0031-3998/90/2704-0327$02.00/0
PEDIATRIC RESEARCH

Vol. 27, No. 4, 1990
Printed in U.S.A.

Brain Blood Flow and Ventilatory Response to Hypoxia in Sedated Newborn Piglets

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ABSTRACT. To evaluate the relationship between brain blood flow and ventilatory response to hypoxia, seventeen sedated, spontaneously breathing newborn piglets were studied. Minute ventilation ($\dot{V}_E$) was measured by pneumotachograph, cardiac output by thermodilution and total brain and brain stem blood flows with radiolabeled microspheres. Measurements were performed while the animals were breathing room air and after 10 min of hypoxia induced by breathing 10% O_2. Two patterns of ventilatory response to hypoxia were observed in the study animals. All animals increased $\dot{V}_E$ during the 1st min of hypoxia, but nine (mean ± SD; age 5 ± 1.3 d; wt 1828 ± 437 g) sustained increased $\dot{V}_E$ after 10 min of hypoxia (↑ $\dot{V}_E$ group). The remaining eight animals (age 5 ± 1.2 d; wt 1751 ± 168 g) had decreased $\dot{V}_E$ at 10 min of hypoxia to values less than their room air baseline (↓ $\dot{V}_E$ group). The decrease in Pa_{O_2} during hypoxia was similar in both groups, however the Pa_{CO_2} decreased significantly only in the ↑$\dot{V}_E$ group. Although cardiac output increased significantly during hypoxia in both groups, the values during normoxia and hypoxia were lower in the ↓$\dot{V}_E$ group ($p < 0.001$). Arterial blood pressure increased significantly during hypoxia only in the ↑$\dot{V}_E$ group. The increase in total brain and brain stem blood flows with hypoxia was similar in both groups, despite the two different patterns of ventilatory response to hypoxia. These data suggest that in this animal model the distinct patterns of ventilatory response to hypoxia are not related to the changes in total brain or brain stem blood flows that occur during hypoxia. (*Pediatr Res* 27: 327–331, 1990)

Abbreviations

$\dot{V}_E$, minute ventilation
CO, cardiac output
BBF, total brain blood flow
BSBF, brain stem blood flow
RA, room air
ABP, arterial blood pressure
V_t, tidal volume
Cdyn, dynamic lung compliance
R_L, pulmonary resistance

The ventilatory response to hypoxia during the first days after birth is characterized in humans and several animal species by a transient initial increase in ventilation (1–2 min), followed by a marked decline in $\dot{V}_E$ to values slightly above or below prehypoxia basal values (1–6). The mechanism responsible for this biphasic response to hypoxia has not been completely elucidated. Various neurotransmitters or modulators released during hypoxia such as endorphins, γ-aminobutyric acid, prostaglandins, and adenosine have been suggested as possible mediators of the late decrease in ventilation (2, 7–10). Other possible explanations have included changes in lung mechanics, a decrease in the metabolic rate, respiratory muscle fatigue, and inhibition of peripheral chemoreceptors (3, 11–14). The increase in cerebral blood flow that occurs in response to hypoxia can induce a decrease in P_{CO_2} and H^+ in the CNS extracellular fluid and this may also account for the decrease in respiratory drive (15). Conversely, the absence of a normal cardiovascular response and the increase in cerebral blood flow that normally occurs during hypoxemia can aggravate CNS hypoxia and lead to CNS depression (16).

We hypothesized that the observed differences in the ventilatory response to hypoxia in newborn piglets may be related to differences in their cardiovascular and brain blood flow response to hypoxia.

Our purpose was to define the relationship between the ventilatory response to hypoxia and the changes in cerebral blood flow in newborn piglets.

MATERIALS AND METHODS

Seventeen piglets ≤7 d of age were anesthetized with ketamine (20 mg/kg intramuscularly) and xylazine (2 mg/kg intramuscularly) for surgical procedures. Lidocaine hydrochloride (0.5%) was used for local anesthesia. The animals were then sedated with chloral hydrate (200 mg/kg p.o. every 3 h) throughout the study period. Experimental trials were performed at least 2 h after administration of ketamine. The left femoral and right brachial arteries and femoral vein were cannulated and used for systemic ABP measurement, blood sampling, and infusion of fluids. The right femoral artery was cannulated with a 3.5 F Argyle catheter (Sherwood Medical, St. Louis, MO), which was advanced into the left ventricle and used for radiolabeled microspheres injection. The left external jugular vein was cannulated and the catheter advanced into the right atrium for injection of cold saline for measurement of CO. A 5 F Swan Ganz catheter was introduced into the right external jugular vein and advanced under fluoroscopy into the left pulmonary artery. CO was measured by thermodilution using a cardiac output computer (95510-A, Edwards Laboratory, Santa Ana, CA). Vascular pressures were measured with pressure transducers (model P23-ID; Gould Instruments, Cleveland, OH) and recorded on a multichannel recorder (model 260, Gould Instruments).

A tracheostomy was performed and a 3.5-mm endotracheal tube inserted while the animals were anesthetized with ketamine and xylazine. The animals did not exhibit signs of pain or discomfort during the study periods under chloral hydrate sedation. The rectal temperature was continuously monitored with a

Received June 22, 1989; accepted December 12, 1989.
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Supported in part by the State of Florida, Department of Health and Rehabilitative Services, Children's Medical Services, and the University of Miami: Project Newborn.

thermistor probe and skin temperature was maintained at 38.5°C by means of a servo-controlled radiant warmer. The animals received an infusion of 6 mL/(kg·h) of 5% dextrose solution through a peripheral vein and a 2.5 mL/h of heparinized saline solution (10 U/mL) through the pulmonary artery catheter.

Handling and care of animals was in accord with the guidelines of the National Institutes of Health and this study protocol was approved by the Animal Care Committee of the University of Miami.

Pulmonary mechanics. Pulmonary mechanics were measured to investigate the possible influence of changes in mechanical factors on the ventilatory response to hypoxia. Respiratory flow was measured by a heated Fleish no. 00 pneumotachograph (OEM Medical, Richmond, VA), a differential pressure transducer (model MP45, Validyne Engineering Co., Northridge, CA) and a pressure amplifier (Gould Instruments). The flow signal was electronically integrated to obtain V_t using a Gould integrator amplifier. Calibration of V_t was done before and after each study using a calibrated glass syringe. $\dot{V}_E$ was obtained by the sum of inspiratory volumes measured over 1-min periods of regular respiration. Esophageal pressure was measured by a water filled 8 F feeding tube placed in the lower third of the esophagus and attached to a pressure transducer (model P23-ID, Gould Instruments) and a Gould pressure amplifier calibrated with a water manometer. Proximal airway pressure was measured by an air filled large-bore catheter attached to a side tap in the endotracheal tube adaptor and to a pressure transducer (model P23-ID, Gould Instruments). Airflow, V_t, and airway and esophageal pressures were recorded on a multichannel recorder (model 260; Gould Instruments). Cdyn and R_L were calculated from this trace (17).

Cerebral blood flow measurements. Regional cerebral blood flow was measured with the tracer microspheres technique (18). Microspheres (15.0 ± 1.0 μm) labeled with ^{141}Ce, ^{85}Sr, ^{46}Sc (3M, St. Paul, MN) and ^{113}Sn (NEN, Boston, MA) were used in random order in each animal. Approximately 0.7–1.2 million microspheres were injected into the left ventricle over a period of 20–30 s. For 10 s before, during, and 60 s after the injection of microspheres, reference arterial blood samples were withdrawn from the right brachial artery at rate of 0.97 mL/min (19). At the end of the experiment the animal was killed and the brain was divided into cerebrum, cerebral gray and white matter, caudate nucleus, hippocampus, thalamus-hypothalamus, midbrain, cerebellum, pons, and medulla. These tissues were placed into counting vials that were weighed without and with tissues. Radioactivity from the tissue and reference blood samples was counted for 5 min by a two-channel γ-counter (model 1191, TM Analytic, Elk Grove Village, IL). Blood flow was calculated with the formula $\dot{Q} = A_t \cdot \dot{Q}r/A_r$, where A_t and A_r are the activity (cpm) in the tissue and reference blood and $\dot{Q}r$ is the rate of withdrawal of the blood sample. Blood flow to each region was expressed by 100 g of tissue. The BSBF included the medulla, pons, and midbrain blood flows. The accuracy of the radiolabeled microspheres technique requires that the number of microspheres in each tissue be more than 385 (18). The mean values ± SEM for the number of microspheres in the tissue samples were: cerebrum 32043 ± 3784, cerebral gray matter 1426 ± 157, cerebral white matter 392 ± 53, caudate nucleus 1167 ± 152, hippocampus 960 ± 133, thalamus-hypothalamus 4210 ± 622, midbrain 2581 ± 329, cerebellum 7487 ± 1002, pons 1395 ± 335, and medulla 2768 ± 437.

To assure that the ligation of both external jugular veins did not increase the cerebral venous pressure and influence cerebral blood flow, four additional newborn piglets were studied before and after both external jugular veins were ligated. A longitudinal scalp incision was made over the sagittal suture, allowing scalp retraction and exposure of the calvarium. A 24-gauge Teflon catheter was inserted through the sagittal suture and dura into the superior sagittal sinus and glued into place. The sagittal venous pressure and brain blood flow were measured before and 1 h after both external jugular vein ligations.

Induction of hypoxia. The animals were allowed a 60-min stabilization period after completion of surgery. After this, the animals were connected to a breathing circuit with a constant bias-flow of 3–4 L/min. After a 10-min period of stable breathing in room air, lung function ($\dot{V}_E$, V_t, Cdyn, and R_L), cardiovascular measurements (ABP and CO), regional brain blood flow and arterial blood gas measurements were obtained and referred to as room air baseline. To induce hypoxia, the FIO_2 was decreased to 0.10 within 6 s and the O_2 concentration was monitored continuously by an oxygen analyzer (OM-15 Beckman Instruments, Anaheim, CA). After 1 and 5 min on FIO_2 of 0.10, cardiovascular measurements were performed and at 10 min of hypoxia all measurements were repeated including cerebral blood flow. All the measurements were taken only when the animals were resting quietly and without signs of distress as evidenced by stable heart rate and ABP recordings.

Data analysis. Changes in cardiovascular and respiratory measurements between RA and during hypoxia were compared by the paired *t* test. Bonferroni correction was used for multiple comparisons.

Repeated measures analysis of variance followed by Duncan's multiple range test was used to compare the pattern of response to hypoxia between the $\uparrow\dot{V}_E$ and $\downarrow\dot{V}_E$ groups at 1, 5, and 10 min of hypoxia for $\dot{V}_E$, ABP, and CO. A one-way analysis of variance was used to compare the arterial blood gas values and respiratory variables between the two groups of animals.

RESULTS

The ventilatory response to hypoxia differed among the animals and for this reason the results were analyzed separately in two groups. Although all animals increased $\dot{V}_E$ during the 1st min of hypoxia, only nine animals (mean ± SD; age 5 ± 1.3 d; wt 1.828 ± 0.437 kg) sustained the increase in ventilation at 10 min of hypoxia ($\uparrow\dot{V}_E$ group). The remaining eight animals (age, 5 ± 1.2 d; wt, 1.751 ± 0.168 kg) had a lower $\dot{V}_E$ at 10 min of hypoxia when compared to their RA baseline ($\downarrow\dot{V}_E$ group) (Fig 1).

The respiratory rate did not change significantly with hypoxia in the $\uparrow\dot{V}_E$ animals, but in the $\downarrow\dot{V}_E$ group the rate was lower than baseline after 10 min of hypoxia. V_t increased significantly with hypoxia only in the $\uparrow\dot{V}_E$ group. Although $\dot{V}_E$ with hypoxia remained 28.1 ± 3.4% above baseline in the $\uparrow\dot{V}_E$ group, in the $\downarrow\dot{V}_E$ group it decreased to values significantly lower than baseline at 10 min of hypoxia (Table 1).

The decrease in Pa_{O_2} while breathing 10% oxygen was similar in both groups but Pa_{CO_2} decreased only in the group of animals

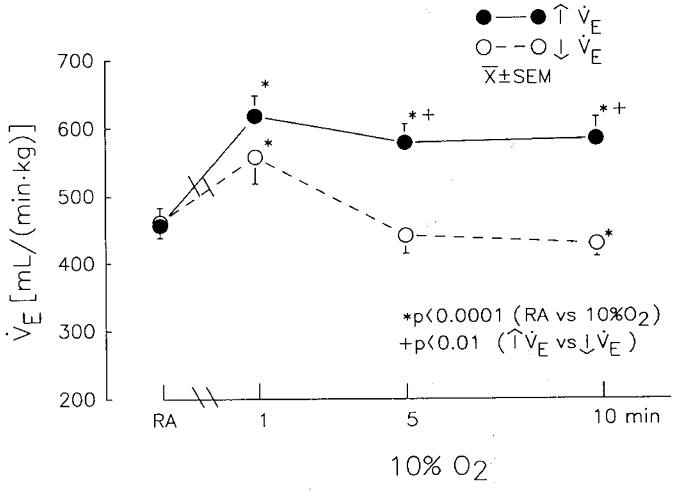

Fig. 1. Changes in $\dot{V}_E$ between normoxia and after 10 min of hypoxia in the $\uparrow\dot{V}_E$ and $\downarrow\dot{V}_E$ groups.

Table 1. *Arterial blood gases, ventilation, BBF and BSBF values obtained during normoxia and after 10 min of hypoxia in the group of animals that sustained (↑ $\dot{V}_E$) and did not sustain (↓ $\dot{V}_E$) increased minute ventilation during hypoxia (mean ± SEM)*

	↑$\dot{V}_E$ ($n = 9$)		↓$\dot{V}_E$ ($n = 8$)	
	Room air	10% O_2	Room air	10% O_2
pH (U)	7.39 ± 0.01	7.40 ± 0.01	7.40 ± 0.02	7.38 ± 0.01
Pa_{O_2} (kPa)	11.5 ± 0.4	3.9 ± 0.1*	11.5 ± 0.5	3.6 ± 0.1*
Pa_{CO_2} (kPa)	5.3 ± 0.3	4.6 ± 0.2*	5.6 ± 0.2	5.5 ± 0.2†
$[HCO^-_3]$ (mmol/L)	23.2 ± 1.1	21.4 ± 1.1*	26.4 ± 1.5	24.6 ± 1.3*
RR (breaths/min)	76 ± 7	85 ± 4	85 ± 6	72 ± 7*
V_t (mL/kg)	6.2 ± 0.5	7.0 ± 0.5‡	5.6 ± 0.4	6.2 ± 0.5
$\dot{V}_E$ [mL/(min·kg)]	456 ± 27	582 ± 32*	461 ± 22	427 ± 19*†
BBF [mL/(min·100 g)]	83 ± 9	157 ± 16*	72 ± 11	141 ± 12*
BSBF [mL/(min·100 g)]	104 ± 14	213 ± 17*	95 ± 18	188 ± 20*

* $p < 0.001$ (RA *versus* 10% O_2).
† $p < 0.05$ (↑$\dot{V}_E$ *versus* ↓$\dot{V}_E$ groups). 1 mm Hg = 0.1333 kPa.
‡ $p < 0.04$ (RA *versus* 10% O_2).

that continued to hyperventilate after 10 min of hypoxia (↑$\dot{V}_E$ group), whereas in ↓$\dot{V}_E$ animals the Pa_{CO_2} remained unchanged (Table 1).

The changes in CO and ABP in the two groups are shown in Figure 2. CO was higher in the ↑$\dot{V}_E$ group while breathing RA and this difference persisted during hypoxia; however, the percentage increase in CO during hypoxia was not different between groups. Conversely, ABP was similar in both groups under basal conditions but increased significantly at 1 and 5 min of hypoxia only in those animals who showed a sustained elevation in ventilation with hypoxia ($p < 0.01$).

The changes in BBF and BSBF with hypoxia are shown in Table 1. Basal values were similar in the two groups of animals.

During hypoxia, total BBF increased by more than 50% and BSBF nearly doubled in both groups ($p < 0.0001$). No correlation was found between the changes in ventilation and BBF or BSBF with hypoxia when the results were analyzed as absolute values or as a percent change from basal values (Fig. 3).

There were no differences in the sagittal venous pressure [10 ± 1 to 10 ± 0.3 mm Hg) and brain blood flow (97 ± 13 to 93 ± 14 mL/(min·100 g)] in the animals before and after both external jugular veins were ligated.

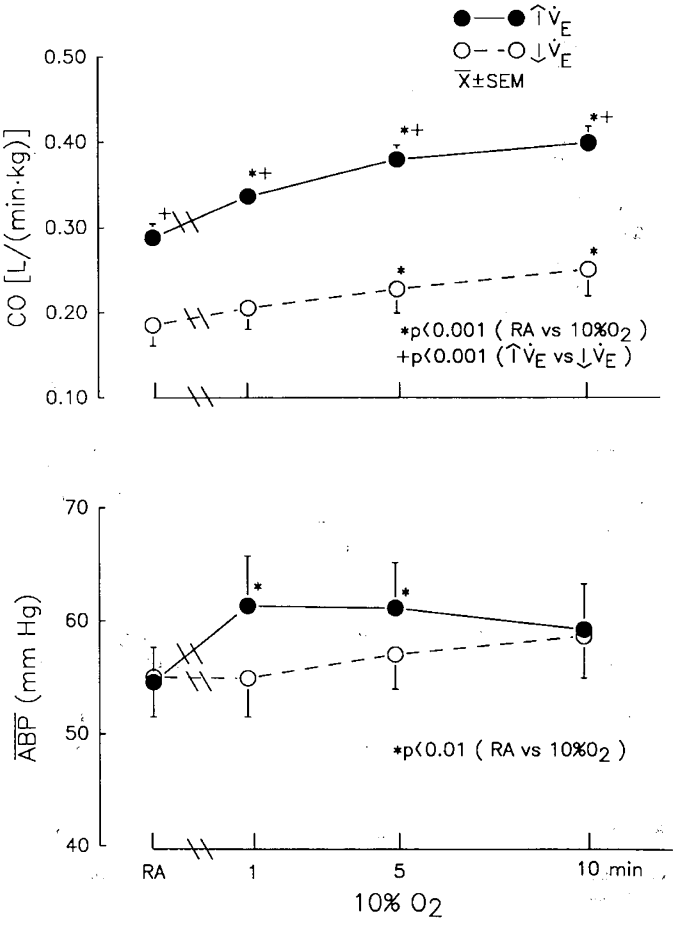

Fig. 2. Changes in CO and mean ABP during hypoxia in the ↑ $\dot{V}_E$ and ↓ $\dot{V}_E$ groups.

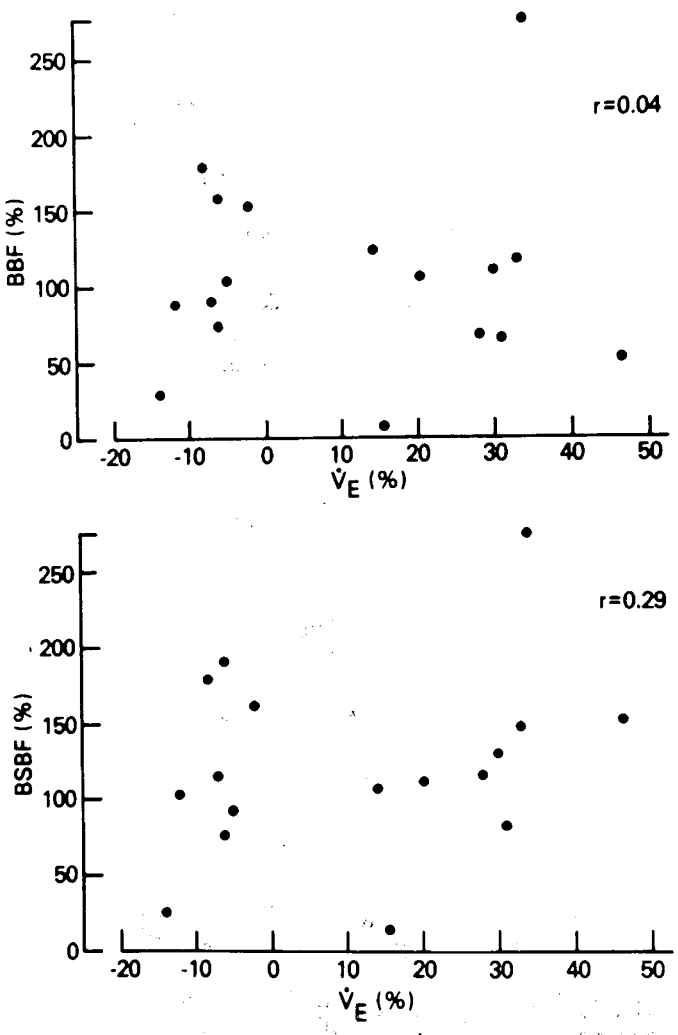

Fig. 3. Changes in BBF and BSBF and $\dot{V}_E$ after 10 min of hypoxia expressed as a percent of change.

Cdyn and R_L were not different between the groups under basal conditions or after 10 min of hypoxia.

DISCUSSION

We have taken advantage of the fact that our studies in the neonatal piglet have revealed that some animals have a ventilatory response to hypoxia similar to the adult response with sustained hyperventilation during hypoxia whereas other animals of a similar age have a neonatal type of response and do not maintain hyperventilation during hypoxia. This provided us with the opportunity to compare the ventilatory and hemodynamic response to hypoxia in these two groups of animals.

Numerous studies have attempted to elucidate the mechanisms responsible for the ventilatory depression that is seen after a few minutes of hypoxia in the neonate (2–5, 7–14). Some investigators have suggested that the ventilatory depression during sustained hypoxia could be due to a relative alkalosis of the brain stem structures produced by a washout of carbon dioxide that result from the increase in brain blood flow that occurs during hypoxia (15, 20). Neubauer *et al.* (15) produced an increase in cerebral perfusion pressure and blood flow by obstructing aortic flow with a balloon in adult chemodenervated cats. This maneuver resulted in a decrease in $\dot{V}_E$ that was attributed to the increase in brain blood flow and rise in the ventral medullary surface pH. However, this mechanism has been questioned by Javaheri and Teppema (21) who showed decrease in $\dot{V}_E$ during hypoxia without changes in ventral medullary extracellular P_{CO_2} or pH. Extending these findings, Brown and Lawson (22) demonstrated an acidotic shift in brain stem extracellular fluid during the late ventilatory depression in neonatal piglets. Also, Suzuki *et al.* (23) recently showed no differences in jugular venous P_{CO_2} (which was used as an index of brain tissue P_{CO_2}) between human adults with sustained and unsustained ventilatory response to hypoxia.

Conversely, Edelman *et al.* (16) showed that adults with familial dysautonomia and goats treated with α-adrenergic blockers have an absence of the normal cardiovascular response to hypoxia that is associated with a depression of the ventilatory response to hypoxia. They attributed the ventilatory depression to hypoxic central depression that was aggravated by a decreased cerebral blood flow due to arterial hypotension. Furthermore, neonatal kittens exposed to 6–12% O_2 display marked ventilatory depression, which in most instances is accompanied by a significant fall in ABP (1).

To our knowledge our data are the first to attempt to establish a relationship between changes in cerebral blood flow and the ventilatory response to hypoxia in newborn animals. Our data are not comparable to those reported by Neubauer *et al.* (15), because they induced an increase in brain blood flow by rapid inflation of an aortic balloon that allowed very short periods of observation and the results were based on only three breaths. Our study does not support the hypothesis that changes in brain stem perfusion during hypoxia influence the pattern of ventilatory response to low inspired oxygen. Although the ventral medullary extracellular pH was not measured in this study, the similar increase in the BBF and BSBF during hypoxia, irrespective of the pattern of the ventilatory response, suggests that possible brain stem alkalosis caused by the increase in brain blood flow is not a major factor for the late ventilatory depression in the newborn piglet.

It has been suggested that changes in pulmonary mechanics may also contribute to the hypoxic ventilatory depression in the newborn (3, 14). However, in our study no significant changes in lung compliance or total R_L occurred in either group of animals studied, eliminating this as a possible explanation for the observed difference in ventilatory response.

A decrease in the metabolic rate during hypoxia has been described in different neonatal animal species and may also explain the decrease in ventilation after a few min of hypoxia (13). Oxygen consumption was not measured in our study but the fact that P_{aCO_2} remained relatively constant during hypoxia in the animals that hypoventilated suggests that any reduction in metabolic rate during hypoxia was not enough to explain the absence of hyperventilation. In addition, recent studies in our laboratory did not demonstrate a clear relationship between changes in oxygen consumption and ventilation during hypoxia in newborn piglets (24).

The finding that the CO and ABP were lower in animals that did not sustain hyperventilation is interesting and raises the possibility that impaired perfusion to respiratory organs such as the respiratory muscles may contribute to the depressed ventilatory response in these animals. However, the magnitude of increase in CO during hypoxia was similar in both groups and ABP values at 10 min of hypoxia did not differ from baseline. We do not have an explanation for the large difference in CO between the two groups, because there were no differences in age, wt, hematocrit, or general condition of the animals that could explain this finding.

Although it is possible that sedation may influence the changes in ventilation during hypoxia, it is unlikely that the different hypoxic ventilatory response was related to the chloral hydrate administration because the dose of the drug was similar in both groups. Also, it has been shown that even at a higher dose (250 mg/kg) than the one used in this study, chloral hydrate does not affect the ventilatory response to hypoxia or hypercarbia in rabbits (25). In addition, a biphasic ventilatory response to hypoxia has been described in anesthetized and unanesthetized newborn animals (1–4, 7, 10, 14). Although it would have been preferable to perform our study in unanesthetized newborn piglets, it would be impossible to obtain all the necessary measurements during normoxia and hypoxia without causing significant distress to the animals.

We do not have a clear explanation for the two different patterns of ventilatory response to hypoxia. However, it has been reported that this response can vary widely among healthy subjects and newborn piglets (4, 22, 26, 27). It has also been suggested that genetic factors may play a significant role in determining this variability, based on studies on identical and nonidentical twins (26, 28). Vizek *et al.* (29) have suggested that the variability of the hypoxic ventilatory response may in part be associated with the differences in peripheral chemoreceptor sensitivity. In contrast, previous reports have demonstrated sustained increase of carotid sinus nerve activity during hypoxia even though there was a late decrease in ventilation (1, 30). However, this does not exclude the possibility that the decline in carotid body chemoreceptor activity during prolonged exposure to hypoxia may contribute to the biphasic respiratory pattern (11).

In conclusion, the results of this study do not support the hypothesis that the hypoxic ventilatory depression in neonatal piglets is related to changes in brain blood flow. Although the cardiovascular response to hypoxia was different in animals with different ventilatory responses, we were unable to establish a clear relationship between the circulatory and ventilatory response to hypoxia in these animals.

Acknowledgments. The authors thank Ralph N. Cicalese and Jean Fleurantin for their invaluable technical assistance, Cristina Varga for her secretarial support, Dr. Shahnaz Duara and Dr. Ronald N. Goldberg for their critical review of the manuscript, and Dr. Maria Delivoria-Papadopoulos and Dr. Craig Wagerle for helpful suggestions concerning microsphere methodology.

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