Global Ischemia in Dogs: Cerebrovascular CO\textsubscript{2} Reactivity and Autoregulation

BY EDWIN M. NEMOTO, PH.D., JAMES V. SNYDER, M.D., ROBERT G. CARROLL, M.D., AND HIDEO MORITA, M.D.

Abstract: Global Ischemia in Dogs: Cerebrovascular CO\textsubscript{2} Reactivity and Autoregulation

One hypothesis on the pathogenesis of post-ischemic-anoxic encephalopathy is impaired cerebral perfusion or the no-reflow phenomenon. Therapies aimed at preventing the development of this phenomenon are increased cerebral perfusion pressure (CPP) and hyperventilation or hypercapnia. Using a dog model in which we have described the progressive development of post-ischemic (PI) cerebral hypoperfusion after 15 minutes of global ischemia induced by aortic and vena cavae clamping, our aims in this study were to determine during the PI cerebral hypoperfusion period: (1) cerebrovascular reactivity to CO\textsubscript{2}, and (2) cerebral blood flow (CBF) autoregulation. Post-ischemic cerebral hypoperfusion to about 50% of normal was not accompanied by raised intracranial pressure (ICP) but cerebrovascular CO\textsubscript{2} reactivity was markedly attenuated while maintaining some kind of autoregulatory phenomenon. Cerebral uptake of oxygen was not significantly affected by changing P\textsubscript{aco} from 20 to 60 torr at constant CPP or by changing CPP from 64 to 104 torr at constant P\textsubscript{aco}. These results suggest that increasing both CPP and hypocapnia/hypercapnia would not significantly attenuate PI neurological deficit after global cerebral ischemia. However, in two dogs inadvertently hemodiluted in the PI period, increasing CPP from 50 to 200 torr increased CBF by 200%, suggesting that hemodilution plus increased CPP may be effective therapy for amelioration of post-ischemic-anoxic encephalopathy. The significance of our findings on cerebrovascular CO\textsubscript{2} reactivity and autoregulation with respect to the mechanism of the no-reflow phenomenon is discussed.

Introduction

A basic assumption in all therapeutic procedures for post-ischemic-anoxic encephalopathy (PIAE) is that the ultimate degree of brain damage sustained after cerebral ischemic-anoxic insult is not entirely due to the initial insult, but that some post-ischemic (PI) pathophysiological changes occur which may be amenable to therapy. Among the pathophysiological changes thought to occur is impaired cerebral perfusion, or the no-reflow phenomenon (NRP) as described by Ames et al.\textsuperscript{1} in rabbits and by Ginsberg and Myers\textsuperscript{2} in monkeys. A likely corollary of the NRP is PI cerebral hypoperfusion as demonstrated by Baldy-Moulinier,\textsuperscript{3} Hossmann et al.,\textsuperscript{4} and us.\textsuperscript{5,6}

In spite of the controversy on the occurrence of the NRP, there is substantial evidence, as previously cited, that cerebral PI hypoperfusion does in fact occur. We have also obtained evidence suggesting that it is not simply decreased cerebral blood flow (CBF) resulting from reduced cerebral metabolic demands.\textsuperscript{8}

The significance of the NRP or PI cerebral hypoperfusion in PIAE is unclear. The data of Levy et al.\textsuperscript{7} show that ischemic cell changes may occur without evidence of flow impairment. However, this observation does not negate cerebral flow impairment as a significant contributory factor to the progressive development of PIAE.

Among the therapeutic procedures aimed at ameliorating PIAE by improving PI CBF are elevated cerebral perfusion pressure (CPP),\textsuperscript{8,9,10} hypercapnia,\textsuperscript{11,12} and in space-occupying lesions of the brain, hyperventilation.\textsuperscript{12,14} Although the efficacy of elevated CPP has been demonstrated in studies on patients with primarily focal ischemic infarct,\textsuperscript{19} this has not been clearly demonstrated after global ischemia. The effect of CO\textsubscript{2} alteration on neurological recovery after global ischemia is also unclear, but the data of Hossmann et al.\textsuperscript{4} suggest that PI cerebrovascular reactivity to CO\textsubscript{2} is markedly attenuated.

Using a dog model in which we have described the progressive development of PI cerebral hypoperfusion during 15 minutes of global ischemia induced by aortic/vena cavae clamping, our aims in this study were to determine during the PI cerebral hypoperfusion period: (1) cerebrovascular CO\textsubscript{2} reactivity, and (2) CBF autoregulation. Briefly, the results show that during the PI hypoperfused state, cerebrovascular reactivity to CO\textsubscript{2} is markedly attenuated (almost no
response), but that some autoregulatory phenomenon occurs, the mechanism of which is not understood.

**Methods**

We used the systemic circulatory arrest model by aortic and vena cavae occlusion as previously described. Briefly, mongrel dogs (15 to 25 kg body weight) were anesthetized with Surital (2.5%), immobilized with gallamine triethiodide (2 mg per kilogram), and ventilated by a constant volume ventilator (Harvard) on 70% N₂O/30% O₂ at tidal volumes of about 20 ml per kilogram. End-tidal CO₂ was monitored with a Beckman infrared CO₂ analyzer and maintained between 5% and 6% by manipulation of FICO₂.

Catheters were inserted into a femoral artery and two femoral veins for pressure monitoring, blood sampling, and I.V. infusions. A catheter inserted rostrally and nonocclusively into the right common carotid artery was used for injection of 13³Xe in 0.2 ml saline for CBF determination. A catheter inserted proximally and nonocclusively into the superior sagittal sinus (catheter tip approximately 2 cm distal to the confluence of the sinuses) was used for cerebral venous blood sampling. A multiple-hole silastic catheter was inserted subdurally over the parietal cortex for intracranial venous blood sampling. A catheter inserted subdurally over the left frontal and parietal lobes. Temporal and parietal musculature were resected out of the view of the scintillation detector used for monitoring of brain ¹³³Xe clearance.

Prior to control measurements arterial base excess (BE) was normalized with NaHCO₃. Three control CBF determinations were made at 60, 30 and 15 minutes pre-ischemia. Other variables monitored at each measurement period were systemic arterial pressure (SAP), ICP, cerebral venous and arterial O₂ content, pHₐ, Paco₂, hematocrit (Hct), central venous pressure (CVP), and rectal temperature (Tr). At time zero, circulatory arrest was induced for 15 minutes and the inspired gas changed to 100% O₂ with end-tidal CO₂ maintained at 5%.

For CBF autoregulation studies, CPP (mean SAP minus mean ICP) was altered to levels of approximately 50, 100, 150, and 200 torr by titrated I.V. infusion of norepinephrine or Arfonad. Paco₂ was maintained near normal throughout. CPP was kept at a given level for at least five minutes before each CPP determination was made. The sequence of CPP changes was randomized.

For CBF CO₂ sensitivity studies, Paco₂ was changed to 20, 40, 60 and 100 torr by manipulation of FICO₂ without changing ventilation rate or tidal volume. Paco₂ was maintained constant at a given level for at least five minutes prior to CPP determination and CPP was maintained normal at each level. The sequence of CO₂ alterations was randomized. All studies were completed between one and four hours PI.

Two dogs were sham-operated and used for control studies without ischemia to determine the normal CBF response to CPP and Paco₂ changes.

CBF was estimated from the brain clearance of 200 to 300 μCi of ¹³³Xe in 0.2 ml of saline injected into the common carotid artery. Ipsilateral brain ¹³³Xe activity was monitored by a focused collimator, 2° × 2° Tl scintillation crystal-preamplifier-spectrometer system (Baird Atomic, Inc.) connected to a linear/log ratemeter with a time constant of one second. The output of the linear/log ratemeter was connected to a strip chart recorder and CBF calculated from the ¹³³Xe clearance curve by the T² method of Waltz et al. The positioning of the probe and the size of the collimator were such that essentially an entire ipsilateral hemisphere was in view of the detector. Therefore, although CBF values will be referred to as regional cerebral blood flow (rCBF), they represent hemispheric (primarily cortical) blood flow. Cerebral metabolic rate for oxygen (CMRO₂) was calculated from CBF multiplied by cerebral arteriovenous oxygen difference.

**Results**

Table 1 shows the changes in rCBF and ICP after 15 minutes of total circulatory arrest. Mean SAP and Paco₂ were maintained normal for up to 60 minutes PI. Mean rCBF was approximately 55 ml/100 gm • minute before ischemia and increased threefold to 160 ml/100 gm • minute at five minutes PI, then decreased to 50% of control (P < 0.05) at 45 and 60 minutes. ICP rose from a pre-ischemic control value

<table>
<thead>
<tr>
<th>Period time (min)</th>
<th>Pre-ischemic</th>
<th>Post-ischemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF (cc/100 gm/min)</td>
<td>54.5</td>
<td>56.5</td>
</tr>
<tr>
<td>ICP (torr)</td>
<td>12.9</td>
<td>14.8</td>
</tr>
<tr>
<td>SAP (torr)</td>
<td>13.1</td>
<td>127.2</td>
</tr>
<tr>
<td>Paco₂ (torr)</td>
<td>35.3</td>
<td>38.9</td>
</tr>
</tbody>
</table>

*Significantly different from pre-ischemic values (P < 0.05).

Results from eight dogs subjected to total circulatory arrest by aortic and vena cavae clamping, 0 time = time of aortic and vena cavae clamp release.

For CBF autoregulation studies, CPP (mean SAP minus mean ICP) was altered to levels of approximately 50, 100, 150, and 200 torr by titrated I.V. infusion of norepinephrine or Arfonad. Paco₂ was maintained near normal throughout. CPP was kept at a given level for at least five minutes before each CPP determination was made. The sequence of CPP changes was randomized.

For CBF CO₂ sensitivity studies, Paco₂ was changed to 20, 40, 60 and 100 torr by manipulation of FICO₂ without changing ventilation rate or tidal volume. Paco₂ was maintained constant at a given level for at least five minutes prior to CPP determination and CPP was maintained normal at each level. The sequence of CO₂ alterations was randomized. All studies were completed between one and four hours PI.
POST-ISCHEMIC CBF REGULATION

CBF autoregulation in the post-ischemic hypoperfused dog brain between one and four hours after 15 minutes of circulatory arrest. Arfonad and Levophed infusions (I.V.) were used for blood pressure manipulation. Blood pressure was maintained at a given level for at least five minutes before rCBF was determined. * = Significantly different from the corresponding nonischemic value (P < 0.05). Numbers in parentheses are mean PaCO₂ ± SEM in torr.

The effect of hemodilution on post-ischemic CBF autoregulation one to four hours after 15 minutes of circulatory arrest. Arfonad and Levophed infusions (I.V.) were used for manipulation of arterial blood pressure. rCBF was determined only after arterial blood pressure was maintained at a given level for at least five minutes. Hemodiluted dogs: ○ Hct, 30% to 33%; ● Hct, 19% to 22%. Normal Hct dogs: ■—■. mean ± SEM.

Cerebrovascular CO₂ sensitivity in the post-ischemic hypoperfused dog brain one to four hours post-ischemia. PACO₂ was varied by alteration of F₂CO₂. rCBF was determined only after PACO₂ was maintained at the desired level for at least five minutes. * = Significantly different from corresponding nonischemic control group value (P < 0.05). Numbers in parentheses are mean cerebral perfusion pressure ± SEM in torr.

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was made to maintain CPP at approximately 100 torr, at \( \text{Paco}_2 \) values of 40 and 65 torr, mean CPPs were significantly lower, while at \( \text{Paco}_2 \) of 100 torr they were significantly higher in the PI dogs compared to the control (nonischemic) dogs.

Alteration of \( \text{Paco}_2 \) from 21 to 61 torr and CPP from 64 to 105 torr in dogs with normal hematocrits had no significant effect on CMRO₂ (table 2).

**Discussion**

Our finding of cerebral reactive hyperemia with subsequent cerebral hyperperfusion (i.e., 50% of preischemic values) differs from the observations of Hussmann et al. and Baldy-Moulinier in cats. In both reports reactive hyperemia did not occur if PI hypoperfusion developed. It is disconcerting to note that in Baldy-Moulinier’s study, global brain ischemia for ten minutes or longer resulted in essentially no return of CBF PI, whereas in Hussmann’s study, after 30 to 60 minutes of global ischemia in some animals, CBF returned. In neither study was ICP measured and therefore CPP could not be quantitated and rigorously compared with our data.

The lack of an increase in CBF with a rise in CPP at normal hematocrit during the low-flow PI state corroborates the findings of Hussmann et al. These data suggest that after global ischemia, hypertension would have no significant effect on neurological recovery. Miller et al. also have observed the constancy of CBF with increased CPP after focal cold-induced cortical injury which was termed “false” autoregulation, since it is unlikely to be comparable to the process of physiological autoregulation observed in normal brain. In contradiction, Wise et al. demonstrated amelioration of neurological deficit by increasing systemic arterial pressure in patients suffering focal ischemic insults. Cantu et al. and Miller and Myers reported that hypotension PI was a significant factor limiting recovery from global cerebral ischemic-anoxic insult. These studies suggest that elevation of CPP affects CBF and neurological recovery, which appear contradictory to our observations that elevation of CPP from 64 to 105 torr had no significant effect on CBF or CMRO₂ (table 2). Although our data on CBF and CMRO₂ are qualified because of possible cerebral arteriovenous shunts, regional inhomogeneity in flow and metabolic rate, the degree of PI hypotension reported by Cantu et al. and Miller et al. is from 20 to 40 torr mean systemic arterial pressure and probably CPPs of 10 to 20 torr, which is clearly out of the range of the CPP values we tested. This degree of hypotension may indeed impede neurological recovery as they have shown. However, in Miller’s study the tacit assumption was made that the PI hypotension was cause and neuropathology effect. It is also likely that the reverse is true — namely, that the neuropathological pattern observed was cause and the PI hypotension the effect, as found in failure of the Cushing response to increased ICP by Langfitt et al.

As we have previously discussed, the no-reflow phenomenon described by Ames et al., by colloidal carbon perfusion, appears to differ in terms of its time course from PI cerebral hyperperfusion. However, the discrepancy is probably a result of methods used rather than the existence of two separate phenomena. Applicable to both phenomena are the findings of Chiang et al., demonstrating capillary “pinching” or narrowing of the capillary lumen due to edema of endothelial cells and astrocyte foot processes. In addition, they described the formation of capillary endothelial “blebs” breaking off the capillary wall and occluding the lumen. We have shown that six hours after 15 minutes of global ischemia CSF pH is still acidotic, indicating that brain arterioles are probably maximally dilated or in vasoparalysis. The lack of cerebrovascular sensitivity to \( \text{CO}_2 \) alterations described in this study (discussed later) also supports the existence of vasoparalysis. Therefore, the data suggest that during PI cerebral hyperperfusion cerebral vessels are in a state of vasoparalysis with obstructed capillaries.

**Table 2**

<table>
<thead>
<tr>
<th>( \text{Pa}_2 \text{CO}_2 ) (torr)</th>
<th>( \text{Paco}_2 )</th>
<th>CPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>21.0</td>
<td>104.5</td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>SEM</td>
<td>2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>CMRO₂ (( \mu \text{mol/100 gm} \cdot \text{min} ))</td>
<td>X</td>
<td>146.8</td>
</tr>
<tr>
<td>( \mu \text{mol/100 gm} \cdot \text{min} )</td>
<td>n</td>
<td>5</td>
</tr>
<tr>
<td>SEM</td>
<td>10.8</td>
<td>24.5</td>
</tr>
<tr>
<td>CPP</td>
<td>X</td>
<td>103.8</td>
</tr>
<tr>
<td>(torr)</td>
<td>n</td>
<td>5</td>
</tr>
<tr>
<td>SEM</td>
<td>16.2</td>
<td>5.3</td>
</tr>
<tr>
<td>CBF (( \text{cc/100 gm} \cdot \text{min} ))</td>
<td>X</td>
<td>23.8</td>
</tr>
<tr>
<td>( \text{cc/100 gm} \cdot \text{min} )</td>
<td>n</td>
<td>5</td>
</tr>
<tr>
<td>SEM</td>
<td>3.8</td>
<td>3.7</td>
</tr>
</tbody>
</table>
POST-ISCHEMIC CBF REGULATION

Our present speculation on the mechanism of "false" autoregulation is as follows. During ischemia the arterioles and other resistance vessels of the brain are maximally dilated as a result of severe lactic acidosis, elevated ADP and AMP, and K+ concentrations. Also, intracellular hyperosmolarity develops due to sodium uptake by the cells from failure of the sodium-potassium pump. This process occurs in capillary endothelial, neuronal and glial cells. Upon restoration of circulation and at normal CPP, marked reactive hyperemia occurs with rapid imbibition of water from the intravascular to the extravascular space of the brain, resulting in hemocoagulation and increased blood viscosity. Focal or regional brain edema develops (not necessarily to the point of a generalized increase in ICP), causing narrowing of the capillary lumen, formation of endothelial blebs and obstruction of capillaries. As a result, cerebral hypoperfusion ensues with continued anoxic state of the brain and CSF acidosis. The arterioles remain in vasoparalysis with capillaries stenosed or occluded, and causing apparent hyperviscosity of blood resulting in an attenuated pressure-flow relationship. These speculations are diagrammatically illustrated in figure 4.

Insight into the mechanism of PI cerebral hypoperfusion could be gained by a thorough examination of the autoregulatory curves for normal and PI brain at the low (CPP: 0 to 50 torr) and high (CPP: 150 to 300 torr) pressures. Figure 5 illustrates the hypothetical autoregulation curves for normal and PI hypoperfused brain. At CPPs from 0 to 50 torr in normal brain, there is a failure of autoregulatory mechanisms as brain vessels are maximally dilated with flow resistance almost entirely due to capillaries. In the post-ischemic brain, a similar state is presumed to exist with the exception that the capillary beds are partially or completely obstructed, thus having a higher resistance to flow. On the other hand, at higher CPPs (at the upper limits of CBF autoregulation in normal brain), autoregulation in the normal brain occurs, while in the PI brain the vessels are still in vasoparalysis; the lack of an increase in CBF may be due to a combination of factors such as blood hyperviscosity (i.e., reversal of Fahraeus-Lindquest effect at small capillary diameters) and capillary obstruction. Therefore, beyond the "breakpoint" of the normal CBF autoregulation curve (CPP: 150 to 200 torr), there should be a marked increase in CBF in normal brain, but not in PI brain unless the capillary obstructions are released by the increased CPP.

In two dogs in which inadvertent hemodilution occurred, we demonstrated a marked effect of increased CPP on CBF. These findings support the concept that blood hyperviscosity is probably a major impediment to the improvement of CBF for adequate oxygenation and substrate delivery to the brain. The effect of hemodilution on CBF is well known and has been tested recently in PI brain by Fischer et al., who demonstrated reduction of flow impairment by hemodilution during the ischemic insult. However, inherent in their studies is the hemodilution resulting from the technique of flow impairment estimation by brain perfusion with colloidal carbon suspension. Although based on scanty data, our findings on the effect of hemodilution on PI CBF suggest that hemodilution may be a promising therapy for PIAE.

During the PI low-flow state, alteration of Paco2 from 20 to 110 torr had no significant effect on either CBF or CMRO2 (table 2). Hossmann et al. reported...
similar results on PI cerebrovascular reactivity to CO₂. For comparison of these results with other studies on PIAE the following are important considerations: (1) the etiology of the initial cerebral ischemic-anoxic insult (i.e., head injury, stroke, tumor, cardiac arrest), (2) the severity or extentiveness of the initial insult, (3) the regionality of the CBF measurement, (4) the duration of exposure to low or high CO₂ before CBF determination, (5) the time post-insult at which cerebrovascular CO₂ sensitivity is tested, and (6) the maintenance of normal or constant CPP during the alteration of PCO₂. The following conditions apply to this study: (1) the cerebral ischemic insult is diffuse and of sufficient severity to cause permanent brain damage without brain death and marked secondary increase in ICP (i.e., brain swelling), (2) CBF measurement is essentially hemispheric and estimates primarily cortical flow, (3) cerebrovascular CO₂ sensitivity was tested in the early PI phase (one to four hours PI) during the low-flow state, and (4) CBF was estimated after five to ten minutes' equilibration at a given PaCO₂ level at constant CPP within the normal autoregulatory range.

Our findings suggest that hyperventilation or CO₂ elevation would have no significant effect on CBF and CMRO₂ (qualifications of CBF and CMRO₂ measurements previously discussed) after global ischemia and perhaps on the degree of brain damage ultimately sustained. However, because the rationale of hyperventilation is based not only on lowering ICP\(^1\),\(^2\) and thereby improving CBF (increased CBF was not observed in these studies) but also on pH normalization of the brain, it may be of benefit in terms of the ultimate degree of brain damage sustained. However, available evidence suggests that aside from the reduction of life-threatening ICP increases, which may occur after acute head injury or space-occupying lesions,\(^1\),\(^2\) hyperventilation is unproved in decreasing mortality rates\(^3\),\(^4\) and may actually be contraindicated because of enhanced cerebral anaerobiosis,\(^4\) tissue hypoxia resulting from impeded unloading of oxygen due to attenuation of the Bohr effect, hypotension and raised CVP and therefore ICP, with intermittent positive pressure ventilation. Therefore, unless ICP is increased, hyperventilation below a PaCO₂ of 25 to 30 torr is not indicated and may result in deleterious rather than beneficial effects. Indeed, several reports indicate that hypercapnia rather than hypocapnia improves CBF and the paradoxical CO₂ response does not occur except in cases involving intracranial space-occupying lesions.\(^5\)

The loss of cerebrovascular reactivity to CO₂ during PI cerebral hypoperfusion also may be the result of arterial vasospasm rather than vasoparalysis. However, papaverine has been shown to be ineffective in improving CBF in the low-flow PI state after global ischemia,\(^6\) suggesting that vasospasm does not explain PI hypoperfusion. In focal ischemic disease, Meyer et al.\(^7\) and McHenry et al.\(^8\) reported improvement of CBF with papaverine administration, which may result from increased CBF through the normal brain areas and thereby improve collateral flow into the ischemic regions. On the other hand, after global ischemic insult, collateral channels may not exist to the extent of improving CBF in damaged, hypoperfused areas.

As is true for much of the studies done in the past on PIAE, a shortcoming of our experiments is that we have evaluated efficacy of therapeutic procedures in physiological response (i.e., CBF and CMRO₂) rather than amelioration of permanent neurological deficit sustained. To evaluate therapy in terms of permanent neurological deficit sustained requires an animal model with a simple, noninvasive and reliable method for producing global brain ischemia and with long-term survival. Highly invasive techniques as in the dog model used in these studies complicate post-ischemic life support and long-term survival. We have recently developed a 16-minute global brain ischemia monkey model using a high pressure neck tourniquet at 30 psi (complete ischemia documented by brain scan and EEG isoelectric in less than 20 seconds after tourniquet inflation) combined with ancillary procedures resulting in severe neurological deficit and survival (24-hour coverage life support) until sacrifice at seven days PI.\(^9\) Having described the natural history of this model in terms of neurological deficit, EEG patterns (quantitation), neuropathology and systemic and intracranial physiological variables, we can now begin to evaluate therapeutic procedures in a clinically relevant model.

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**Figure 3**

Hypothetical CBF autoregulation curves for normal (—) and post-ischemic (---) "low flow state" brain. Autoregulation divided into three segments in reference to "normal" curve: (A) loss of autoregulation, (B) range of autoregulation, and (C) "breakpoint" of autoregulation. See text for discussion.
POST-ISCHEMIC CBF REGULATION

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