Mechanisms of Postischemic Brain Edema: Contribution of Circulatory Factors

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SUMMARY Controlled cerebral ischemia was produced in rabbits by bilateral occlusion of the common carotid arteries and restriction of collateral blood flow by a decrease of the systemic arterial pressure to a desirable level (by hemorrhage into a pressurized reservoir system). The following circulatory parameters were simultaneously monitored: systemic arterial pressure (SAP), pressure in the circle of Willis (Pcw), systemic venous pressure (SVP), and pressure in the sagittal venous sinus of brain (Pvs). The cerebral blood flow (CBF) was measured by means of the H2-clearance method, and the brain volume (BrV) changes were evaluated with a mechanical system of the stereotaxic device. It has been concluded that the pre-edematous changes in the brain tissue arise during deep ischemia but an important factor in the brain edema development is the recovery of the CBF with an increase of the intravascular pressure closely related to the brain blood volume augmentation. The latter may be pronounced because of diminution of the blood outflow from the brain when the SVP is increased. The compensation for the BrV increase (caused either by brain blood volume augmentation or by brain edema) is obtained by Pcw decrease probably due to resistance rise in the internal carotid and vertebral arteries. The brain edema may be additionally compensated by an active decrease of the systemic arterial pressure.

Introduction

SINCE CEREBRAL ISCHEMIA, with ensuing hypoxia and hypercapnia, is one of the most frequent causes of brain lesions in man, the postischemic pathological changes, brain edema in particular, have been the subject of numerous experimental investigations. Though it is generally believed that brain hypoxia and ischemia may result in edema, the conditions of its development have not yet been fully clarified. Pure hypoxia has been shown not to cause brain edema, but the latter does develop if the brain is simultaneously affected by some additional factors, e.g., hypercapnia, or if there was mere and prolonged ischemia. Blood-brain barrier permeability is increased during hypoxic-ischemic conditions, but its changes are not parallel with the development of postischemic brain edema.

It is obvious that the disturbance of water exchange between blood and cerebral tissue during postischemic edema development should be largely dependent on the circulatory parameters. However, the role of the latter has not been analyzed enough as yet. The purpose of the present study is to examine the influence of different circulatory factors on the development of postischemic brain edema and, in particular, to elucidate: (a) which of them, and how, may play a pathogenic role in brain edema development, and (b) how cerebral edema might be compensated for by the hemodynamic factors under natural conditions.

Methods

The experiments were carried out with 74 adult rabbits of both sexes weighing 2 to 2.5 kg. The animals were either unanesthetized (the preparatory surgical procedure was performed under local novocaine anesthesia), or anesthetized with ketamine (up to 1 gm per kilogram of body weight, intravenously), but no clear-cut differences in the experimental results have been observed in these two groups of rabbits. The preparatory surgical procedure was of two types. (1) In the routine experiments after tracheotomy both common carotid arteries and the right external jugular vein were exposed. All branches of the right carotid artery were ligated except the internal carotid. Then the external iliac artery was exposed extraperitoneally. A large craniotomy hole was made in the parietal region of the cerebral hemisphere. The dura mater was kept intact until the beginning of the experiment. (2) For a reliable stabilization or controlled change of both the systemic arterial and venous pressures the "chest-head preparation" was applied. The abdominal aorta and vena cava caudalis were exposed under the diaphragm and connected with pressurized reservoir systems. Both arteries and veins subclaviae were then exposed and ligated. Thus, it appeared that the systemic arterial, as well as venous, circulation was restricted mainly by the regions of head, neck and chest of the experimental animal.

To prevent blood coagulation heparin was injected intravenously (about 1,500 units per 1 kg of body weight) at the beginning of the experiment.

Monitored Circulatory and Other Parameters

Blood pressure levels were measured in four regions of the circulatory system. (1) The systemic arterial pressure (SAP) was recorded through the right internal carotid artery and vertebral arteries. The brain edema may be additionally compensated by an active decrease of the systemic arterial pressure.

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*The preliminary results of the present studies were published elsewhere.
pressure (SVP) was recorded through a catheter inserted into the external jugular vein and led to the cranial vena cava; in the "chest-head preparation" it could be stabilized at a desirable level by connecting the caudal vena cava with a pressurized reservoir system (other than the one for the SAP). (4) The venous pressure in the sinuses of the brain (Psv) was measured through a glass cannula inserted into the sagittal sinus. The recording of the above blood pressures was performed with electromanometers and Mingraf 81 (Elema, Sweden). The pressure transducers (type EMT 35) were set at the same level as the animal's heart auricle. The mean pressures were recorded by electrical integration. The ECG was recorded with the Mingraf 81.

The cerebral blood flow (CBF) was measured with the hydrogen clearance method.11 A platinum needle-shaped anode with a 2-mm² surface was inserted to the depth of 2 to 3 mm into the cerebral cortex (parietal area). The platelike iron cathode with approximately 20-cm² surface was fastened under the skin of the neck. The potential of the cathode with respect to the anode was +0.3 volt. The electric signal which appeared with saturation of the brain with hydrogen and during the subsequent clearance from the latter was amplified with the pH-meter LPU-01 and registered on the recorder KSP-4. The clearance curve having an exponential shape was further analyzed by the method described elsewhere.12,13

The respiration rate was recorded using a pneumotachograph connected with the tracheotomy tube, as well as with the pressure transducer EMT 32 and electromanometer (Elema, Sweden). When necessary, artificial respiration was applied.

The brain volume (BrV) changes were evaluated with a mechanical system of the stereotactic device and were expressed in millimeters of the brain surface expansion from the craniotomy hole.

The water content in the brain was determined as percentage of its wet weight. The brain was removed from the skull. All free fluid was carefully wiped out of the ventricles with filter paper. After determining the fresh weight of the brain tissue the brain was placed in a thermostat at about 100°C for 12 to 14 days until its constant weight was reached.

The experimental results were treated statistically and are presented below as mean values and standard errors.

Experimental Model of Cerebral Ischemia

This model has been previously described elsewhere.14 Ischemia of cerebral hemispheres was produced by two simultaneous procedures: occlusion of both carotid arteries and restriction of collateral blood supply to the brain hemispheres from the vertebral arteries by a decrease of the SAP to about 20 to 25 mm Hg. Under these conditions the blood supply to the medulla was usually sufficient to maintain spontaneous respiration, but the next small drop of SAP immediately resulted in a disturbance of respiration. To obtain deeper ischemia of the cerebral hemispheres the SAP was lowered below this level so that artificial respiration was required. To return the SAP to its initial level after ischemia, the reservoir had to be raised and, thus, blood returned into the vascular system until the arterial pressure reached a mean of 100 mm Hg.

Criteria of Brain Edema Appearance

These were (1) increased brain volume after lowered venous pressure and hence decreased brain blood volume, and (2) significantly increased water content in the brain tissue as compared to control values.

Results

The time course of the studied processes could be divided into three periods. (1) Cerebral ischemia: CBF decreased from initial values of 48 ± 6 ml per gram per minute to 10% to 20%; the SAP decreased from mean 98 ± 1.3 to about 20 to 25 mm Hg (that was one of the necessary experimental procedures which caused cerebral ischemia — see above); the SVP decreased from mean 0.5 ± 0.6 mm Hg by about 1 mm Hg. (2) Postischemic hyperemia which appeared within two to three minutes after removal of the carotid occlusion and restoration of the SAP (due to blood retransfusion): SAP usually reached its initial level because of the connection of the animal's arterial system with the pressurized reservoir; CBF increased to 107 ± 9 ml per gram per minute (if the perfusion pressure was about the normal range); SVP had a regular tendency to increase by 8 to 12 mm Hg, probably because of reversible heart insufficiency after considerable hypotension; postischemic hyperemia lasted about five minutes and then gradually disappeared. (3) The postischemic state after disappearance of the arterial hyperemia: CBF diminished and reached its initial values; SAP was still maintained at a normal range; SVP gradually decreased toward its initial level.

Brain volume (BrV) changes, as well as arterial and venous pressures, are shown in figure 1 (mean values and standard errors from 17 experiments). During ischemia the BrV decreased and during the subsequent postischemic hyperemia it increased simultaneously with respective changes of the arterial and venous pressures. However, in the following period of the postischemic state the BrV had two tendencies: (1) either it decreased simultaneously with the drop of the venous pressure in the vena cava and sinuses of the brain (fig. 1, top) and was assumed to be dependent on the blood volume changes in cerebral blood vessels, or (2) the BrV remained high despite the decrease of blood pressure in the vena cava and venous sinus of the brain (fig. 1, bottom) and was interpreted as a result of brain edema. There was other evidence that brain edema actually appeared in such cases, i.e., the increase of water content in the brain tissue. While in cases without edema it was 79.1 ± 0.15%, in cases with edema the water content increased to 80.3 ± 0.05%, the difference being significant (P < 0.02). Postischemic brain edema appeared in those experiments when ischemia was especially deep (because of considerable drop of the SAP) and/or when cerebral ischemia was repeated several times with intervals of 15 to 30 minutes.

The increase of BrV due to brain blood volume changes and/or brain edema was dependent on both SAP and SVP. The correlation between their changes was clearly seen in the experiments performed without artificial stabilization of SAP after blood retransfusion. After recovery from ischemia and establishment of steady state (within about 5 to 15 minutes) the rabbits were differentiated according to the changes of SVP in three groups: Group A, no-
siderable changes of SVP: from $-0.1 \pm 0.05$ to $0.4 \pm 0.2$ mm Hg ($n = 16$); Group B, with moderate changes of SVP: from $-0.5 \pm 0.2$ to $5 \pm 1.5$ mm Hg ($n = 12$); and Group C, with considerable changes of SVP: from $-0.6 \pm 0.22$ to $8 \pm 0.7$ mm Hg ($n = 16$). In the first two groups the SAP did not change significantly, from $114 \pm 0.4$ to $117 \pm 2.3$ mm Hg and from $112 \pm 3.3$ to $111 \pm 5.1$ mm Hg (Groups A and B, respectively), but in the last group it decreased considerably, from $111 \pm 3.2$ to $48 \pm 4$ mm Hg (Group C). However, the BrV (always being independent of the SAP) invariably changed parallel to the SVP: in Group A the brain surface raised by $0.3 \pm 0.03$ mm, in Group B by $1 \pm 0.26$ mm and in Group C by $2.4 \pm 0.1$ mm. These data (from randomly selected experiments) are presented in figure 2.

The dependence of BrV on SVP and not on SAP was shown better in experiments in which an isolated increase of SAP or SVP was produced in the postischemic period. The intravenous injection of adrenalin (0.5 mg) caused an increase of the SAP from $64 \pm 3.4$ to $108 \pm 3.2$ mm Hg within about one minute, while the SVP decreased from $5.5 \pm 0.7$ to $1.6 \pm 0.4$ mm Hg ($n = 11$). On the other hand, an artificial increase of the intrathoracic pressure (similar to the Valsalva maneuver) caused an increase of the SVP from $1.7 \pm 0.3$ to $10.4 \pm 0.5$ mm Hg within about 0.5 minute, while SAP decreased from $106 \pm 6$ to $51.3 \pm 11.2$ mm Hg ($n = 10$). Under these conditions the changes of the BrV were even opposite in direction to those of the SAP, but regularly followed the SVP changes: the brain surface lowered by $0.6 \pm 0.05$ mm following adrenalin injection and raised by $1.5 \pm 0.4$ mm during the Valsalva maneuver (fig. 3).

To elucidate the quantitative dependence of the BrV on both SVP and SAP, experiments were carried out under conditions when the SAP was artificially changed in the "chest-head preparation" by means of a pressurized reservoir system, while the SVP was reliably stabilized by another pressurized reservoir system, or, on the contrary, the SVP was changed while the SAP was reliably stabilized ($n = 17$). The results are summarized in figure 4, which shows that both SAP and SVP affect BrV, but the degree of in-

FIGURE 1. The BrV changes related to venous pressures (SVP and $P_{vs}$) and the SAP in the course of ischemia (Isch.), postischemic hyperemia (Hyp.) and the postischemic state (P. state) (see text). Top: BrV decreased in the postischemic state simultaneously with the drop of venous pressures and was interpreted as a result of the brain blood volume rise. Bottom: BrV did not decrease in the postischemic state simultaneously with the drop of venous pressures and was considered to be caused by brain edema.

FIGURE 2. The dependence of the BrV changes on the SVP when the SAP affects them slightly in the postischemic period in three groups of experimental animals (see text). The data were obtained from several randomly selected experiments.
fluence is different: SVP affects BrV about 6.5 times more than SAP.

The dependence of the BrV on the SVP should not be direct but mediated through the changes in the brain venous pressure. By studying the correlation \( n = 13 \) of the SVP and the pressure in the sagittal sinus of the brain \( (P_{sv}) \), the quantitative dependence appeared to be linear (fig. 5).

The BrV changes, dependent on either the brain blood volume changes or edema appearance, were found to affect in turn both the blood pressure in the circle of Willis \( (P_{cw}) \) and the SAP. The influences were found not to be similar when there were either brain blood volume changes or edema (the latter was identified according to the criteria mentioned above). Figure 6 shows that the \( P_{cw} \) invariably decreased in both cases even if the SAP was stabilized, but not similarly: in cases of brain blood volume increase (without edema) the \( P_{cw} \) decreased by \( 18 \pm 2.8\% \) \( (n=7) \), but when brain edema developed its decrease was \( 26 \pm 4.2\% \) \( (n=9) \), the difference being significant \( (P < 0.001) \). The SAP did not decrease when there was only a brain blood volume increase (without edema). But when brain edema developed there was a regular drop of the SAP by \( 29 \pm 4.8 \) mm Hg \( (n=10) \) (fig. 7).

Discussion

In spite of cessation of blood flow in individual major arteries of the brain the disturbances of CBF may be fully abolished due to well-developed collateral pathways. The presently applied experimental model of cerebral ischemia caused by bilateral carotid occlusion has the following ad-
FIGURE 6. The effects of postischemic increase of the brain blood volume (BBV) and of the appearance of postischemic brain edema (BE) on the pressure in the circle of Willis (Pcw). I = initial pressure levels, P = postischemic pressure levels.

FIGURE 7. The effects of postischemic increase of the brain blood volume (BBV) and of the appearance of postischemic brain edema (BE) on the SAP. I = initial pressure levels, P = postischemic pressure levels.

Advantages in comparison with others: (1) By changing the level of the SAP, collateral blood supply to the cerebral hemispheres and hence the severity of their ischemic changes may be controlled. (2) By restoring both the blood flow in the carotid arteries and the initial level of the SAP at the desirable time the length of the cerebral ischemia may be controlled. Elimination of one of the carotid arteries from circulation during the experiments (for recording some circulatory parameters) should not influence considerably the blood supply to the cerebral hemispheres under conditions of sufficiently high perfusion pressure. The large craniotomy was necessary for measurement of some parameters (BrV changes, Pcw, CBF) in the present experiments and even had additional advantages, since it led to stabilization of the intracranial pressure which could be an additional factor complicating the analysis of the experimental results.

The recorded parameters yielded information on most of the circulatory factors which might influence the postischemic edema development: (a) SAP was directly measured in mm Hg. (b) The blood inflow to the brain was ascertained as CBF in milliliters per gram per minute. (c) The functional behavior of the major arteries of the brain (internal carotids and vertebrals) was evaluated proceeding from pressure gradient from the aorta to the circle of Willis and of the pial arterial system was evaluated from direct studies in the previous investigations. (d) The brain blood volume was adopted as the brain volume which was dependent on changes of venous pressure in the cerebral venous system. (e) The blood pressure in the brain capillaries was ascertained from the blood pressures in the sagittal venous sinus and in the circle of Willis. (f) The segmental resistance in the venous system of the brain and the blood outflow from the brain were estimated by the pressure gradient between the brain venous sinuses and the vena cava. (g) Systemic blood stagnation in the venous system caused by transient heart insufficiency was ascertained from the level of the systemic venous pressure. The present studies were carried out under conditions when it was possible to obtain all the mentioned information in the course of the following events which lasted one and one-half to two hours: (1) an ischemic diminution of CBF which was more or less sufficient to cause brain edema, (2) postischemic hyperemia and, at last, (3) normalization of CBF when it again reached its normal value. But at the same time the conditions of the present experiments did not allow study of ischemic cerebral edema which could develop in the regions remaining continuously ischemic, or edema reaching a maximum several hours or even days after the onset of ischemia.

The present studies showed that brain edema does not develop during cerebral ischemia lasting 15 minutes and appears only in the postischemic period when the brain becomes hyperemic. However, the pre-edematous changes in the brain tissue which are crucial for the development of edema appear certainly during ischemia. The evidence for this conclusion is that edema developed only if cerebral ischemia was deep and/or repeated several times. In the present studies, postischemic brain edema appeared simultaneously with postischemic hyperemia when (a) the blood inflow to the brain was considerably increased, (b) the brain blood volume was increased because of increased blood inflow and decreased outflow (due to systemic venous stagnation because of transient heart insufficiency in the present studies), and (c) the blood pressure in the brain capillaries was increased because of dilatation of the pial arterial
system and especially because of deficient blood outflow from the brain due to systemic blood stagnation in the venous system.

The present studies showed that the level of the SAP influences edema development in the postischemic period, as it had been shown previously for traumatic brain edema. But the brain venous pressure has now been found to be much more significant for postischemic edema development. No local mechanisms affecting blood pressure in the venous system of the brain have been ascertained in the present studies, since the dependence of the pressure in the venous sinuses on that in the vena cava was about linear. SVP influenced brain blood volume and intracapillary pressure, and in this way considerably promoted the fluid filtration from blood into cerebral tissue and hence development of edema.

When BrV increased because of brain blood volume rise or edema development, these pathological processes might be compensated for by different mechanisms and in particular by the circulatory factors themselves. The present study showed how this might be realized. Though the effect of the venous system on brain edema development is considerably potent (in comparison with the arterial system), the compensation cannot be realized through it, since the normal range of the venous pressure is near zero and this means that it cannot be additionally decreased. Even in cases when it was increased because of heart insufficiency this meant that the compensatory mechanisms could not overcome this pathological change. Therefore, the compensation, which usually is a manifestation of normal controlling mechanisms, should be realized only through the arterial system, i.e., either by change of the SAP or by changes of the cerebrovascular resistance. The present experiments showed that a decrease of the SAP was not observed when there was only a BrV increase because of blood volume augmentation in its blood vessels, but if there was postischemic edema, the SAP dropped regularly. Hence the decrease of the SAP might be considered as one of the possible compensatory mechanisms of development of brain edema.

On the other hand, a decrease of arterial pressure in the circle of Willis may be a manifestation of the resistance rise in the major arteries of the brain, i.e., internal carotids and vertebrea. This phenomenon was observed in the present experiments even when SAP was stabilized both during brain blood volume increase and edema development, in the latter case being significantly more pronounced. The constriction of the major arteries of the brain had been observed during traumatic brain edema. This cannot but result in an increase in cerebrovascular resistance and in comparative decrease of the CBF, as has been shown within several minutes following experimental brain injury.

Hence, the present study investigated the contribution of the circulatory factors in the development of postischemic brain edema and concludes the following.

The primary changes in the brain that seem to account for edema development appear during ischemia, but in the course of the latter there are no adequate conditions for the development of brain edema. That is why, if it develops, it does so only after a considerable delay.

An important role in brain edema development is played by postischemic (reactive) hyperemia in the brain, probably because of an increase in CBF, augmentation of blood volume in the cerebral vessels, and rise of intravascular pressure.

Postischemic hyperemia in the brain thus has a dual significance: being a compensatory mechanism that contributes to abolishment of the CBF deficiency while at the same time promoting edema development. Hence, the reperfusion of blood to the ischemic brain might be very dangerous from the viewpoint of edema development.

If the previous studies had shown that the systemic blood stagnation as such does not cause brain edema, the present experiments proved that it might be one of the most potent circulatory factors that can contribute to brain edema development if the previous changes of the cerebral tissue were sufficiently deep.

Brain edema development may be compensated for inside the circulation by decrease of the SAP and constriction of the major arteries of the brain (maybe also of the smaller ones), increasing the cerebrovascular resistance and therefore decreasing CBF, BrV, and intravascular pressure in the brain capillaries.

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Carotid Blood Velocity During Cough: Studies in Man

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SUMMARY Utilizing a Doppler ultrasonic flowmeter catheter, right carotid artery blood velocity was measured during 91 coughing episodes in 16 patients. Such coughing reduced carotid blood velocity by 40 ± 22% (control = 34 ± 8 cm per second, cough = 20 ± 9 cm per second, p < 0.001). There was an insignificant low degree of correlation between the level of simultaneously recorded mean right pressure and the percent decline of peak carotid blood velocity, suggesting that impaired venous return was not the only factor responsible for the observed changes. It is concluded that (1) coughing diminishes phasic carotid blood velocity and (2) reduced cerebral perfusion may play a role in the pathogenesis of cough syncope.

Methods

Sixteen patients comprised the study group; there were 12 men and four women whose ages ranged from 23 to 58 with a mean of 44 years. Eight subjects had normal cardiovascular function and seven had coronary artery disease. One patient had mitral stenosis. No subject had symptoms suggestive of cough syncope. All diagnoses were established on the basis of right and left heart catheterization, indicator dilution curves and selective coronary cineangiography. Normal subjects were studied because of the presence of chest pain or systolic murmurs originally thought to represent heart disease. Patients were studied in a supine position in the postabsorptive state.

Phasic instantaneous right carotid artery blood velocity was measured with a Doppler ultrasonic flowmeter catheter as previously described. Under local anesthesia (1% lidocaine), the crystal-tipped catheter was introduced into a brachial arterial incision and advanced to the origin of the right carotid artery. In addition, a standard fluid-filled catheter connected to a Statham P23Db strain gauge was advanced from a medial antecubital vein to the right heart for the purpose of obtaining right atrial pressures. All subjects were instructed to cough in varying degrees while phasic carotid artery blood velocity, mean right atrial pressure and lead II of the ECG were recorded. Catheter tip position and stability were monitored by means of constant fluoroscopic image intensification. In six subjects, phasic aortic blood velocity also was recorded during cough.

The Doppler catheter utilized in this study measured the velocity of blood cells flowing past its tip and reflected volumetric flow only as a function of stable arterial lumen diameter.

Results

Ninety-one coughing episodes in the study group reduced peak carotid artery blood velocity by an average of 40 ± 22%. Mean (±1 SD) values for carotid blood velocity were 34 ± 8 cm per second in the control period and 20 ± 9 cm per second during the tussive efforts (fig. 1). There is a significant (p < 0.001) difference between the mean values.

The cough-induced decline of peak carotid blood velocity was immediate in onset and uniformly occurred within one second of each tussive effort (fig. 2). When the diminution of peak carotid blood velocity was plotted as a function of the rise of mean right atrial pressure, there was a low degree of correlation which was not statistically significant. The greatest reduction of phasic carotid blood velocity, however, was generally observed at the peak rise of mean right atrial pressure in the individual case.

In the six patients studied, there were minimal or no significant tussive-related alterations of peak aortic blood
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