

The Effect of Hypocapnia on the Cardiovascular System of Puppies

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Summary

Respiratory alkalosis (hypocapnia) is used to treat persistent pulmonary hypertension in newborns. With the exception of the brain, there are no data on the effects of hypocapnia on organ blood flow in the neonate. Therefore, we examined the effects of 2 h of hypocapnia on blood pressure, oxygen consumption, cardiac output and organ blood flows in puppies.

In six animals (group I), reducing the P_{aCO_2} to 21.8 ± 1.5 mm Hg (pH 7.62 ± 0.04) caused an immediate and sustained reduction in cerebral blood flow (40%) and in myocardial blood flow (25%). There were no significant changes in arterial blood pressure, total body oxygen consumption, cardiac output, right and left ventricular rate-pressure product, or blood flow to the gut, liver, muscle, and kidneys.

In four control animals (group II) (P_{aCO_2} 39.8 ± 3.0 , pH 7.38 ± 0.04), there were no changes in any of the measured variables (arterial blood pressure, total body oxygen consumption, cardiac output, or blood flow to any organ, including brain and heart) during 2 h of normocarbic ventilation.

We did not determine whether the reductions in cerebral and myocardial blood flows were detrimental. We suspect that they were not because the animals did not develop metabolic acidosis and they had normal cardiac outputs, and ventricular rate-pressure products throughout the study.

Respiratory alkalosis is used to treat the pulmonary hypertension associated with meconium aspiration (14), infection (15), polycythemia (15), maternal indomethacin and aspirin ingestion (9), hyaline membrane disease (7), and pulmonary hypoplasia (diaphragmatic hernia) (36). Alkalosis is also used to treat idiopathic pulmonary hypertension (46). In all of these cases, it is occasionally necessary to raise the pH to 7.60 (P_{aCO_2} 20 mm Hg) to cause the desired reduction in pulmonary artery pressure. There is concern among clinicians that this degree of hypocapnia may alter cardiac output and its distribution.

The effects of P_{aCO_2} on regional blood flow have been studied in adult animals but not in newborns. In the adult, hypocapnia either decreases myocardial blood flow (32, 42, 45) or maintains it constant (21, 42, 45, 48). Gastrointestinal blood flow decreases. A similar reduction in gut blood flow in the neonate may cause necrotizing enterocolitis, an entity thought to result from hypoperfusion (30).

We felt it important to determine the effects of respiratory alkalosis ($P_{aCO_2} \sim 20$ mm Hg) on the regional blood flow of newborn animals before this form of therapy is widely used in human infants. To do so, we measured the cardiac output and organ blood flow of 5–10-day-old puppies before and after their P_{aCO_2} was reduced to 21.8 ± 1.5 mm Hg. Puppies were used for these studies because they, like human babies, are immature at birth.

MATERIALS AND METHODS

We studied 12 5–10-day-old mongrel dogs who weighed 505–855 g. They were anesthetized with 70% nitrous oxide throughout the study and paralyzed with 0.1 mg/kg of pancuronium. Their tracheae were intubated, and their lungs were mechanically ventilated with a Harvard small animal volume ventilator. Their tracheal pressures were continuously recorded from an 18-gauge needle; the needle tip was positioned near the tracheal end of the endotracheal tube. The needle was connected by stiff pressure tubing to a Gould-Statham 823DB pressure transducer. The response time of the needle, catheter, and strain gauge was flat to 15.1 Hz.

The right groin and both sides of the neck were infiltrated with 0.5 ml of 1% xylocaine and catheters were inserted into the femoral artery and vein, left ventricle (via left carotid artery), and right ventricle (via right jugular vein). The femoral vein catheter was used to infuse 10% dextrose in 0.2 normal saline (2–4 ml/kg/h), transfuse blood, and administer pancuronium bromide. The femoral artery catheter was used to monitor arterial blood pressure, blood gases, and pH, and to withdraw blood for reference samples during microsphere injections (28). The left ventricular catheter was used to inject radionuclide-labeled microspheres. The right ventricular catheter was used to measure right ventricular pressures, and to withdraw blood for determination of mixed venous blood gases and pH. We were unsuccessful in advancing catheters into the pulmonary arteries of these small animals so we used right ventricular systolic pressure as an index of pulmonary artery pressure.

After allowing 30 min for recovery from the surgical manipulations, we measured blood gases and pH. We found them to be normal in all but two animals. These two had a small amount of metabolic acidosis which was corrected with 2 meq/kg of sodium bicarbonate. Two-tenths ml of blood was withdrawn from the femoral artery and from the right ventricle before each microsphere injection. With each sample, we determined pH, PO_2 , PCO_2 , oxygen saturation, and hemoglobin concentration. Blood gases and pH were measured with a Corning 175 blood gas analyzer and corrected for body temperature and pH. Hemoglobin concentration and oxygen saturation were determined with a Radiometer Hemoximeter. Next, microspheres were injected into the left ventricle to determine control (normocarbic) cardiac output and organ blood flow. The microspheres were injected over 20–30 sec and 5 ml of arterial blood ("reference organ sample") were withdrawn over a 2-min period. An equal volume of maternal blood was infused into the femoral vein during the withdrawal to maintain a constant blood volume. We injected 200,000 to 800,000 15- μ m radionuclide microspheres during each cardiac output measurement to ensure that there was an adequate number of microspheres present to accurately determine organ blood flows (28). Because injecting the spheres did not affect the arterial blood pressure, we conclude that they did not significantly obstruct the circulation. The rectal temper-

Table 1. Variables measured during a 2-h period of controlled ventilation*

Variable	During normocarbic ventilation		
	Control	15 min	120 min
Arterial PO ₂ (mm Hg)	141.5 ± 16.2	135.7 ± 26.0	132.2 ± 18.5
Arterial oxygen saturation (%)	100 ± 0.0	100 ± 0.0	100 ± 0.0
Arterial PCO ₂ (mm Hg)	41.3 ± 2.5	37.7 ± 4.9	42.3 ± 3.0
Arterial pH	7.34 ± 0.03	7.37 ± 0.02	7.33 ± 0.01
Venous PO ₂ (mm Hg)	32.5 ± 3.5	35.0 ± 2.8	41.0 ± 2.8
Venous oxygen saturation (%)	60.5 ± 5.6	63.1 ± 4.2	65.7 ± 8.3
Arterial oxygen content (ml/100 ml)	14.58 ± 2.6	14.56 ± 2.1	14.30 ± 1.8
Venous oxygen content (ml/100 ml)	8.69 ± 1.7	8.42 ± 0.9	9.13 ± 0.4
Arterial-venous oxygen content difference (ml/100 ml)	5.89 ± 1.9	6.15 ± 1.5	5.17 ± 1.4
Oxygen consumption (ml/kg/min)	14.94 ± 3.7	15.17 ± 2.8	13.85 ± 1.4
Mean arterial blood pressure (mm Hg)	74.5 ± 22.9	70.3 ± 21.6	58.0 ± 15.3
Systemic vascular resistance	523 ± 265	478 ± 237	419 ± 169
Cardiac output (ml/kg/min)	232 ± 60	238 ± 59	227 ± 87

* PaCO₂ = 38–42 mm Hg. Values are means ± SD.

Table 2. Tissue blood flow (flow/100 g/min) during a 2-h period of controlled ventilation*

	Normocarbica (control)	Normocarbica (15 min)	Normocarbica (120 min)
Brain	41.20 ± 6.69	34.27 ± 9.26	40.27 ± 7.55
Heart	124.83 ± 13.61	110.65 ± 19.66	121.7 ± 48.18
Gut	63.67 ± 18.49	78.03 ± 17.51	68.05 ± 32.81
Kidney	166.67 ± 23.95	175.05 ± 26.71	174.17 ± 31.89
Spleen	110.93 ± 67.78	147.1 ± 121.61	105.85 ± 60.96
Liver	34.75 ± 9.64	33.05 ± 5.40	33.00 ± 15.18
Lung	77.67 ± 42.41	63.12 ± 32.00	49.02 ± 39.14
Lower carcass	11.79 ± 5.04	12.56 ± 4.86	13.05 ± 6.25
Upper carcass	13.87 ± 5.33	13.97 ± 4.54	13.37 ± 6.97

* PaCO₂ = 38–42. Values are means ± SD.

atures of the puppies were continuously monitored and maintained at 38.5 ± 0.3°C (their normal body temperature) with a Servo-controlled heating lamp and a heated water blanket. The animals were covered with Saran wrap to reduce evaporative heat loss.

Eight animals (group I) were then hyperventilated to a pH of 7.62 ± 0.04 and a PaCO₂ of 21.8 ± 1.5 mm Hg by increasing the rate of the ventilator. Fifteen, 30, 60, and 120 min later, we determined arterial and venous blood gases, pH, oxygen saturation, hemoglobin concentration, and cardiac output and its distribution.

Four animals (group II) were ventilated to maintain their blood gases and pH at normal for 2 h. They were used to control for the effect of time on the preparation. Microspheres were also injected after 15, 30, 60, and 120 min of mechanical ventilation.

Two additional animals (group III) were prepared the same way. In addition, their ductus arteriosus was ligated. These animals allowed us to determine normal bronchial blood flow in the puppy and to check for immediate recirculation of microspheres. We tested for recirculation by injecting microspheres into the left ventricle and simultaneously withdrawing blood from the right ventricle. Radioactivity in right ventricular blood would indicate that some microspheres were not trapped by the arterial microcirculation.

At completion of the study, all animals were killed with an overdose of intravenous sodium pentobarbital and their organs were removed, weighed, and ashed. The brain was divided into left and right hemispheres, cerebellum, and brain stem; the heart was divided into atria, left and right ventricles, and ventricular septum; the right and left lungs and kidneys were separated; and the spleen, stomach, small bowel, large bowel (minus its con-

Table 3. Tissue blood flow (% of cardiac output) during a 2-h period of controlled ventilation*

	Normocarbica (control)	Normocarbica (15 min)	Normocarbica (120 min)
Brain	4.21 ± 1.00	3.27 ± 0.25	4.5 ± 1.92
Heart	4.09 ± 0.69	3.52 ± 0.79	4.13 ± 1.85
Gut	14.44 ± 2.24	17.10 ± 0.62	15.37 ± 2.49
Kidney	12.54 ± 2.54	12.89 ± 3.42	14.43 ± 7.21
Spleen	2.23 ± 1.08	3.03 ± 1.90	2.32 ± 0.69
Liver	9.55 ± 5.28	8.39 ± 3.15	8.45 ± 3.78
Lung	7.44 ± 2.17	5.85 ± 2.00	4.21 ± 1.97
Lower carcass	13.45 ± 3.38	14.11 ± 2.38	15.41 ± 2.84
Upper carcass	30.70 ± 5.57	30.55 ± 2.39	29.86 ± 7.22

* PaCO₂ = 38–42 mm Hg. Values are means ± SD.

Table 4. Variables measured before and during hyperventilation in six newborn dogs*

Variable	Before hyperventilation	During hyperventilation	
		15 min	120 min
Arterial PO ₂ (mm Hg)	128.3 ± 12.2	128.5 ± 16.3	146.3 ± 12.2
Arterial oxygen saturation (%)	99.1 ± 1.3	98.2 ± 2.17	98.9 ± 1.4
Arterial PCO ₂ (mm Hg)	38.0 ± 4.7	21.8 ± 1.5†	19.7 ± 3.5†
Arterial pH	7.37 ± 0.02	7.62 ± 0.04†	7.59 ± 0.05†
Venous PO ₂ (mm Hg)	31.5 ± 2.1	24.8 ± 4.5†	24.3 ± 2.6†
Venous oxygen saturation (%)	48.1 ± 5.6	43.1 ± 7.9	40.0 ± 8.8
Arterial oxygen content (ml/100 ml)	12.15 ± 2.45	12.10 ± 1.72	12.95 ± 2.14
Venous oxygen content (ml/100 ml)	5.97 ± 1.8	5.14 ± 0.68	4.94 ± 1.36
Arterial-venous oxygen content difference	6.19 ± 1.74	6.96 ± 1.42	8.01 ± 1.37
Oxygen consumption (ml/kg/min)	16.41 ± 6.54	16.87 ± 6.97	14.57 ± 3.48
Mean arterial blood pressure (mm Hg)	69 ± 18	58 ± 21	54 ± 25
Systemic vascular resistance	403 ± 181	360 ± 168	352 ± 149
Cardiac output (ml/kg/min)	268 ± 86	248 ± 102	184 ± 46

* Measurements made at 30 and 60 min after commencing hyperventilation are not included, but were not significantly different from those at 15 min.

† Significantly different from value before hyperventilation, *P* < 0.001 (mean ± SD).

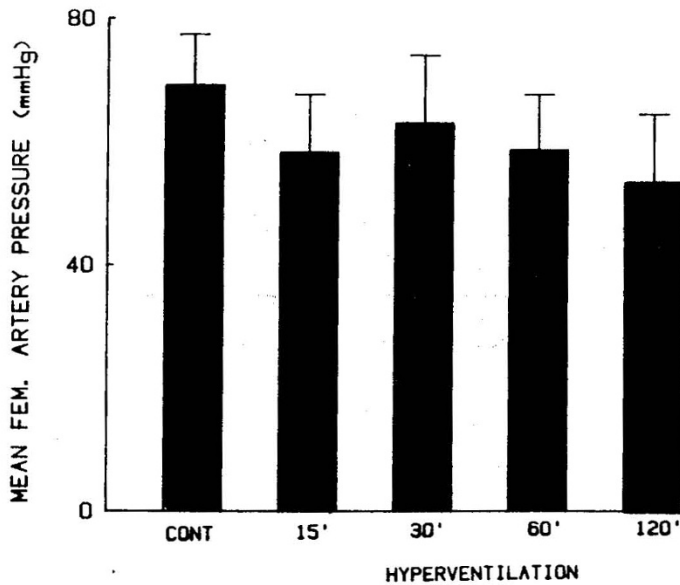


Fig. 1. The effects of respiratory alkalosis ($\text{pH } 7.62 \pm 0.04$) and time on mean arterial blood pressure. *Cont.*, control, normal PaCO_2 .

Table 5. Tissue oxygen delivery ($\text{ml}/\text{min}/100 \text{ g of tissue}$)*

	Before hyperventilation	During hyperventilation	
		15 min	120 min
Brain	0.73 ± 0.21	0.4 ± 0.07	$0.4 \pm 0.10^\dagger$
Heart	1.12 ± 0.4	0.82 ± 0.26	0.83 ± 0.44
Gut	3.03 ± 1.01	3.02 ± 0.59	2.08 ± 1.26
Kidney	2.62 ± 0.70	2.66 ± 0.26	2.38 ± 0.89

* Values are means \pm SD.

$^\dagger P < 0.01$ = different from normocarbica.

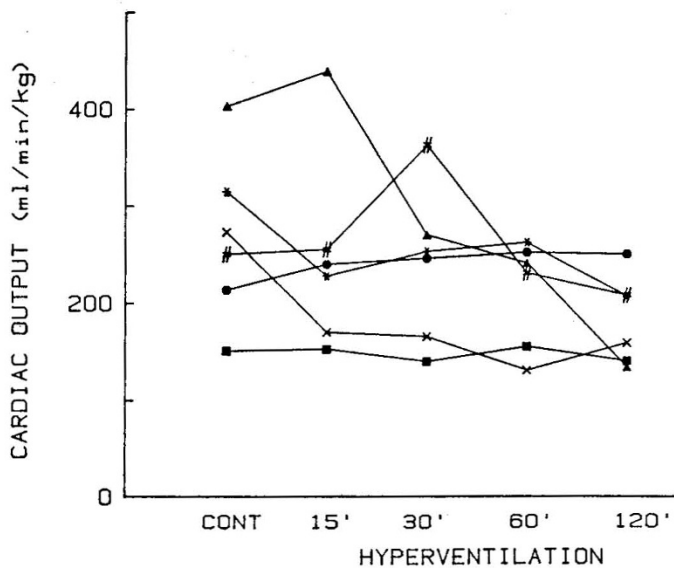


Fig. 2. The effects of respiratory alkalosis ($\text{pH } 7.62 \pm 0.04$) and time on cardiac output. Each *symbol* represents an individual animal. *Cont.*, control, normal PaCO_2 .

tents), and liver were weighed and evaluated separately. The body of each animal was divided at the diaphragm and the two parts of the body were counted as upper and lower carcass.

Calculations and statistics. Arterial and venous oxygen contents were calculated by assuming an oxygen-hemoglobin affinity of $1.34 \text{ ml O}_2/\text{g hemoglobin}$ at 100% saturation. Total body oxygen uptake was calculated by multiplying the arterial-venous

Table 6. Tissue blood flow ($\text{ml}/100 \text{ g}/\text{min}$) before and after the induction of hypocarbica*

Organ	Normocarbica	Hypocarbica (15 min)	Hypocarbica (120 min)
Brain	39.65 ± 7.30	$21.90 \pm 3.04^\dagger$	$18.27 \pm 2.61^\dagger$
Heart	177.47 ± 57.45	$107.30 \pm 28.25^\dagger$	$116.45 \pm 46.30^\dagger$
Gut	82.35 ± 24.84	82.05 ± 15.57	62.33 ± 23.85
Kidney	183.12 ± 20.71	194.07 ± 44.60	156.17 ± 36.90
Spleen	96.15 ± 32.07	90.47 ± 72.90	67.82 ± 18.82
Liver	12.09 ± 6.63	10.16 ± 3.35	17.89 ± 7.05
Lung	47.15 ± 31.37	30.35 ± 22.13	14.30 ± 10.50
Lower carcass	19.20 ± 10.55	18.78 ± 13.89	13.94 ± 6.18
Upper carcass	17.35 ± 8.53	16.10 ± 9.48	11.53 ± 4.02

* PaCO_2 $21.8 \pm 1.5 \text{ mm Hg}$. Values are means \pm SD.

$^\dagger P < 0.001$ = different from normocarbica.

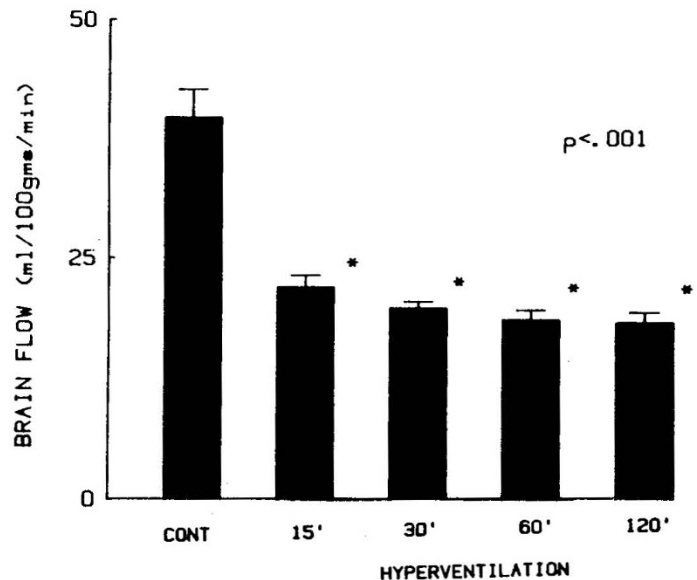


Fig. 3. The effects of respiratory alkalosis ($\text{pH } 7.62 \pm 0.04$) and time on brain blood flow. Note that alkalosis significantly reduced cerebral blood flow. Also note that it did not increase with time. *Cont.*, control, normal PaCO_2 . *, $P < 0.001$ = different from normocarbica.

oxygen content difference by cardiac output. The rate-pressure product (heart rate \times peak systolic pressure) was calculated as an index of myocardial oxygen requirement (13).

The data were analyzed by one-way or two-way analysis of variance and Newman-Keuls testing. A Bonferroni correction was used. A P value < 0.05 was considered significant.

RESULTS

Two animals were excluded from the analysis, one because 50% of cardiac output entered the lung, and the other because there was unequal distribution of microspheres between left- and right-sided organs. The following data are from the remaining 12 animals (6 hyperventilated, 4 nonhyperventilated controls, 2 ductus arteriosus ligation).

On four separate determinations, the bronchial blood flow was $2.6 \pm 1.3\%$ of the cardiac output in the two group III animals. It was arbitrarily decided to accept studies in which the blood flow to the lung was as high as 11% of the cardiac output as representing an acceptably small left-to-right shunt through the ductus arteriosus. There was no evidence of recirculation of microspheres.

Ventilation and hemodynamic changes. The ventilator rate of groups I and II was 32 ± 1.6 (SD) breaths/min during the control period. The peak airway pressure was $6.6 \pm 0.5 \text{ mm Hg}$ and the end expiratory pressure was 0 mm Hg . Hyperventilation was

easily accomplished in group II by increasing the ventilator rate to 78.2 ± 4.9 breaths/min while maintaining a constant tidal volume. This resulted in a peak airway pressure of 10 ± 1.5 mm Hg and an end expiratory pressure of zero. The desired P_{aCO_2} and pH were easily achieved and maintained throughout the experiments.

In group I, there were no significant changes in any of the measured or calculated variables, including cardiac output and organ blood flows (Tables 1-3). Intravascular pressures remained within normal limits.

In group II, there were no significant changes in hemoglobin concentration, arterial oxygen tension, saturation, or content, venous oxygen saturation or content, or arteriovenous oxygen content difference, although there was a tendency for the venous oxygen content to fall and the arteriovenous oxygen difference to increase (Table 4). There was significant difference in venous PO_2 between the control and the hyperventilated states in group II, due to the Bohr effect (4). This resulted in a lower PO_2 at the same oxygen saturation.

There was no significant change in mean arterial blood pressure (Fig. 1) in group II, although it fell from 80 to 35 mm Hg in one animal due to a marked reduction in systemic vascular resistance. This fall occurred with the onset of hyperventilation and remained constant thereafter. In two other animals, the mean arterial pressure fell 15-20% during the last hour of the study. On average, there was no change in the systemic vascular resistance during the study period (Table 4). There was also no change in either the right or the left ventricular rate-pressure products.

Oxygen consumption and delivery. There was no significant change in group II in total body oxygen consumption (Table 4) or in oxygen delivery (tissue blood flow \times oxygen content of arterial blood) (Table 5) to any organ except the brain in group II. Oxygen delivery to the brain was reduced 46% by hypocarbia and remained constant throughout the remainder of the study.

Cardiac output and organ blood flows. Hyperventilation had no significant effect on cardiac output (Fig. 2). There was, however, a tendency for it to decrease 20-30% in some animals after 2 h of hyperventilation. This did not occur in the control animals (Table 1).

Only the brain and heart showed a significant change in blood flow/min/100 g during hyperventilation. Cerebral blood flow was decreased 40% (39.7 ± 7.3 to 21.9 ± 3.03 ml/min/100 g) ($P < 0.01$) by hyperventilation (Table 6 and Fig. 3). This reduction

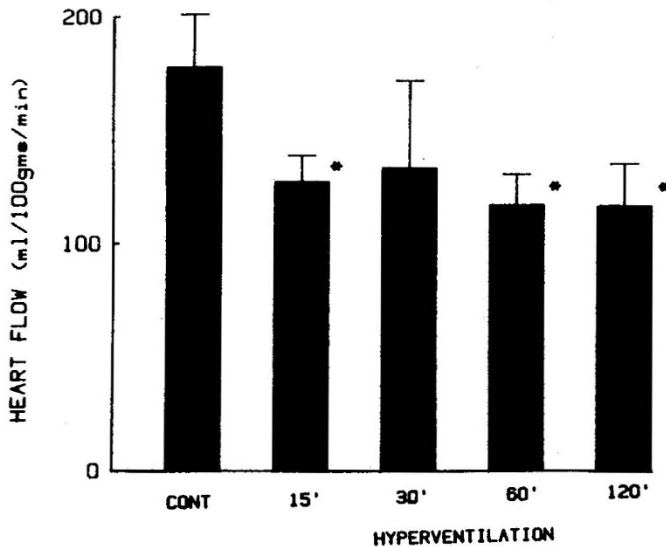


Fig. 4. The effects of respiratory alkalosis (pH 7.62 ± 0.04) and time on cardiac blood flow. Blood flow was significantly reduced by alkalosis. Flow did not increase with time. *Cont.*, control, normal P_{aCO_2} . *, $P < 0.01$ = different from normocarbia.

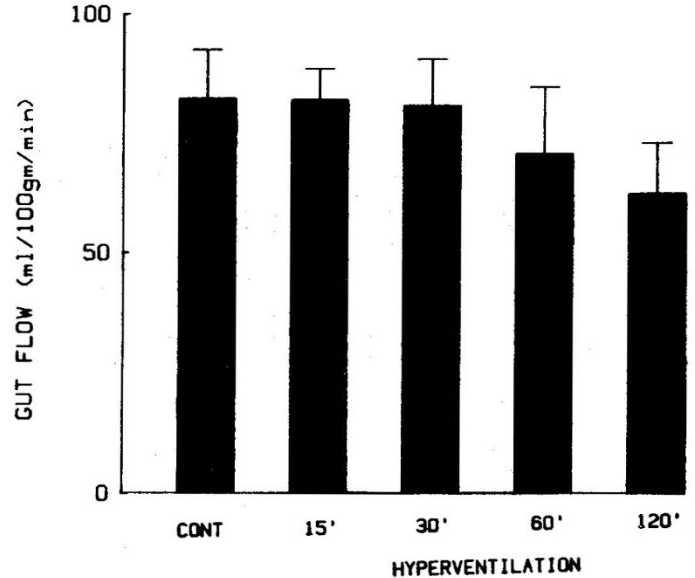


Fig. 5. The effects of respiratory alkalosis (pH 7.62 ± 0.04) and time on gut blood flow. *Cont.*, control, normal P_{aCO_2} .

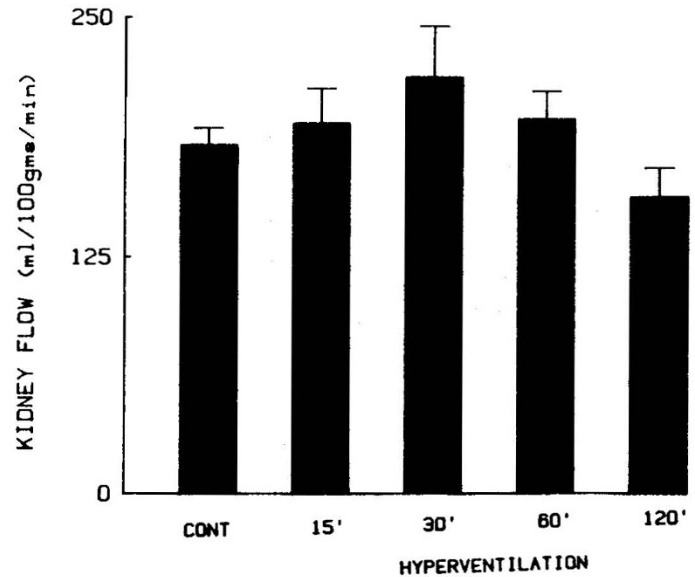


Fig. 6. The effects of respiratory alkalosis (pH 7.62 ± 0.04) on kidney blood flow. *Cont.*, control, normal P_{aCO_2} .

Table 7. Tissue blood flow (% cardiac output) before and after the induction of hypocarbia*

Organ	Normocarbia	Hypocarbia (15 min)	Hypocarbia (120 min)
Brain	3.61 ± 1.11	2.18 ± 0.54	2.39 ± 0.64
Heart	5.39 ± 1.07	4.51 ± 1.59	5.29 ± 1.29
Gut	14.55 ± 2.24	16.45 ± 3.12	14.07 ± 3.11
Kidney	13.07 ± 4.01	14.63 ± 2.80	15.89 ± 5.81
Spleen	2.04 ± 0.60	2.01 ± 1.57	2.07 ± 1.10
Liver	3.16 ± 2.26	2.91 ± 1.62	6.16 ± 3.41
Lung	5.80 ± 3.50	4.02 ± 2.16	2.99 ± 1.90
Lower carcass	19.15 ± 5.28	19.80 ± 5.21	18.73 ± 4.03
Upper carcass	31.85 ± 5.30	32.00 ± 4.83	31.80 ± 5.50

* P_{aCO_2} 21.8 ± 1.5 mm Hg. Values are means \pm SD.

in flow occurred within 15 min of the onset of hyperventilation and persisted throughout the remainder of the study. Blood flow to the right and left cerebral hemispheres and the various areas of the brain were similar whether or not the left carotid artery was ligated during insertion of the left ventricular catheter.

Myocardial blood flow decreased 25–40% (27.8 ± 23.8) within 15 min of initiating hyperventilation ($P < 0.01$) (Fig. 4), and remained constant thereafter. The decrease in flow was equal in all parts of the heart.

Gastrointestinal blood flow was not significantly altered by hyperventilation, but there was a tendency for it and the cardiac output to decrease during the last hour of the study (Fig. 5). All parts of the gastrointestinal tract responded similarly to hyperventilation. Liver, kidney (Fig. 6), spleen, and carcass blood flow were also unaffected by hyperventilation. There was no change in the percentage of cardiac output distributed to any of the organs, including that to heart and brain (Table 7).

DISCUSSION

We induced hyperventilation in group II by increasing the ventilator rate. It might be argued that we should have hyperventilated both groups I and II initially and then added enough CO_2 to the inspired gas to maintain a normal PaCO_2 . This would have allowed us to withdraw the added CO_2 in group II to produce alkalosis without altering the ventilator settings. We did not do this for two reasons: 1) because we had difficulty maintaining a constant PaCO_2 when we attempted to add CO_2 to the inspired gas, 2) because it is unknown what effect a previous period of hyperventilation has on the cardiovascular system when it is followed by a period of normocarbica. A recent study suggests that the effect on the brain may be significant (24).

The initial resting myocardial blood flow differed in both groups I and II. It was 124 ± 13.6 ml/100 g/min in group I and 178 ± 56 ml/100 g/min in group II. Cardiac output, oxygen consumption, and the arteriovenous oxygen difference were slightly greater in group II. The venous oxygen saturation and arterial pH were also higher in group II. Systemic vascular resistance and mean arterial pressure were lower in group II. There was no difference in the body weight, environmental or body temperatures, or the time of year the studies were done. Except for myocardial blood flow, the differences between the two groups were not significantly different by unpaired *t* test. The initial values for myocardial flow in group I were 104–134 ml/100 g/min. Those for group II were 116 to 273 ml/100 g/min. In group II, myocardial blood flow decreased when the initial flow exceeded 190 ml/100 g/min. It did not change when the initial flow was less than 150 ml/100 g/min. Five of six animals in group II had initial myocardial flows that were greater than those in group I. It is not clear why these differences existed. After the initial decrease in myocardial blood flow, the flows were similar in both groups. Reductions in myocardial blood flow similar to those found in group II have been reported in adults (42, 45). While the cause(s) are unknown, they might be related to a decrease in ionized calcium, tissue catecholamine levels, or myocardial oxygen consumption. We did not measure these variables in this study. Despite the decrease in myocardial blood flow, it does not appear that oxygenation of the heart was impaired because the rate-pressure-product of both ventricles [an indication of myocardial oxygen consumption (13)] remained normal and constant. The myocardial oxygen consumption of adults is unchanged (42) or increased (47) by hyperventilation. In adult dogs, myocardial oxygen consumption is decreased by hyperventilation (44). This does not appear to be detrimental because the phosphorylated nucleotide content of the heart remains constant (45).

The cardiac output of adult animals (21, 32) and humans (16, 29, 41, 42) is either unchanged or decreased by hypocarbica. The systemic vascular resistance and blood pressure often decrease for the first 1–7 min of hyperventilation and then return to control levels (16, 40). In our animals, neither cardiac output nor peripheral vascular resistance changed significantly.

Respiratory alkalosis reduces the cerebral blood flow of neonates and adults (22, 23, 27, 37, 49). The relationship between PaCO_2 and cerebral blood flow is linear when the PaCO_2 is between

20 and 80 mm Hg (22, 37, 43). The absolute level of cerebral blood flow and the flow/100 g of brain are both lower in newborns than in adults of the same species (8, 22, 35, 37). The changes in cerebral blood flow per mm Hg change in PaCO_2 are either smaller (27, 37, 43) or larger (30) than they are in adults.

This study confirms previous observations in adults (8, 40, 43, 49) and neonates (37, 43) that cerebral blood flow is reduced by hyperventilation. Unlike adults, there was no tendency for cerebral blood flow to return to normal with time. There is disagreement about whether the reduction in cerebral blood flow and oxygen delivery caused by hypocarbica is harmful. Cerebral cortical PO_2 decreases when adults are hyperventilated (2, 3). The dominant frequency of the electroencephalograph decreases (2, 33, 38, 39) when the PaCO_2 is less than 20 mm Hg. This slowing can be reversed by administering 100% oxygen at 3 atm pressure (37). Newborn lambs and adult humans (1, 10, 24, 33, 39) maintain constant cerebral metabolic rates for oxygen and glucose at PaCO_2 values of 20–25 mm Hg (23). The high energy phosphates in the brains of adult rats and cats remain normal until their PaCO_2 is below 12 mm Hg (10, 17–19, 25), suggesting normal citric acid cycle activity above this PaCO_2 . Both lines of evidence (normal cerebral metabolic rates for oxygen and glucose and normal levels of high energy phosphate) suggest that hypoxic-ischemic brain damage is unlikely to occur at the levels of hypocarbica used in our study (PaCO_2 of 20–25 mm Hg).

The increased concentration of lactate in the brains of hypocarbica adults (3, 17, 19, 20, 25) is probably the result of increased glycolytic activity (10), which is due in turn to increased phosphofructokinase activity (17). In 1–5-day-old lambs, the increased cerebrospinal fluid lactate concentration is caused in part by the uptake of lactate from arterial blood (23). It appears that lactate provides an additional source of energy during hyperventilation, as it does in 1–3-week-old hypoglycemic puppies (44).

Since it was easy to produce respiratory alkalosis without causing high airway pressures, it is unlikely that changes in intrathoracic pressure contributed significantly to changes in myocardial and cerebral perfusion, especially since blood flow to other organs was not affected.

Previous reports indicate that hyperventilation has no effect (16, 42, 47) on or increases total body oxygen consumption of adults. Hyperventilation had no effect on the oxygen consumption of our neonatal lambs.

Long-term follow-up of hyperventilated infants is not extensive. The outcome of such infants is variable. Most are normal (5); however, some have severe neurological handicaps (46). It is unknown whether the poor outcome of some infants is the result of the primary disease or of the hyperventilation.

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