Amelioration of Cerebral Ischemia by Prior Treatment of Hypertension

JAMES H. HALSEY, JR., M.D., MICHAEL O'BRIEN, M.D., AND EDWARD R. STRONG

SUMMARY Bilateral carotid artery ligation was made in 14 SHR while rCBF was serially measured with hydrogen clearance. Blood pressure was controlled with an intra-arterial catheter connected to a reservoir. There was no significant correlation between blood pressure and rCBF prior to the carotid occlusion, but afterwards there was a progressively increasingly negative correlation between mean arterial blood pressure and rCBF with time. These observations indicate that the severity of ischemia is greater in the presence of hypertension if the hypertension is present prior to the onset of ischemia and the blood pressure maintained constant thereafter.

Epidemiologic studies over the past 2 decades have established a clear pathogenetic relationship between pre-existing hypertension and stroke morbidity and mortality, and even recurrence rate. The mechanism of action of hypertension has been presumed to be principally the acceleration of atherosclerosis.

An important contribution in experimental stroke research has been the introduction of the spontaneously hypertensive rat (SHR) developed from the Wistar strain. In an important contribution, Choki, et al. have shown that 2 hours following bilateral carotid artery ligation, rCBF, measured autoradiographically with $^{14}$C-antipyrine was significantly lower in SHR than in normotensive control rats (NTR). Although this report has the important potential implication for the management of human patients that the severity of clinical outcome of a stroke will be influenced by the blood pressure prior to the stroke, this interpretation must be limited by some details of the experiment. Since more than 32 generations of selective inbreeding separate the SHR from the NTR parent Wistar stock which served as controls, there is the concern that some other genetic determinant of stroke outcome, unrelated to blood pressure, might be present in the SHR. Further, during the 2 hours between the carotid ligation and the rCBF measurement in that study, the mean arterial blood pressure rose progressively in the NTR while it was declining in the SHR during at least the last 45 minutes of the experiment, raising the possibility that the rCBF differences were due to the changing mean arterial blood pressure (MABP) in the presence of defective autoregulation, rather than to the absolute blood pressure levels. Finally, the nature of the rCBF measurement provided no information about the time course of flow changes following the carotid ligation, though this in itself would not invalidate the essential observation.

In view of the potential clinical importance of this study, we have performed some further experiments with attention to these foregoing details in order further to confirm and amplify the original finding of Choki, et al.

Methods and Materials

SHR

SHR of the Okamoto-Aoki strain were obtained from Charles River Laboratories, Wilmington, MA. Body weight was 200-350 grams and age was 12-26 weeks. The animals were randomly assigned to treatment or no-treatment groups. The treatment consisted of addition to their drinking water of 1.5 mg reserpine, 160 mgm hydralazine, and 1.5 gm chlorothiazide/liter. There was no other difference in care between the 2 groups. There was no mortality in either group between their delivery to the laboratory and the performance of the experiment, an interval of 2-4 weeks.

rCBF

Two to five days prior to the experiment, 4 bare platinum electrodes, 125 microns in diameter, with 1 mm exposed tip length, otherwise insulated with epoxy, were implanted stereotaxically, one in the anterior corpus striatum and one in the dorsal hippocampus of each hemisphere. These were anchored to the skull with dental acrylic. An Ag-AgCl wire

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placed subcutaneously during the experiment served as reference. The electrodes were polarized at +600 mV and an H$_2$ oxidation current was monitored with a circuit described previously. We have found that the +600 mV polarizing voltage makes unnecessary any platinization or other pretreatment of the electrode. Bipolar EEG was monitored from the polarized electrodes, linking the striatal pair of electrodes in one channel and the hippocampal pair in the other. At the slow paper speed of recording (1 cm/min) only the EEG amplitude could be determined by inspection. This was therefore supplemented by on-line sampling of the power spectrum using a Fast Fourier Transform program, sampling 3 sec epochs. The blood flow measurement was calculated from the clearance rate of H$_2$ administered by inhalation. We have utilized a flow index = 0.693 + T'/i cc X gm$^{-1}$ X min$^{-1}$, where T'/i is the time required for clearance of 50% of the tissue hydrogen content, beginning 45 seconds after the termination of the H$_2$ inhalation, by which time arterial recirculation is complete in these small animals. We have found this flow index to be more reliable than compartmental analysis in these small animals because of the instability of flow compartments and variable intercompartmental diffusion of indicator. In the presence of a monoexponential clearance, our flow index would be identical to the single compartment blood flow, while in a biexponential clearance, our index would be relatively more influenced by the fast compartment unless it were very small. We have discussed some of these problems extensively elsewhere.

Anesthesia, Control of Respiration and Blood Pressure

Animals were prepared for experiments with a single intraperitoneal injection of pentobarbital 6 mgm/kg. They were paralyzed with d-tubocurarine and maintained on a ventilator via tracheostomy. The left common carotid artery was ligated and a catheter introduced proximally into the aortic arch. This was connected to a strain gauge transducer for monitoring blood pressure, and, via a Y adapter, to a 20 cc reservoir placed at an elevation above the animal approximately equal to the desired blood pressure, recalculated to centimeters of water. The tubing connecting the animal to the reservoir was filled with heparinized saline and the reservoir contained 5-15 cc of heparinized blood taken from a donor animal. This reservoir system served to fix the mean arterial blood pressure at the level of the reservoir by automatically controlling the animal's blood volume. In most cases, an attempt to elevate the MABP above the level found initially resulted in death due to pulmonary edema. For these experiments, we therefore set the reservoir at a level equal to about 10 mm Hg less than the MABP initially found. In order to prevent over-transfusion, which had occurred in a few animals in pilot studies, 0.1 mgm metaraminol was added.

A blood sample for measurement of PO$_2$, PCO$_2$, pH, and hemoglobin was taken when the animal was in a steady state. The respirator setting was not changed thereafter. Rectal temperature was monitored with a thermistor and maintained at 37.5°C ± 0.5°C with a heat lamp.

Two rCBF measurements were made after the steady state was achieved, before ischemia, which was then induced by ligation of the remaining right carotid artery. Thereafter, rCBF was measured as frequently as possible, allowing for adequate indicator saturation and desaturation of each curve. Not more than 2 per hour could be made in the presence of very slow flow.

Results

Blood pressure was lower in the treated than in the untreated animals but the difference between the groups was not statistically significant. Nonetheless, a satisfactory range of blood pressures over the 14 experiments was achieved. As can be seen in figures 1 and 2, the MABP 170 mm Hg appeared to be critical. Six of the seven animals with the higher MABP...
developed progressively falling rCBF to less than 0.25 cc × gm⁻¹ × min⁻¹, and isoelectric EEG in less than 4 hours, while 5 of the 7 animals with MABP lower than 170 mm Hg survived this period with active EEG and rCBF greater than 0.30 cc × gm⁻¹ × min⁻¹. The time course of flow changes at all 4 electrode positions was similar. From these figures, the blood flow at 30, 60, 120, and 240 minutes postocclusion was obtained by interpolation. These values for each electrode position for each time interval were plotted as in figure 3 and a linear regression expressing rCBF as a function of MABP, rCBF = a + b × MABP was calculated.

In table 1 are summarized the slopes (b) of this regression relationship together with their correlation coefficients and statistical probabilities. One can see that there was very little relation between MABP and rCBF prior to occlusion (both the slope and correlation coefficients are very small). Following ischemia, at all 4 electrodes there emerged an increasingly steep negative relationship (the higher the MABP, the lower the rCBF) and progressively increasing correlation coefficient at each electrode position.

Similar analyses were made for hemoglobin and for arterial Pco₂. Prior to ischemia the relationship between hemoglobin and rCBF was negative (the higher the hemoglobin, the lower the rCBF) with modest correlation coefficients (0.45 to 0.64) except at the left hippocampal location where there was a positive relationship but a relatively weak correlation coefficient of 0.23. Following ischemia at all time intervals at all 4 electrode positions, the effect of hemoglobin was not significant (correlation coefficients 0.0007 to 0.415) though at the 2 striatal electrode positions and the right hippocampal electrode there was a trend for the slope to become progressively more negative and the correlation coefficients to strengthen with time, though none became statistically significant. These trends can be seen in table 2.

There was no significant relationship between rCBF and arterial Pco₂ (correlation coefficients 0.013 to 0.270) with no consistent trends.

**Discussion**

The term “ischemia” needs some qualification here. Prior to the first preocclusion rCBF the animals had been prepared with ligation of the left common carotid artery in order to permit its catheterization. Some reduction in the rCBF at both left hemisphere electrodes resulted from this. In all cases, however, this procedure had no effect on the EEG, and in preliminary experiments there was never any clinical disability resulting from unilateral carotid ligation. Clearly, the flow input to the circle of Willis from the
right carotid and basilar arteries is adequate for functional survival of the left hemisphere so that the major event for the brain in these experiments was the subsequent right carotid occlusion after which the pathophysiologic events developed regularly.

Systemic Heparinization

Because of the reservoir system to control the MABP most of the animals received variable doses of heparin. The effect of this, if any, should have been to ameliorate the progressive ischemic process. In fact, the largest doses were received by the animals developing the most severe ischemia, these tending to take more blood from the reservoir late in the experiment. It seems improbable, therefore, that the heparin could have played a significant role.

Vasopressor Drug

The largest amount of metaraminol was similarly received by the most severely ischemic animals, having been added to the reservoir to limit the amount of transfusion necessary to prevent a fall in blood pressure. In previous unpublished experiments in cats, rabbits, and rats, we have seen no effect on rCBF, nor on continuously recorded brain tissue Po2 or EEG on intracarotid injection of metaraminol until recirculation evoked a blood pressure response, when the rCBF and Po2 changes simply reflected the quality of autoregulation.

Changing Hemoglobin

A single hemoglobin measurement was made prior to ischemia in each animal. This was found to have a modest negative relation to rCBF, as has been noted by others. Following ischemia, this effect was essentially lost, what correlation remained appearing to be random and not statistically significant. The changes in hemoglobin thereafter, which might have occurred in these experiments, would be difficult to predict, being affected by continuous fluid loss via the lungs, and by fluid and hemoglobin gain by transfusion from the reservoir. Since the reservoir contained blood mixed with saline, probably mild hemodilution occurred in the more severely affected animals. Insofar as one might be concerned about an independent hemoglobin effect, it can be noted from table 2 that the correlation coefficients were substantially weaker 30 minutes postocclusion than preocclusion, did not change systematically thereafter, and were in no instance statistically significant. A substantial hemoglobin effect therefore seems unlikely.

Absence of a CO2 Effect

Although a generation of physicians has known that CO2 has a potent effect on CBF, reflection on the many studies which have demonstrated this reveals that this has always been in the context of acute or sudden PCO2 changes in the individual patient or animal, comparing flow measurements before and

### Table 1: MABP

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<th>Corpus striatum</th>
<th>Dorsal hippocampus</th>
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<td></td>
<td>Pre Ocell</td>
<td>Min Post Ocell</td>
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<td>Slope</td>
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<td>(b) X 10^-2</td>
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<td>Correl coeff</td>
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<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Ocell</td>
<td>.067</td>
<td>.092</td>
</tr>
<tr>
<td>Min Post Ocell</td>
<td>.255 &lt;.25</td>
<td>.703 &lt;.25</td>
</tr>
<tr>
<td>30</td>
<td>.073 &gt;.25</td>
<td>.180 &lt;.25</td>
</tr>
<tr>
<td>60</td>
<td>.338 &lt;.25</td>
<td>.311 &lt;.01</td>
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<tr>
<td>120</td>
<td>.25 &gt;.25</td>
<td>.262 &lt;.025</td>
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<td>240</td>
<td>.25 &gt;.25</td>
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Slope, correlation coefficient, and probability for the regression relationship rCBF = a + b X MABP for each electrode location, at each time interval. In all cases the slopes are negative.

### Table 2: Hemoglobin

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<tr>
<td>Pre Ocell</td>
<td>-2.840 .563 &lt;.05</td>
<td>-2.480 .638 &lt;.01</td>
</tr>
<tr>
<td>Min Post Ocell</td>
<td>.098 &gt;.25</td>
<td>-2.650 .163 &gt;.25</td>
</tr>
<tr>
<td>30</td>
<td>.018 &gt;.25</td>
<td>-2.680 .189 &gt;.25</td>
</tr>
<tr>
<td>60</td>
<td>.707 &gt;.25</td>
<td>-1.150 .257 &lt;.25</td>
</tr>
<tr>
<td>120</td>
<td>-.011 &gt;.25</td>
<td>-2.470 .415 &lt;.10</td>
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<tr>
<td>240</td>
<td>-1.574 .276 &gt;.10</td>
<td>-2.470 .415 &lt;.10</td>
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Slope, correlation coefficient, and probability for the regression relationship rCBF = a + b X Hgb, for each electrode location, at each time interval.
after the Pco₂ change. More recently and slowly accumulating observations of CBF without imposed changes in Pco₂, or during prolonged periods at altered Pco₂, have revealed that CBF is strongly affected by the state of alertness and neuro-psychologic activation of the normal brain and that this usually overrides any secondary effects on CBF of simultaneously occurring CO₂ changes which themselves are determined by the activity state of the brain. Following ischemia, we and others have previously commented on the absence of an effect by the steady state Pco₂ in the course and outcome of cerebral ischemia. Reasons for this would include the foregoing discussion about the normal brain, but, in addition, during ischemia is the fact of altered regional CO₂ reactivity, i.e. sometimes attenuated, sometimes absent, sometimes paradoxically reversed.

Effect of MABP

Subject to the foregoing uncertainty about hemoglobin, this study confirms the earlier observations of Choki, et al., that for the same arterial lesion, ischemia is indeed more severe as a function of hypertension. The details of our experiments satisfactorily exclude genetic differences between hypertensive and control animals, and also exclude a potential artifact due to changing MABP in the presence of defec-
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The effect of the hypertension is probably to make the cerebral collateral circulation, including the circle of Willis, less competent, an interpretation consistent with the observation by Fujishima and Omae, that the carotid stump back-pressure, after ligation, is lower in SHR than in NTR, though the reservation about possible genetic differences discussed previously would still apply there.

How the effect of high blood pressure on the brain circulation takes place might be suggested by the direct observation on the leptomeningeal blood vessels reported by Byrom in the rat, and by Rodda and Denny-Brown in the monkey, both studies of renal hypertension. These studies reported the development of segmental vasospasm of the pial vessels as a function of both duration and severity of hypertension. To account for our observation of not much effect of MABP on rCBF prior to ischemia, and a progressive deterioration thereafter, one might suggest that the main pathologic effect of the hypertension is on the leptomeningeal and circle of Willis anastomotic vessels rather than on the intraparenchymal resistance vessels or the major afferent trunks, the carotid and basilar arteries as well as the anterior, middle, and posterior cerebral arteries. In this formulation, the posterior communicating arteries appear to represent an anomaly since they would seem to have more in common with the major trunk vessels than with the leptomeningeal vessels. The only reason to suspect a functional difference between the posterior communicating and the major trunk vessels would be that in the normal state there is no, or only a low pressure gradient across the posterior communicating arteries. Only further research can resolve this speculation.

We do not have a clear explanation for our observation that the rCBF declines progressively with time post occlusion. One possibility we have been considering is that edema, evolving as a consequence of the ischemia, causes secondarily compression of the collateral circulation, further aggravating the ischemia. An alternate or additional hypothesis is that some product of the evolving tissue necrosis, other than edema, exerts a toxic effect on the collateral circulation. This topic will be discussed in detail in a subsequent paper in which we will present measurements of cerebral edema which indicate that if edema plays a role at all, it is only secondary, taking effect only after the primary determination of collateral circulation competence by the blood pressure.

The clinical implication of these studies, insofar as laboratory observations in the rat can be applied to the human patient at the bedside, is that if cerebral ischemia occurs, its outcome will be less severe if the pre-ischemic blood pressure had been made normal, than if it remained high. This is consistent with the many clinical studies which reveal a reduction in stroke incidence due to treatment of hypertension. But further, especially high priority for reduction of blood pressure might be accorded the patient who might face an episode of cerebral ischemia, as during elective angiography, vascular reconstruction, or aneurysm ligation. How long the blood pressure must have been reduced, before useful protection might be realized, cannot be determined from these experiments, nor can we objectively comment on the important question of what to do about hypertension in the acute phase of a stroke when autoregulation might be defective.

References

Physiological Mechanisms Controlling Cerebral Blood Flow

GEORGE MCHEDLISHVILI, M.D.

SUMMARY The major conceptions of cerebral blood flow (CBF) control developed in the 19th and 20th centuries are listed. The systems of CBF regulation are considered from the viewpoint of automatic control. In the classification of CBF regulation mechanisms, 4 types are identified. The effectors of CBF regulation, i.e. the specific arterial segments through which each type of regulation is accomplished, were found to be mainly the major arteries of the brain and the small pial arteries rather than the intracerebral arterioles. Review of controlling influences on these effectors of regulation, (myogenic, humoral and neurogenic), show that priority should be given to neurogenic mechanisms. Several criteria governing efficiency of CBF regulation are proposed. Review of interactions of different types of CBF regulation shows that there may be both synergistic and antagonistic relationships. Information about the processes is important for medical practice.

SEVERAL CONCEPTIONS of the physiological mechanisms controlling cerebral blood flow (CBF) regulation were developed during the 19th and 20th centuries. The earliest was the Monro-Kelly doctrine,\(^1\) which postulated that there are 3 incompressible constituents inside the skull: cerebral tissue, cerebrospinal fluid, and blood. Therefore, the amount of blood and, hence, the CBF, should remain constant under any physiological and pathological conditions. The doctrine actually meant an absence of active control of CBF.

By the end of the 19th-century evidence had accumulated to show that CBF may, nevertheless, change.\(^1\) According to this new concept, although the diameter of cerebral blood vessels remained unchanged, CBF could be altered and was thus controlled by changes of the systemic arterial and/or venous pressures.

The next concept concerning regulation of CBF was developed in the 1930s when studies by Forbes and associates\(^2\) showed that the pial arteries may actively constrict and dilate. During the 1940s and 1950s further evidence accumulated for an active role of the cerebral blood vessels in regulation of CBF.\(^2\) Investigators, being unaware of which blood vessels were responsible for CBF regulation, speculated that arterioles were responsible as arterioles were the smallest precapillary arteries with one layer of smooth muscle cells. The control of dilatation or constriction of cerebral blood vessels was believed to be the direct effect of metabolic agents, e.g. CO\(_2\) and O\(_2\).

In the 1960s specific responses of particular portions of cerebral arteries (i.e. of the major, pial and intracerebral arteries) were found to be under different control.\(^5,6\) In this period experimental evidence accumulated on the important role of neurogenic control of CBF.\(^12-24\)

The conceptions of the physiological mechanisms regulating CBF mentioned above are schematically summarized in the figure.

Regulation of CBF: Automatic Control

The physiological mechanisms for regulation of CBF are triggered by disturbances such as a primary decrease in cerebral blood flow or by increase in cerebral blood volume. In response to such disturbances, a regulatory mechanism becomes active and adjusts CBF to the new conditions within possible limits. The mechanisms consist of 3 links: 1) afferent information indicating the type of disturbances in...
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