Regional Cerebral Blood Flow and Cerebral Metabolic Rate of Oxygen during Hyperventilation in the Newborn Dog

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ABSTRACT. Cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) were measured during normocarbica and during both moderate and severe hypocarbica. Eighteen newborn mongrel dogs, 1 to 7 days of age, were given pancuronium and ventilated with 70% N₂O and 30% O₂. The respirator was adjusted to achieve a PaCO₂ of 15 torr, all subsequent changes to 25 and 40 torr were made by adjusting the inspired concentration of CO₂. The sequence of PaCO₂ levels was randomized. CBF was measured by microsphere technique and CMRO₂ calculated as arterial-sagittal sinus O₂ content difference times hemispheric blood flow. All measurements were made after 30 min at each PaCO₂. Total CBF was reduced at a PaCO₂ of 25 torr ($p < 0.001$), further reduction in PaCO₂ to 15 torr resulted in a significant decrease in total CBF ($p < 0.01$) compared to 25 torr CO₂. All regional cerebral blood flows were reduced at a PaCO₂ of 25 torr ($p < 0.001$), and most regional CBFs had further significant decreases in flow at a PaCO₂ of 15 torr. CMRO₂ was 1.28 ± 0.47 ml/100 g/min at a PaCO₂ of 40 torr and fell to 1.09 ± 0.34 ($p < 0.05$) and to 1.04 ± 0.28 ($p < 0.025$) ml/100 g/min at PaCO₂ values of 25 and 15 torr, respectively. Cardiac output was calculated to be 169 ± 71 ml/kg/min at a PaCO₂ of 40 torr and fell to 135 ± 27 ($p < 0.025$) and to 127 ± 36 ($p < 0.005$) ml/kg/min at PaCO₂ values of 25 and 15 torr, respectively. Regression analysis of the relationship between PaCO₂ and CBF for values of PaCO₂ between 10 and 50 torr was nonlinear ($\ln \text{CBF} = a + b \cdot \text{PaCO}_2$). A series of regression curves for regional CBF are presented with R values between 0.69 and 0.81 ($p < 0.001$). It is concluded that hypocarbica to PaCO₂ values of 25 and 15 torr results in significant decreases in total as well as regional cerebral blood flows. CMRO₂ and cardiac output also show significant decreases at PaCO₂ values of both 25 and 15 torr compared to normocarbica. A nonlinear relationship is demonstrated between regional CBF and PaCO₂ between 10 and 50 torr. (*Pediatr Res* 20: 1102-1106, 1986)

Abbreviations

CBF, cerebral blood flow
CMRO₂, cerebral metabolic rate of oxygen
rCBF, regional CBF
CPD, citrate phosphate dextrose
CPM, counts per minute

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Hypocarbica is a known depressant of CBF in neonatal animals of several species (1-5). Since hyperventilation, for persistent pulmonary hypertension of the newborn, is a common practice in many intensive care nurseries, concern is raised as to whether decreased oxygen delivery to the brain secondary to decreased CBF during hypocarbica could be of such severity as to cause cerebral hypoxia. In separate studies, both Kennealy *et al.* (6) and Sugioka and Davis (7) have demonstrated significant decreases in cerebral tissue PO₂ during hyperventilation in adult dogs. Similarly, hypocarbica has been shown to increase cerebral venous (8) and CSF lactate levels (9) in dogs and to cause electroencephalographic changes in man (10).

The CMRO₂ was reported by Gregoire *et al.* (11) for newborn dogs during mild hypocarbica. Their value for CMRO₂ was not different from that measured during normocarbica but PaCO₂ was lowered only to 31 torr. We decided to test the hypothesis that the decrease in CBF during hyperventilation can result in a reduction in the cerebral metabolic rate of oxygen. The current study was therefore designed to measure total and rCBF and total CMRO₂ in the newborn dog during normocarbica and during both moderate and severe hypocarbica.

MATERIALS AND METHODS

Surgery. Eighteen newborn mongrel dogs, 1 to 7 days of age, weighing 265 to 475 g, were removed from the litter on the morning of study. The animals were given an intravenous injection of 0.1 mg/kg of pancuronium, immediately intubated (2.5-3.0 Portex endotracheal tube) and ventilated (Harvard Rodent Respirator, Harvard Apparatus Co. Natick, MA) with 70% nitrous oxide and 30% oxygen. A rectal temperature probe was inserted and the animal placed on an electric heating pad and servocontrolled to 37.5° C. Halothane (1 to 1.25%) was administered during surgical procedures which included catheterization of the femoral artery and vein with PE-50 tubing. The femoral artery catheter was advanced to the level of the sternum for aortic pressure monitoring (Statham physiologic pressure transducer, Gould pre-amp and recorder) and procurement of reference flow samples. A left ventricular catheter for injection of microspheres was inserted in the following manner. The left common carotid artery was exposed and elevated onto the blades of an iris forceps. Temporary occlusion occurred at the two sites of contact with the forceps. The 1-cm section of artery between the forcep blades was punctured with a 23-gauge needle and catheterized with a tapered PE-50 catheter which was advanced into the left ventricle. The puncture site was sealed by the catheter and after removal of the forceps a nonligated artery with pulsation proximal and distal to the site of catheter insertion remained. An incision was made over the dorsal skull exposing the sagittal suture. A 22 gauge Jelco catheter (Critikon, Inc., Tampa, FL) was inserted through the sagittal suture into the underlying

sagittal sinus. The catheter entered the rostral portion of the sinus at the junction of the frontoparietal (coronal) and sagittal suture. The catheter was advanced through the sagittal suture 2 to 4 mm to obtain a blood return, the plastic sheath was then advanced 2 mm further after which the metal trocar was withdrawn. Estimated caudal penetration would be 4–6 mm. The hub of the catheter was severed and the indwelling catheter connected to PE-50 tubing with a 23-gauge needle shaft. Sagittal sinus blood samples were slowly withdrawn over a 2-min period to minimize potential changes in sinus pressure. Upon completion of surgery, incision sites were infiltrated with 1% xylocaine and halothane discontinued, the animal was ventilated with 70% nitrous oxide and 30% oxygen for the duration of the study. After surgery, a 1-h period was allowed for the animal to stabilize.

Experimental design. Immediately after completion of surgery the respirator rate was increased to 75 cycle/min and stroke volume increased to achieve an arterial carbon dioxide tension of 15 torr. Respirator settings remained unchanged for the remainder of the study. Carbon dioxide was immediately bled into the system to achieve a PaCO₂ of 40 torr during the one hour period of recovery. All subsequent changes in PaCO₂ during the experimental conditions were accomplished by adjusting the inspired carbon dioxide concentration. Peak airway pressure was measured by a manometer, connected by a T-piece near the proximal end of the endotracheal tube.

Measurements of CBF and CMRO₂ were to be made at PaCO₂ values of 40, 25, and 15 torr. To control for time and possible effects of sequence, the order of experimental periods was randomized. Randomization was achieved by ordering the three experimental periods in every possible combination (3 factorial = 6). The six possible sequences were studied in triplicate to arrive at a total of 18 experimental animals.

At the end of the 1 h recovery, PaCO₂ was adjusted to 40, 25, or 15 torr. After 30 min, blood was drawn from the femoral artery and sagittal sinus for blood gas (Radiometer BMS 3, Radiometer America, Louisville, KY), O₂ content (Lex-O₂-Con, Woodland Associates, Wrentham, MA), and hematocrit determinations. Approximately 800,000 15 μ microspheres (3-M, St. Paul, MN) labeled with 85-Sr, 51-Cr, or 141-Ce, were reagentized and flushed into the left ventricle over 30 s with 2 ml of warmed saline. Aortic reference samples were procured via the femoral catheter by an infusion/withdrawal syringe pump (Harvard Apparatus) at a rate of 1.36 ml/min. The withdrawal pump was started 10 s prior to microsphere injection and continued for a total of 2 min. After each microsphere injection was complete a replacement transfusion of CPD adult dog donor blood was given. After each experimental period the PaCO₂ was returned to 40 torr for 15 min before proceeding to the next prescribed PaCO₂. Upon completion of the third period the animal was sacrificed with pentobarbital and the brain removed, weighed, and placed in 5% glutaraldehyde. After 7 days, the gross brain was divided into the right and left hemispheres, brainstem and cerebellum; the hemispheres were further dissected into cortical gray matter, subcortical white matter, and thalamus (12). CPM in each sample were determined with a Packard auto γ scintillation spectrometer; isotope cross-overs were corrected by simultaneous equations. Blood flow was calculated as tissue blood flow = tissue CPM per 100 g/CPM of reference sample $\times$ reference withdrawal rate (13). Cardiac output was calculated as CPM injected/CPM of reference sample $\times$ reference withdrawal rate. All regional tissue samples had greater than 400 microspheres as recommended by Buckberg *et al.* (14) and all reference samples contained greater than 7000 microspheres.

Verification of sagittal sinus sampling. The use of sagittal sinus sampling to determine the cerebral metabolic rate of oxygen, or indeed any substance, is based on the assumption that there is no significant drainage of extracerebral venous blood into the sagittal sinus. Any contamination of the sagittal sinus blood with extracerebral venous blood would lead to erroneous calculations of cerebral metabolic rates, particularly during periods of low

cerebral blood flow. In the newborn dog, there are significant anastomoses of the distal branches of the maxillary artery with the cerebral arterial circulation (15) which thus preclude the use of intraarterial injections of indicator (Evans Blue) as a method for testing for the presence of extracerebral venous blood in the sagittal sinus. Instead, we chose a modification of the hydrogen polarographic technique as described by Aukland *et al.* in 1964 (16). Briefly, an electrode polarized to 0.620 mV will accept electrons from H₂ thus generating a current which can be amplified and recorded (Hydrogen Flow Monitoring Instrument, Scientific Computer Technology, 1706 Iliff, Cincinnati, OH). If H₂ is infiltrated into a region drained by the sagittal sinus, a current will be generated from a sagittal sinus electrode as H₂ is washed out of the tissue by the local blood flow.

Four newborn dogs were prepared as previously described except that 20 mg/kg of pentobarbital was administered due to the more invasive nature of this study. A hydrogen electrode (0.004 inches in diameter) was inserted through the sagittal sinus catheter into the sagittal sinus and polarized to +0.620 mV. A silver-silver chloride wire was placed subcutaneously to serve as the reference electrode. Injections of 1.5 ml of normal saline saturated with hydrogen gas was injected during both normocarbica and during hypocarbica into two distinct locations: 1) percutaneous injections into the cerebral hemispheres and 2) subcutaneous injections into the occipital, parietal, frontal, and periorbital regions. Injection of the hydrogen saturated saline into the cerebral hemispheres resulted in an immediate spike (within 15 s) in the hydrogen generated current as recorded from the sagittal sinus electrode during both normo- and hypocarbica. Subcutaneous injections of hydrogen saturated saline resulted in no deviation from baseline in the hydrogen generated current during the subsequent 5 min of observation during either normo- or hypocarbica. Our interpretation of these findings is that there is no significant drainage of extracerebral venous blood into the sagittal sinus during conditions of normo- or hypocarbica.

Additional studies. In order to more uniformly distribute the data for regression analysis, six additional newborn dogs were studied to generate data points between 15 and 25 torr and between 25 and 40 torr PaCO₂. The measurements were made under the exact same conditions as the previous 18 animals. Three microsphere injections were performed in each and a given PaCO₂ induced 30 min prior to each CBF determination. Data from these six animals were combined with the previous 18 animals for regression analysis only.

Statistical analysis. All measurements were compared at each of the three levels of PaCO₂ by analysis of variance for repeated measures. Comparisons resulting in a significant F value were further evaluated by the Newman-Keuls multiple range test. Regression analyses were performed on a CLINFO computer by least-squares.

RESULTS

Right and left hemispheric blood flows were compared for all 54 (18 $\times$ 3) microsphere injections by analysis of variance. There was no significant difference between right and left hemispheric blood flows indicating adequate mixing of microspheres and no detectable disturbance of blood flow by the carotid catheter.

Due to variations in gas flow rates, the PaCO₂ was not maintained at exactly 40, 25, and 15 torr. Mean PaCO₂ ($\pm$ SD) for the three levels was 42.2 $\pm$ 3.7, 27.7 $\pm$ 2.3 and 13.2 $\pm$ 2.8 torr. Table 1 lists physiologic variables including arterial and sagittal sinus blood gases, hematocrits and O₂ contents for each of the three periods. Despite a decrease in PaO₂ at 25 and 15 torr CO₂, the arterial O₂ content was stable as was the hematocrit. PaO₂ measurements would be expected to decrease with progressive hypocarbica due to the leftward shift of the oxyhemoglobin dissociation curve seen with hypocarbica (17).

Mean values for arterial blood pressure and cardiac output are also seen in Table 1. Mean arterial blood pressure was 10% lower

at a PaCO₂ of 15 torr compared to 40 torr PaCO₂ ($p < 0.05$). Blood pressure at a PaCO₂ of 25 torr was not different from either 15 or 40 torr PaCO₂. Compared to normocarbica, cardiac output fell significantly when the PaCO₂ was 25 ($p < 0.025$) and 15 ($p < 0.005$) torr. There was no change in cardiac output between 25 and 15 torr PaCO₂. As the ventilator stroke volume and respiratory rate were not changed during the study, the peak airway pressures remained relatively constant at 11.9 ± 1.5 , 11.9 ± 1.4 , and 12.4 ± 1.4 cm H₂O at PaCO₂ values of 40, 25, and 15 torr, respectively.

Table 2 lists CBF, rCBF, (A-V)O₂, and CMRO₂ at each level of PaCO₂. Compared to normocarbica, all blood flows were significantly reduced at PaCO₂ values of 25 ($p < 0.001$) and 15 ($p < 0.001$) torr. Mean blood flows for total and all regional samples were lower at a PaCO₂ of 15 compared to 25 torr with only brainstem and thalamic flows ($0.10 > p > 0.05$) failing to reach the $p < 0.05$ level of significance. Cerebral oxygen transport (total hemispheric flow $\times$ arterial oxygen content) fell significantly ($p < 0.001$) at each level of hypocarbica. Cerebral oxygen extraction increased with progressive hypocarbica, *i.e.* (A-V)O₂ and the percent extraction at each level of PaCO₂ was significantly different from the other two ($p < 0.001$). Since (A-V)O₂ measured at the sagittal sinus does not reflect brainstem or cerebellar extraction, CMRO₂ was calculated as (A-V)O₂ $\times$ hemispheric blood flow. CMRO₂ fell by 14.8% at a PaCO₂ of 25 torr ($p < 0.05$) and 18.8% at a PaCO₂ of 15 torr ($p < 0.025$).

Figure 1 depicts all 72 total and rCBF measurements in 24 animals plotted against PaCO₂. Regression equations, R and p values are listed in Table 3.

DISCUSSION

The current study clearly demonstrates that progressive decreases in PaCO₂ are associated with progressive decreases in total CBF even beneath a PaCO₂ of 25 torr. Moreover, the observed decreases in total CBF were reflected in decreases in each of the rCBF examined. Total CBF has been reported during moderate hypocarbica in newborn dogs by both Hernandez *et al.* (18) and Gregoire *et al.* (11). Our reported value of 18 ml/100 g/min compares well with the reported value of Hernandez *et al.* (18) of 16 ml/100 g/min at a PaCO₂ of 28 torr, although his normocarbica value of 23 ml/100 g/min is much lower than ours. Gregoire *et al.* (11) reported a higher value of 38 ml/100 g/min at a PaCO₂ of 31 torr. It should be noted that although both investigators modified the Kety and Schmidt (22, 23) technique by using 133-Xe as an indicator, they determined quite different blood-brain partition coefficients of 0.51 and 0.74. This difference in partition coefficients explains a large portion of the differences in their reported values for CBF. Our data compares very well with that of Cartwright *et al.* (1) who also used the microsphere technique to measure total CBF at PaCO₂ values of 38 and 22 torr. In that study, CBF fell from a normocarbica value of 40 to 22 ml/100 g/min during hyperventilation.

Table 1. Physiologic variables at PaCO₂ values of 40, 25, and 15 torr (mean $\pm$ SD, $n = 18$)

		PaCO ₂ level		
		40 torr	25 torr	15 torr
pH	Arterial	7.33 $\pm$ 0.06	7.50 $\pm$ 0.06*	7.71 $\pm$ 0.07*†
PaCO ₂	Arterial	42.9 $\pm$ 3.7	27.7 $\pm$ 2.3*	13.2 $\pm$ 2.8*†
PaO ₂	Arterial	130 $\pm$ 56	111 $\pm$ 48‡	80 $\pm$ 33*†
Base excess	Arterial	-3.7 $\pm$ 4.1	1.1 $\pm$ 3.7*	3.8 $\pm$ 4.3*†
Hematocrit (%)	Arterial	47.9 $\pm$ 4.5	48.2 $\pm$ 5.2	47.9 $\pm$ 5.4
O ₂ Content (vol%)	Arterial	16.0 $\pm$ 2.5	16.3 $\pm$ 2.9	16.4 $\pm$ 2.6
pH	Sagittal	7.30 $\pm$ 0.05	7.42 $\pm$ 0.05*	7.57 $\pm$ 0.06*†
PvCO ₂	Sagittal	46.5 $\pm$ 5.8	35.2 $\pm$ 3.2*	22.8 $\pm$ 3.7*†
PvO ₂	Sagittal	53.3 $\pm$ 18.4	34.3 $\pm$ 9.4*	23.6 $\pm$ 8.3*†
Base excess	Sagittal	-4.9 $\pm$ 3.9	0 $\pm$ 3.5*	2.9 $\pm$ 3.5*†
Cardiac output (ml/Kg/min)		169 $\pm$ 71	135 $\pm$ 27‡	127 $\pm$ 36‡
Blood pressure (mm Hg)		55.8 $\pm$ 11.3	53.4 $\pm$ 12.4	50.5 $\pm$ 11.9‡

* $p < 0.001$ compared to 40 torr.

† $p < 0.001$ compared to 25 torr.

‡ $p < 0.05$ compared to 40 torr.

Table 2. Regional CBFs and indices of cerebral O₂ metabolism at PaCO₂ levels of 40, 25, and 15 torr (mean $\pm$ SD, $n = 18$)

		PaCO ₂ level		
		40 torr	25 torr	15 torr
Total brain (ml/100 g/min)		36.5 $\pm$ 12.3	17.8 $\pm$ 5.6*	11.8 $\pm$ 3.6*†
Cerebellum		52.7 $\pm$ 16.6	28.6 $\pm$ 8.9*	21.7 $\pm$ 4.6*†
Brainstem		44.4 $\pm$ 18.3	18.8 $\pm$ 6.6*	13.3 $\pm$ 4.2*
Hemispheres		34.5 $\pm$ 11.7	17.1 $\pm$ 5.6*	11.1 $\pm$ 3.6*†
Gray		66.2 $\pm$ 23.3	32.2 $\pm$ 12.5*	20.6 $\pm$ 7.0*†
White		18.1 $\pm$ 5.8	9.4 $\pm$ 2.5*	6.7 $\pm$ 2.0*†
Thalamus		40.7 $\pm$ 16.3	16.2 $\pm$ 4.4*	10.4 $\pm$ 2.8*
Cerebral oxygen transport (ml/100 g/min)		5.56 $\pm$ 2.3	2.71 $\pm$ 1.04*	1.82 $\pm$ 0.70*†
Cerebral (A-V)O ₂ (vol%)		3.9 $\pm$ 1.4	6.8 $\pm$ 2.3*	9.7 $\pm$ 2.5*†
% O ₂ extraction		24.3 $\pm$ 6.8	41.7 $\pm$ 11.3*	58.9 $\pm$ 11.7*†
CMRO ₂ (ml/100 g/min)		1.28 $\pm$ 0.47	1.09 $\pm$ 0.34‡	1.04 $\pm$ 0.28‡

* $p < 0.001$ compared to 40 torr.

† $p < 0.05$ compared to 25 torr.

‡ $p < 0.05$ compared to 40 torr.

Fig. 1. Relationship between PaCO₂ and total and rCBF between 10 and 50 torr. Regression equations, *R* and *p* values are listed in Table 3. Regression curves were generated by taking the antilogs of the solutions to the regression equations.

Table 3. Regression equations and *R* values for PaCO₂ vs rCBF

Equation	<i>n</i>	<i>R</i>	<i>p</i>
ln total CBF = 1.89 + 0.036 PaCO ₂	72	0.78	<0.001
ln brainstem = 1.94 + 0.037 PaCO ₂	72	0.74	<0.001
ln cerebellum = 2.63 + 0.027 PaCO ₂	72	0.69	<0.001
ln gray = 2.39 + 0.038 PaCO ₂	72	0.78	<0.001
ln white = 1.39 + 0.032 PaCO ₂	72	0.77	<0.001
ln thalamus = 1.64 + 0.043 PaCO ₂	69	0.81	<0.001

Shapiro *et al.* (2) provide the only previous data for rCBF during hypocarbia in the newborn dog. Using a [¹⁴C]antipyrine autoradiographic technique, they reported rCBF to the cortical gray and subcortical white matter at a PaCO₂ of 22 torr to be 22.5 and 6 ml/100 g/min, respectively. In contrast to Shapiro *et al.* (2) who did not find a significant reduction in gray matter flow below a PaCO₂ of 36 torr, the present study demonstrated significant reductions in total as well as cortical gray and white matter flows between PaCO₂ values of 25 and 15 torr. Our data do not support the suggestion of Shapiro *et al.* (2) that the newborn mammal has a higher threshold PaCO₂ which would thereby limit CBF reduction during severe hypocarbia.

The nonlinearity of the PaCO₂ versus CBF relationship between PaCO₂ values of 10 and 50 torr is demonstrated for total as well as rCBF. The linear relationship described by Shapiro *et al.* (2) was between 22 and 65 torr CO₂. The weight of our data points between PaCO₂ values of 10 to 22 torr contributes heavily to the nonlinear relationship. A nonlinear relationship between PaCO₂ and total CBF is consistent with data from adult dogs (19) and from the piglet (4). Our data differ from the study by Hansen *et al.* (4) in the piglet in that we observed significant reactivity of the hindbrain structures to hypocarbia.

CMRO₂ measurements in the newborn dog at normocarbia found in the current study are similar to the 1.13 ml/100 g/min of Hernandez *et al.* (18) and somewhat lower than 2.15 ml/100 g/min reported by Gregoire *et al.* (11). The CMRO₂ measurements by Hernandez *et al.* (18) and Gregoire *et al.* (11) are also influenced by their different Xenon partition coefficients as was just discussed. CMRO₂ for adult dogs have been reported at 3–4 ml/100 g/min, twice that of the newborn dog (8, 20). Newborn

lambs studied by Rosenberg *et al.* (5) had CMRO₂ values equal to or greater than those in adult sheep. The reason for the low CMRO₂ in the newborn dog is likely due to its CNS immaturity at birth.

Adult studies in both animals (8, 20) and humans (21–23) suggest that CMRO₂ is maintained constant during severe hypocarbia. Other neonatal studies in which CMRO₂ has been evaluated during a significant degree of hypocarbia were performed using fetal and newborn lambs and piglets. Gregory *et al.* (3), in an abstracted report, did not find a significant decrease in CMRO₂ in newborn lambs when PaCO₂ was lowered to 22 torr. Similarly, Rosenberg *et al.* (5) found no correlation between CMRO₂ and PaCO₂ in fetal and newborn lambs when PaCO₂ was varied between 25 and 70 torr. A recent report observed the newborn piglet to have a decrease in CMRO₂ after 30 min of hyperventilation but CMRO₂ returned to baseline by 1 h during continued hyperventilation (24). Although species difference may explain the difference in CMRO₂ response between lambs and newborn dogs, a more likely explanation would be the difference in neurologic maturity at birth. Comparing sensory-motor function, the lamb would appear to be significantly more mature than the newborn dog at birth. Histologically, the brain of the newborn dog at term gestation has a germinal matrix (25) and the cortical gray matter demonstrates minimal stratification of neuronal layers at birth (Reuter JH, personal observation).

Although it may be tempting to attribute the decrease in CMRO₂ solely to the large decreases in CBF and oxygen transport to the brain during hypocarbia, this is not the only possible interpretation of the data. There was no increase in base deficit in sagittal sinus blood during hypocarbia, this could be taken as evidence against cerebral hypoxia and increased anaerobic glycolysis. Also, the 15% decrease in CMRO₂ during hypocarbia occurred despite the fact that cerebral venous blood was still at least 50% saturated (PvO₂ 24–34 torr); this would suggest that there may be a reduced demand for O₂. Hypocarbia, with large increases in pH, may possibly have an effect on cerebral metabolism, thus reducing the demand for O₂ uptake. Alkalosis has been shown to diminish respiration in mitochondria isolated from avian cardiac muscle (26). Similarly, Howell *et al.* (27) have recently discussed a possible role of alkalosis in inhibition of oxidative phosphorylation.

CSF and brain lactate levels increase during hyperventilation, however, the etiology of this increase in lactate remains unclear. Alkalosis alone is thought to increase lactate production by stimulating the activity of phosphofructokinase (28). Huckabee (29) has proposed that lactic acid production may be a mechanism of acid-base homeostasis by reducing body bicarbonate during alkalosis. Alternately, Plum *et al.* (30) have observed decreased cerebral lactate accumulation in dogs hyperventilated under hyperbaric-hyperoxic conditions, thus suggesting hypoxia may be at least contributing to lactate accumulation during hypocarbia. Regardless of the etiology, there remains the question as to whether an immature brain is adversely affected by lactic acid. Results of several laboratories do suggest adverse effects of lactic acid on the CNS (31–33).

At the onset of hypocarbia, it was common to observe a significant decrease in blood pressure which then gradually returned toward baseline. This observation has been reported previously in adult humans (34). The small (10%) but statistically significant drop in blood pressure we observed indicates baseline blood pressure had not been achieved after 30 min of hypocarbia (PaCO_2 of 15 torr).

The 20 and 25% decreases in cardiac output found at PaCO_2 values of 25 and 15 torr, respectively, is a new finding in newborn dogs. This decrease cannot be attributed to changes in ventilatory pattern since neither respirator rate or volume were changed. Unfortunately, we do not have measurements of heart rate, central venous pressure, or an index of myocardial contractility to further characterize this decrease in cardiac output. Cartwright *et al.* (1) did not report a significant fall in cardiac output during hyperventilation to a PaCO_2 of 22 torr. Although their mean cardiac output measurement fell by 84 ml/kg/min after 2 h of hyperventilation, the number of animals studied ($n = 6$) may not have rendered adequate statistical strength. Cartwright *et al.* (1) did, however, report a significant decrease in myocardial blood flow during hypocarbia. Studies in anesthetized adult dogs have demonstrated both decreases (35, 36) and no change (37) in cardiac output in response to hypocarbia induced by passive hyperventilation.

It must be stressed that the findings of the current study were derived from experiments in which there was only a short period of hypocarbia. Work in piglets suggests the decrease in CMRO_2 may be a transient observation (24). Our measurements of CMRO_2 are, obviously, estimates of aerobic metabolism only; possible anaerobic contributions to cerebral metabolism during hypocarbia in the newborn dog await further study.

In conclusion, there is a nonlinear positive relationship between PaCO_2 and rCBF from PaCO_2 values of 10 to 50 torr in the newborn dog. The cerebral metabolic rate of oxygen is also reduced by hyperventilation to PaCO_2 values of 25 and 15 torr. Whether the decrease in CMRO_2 is due to the decrease in oxygen delivery or to a decrease in oxygen demand cannot be precisely determined from the present data. On the basis of sagittal sinus blood having 1) an oxygen saturation of approximately 50% and 2) no increase in base deficit, we speculate the observed decrease in CMRO_2 during respiratory alkalosis may be due to a decrease in cerebral oxygen demand.

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