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THE "NO REFLOW" PHENOMENON IN THE CEREBRAL CORTEX IN THE EARLY POSTISCHEMIC PERIOD

V. V. Semchenko and N. N. Klassen

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During the first minutes of the resuscitation period after total profund cerebral or general ischemia the volume blood flow of the brain tissue rises sharply [3, 4]. Meanwhile investigations have demonstrated local postischemic hypoperfusion of the cerebral cortex as the earliest manifestation of cerebrovascular disturbance [7, 9]. The contradictory nature of these data and the absence of agreement on the nature of the phenomenon of occlusion of the cerebral vessels in the early postischemic period motivated a morphological and functional investigation of the microcirculation of the cerebral cortex during ischemia and in the early recovery period.

EXPERIMENTAL METHOD

Experiments were carried out on 50 male albino rats weighing 180-220 g anesthetized with ether. Ischemia was produced by a model of clinical death lasting 5 min from blood loss through the external iliac artery followed by resuscitation. Material for analysis was taken from the experimental animals at the end of clinical death and 5, 10, and 30 min after resuscitation. Ten animals served as controls.

The cerebral vessels were injected with gelatin medium with high-grade purified Mark PM-50 soot. Perfusion was carried out intravitally at 37°C under a pressure of 120 mm Hg for 20 min. The brain, perfused with ink, was fixed in 96° alcohol and embedded in celloidin. The angioarchitectonics of the cortex and deep brain formations was studied in cleared preparations 200 μm thick. The vascular network of the sensomotor cortex was subjected to morphometric analysis: The density of the vascular network was determined [1] in sections 20 μm thick and the internal diameter of the vessels measured. Filling of the vessels with blood was studied by a histochemical method of hemoglobin determination [8]. For ultrastructural analysis the cortex was fixed by perfusion with 2.5% glutaraldehyde and immersion in the same fluid and postfixation in 1% OsO_4. Oriented pieces of neocortex were embedded in Epon-812. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in the EVN-100LM electron microscope. The numerical results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

At the end of ischemia a small decrease in density of the vascular network was found in the cerebral cortex (Fig. 1). The mean diameter of the vessels increased to 7.02 ± 0.47 μm compared with 5.12 ± 0.12 μm in the control ($P < 0,01$). Some microvessels were highly constricted, others extremely dilated, i.e., there was a wide range of variations of their diameter. The residual content of blood in the vessels was minimal.

Evidence of slight swelling of the pericapillary astroglia, and moderate translucency of the cytoplasm of some and hyperchromia of other endotheliocytes of the blood capillaries were observed electron-microscopically during ischemia.

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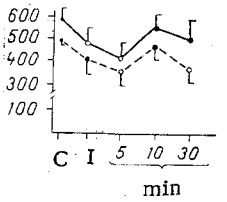

Fig. 1. Density of vascular network in sensomotor cortex in postischemic period. Continuous line, upper level; broken line, lower level of cortex. Filled circles $P > 0.05$, empty circles $P < 0.05$. Abscissa, C) control, I) ischemia 5, 10, and 30 min of postischemic period; ordinate, density of vascular netowork (in units/mm^2).

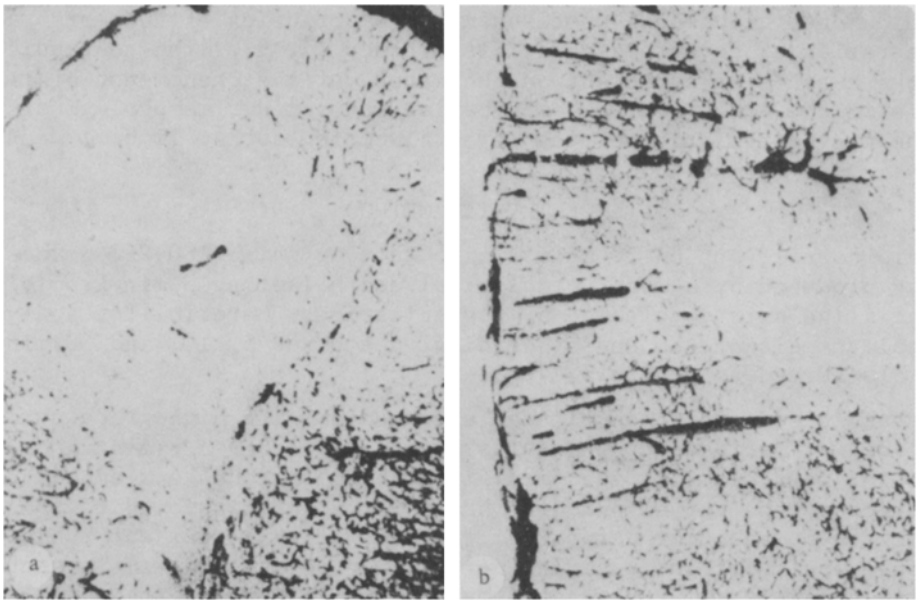

Fig. 2. "No reflow" focus extending to all layers (a) and located in the lower level (b) of the cortex in the postischemic period. a) 5 min, b) 30 min of postischemic period. Injected with ink. 48 ×.

At the 5th minute of recirculation local extensive areas of incomplete filling of vessels 1-3 μm in diameter with ink against the background of well perfused tissue were found on the surface of the cerebral hemispheres. These regions, one to three in number on each brain, were found in the frontal, parietal, occipital, and other parts of the brain. Regions of incomplete filling of the vessels were as a rule located in the surface layers of the cortex, but sometimes extended to the white matter, which corresponded to the territory of distribution of fairly large branches of the intracerebral arteries (Fig. 2a). On the whole the density of the vascular network at the 5th minute of the recovery period was already significantly lower than in the control. The mean diameter of the vessels was close to that in the control. In "no reflow" regions a very low density of the perfused network was found, and they can consequently be regarded as regions with very weak perfusion. Histochemical staining for hemoglobin also revealed zones with defective blood filling of the vessels.

Electron-microscopically, at the 5th minute of the recovery period sludging of erythrocytes, infrequent platelet aggregates, and protein bands in contact with endotheliocytes were discovered about equally in degree in the lumen of the small blood vessels in the "no reflow" and adjacent regions. In zones with better perfusion, swelling of fragments of hyperchromic endothelial cells were observed more frequently in the lumen, with signs of microclasmatosis; these changes progressed at subsequent times.

At the 10th-30th minute of the recovery period marked focal disturbances of patency of the vascular network were no longer observed, emphasizing their reversible character in the earlier stages. By this time signs of reactive hyperemia had developed in the brain, as shown by moderate vasodilatation, an increase in density of the vascular network compared with the previous time, and good filling with blood. Widespread generalized hyperemia was observed in 10% of cases. In most animals irregularity of filling of the vessels with blood was observed at this time, but regions of reduced perfusion were located more often in the deep layers of the cortex (Fig. 2b) and subcortical structures and were better filled with blood than in "no reflow" regions.

Ultrastructural analysis showed that during 30 min of the recovery period there were no signs of any marked degree of generalized swelling of endotheliocytes or pericapillary astroglia or of compression of the vessels. At the 30th minute signs of congestive venous hyperemia were observed in the brain.

Most workers who have described the phenomenon of postischemic hyperfusion studied the total blood flow of the whole brain or its major regions. However, in experiments involving the use of a large number of electrodes, nonhomogeneity of perfusion was demonstrated in the neocortex in the early postischemic period [7], which is in agreement with the results of the present investigations. Postischemic formation of regions of incomplete vascular filling can be explained by changes in the rheologic properties of blood in the vessels during the period of ischemia, by edema of endotheliocytes and pericapillary astroglia, and by bubble formation [6]. However, in the present experiments the residual content of blood in the cerebral vessels during clinical death was small and could have had no significant effect on the development of the phenomenon of vascular occlusion. There was no compression of the microvessels by swollen processes of astrocytes. The morphological changes in the vessels were thus themselves not sufficient to induce a "no reflow" phenomenon during recirculation.

The facts described above suggest that the reduction in diameter of the group of cerebral cortical microvessels in the early postischemic period is functional in nature; spasm of the intracortical arteries, arterioles, and precapillary sphincters. Acute arterial hypertension causes a sharp increase in tone of the intracortical vessels [2]. Consequently, transient arterial hypertension in the first minutes of postischemic recirculation, along with other factors (hypercatecholaminemia, disturbance of autoregulation) [5], causes transient spasm of the vessels, producing a sharp focal reduction in perfusion of the brain tissue with blood during this period. Since there are no arteriolo-venular anastomoses in the cerebral cortex, the shunting of "excess blood" is evidently effected by the main capillaries.

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