The Effects of Profound Hypocapnia and Dilutional Anemia on Canine Cerebral Metabolism and Blood Flow

John D. Michenfelder, M.D.,* and Richard A. Theye, M.D.†

The effects of hypocapnia and dilutional anemia on cerebral metabolism and circulation were examined in 20 anesthetized dogs. In ten dogs, a reduction in P_{aco}, to 11 mm Hg did not alter the cerebral oxygen consumption rate (CMRO_{2}), but with subsequent dilution of hemoglobin to 5 gm/100 ml of blood, a significant decrease in CMRO_{2} was observed. In ten other dogs, anemia alone did not alter CMRO_{2}, but with the addition of hypocapnia, a reduction in CMRO_{2} similar to that of the first group was observed. An increase in cerebral glucose consumption rate and a decrease in the oxygen-glucose index were observed in both groups of dogs prior to changes in CMRO_{2}. Changes in cerebral blood flow and cerebrovascular resistance (CVR) due to hypocapnia alone or hemodilution alone were of the expected directions and magnitudes. However, in dogs hyperventilated after hemodilution, no change in CVR occurred. In these dogs, the reduction in CMRO_{2} that occurred was secondary to a reduction in O_{2} extraction from the blood. (Key words: Cerebral metabolism; Cerebral blood flow; Hypocapnia; Anemia.)

In both man and experimental animals, hypocapnia is, in most circumstances, associated with a significant reduction in cerebral blood flow (CBF).† Concern has been expressed regarding the possible consequences of this effect in relation to cerebral metabolism.

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Alexander and associates, in anesthetized volunteers, originally noted alterations in cerebral carbohydrate metabolism at profound levels of hypocapnia (P_{aco}, approximately 10 mm Hg) and subsequently reported a 10 percent decrease in cerebral oxygen consumption rate (CMRO_{2}). They concluded from indirect evidence that the alkalois produced by hyperventilation shifted the O_{2}-Hb dissociation curve (Bohr effect) sufficiently to result in restricted O_{2} extraction from the blood, thereby contributing significantly to the observed alterations in cerebral metabolism. Such profound levels of hypocapnia have not otherwise been studied in man. In dogs, Cain did not detect alterations in cerebral metabolism secondary to hypocapnia (P_{aco} = 10 to 13 mm Hg).

The alterations in carbohydrate metabolism reported by Alexander and associates were interpreted as evidence of cerebral hypoxia. They observed similar changes during hypoxia produced in the absence of hypocapnia. However, these changes in carbohydrate metabolism can also be produced, in vitro, in response to alkalois without hypoxia. It is, therefore, not established whether the alterations in cerebral carbohydrate metabolism, produced by hypocapnia are due to cerebral hypoxia or alkalois or both.

The present study is concerned with the response of canine cerebral metabolism to profound hypocapnia or dilutional anemia or both. No alteration in CMRO_{2} was observed in response to hypocapnia alone, but in other respects the findings were generally in agreement with those reported by Alexander and associates. The basis for the potential hypoxic stress of hypocapnia was further elucidated, and, under the circumstances of this
study, the restriction on blood O₂ extraction imposed by the Bohr effect proved a more potent influence than that resulting from alterations in CBF.

Methods

Twenty unanesthetized, clipped dogs weighing 12 to 16 kg were studied in the prone position. Anesthesia was induced and maintained with halothane (1.0 per cent) in nitrogen (60 to 70 per cent) and oxygen. After injection of succinylcholine (30 mg), the trachea was intubated with a cuffed tube and ventilation was controlled with a Harvard pump. Muscle paralysis was maintained with intravenously administered succinylcholine (150 mg/hr). Catheters were inserted in a femoral vein, a femoral artery, and the cervical subarachnoid space. Body temperature was controlled by partial immersion of the dog in a water bath.

Sagittal sinus blood flow was measured directly as previously described. The technique includes interruption of the extracerebral vessels draining into the sagittal sinus, exposure and cannulation of the posterior portion of the sinus, and occlusion of the sinus posterior to the cannula. By these means, sagittal sinus flow is isolated and drained into a reservoir maintained at the level of the sinus. Flow was measured by automatic, timed collection. With this technique, 43 per cent of the total brain weight as determined at autopsy (primarily cerebral hemispheres) is drained by the isolated sagittal sinus. Using this factor, flow units may be converted from ml/min to ml/100 gm brain/min. In validation studies, flows so determined were not significantly different from simultaneously determined flows obtained by the modified Ketty-Schmidt method (krypton-85) over a range of 28 to 98 ml/100 gm/min.

In 16 dogs the oxygen content of arterial and sagittal sinus blood was calculated from measured oxygen tension (IL electrodes), hemoglobin concentration, and oxygen saturation (IL 182 CO-oximeter). This method had been previously validated by comparison with Goldstein’s modification of the Van Slyke technique for determination of O₂ content. In addition, both methods were used in one of the dogs studied. In four dogs, O₂ contents

![Graph of CMRO₂ vs. Pco₂ and Hb concentration in control and hypocapnia conditions.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931599/)

**Fig. 1.** Response of CMRO₂ to hypocapnia and subsequent dilutional anemia (group I, ten dogs). In this and subsequent figures, individual values are plotted as percentages of their controls. Spacing of points does not reflect time or rate of change. Mean values for PaO₂ and hemoglobin concentration identify the conditions of the experiment. Hypocapnia did not alter CMRO₂. With dilution of blood hemoglobin level to 8.0 gm/100 ml, a reduction in CMRO₂ was observed in four of nine dogs. This trend became significant with the final dilution.

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Table 1. Cerebral Metabolism, Cerebral Circulation, and Blood Measurements in Hypocapnia Followed by Anemia (Group I)

<table>
<thead>
<tr>
<th>Factor</th>
<th>1 Control (10 dogs)</th>
<th>2 Hypocapnia (10 dogs)</th>
<th>3 Hypocapnia and moderate anemia (0 dogs)</th>
<th>4 Hypocapnia and extreme anemia (6 dogs)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, SE</td>
<td>Mean, SE</td>
<td>Mean, SE</td>
<td>Mean, SE</td>
<td></td>
</tr>
<tr>
<td>CMRO₂, ml/100 gm/min</td>
<td>4.48 ± 0.27</td>
<td>4.49 ± 0.28</td>
<td>4.27 ± 0.30</td>
<td>3.54 ± 0.29</td>
<td>NS*</td>
</tr>
<tr>
<td>CMR glucose, mg/100 gm/min</td>
<td>6.65 ± 0.49</td>
<td>7.30 ± 0.51</td>
<td>7.03 ± 0.61</td>
<td>8.14 ± 0.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oxygen-glucose index</td>
<td>0.92 ± 0.05</td>
<td>0.86 ± 0.04</td>
<td>0.83 ± 0.04</td>
<td>0.63 ± 0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cerebral blood flow, ml/100 gm/min</td>
<td>73 ± 6</td>
<td>48 ± 4</td>
<td>71 ± 5</td>
<td>112 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular resistance, mm Hg/ml/100 gm/min</td>
<td>1.3 ± 0.12</td>
<td>1.8 ± 0.11</td>
<td>1.1 ± 0.09</td>
<td>0.7 ± 0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>88 ± 2</td>
<td>81 ± 2</td>
<td>75 ± 3</td>
<td>76 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>142 ± 6</td>
<td>165 ± 10</td>
<td>103 ± 10</td>
<td>101 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>38 ± 1.0</td>
<td>11 ± 0.4</td>
<td>10 ± 0.6</td>
<td>11 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pao₂, mm Hg</td>
<td>35 ± 1.2</td>
<td>17 ± 0.8</td>
<td>19 ± 1.1</td>
<td>21 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SSO₂, %</td>
<td>63 ± 1.8</td>
<td>39 ± 2.0</td>
<td>46 ± 3.6</td>
<td>53 ± 4.7</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.71 ± 0.03</td>
<td>7.72 ± 0.03</td>
<td>7.61 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, gm/100 ml</td>
<td>11.8 ± 0.4</td>
<td>11.8 ± 0.2</td>
<td>8.0 ± 0.2</td>
<td>5.0 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Not significant.
† PaO₂ of sagittal sinus blood.
‡ O₂ saturation of sagittal sinus blood.

of blood were determined by an O₂-electrode (IL) method.¹⁰ Glucose concentrations of arterial and sagittal sinus blood were determined by an enzymatic method.¹¹ Additional measurements included arterial pH and PaCO₂ (IL electrodes), inspired halothane concentration (gas chromatography), midesophageal and parietal epidural temperatures (thermistors), and arterial and cerebrospinal fluid (CSF) pressures (strain gauge). In ten dogs, the EEC was recorded from the cortical surface.

Studies were initiated one to two hours after induction of anesthesia, after establishment of a PaCO₂ of 35 to 45 mm Hg, an inspired halothane concentration of 0.9 to 1.1 per cent, a hemoglobin concentration of more than 10.5 gm/100 ml of blood, a mean arterial pressure of more than 70 mm Hg, and an epidural temperature of 36.9 to 37.1 C. Control and experimental values were based on ten to 20 sequential determinations of CBF and differences in arterial–sagittal sinus O₂ content [C(a–ss)]O₂ and on a minimum of three determinations of arterial and sagittal sinus blood glucose concentrations. Because of the relative delay in the movement of glucose across
the blood–brain barrier, samples for glucose analysis were taken only if preceded by a five-minute period of steady CBF. After control values were established, the 20 dogs were divided into two groups of ten based on the sequence of the events studied. In group I, hypocapnia (P_{\text{a}CO_2} less than 13 mm Hg) was studied first, then hypocapnia with moderate anemia (hemoglobin value approximately 8.0 gm/100 ml), and finally hypocapnia with extreme anemia (hemoglobin value approximately 5.0 gm/100 ml). In group II, moderate anemia at normocapnia was studied first, then extreme anemia, and last hypocapnia with extreme anemia. Hypocapnia was produced by a single-step increase in both respiratory rate and tidal volume. Anemia was produced by simultaneous arteriotomy and infusion of either dog plasma or low-molecular-weight dextran. After a change in either P_{\text{a}CO_2} or Hb concentration, a 30- to 45-minute period was allowed for establishing steady values for arterial blood pressure, temperature, P_{\text{a}CO_2}, Hb concentration, and inspired halothane concentration. If either hyperventilation or hemodilution resulted in a mean arterial pressure of less than 70 mm Hg, the study was terminated; this was necessary during the final one or two steps in eight of the 20 dogs. The duration of each completed experiment was six to eight hours.

CMRO_2, cerebral glucose consumption rate (CMR glucose), and cerebrovascular resistance (CVR) were calculated in the usual manner. The oxygen–glucose index (OGI) was calculated in the manner described by Cohen and associates. The data were analyzed for statistical significance by Student’s t test for dependent (paired) data.
Results

In the group I dogs, hypocapnia, in the absence of anemia, was not associated with a change in the mean CMRO₂ (fig. 1, table 1). A random variation in CMRO₂ values of 6 per cent or less was observed. With additional moderate anemia, a reduction in CMRO₂ exceeding 10 per cent occurred in four of nine dogs, but the mean decrease for the group was not significant. In six dogs, when the hemoglobin level was reduced further (extreme anemia), a significant reduction in CMRO₂ was observed. Changes in CMR glucose were observed prior to the decrease in CMRO₂ (table 1). Hypocapnia alone produced a small but significant increase in the mean value for CMR glucose. This increase was not sufficient to decrease the mean OGI significantly. With the addition of moderate anemia, CMR glucose remained elevated and a further reduction in the OGI became significant. With extreme anemia, the reduction in CMRO₂ was associated with a further reduction in the OGI. These maneuvers significantly altered CBF and CVR (fig. 2, table 1). Hypocapnia alone produced a 33 per cent reduction in CBF due primarily to an increase in CVR. With hemodilution, a progressive decrease in CVR and an increase in CBF occurred. In the presence of extreme anemia, the CBF values in five of six dogs increased above the individual control values.

In the group II dogs, anemia in the absence of hypocapnia was not associated with an alteration in the mean CMRO₂ (fig. 3, table 2). With moderate anemia, the variation in individual CMRO₂ values in nine of the ten dogs was less than 5 per cent; and, with the production of extreme anemia, CMRO₂ remained essentially unchanged in seven of eight dogs. The addition of hypocapnia to extreme anemia in six dogs produced a consistent and significant decrease in the CMRO₂ similar to that observed in the group I dogs. Changes in CMR glucose were again observed prior to the decrease in CMRO₂ (table 2). In the presence of extreme anemia without hypocapnia, the mean CMR glucose was increased significantly and accounted for a significant decrease in the mean OGI. With the addition of hypocapnia, a further reduction in the OGI resulted from the reduction in the CMRO₂. As in the group I dogs, progressive hemodilution was accompanied by a progressive increase in the CBF (fig. 4, table 2), due primarily to a decreasing CVR. However, in these dogs, no change in the mean CVR occurred when PaCO₂ was reduced to hypocapnic levels. The slight decrease in CBF that occurred after hyperventilation in five of the six dogs was accounted for...
solely by a modest reduction in the mean arterial pressure.

In both groups of dogs, no significant change in buffer base occurred during the study, and the observed changes in pH were due primarily to changes in $\text{Pa}_2$ (tables 1 and 2). $\text{Pa}_2$ increased moderately after hyperventilation and was thereafter maintained at that level. In group I, a marked decrease in the $\text{Pa}_2$ of sagittal sinus blood ($\text{Fss}_2$) occurred after hyperventilation, and thereafter increased slightly with hemodilution. In group II, a progressive and moderate decrease in $\text{Pss}_2$ occurred with hemodilution, followed by a marked decrease with hyperventilation. Changes in the oxygen saturation of sagittal sinus blood ($\text{Sss}_2$) were appropriate for the changes in $\text{Fss}_2$ and $\text{PH}$ and were in agreement with the nomogram constructed by Rossing and Cain.2

The mean control values for all measured and calculated variables were similar in both groups of dogs. The combination of hypoapotnia and extreme anemia, no matter how achieved, produced remarkably similar changes in these values.
FIG. 4. Response of CBF to dilutional anemia followed by hypocapnia (group II, ten dogs). CBF increased in all dogs during progressive hemodilution. With hypocapnia, a moderate decrease occurred in two dogs; in the remaining four dogs, the decrease in CBF was minimal. In all but one dog (no. 4), CVR did not change, and the decrease in CBF was due to a decrease in arterial pressure only.

There was no significant difference between groups of dogs or among individual dogs throughout the studies in inspired halothane concentration, CSF pressure, and temperature. No systematic differences resulting from the different methods used for measuring the oxygen content of blood were apparent. Changes in the EEC produced by hypocapnia (increased amplitude, decreased frequency) were not significantly altered by the addition of anemia.

Discussion

These findings further clarify the potential effects of hypocapnia on cerebral metabolism and circulation. Contrary to the observations of Alexander and associates, no change in CMRO₂ (and, as a result, no significant change in the OGI) was seen in response to a reduction in PAO₂ alone. Such a response could be elicited only by the addition of dilutional anemia. Similarly, anemia in the absence of hypocapnia was not associated with a reduction in CMRO₂, but with the combination of extreme anemia and profound hypocapnia, a reduction occurred in all dogs. The discrepancy between these observations and those of Alexander and associates might be explained by differences in methodology or species. It is also possible that the cerebrovascular response to hypocapnia in the presence of halothane anesthesia (this study) differs in degree from that which occurs in the presence of thiopental and nitrous oxide anesthesia. However, the validity of their conclusions also may be questioned, since the mean decrease in CMRO₂ they observed was small (10 per cent), significant only at the 0.05 level.

The alterations in cerebral carbohydrate metabolism that were observed in response to hypocapnia are similar to those reported by Alexander and associates. In group I dogs, hypocapnia alone produced a significant increase in the CMR glucose, although not sufficient to decrease the OGI significantly. With the addition of anemia, a reduction in the OGI was observed prior to a significant reduction in CMR glucose. The possibility that these effects were secondary only to changes in the pH and PAO₂ cannot be excluded. However,
in the group II dogs, an increase in the CMR glucose and decrease in the OGI were observed in the absence of change in pH or \( \text{Pa}_{\text{CO}_2} \). When these dogs were hyperventilated, no further increase in CMR glucose occurred despite the production of profound alkalis.

In both groups of dogs, the observed alterations in carbohydrate metabolism were quantitatively similar. These combined observations suggest that in all dogs the increase in CMR glucose and the decrease in the OGI were secondary to cerebral hypoxia. Furthermore, as previously observed by Alexander and associates,\(^2\) these changes were an early indication of cerebral hypoxia and occurred prior to a significant reduction in \( \text{CMR}_{\text{O}_2} \).

Blood lactate and pyruvate concentrations were not measured in this study. Previous efforts to obtain meaningful information about cerebral lactate metabolism from blood analysis have been disappointing.\(^3\) Investigations by others\(^4\) have demonstrated potentially-large differences in the concentrations of lactate and pyruvate in brain, CSF, and the blood draining the brain. This is presumably accounted for by the blood-brain and blood-CSF barriers, which prevent free passage of these molecules. Equilibration between these compartments probably occurs only during prolonged steady-state conditions. Such conditions cannot be achieved in an acute experiment requiring exaggerated changes in \( \text{Pa}_{\text{O}_2} \) and CBF. These considerations are of less significance as regards glucose, which moves with relative freedom across the blood-brain barrier.\(^5\)

The effects of hypocapnia on CVR and CBF were strikingly different in the two groups of dogs. In hyperventilated before hemo-
dilution, a 33 per cent decrease in CBF occurred in response to a 39 per cent increase in CVR and a modest decrease in arterial pressure. These changes are the expected response to a reduction in \( \text{Pa}_ {\text{CO}_2} \). With subsequent hemo-
dilution, a progressive decrease in CVR and increase in CBF was observed. This cannot be accounted for solely by vasodilatation since blood viscosity was decreasing progressively. In the second group of dogs, hemo-
dilution at a normal \( \text{Pa}_ {\text{CO}_2} \) produced quantitatively similar changes in CVR and CBF. In these dogs, a subsequent reduction in \( \text{Pa}_ {\text{CO}_2} \) from 40 to 10 mm Hg did not increase CVR. Thus, in the presence of extreme anemia, the cerebrovascular bed was presumably maximally dilated and unresponsive to change in \( \text{Pa}_ {\text{CO}_2} \). Others have demonstrated a similar lack of response to CO\(_2\) in the presence of severe hypotension\(^6\) or low arterial oxygen tensions\(^7\) and have accordingly postulated "threshold" or "critical" levels for arterial pressure and \( \text{Pa}_ {\text{O}_2} \). The present study supports the concept of a "threshold" concentration of hemoglobin. It is probable that the attainment of these various threshold levels can be accounted for by a single mechanism which is triggered by a progressive restriction in the amount of oxygen delivered to the brain. Severinghaus and Lassen\(^8\) postulated that the pH of the extracellular fluid of arteriolar smooth muscle is the ultimate mechanism controlling CBF. According to this hypothesis, cerebral hypoxia, no matter how produced, ultimately will reduce the pH of the arteriolar extracellular fluid; this, in turn, will cause vasodilatation.

Although CBF was well maintained in the presence of hypocapnia and extreme anemia, a reduction in \( \text{CMR}_{\text{O}_2} \) did occur. The observations indicate that this reduction was primarily due to a reduction in \( \text{O}_2 \) extracted from the blood secondary to the shift in the \( \text{O}_2-\text{Hb} \) dissociation curve (Bohr effect) resulting from the alkalisosis produced by hyper-
ventilation. This was most clearly demonstrated in the group II dogs. In these dogs, extreme anemia at normocapnia did not alter \( \text{CMR}_{\text{O}_2} \) but, with the addition of hypocapnia, \( \text{CMR}_{\text{O}_2} \) was reduced 12 per cent. This occurred despite the fact that the amounts of \( \text{O}_2 \) delivered to the brain during both normocapnia and hypocapnia were virtually unchanged (8.9 and 8.6 ml/100 gm/min, respectively). However, during hypocapnia, the \( \text{O}_2 \) bound by hemoglobin (\( \text{SSo}_2 \)) increased 5 per cent despite a 10-mm decrease in \( \text{PSS}_2 \). This "shift to the left" of \( \text{O}_2-\text{Hb} \) dissociation was apparently sufficient to limit \( \text{O}_2 \) extraction and to result in a reduction in the C(a-ss)\(_{\text{O}_2} \). Under these circumstances, the amount of \( \text{O}_2 \) extracted from the hemoglobin could have been maintained at the normocapnic levels.
only by a further reduction in the PsO₂. However, such a mechanism was not available, since the critical PsO₂ value for these circumstances already had been achieved, as evidenced by the observed reduction in CMR O₂.

A single critical value for cerebral venous PO₂ was not established in this study. The lowest mean PsO₂ achieved was 17 mm Hg, identical to that observed by Alexander and associates in man. This possibly represents the minimal PO₂ adequate to provide a sufficient gradient for oxygen extraction from cerebral tissue. However, this does not mean that a PO₂ of more than 17 mm Hg is, in all circumstances, adequate. The PsO₂ values of dogs stressed to the point of a reduction in CMR O₂ were always more than 17 mm Hg, and averaged 20 to 21 mm Hg. Thus, the "critical" cerebral venous PO₂ is not a fixed value; rather, it must depend on the interrelationship of several factors, including pH, CBF, CMR O₂, and hemoglobin concentration. In addition, Lawson and Forster have demonstrated an effect of hemoglobin concentration and pH on the PO₂ gradient between plasma and erythrocytes. This gradient, normally considered to be negligible, may increase to 1.5 mm Hg in the presence of anemia and alkalosis. Such an increase, although small, may have affected the critical PO₂ value in this study.

References