Physiological Modification of Immediate Ischemia due to Experimental Middle Cerebral Occlusion—Its Relevance to Cerebral Infarction

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Abstract:
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In cats subjected to middle cerebral artery occlusion, the resulting ischemia was unaffected by the blood pressure at the time of occlusion when arterial P_{CO_2} was normal or low. At normal and elevated blood pressures, hypercapnia established prior to occlusion minimized the ischemia and hypocapnia aggravated it. Re-occlusion during postischemic reactive hyperemia resulted in ischemia of the same severity as during the initial occlusion, provided P_{CO_2} and blood pressure were not changed. These observations suggest that a general determinant of the severity of immediate ischemia in this preparation is the competence of the collateral circulation.

This conclusion suggests that proper analysis of the pathogenesis of cerebral infarction requires consideration of immediate ischemia separately from the subsequent course of the ischemic lesion. There are so many variables bearing on the pathogenesis of cerebral infarction that a rational therapy of acute stroke can only be visualized when there is knowledge of the specific arterial lesion, frequent or continuous measurement of regional cerebral blood flow, regional metabolism or neuronal activity, intracranial pressure, and some way of distinguishing paralyzed but viable tissue from infarction.

ADDITIONAL KEY WORDS: regional cerebral blood flow, hypocapnia, hypercapnia, oxygen availability, collateral circulation

Introduction

It is now widely held that cerebrovascular reactivity to changes in systemic blood pressure and P_{CO_2} is altered in acute regional ischemia. Regional blood flow becomes passively responsive to altered blood pressure and may not change or in some cases may decrease during hypercapnia.1-3 The purpose of this study has been to examine some of the effects of changes in blood pressure and P_{CO_2} made immediately prior to vascular occlusion, on the severity of the resulting ischemia.

Methods

Bare platinum polarographical electrodes were chronically implanted through the intact cranium in various areas of the cerebral cortex of cats. This method after a few days permits continuous monitoring of regional oxygen availability which, in our hands, has been a reliable semiquantitative index of regional cerebral blood flow. For a given electrode, serial and continuous measurements are quantitatively reproducible. Changes in oxygen availability indicate changes in blood oxygen content or regional blood flow. Techniques of electrode construction, implantation, and recording are as described previously.6,7

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Occlusion of middle cerebral artery at low and high \( P_{CO_2} \) in same animal. Abrupt fall in oxygen availability on occlusion with rapid recovery on removal of occluding clip. Ischemia is less severe at high \( P_{CO_2} \).

Though simultaneous recordings from multiple regions were made, the data reported here were all obtained from the electrodes designated "sylvian," i.e., those located in the anterior and posterior sylvian gyri, the inferior part of the ectosylvian gyri, and rarely the lower part of the posterior ectosylvian gyri. This is the most ischemic region of the accessible cerebral convexity following middle cerebral occlusion, the most likely to become infarcted, and the locus of the most severe alterations in cerebral vascular reactivity.6

Monopolar EEG was simultaneously recorded from the same electrodes, utilizing an external average reference obtained by connecting each cerebral electrode to the reference via a 25,000 ohm resistor. With meticulous attention to grounding, shielding, and sources of artifact, polarization of the electrodes does not interfere with EEG except for a slow baseline sway of three to eight/minute which is due to rhythmic local fluctuations of oxygen availability.6-9

Under pentobarbital anesthesia, the origin of the middle cerebral artery was exposed by the retro-orbital extradural approach of Sundt and Waltz.10 The animals were paralyzed and artificially ventilated. Expired CO2 and mean arterial blood pressure were continuously monitored. Arterial \( P_{O_2} \), \( P_{CO_2} \), and pH were determined immediately after each episode of regional ischemia. Arterial \( P_{O_2} \) was maintained between 120 and 180 mm Hg to minimize changes in blood oxygen content. Rectal temperature was maintained between 36° and 38°C. Blood pressure was manipulated by intravenous infusion of nitroprusside and metaraminol.

Occlusion of the middle cerebral artery at its origin causes an abrupt fall in regional oxygen availability, rapidly reaching a low plateau, and, if the occluding clip is left in place, a gradual rise over subsequent hours.9

In these experiments the clip was removed within a few minutes, when the oxygen availability had reached a stable low level or had begun to rise. The brain was allowed to rest until oxygen availability and EEG became stable, the blood pressure or \( P_{CO_2} \) was then altered and the clip reapplied. Expired CO2 and blood pressure were held constant during each period of occlusion. An attempt was made to obtain in each animal occlusions at low and high \( P_{CO_2} \) in combination with low, medium, and high blood pressure. This report is based on observations in 13 animals, comprising 150 occlusions.

**Results**

**THE EFFECT OF \( P_{CO_2} \)**

Figure 1 shows the oxygen availability record from the same electrode at low and high \( P_{CO_2} \) at similar blood pressures. This was a fairly consistent observation. In nearly all animals, hypercapnia induced prior to occlusion resulted in less severe ischemia. The only exception was that in a few animals at mean blood pressures below 90 mm Hg this protective effect was lost and rarely hypercapnia aggravated the ischemia, notwithstanding an increase in oxygen availability prior to occlusion caused by the
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Occurrence of mild hypercapnia, regardless of the blood pressure level (fig. 2). In all animals with mean blood pressure above 90 mm Hg, hypercapnia induced prior to occlusion resulted in less severe ischemia than did hypocapnia for the range of arterial P CO₂ 15 mm Hg to 100 mm Hg (figs. 3 and 4). In some cases simultaneous EEG monitoring from the same electrodes revealed loss of EEG activity during occlusion at low P CO₂ but preservation of it during occlusion at higher levels of P CO₂.

THE EFFECT OF BLOOD PRESSURE

In most animals when occlusions were performed at P CO₂ below 35 mm Hg, the blood pressure prior to occlusion had no effect on the oxygen availability during occlusion, provided the blood pressure remained constant during the occlusion. (This is notwithstanding the invariable loss of regional autoregulation during occlusion.) The only exception was in a few cases where autoregulation was somewhat defective, allowing oxygen availability prior to occlusion to vary slightly with blood pressure (fig. 5). Indeed, in all cases, when autoregulation was abolished by hypercapnia, the ischemia during occlusion was less severe at high blood pressures established prior to occlusion and maintained constant during occlusion (fig. 6).

THE EFFECT OF REGIONAL VASODILATION

Following removal of the occluding clip at low and normal P CO₂, regional oxygen availability rises abruptly to a level substantially higher than preocclusion, gradually returning to the preocclusion level over a few minutes. This is presumed to represent posts ischemic reactive hyperemia due to regional vasodilation.

If the clip is reapplied at the peak of hyperemia, ischemia immediately re-occurs (fig. 7) identical in severity with that resulting at the initial occlusion (assuming P CO₂ and blood pressure have remained constant). This observation could not be tested during hypercapnia because hyperemia does not then occur, pre-

FIGURE 3

Same as figure 2. Mean arterial blood pressure 90 to 120 mm Hg. Preocclusion vasodilation has protective effect in all cases.

FIGURE 4

Same as figure 2. Mean arterial blood pressure above 120 mm Hg.
During occlusion (pCO₂ < 35 mm Hg). Hypertension has no protective effect.

**Discussion**

The circumstances of these experiments eliminated significant changes in blood oxygen content, leaving regional blood flow as the main determinant of oxygen availability. However, there are two other possible factors which may modify this direct relationship. The Bohr effect, resulting in increased oxyhemoglobin dissociation during the acidosis resulting from hypercapnia, might conceivably increase the oxygen availability beyond that due to a simple increase in flow. If this were significant, it would not invalidate the empiric observation of a protective effect of prior hypercapnia but it might require modification of the conclusions reached below. This artifact should have been minimized in the absence of ischemia, by the provision of 100% oxygen saturation. It remains conceivable, however, that increased local tissue acidosis during ischemia might be operative in some cases. There are limited quantitative data available bearing on this point.

Relevant is an important but neglected study by Meyer and Denny-Brown which demonstrated decrease in local cortical pH of the order 0.1 to 0.5 unit during cortical ischemia sufficient to flatten the EEG and initiate a steady potential shift. Simultaneous monitoring of oxygen availability and cortical temperature indicated that there was not a substantial qualitative distortion of the relationship between oxygen availability and blood flow. In some of our experiments, simultaneous monitoring of EEG from the same electrode revealed preservation of EEG activity at the higher oxygen availability which resulted from ischemia during hypercapnia, while EEG activity was lost as a result of ischemia during hypocapnia when local tissue acidosis might be...
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presumed to have been greater. The balance achieved between local acidosis and systemic alkalosis is unknown, however.

Questions may also be raised about the effect of altered tissue metabolism on oxygen availability. It could be argued that in states of decreased oxygen consumption the oxygen available to the electrode might be increased. The observation by Waltz of red venous blood after prolonged ischemia despite demonstrably reduced flow is germane to this argument. This consideration is particularly important in interpreting the results of the experiments in which re-occlusion was made during postischemic reactive hyperemia.

A final resolution of this issue is not at hand. One study by Meyer and Denny-Brown in which flow was inferred from cortical temperature and monitored together with oxygen availability tends to support the interpretation advanced here.

It may be noted further that whenever simultaneous monitoring of EEG and oxygen availability is made during ischemia, loss of EEG activity always occurs at a low or declining oxygen availability. In more than 100 such experiments we have never observed a sudden rise in oxygen availability on disappearance of EEG activity. Moreover, following brief ischemia during which EEG flattening occurs, on restoration of flow EEG activity may return during the postischemic reactive hyperemia. The crucial experiment of monitoring quantitative flow and oxygen availability during ischemia remains to be done.

Other pertinent experiments have been reviewed elsewhere and the tentative conclusion reached that in this preparation at 100% oxygen saturation, oxygen availability is a valid qualitative index of flow. Though the Bohr effect and altered metabolism may somewhat affect this relationship, they probably do so in only minor degree and do not invalidate the arguments advanced here.

SIGNIFICANCE OF THE PATHOPHYSIOLOGICAL OBSERVATIONS

A summary statement valid for most of these experiments would be that ischemia was more severe in situations where cerebral blood flow immediately prior to occlusion was reduced, and less severe if it had been made to increase, provided the increase in blood flow was general and not local. It would follow that an important determinant of the severity of the regional ischemia due to arterial occlusion is the competence of the collateral circulation.

In the controversial area of the determinants of the course of cerebral infarction, the limitations on the significance of these observations should be made clear: they pertain only to the severity of immediate ischemia. They do not controvert other observations which indicate that vascular reactivity to P<sub>O</sub><sub>2</sub> and blood pressure, after ischemia is induced, differs from the normal state. The occurrence and course of cerebral infarction must depend greatly on what happens in the brain during a period of many minutes or hours following the immediate ischemia due to the arterial occlusion.

Only in such a context can meaningful correlation be made between this and other published studies of experimental cerebral infarction. An important one is that by Soloway et al., in which cerebral infarction in dogs was found to be less severe when hyperventilation was commenced prior to arterial occlusion and continued for two hours postocclusion. Two reservations should be mentioned about this study. Body temperature was lower in the hyperventilated group, though the authors thought not significantly so. The arterial lesion consisted of occlusion of the middle cerebral artery and in addition of the internal carotid between the anterior cerebral and posterior communicating, which would seem to result in an anatomically less competent collateral circulation. Since regional blood flow was not measured in this study, one can only speculate that perhaps the effect of hyperventilation, though it might have aggravated initial ischemia, was ultimately beneficial by its effect on the course of the ischemic lesion by reducing cerebral edema or by the paradoxical increase in blood flow in the ischemic region which might be predicted to occur in response to hypocapnia.

Soloway et al. have subsequently reported that hyperventilation begun one hour after occlusion in monkeys resulted in a slightly, but not statistically significantly, larger infarction. Battistini et al., beginning hyperventilation 30 minutes after occlusion, found a beneficial effect in normotensive cats but not in hypertensive cats. Yamaguchi et al., beginning hyperventilation four to six hours after occlusion in cats, studied the regional...
The Pathogenesis of Cerebral Infarction

I. Immediate ischemia
   A. The specific arterial lesion
   B. The anatomical disposition of the collateral circulation
   C. Physiological modification of the collateral circulation
      1. Blood pressure
      2. P\text{CO}_2
      3. Blood oxygen content
      4. Blood viscosity
      5. Body temperature

II. The course of the ischemic lesion
   A. Size of the ischemic lesion
   B. Duration of the ischemic lesion
   C. Altered reactivity of the collateral circulation
      1. Loss of responsiveness to CO\text{2} changes and occasional paradoxical responsiveness
      2. Loss of autoregulation to systemic blood pressure and intracranial pressure changes
   D. The development of regional cerebral edema
   E. Blood oxygen content
   F. Body temperature
   G. Blood viscosity

Determinants of immediate ischemia: the specific arterial lesion would appear of major self-evident significance and not require extensive discussion. The anatomical disposition of the collateral circulation includes such considerations as whether the occlusion is above or below the circle of Willis, the competence of the circle of Willis, the competence of the leptomeningeal anastomosis, and the absence of significant collateral circulation in the lenticulostriate region.

Physiological modification of the collateral circulation prior to occlusion would result principally from manipulation of blood pressure and P\text{CO}_2 prior to occlusion. It appears from the present study that, to the extent that there is a collateral circulation, hypertension at normocapnia has no beneficial effect but hypercapnia at normal levels, and particularly at hypertensive levels, may significantly augment the collateral circulation. Unpublished data being accumulated would indicate that blood oxygen content is a further independent variable, depending on oxygen saturation and hemoglobin level, while the latter may influence viscosity and vascular resistance. There is probably an optimal midrange for hemoglobin levels, between very high levels resulting in excessive viscosity and very low levels which produce dangerously low levels of oxygen content.

Determinants of the course of the ischemic lesion: the altered reactivity of the circulation in ischemic regions is now well established. Regional blood flow becomes passively responsive to blood pressure changes and either unresponsive or occasionally paradoxically reduced by hypercapnia. It appears likely that the size of the lesion and its duration may quantitatively modify this altered reactivity, with a tendency toward normalization of reactivity to blood pressure and P\text{CO}_2 with time after occlusion, and in smaller lesions.

The duration of the specific arterial lesion also has a self-evident function in that restoration of flow prior to infarction would yield recovery, while restoration after infarction would cause an aggravation of regional edema, perhaps combined with a beneficial protective effect on a marginal zone of ischemic but uninfarcted tissue.

Increased intracranial pressure probably affects the course of an ischemic lesion.
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principally by reducing regional cerebral blood flow, rather than by a direct effect on brain tissue. It appears that the low perfusion pressure in an ischemic region is exquisitely sensitive to extravascular pressures in contrast to the capability of normal brain to maintain its flow by autoregulation in the face of intracranial pressure changes up to about 400 mm H2O.21, 22 It is easy to visualize a malignant cycle: infarction → local edema → increased intracranial pressure → decreased regional blood flow → extension of infarction.

Hyperventilation-induced hypocapnia may interrupt this cycle by (paradoxically) increasing blood flow in the ischemic region, and by a general reduction in intracranial pressure. It is not clear whether hyperventilation can also act specifically on the edema in an infarction.

Decreased body temperature might affect the outcome by reducing the rate of edema formation in the infarct and by increasing the tolerance of brain tissue to ischemia.

Blood oxygen content and blood viscosity probably further affect the outcome mainly at the extremes of hemoglobin levels, though oxygen content may be altered independently by systemic hypoxia and hyperbaria.

IMPLICATIONS FOR TREATMENT OF ACUTE STROKE

There is no reason to assert that the foregoing discussion is complete, nor that the elements in it are entirely correct. To the extent that it is relevant, it indicates that rational stroke therapy cannot depend on some formula of PCO2, blood pressure, hemoglobin level, etc. It would, of course, be possible to evaluate such a formula statistically in terms of stroke outcome, though the total number of cases needed for a properly randomized study would exceed the clinical resources of any institution. More hopeful would be a scientific stroke treatment for the individual case, recognizing that this might change from day to day and perhaps hour to hour. This would require a knowledge of the specific arterial lesion and frequent or continuous measurement of regional cerebral blood flow and regional metabolism or neuronal activity and of intracranial pressure. One would also like to be able to distinguish between functionally paralyzed, metabolically inactive regions and those which are actually infarcted. It is possible that evoked potential24, 25 might provide some of this information. All of these can be brought to bear in the laboratory and most, in principle, can be utilized in the operating room. Barriers to their application at the bedside are more formidable.

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