Effect of CO₂ on cerebrovascular autoregulation in hyperthermic dogs

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Cerebral blood flow (CBF) response to arterial blood CO₂ tension (PACO₂) was increased during hyperthermia (Am. J. Physiol. 223: 1041-1043, 1972). Cerebrovascular control during hyperthermia was further explored in the present study by examining the effect of mean arterial pressure (MAP) on CBF at different PACO₂. CBF was determined in dogs by a ¹³³Xe-desaturation technique at MAPs of 50, 80, and 110 mmHg with PACO₂ values of approximately 20, 40, and 57 torr, respectively. Responses at body temperatures (Tₜᵣₑ) of 37.5 and 41.5°C were compared. As expected, increased PACO₂ increased CBF. MAP did not significantly affect CBF at low PACO₂. At the highest PACO₂, the CBF response to MAP was increased at Tₜᵣₑ 41.5 compared to 37.5°C. CBF sensitivity (ΔCBF/ΔPACO₂) during hyperthermia was affected by MAP.

AT NORMAL BODY TEMPERATURE (Tₙ) hypocapnia caused a decrease in cerebral blood flow (CBF) (11). During hyperthermia, however, CBF did not change despite a decreased PACO₂ (14). An increased CO₂ sensitivity, i.e., ΔCBF/ΔPACO₂, was reported for dogs at a Tₜᵣₑ of 41.7°C (3). Whether the altered CO₂ sensitivity represented a loss of CBF autoregulation or a change in the responsivity of the control mechanisms was not clear. CBF autoregulation has been demonstrated at normal Tₜᵣₑ during normo- and hypocapnia (8). There have been no reports on the response to elevated Tₜᵣₑ when PACO₂ is normally decreased by thermal polypnea. As one approach to understanding the mechanism of the hyperthermic response we examined CBF autoregulation at high Tₜᵣₑ. Specifically, our study was undertaken to characterize the CBF-arterial blood pressure response during hyperthermia and to determine if there was any alteration in the effect of PACO₂ on the response.

METHODS

Two groups of dogs were used for CBF determinations. Mongrels weighing 10 to 25 kg were used in studies in which PACO₂ was maintained hypocapnic. Purebred beagles, weighing 10 to 15 kg, were used for hyper- and hypocapnic studies. All animals were pretreated with 0.6 mg/kg of acetylpromazine maleate (Ayerst Laboratories) 1 h before sodium pentobarbital (30 mg/kg, i.v.) anesthesia. A metal cannula was placed in the trachea and polyethylene cannulas were placed in the a) right femoral vein, b) abdominal aorta (via the right femoral artery), and c) carotid artery (via the cranial thyroid artery). To minimize extracerebral isotope contamination during CBF determinations, the cranial musculature (m. temporalis) was resected. All animals were heparinized.

For the purpose of comparing temperatures at different locations in the body, calibrated thermistors were placed a) 10–15 cm into the rectum, b) 20 cm down the esophagus, c) 5 cm below the bifurcation of the common carotid artery, and d) into the deltoideus muscle of three mongrel dogs.

After surgical preparation the dogs were placed in a small, controlled-temperature chamber in order to regulate Tₜᵣₑ. Temperature was monitored using calibrated thermistors and a Yellow Springs Instrument Co. Thermistor and telethermometer. For temperature distribution studies, the dog's Tₜᵣₑ's were maintained constant at 37.5 (normothermic) and 41.5°C (hyperthermic) for 2 h, during which time temperatures were monitored at 30-min intervals. The dogs were hyperventilated using a Harvard Apparatus Co. respirator (model 606), which was set at a frequency of 30 breaths/min with a tidal volume of 1.7 times the value determined from a nomogram of tidal volume vs. body weight and rate. The nomogram was prepared by Kleinman and Radford and was obtained from the Harvard Apparatus Co.). PACO₂ was controlled in the dog by administration of gas mixtures of 0, 4, or 7% CO₂ in 21% O₂ and the balance N₂. This procedure produced hypocapnia, normocapnia, or hypercapnia, respectively.

Mean arterial blood pressure (MAP) was measured in the abdominal aorta cannula. The cannula was also used to collect arterial blood samples. Blood samples were collected anaerobically in 1-ml tuberculin syringes and analyzed immediately. Analyses of PACO₂, PAO₂, and arterial pH (pHₐ) were made at temperatures equivalent to the Tₜᵣₑ of the dog, using a Instrumentation Laboratory model 127 constant-temperature bath and appropriate electrodes.

Cerebral blood flow was calculated from the rate of brain clearance of an intra-arterial injection of xenon-133 (2, 17). Approximately 1 mCi of ¹³³Xe (Amersham/Searle Corp.) dissolved in 0.1 ml of saline was rapidly injected
into the carotid artery cannula and washed in with approximately 0.4 ml of saline. Collimated (1 inch diam) sodium iodide-scintillation crystals (2 inch x 1 inch) placed on either side of the head were used to monitor cerebral radioactivity. Radioactivity was measured at 1-s intervals for the first 20 s; 10-s intervals were used for the next 9 min 40 s of each CBF determination. Resolution of the washout curve and stochastic calculation of mean CBF was carried out using the program of deValois et al (6) modified to operate on an IBM 360 computer.

Cerebral blood flow was determined at MAP levels of 50, 70, 90, and 110 mmHg in mongrel dogs which were maintained normocapnic. In purebred dogs, CBF at three MAP levels (50, 80, 110 mmHg) was determined during hypo- or hypercapnia. The order of MAP levels was randomized for each dog at normal Tm and during hyperthermia. A given MAP level was obtained by either slowly removing or reinfusing blood via the femoral vein cannula. MAP was maintained constant for at least 10 min prior to any CBF determination. In this study autoregulation was considered to be present when mean CBF did not change significantly with changes in MAP between 50 and 110 mmHg at a constant Paco2.

Analysis of variance for the data was determined using the ANOVAR program and the IBM 360 computer of the Rutgers University Center for Computer and Information Services. For purposes of comparison of these data, a P value of ≤0.05 was considered significant and least-significant differences (LSD) were calculated at a 95% confidence interval by the formula: LSD = (mean sum of squares/n) X 2 X 2.571. The coefficient of variation (CV) was calculated to compare the responses of mongrel and pure-bred dogs by the formula: CV = variance of all data/mean of all data.

RESULTS

During a steady-state thermal condition that lasted 2 h or longer, Tm and carotid blood temperature measured simultaneously were within 0.1°C of each other at both 37.5 and 41.5°C. During the transient elevation of Tm from 37.5 to 41.5°C, carotid blood temperature was as great as 0.4°C higher. Esophageal temperature was consistently lower than Tm and varied as much as 1.3°C from Tm. Muscle temperature reflected the state of the environmental chamber, i.e., during exothermic heating, muscle temperature was consistently higher than Tm but could not be correlated with Tm in our study.

In the normocapnic mongrel dogs PaCO2 averaged 39 mmHg at 37.5 and 41 mmHg at 41.5°C and was not significantly affected by the MAP conditions. PaCO2 was not significantly different for the normothermic and hyperthermic animals. The hyperthermic dogs did have a significantly lower pHa than the normothermic ones (Table 1). Mean CBF in a group of six dogs in which complete sets of data at MAPs of 50, 70, 90, and 110 mmHg were obtained was 34.7 and 50.5 ml/100 g per min for normothermia and hyperthermia, respectively. Analysis of variance of those data showed no significant effect of Tm or MAP. It was noteworthy that variability of response was high in this group (CV = 29.8%). The level of variability for the purebred animals was less than half that found in the mongrel group, viz., CV = 13.5%.

In hypocapnic purebred dogs, average PaCO2 was 93 mmHg and was not significantly different at different MAP and Tm conditions (Table 1). PaCO2 was over 100 mmHg and the animals were alkalotic. Mean CBF was 28.6 ml/100 g per min over the MAP range from 50 to 110 mmHg at normothermia and 32.6 ml/100 g per min at hyperthermia. There was no significant effect of MAP on CBF at either Tm, i.e., autoregulation was present during hypocapnia (see Fig. 1). Least significant difference for the hypocapnic CBF data was 6.6 ml/100 g per min.

In the hypercapnic studies on purebred dogs, average PaCO2 was 56 mmHg at normothermia and averaged 2 mmHg greater in the dogs during hyperthermia (see Table 1). There was no significant difference in the PaCO2 or pHa values with Tm. An analysis of variance for CBF as effected by PaCO2, MAP, and Tm in the purebred dogs showed that CBF was effected significantly by MAP during hypercapnia, i.e., the dogs did not autoregulate CBF (see Fig. 1). In addition, the CBF response to MAP was increased by increased Tm, during hypercapnia. For example, mean CBF at MAP of 50 mmHg was 49.2 and 44.7 ml/100 g per min at normothermia and hyperthermia, respectively. It was 66.2 and 87.3 ml/100 g per min at an MAP of 110 mmHg for normothermia and hyperthermia, respectively. The least significant difference for the hypercapnic CBF data was 10.7 ml/100 g/min.

Calculated cerebral vascular resistance (CVR = MAP/PCBF)
CBF) for hypocapnia and hypercapnia experiments was used to indicate the response of the cerebral vasculature. There was a significant MAP effect on resistance, i.e., CVR increased with increasing MAP. The combination of low MAP and high PaCO₂ gave the greatest vasodilatory effect (lowest CVR). There appeared to be a minimum CVR value close to 1.0 for our study. At all three MAP levels CVR was significantly less with hypercapnia (Table 2).

**DISCUSSION**

Our results showed a close correspondence between Tₑₐ and carotid blood temperature during a steady state, this validated the use of Tₑₐ as a measure of heat content since it could be related to average cerebral tissue temperature in this study. We did not wish to interfere with the cerebral blood supply nor did we wish to damage and possibly disrupt cerebral tissue during our CBF measurements. Cerebral tissue temperature has been reported to vary with location and local metabolic activity (4, 10). For this reason single local measurements would not estimate average cerebral tissue heat content. The argument that the rete system found in the dog could cause disparity between carotid blood and cerebral artery blood temperature (1, 13) would not apply in our study. The tracheal cannula, used for ventilating the animal, bypassed the nasopharyngeal area so that respiration did not serve to cool the rete blood as is normally the case. In addition, respiration was controlled and constant through the experiment.

When the data were presented in a form that combined the effects of PaCO₂, MAP, and the regulation of CBF, their interdependence was more easily recognized (Fig. 2). At an MAP of 50 mmHg, CVR appeared to be approaching a minimum limit close to 1.0 unit peripheral resistance (PRU). The CO₂ effect between 58 and 20 mmHg was an increase in CVR of approximately 70% above the CVR value at 58 mmHg. That observation would suggest a relatively limited ability to adjust to hypocapnia when the vessels approach maximum vasodilation. At an MAP of 110 mmHg CVR was well above the minimum found at 50 mmHg and the CO₂ effect on CVR was a change of approximately 140%. A similar response was found during hyperthermia. In order to determine if our interpretation of the interplay between MAP and CO₂ was consistent with the data obtained by others we extrapolated data from a report by Paulson (16) on dogs at normal Tₑₐ (his Fig. 3) and used them to calculate CVR during hypotocapnia. Paulson's data also demonstrated a decreased ability to adjust CVR at an MAP of 50 mmHg.

The CO₂ effect on CVR in his data was 110% at an MAP of 50 mmHg compared to 250% at 110 mmHg.

Cerebrovascular autoregulation was demonstrated in normo- and hypocapnia at both thermal conditions. It was not found at either Tₑₐ during hypercapnia, although CBF responded more to MAP during hyperthermia. Comparison of the PaCO₂, effects at an MAP of 50 and 110 mmHg demonstrated the Tₑₐ effect more clearly (Fig. 3). Increased CO₂ sensitivity (ACBF/APaCO₂) was demonstrated at 110 mmHg, similar to the response reported previously (3). Demers et al. (5) reported a shift in the CBF-PaCO₂ line to the left but no change in the CO₂ sensitivity (slope) during hyperthermia. In our study at MAP of 50 and 80 mmHg a change from hypocapnia to hypercapnia changed CBF approximately the same amount whether the dogs were normo- or hyperthermic, i.e., CO₂ sensitivity remained approximately constant. The PaCO₂-CBF effect during hyperthermia, therefore, was MAP dependent. An MAP greater than 80 mmHg was required to demonstrate the change in CO₂ sensitivity. Demer's group did not report MAP levels in their dogs.

The mechanism for cerebral autoregulation is not clear. Several hypotheses have been suggested to explain the phenomenon, among them are metabolic, mechanical and myogenic mechanisms (2). The observation that the pressure response was still sensitive during hypercapnia at normothermia, i.e., some adjustment did occur (CVR 1.1 at 50 and 1.7 at 110 mmHg) and that the sensitivity was removed during hyperthermia could be used to argue that a metabolic mechanism, increased by increased term-

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**TABLE 2. Mean cerebrovascular resistance in hypo- and hypercapnic dogs as affected by Tₑₐ and MAP**

<table>
<thead>
<tr>
<th>MAP, mmHg</th>
<th>50</th>
<th>80</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tₑₐ, °C</td>
<td>37</td>
<td>41.5</td>
<td>37</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1.9</td>
<td>1.7</td>
<td>2.7</td>
</tr>
<tr>
<td>58</td>
<td>1.1</td>
<td>1.2</td>
<td>1.4</td>
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CEREBROVASCULAR AUTOREGULATION IN HYPERThERMA

Temperature, was a primary contributor to autoregulation. At high metabolic rates or with the accumulation of metabolites, e.g., CO₂, complete relaxation of cerebrovascular smooth muscle occurred and the autoregulatory response was blocked. If it were a mechanical response, blocking as a result of a thermal effect would not normally be expected. If the response was simply myogenic, some type of vascular adjustment should also have occurred at the higher temperature level as it did at normal Tₑ. Increased temperature has been reported to result in dilation of cutaneous veins in vivo (20) and in vitro (19). Maximal cerebrovascular dilation at the worst condition, during hypercapnia and hyperthermia, could conceal any responsiveness to MAP so that a myogenic response was not ruled out. Test.

REFERENCES


