Cerebral Circulation and Perfusion in Experimental Increased Intracranial Pressure*

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To study the pathological changes in different areas of the brain of cats subjected to increased intracranial pressure, the animals were perfused with glutaraldehyde to ensure in situ fixation of the tissue for light- and electronmicroscopy. Intracardiac perfusion of the glutaraldehyde gave excellent fixation of the brain in five cats studied as controls. However, in one animal when a marked increase of intracranial pressure was produced by inflation of an extracranial balloon, the glutaraldehyde barely reached brain tissue and merely filled some of the large cortical vessels. A second experiment revealed identical findings except that the cerebellum was partially fixed. Since the perfusion material was injected at the terminal stage when the compressing balloon had been evacuated and intracranial pressure had returned to zero following a marked elevation, the finding appeared to have considerable significance.

To explore the cause of this failure of perfusion, further experiments were done and different dyes were used. In some animals the cerebral circulation was also observed through a cranial window, to compare the results with those of perfusion.

Technique

The technique of insertion of the extracranial balloon and the monitoring of the vital signs has already been described in the preceding paper (see pp. 16–20). The glutaraldehyde was perfused essentially with the same technique as that described by Palay, et al.,4 for osmium tetroxide, and by Rewcastle5 for glutaraldehyde. The chest was incised in the midline and the pericardium opened. The descending aorta was clamped just above the diaphragm and a large cannula inserted into the left ventricle. The right ventricle was then opened, and 1000 ml of 5% glutaraldehyde in cacodilate buffer were injected in 30 minutes. The glutaraldehyde flask was encompassed by ice chips in a bottle held 5 feet above the animal.

In addition to perfusion with glutaraldehyde, in 40 cats we used Evans blue, barium sulfate, and India ink in smaller amounts; 50 ml (60% suspension of barium, or 2 ml/kg of Evans blue or India ink) were injected into the left ventricle. In all animals the right ventricles were opened for free drainage of the venous blood. The technique of perfusion was identical for the controls and for the animals with cerebral compression.

Tracheostomy was performed at the beginning of all experiments. Initially, artificial respiration was used when the chest was opened for perfusion. As experience was gained, the time required to open the chest and initiate perfusion was shortened to 15 or 30 sec, and artificial respiration became unnecessary.

In 15 animals an additional burr hole was made just behind the recording balloon, and a circular area of the dura was removed. A glass window made to fit the burr hole was inserted in the opening and fixed in place by a plastic washer, sealed to the skull with dental cement. The cortical vessels were observed through an operating microscope, using magnification of 25 to 100. Photographs and motion pictures were taken through the microscope. These animals were also perfused at the end of the experiment, and the results of observations through the windows were compared with the results of perfusion.

In each animal the perfusion was done at a different stage during the rise of intracranial pressure.
nial pressure, so that a clinical correlation could also be made. Following the perfusion, the brains were immediately removed, photographed, and sectioned for histological studies.

Results

Perfusion in Normal Animals Without Cerebral Compression. Perfusion was carried out in ten control animals without cerebral compression (glutaraldehyde in five animals, Evans blue in two, India ink in two, and barium sulfate in one). The brains were well perfused; the cortex of the cerebrum and cerebellum, the central gray matter, and the nuclei were denser in color than the white matter, appearing as dark yellow, dark blue (Figs. 1 A and 2 A), and bluish black respectively. The brains were fixed well with glutaraldehyde similar to brains fixed for weeks in formalin. The vessels were stained with Evans blue and with India ink, but Evans blue penetrated the brain slightly better, probably because it combined with plasma albumin. Although the vessels were fixed with glutaraldehyde they could not be seen well because of their light yellow color. The cortex of the brain of one animal in which barium sulfate was perfused appeared white, but the deep and fine capillaries were not perfused, presumably because of the size of the barium particles.

Cerebral Perfusion at Different Stages of Cerebral Compression and Increased Intracranial Pressure. Animals perfused at different stages of the rising intracranial pressure were divided into five groups. (In Groups 4 and 5 the perfusion was done after deflation of the balloon to study the cerebral perfusion following cerebral decompression.)

Group 1. In 10 animals the balloon was inflated gradually until the arterial and intracranial pressures rose to the highest peak and then gradually declined. The perfusion was performed when the intracranial pressure had returned to about zero. When respiration stopped and the arterial pulse was barely present, the chest was opened and the intracardiac perfusion was done. However, the perfusion substances did not reach the brain tissue (Figs. 1 B and 2 B). The vessels were either filled with clotted blood or empty. Frequently, the larger vessels were perfused but the dye did not fill the capillaries (Figs. 1 C and Fig. 4). Sometimes cerebellum was partially perfused (Fig. 1 D).

In these animals, as in the controls, the pericranial and facial muscle, the eyes, the tongues, and mucuous membranes were well fixed or stained with Evans blue or India ink. But unlike the control animals, the brains were not perfused.

Group 2. In five animals the perfusion was done when one or both pupils were enlarged but before the blood pressure became elevated or as it was just beginning to rise. At this stage the respiration and the pulse rates were decreased. The slow waves and lower amplitude in the EEG were present on the ipsilateral side, and to a lesser degree on the contralateral side. In these animals the larger vessels were stained but capillary perfusion was markedly decreased (Fig. 2 C).

Group 3. In two animals the brain was perfused when the respiration began to change. The amount of Evans blue reaching the brains was more than the previous groups but not adequate (Fig. 2 D).

Group 4. In five animals the balloon was inflated until both pupils were dilated, the EEG was flat, and the intracranial and arterial pressures were at their peak or declining. Then the balloon was deflated. The intracranial pressure returned to zero or near it. Four animals died within 30 minutes. One animal whose respiration was artificially supported for 15 minutes died 5 hours later; during these five hours the intracranial and arterial pressure were normal but the electroencephalograms were almost flat. It is of utmost interest that, in spite of deflation of the balloons, the perfusion material did not reach the brains in this group in which the brains were almost identical with those in the first group (Fig. 3 A).

Group 5. In three animals the balloons were deflated before the marked rise of the arterial pressure and complete dilatation of the pupils occurred. Perfusion of the brain was then decreased. Better staining, however, was obtained if the brain was not perfused immediately after deflation of the balloon. Figure 3 B shows the
Fig. 1. Comparison of the cerebral perfusion in animals subjected to cerebral compression (B, C, D) with that of a normal control (A). The cerebral compression was carried out until both pupils were dilated and the vital signs failed. Note that the spinal cord in B and cerebellum in D are perfused with Evans blue. The large arteries are filled in C but the capillaries are not perfused. The brain in C was perfused with India ink. The control brain with India ink appears almost exactly like A.

Fig. 2. A comparison of the cerebral perfusion at different stages of alteration of vital signs with that of a control (A). The brain was perfused in B when all vital signs failed, in C when one pupil was dilated, in D when the respiration slowed. (The brain in B is the cross section of the one in Fig. 1 B and both are from the animal whose record was used to illustrate the sequential alteration of vital signs in the preceding paper. The brain in A is a cross section of the one in Fig. 1 A).

Fig. 3. Cerebral perfusion in animals following the deflation of the balloon. In A the balloon was deflated when both pupils were dilated, EEG was flat, and arterial pressure was raised. In B the balloon was deflated when the pupils were partially dilated (this brain was perfused 50 days following decompression).

Fig. 4. Cerebral perfusion with India ink as soon as the vital signs failed due to cerebral compression. These blood vessels, under the cranial window, were photographed through the microscope. A large artery and a few arterioles are perfused with India ink. The circulation of the vein, in the center, was stopped, and it was filled with intravascular clots. Note that vein and most capillaries are not perfused.
brain of a cat in which the balloon was deflated when both pupils were partially dilated. The brain was perfused 50 days after deflation. During this period the animal was conscious and able to walk.

Normal Cortical Vessels Before Inflation of the Balloon. Observation of the cerebral cortex through the microscope shows that the diameters of the cortical vessels are variable but can be divided into three groups: 1) large arteries and veins, such as the main branches of the middle cerebral arteries and the veins entering the sagittal sinus, 2) the middle-sized arteries (arterioles) and veins (venules), and 3) the arterial and venous capillaries.

The blood flow in the larger arteries and veins cannot usually be seen under the microscope due to the faster speed of the cells. The individual red cells can be clearly seen as they pass through the capillaries. The flow can be seen in arterioles, and particularly in the venules, at a certain segment of the vessels especially as they turn or as they cross the other vessels. Some arteries display a serpentine movement with each pulsation.

Cortical Vessels During the Inflation of the Balloon and Rising Intracranial Pressure. In 15 animals the cortical vessels and their blood flow were observed as the balloon was gradually inflated. Usually there was no change in the cerebral blood flow following the first few increments of injection of 0.2 ml saline in the balloon. As additional increments were injected the first noticeable change occurred in the circulation of the capillaries. The flow decreased in some of the capillaries immediately after the injections, but it returned to normal flow several minutes later. There was no visible change in the flow of the arteries and veins, but a slight reduction of the flow was noticeable in the venules. At this stage there were no conspicuous changes in vital signs and EEG.

As increments of saline were added, marked reduction of the blood flow occurred in the venules and later in the arterioles. Usually the electroencephalographic changes began to appear at this stage. Gradually some of the venules and veins dilated (Fig. 5 B and C). The dilation and reduction of the flow was not universal in all vessels; it occurred in some of the veins while it was not present in others. Sometimes only a segment of the vein was dilated, particularly that next to a region of obstruction where the veins were compressed against a crossing artery, at a narrowed sulcus, or at the edge of the sagittal sinus (Fig. 6). The direction of the flow reversed or changed in some of the veins, taking whatever path was open. The amplitude and frequency of the electroencephalogram decreased markedly and the respiration and the pulse slowed.

When a sinusoid wave of the arterial pressure appeared, a simultaneous change occurred in the speed of the already decreased blood flow. The blood flow became faster as the blood pressure increased and became slower as the blood pressure decreased. At this and the following stages, the blood flow was not continuous in most vessels, and the cells appeared as if they were marching to the same rhythm as the heart beat. Similarly, the blood flow became slightly faster immediately following each respiration and slowed in between, as if the cells were being pulled forward with respiration. Gradually, the red blood cells began to sludge (Fig. 5 D) and the venous blood appeared bright red, looking like arteries. Usually one or both pupils were partially dilated at this time.

With additional increments of fluid and with the sudden rise in arterial and intracranial pressure, the blood flow decreased markedly in both veins and arteries. The sludging of the cells became prominent in the vessels. The cerebral cortex became pale, and a majority of the cortical vessels were either empty of blood or were occluded by the sludged cells (Figs. 5 E and Fig. 6). The sagittal sinus was collapsed and flow in it decreased. The electroencephalogram was flat, and the pupils were dilated.

Finally, when the cranial and arterial pressure failed and declined simultaneously, the blood flow ceased almost entirely. Sludged red cells and large emboli, separated from the plasma (Fig. 5 E), wandered in the arteries and veins in different directions. Frequently, the intracranial and arterial pressures rose slightly and temporarily a few times as they declined; with each elevation there was a slight return of the flow in some of the vessels. Within several minutes both respiration and heart beats stopped.

In five animals the balloon was deflated as
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Fig. 5. Vascular alteration in cerebral compression and rising intracranial pressure. The pial vessels under the cranial window appear as they are seen through the operating microscope and photographed. These frames are reproductions from motion pictures and are selected from different stages. Note that before the inflation of the balloon in A the inverted Y shaped vein (V) is crossed by the artery. As the intracranial pressure increased, the vein dilated (B) and its blood flow decreased (C). Finally, the sludging of the red cells (C and D) and intravascular clotting and embolus formation (E) occurred. After the deflation of the balloon the blood flow returned (F) moving these emboli forward. Note the vein is dilated more proximal to the artery where it was compressed. The artery is slightly dilated.

the intracranial and arterial pressures were at their highest peak or when they were declining. Immediately after deflation of the balloon, a sudden return of the flow occurred in some arteries and veins (Fig. 5 F), moving the sludged cells and emboli forward. But the flow did not return in most of the small vessels and capillaries. However, the flow ceased again, and all animals died. In the single animal that received artificial respiration following deflation of the balloon, the cranial and arterial pressures returned to normal immediately and the respiration became spontaneous within 15 minutes. Similarly, in this animal the blood flow returned in the large arteries and veins but not in the majority of the small vessels and capillaries. The intracranial pressure remained around zero and the animal died 5 hours later.

Perfusion of the brain with Evans blue and India ink in these five animals confirmed the presence of obstruction of capillaries in the brain.

Discussion

Cushing observed the cortical pial vessels in dogs through a cranial window while cerebral compression was produced by allowing mercury to enter a bag inserted inside the skull. He noted that the larger veins remained full of dark non-circulating blood and looked as though they were broken in places. The arteries were mere threads and barely distinguishable while the cortex was completely blanched. He also reported that the longitudinal sinus might be completely collapsed by increased intracranial tension. Exactly similar findings were observed in these experiments. But as Cushing himself stated, these were findings in the later stages of increased intracranial pressure when the local compression against the hemisphere was considerably in excess of the measured arterial pressure. Nevertheless, in our experiments with cats, the intracranial pressure did not have to be higher than the arterial pressure in order to produce the above circulatory changes.

Wolf and Forbes confirmed Cushing's observations with similar experiments. They reported that, as the intracranial pressure was raised, there was a slowing of the blood flow through the veins, dilatation of the veins and arteries, slowing of the blood flow
through the arteries, and, finally, complete emptying of these vessels and blanching of cortex. Our observations are comparable except that, when dilation of the cortical arteries occurred, it was slight. In fact, frequently the arterial diameter was narrowed.

Walker, in experimental studies on concussion, found dilatation, intravascular agglutination, and slowed blood flow in the cortical vessels, findings that we observed in the later stages of cerebral compression.

We paid special attention to the circulation of the small vessels and capillaries, because through the perfusion studies we had discovered that as the intracranial pressure was raised decreasing amounts of dye reached the brain until ultimately no dye reached the brain. Since the larger vessels were stained (Fig. 1 C), the obstruction to the flow must have been at the level of the capillaries and small vessels (Fig. 4).

As the intracranial pressure increased, the capillary circulation decreased even before there was a conspicuous change in EEG, respiration, and pulse. The flow gradually stopped in an increasing number of them. Later, the flow decreased in the larger veins and then in the arteries. While most of the capillaries were completely collapsed or obstructed, an inefficient circulation was maintained in the others (Fig. 6). Since obstruction and cessation of the flow were often present in those vessels which were compressed by other anatomical structures, the reduction of the circulation cannot be considered due entirely to the so-called vasomotor phenomena so frequently mentioned in the literature. Also, the dilation was noted mainly in the segments of the vein proximal to an obstructed region. Our exper-

Fig. 6. Injection of Evans blue in the aorta before inflation of the balloon. The dye extravasated gradually in subarachnoid space. The vessels themselves were stained. (The bluish-stained walls of vessels cannot be seen clearly in the black and white reproduction.) As the intracranial pressure rose, the flow in the artery (A) narrowed; but the artery itself was not narrow, suggesting the swelling of the vessel's wall. Note that the vein (V) dilated on the right, but not so much in the middle. The dilation was proximal to the sagittal sinus. Note that the flow is stopped in that portion of the venules (VL) which is compressed by the artery. Flow was maintained through a feeding capillary (upper arrow). Note the sludged cells and microemboli in the vessels. The circulation has stopped in the majority of the capillaries with stagnant blood and microemboli (lower arrow).
ments therefore suggest involvement of a mechanical factor in the production of venous dilatation and increased intracranial pressure in cerebral compression. There was no evidence regarding the presence or absence of a vasomotor factor.

The contents of the posterior fossa were somewhat more perfused in few of the animals. This may have been due to the protective effect of the tentorium. On the other hand, tentorial herniation may have been the reason for the decreased blood flow in the supratentorial region. But since the decreased perfusion and the obstruction of capillaries were seen from the early stages of increased intracranial pressure, the tentorial herniation probably represented a terminal factor rather than the only one involved in the production of the cerebral ischemia. Furthermore, in some animals (Fig. 1 C) the main arterial branches remained open while the obstruction occurred in capillaries; this could not be the result of a tentorial herniation.

The deflation of the balloon at different stages of intracranial pressure revealed different degrees of uptake of dyes in the cerebral capillaries. When intracranial pressure was higher, a lesser degree of perfusion occurred. However, the observation of the cerebral blood vessels during rising intracranial pressure and the further observation of perfusion of the same brains suggest that the obstructed and occluded blood vessels prevented the injected materials from reaching the brain.

Following deflation of the balloon, the circulation was not reestablished in a majority of small vessels and capillaries which were compressed or occluded. This failure of blood flow to return throws considerable light on the cause of the marked brain damage or death which commonly follows severe head injuries and cerebral compressions. (Recently we observed through the microscope the cerebral cortex of a 53-year-old woman with head injury and bilaterally dilated pupils after an acute subdural hematoma had been removed. Although the pulsation of the brain returned and the vessels appeared essentially unchanged to the naked eye, microscopic observation revealed no flow in many of the capillaries. Also, the red cells were sludged as they passed through the vessels. This patient died the following day.)

The fact that the blood flow continued in the larger arteries and veins suggests a shunting system, by-passing the capillaries. The change of the venous blood to a reddish color also suggests a shunting system.

Weinstein, et al., in an experimental study of patterns of brain distortion and ischemia in the presence of intracranial masses, found that rapid inflation of a subdural balloon not only caused ischemia of the brain adjacent to the balloon but in remote portions of the brain as well. Our perfusion studies are in agreement with their findings. Since they froze the animal’s heads in liquid nitrogen, their experiments demonstrated the distortion of brain substance. In the present experiments the indentation on the brains caused by the balloon were clearly visible at the time of opening of the skulls, but the brains returned almost to their normal configuration without a remarkable shift of the midlines. This phenomenon, together with the observations made through the cranial window, suggests that the rising intracranial pressure in acute cerebral compression is due to vascular dilatation rather than brain swelling and supports the conclusion made by Langfitit, et al., that cerebral vascular dilatation was a constant response to increase in intracranial pressure.

Observation of the vessels through the window, however, indicates that this vascular engorgement occurs mainly in the veins rather than the arteries. The dilatation of the arteries was slight and mostly inconspicuous. In fact, x-ray study with the injection of barium sulfate (Fig. 7) disclosed that the cortical arteries were narrowed, as when cerebral angiography is performed in patients with increased intracranial pressure. The reason for this narrowing of the arteries is not yet clear. In one experiment Evans blue was injected in the aorta before the intracranial pressure was raised. The dye extravasated around the blood vessels and outlined their external surface as the cranial pressure was rising (Fig. 6). Since the blood stream was narrowed in the arteries but the arteries themselves were not in spasm, it may suggest that the swelling had occurred in the vessel walls.

Conclusion

In rising intracranial pressure the altera-
tion of vital signs occurs in a sequence starting with slowing of the respiration, followed by slowing of the pulse, dilatation of pupils, and rising blood pressure. The electroencephalographic changes occur prior to the alteration of respiration.

Cerebral circulation decreases as the intracranial pressure increases. The cerebral circulation decreases in the venous capillaries even before the alteration of electroencephalogram and is gradually reduced in the veins and arteries as other alterations occur. The cerebral circulation is markedly decreased in the capillaries and veins when there is slowing of respiration and pulse. Both venous and arterial circulations are decreased when the pupils begin to dilate, and the flow is almost completely stopped when both pupils are dilated. The electroencephalogram is flat when the cranial and arterial pressures are at their peak.

Obstruction of blood flow is commonly caused by the compression of vessels against other intracranial components, and occlusion of the vessels occurs due to the sludging of blood cells which form microemboli. When compression is the cause of obstruction, the blood vessels, commonly the veins, are squeezed against the artery, an obstructed sulcus, or the edge of the sagittal sinus. The sagittal sinus is also collapsed with decreased blood flow. When a vessel is obstructed distally, the blood flow diverts or reverses proximally in any direction in which the flow can be maintained. These findings suggest the involvement of a mechanical factor in the production of venous dilatation and cerebral ischemia.

When the intracranial pressure is raised high enough to cause dilatation of both pupils, flattening of the EEG and sudden rise of the arterial pressure occur, and the animal dies within a few minutes. If the balloon is deflated the blood does not return in the majority of the small vessels and capillaries but it does return in larger arteries and veins. The findings suggest that following a marked rise in intracranial pressure there is diffuse and massive infarct of the brain caused by microemboli and obstruction of small vessels.

If the balloon is deflated before the dilatation of both pupils, flattening of EEG, and sudden rise of the arterial pressure, considerable blood flow will return in the capillaries. Since deflation of the balloon does not reestablish flow in the majority of the capillaries and small vessels, but flow does return in larger vessels, there must be shunting of blood between the arteries and veins. Therefore, since cerebral angiography visualizes the larger vessels, it does not, in its present
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form, seem to be of value in the evaluation of cerebral circulation at the capillary level where the nutrient material reaches the brain. A similar objection can be raised to the techniques of measuring the cerebral circulation via the carotid blood flow.

Summary

Increased intracranial pressure was produced by an extradural balloon. The EEG, respiration, and blood pressure were monitored simultaneously. The cortical blood vessels were observed through a cranial window with a microscope, and brains were perfused at the end of the experiment with glutaraldehyde, Evans blue, barium sulfate, or India ink. The cerebral circulation and perfusion were studied at different stages of rising intracranial pressure and with each change of vital signs. The resulting alteration in the cerebral circulation can be summarized as follows:

1. With rising intracranial pressure the cerebral circulation and perfusion gradually decreased and finally ceased in the capillaries and later in the larger vessels.

2. The reduction and cessation of the circulation and perfusion was caused by external compression on the vessel by other intracranial components, and by internal occlusion by sludged cells, microemboli, and intravascular clotting.

3. Following the deflation of the balloon, cerebral circulation and perfusion did not return in the majority of the capillaries and small vessels if the pupils were dilated, the EEG was flat, and the blood pressure elevated. The flow did return to a considerable degree if these signs were not fully developed.

4. The failure of the circulation to return is considered to be due to capillary obstructions.

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References