The Course of Experimental Cerebral Infarction—The Development of Increased Intracranial Pressure

BY JAMES H. HALSEY, JR., M.D., AND NORMAN F. CAPRA, B.S.

Abstract:
The Course of Experimental Cerebral Infarction—The Development of Increased Intracranial Pressure

In cats being subjected to surgical occlusion of the middle cerebral artery, regional oxygen availability (O$_2$a) was monitored continuously from four open-tip platinum electrodes in the ischemic hemisphere and one in the control hemisphere. Extradural pressure over the convexity of the ischemic hemisphere was measured hourly. The animals were killed 24 hours after occlusion. Ten animals developing substantial increases in extradural pressure as a consequence of cerebral infarction were compared with ten which did not. The two groups did not differ in severity of the initial ischemic insult resulting from the arterial ligation, in blood pressure following occlusion, or in hematocrit, P$_{CO_2}$, or oxygen saturation.

The most important difference between the two groups was in the course of regional O$_2$a in the ischemic hemispheres following occlusion. In the animals which ultimately developed increased intracranial pressure the recovery of regional O$_2$a was slower and less complete. After the ninth hour postocclusion O$_2$a declined progressively, clearly related to rising intracranial pressure. In the animals which developed increased extradural pressure, it rose progressively to a mean of 40 mm Hg by 24 hours postocclusion. The intracranial pressure changes during the first few hours seemed insufficient to account for the early failure of recovery of regional O$_2$a, unless they are viewed as averages which obscure important regional intracerebral pressure changes.

Introduction

A substantial result of the last decade of cerebrovascular physiological research has been the demonstration of altered vascular reactivity in ischemic regions of the brain.$^{1-6}$ This important finding, together with the natural tendency for ischemic and infarcted tissue to become edematous, make extremely complex the effort to analyze and ultimately to predict the result of a major arterial occlusion.

Additional Key Words
regional cerebral blood flow
O$_2$a
P$_{CO_2}$

This is a preliminary report of a continuing effort to elucidate this process. Here we wish to draw attention to some interrelationships among the systemic determinants of the collateral circulation, the intrinsic anatomical predisposition of the collateral circulation, and the development of intracranial pressure during the process of infarction. We wish to re-emphasize in this context that the severity of initial ischemia at the time of occlusion is determined differently than is the subsequent course of the ischemic lesion.$^7$

Methods
Cerebral infarction was made by surgical occlusion of the middle cerebral artery at its origin by a miniature Mayfield clip.$^8$ The surgical approach consisted of resection of a portion of the sphenoid wing. The dura and arachnoid were opened only...
EXPERIMENTAL CEREBRAL INFARCTION

over the optic nerve to permit access of the clip to the origin of the artery. No attempt at closure of this dural opening was made but the brain was otherwise not exposed. The cranium was intact except for the sphenoid wing craniectomy. At the time of occlusion intracranial pressure was presumed to be zero because of cerebrospinal fluid drainage through this small dural and arachnoidal opening. Arterial occlusion by the clip was confirmed at postmortem.

Regional oxygen availability (O₂a) was monitored continuously from chronically implanted polarographical electrodes. Three electrodes were placed in the cortical convexity, and one in the head of the caudate nucleus of the ischemic hemisphere, and one in the convexity of the control hemisphere. Techniques of electrode construction, implantation, and recording were as described previously. We hold that O₂a is a semiquantitative measurement which is probably linearly proportional to tissue oxygen tension. Its biological significance has been discussed elsewhere.

Intracranial pressure was measured as the manometric pressure required to separate a pair of electrode contacts on the dura overlying the convexity of the ischemic hemisphere. The transducer is illustrated in figure 1. Each transducer was calibrated in vitro prior to use. The calibration was linear in the pressure range 0 to 100 mm Hg with an error of about ±1 mm Hg, unaffected by physiological temperature.

**FIGURE 1**

Schematic diagrams of the extradural pressure transducer. Manometrically measured pressure is delivered into the transducer via the 20-gauge needle. Separation of the rivet and 25-gauge needle is indicated by an ohmmeter between the 20-gauge needle and the varnish-covered copper wire. The pressure at which this separation occurs is taken as the measurement of intracranial pressure.
changes. The extradural transducer was placed an hour or more prior to middle cerebral artery occlusion and anchored rigidly with dental acrylic. Its relationship with the dura was confirmed at postmortem. This method has the disadvantage of a maximum measurement frequency of about one per minute. Its major advantages are freedom from mechanical and electronic artifacts and, hence, provision of reliable drift-free measurements over long periods. It is subject to the same limitations and interpretations as any other extradural estimate of intracranial pressure.

EEG was monitored continuously from the oxygen electrodes utilizing linkages between adjacent pairs in the ischemic hemisphere and a convenient pair in the control hemisphere. Polarization of the electrodes did not affect EEG except for a slow baseline sway of three to eight per minute which was due to rhythmic changes in local oxygen availability.

These experiments were carried out under pentobarbital anesthesia and gallamine paralysis with artificial respiration. Respiratory CO₂ was monitored continuously, and was held constant for the duration of the experiment beginning at least one hour before middle cerebral artery occlusion. Arterial P₀₂, PO₂, pH, and hematocrit were measured every four hours. In regular rotations, experiments were performed at low P₀₂ (15 to 20 mm Hg), normal P₀₂ (28 to 32 mm Hg), and high P₀₂ (40 to 60 mm Hg). Arterial P₀₂ was maintained between 120 and 180 mm Hg. Rectal temperature was maintained between 36°C and 38°C. Mean arterial blood pressure was monitored continuously but allowed to fluctuate spontaneously except that intravenous infusion of metaraminol was used in some cases in an effort to prevent reduction below 80 mm Hg.

Unless death occurred earlier, the animals were killed at 24 hours after occlusion. The brains were fixed by immersion in neutral buffered formalin and subsequently studied by routine histological technique. In order to study blood-brain barrier abnormalities 5 cc of Evans blue was injected intravenously shortly following arterial occlusion.

**Results**

**INTRACRANIAL PRESSURE**

Fourteen animals developed increased intracranial pressure, in each case more than 25 mm Hg at some point in time postocclusion, while in 13, intracranial pressure was continuously below 15 mm Hg. The mean and standard deviation for each group at hourly
EXPERIMENTAL CEREBRAL INFARCTION

FIGURE 3
Hourly measurements of oxygen availability, all animals.

FIGURE 4
Hourly measurement of mean arterial blood pressure, all animals.
OXYGEN AVAILABILITY
For each animal, the oxygen electrode showing the greatest change at occlusion has been selected. Oxygen availability following occlusion is expressed as a percentage of the preocclusion level for each electrode. The mean and standard deviation for O2a in the two groups following occlusion is shown in figure 3.

In the animals which did not develop increased intracranial pressure, the O2a rose rapidly from the immediate postocclusion mean of 38% (time 0) to above 60% by the first postocclusion hour. By contrast, in the animals which ultimately developed increased intracranial pressure, the immediate ischemia was more severe (mean 23%), the recovery was slower (less complete), and it was followed by a tendency to decline subsequently. The O2a differences between the two groups are statistically significant (p < 0.05) at every hour.

EEG CHANGES AT OCCLUSION
EEG flattening occurred regionally in nine of the animals which subsequently developed increased intracranial pressure and in four of the animals which did not. These numbers are not statistically significant (p > 0.05) though they comprise a trend reflecting the differences in initial ischemia quantitatively recorded by the oxygen electrodes. In most cases the EEG recovered in the animals which did not develop increased intracranial pressure, while several additional animals, which ultimately developed increased intracranial pressure, progressively lost EEG activity one to several hours postocclusion. In all cases, regional loss of EEG activity preceded substantial increases in intracranial pressure. A detailed exposition of these changes will be the subject of a subsequent report.

PATHOLOGICAL CHANGES
All of the animals which developed increased intracranial pressure had large infarcts extending from the head of the caudate nucleus to the cortical convexity, usually to the suprasylvian gyrus. In all but one of the animals which did not develop increased intracranial pressure, there was either no infarct or only a small one confined to the caudate nucleus and internal capsule. A detailed exposition of pathological changes will be the subject of a subsequent report.

BLOOD PRESSURE
The mean and standard deviation for each group is shown in figure 4. During the first six hours, blood pressure was slightly higher in the animals which ultimately developed increased intracranial pressure and subsequently it was somewhat lower. None of the differences is statistically significant except for the eighteenth hour (p < 0.05). The late tendency for lower blood pressure in the high intracranial pressure group reflects generally declining blood pressure in association with early stages of brain ischemia.
EXPERIMENTAL CEREBRAL INFARCTION

stem compression, notwithstanding well-developed Cushing reflexes in most of the cases which were supported to the point of medullary compression. In order to have better quality tissue for histological study it has become our practice to terminate the experiment when both pupils are dilated or bilateral EEG flattening has occurred.

The arterial $P_{CO_2}$ was similar in the two groups as shown in figure 5.

OTHER

There was no significant difference between the two groups in $P_{O_2}$, pH, hematocrit, oxygen content, or rectal temperature.

*Figure 6*

Hourly measurements of extradural pressure, subgroups matched for severity of initial ischemia.

*Figure 7*

Hourly oxygen availability measurements, subgroups matched for severity of initial ischemia.
SUBGROUPS MATCHED FOR SEVERITY OF IMMEDIATE ISCHEMIA

For reasons detailed in the Discussion, we have matched the groups for severity of immediate ischemia. This was achieved by arbitrarily excluding from the group which developed increased intracranial pressure the four with the most severe initial ischemia, and from the group which did not develop increased intracranial pressure, the three with the least severe initial ischemia. In making these exclusions, no attention was paid to blood pressure, $P_{CO_2}$, or subsequent course.

The time course of intracranial pressure changes, $O_2a$, blood pressure and $P_{CO_2}$ are depicted in figures 6 through 9. These subgroups did not differ in hematocrit, $P_{O_2}$, pH, oxygen content, and rectal temperature. Regional EEG flattening occurred at occlusion in six of these animals which subsequently developed increased intracranial pressure and in four which did not (difference not significant).

Discussion

THE PROBLEM OF $O_2a$ CALIBRATION

Previous papers have discussed at some length the theoretical obstacles to calibration of the in vivo $O_2a$ measurement in terms of absolute $P_{O_2}$. In essence, these are due to the unknowable electrode-tissue and electrode-microcirculation relationship. Though this is presumably a constant relationship for a single electrode in healthy brain, it might become altered during the process of infarction. This theoretic problem does not appear greatly to impair the empiric use of the measurement for continuous monitoring from a single electrode, nor for the averages of many electrodes as in the present work.

However, there is a systematic error in the calculation of the postocclusion $O_2a$ as percentage of the immediate preocclusion of $O_2a$. Since the denominator of this calculation is greater in the high $P_{CO_2}$ experiments and smaller in the low $P_{CO_2}$ experiments, the calculated $O_2a$ percent is underestimated at
Arterial $P_{CO_2}$ measured at four-hour intervals, subgroups matched for severity of immediate ischemia.

high $P_{CO_2}$ and overestimated at low $P_{CO_2}$, or by reference to some standard, the average postocclusion $O_2a$ should be somewhat higher in the high $P_{CO_2}$ experiments and lower in the low $P_{CO_2}$ experiments than is indicated in the data presented here. To the extent that this error is significant, it would cause underestimation of the differences reported here.

In ten animals studied separately, in the $P_{CO_2}$ range 18 to 100 mm Hg, the $O_2a$ was noted to double in response to a mean $P_{CO_2}$ change of 50 mm Hg (S.D. = ± 15 mm Hg) or about 2% per mm Hg change in $P_{CO_2}$.

Since this problem has been recognized we have attempted to relate $O_2a$ changes to preocclusion standard recording conditions of $P_{CO_2}$ 30 mm Hg, $O_2$ saturation 100%, at 37°C. Reanalysis of the data in these terms does not alter statistical significance because a smaller sample is available, and the mean $P_{CO_2}$ differences are not great.

**SIGNIFICANCE OF THE SERIAL $O_2a$ CHANGES—IMMEDIATE ISCHEMIA**

Inspection of figure 2 reveals a significant difference in immediate ischemia, more severe in the animals ultimately developing increased intracranial pressure. Our previous study indicated that immediate ischemia is determined largely by the nature of the arterial occlusion, and by the competence of the collateral circulation. Therefore, it was a surprise that there was not a $P_{CO_2}$ difference at this point. It will be remembered, however, that $P_{CO_2}$ has two differing effects on cerebral ischemia—an orthodox effect in determining immediate ischemia, and a sometimes paradoxical effect following ischemia. It is probable that these contrary effects are largely cancelled in the context of this protocol in which the ultimate outcome of a constant $P_{CO_2}$ set before occlusion is evaluated.

That this may be so can be supported by reanalyzing the data in terms of the determinants of immediate ischemia rather than the ultimate outcome, utilizing EEG change at occlusion as the criterion. Among the 13 animals whose EEGs were substantially altered at occlusion, regional $O_2a$, $P_{CO_2}$, and blood pressure were all significantly lower than among the 14 without EEG changes. From these, subgroups matched for blood pressure were constructed by excluding from the group with unchanged EEG at occlusion the three animals with the highest blood pressures at occlusion (165, 150, and 135 mm Hg) and from the group with altered EEG the three animals with the lowest blood pressures (80, 90, and 100 mm Hg). These subgroups matched for blood pressure are compared in table 1, and reveal significant differences in regional $O_2a$ and in arterial $P_{CO_2}$. They did not differ in

---

**Figure 9**

Arterial $P_{CO_2}$ measured at four-hour intervals, subgroups matched for severity of immediate ischemia.
PO₂, hematocrit, or temperature. It is important to emphasize that these data differ from the determinants of the ultimate outcome.

In the absence of any significant difference in systemic determinants of cerebral vascular reactivity and ischemia (PO₂, PCO₂, pH, Hct, BP, temp), an intrinsic structural or physiological difference in cortical collateral circulation between the two groups might be considered. Inspection of the occluding clip location at autopsy did not reveal any proximal middle cerebral branches escaping occlusion in any animal or any other anatomical variant systematically different in the two groups, though peculiarities in clip positioning, e.g., compression of anterior cerebral, posterior communicating, or anterior choroidal artery during life, could have escaped postmortem examination. Differences in brain trauma during the surgical approach to the middle cerebral artery and placement of the extradural transducer might result in differences in quality of reactivity of cortical vessels.

Pertinent to this question is the recent paper by Yamaguchi and Waltz which reported no correlation between regional cerebral blood flow and cortical arterial diameter in the cortical convexity, following puncture of the middle cerebral artery at its origin. The surgical exposure was by the same technique as used in this study, though with in addition extensive bilateral craniectomies required for cortical observation. Their conclusion, with which we agree, was that the effects of trauma and spasm were largely confined to the proximal trunk of the middle cerebral artery. These may be negligible in experiments such as the present series in which the middle cerebral artery was occluded, without subarachnoid hemorrhage, and with less manipulation of the artery than was required in their experiments.

**TABLE 1**

<table>
<thead>
<tr>
<th>Determinants of Immediate Ischemia</th>
<th>EEG altered at occlusion</th>
<th>EEG unchanged at occlusion</th>
<th>Difference significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>O₂a</td>
<td>19.7</td>
<td>43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PCO₂</td>
<td>24.5</td>
<td>34.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BP</td>
<td>112.8</td>
<td>114.4</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**SUBSEQUENT COURSE OF THE ISCHEMIC LESION**

In the animals ultimately developing increased intracranial pressure the slower, less complete recovery during the early hours following occlusion may reflect a less competent collateral circulation, for whatever reason, as well as the obviously larger initial lesion. The late decline, after about the twelfth hour, is clearly associated with rising intracranial pressure.

In the subgroups matched for severity of initial ischemia, such artifacts as surgical trauma, as well as extent of the initial lesion, are presumably similar. In these, the difference in early course between the two subgroups is probably due to an inherent structural or physiological difference in the ability of the collateral circulation to adjust rapidly to compensate for the ischemia before infarction occurs.

The minor difference in EEG changes between the two subgroups, though not statistically significant, may leave a lingering suspicion of a trend toward more severe initial ischemia in the subgroup which ultimately developed increased intracranial pressure, notwithstanding the nearly identical ischemia as measured by O₂a.

**THE NONSIGNIFICANCE OF THE PO₂**

The evidence is now massive—and this study adds to it—that altered arterial PO₂ maintained over many hours during an infarction will have relatively little effect on the outcome in an average group of major cerebral arterial occlusions. Many of these studies are reviewed in a previous report. The same finding has now been made in man. This surprising conclusion, in view of the very pronounced transient effects PCO₂ has on cerebral blood flow, might have been predicted simply from the violence of debate on the subject during the recent past. However, it does not follow that in the individual case altering PO₂ may not affect the outcome for better or worse. Upon analysis, it appears that the PO₂ is not unimportant but that its effects are so many, and their interrelations so complex, that their average over a several-hour period will be unsubstantial in a group of cases. Some of these effects are summarized in table 2. There may be a place for altering the PO₂ in some cases at some point in the evolution of the infarction, recognizing that it would be hard to predict in advance in which direction to make.
TABLE 2

Some Effects of Hypercapnia in Cerebral Infarction

1. Increase regional blood flow if collateral circulation is competent.
2. Reduce regional blood flow if collateral circulation is incompetent.
3. May facilitate development of collateral circulation over a time period if changed gradually.
4. Increase in intracranial pressure.
5. May aggravate cerebral edema.
6. May aggravate regional acidosis.

The change, how rapidly to do it, and that the same change may have different effects at different times after the arterial occlusion.

Thus, in many animals we have seen at one point in time following a major vessel occlusion that elevation of \( P_{\text{CO}_2} \) might cause a decrease in regional \( O_2 \), at a subsequent time no change, and still later an increase. The reverse sequence also has been seen in progressing lesions. Even within this context there may be variations, e.g., whereas a sudden \( P_{\text{CO}_2} \) change from 20 to 60 mm Hg might aggravate regional ischemia, a gradual change from 20 to 30 mm Hg might ameliorate it. A minimum requirement for therapeutic manipulation of the \( P_{\text{CO}_2} \) would be continuous monitoring or frequent measurement of regional cerebral blood flow.

SIGNIFICANCE OF THE INTRACRANIAL PRESSURE CHANGES

From examination of figure 6, there can be no reasonable doubt that beyond the tenth hour, progressively rising intracranial pressure accounted for the falling \( O_2 \). The greater uncertainty is during the first few hours. Whereas at one hour postocclusion there is already a significant \( O_2 \) difference between the two subgroups, reflecting slower collateral recovery in the group which subsequently developed increased intracranial pressure, a significant intracranial pressure difference (7 mm Hg) was not evident until the second hour. Though this seems a rather trivial difference, in fact it may be a very substantial fraction of the arterial or tissue perfusion pressure in the ischemic region or its border zone. A recent important study by Symon revealed arterial pressures in catheterized branches of the middle cerebral artery distal to an occlusion in the range of 8 to 22 mm Hg.

A more speculative point is whether the 1 mm Hg difference at one hour postocclusion obscures substantial regional pressure gradients within the brain in some animals.

Whether important regional pressure gradients develop within the brain during infarction, and whether they adequately explain the differences between the determination of immediate ischemia and the determination of the ultimate outcome of a cerebral vascular occlusion, is a subject for further research.

References

3. Waltz AG: Effect of \( P_{\text{CO}_2} \) on blood flow and microvasculature of ischemic and nonischemic cerebral cortex. Stroke 1: 27-37, 1970


The Course of Experimental Cerebral Infarction--The Development of Increased Intracranial Pressure
James H. Halsey, JR. and Norman F. Capra

Stroke. 1972;3:268-278
doi: 10.1161/01.STR.3.3.268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/3/3/268

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/