

Response of the Cerebral Circulation to Hypocarbica in Postasphyxia Newborn Lambs

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ABSTRACT. Respiratory alkalosis is used in the treatment of newborn infants with persistent pulmonary hypertension. Many of these infants have suffered a prior asphyxial insult. Previous studies in a newborn lamb postasphyxia model have demonstrated abnormalities in the response of the cerebral circulation to hypoxia and to changes in blood pressure. Although vasodilation in response to these stimuli was impaired, the ability of the brain to extract oxygen was not. Therefore, because the principal response of the cerebral circulation to lowering arterial carbon dioxide tension is vasoconstriction with a compensatory increase in oxygen extraction, it was hypothesized that the postasphyxia response of the cerebral circulation to decreases in carbon dioxide tension would be intact. Ten newborn lambs were subjected to an asphyxial insult. Postasphyxia whole brain and regional blood flows were measured at three to four different levels of arterial carbon dioxide tension using the radiolabeled microsphere technique. In addition, arterial and venous oxygen content and blood gases were measured in the brachiocephalic artery and the sagittal sinus. The response of whole brain cerebral blood flow (CBF) to changes in arterial carbon dioxide tension (P_{aCO_2}) is described by $\ln CBF = 0.031 P_{aCO_2} + 3.15$ ($r = 0.83$, $p < 0.001$). Responses of individual brain regions did not differ from whole brain flow. Cerebral oxygen consumption remained stable, and fractional O_2 extraction (E) increased according to the relationship $\ln (1 - E) = -0.023 P_{aCO_2} - 1.35$ ($r = 0.89$, $p < 0.001$). No significant differences in responses of cerebral hemodynamics to hypocarbica were found in comparison of data from this study with previous work in nonasphyxiated lambs. Thus, the response of the cerebral circulation to hypocarbica is not affected by a prior asphyxial insult in the newborn lamb. (*Pediatr Res* 32: 537-541, 1992)

Abbreviations

CBF, cerebral blood flow
CMRO₂, cerebral oxygen consumption
OD, cerebral oxygen delivery
E, cerebral fractional oxygen extraction
PaCO₂, arterial carbon dioxide tension
PaO₂, arterial oxygen tension

newborn animals (2-5), concerns have existed about the safety of prolonged hyperventilation in these infants (6, 7). Previous data from my laboratory (5) as well as that from Hansen *et al.* (8) have shown that, despite the decrease in CBF with hypocarbica, CMRO₂ is maintained at constant levels by an increase in E as CBF decreases. The studies described above were performed in nonstressed newborn lambs (5) and piglets (8).

Many infants with persistent pulmonary hypertension of the newborn have previously suffered an asphyxial insult. In previous studies, I have demonstrated abnormalities in autoregulation and in the response to hypoxic hypoxia of the cerebral circulation after an asphyxial insult in the newborn lamb (9). During hypoxia, the increase in CBF was less than that seen in control animals; with changes in blood pressure, CBF decreased as blood pressure decreased, which is indicative of impaired cerebral autoregulation. In both cases, however, E increased appropriately in response to diminished OD.

The present investigation was designed to address two issues. The primary goal was to examine the vasoconstrictive response postasphyxia to a decrease in PaCO₂. The second issue addressed the hypothesis that, if CBF and OD did fall postasphyxia in response to hypocarbica, CMRO₂ would be preserved by an intact increase in E.

MATERIALS AND METHODS

Ten 1- to 3-d-old newborn lambs were operated on under pentobarbital anesthesia. In each lamb, polyvinyl chloride catheters (0.034 inches inner diameter × 0.054 inches outer diameter; Martech Medical Products, Lansdale, PA) were placed in the left ventricle via a femoral artery, in the brachiocephalic artery via an axillary artery, in the abdominal aorta via a femoral artery, in the inferior vena cava via a femoral vein, and in the posterior sagittal sinus proximal to the confluence of the veins via a 1-inch diameter burr hole in the middle proximal to the lambdoid sutures. The catheters entering the lamb'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 lambs were returned to their mothers and allowed 24 h to recover. At the time of study, all lambs were standing and feeding normally. Previous work has demonstrated that this recovery period is adequate to eliminate any pentobarbital effect on CBF (10).

Whole and regional brain blood flows were measured using the reference organ radiolabeled microsphere technique as previously described (10). The reference organ was withdrawn through the brachiocephalic artery catheter into a counting vial by a precalibrated pump (2.40 mL/min; Harvard Apparatus, Dover, MA). This withdrawal rate is sufficient to prevent errors in the calculation of brain blood flows due to hematocrit differences (11). After completion of the study, the lambs were killed with T-61 Euthanasia Solution (American Hoechst, Somerville, NJ), position of the catheters was checked, and the brains were removed. The brain was divided into brainstem, cerebellum, midbrain-diencephalon, left and right frontal lobes, left and

Prolonged respiratory alkalosis is frequently used in the treatment of infants with persistent pulmonary hypertension (1). Because decreasing PaCO₂ results in cerebral vasoconstriction in

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right temporal lobes, left and right occipital lobes, and left and right parietal lobes. The radioactivity in each sample was determined using a three-channel gamma counter (Tracor Analytic, Des Plaines, IL), and regional blood flows were calculated as previously described (12). Whole-brain blood flow was calculated using the sums of the radioactive counts and regional brain weights for all regions rostral to the pons. Adequate central mixing of microspheres using the left ventricular injection site has previously been confirmed in newborn lambs (11). All reference blood samples and all tissue samples contained > 400 microspheres (13).

Blood samples for pH, P_{aCO_2} , P_{O_2} , and oxygen content were withdrawn anaerobically into heparinized Natelson glass pipettes from the brachiocephalic artery and sagittal sinus catheters. P_{O_2} , P_{aCO_2} , and pH were measured at 39.5°C using a Radiometer BMS3 Mk2 blood gas analyzer (Radiometer, Copenhagen, Denmark). Hb concentration and oxygen saturation were measured colorimetrically in duplicate by a hemoximeter (Radiometer), and oxygen content was calculated as the product of Hb and oxygen 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.

On the day of study, the lambs were paralyzed with 0.1 mg/kg pancuronium, anesthetized with 20 μ g/kg initial dose of fentanyl followed by an infusion of 10 μ g/kg/h, intubated, and ventilated with an infant ventilator (Bird Co., Palm Springs, CA) with a baseline gas mixture of 30–35% O_2 and 65–70% N_2 to provide P_{aO_2} of 10.7–16.0 kPa (80–120 mm Hg) and a baseline ventilator rate of 25–35 breaths/min to provide P_{aCO_2} of 4.7–5.3 kPa (35–40 mm Hg). Pancuronium and fentanyl have been shown at the doses used in this study to have no effect on CBF and $CMRO_2$ (9, 14). Animal body temperature was maintained with a heating pad placed below the chest and abdomen.

The lambs were then subjected to a gradual asphyxial insult by altering inspired gas concentrations and ventilator rate as previously described (12). In a stepwise fashion over 30 min, P_{aO_2} was lowered to 2–2.9 kPa (15–22 mm Hg), arterial oxygen content was lowered to 0.66–1.11 mM, and P_{aCO_2} was increased to 8–9.3 kPa (60–70 mm Hg). Approximately 1 h into the asphyxia, heart rate and mean arterial blood pressure began a gradual decline over 15–30 min to a heart rate of 30–60 beats/min and a blood pressure of 3.3–4.7 kPa (25–35 mm Hg). Final heart rate values were 12–25% of the control heart rate of 250 beats/min, and mean arterial blood pressure dropped to 30–40% of the control blood pressure of 10.7 kPa (80 mm Hg). The lambs were then returned to baseline ventilator settings and inspired oxygen concentration. The initial measurements of brain blood flows, arterial and venous blood gases, and O_2 content were made 2 h after the end of the asphyxial insult. P_{aCO_2} was then altered by adjusting the ventilator rate; P_{aO_2} was maintained with small adjustments in fraction of inspired oxygen. Each lamb was allowed to stabilize for 30 min at each P_{aCO_2} level. After measurements were made at each P_{aCO_2} , the lamb was returned to control ventilator settings for 30 min. The order of treatments (low versus higher P_{aCO_2}) was varied among lambs. Three to four determinations were made in each lamb with P_{aCO_2} varying from 2.3–6.9 kPa (17–52 mm Hg). At the completion of the study, the lambs were killed and their brains were removed.

The responses of whole and regional brain blood flows, OD, and E to changes in P_{aCO_2} were evaluated using least squares linear regression analysis after natural log transformation. For regional flows, left and right samples were combined because they did not differ. After determination of the standard error of the slope, significance of the slope compared with $b = 0$ was assessed at $p < 0.05$ using t tests. Regional flow slopes were compared with each other using two-tailed t tests and a $p < 0.05$ level of significance. The response of $CMRO_2$ to changes in P_{aCO_2} was evaluated without transformation. Finally, the responses of whole brain flow, regional flows, and extraction to

changes in P_{aCO_2} in the present investigation were compared with data from a prior investigation that used nonasphyxiated lambs (5) using two tailed t tests. The nonasphyxiated lamb studies were performed in 10 1- to 7-d-old lambs using an identical surgical approach, 24-h recovery period, and study anesthesia as in the present investigation. The experimental protocol used the same design as the present study except for the absence of the asphyxial insult and 2-h recovery period after asphyxia. The total study time in the nonasphyxiated lambs was 3 h shorter than that in the present investigation. P_{aCO_2} ranged from 1.6 to 6.1 kPa (12–46 mm Hg) with three to four different determinations made in each animal after a 30-min equilibration period at each level of P_{aCO_2} . Other physiologic parameters in the present investigation (P_{aO_2} , arterial O_2 content, blood pressure, heart rate, hematocrit) were compared during normocarbica (4–5.3 kPa; 30–40 mm Hg), mild hypercarbia (>5.3 kPa), and hypocarbica (<4 kPa) using one way analysis of variance. If the overall F test was significant, individual conditions were compared using paired t tests with a Bonferroni correction for multiple comparisons.

RESULTS

The response of CBF to changes in P_{aCO_2} over the range 2.3–6.9 kPa (17–52 mm Hg) is depicted in Figure 1. The relationship is nonlinear and is described by the equation $\ln CBF = 0.031 P_{aCO_2} + 3.15$ ($r = 0.83$, $p < 0.001$). The responses of regional flows were quite similar. For all brain regions examined, the slopes ranged between 0.025 and 0.033 \ln (mL/100 g/min/mm Hg), with r between 0.72 and 0.85, all significant at $p < 0.001$ (Table 1). The response of OD to changes in P_{aCO_2} is depicted in Figure 2 and is described by the equation $\ln OD = 0.031 P_{aCO_2} + 1.36$ ($r = 0.78$, $p < 0.001$). The relationship between E and P_{aCO_2} is depicted in Figure 3 and is described by the equation $\ln(1 - E) = -0.023 P_{aCO_2} - 1.35$ ($r = 0.89$, $p < 0.001$). $CMRO_2$

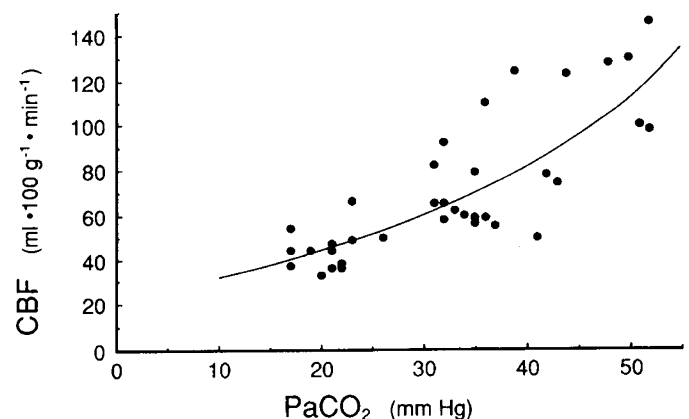


Fig. 1. Scatter plot of CBF vs P_{aCO_2} in 10 hyperventilated postasphyxia newborn lambs. SI unit conversion: 1 mm Hg = 0.1333 kPa.

Table 1. Regression equations for P_{aCO_2} vs whole brain and regional blood flows for 10 hyperventilated newborn lambs*

Equation	r
\ln (Whole brain) = $0.031 P_{aCO_2} + 3.15$	0.83
\ln (Brainstem) = $0.033 P_{aCO_2} + 3.06$	0.85
\ln (Cerebellum) = $0.031 P_{aCO_2} + 3.21$	0.80
\ln (Midbrain/diencephalon) = $0.030 P_{aCO_2} + 3.12$	0.82
\ln (Frontal cortex) = $0.028 P_{aCO_2} + 2.90$	0.82
\ln (Temporal cortex) = $0.030 P_{aCO_2} + 2.92$	0.78
\ln (Occipital cortex) = $0.028 P_{aCO_2} + 3.41$	0.72
\ln (Parietal cortex) = $0.029 P_{aCO_2} + 3.31$	0.80
\ln (Caudate nuclei) = $0.033 P_{aCO_2} + 3.40$	0.81
\ln (Hippocampi) = $0.025 P_{aCO_2} + 2.96$	0.71

* $n = 36$, $p < 0.001$ for all equations.

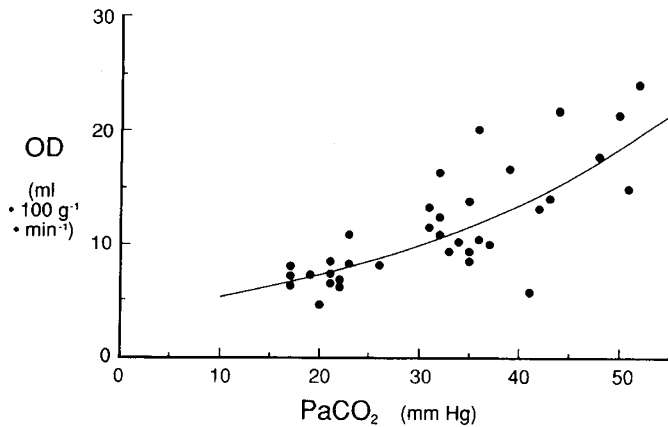


Fig. 2. Scatter plot of OD vs PaCO_2 in 10 hyperventilated postasphyxia newborn lambs. SI unit conversion: 1 mm Hg = 0.1333 kPa.

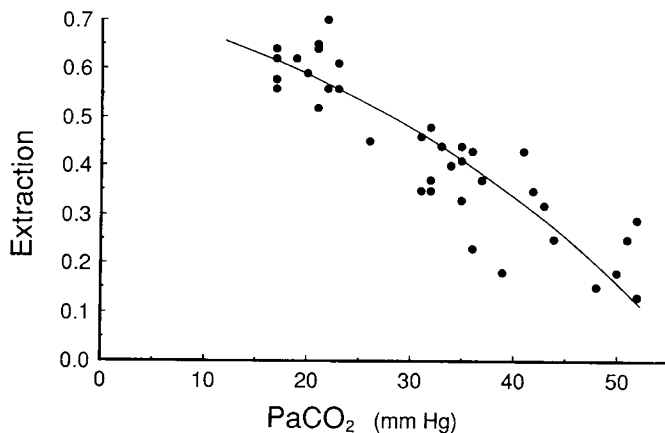


Fig. 3. Scatter plot of E vs PaCO_2 in 10 hyperventilated postasphyxia newborn lambs. SI unit conversion: 1 mm Hg = 0.1333 kPa.

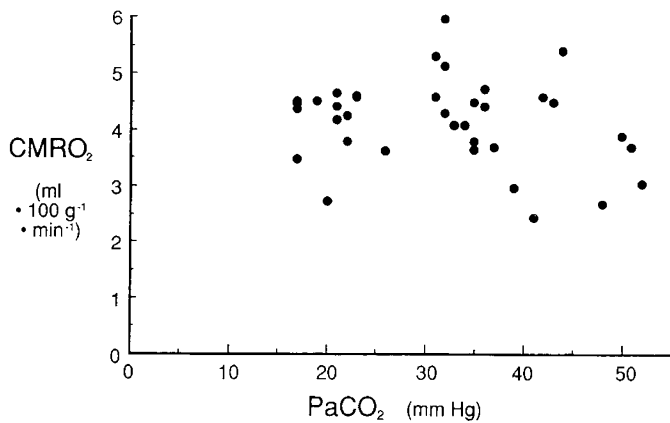


Fig. 4. Scatter plot of cerebral metabolic rate for oxygen (CMRO_2) vs PaCO_2 in 10 hyperventilated newborn lambs. SI unit conversion: 1 mm Hg = 0.1333 kPa.

did not change with PaCO_2 ($\text{CMRO}_2 = -0.021 \text{ PaCO}_2 + 4.88$; $r = -0.25$, $p > 0.05$) (Fig. 4). During the postasphyxia study period, no significant differences in PaO_2 , arterial oxygen content, blood pressure, heart rate, or hematocrit were present at different levels of PaCO_2 (Table 2).

Table 3 presents a comparison of the responses of CBF, OD, CMRO_2 , and E to changes in PaCO_2 postasphyxia and in nonasphyxiated lambs (5). No significant differences in responses were present between groups for any of the cerebral hemodynamic variables. In addition, no significant differences existed in regional flow responses to PaCO_2 between nonasphyxiated and asphyxiated lambs.

DISCUSSION

The data from this investigation demonstrate that the responses of the cerebral circulation to hypocarbia are not affected by a prior asphyxial insult. As in the nonasphyxiated lamb, the decreases in whole brain and regional blood flows to decreasing PaCO_2 were nonlinear, with no significant differences noted among regions. In addition, CMRO_2 was unchanged even during severe hypocarbia due to a compensatory increase in E and an attenuation of cerebral vasoconstriction at very low levels of PaCO_2 .

This study is the first to examine responses to hypocarbia after an asphyxial insult in a neonatal model. Some comparison data is available from adult global ischemia models. Although the type of insult is different, these data do provide a framework against which the data from the present investigation can be considered. Nemoto *et al.* (15), using a model of 15 min of global ischemia in dogs, showed no change in CBF from normocarbia as PaCO_2 was lowered to 2.7 kPa (20 mm Hg) during the period of postischemic recirculation. Koch *et al.* (16) also in dogs, showed a similar response after 12 minutes of ischemia. In contrast, Miller *et al.* (17), using 5 min of global ischemia in dogs, did show a decrease in CBF with hypocarbia. The insult in the later study is most comparable to the present investigation in which blood pressure below the limits of autoregulation in the lamb (mean arterial pressure <5.3 kPa; 40 mm Hg) and bradycardia (heart rate <100 beats/min) are present during the final 5–10 min of the insult. These data would support a conclusion that the response to hypocarbia postasphyxia/ischemia remains intact with less severe insults. In addition, data in newborn piglets subjected to complete ischemia have demonstrated depressed pial arteriolar and CBF responses to hypo- and hypercarbia (18–20). These data also support the above conclusion that the findings of an intact response to decreases in PaCO_2 in the present investigation are related to the severity of the insult and, in addition, are not related to maturity of the brain.

Previously studied nonasphyxiated controls were used to compare the response of the cerebral circulation to changes in PaCO_2 with that in the present postasphyxia lambs. The experimental protocols in the two studies were similar except for the asphyxial insult and 2-h recovery period in the present investigation. The 3-h increase in the time of the present investigation and the associated longer exposure to pancuronium and fentanyl compared to "controls" are unlikely to have influenced the results. Previous work from my laboratory has demonstrated the stability of CBF and CMRO_2 in the pancuronium- and fentanyl-anesthetized lamb over an 8-h period (unpublished results). There is also a small difference in the range of PaCO_2 in each study that must be addressed to completely interpret the data (1.6–6.1 kPa, 12–46 mm Hg in controls; 2.3–6.9 kPa, 17–52 mm Hg in the present study). In addition, there was an overall skew in the data to higher levels of PaCO_2 in the present study. However, the response of the cerebral circulation to changes in PaCO_2 was identical in both studies, making it unlikely that these small differences in range and distribution of data points were important.

The ability to increase E in response to a decrease in OD is consistent throughout all of our studies on postasphyxia cerebral hemodynamics (9, present investigation). This capability has a ready explanation in previous work that examined postasphyxia mitochondria function in newborn lambs (21). These data demonstrated a restoration of previously impaired mitochondria function by 2 h postasphyxia. This would support a concept that oxygen present can be used and necessary amounts extracted to preserve CMRO_2 in the face of diminished oxygen delivery.

Regional blood flow responses were the same in all regions and did not differ from control regional blood flow responses to hypocarbia. Hansen *et al.* (3) demonstrated a greater percentage of decrease in CBF compared with cerebellar, thalamic, or brainstem regional blood flows as PaCO_2 decreased from 4.7–2.0 kPa (35–15 mm Hg) in piglets. Shapiro *et al.* (22), in newborn

Table 2. *Physiologic parameters with changes in PaCO₂ in 10 newborn lambs**

Condition	n	PaO ₂ (kPa)	PaCO ₂ (kPa)	CaO ₂ (mM)	MABP (kPa)	HR (beats/min)	HCT
Hypocarbica (PaCO ₂ < 4 kPa)	14	15.2 ± 0.7	2.7 ± 0.1	7.4 ± 0.2	9.5 ± 0.5	250 ± 11	35 ± 1
Normocarbica (PaCO ₂ 4–5.3 kPa)	13	15.3 ± 0.5	4.5 ± 0.1†	7.5 ± 0.2	10 ± 0.3	242 ± 13	36 ± 1
Mild hypercarbica (PaCO ₂ > 5.3 kPa)	9	14.9 ± 0.8	6.3 ± 0.2†‡	6.9 ± 0.4	10.1 ± 0.5	222 ± 16	33 ± 2

* Values are mean ± SEM. 1 kPa = 7.5 mm Hg. CaO₂, arterial oxygen content; MABP, mean arterial blood pressure; HR, heart rate; HCT, hematocrit.

† $p < 0.001$ compared to hypocarbica.

‡ $p < 0.001$ compared to normocarbica.

Table 3. *Regression equations for PaCO₂ vs cerebral hemodynamic variables for asphyxiated and nonasphyxiated lambs**

Asphyxia	No asphyxia†
$\ln(\text{CBF}) = 0.031 \text{ PaCO}_2 + 3.15$	$\ln(\text{CBF}) = 0.025 \text{ PaCO}_2 + 3.38$
$\ln(\text{OD}) = 0.031 \text{ PaCO}_2 + 1.36$	$\ln(\text{OD}) = 0.026 \text{ PaCO}_2 + 1.50$
$\ln(1 - E) = -0.023 \text{ PaCO}_2 - 1.35$	$\ln(1 - E) = -0.023 \text{ PaCO}_2 - 1.37$
$\text{CMRO}_2 = -0.021 \text{ PaCO}_2 + 4.88$	$\text{CMRO}_2 = 0.0065 \text{ PaCO}_2 + 4.39$

* No significant difference in slopes between groups.

† No asphyxia animals are data from historical controls from reference 5.

puppies, showed significant decreases only in subcortical white matter with decreases in PaCO₂; multiple gray matter regions showed no decreases in blood flow. Young and Yagel (23), also in newborn puppies, demonstrated regional differences in blood flow responses with hypocarbica. There are several possible explanations for the differences in the data from my newborn lamb studies (present, 5) and the above cited investigations in piglets and puppies. Methodologic differences in study design, blood flow measurement techniques, anesthesia, and difficulty in demonstrating significance when absolute changes are small and experimental variability is high constitute one series of explanations. In addition, species differences offer another explanation because the newborn lamb has a more mature brain at birth than either puppies or piglets. However, it is more likely that the discrepancies relate to methodology rather than species-specific maturational differences. This is supported by the work of Reuter and Disney (4) in puppies demonstrating regional blood flow responses similar to those seen in newborn lambs. Regional blood flow decreased in a nonlinear fashion and to a similar degree in all regions examined (4). This last study is most similar to the newborn lamb studies in design and method of blood flow measurement.

Despite the availability of several studies, disagreement still exists about whether reduction of CBF with hypocarbica is harmful. Work in adult animals and humans has shown decreases in cerebral tissue PO₂, the development of abnormalities in electroencephalographic recordings, and decreased CMRO₂ during hyperventilation (24–28). These data were supported by the demonstration by Reuter and Disney (4) of decreased CMRO₂ with acute hypocarbica in newborn puppies. In contrast, both Hansen *et al.* (8) and my laboratory (5) have provided data supporting the safety of hypocarbica. Hansen *et al.* (8) studied changes in CMRO₂ in newborn piglets during both acute and more prolonged (2 h) hypocarbica. After 30 min of hypocarbica, both CBF and CMRO₂ were significantly decreased; however, by 60 min CMRO₂ had returned to baseline. Our prior work showed stable CMRO₂ in the newborn lamb with PaCO₂ lower than 2.7 kPa (20 mm Hg) (5). Furthermore, work in both newborns and adults has demonstrated normal levels of high-energy phosphates with PaCO₂ as low as 1.6 kPa (12 mm Hg) (23, 29, 30). All of these studies were done in nonasphyxiated animals. However, the infants on which therapeutic hyperventilation is often applied (those with persistent pulmonary hypertension) (1) have frequently suffered a prior asphyxial insult. Thus, these data evaluating the response to hypocarbica postasphyxia are germane to

that issue. To the extent that a stable CMRO₂ is indicative of a successful adaptation to hypocarbica, these data are reassuring regarding the use of respiratory alkalosis in the treatment of pulmonary hypertension. It is important to note, though, that the use of radiolabeled microspheres precluded an assessment of histologic injury in this model. Therefore, conclusions about the safety of therapeutic respiratory alkalosis must be considered in this regard. However, these data are consistent with outcome data in neonates who have been hyperventilated for treatment of persistent pulmonary hypertension (6, 7). Despite representing an extremely high-risk group for CNS damage, their outcome is generally favorable.

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Announcement

Call for Abstracts

The American Pediatric Society and The Society for Pediatric Research announce that the abstract deadline for the 1993 Annual Meeting (May 3-6, 1993, Sheraton Washington Hotel, Washington, DC) has been set as *January 5, 1993*. For further information contact: APS/SPR Association Headquarters, 141 Northwest Point Blvd., P.O. Box 675, Elk Grove Village, IL 60009-0675.