analyzed in this fashion because the time after asphyxia of lowest CBF was variable (see "Results"). Parameters compared included measured physiologic variables (oxygen contents, blood gases, microsphere whole brain, and regional blood flows) as well as calculated variables. $CMRO_2$, OD, fractional extraction of oxygen, CBF per unit O_2 consumption [1/(CaO_2-CvO_2)] were calculated as described previously (10, 15).

Statistical analysis among the four groups for measured and calculated variables were made using one-way analysis of variance. If the overall F test was significant, individual comparisons were made by paired t tests using the Bonferroni correction for multiple comparisons (16).

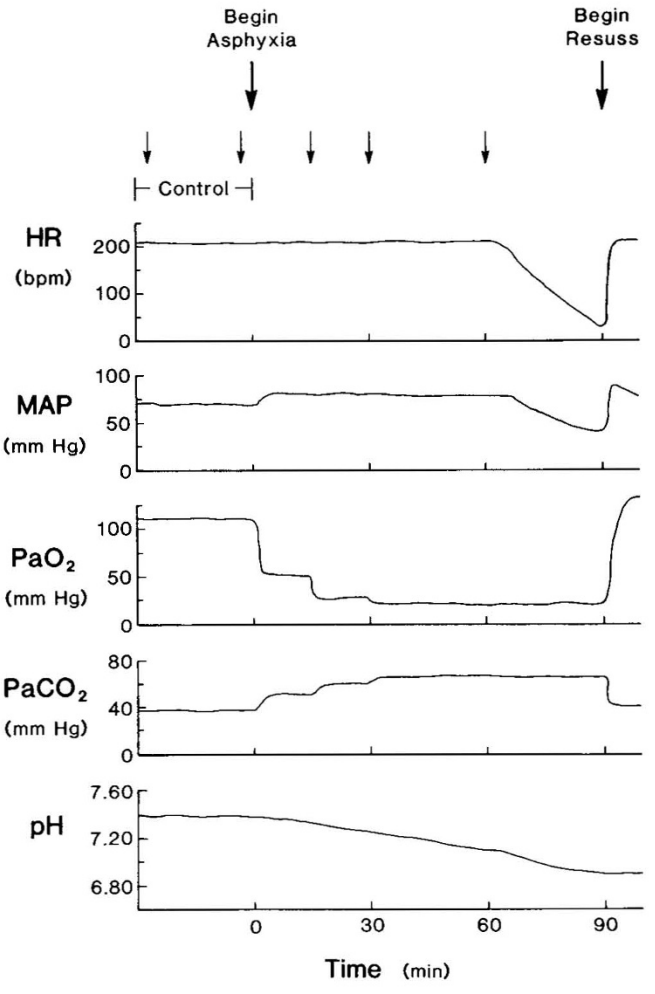

Fig. 1. Physiologic variables with asphyxia. *HR* (heart rate) in beats per minute (*bpm*), *MAP* (mean arterial pressure), arterial O_2 tension (PaO_2), arterial CO_2 tension ($Paco_2$), and pH are presented over time. Blood pressure and heart rate were monitored continuously with the mean for n = 9 animals calculated every 10 min. Blood gases were measured at the times noted by the *small arrows* and averaged for n = 9 animals.

RESULTS

The physiologic variables are presented in Table 1. There were no significant differences in CaO_2, $Paco_2$, or mean arterial blood pressure among control and postasphyxia measurements to explain changes in cerebral hemodynamics. CBF (mean ± SEM) at control, 5 min after asphyxia, and late after asphyxia is depicted in Figure 2. Control CBF was 82 ± 7 (ml·100 g^{-1}·min^{-1}), 5 min after asphyxia 239 ± 22 ($p < 0.01$ from control) and late 52 ± 4 ($p < 0.01$ from control). In the "late" period after asphyxia, all nine animals decreased CBF to a level significantly below control. However, the time of lowest flow was variable. In three animals it was reached at 30 min after asphyxia, in one at 60 min, in two by 2 h, and in the other three by 4 h. In the 6 animals who reached their lowest CBF prior to the measurement at 4 h, CBF remained stable below control values out to 4 h after asphyxia. The average CBF at 4 h after asphyxia was 59 ± 5 ($p < 0.05$ from control). All regions of the brain examined demonstrated similar flow patterns (Table 2). This pattern was also seen when cerebral perfusion was assessed by 1/(CaO_2-CvO_2). At control 1/(CaO_2-CvO_2) was 0.179 ± 0.017 (mean ± SEM, ml·ml^{-1}), 5 min after asphyxia, 0.915 ± 0.220 ($p < 0.01$ from control), 0.153 ± 0.006 late after asphyxia ($p <$

0.05 from control), and 0.145 ± 0.008 4 h after asphyxia ($p <$ 0.05 from control).

The changes in $CMRO_2$, OD, and E are presented in Table 3. The reactive hyperemia present 5 min after asphyxia was associated with a significant fall in $CMRO_2$ when compared to control despite the marked increase in O_2 delivery. Thus cerebral fractional O_2 extraction was significantly decreased when compared to control. In the late period after asphyxia, both $CMRO_2$ and O_2 delivery were significantly decreased compared to the control period.

DISCUSSION

Although Myer's elegant studies (4) detailed clinical and pathologic changes seen with neonatal asphyxia and emphasized the role of hypoxic ischemic insults in brain damage, little work is available in a neonatal model on mechanisms of subsequent damage incurred during the postasphyxia period of cerebral recovery. The importance of postischemic events has been emphasized by work in several ischemia models. Neuronal damage in the neocortex and hippocampus of rats exposed to four-vessel occlusion worsened for hours to days after relatively brief forebrain ischemia (17). Furthermore, central nervous system damage has been minimized by posthypoxic-ischemic pharmacologic interventions designed to improve CBF (18–20). Potential mechanisms of damage during the postischemic recovery period likely involve abnormalities of CBF regulation and cerebral metabolism. Serial measurements of CBF have been examined after fetal/neonatal hypoxia (21–23), but the degree of hypoxia did not approach that induced by Myers and there was no evidence of post hypoxic interference with CBF. Reivich *et al.* (24) measured CBF status post asphyxia in Myer's nonhuman primate model and found CBF to be depressed from control. However, no assessment of oxygen metabolism was made. More recently, McPhee *et al.* (25) examined the response of CBF and cerebral perfusion pressure after acute asphyxia. They demonstrated a marked hyperemia immediately after asphyxia, but only made determinations out to 40 min after asphyxia. $CMRO_2$ was again not assessed. With this background in mind, the goals of these experiments were to establish a reproducible neonatal animal model for the study of the cerebral circulation during the 4 h after asphyxia and to describe changes present in CBF and oxygen metabolism during this period.

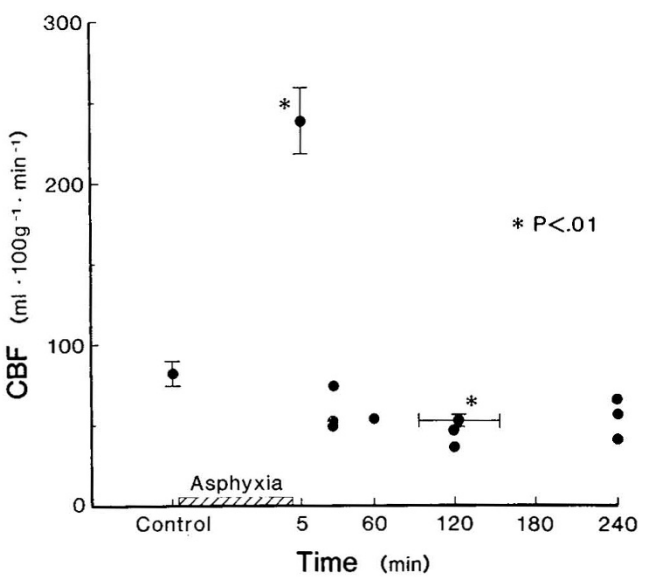

Fig. 2. CBF after asphyxia. Control and 5 min after asphyxia are mean ± SE for measurements in $n = 9$ animals. The lowest CBF late after asphyxia is depicted by an individual *point* for each animal; 3 at 30 min, 1 at 60 min, 2 at 2 h, and 3 at 4 h. The mean ± SE of these nine measurements is depicted as well as the mean ± SE for the time of lowest CBF. The mean at 5 min after asphyxia and the mean late after asphyxia differ significantly from control ($p < 0.01$).

The neonatal lamb was chosen for these studies because it is a well-established model for the evaluation of the cerebral circulation (10, 15, 26). The surgical procedures are tolerated nicely and an indwelling sagittal sinus catheter for sampling cerebral venous drainage can be reliably placed. The animals were very stable after the asphyxial insult from the cardiopulmonary standpoint allowing for repetitive assessments of the cerebral circulation without the influence of variable blood pressure, PaO_2, or $PaCO_2$.

These studies demonstrated important changes in CBF and $CMRO_2$ after asphyxia. Immediately after asphyxia, there was no evidence in the regional flow data of a failure to reperfuse. Rather, a state of reactive hyperemia existed. However, despite this cerebral overperfusion, $CMRO_2$ was depressed. Finally, all animals demonstrated significant depressions in CBF, OD delivery, and $CMRO_2$ during the late period after asphyxia. These changes may certainly be potential sources of extension of cerebral injury during the period of "cerebral recovery."

Failure to reperfuse ischemic regions after a cerebral insult has been called the "no reflow" phenomenon. It was originally described in an adult rabbit cerebral ischemia model (5) and has subsequently been observed in several other species including nonhuman primates (27). Failure to reperfuse precludes restoration of cerebral metabolism or function. Proposed mechanisms for no-reflow include postischemia hypotension (28), increased blood viscosity in the cerebral microvasculature (5), or swelling of cells in and around capillary walls decreasing vessel caliber (5, 29). In the newborn lamb model, no-reflow did not occur in any of the regions studied. Two likely explanations are that blood pressure was promptly restored during the resuscitation (Fig. 1) and that the model is one of incomplete rather than complete cerebral ischemia. Sludging of red cells in the microvasculature is likely to be more of a problem with complete ischemia.

Table 1. *Physiologic measurements**

	Control	5 min postasphyxia	Late†	4 h postasphyxia
PaO_2 (mm Hg)	113 ± 8	130 ± 19	103 ± 3	111 ± 7
$PaCO_2$ (mm Hg)	38 ± 2	41 ± 2	37 ± 2	34 ± 2
pH	7.39 ± 0.03	6.98 ± 0.06‡	7.28 ± 0.04	7.36 ± 0.03
CaO_2 (ml·100·ml^{-1})	15.8 ± 0.7	16.1 ± 0.9	16.1 ± 0.8	15.5 ± 0.6
Mean arterial pressure (mm Hg)	71 ± 2	74 ± 4	67 ± 4	67 ± 3
Heart rate (beats·min^{-1})	208 ± 12	211 ± 10	234 ± 11	238 ± 11

* All values mean ± SE for $n = 9$ animals at each time period.

† Time of lowest CBF.

‡ $p < 0.05$ from control, t test with Bonferroni correction.

Table 2. *Regional brain blood flows**

Region	Control	5 min postasphyxia	Late†	4 h postasphyxia
Brainstem	85 ± 7	292 ± 60‡	51 ± 4‡	55 ± 4‡
Cerebellum	96 ± 8	289 ± 22‡	70 ± 6	75 ± 6
Midbrain and diencephalon	95 ± 11	303 ± 53‡	59 ± 7‡	60 ± 6‡
Left frontal	82 ± 8	225 ± 18‡	51 ± 4‡	58 ± 7‡
Right frontal	83 ± 8	228 ± 21‡	53 ± 4‡	59 ± 5‡
Left occipital	81 ± 8	232 ± 22‡	54 ± 4‡	62 ± 7§
Right occipital	85 ± 7	230 ± 20‡	56 ± 5‡	67 ± 7§
Left temporal	67 ± 7	211 ± 24‡	43 ± 3‡	46 ± 5‡
Right temporal	69 ± 6	214 ± 24‡	42 ± 5‡	47 ± 3‡
Left parietal	86 ± 7	239 ± 19‡	57 ± 5‡	65 ± 6‡
Right parietal	83 ± 7	224 ± 21‡	52 ± 5‡	58 ± 5‡
Hippocampus	50 ± 6	198 ± 39‡	30 ± 3§	38 ± 10
Caudate	114 ± 11	322 ± 29‡	63 ± 5‡	63 ± 7‡
White matter	56 ± 7	155 ± 15‡	31 ± 4§	30 ± 6§

* All values mean ± SE; ml·100 g^{-1}·min^{-1} for $n = 9$ animals at each time period.
† Time of lowest CBF.
‡ $p < 0.01$ from control, t test with Bonferroni correction.
§ $p < 0.05$ from control, t test with Bonferroni correction.

Table 3. *Cerebral hemodynamics**

	Control	5 min postasphyxia	Late†	4 h postasphyxia
CBF (ml·100 g^{-1}·min^{-1})	82 ± 7	239 ± 22‡	52 ± 4‡	59 ± 5§
$CMRO_2$ (ml·100 g^{-1}·min^{-1})	4.75 ± 0.42	3.42 ± 0.46§	3.34 ± 0.24§	3.88 ± 0.30
O_2 delivery (ml·100 g^{-1}·min^{-1})	12.87 ± 1.20	37.40 ± 3.40‡	7.94 ± 0.50‡	9.21 ± 0.80§
Fractional O_2 extraction	0.38 ± 0.03	0.09 ± 0.02‡	0.42 ± 0.02	0.43 ± 0.04

* All values mean ± SEM for $n = 9$ animals at each time period.
† Time of lowest CBF.
§ $p < 0.05$, t test with Bonferroni correction.
‡ $p < 0.01$, t test with Bonferroni correction.

Reperfusion in the newborn lamb was characterized by a reactive hyperemia. This phenomenon has been described in adult ischemia models (7, 30) and has been attributed to vasodilation due to accumulation of hydrogen ion during asphyxia (30). This mechanism is a possibility in the newborn lamb as the systemic pH in the immediate postasphyxia period was markedly depressed. Another potential mechanism for this reactive hyperemia that merits future consideration is the potential role of free O_2 radicals. McCord (31) has demonstrated in several organ systems the importance of injury occurring during recirculation and has implicated free oxygen radicals in this process. Oxygen radicals have also been implicated as mediators of cerebral vascular damage in acute severe hypertension (32) and in experimental percussion brain injury (33). In both of these circumstances, there is morphologic damage to arterioles as well as a sustained vasodilation.

Of even greater concern is the depression in $CMRO_2$ immediately after asphyxia despite the marked increase in O_2 delivery. This circumstance suggests mitochondrial dysfunction in that oxygen is available but not utilized. These data correlate nicely with previous work in other models demonstrating postischemic derangements in brain energy metabolism (34) and mitochondrial function (35, 36).

In the late period after asphyxia both CBF and $CMRO_2$ are depressed. This delayed hypoperfusion has been described in adult postischemia models (6, 7). The potential role of late hypoperfusion in injury is supported by work demonstrating improved postischemic blood flow induced by nimodipine results in improved neurologic outcome (18). One suggested mechanism for late hypoperfusion is the development of cerebral edema impinging on capillaries, causing decreased cerebral perfusion (7). Cerebral edema as a complication of neonatal asphyxia has been documented pathologically in Myer's nonhuman primate model (37). The microsphere technique prevented evaluation of the brains in this study for evidence of cerebral edema.

A second potential mechanism for late hypoperfusion is a disturbance in the regulation of blood flow. The phenomena could be mediated by the production in excess of cerebral vasoconstrictors. During ischemia, there is extensive release of free fatty acids including arachidonate (38). During recirculation, the presence of oxygen allows utilization of arachidonate along both the cyclooxygenase and lipoxygenase pathways. Under normal circumstances there is a balance in production between the potent cerebral vasodilator prostaglandin I_2 and the platelet derived vasoconstrictor thromboxane A_2 (39). Both prostaglandin I_2 and thromboxane A_2 are products of the cyclooxygenase pathway. If thromboxane A_2 is produced in excess postischemia, this would lead to vasoconstriction. Two lines of evidence exist to support this hypothesis. Obrenovitch and Hallenbeck (40) demonstrated platelet accumulation 4 h after an ischemic insult in regions of low CBF (40). Improved neurologic outcome (19) and amelioration of postischemic delayed hypoperfusion (20) by administration of indomethacin, a cyclooxygenase inhibitor, have been demonstrated in other postischemia models. The lipoxygenase pathway of arachidonate metabolism is also important to consider in this regard. Leukotrienes are cerebral vasoconstrictors (41) and their production has also been shown to be increased during recirculation after cerebral ischemia (42).

$CMRO_2$ is also depressed during the late period after asphyxia. Previous studies in a model of incomplete ischemia demonstrated mitochondrial dysfunction out to 1 h after recirculation (35). Thus one explanation for the persistent decrease in $CMRO_2$ is failure of mitochondrial recovery. A second, more likely explanation in the newborn lamb model is normal physiologic coupling of CBF and $CMRO_2$. Evidence for this is provided from studies in which $CMRO_2$ was decreased 50% by pentobarbital

coma resulting in a 50% decrease in CBF (43). Furthermore, in the present study fractional O_2 extraction returned to control levels which provide at least presumptive evidence of intact mitochondrial function.

These initial studies on the regulation of CBF after neonatal asphyxia have realized the experimental goals outlined. A model for the study of the cerebral circulation after asphyxia has been developed. Important changes in CBF and $CMRO_2$ have been demonstrated during the 4-h period after a severe asphyxial insult. These changes may have major implications in the development of subsequent brain injury. The specific mechanisms of these abnormalities as well as their specific role in brain injury remain to be elucidated.

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