Prolonged Hypercarbia in the Awake Newborn Piglet: Effect on Brain Blood Flow and Cardiac Output

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ABSTRACT. In adults, exposure to prolonged hypercarbia results in a normalization of the extravascular brain pH associated with a reduction in brain blood flow (BBF). Following prolonged hypercarbia, sudden normalization of the arterial PCO_2 also produces a change in the extravascular brain pH to an alkaline state, resulting in a marked decrease in BBF. We examined these physiologic phenomena in newborn subjects by exposing seven awake, spontaneously breathing newborn piglets to 4 h of sustained hypercarbia (PaCO_2 : 60–70 mm Hg) followed by a 45-min normocarbic period. Total and regional BBF, cardiac output (radionuclide-labeled microsphere method), arterial blood pressure, plasma catecholamine and lactate concentrations, blood gases, oxygen contents, and hematocrits were measured during a baseline period, at $\frac{1}{2}$, 2, and 4 h of sustained hypercarbia and $\frac{1}{4}$ and $\frac{3}{4}$ h following an abrupt onset of normocarbic. The initial 2.5-fold increase in total BBF during hypercarbia persisted for 2 h and at 4 h decreased significantly below the level of the 30-min hypercarbic measurement, although the values still remained 2-fold above the baseline values. Brain tissue pH was reduced at the onset of hypercarbia, remaining unchanged throughout the hypercarbic period. Both total BBF and brain tissue pH returned to baseline values following the return to normocarbic. Changes in regional BBF were similar to that of total BBF with the exception of the boundary zone (periventricular area in the frontoparietal region of the cerebrum, adjacent to the caudate nucleus) and the parietal area (site of the brain tissue pH electrode), where a significant decrease from the peak hyperemia was not observed. Choroid plexus blood flow demonstrated a small initial increase over normocarbic baseline values. Plasma bicarbonate concentrations did not change during the studies. Following the onset of hypercarbia, heart rate and cardiac output increased significantly whereas plasma lactate concentrations decreased significantly. There was also an increase in the percentage of cardiac output distributed to the brain. The increase in cardiac output persisted throughout the hypercarbic period and returned to baseline levels during normocarbic. Mean arterial blood pressure increased significantly at the 4-h hypercarbic period and this increase persisted during normocarbic. We conclude that in newborn piglets 1) hypercarbia resulted in cerebral hyperperfusion, accompanied by marked fall in brain tissue

pH, 2) prolongation of hypercarbia for 4 h was associated with a slight but significant reduction in the cerebral hyperperfusion independent of changes in brain tissue pH, and 3) in contrast to that observed in adult subjects, the abrupt normalization of arterial PCO_2 was not associated with a fall of BBF below the prehypercarbic values. (*Pediatr Res* 21: 29–33, 1987)

Abbreviations

BBF, brain blood flow
IVH, intraventricular hemorrhage
MABP, mean arterial blood pressure

Hypercarbia results in cerebral vasodilation and increased BBF in fetal and newborn animals (1–3) and may be an important factor in the development of IVH in premature infants (4). In infants with respiratory disorders, PaCO_2 may exceed the physiologic range for considerable amounts of time despite appropriate ventilatory therapy.

In adult animals and humans, acid-base adjustments normalize the brain tissue pH during prolonged hypercarbia, resulting in a diminution of cerebral vasodilation (5–7). Because the blood brain barrier is readily permeable to carbon dioxide and relatively impermeable to bicarbonate ion, acute normalization of systemic PaCO_2 and pH in chronically hypercapnic adult humans and dogs results in an alkalization of extravascular brain pH and markedly reduces BBF (6, 7). Whether this phenomenon also exists in newborns is not known and may if present contribute to the development of central nervous system abnormalities in the neonatal period.

We hypothesized that 4 h of hypercarbia in newborns may result in a normalization of extravascular brain pH and BBF, and an acute normalization of PaCO_2 following this 4-h period of hypercarbia may result in a reduction of BBF below prehypercarbic levels.

MATERIALS AND METHODS

Seven 2- to 4-day-old newborn piglets with a mean weight of 1.21 kg (range 1.05–1.43) were obtained from a local farmer. The piglets remained with the sows until the morning of the study. Catheter placement was performed on an infant radiant warmer under general anesthesia using a mixture of 70% nitrous oxide and 30% oxygen administered via a head hood and local anesthesia with 1% lidocaine. A Sentinel line catheter (ID 0.67 mm, OD 1.05 mm, Argyle, St. Louis, MO) was introduced into the left ventricle via the right brachial artery for injection of radionuclide-labeled microspheres. Polyvinyl catheters (ID 0.58

Received January 27, 1986; accepted August 11, 1986.

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Supported by the National Research Training Grant IT 32-HD-07232, National Institute of Child Health and Human Development Bethesda, MD and a grant-in-aid from the American Heart Association with funds contributed in part by the Rhode Island Affiliate. A.M.B. was supported by Leiden University, Leiden, The Netherlands.

mm, OD 0.9 mm, Bolab Inc. Lake Havasu, AZ) were placed in: 1) the left brachial artery for withdrawal reference blood samples, 2) the abdominal aorta via the femoral artery for determination of blood pressure, heart rate, arterial blood gases, hematocrit, and plasma catecholamine and lactate concentrations, and 3) the inferior vena cava via the femoral vein for continuous infusion of 5% glucose and replacement of blood during the study. All incisions were infiltrated with a 2% oxylocaïne gel before closure of the skin to insure prolonged analgesia.

The animals were then removed from the head hood, restrained in a prone position, and ventilated via a veterinary mask connected to an Isolette Amsterdam type infant ventilator (Narco, Warminster, PA) with 70% nitrous oxide and 30% oxygen. Following local anesthesia and incision of the periosteum, a small burr hole (approximately 5 mm in diameter) was made in the left parietal region of the skull with a hand held drill. A rubber stopper with a similar diameter was then secured with sutures over the burr hole between the bone and skin. The dura was then pierced with a stylette, care was taken to avoid blood vessels, and a Roche glass pH tissue electrode (Roche Laboratories Electronics Inc., Cranbury, NJ) was inserted approximately 4 mm into the brain tissue via the rubber stopper. The electrode was then secured to the rubber stopper with plaster of Paris and this cast fixed to the scalp with surgical steel sutures.

Following surgery the animals were allowed to recover in a padded enclosed box where they remained for the duration of the study, therefore the awake unrestrained newborn piglets were studied with a minimum of external stimulus. The tissue pH electrode cord and catheters were exteriorized via small openings in the box. Microspheres ($15 \pm 5 \mu\text{m}$, New England Nuclear, Boston, MA) labeled with ^{51}Cr , ^{46}Sc , ^{95}Nb , ^{113}Sn , ^{103}Ru , and ^{57}Co were utilized to measure brain blood flow and cardiac output according to the method of Heymann *et al.* (8). For each blood flow measurement, approximately 9×10^5 radionuclide-labelled microspheres suspended in 10% dextran and 0.01% Tween were injected over 30 s into the left ventricle. The reference blood sample from the axillary artery was collected continuously for 2 min beginning 15 s prior to the microsphere injection at a withdrawal rate 1.03 ml/min using a constant withdrawal pump (Harvard Apparatus, Millis, MA). Blood losses from study sampling were replaced with an equal volume of blood obtained from a young donor piglet. Adequate mixing of microspheres in the left ventricle were confirmed by comparing blood flow to the left and right cerebrum ($r = 0.98$, $p < 0.001$, $n = 7$).

Following baseline blood flow determinations, a gas mixture containing 15% CO_2 , 20% O_2 with balance nitrogen was introduced into the enclosed vented box in order to obtain a PaCO_2 between 60 and 70 mm Hg. This level of hypercarbia was maintained for 4 h. The gas mixture was humidified and heated to 28°C in order to prevent alterations in the piglets body temperature. Blood flow was measured $\frac{1}{2}$, 2, and 4 h following the onset of hypercarbia. Immediately following the third hypercarbia measurement, after 4 h of carbon dioxide exposure, the gas mixture was withdrawn and compressed air was substituted. The box containing the piglet was then flushed with 8 liter/min

of compressed air in order to immediately reduce the ambient carbon dioxide concentration. Following this initial reduction of ambient carbon dioxide from the box containing the piglet, compressed air was delivered at 2 liter/min for the remainder of the study and repeat measurements as indicated above were obtained $\frac{1}{4}$ and $\frac{3}{4}$ h after the return to normocarbica.

MABP was continuously monitored during the study using a Hewlett Packard 1280 B pressure transducer and recorded on a Hewlett Packard 7754 A polygraph (Lexington, MA). MABP and heart rate represented the mean of five determinations during each blood flow measurement. Lactic acid concentration was determined according to the method of Marbach and Weil (9). Plasma epinephrine and norepinephrine concentrations were obtained by collecting 2 ml of arterial blood in a chilled heparinized tube containing reduced glutathione. The blood was centrifuged at 0°C and the plasma stored at -70°C until the time of the assay. Determinations of plasma catecholamine concentrations were performed by liquid chromatography using the electrochemical detection method of Hjendahl *et al.* (10). The coefficient of the variation for norepinephrine with this method was 9.5% and for epinephrine 9.4%. The lower limit of sensitivity was approximately 20 pg for injected norepinephrine and 30 pg for injected epinephrine. Recovery of catecholamine from plasma was between 70–80%. Following each blood flow determination PaCO_2 , PaO_2 , pH, and bicarbonate were measured using a Corning 175 Corning Blood Gas Analyzer (Medfield, MA). Oxygen contents were measured with a Lex-O₂-Con (Lexington Instruments, Waltham, MA). Arterial hematocrit was measured using the microhematocrit method.

The brain pH electrode was calibrated with two test solutions with a pH of 7.0 and 7.4, respectively, prior to placement into the brain tissue. Brain tissue pH was monitored continuously on a recorder. The calibration was verified following each study. Because of technical difficulties with the pH electrode placement, brain tissue pH was measured in five of the seven study animals. Figure 1 illustrates a representative brain tissue pH recording during the study.

At the end of the study the animals were sacrificed with an overdose of sodium thiamylal, the catheter placement was confirmed by autopsy, the pH electrode removed, and the brain removed and weighed prior to and following fixation with 10% formaldehyde.

For determination of regional BBF, the brain was divided into the following sections: cerebrum, brain stem (from the superior colliculus to the spinal cord), cerebellum, thalamus, caudate nuclei (floor of the lateral ventricles), the boundary zone (periventricular area in the frontoparietal region of the cerebrum, adjacent to the caudate nucleus), and the choroid plexus. In order to determine if the insertion of the pH electrode into the brain tissue altered local brain blood flow, the electrode site in the parasagittal left side of the cerebrum and the corresponding right side were also isolated. After removal of the brain, the remaining organs and the carcass were weighed and incinerated for 96 h for cardiac output determination as previously described (1, 8).

Fig. 1. A representative brain tissue pH recording during the study.

Changes from baseline during prolonged hypercarbia followed by normocarbica and changes during prolonged hypercarbia were examined by analysis of variance for repeated measurements. If a significant difference was found ($p < 0.05$), the Dunnett's multiple range t test was used to compare the means to the baseline values, during prolonged hypercarbia the 2- and 4-h determinations were compared to the 30-min measurement. Analysis of variance with the multiple comparison Newman-Keuls *post hoc* test was also used to detect significant differences in blood flow among the brain regions during the baseline, the three hypercarbic, and two normocarbica measurements. All values are expressed as mean $\pm$ SEM.

RESULTS

Table 1 summarizes the blood gas, hematocrit, oxygen content, and bicarbonate and plasma lactic acid values during the studies. The rise in PaCO_2 obtained at 30 min of hypercarbia remained unchanged during the ensuing 4 h. Following the termination of hypercarbia, PaCO_2 returned to normocarbica levels for newborn piglets, however, during the first of the two normocarbica measurements PaCO_2 was still slightly, but significantly elevated, compared with the baseline values. The respiratory acidosis was associated with a significant decrease in the base excess. The PaO_2 and hematocrit values did not change. Oxygen content decreased slightly but significantly at 30 min of hypercarbia, the remainder of the values were similar to baseline. There were no significant changes in the plasma bicarbonate values. A significant decrease in lactic acid concentration occurred during the third hypercarbic measurement period.

As shown in Figure 2, total BBF increased approximately 2.5 times the baseline value during the induction of hypercarbia and remained elevated during the first 2 h of hypercarbia. At 4 h of hypercarbia, total BBF was reduced significantly compared to the 30-min hypercarbic determination. Reduction of the PaCO_2 to the normocarbica range resulted in a reduction of BBF to baseline levels. As expected, the brain tissue pH was significantly decreased at 30 min of hypercarbia. During the remainder of the hypercarbic period, brain tissue pH increased slightly, however, significant changes were not observed. A return to baseline levels was observed during the normocarbica period.

Blood flow to all regions of the brain increased significantly during the first 30 min of hypercarbia (Table 2). Blood flow to the brain stem and thalamus was significantly greater than to the cerebrum during the 30-min hypercarbic period. Compared to the peak hyperemic value at 30-min of hypercarbia, significant reductions in regional blood flow were observed in the cerebrum, cerebellum, brain stem, thalamus, and caudate nucleus following 4 h of hypercarbia. The blood flow to the boundary zone and parietal area also declined when compared with the 30-min hypercarbia period, but these changes were not statistically sig-

nificant. Choroid plexus blood flow was higher than blood flow to the cerebrum and increased significantly during the first 30 min of hypercarbia and remained elevated during the hypercarbic periods. There were no significant differences from the baseline blood flow values to any brain region examined following the return to normocarbica.

Table 3 summarizes the changes in total BBF expressed as percentage of cardiac output, cardiac output, heart rate, plasma catecholamine concentrations, and MABP during the study periods. The percentage of cardiac output distributed to the brain was significantly increased during hypercarbia, decreased significantly at 4 h of hypercarbia compared with the 30-min determination and returned to baseline during normocarbica. Cardiac output increased significantly and remained elevated and unchanged throughout the three hypercarbic periods. The return to normocarbica resulted in a decrease in cardiac output. The induction of hypercarbia resulted in a temporary increase in the heart rate and catecholamine concentrations: the heart rate, epinephrine, and norepinephrine levels were significantly elevated during

TOTAL BRAIN BLOOD FLOW

BRAIN TISSUE pH

Fig. 2. BBF and brain tissue pH during baseline and 30, 120, and 240 min of hypercarbia and 15 and 45 min following return to normocarbica. $n = 7$ except when indicated in parentheses.

Table 1. Blood gases, hematocrit, oxygen content, bicarbonate, and lactic acid values during the six study periods [mean $\pm$ SEM ($n = 7$)]

Variable	Baseline	Hypercarbia			Normocarbica	
	0 min	30 min	120 min	240 min	255 min	285 min
pH	7.44 $\pm$ 0.01	7.20 $\pm$ 0.01*	7.19 $\pm$ 0.01*	7.22 $\pm$ 0.02*	7.38 $\pm$ 0.02*	7.42 $\pm$ 0.01
PaCO_2 (mm Hg)	39.6 $\pm$ 1.8	66.4 $\pm$ 2.0*	67.9 $\pm$ 1.5*	67.4 $\pm$ 1.7*	44.9 $\pm$ 0.3*	42.6 $\pm$ 1.3
BE (mEq/liter)	4.1 $\pm$ 1.0	-1.5 $\pm$ 1.8*	-1.6 $\pm$ 1.7*	-0.3 $\pm$ 1.5*	2.8 $\pm$ 1.6*	4.1 $\pm$ 1.4
PaO_2 (mm Hg)	87.3 $\pm$ 3.8	97.7 $\pm$ 8.5	97.1 $\pm$ 9.0	95.1 $\pm$ 12.8	78.9 $\pm$ 4.8	79.0 $\pm$ 5.1
Hematocrit (%)	26 $\pm$ 2	25 $\pm$ 2	26 $\pm$ 2	26 $\pm$ 2	26 $\pm$ 2	26 $\pm$ 2
O_2 content (ml/dl)	9.1 $\pm$ 0.7	8.4 $\pm$ 0.7*	8.6 $\pm$ 0.5	8.6 $\pm$ 0.7	8.6 $\pm$ 0.6	9.2 $\pm$ 0.6
HCO_3^- (mEq/liter)	26.4 $\pm$ 0.9	25.8 $\pm$ 1.2	25.5 $\pm$ 0.7	26.5 $\pm$ 1.2	26.5 $\pm$ 1.2	27.0 $\pm$ 1.3
Lactic acid (nM/liter)	2.99 $\pm$ 0.57	2.75 $\pm$ 0.54	2.03 $\pm$ 0.38	2.06 $\pm$ 0.46†	3.45 $\pm$ 0.66	3.05 $\pm$ 0.74

* $p < 0.05$ versus baseline.

† $p < 0.05$ versus 30 min of hypercarbia.

Table 2. Regional BBF during the six study periods (mean $\pm$ SEM)*

Region	Baseline 0	Hypercarbia			Normocarbica	
		30	120	240	255	285
Q cerebrum	80 $\pm$ 6	182 $\pm$ 19†	179 $\pm$ 23†	145 $\pm$ 11†‡	97 $\pm$ 10	96 $\pm$ 7 (6)
Q cerebellum	94 $\pm$ 6	275 $\pm$ 34†	241 $\pm$ 37†	189 $\pm$ 19†‡	100 $\pm$ 8	108 $\pm$ 8 (6)
Q brainstem	86 $\pm$ 5	304 $\pm$ 31†§	267 $\pm$ 33†	197 $\pm$ 18†‡	92 $\pm$ 9	97 $\pm$ 8 (6)
Q thalamus	98 $\pm$ 6	314 $\pm$ 27†§	287 $\pm$ 32†	217 $\pm$ 18†‡	106 $\pm$ 10	113 $\pm$ 9 (6)
Q caudate nucleus	104 $\pm$ 9	230 $\pm$ 24†	217 $\pm$ 29†	184 $\pm$ 19†‡	115 $\pm$ 17	124 $\pm$ 11 (6)
Q boundary zone	82 $\pm$ 6	206 $\pm$ 21†	204 $\pm$ 24†	167 $\pm$ 15†	110 $\pm$ 15	99 $\pm$ 5 (6)
Q parietal right	92 $\pm$ 8	228 $\pm$ 30†	232 $\pm$ 39†	186 $\pm$ 18†	120 $\pm$ 12	117 $\pm$ 8 (6)
Q parietal left (pH electrode site)	94 $\pm$ 7	224 $\pm$ 28†	239 $\pm$ 38†	202 $\pm$ 24†	124 $\pm$ 11	123 $\pm$ 9 (6)
Q choroid plexus	389 $\pm$ 70§	545 $\pm$ 85†§	534 $\pm$ 97§	534 $\pm$ 82§	353 $\pm$ 47§	414 $\pm$ 62§ (6)

* Q, blood flow (ml $\cdot$ min⁻¹ $\cdot$ 100 g⁻¹), number of animals = 7, except as indicated in parentheses.

† $p < 0.05$ versus baseline.

‡ $p < 0.05$ versus 30 min of hypercarbia.

§ $p < 0.05$ versus cerebrum for each time period.

Table 3. Cardiac output, BBF as percentage of cardiac output, plasma catecholamine concentrations, heart rate, and MABP and pulse pressure during the six study periods (mean $\pm$ SEM)*

Variable	Baseline 0 min	Hypercarbia			Normocarbica	
		30 min	120 min	240 min	255 min	285 min
BBF (% cardiac output)	5.4 $\pm$ 0.4	10.1 $\pm$ 0.8†	9.3 $\pm$ 0.6†	7.8 $\pm$ 0.6†‡	5.1 $\pm$ 0.3	5.5 $\pm$ 0.4 (6)
Cardiac output (ml $\cdot$ min ⁻¹ $\cdot$ kg ⁻¹)	379 $\pm$ 15	523 $\pm$ 51†	539 $\pm$ 60†	522 $\pm$ 31†	477 $\pm$ 38	476 $\pm$ 45 (6)
Heart rate (beats/min)	200 $\pm$ 6	228 $\pm$ 5†	213 $\pm$ 7	217 $\pm$ 8	206 $\pm$ 10	191 $\pm$ 11
Epinephrine (pg/ml)	288 $\pm$ 55	416 $\pm$ 61†	356 $\pm$ 75	265 $\pm$ 51‡	202 $\pm$ 38	191 $\pm$ 48
Norepinephrine (pg/ml)	427 $\pm$ 71	928 $\pm$ 180†	803 $\pm$ 145†	615 $\pm$ 91	443 $\pm$ 85	304 $\pm$ 48
MABP (mm Hg)	61 $\pm$ 2	65 $\pm$ 2	66 $\pm$ 3	69 $\pm$ 4†	73 $\pm$ 3†	74 $\pm$ 3†

* Number of animals = 7, except where indicated in parentheses.

† $p < 0.05$ versus baseline.

‡ $p < 0.05$ versus 30 min of hypercarbia.

the 30-min hypercarbic measurement and the norepinephrine levels remained elevated during the second hypercarbic measurement (120 min). Mean arterial blood pressure increased significantly during the final hypercarbic measurement (240 min) and remained elevated during normocarbica.

DISCUSSION

Cerebral vasodilation occurring during hypercarbia is mediated in part through a reduction in the brain extracellular fluid pH surrounding the blood vessels (11). Following 3 h of elevated arterial PCO₂ values in adult dogs, the intracellular pH of the brain has been demonstrated to return to normal (6). In addition, because the ependyma offers little resistance to diffusion of ionic charged molecules, the brain extracellular fluid pH surrounding the blood vessels also returns to normal (12). Moreover, following prolonged periods of hypercarbia, the pial arteriolar vasodilator response to hypercapnia is diminished (5), suggesting that brain blood flow might also be reduced. The major objective of the current study was to determine the effect of 4 h of hypercarbia on brain tissue pH and blood flow in newborn subjects. In contrast to that observed in adult dogs (6), our results showed that for yet undetermined reasons, the buffering adjustments within the central nervous system did not result in the anticipated return of the brain tissue pH to baseline values (Fig. 2) within the time frame examined. Therefore, while there was a slight, however, significant reduction in blood flow to the total brain and some of its regions, hyperperfusion of the central nervous system persisted. In contrast to that observed in the adult dogs (6), it is possible that in the newborn piglet a longer period of hypercarbia, than the 4 h examined in our study, is required in order to return the brain tissue pH to normal values, and thereby

reduce BBF to baseline levels. It is also possible that the elevation in brain tissue pH to normal values was more rapid (3 h) in the study by Arieff *et al.* (6) because the arterial PCO₂ was higher (85 mm Hg) than in the current study (67 mm Hg). The mechanism for the modest reduction in total and regional BBF in our newborn piglets at 4 h compared with 30 min of hypercarbia is as yet unexplained.

A critical issue that should be considered in interpreting the data is the validity of brain tissue pH measurement. One element that may influence its validity is the unavoidable tissue damage during the application of the electrode (14). However, the results we obtained were most likely accurate because each of the five animals demonstrated similar marked changes in brain tissue pH during the induction of hypercarbia and the return to normocarbica (see Fig. 1 as an example) suggesting that the qualitative changes are consistent within each animal. Our baseline brain tissue pH values (7.24 $\pm$ 0.05) are somewhat lower than previously reported cerebrospinal fluid values in adult man (15) and higher than intracellular brain pH values reported in adult dogs using the distribution of ¹⁴C-labeled dimethadione (6).

During hypercarbia differences in the blood flow among the various regions in the brain are similar to previous findings by us and others in newborn animals (1, 16, 17). This has been attributed to higher metabolic requirements in the more caudal portions of the brain. During prolonged hypercarbia, BBF in most regions remained elevated suggesting that the buffering shifts in these regions were such that the tissue pH in these areas remained unchanged. Thus, there were no major alterations in the state of perfusion.

Prolonged hypercarbia was also associated with significant increases in cardiac output and the percentage of cardiac output distributed to the brain. These elevations in cardiac output were

associated with significant increases in circulating catecholamine concentrations.

Because the blood brain barrier is permeable to carbon dioxide and relatively impermeable to HCO_3^- (18), acute normalization of PaCO_2 following prolonged hypercarbia may potentially result in an alkaline shift in the extracellular pH of the brain. In chronically hypercapnic adult humans, this alkaline shift has been shown to result in a very low BBF following a reduction in PaCO_2 after a period of prolonged hypercarbia (7). In the newborn piglets, both brain tissue pH and BBF returned to baseline values following the normalization of PaCO_2 . The maintenance of brain tissue pH at acidotic ranges during hypercarbia indicates a lack of shift in HCO_3^- in the cerebrospinal and extracellular fluid; therefore the lack of a precipitous fall in BBF due to an "alkaline shift" in tissue pH when normocarbia followed prolonged hypercarbia is to be expected. However, the increase in mean arterial blood pressure following the return to normocarbia may have influenced the changes in BBF following the termination of hypercarbia. If BBF autoregulation were impaired by 4 h of hypercarbia, this elevation in blood pressure may have prevented the anticipated reduction in BBF following the return to normocarbia. Alternatively, a longer duration of hypercarbia prior to the return to normocarbia may have resulted in reductions in BBF to values below the baseline levels.

Acknowledgments. The authors acknowledge the excellent technical assistance of Donna Piva.

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