

## Alterations in Cerebral Blood Flow and Oxygen Consumption during Prolonged Hypocarbica

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**ABSTRACT.** The effect of prolonged (2 h) hypocarbica on cerebral blood flow, oxygen delivery, extraction, and consumption was studied in eight, 1- to 4-day-old piglets. Hyperventilation to  $P_{aCO_2} < 20$  mm Hg acutely (30 min) decreased cerebral blood flow and oxygen consumption. Cerebral oxygen consumption was subsequently restored via increases in cerebral blood flow and thus, cerebral oxygen delivery. Cerebral oxygen extraction rose from a normocarbica baseline of 50 to 75% with acute hypocarbica and was maintained at this level. The percent decrease in blood flow to the cerebrum was greater than that to other brain regions during hypocarbica. (*Pediatr Res* 20: 147-150, 1986)

Hyperventilation-induced respiratory alkalosis is a principal form of therapy used in newborn infants with persistent pulmonary hypertension. A potential complication of this therapeutic modality is brain ischemia, caused by hypocarbica-induced vasoconstriction of the cranial arteries. In several newborn animal species, acute respiratory alkalosis reduced brain blood flow to 50% of normocarbica levels indicating that significant brain oxygen deprivation might occur during hypocarbica alkalosis (1, 2). However, follow-up studies of infants managed with prolonged hypocarbica alkalosis have demonstrated a paucity of significant neurologic sequelae, despite the anticipated impact of hyperventilation on the cerebral circulation (3, 4). The apparent discrepancy between human and animal studies might be explained by variations in the response of the cerebral vasculature to extreme hypocarbica over time (5). Thus, we hypothesized that there may be an "escape" from the acute vasoconstrictive effects of hypocarbica, such that brain blood flow returns toward baseline despite the persistence of hypocarbica alkalosis. The purpose of this study was to characterize brain blood flow, oxygen delivery, and utilization over time during constant severe hypocarbica in the newborn piglet.

### MATERIALS AND METHODS

**Animal preparation.** Twelve, 1- to 4-day-old farm bred piglets were obtained on the morning of the study. The weight of the piglets was  $1.7 \pm 0.5$  kg. All surgical procedures were performed under nitrous oxide inhalation (70%) with local infiltration of the surgical incisions with 1% lidocaine. Catheters were positioned in the left ventricle (via femoral artery), ascending aorta (via axillary artery), and lower abdominal aorta (via femoral artery). A tracheotomy was performed and muscle paralysis

induced with pancuronium bromide (0.5 mg/kg). The piglet was subsequently ventilated with a Bourne LS104 infant ventilator. The sagittal sinus was exposed via a burr hole in the anterior skull, and a catheter was introduced through a 22 gauge needle puncture.

**Experimental protocol.** All animals were maintained with normal arterial blood gas values for 120 min following the completion of surgery. Body temperature was continuously monitored and maintained at  $39 \pm 1^\circ$  C throughout the study with an electric heating pad. The nitrous oxide gas mixture was replaced with compressed air and 25% oxygen at the beginning of this period. The study consisted of four blood flow determinations. During each, cardiac output, brain blood flow, arterial and sagittal sinus  $O_2$  contents, arterial blood gas tensions, and hematocrits were obtained. A baseline (time 0) measurement was made under normoxic and normocarbica conditions. Respiratory alkalosis ( $P_{aCO_2} < 20$  mm Hg) was induced by increasing the tidal volume by 30% and the respiratory rate by 50% in eight piglets. Three additional measurements were made 30, 60, and 120 min following the initiation of hyperventilation. A constant degree of respiratory alkalosis was maintained throughout the study. Blood volume was maintained by replacing the blood withdrawn with age-matched piglet blood. Following the 120-min blood flow determination, the piglet was sacrificed with pentobarbital and the brain removed and preserved in 10% formalin for 5-7 days. The brain was then divided into the following right and left sections; cerebrum, thalamus, cerebellum, and brain stem.

Four piglets served as normocarbica controls to assess the stability of this animal preparation. They were treated in a similar manner to the study piglets but were not hyperventilated.

**Methodology.** Blood flow and cardiac output were measured with microspheres ( $15 \pm 2$   $\mu$ m diameter) with the following nuclides: 113 Sn, 46 Sc, 57 Co, and 103 Ru (New England Nuclear, Boston, MA). The radioactivity per unit weight of the microsphere solution was determined just prior to the microsphere injection. Approximately  $9 \times 10^5$  microspheres were injected into the left ventricle and the catheter was flushed with 5 ml of heparinized saline over 15-20 s immediately following the microsphere injection. The reference organ withdrawal sample from the ascending aorta was collected for 2 min beginning 10 s prior to the microsphere injection, at a constant withdrawal rate of 1.03 ml/min. No change in mean arterial pressure was observed during the microsphere injection and the criteria necessary to ensure measurement accuracy to within 5% were met during the study (6). A small sample of lung tissue was removed at the end of the study to monitor for shunting of blood through the ductus arteriosus (from the aorta to pulmonary artery). We predetermined that a blood flow measurement would be discarded if there was a change of 20% or greater (compared to baseline normocarbica value) in the percentage cardiac output delivered to the lung, however, this did not occur during any of the hypocarbica determinations.

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Blood, tissue, and microsphere solution radioactivity were measured using a Packard gamma spectrometer and blood flow data generated with software written for an IBM PC. The program corrected for isotope spillover and decay. Blood flow was calculated by determining the ratio of cpm in the brain and reference blood sample and the rate of withdrawal of the reference blood sample (7). Similarly, cardiac output was calculated from the following equation:

$$\text{cardiac output} = \frac{\text{cpm injected}}{\text{cpm reference sample}} \times \text{rate of withdrawal of reference sample} \quad (7)$$

The radioactivity of the microsphere solution injected was determined by obtaining (in triplicate) small aliquots of the microsphere solution ( $0.02 \pm 0.005$  g) just prior to injection and by determining the exact weight of microsphere solution injected. Residual amounts of microsphere solution remaining in the injection syringe and stopcock were measured by flushing the syringe and stopcock into counting vials with 10–20 ml of normal saline. Blood flow to the brain was expressed as ml/min/100 g wet (nonfixated) weight, and cardiac output as ml/min/kg body weight.

O<sub>2</sub> contents of the arterial and sagittal sinus blood samples were measured with a Lex-O<sub>2</sub>-Con O<sub>2</sub> analyzer and arterial blood gas tensions measured using standard electrodes (Instrumentation Labs, Waltham, MA). Hematocrit was measured by the microhematocrit method.

**Data analysis.** Cerebral oxygen delivery and consumption were calculated using the Fick equation. O<sub>2</sub> delivery = cerebral blood flow  $\times$  arterial O<sub>2</sub> content (CaO<sub>2</sub>); O<sub>2</sub> consumption = cerebral blood flow  $\times$  [arterial O<sub>2</sub> content – sagittal sinus O<sub>2</sub> content (CvO<sub>2</sub>)]. Cerebral extraction fraction was determined by:  $\text{CaO}_2 - \text{CvO}_2 / \text{CaO}_2 \times 100$ .

Analysis of variance for repeated measurements was used to detect statistical significance. If a significant difference was found, the Dunnett's multiple range *t* test was used to compare the means. A two-way analysis of variance was used to interpret the interaction between regional changes in brain blood flow and time. Control animals were not compared directly with study animals but were used to assess stability of brain blood flow and oxygen consumption over time. All data are expressed as mean  $\pm$  SD.

## RESULTS

Table 1 summarizes the heart rate, mean arterial blood pressure, and arterial blood gas values during the study. There were no changes in heart rate, mean arterial blood pressure, and PaO<sub>2</sub>. As expected, hyperventilation resulted in increases in arterial pH as a result of hypocarbia. It should be noted that a constant level of respiratory alkalosis was maintained throughout the 120-min study period. The hematocrit values remained stable throughout the study ( $30 \pm 5\%$ ).

Figure 1 and 2 depict hypocarbic induced changes in total brain blood flow and cardiac output. Brain blood flow decreased (40%) at 30 min following the induction of respiratory alkalosis and remained decreased during the entire study. However, there was a gradual increase in brain blood flow over time, so that by 120 min, there was greater brain blood flow than at the 30-min

Table 1. Heart rate (HR), mean arterial pressure (MAP), and arterial blood gas values during the study (mean  $\pm$  SD) (*n* = 8)

Time	B	30	60	120
HR (bpm)	225 $\pm$ 33	246 $\pm$ 40	237 $\pm$ 39	234 $\pm$ 41
MAP (mm Hg)	85 $\pm$ 14	79 $\pm$ 16	83 $\pm$ 17	81 $\pm$ 15
pH	7.42 $\pm$ 0.04	7.65 $\pm$ 0.07	7.67 $\pm$ 0.07	7.66 $\pm$ 0.08
pCO <sub>2</sub> (mm Hg)	38 $\pm$ 2	16 $\pm$ 3	17 $\pm$ 3	16 $\pm$ 3
pO <sub>2</sub> (mm Hg)	107 $\pm$ 31	109 $\pm$ 30	105 $\pm$ 28	105 $\pm$ 29

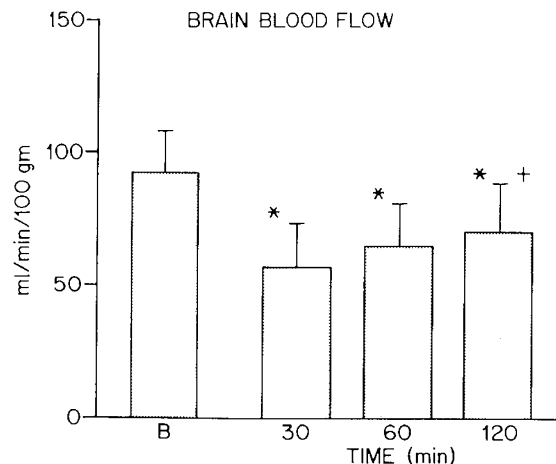


Fig. 1. Total brain blood flow during normocarbica baseline (B) and following hyperventilation (mean  $\pm$  SD). The asterisk designates a significant difference ( $p < 0.05$ ) from baseline measurement. The dagger designates a significant difference from 30-min hypocarbic measurement (*n* = 8).

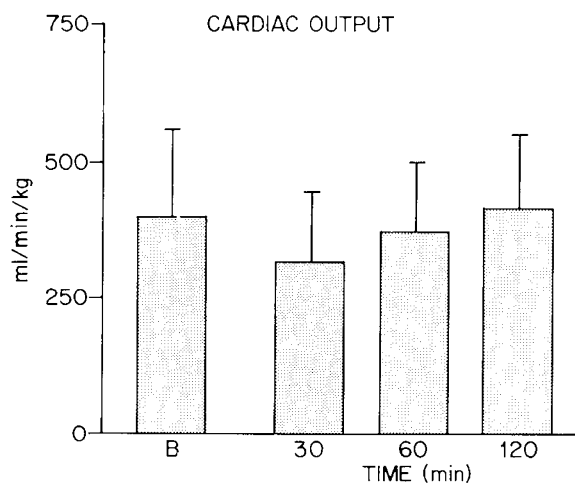


Fig. 2. Cardiac output during normocarbica baseline (B) and following onset of hyperventilation (mean  $\pm$  SD) (*n* = 8).

determination. Cardiac output did not vary significantly, although there was a trend toward decreased cardiac output with the induction of hyperventilation. The percent cardiac output reaching the brain decreased from  $5.8 \pm 1.5\%$  during normocarbica to  $4.3 \pm 0.9\%$ ,  $4.0 \pm 0.8\%$ ,  $4.4 \pm 1.7\%$  at 30, 60, and 120 min. Only the 60 min was statistically lower than the normocarbica baseline.

Figure 3 depicts the regional changes in brain blood flow during hypocarbia. To correct for regional flow differences observed during the baseline determination, the flows are expressed as percentage change from baseline flow to that region. The percentage decrease in flow to the cerebrum was greater than that observed in the other regions at the 30- and 60-min determinations.

Figure 4 summarizes the changes in cerebral oxygen delivery, oxygen extraction, and oxygen consumption. Hypocarbic-induced vasoconstriction decreased cerebral oxygen delivery during all three hypocarbic determinations. However, by 120 min oxygen delivery had significantly increased from the 30-min value. Cerebral oxygen extraction rose and was maintained at a consistent level during all three hypocarbic determinations. Cerebral oxygen consumption was decreased at only the 30-min determination.

Table 2 summarizes the data from the four control animals maintained with normocarbica throughout the entire study. There

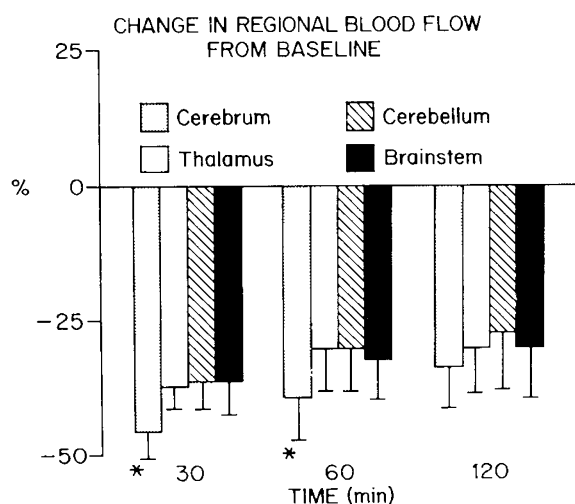


Fig. 3. Regional blood flow during hyperventilation expressed as percentage change in blood flow to that region during normocarbica. Asterisk denotes a significant difference ( $p < 0.05$ ) between regions (mean  $\pm$  SD) ( $n = 8$ ).

were no significant changes in arterial blood gases, heart rate, mean arterial pressure, cardiac output, or brain blood flow. Similarly, cerebral oxygen consumption extraction ratio remained constant.

#### DISCUSSION

In this study, hypocarbic alkalosis was achieved by increasing both the tidal volume and respiratory rate in paralyzed piglets. Positive pressure hyperventilation has the potential to impede venous return to the heart and consequently decrease cardiac output. There was a trend toward increased heart rate and decreased arterial blood pressure during hyperventilation but no significant alterations in cardiac output were observed. Hyperventilation did result in cerebral vasoconstriction as demonstrated by the changes in percentage cardiac output going to the brain. Only the 60-min determination was significantly lower than baseline due to large variations in cardiac output. Intracranial pressure and/or cerebral venous pressure were not monitored during this study. Intracranial pressure would be expected to decrease with hyperventilation due to the reduction in cerebral arterial blood flow. However, positive pressure ventilation has the potential of impeding cerebral venous return and this would have an opposite effect on intracranial pressure. Further studies of the effects of hyperventilation on intracranial pressure and cerebral venous pressure are needed to clarify this question.

The four control animals were studied to assess the stability of this surgical preparation. We did not demonstrate a gradual decrease in cerebral blood flow over time, as has been observed by other investigators studying acutely instrumented artificially ventilated animals (8). This observation may have been due to differences in anesthesia, body temperature maintenance, or be secondary to a longer stabilization period following surgery in both our control and hyperventilated animals. Muscle paralysis was initiated following surgery in both groups. Although transient changes in heart rate and arterial pressure have been reported in human neonates following pancuronium administration (9), no significant alterations in cerebral blood flow or oxygen consumption have been observed in the newborn lamb (10).

The magnitude of the decrease in cerebral blood flow (40%) at 30 min following the induction of hyperventilation is similar to that observed in previous studies (1, 2). Whether hypocarbic-induced vasoconstriction results in significant cerebral ischemia remains controversial (11). Earlier work does not support the concept of significant brain hypoxia subsequent to acute hypocarbic induced vasoconstriction (11); however, several recent

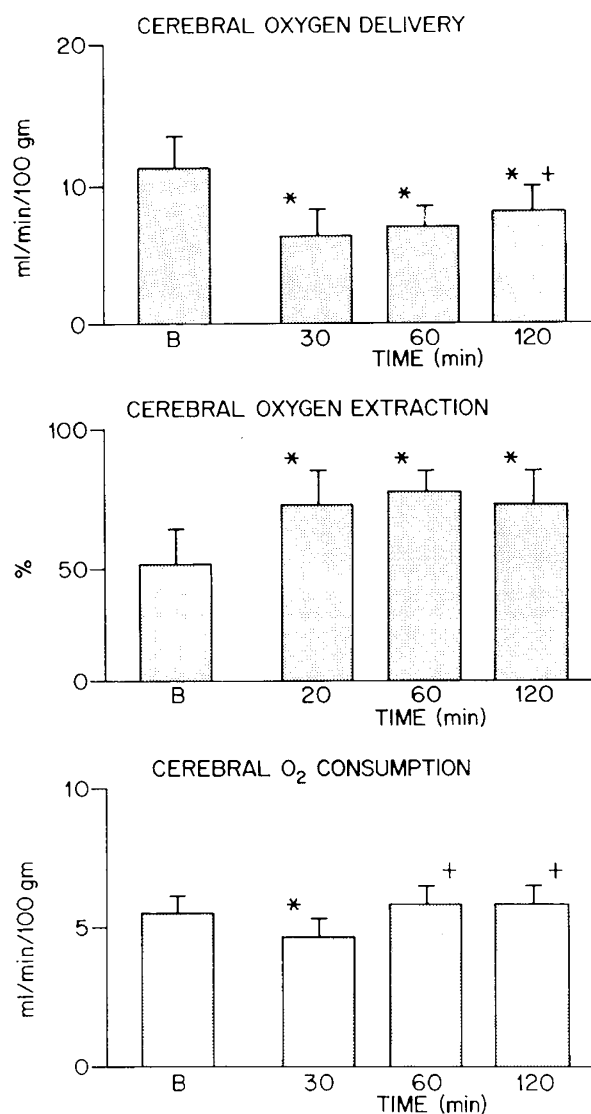


Fig. 4. Cerebral oxygen delivery, cerebral oxygen extraction, and cerebral oxygen consumption during normocarbic baseline (B) and following hyperventilation. The asterisk designates a significant difference ( $p < 0.05$ ) from baseline measurement. The dagger designates a significant difference from the 30-min measurement (mean  $\pm$  SD) ( $n = 8$ ).

Table 2. Blood gas, cardiac output (CO), brain blood flow (BBF), cerebral oxygen consumption ( $VO_2$ ), and extraction ( $EO_2$ ) values in control ( $n = 4$ ) animals maintained with normocarbica throughout the study (mean  $\pm$  SD)

Time	B	30	60	120
pH	7.39 $\pm$ 0.03	7.39 $\pm$ 0.03	7.38 $\pm$ 0.03	7.37 $\pm$ 0.04
pCO <sub>2</sub> (mm Hg)	41 $\pm$ 3	39 $\pm$ 2	41 $\pm$ 3	40 $\pm$ 3
pO <sub>2</sub> (mm Hg)	102 $\pm$ 19	103 $\pm$ 24	100 $\pm$ 19	105 $\pm$ 21
CO (ml/mm/kg)	481 $\pm$ 176	401 $\pm$ 179	475 $\pm$ 208	467 $\pm$ 149
BBF (ml/min/100 g)	94 $\pm$ 5	97 $\pm$ 9	96 $\pm$ 11	98 $\pm$ 6
VO <sub>2</sub> (ml/min/100 g)	5.7 $\pm$ 0.7	5.9 $\pm$ 0.6	5.6 $\pm$ 0.8	5.7 $\pm$ 0.7
EO <sub>2</sub> (%)	52 $\pm$ 4	54 $\pm$ 2	52 $\pm$ 2	52 $\pm$ 4

studies have demonstrated hyperventilation induced cerebral hypoxia (12, 13). Our data demonstrate an acute but transient decrease in cerebral oxygen consumption in response to hypocarbic induced cerebral vasoconstriction. The physiologic signif-

icance of this 15% decrease in oxygen consumption cannot be determined from this study.

The striking finding in this study is the gradual increase in cerebral blood flow over the 2-h period of hyperventilation. This increase in cerebral blood flow serves to restore cerebral oxygen consumption, following the acute decrease in cerebral blood flow noted with the onset of hyperventilation. The finding of gradually increasing cerebral blood flow during prolonged hypocarbia differs significantly from previous observations in newborn lambs and puppies (1, 14). This discrepancy may be species specific, but could also be related to experimental methodology as several studies have shown that cerebral blood flow gradually decreases during prolonged anesthesia (8, 15).

The mechanism responsible for the gradual increase in cerebral blood flow during prolonged hypocarbia cannot be clearly elucidated from our data. One likely explanation may be the coupling of cerebral metabolism to blood flow (16). Decreases in oxygen and other substrate availability may induce locally mediated changes in vascular resistance overriding the influence of hypocarbia on the cerebral circulation. Thus, the initial effect of hypocarbia was to induce a state of ischemic hypoxia; this, in turn, may have resulted in the local release of vasoactive substances which counteracted the hypocarbic induced cerebral vasoconstriction. This vascular escape phenomenon associated with prolonged severe hypocarbia may be the explanation of the discrepancy between the observation in animal studies of significant hypocarbia induced reductions in cerebral blood flow and the lack of long-term evidence of ischemic sequelae in human neonates treated with prolonged hyperventilation for several days.

Oxygen consumption depends on both oxygen delivery and oxygen extraction (17). Under most circumstances, cerebral oxygen consumption is maintained by alterations in oxygen delivery, and thus, cerebral blood flow rather than alterations in oxygen extraction (17, 18). Hypocarbia is the one notable exception during which extraction increases dramatically (17). As the fetus and newborn of many species have erythrocytes with increased oxygen affinity (19, 20), theoretically they would be expected to have a limited ability, when compared to mature animals, to increase oxygen extraction in the face of severe hypocarbic-induced vasoconstriction. In the present study, cerebral oxygen extraction increased during hypocarbia, however, the increase was not adequate to compensate for the decrease in oxygen delivery occurring at this time, and oxygen consumption therefore decreased. It appears that the piglet cerebrum is limited in the amount of oxygen it can extract. Data from this study suggest this level to be near 75%.

In summary, gradual increases in cerebral blood flow during prolonged hypocarbia restored oxygen delivery and subsequently

restored cerebral oxygen consumption. The regional differences in cerebral blood flow during hypocarbia are similar to those observed in previous studies (2). Whether these differences are due to regional differences in metabolic rate remain to be determined.

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