Respiratory Influence on the Total and Regional Cerebral Blood Flow Responses to Intracranial Hypertension

ASRAR B. MALIK, PH.D., JOHN A. KRASNEY, PH.D., AND GEORGE J. ROYCE, PH.D.

SUMMARY The effect of respiration on the cerebrovascular response to elevated intracranial pressure (ICP) was studied in anesthetized dogs. Total and regional cerebral blood flows were measured using labelled microspheres. In spontaneously breathing dogs total and regional cerebral blood flows increased when cerebral blood flow pressure was reduced to 20 mm Hg. The increase in cerebral blood flow during elevated ICP in spontaneously breathing dogs is secondary to the development of hypoxemia and respiratory acidosis since cerebral vessels retain reactivity to carbon dioxide during cerebral vaso- dilatation and reduced blood flow. Therefore, the potential exists for the alteration in the cerebrovascular response to elevated ICP due to the development of hypoxemia and respiratory acidosis. The purpose of the study was to determine the role of brain blood and pH alterations occurring during elevated ICP in spontaneously breathing dogs on the total and regional cerebrovascular response to elevated ICP.

Methods

Fifteen mongrel dogs (mean weight 11.2 ± 1.5 kg) were anesthetized with 30 mg/kg sodium pentobarbital and intubated. Teflon catheters were positioned in a femoral artery.
and in the left ventricle via the other femoral artery under fluoroscopic guidance. The arterial pressure catheter was connected to a Statham P23Db pressure transducer for pressure measurements. Intracranial pressure (ICP) was elevated by infusing saline subdurally via a brass plug inserted into a trephine hole in the left parietal bone. The infusion was from a pressure bottle connected to a Statham P23AC pressure transducer. ICP was elevated to 20 mm Hg below the mean arterial pressure rapidly within 5 to 10 seconds. In each case, ICP was regulated at 20 mm Hg below the mean arterial pressure manually by varying the ICP with changes in the arterial pressure.

Cardiac output was measured using the dye dilution technique, with indocyanine green dye injected into the left ventricle and sampled in the femoral artery. A Giford cuvette-densitometer was used to monitor the concentration of the dye in-the blood. All dye curves were recorded in triplicate. Air flow, measured using a pneumotachometer, was integrated to give tidal volume measurements. Pressures, tidal volumes, and dye curves were recorded on a PR-7 Electronics for Medicine recorder. Systemic vascular resistance was calculated as the ratio of mean arterial pressure to cardiac output.

Arterial oxygen tension (PaO₂), carbon dioxide tension (PaCO₂) and pH were recorded using a Radiometer BMS-3 blood gas and pH analyzer. The blood gas values were corrected for body temperature recorded by a rectal thermometer.

Regional cerebral blood flow was measured with labelled microspheres (15 ± 5 μm in diameter) using the reference sample method.5* * Tween 89 was added to the microsphere suspension, and the spheres were dispersed in a sonicator for 30 minutes prior to injection. The 15 ± 5 μm diameter microspheres were injected in the left ventricle over a 40 second period and a reference blood sample simultaneously withdrawn from the femoral arterial catheter using a Harvard withdrawal pump. Approximately 3.5 × 10⁶ spheres of each type were injected. The spheres did not alter the blood pressure, cardiac output, blood gases and pH. A sufficient number of spheres were present in each tissue sample to meet the criteria for measurement of blood flow using this technique.5 The microsphere injections were made during the control period and during elevated ICP when a circulatory steady state had been attained. The spheres were labelled with ⁵¹Sr, ¹⁸¹Ce, or ⁶⁷Cr. The counts for each isotope were obtained by separating the three activities by gamma pulse height analysis.8 At the end of the experiment the dogs were killed with KCl injection, and the brain removed. The intact brain was steeped in 10% formalin for 5 to 7 days. The left and right hemispheres were then cut into discrete areas using a dissecting microscope.9 Each hemisphere was cut into the following areas: gyrus lateralis, motor cortex, gyrus frontal, gray matter of ectolateral gyrus, white matter of ectolateral gyrus, posterior sylvian gyms, anterior sylvian gyrus, pyriform cortex, olfactory bulb, olfactory tract, corpus callosum, caudate nucleus, the rest of telencephalon, thalamus, hypothalamus, the rest of mesencephalon, cerebellum, pons, upper medulla, lower medulla, and cervical spinal cord. Each section from both hemispheres was weighed and activities counted on a Nuclear-Chicago gamma well counter. Cerebral vascular resistance was determined as the ratio of arterial pressure to total cerebral blood flow.

Studies were carried out in three groups: Group I (n = 5) Elevation in ICP to 20 mm Hg below the mean arterial pressure in spontaneously breathing dogs. The cerebral perfusion pressure (CPP) was regulated at 20 mm Hg until a steady arterial pressure was attained, usually within 10 minutes. Cerebral blood flow, blood pressure, blood gas, pH, respiratory rate and tidal volume measurements were taken during the control period, and at 10 min of intracranial hypertension. Group II: (n = 5) The ICP was increased and CPP was also regulated at 20 mm Hg. The dogs were artificially ventilated at their resting tidal volumes and respiratory rates, using a Harvard respirator to maintain blood gases and pH in the normal range. Measurements were taken during the control period, and at 10 minutes of intracranial hypertension. Group III: (n = 5) Dogs were also artificially ventilated but breathed 5% CO₂/room air mixture while ICP was elevated. Measurements were taken during the control period, at 10 min of elevated ICP, and at 15 min of continued elevation in ICP while breathing 5% CO₂.

The ICP was maintained manually at a constant level 20 mm Hg below the mean arterial pressure in the three groups. Intracranial pressure in each case was regulated by altering ICP as arterial pressure changed so as to maintain CPP at 20 mm Hg.

The significance of changes from control levels was tested using the paired t-test, and significance between mean values was tested using the Student's t-test.

Results

The cerebral perfusion pressure (CPP) was regulated at 20 mm Hg during elevation in intracranial pressure (ICP) in the 3 groups: Group 1, spontaneously breathing; Group II, artificially ventilated; and Group III, artificially ventilated dogs breathing 5% CO₂/room air mixture.

The blood gas and pH values in the 3 groups are shown in table 1. The spontaneously breathing dogs became hypoxic, PaO₂ decreasing from 73.7 ± 2.3 to 57.2 ± 1.0 mm Hg, and developed respiratory acidosis, PaCO₂ increasing from 31.5 ± 2.1 to 44.9 ± 1.9 mm Hg and pH decreasing from 7.34 ± 0.32 to 7.26 ± 0.021. These changes were associated with a decrease in tidal volume from 278 ± 15 to 185 ± 12 ml (BTPS) (p < 0.05) and in respiratory rate 17 ± 2 to 11.3 breaths/min (p < 0.05). The blood gases and pH were maintained at control levels in the artificially ventilated groups while breathing room air (table 1).

The arterial pressure increased from 122 ± 3 to 145 ± 2 mm Hg (p < 0.05) in spontaneously breathing dogs and from 125 ± 3 to 153 ± 2 mm Hg (p < 0.05) in the artificially ventilated dogs in Group II during elevated ICP. The increase in arterial pressure in spontaneously breathing group was significantly greater (p < 0.05). Breathing 5% CO₂ during elevated ICP resulted in a fall in aortic pressure from 132 ± 3 mm Hg during elevated ICP to 127 ± 3 mm Hg (p < 0.05) in the artificially ventilated dogs (Group III). Cardiac output decreased slightly in spontaneously breathing dogs from 2.23 ± 0.15 to 2.17 ± 0.15 l/min. The decrease in cardiac output from control of 2.54 ± 0.22 to 2.00 ± 0.1
TABLE 1 Effects of Elevated Intracranial Pressure (Cerebral Perfusion Pressure = 80 mm Hg) in Spontaneously Ventilating Dogs and Controlled Ventilated Dogs. Mean Values ± 1 SEM are Shown

<table>
<thead>
<tr>
<th></th>
<th>Spontaneously Breathing</th>
<th>Controlled Ventilated</th>
<th>Controlled Ventilated</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PaO2</td>
<td>Paco2</td>
<td>pH</td>
</tr>
<tr>
<td>Control</td>
<td>73.7</td>
<td>31.5</td>
<td>7.34</td>
</tr>
<tr>
<td>CPP = 20</td>
<td>± 2.3</td>
<td>± 2.1</td>
<td>± 0.032</td>
</tr>
<tr>
<td>mm Hg (10 min)</td>
<td>± 1.9</td>
<td>± 1.9</td>
<td>± 0.021</td>
</tr>
<tr>
<td>CO2 (15 min)</td>
<td>57.2</td>
<td>44.9</td>
<td>7.26</td>
</tr>
</tbody>
</table>

1/min during elevated ICP was greater (p < 0.01) in artificially ventilated dogs. Hypercapnia during elevated ICP resulted in increase (p < 0.01) in cardiac output from 1.80 ± 0.058 1/min during elevated ICP to 2.20 ± 0.40 1/min during 5% CO2 breathing while ICP continued to be elevated. Systemic vascular resistance increased from 54.7 ± 3.4 to 66.8 ± 4.5 mm Hg/1/min in the spontaneously breathing group (p < 0.01) and from 49.2 ± 3.5 to 65.0 ± 2.2 mm Hg/1/min in artificially ventilated group (p < 0.01). The systemic vascular resistance decreased from 73.3 ± 4.2 mm Hg/1/min during elevated ICP to 57.7 ± 2.4 mm Hg/1/min during breathing 5% CO2 while ICP continued to be elevated (p < 0.01).

The regional cerebral blood flows (rCBF) during the control period in the spontaneously breathing dogs are shown in figure 1. The control values in spontaneously breathing dogs were not different from control values in the artificially ventilated dogs. The rCBF values obtained in the right and the left cerebral hemispheres were also not significantly different (fig.1). The rCBF values during elevated ICP in spontaneously breathing dogs are shown in figure 2 and the values during elevated ICP in the artificially ventilated dogs are shown in figure 3. The effects of breathing 5% CO2 in room air mixture on rCBF during elevated ICP are also shown in figure 3. The rCBF values increased during elevated ICP in spontaneously breathing dogs, and decreased in the artificially ventilated group. The observed decrease in rCBF in the artificially ventilated dogs during elevated ICP was reversed when the dogs were ventilated with 5% CO2 while ICP continued to be elevated (fig. 3). The control cerebral vascular resistance averaged 3.13 ± .14 mm Hg/ml/min/100g. The resistance decreased (p < 0.001) to 0.23 ± .090 mm Hg/ml/min/100g in spontaneously breathing dogs during elevated ICP. The decrease in resistance to 1.05 ± .15 mm Hg/ml/min/100g in artificially ventilated dogs during elevated ICP was significantly smaller (p < 0.05). The resistance decreased further (p < 0.001) to .20 ± .081 mm Hg/ml/min/100g in artificially ventilated dogs breathing 5% CO2 during elevated ICP.

The percent changes in total and regional cerebral flows from control levels in the different groups are summarized in figures 4 and 5. The increases in regional flows from control levels during elevated ICP were not significantly different in the regions of the supratentorial compartment (averaging 75 ± 5%) in the spontaneously breathing dogs (fig. 4). The increases in flow were similar in both right and left hemispheres (fig. 4). However, the percent increases in regional flows during elevated ICP in spontaneously breathing dogs in the intratentorial compartment, cerebellum, pons, upper and lower medulla, and cervical spinal cord, were significantly greater (p < 0.05) (averaging 160 ± 8%) (fig. 5). The decreases in regional flows in the artificially ventilated group averaged 58 ± 4% from control levels in the supratentorial compartment (fig. 4). The decreases in flows in the cerebellum, pons, upper and lower medulla, and cervical spinal cord averaged 31 ± 3% from...
Figure 2. Regional and total cerebral blood flow values in right and left hemispheres in spontaneously breathing dogs during elevation in intracranial pressure (cerebral perfusion pressure = 20 mm Hg). Mean values ± 1 SEM.

Figure 3. Regional and total cerebral blood flow values in right and left hemispheres in controlled ventilated dogs during elevation in intracranial pressure (cerebral perfusion pressure = 20 mm Hg) (lower bars). Also shows effects of breathing 5% CO₂ mixture in increasing cerebral blood flow at cerebral perfusion pressure of 20 mm Hg (upper bars) in the same controlled ventilated dogs. Mean values ± 1 SEM.
The reference sample method using labelled microspheres has been employed in animals to measure regional cerebral blood flows. The technique requires adequate mixing of the microspheres prior to their impaction in peripheral vessels. Microspheres have no untoward effects on the flows being measured and there is no significant recirculation of spheres. In the present study, the spheres were injected into the left ventricle and adequate mixing was evident by the finding that flows to the two hemispheres were not significantly different. Cerebral blood flow measured during the control period was in the range reported using the inert gas elimination method and labelled microspheres in anesthetized animals. There were no alterations in cardiac output, arterial pressure, blood gas and pH during or after injection of the spheres. Less than 2% of the 15 μm diameter microspheres injected in the left heart are recovered from sagittal sinus blood. Larger spheres reduce the recirculation, but decrease the ability to resolve flows to discrete areas. Activities above the background activity were not observed in samples of jugular venous blood during the control period and the elevation in intracranial pressure. These results are consistent with studies using 15 ± 5 μm spheres. Regional blood flows measured with the microspheres did not differ significantly in the same area of both hemispheres; however, regional variations in flows were noted as reported previously using other techniques. Flows were significantly greater in areas such as the hypophysis, motor cortex, gyrus frontalis, gray matter of the ectolateral gyrus, olfactory bulb, caudate nucleus, and cerebellum than in the other areas examined.

In the present study we determined the role of blood gas and pH alterations occurring in spontaneously breathing animals during an acute increase in intracranial pressure. The aim was to determine the cerebrovascular response to elevated pressure. The total and regional cerebral blood flows increased in the spontaneously breathing dogs when cerebral perfusion pressure (the mean arterial-intracranial pressure gradient) is reduced to 20 mm Hg. The increase in the flows was associated with hyperventilation, and the development of hypoxemia and respiratory acidosis. However, in dogs in which blood gases and pH were regulated at resting levels by artificial ventilation, a similar decrease in cerebral perfusion pressure resulted in decrease in the total and regional cerebral blood flows. The findings in the artificially ventilated dogs are consistent with observations that cerebral blood flow is decreased when cerebral perfusion pressure falls below the range of 40 to 70 mm Hg, however, a decrease in cerebral blood flow has been
an equivocal finding during elevated intracranial pressure. The variability in results was attributed to differences in the level of intracranial pressure, rate of pressure development, method of production of intracranial hypertension, and degree of associated arterial hypertension. In the present study, the changes in these variables were not significantly different in the three experimental groups. The rates of rise in intracranial pressure were similar, and the intracranial pressure was elevated to 20 mm Hg below the mean arterial pressure and regulated at this level.

It has been suggested that blood gas and pH changes affect the cerebrovascular response to elevated intracranial pressure since cerebral vessels retain their reactivity to carbon dioxide during autoregulatory vasodilation. We tested the hypothesis that the increase in cerebral blood flow during intracranial hypertension in spontaneously breathing dogs was due to the associated blood gas and pH alterations. This was done by ventilating the dogs with 5% CO2 in room air mixture during the elevated intracranial pressure when cerebral blood flow was decreased. Hypercapnia resulted in increased total and regional cerebral flows to above control levels at a time when the cerebral perfusion pressure was held constant at 20 mm Hg. The increases in total and regional cerebral blood flows while breathing 5% CO2 at reduced cerebral perfusion pressure were comparable to the increases observed during similar increase in PacO2 at normal cerebral perfusion pressure. These findings suggest that the increases in cerebral blood flow in spontaneously breathing dogs during decrease in cerebral perfusion pressure are due to the concomitant blood gas and pH alterations. Thus, the blood gas and pH alterations in spontaneous breathing dogs may be a mechanism which serves to maintain cerebral flow during elevated ICP. The reduction in cerebral blood flow in the artificially ventilated dogs occurs because the autoregulatory vasodilation was not sufficient to compensate for the decrease in perfusion pressure. In spontaneously breathing dogs, the development of respiratory acidosis and hypoxemia resulted in further dilation during elevated ICP, which was sufficient to compensate for the markedly reduced cerebral perfusion pressure.

The changes in cerebral blood flow are passively dependent on the cerebral perfusion pressure at a perfusion pressure of 20 mm Hg. In the present study, the cerebral perfusion pressure was regulated at 20 mm Hg by altering the intracranial pressure with changes in arterial pressure. Therefore, the changes in regional cerebral blood flows were not due to the variations in arterial pressure induced by elevated intracranial pressure and the resulting alterations in cerebral perfusion pressure. The influence of high PacO2 on the cerebral vessels at reduced cerebral perfusion pressure suggests that the cerebral vessels are capable of further dilation in spite of the extreme reduction in perfusion pressure with presumably exhausted autoregulatory vasodilation. These results are consistent with the findings of Ekstrom-Jodal et al., Haggendahl et al. and Zwetnow. In cases of cerebral infarction and autonomic nervous system impairment (Shy-Drager syndrome) the loss of cerebral autoregulation following a decrease in arterial blood pressure, with preservation of the responsiveness of cerebral vessels to variations in PacO2 ("partial vasoparalysis"), has also been demonstrated (Feischi et al., Lassen and Paulson, and Gotof et al.).

The present findings indicate that there are significant regional perfusion variations during elevated intracranial pressure. The decreases in the regional flows in the artificially ventilated group during elevated intracranial pressure were significantly greater in the supratentorial areas than in the cerebellum, pons, upper and lower medulla, and cervical spinal cord. Similarly, the increases in flows in the infratentorial areas were greater in the spontaneously breathing dogs during elevated intracranial pressure, and in the artificially ventilated dogs breathing 5% CO2 during elevated intracranial pressure. The findings support the contention that there are intracranial pressure gradients during intracranial hypertension, such as across the tentorium cerebelli between supratentorial and infratentorial compartments. The pressure gradients may be responsible for the non-uniform regional cerebrovascular response to elevated intracranial pressure.

In summary, in spontaneously breathing dogs the cerebral blood flow increased during elevated intracranial pressure at cerebral perfusion pressure of 20 mm Hg. The increase in cerebral flow was associated with the development of hypoxemia and respiratory acidosis. In contrast, in the controlled ventilated dogs, in which the arterial blood gas and pH variations were prevented, cerebral blood flow decreased during elevated intracranial pressure. In the controlled ventilated dogs breathing 5% CO2 during elevated intracranial pressure, the cerebral blood flow increased. Thus, hypercapnia reversed the decrease in cerebral blood flow induced by elevated intracranial pressure in controlled ventilated dogs. Therefore, the increase in flow in the spontaneously breathing animals may be due to the co-existing hypoxemia and respiratory acidosis resulting from the decrease in ventilation. The decreases in flows during elevated intracranial pressure in spontaneously breathing dogs and controlled ventilated dogs breathing 5% CO2 were associated with further cerebral vasodilation suggesting that increased dilation compensated for the reduction in perfusion pressure and reversed the decrease in flow. The present findings also indicate differences in regional flow response during intracranial hypertension in the cerebellum, pons, medulla, and cervical spinal cord from the response in the supratentorial areas. This suggests that pressure gradients across the supratentorial and infratentorial compartments determine the regional cerebrovascular response to elevated intracranial pressure.

References

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Coagulopathy Following Experimental Cerebral Ischemia

Konstantin-Alexander Hossmann, M.D., Ph.D. and Volker Hossmann, M.D.

SUMMARY In adult normothermic cats cerebral blood flow was interrupted for 1 hour by clamping the innominate and subclavian arteries. Following ischemia the brains were recirculated with blood, and the coagulation system was investigated by measuring coagulation times and blood content of fibrinogen and platelets.

Ischemia induced progressive consumption coagulopathy with an increase in coagulation times and a decrease of platelets and fibrinogen by more than 40%. Coagulopathy was accompanied by a respiratory distress syndrome with a significant increase in the alveolar-arterial carbon dioxide gradient from $-3.3$ to $-13.5$ mm Hg.

A correlation was found between plasma fibrinogen concentration, cerebral blood flow and electrophysiological function, indicating that a relationship exists between the severity of postischemic coagulopathy and functional recovery following prolonged cerebral ischemia.

DISSEMINATED INTRAVASCULAR coagulation is a serious complication which accompanies various pathological conditions such as septicemia, intravascular hemolysis, endothelial damage, and severe shock. Less known is its occurrence in anoxia or ischemia, especially in that of the central nervous system.

Following transient cerebral ischemia disseminated intravascular coagulation may interfere directly or indirectly with the recovery by means of three different mechanisms: a) impairing the microcirculation of the brain; b) producing pulmonary microembolization and c) eliciting reactive fibrinolysis.

Microrcirculatory disorders have been demonstrated to be of importance in the pathogenesis of the so called no-reflow phenomenon which is one of the limiting factors for recovery after prolonged cerebro-circulatory arrest.

Pulmonary microembolization may cause a respiratory distress syndrome and reactive fibrinolysis bears the risk of promoting hemorrhagic infarction of the ischemic brain.

In the present investigation the occurrence of disseminated intravascular coagulation was studied in animals which were subjected to one hour's complete selective ischemia of the brain. This experimental model has been used in our laboratory for the study of functional recovery after prolonged ischemia, and information is available on various physiological, biochemical and morphological aspects of the recovery process. The comparison of these data with the changes in coagulation parameters following ischemia indicates that disseminated intravascular coagulation may present a problem for the revival of the brain following cerebro-circulatory arrest.

Methods

Fifty adult cats were anesthetized with pentobarbital (30 mg/kg Nembutal® intraperitoneally), immobilized with
Respiratory influence on the total and regional cerebral blood flow responses to intracranial hypertension.

A B Malik, J A Krasney and G J Royce

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