EXPERIMENTAL INVESTIGATION OF THE "NO-REFLOW" PHENOMENON

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The state of the vascular network of the brain was studied in 29 dogs by perfusion with ink after complete temporary arrest of the blood flow (ABF) for 5-20 min by mechanical asphyxia or fibrillation of the heart. In both groups extensive areas unfilled with ink were obtained for 7-8 min after ABF (the primary no-reflow phenomenon). The primary no-reflow phenomenon disappeared completely or became negligible after ABF for 10 min, and it reappeared in another form after ABF for 12-20 min (secondary no-reflow phenomenon). The no-reflow phenomenon was independent of the method of ABF and, consequently, of the presence or absence of hypercapnia and hypoxemia preceding the ABF, and it was determined only by the duration of the latter. The primary no-reflow phenomenon cannot be explained either by closure of the vessels by swollen processes of astrocytes or by thrombosis of the vessels.

KEY WORDS: resuscitation; cerebral circulation.

Investigations linking the development of irreversible postischemic changes in the brain with disturbances of the microcirculation have been published recently [2, 4, 6]. Ames et al. [2] showed that immediately after cessation of the blood flow (occlusion of the aorta) for a period of more than 5 min, zones whose blood vessels were impermeable to blood appeared in the rabbit's brain. The regions excluded from the circulation were demonstratively revealed as white patches after perfusion of the brain with ink. Since these zones were found also for a short time after restoration of the general blood circulation the condition was named the no-reflow phenomenon.

The object of the present investigation was to reproduce this phenomenon in dogs after complete circulatory arrest induced by various methods.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized dogs. Arrest of the blood flow (ABF) was produced either by mechanical asphyxia, which leads to total cessation of respiration and cardiac activity, or by ventricular fibrillation produced by electric shock. The duration of ABF was counted from the moment that the heart stopped. Experiments were carried out on 29 dogs, in 14 of which ABF was produced by asphyxia, and in 13 by electric shock. Two dogs acted as the control. The duration of ABF was from 5 to 20 min. Pantopon (4 mg/kg) was injected into the dogs before the experiment. After the end of the assigned period of ABF the brain was perfused with ink through both common carotid arteries (perfusion pressure 120 mm Hg). Some of the animals were heparinized (500 units/kg).

Seven blocks were prepared from the cerebral hemispheres, the vermis of the cerebellum was investigated in sagittal section, and the brain stem and cerebellar hemispheres in frontal sections. To as-

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TABLE 1. Dependence of Area of Brain Sections Unfilled with Ink on Duration of Preceding ABF

Group	No. Expt.	Method of ABF	Duration of ABF	Area (in %) of brain zones unfilled with ink
1	Control		0	0
	Control		0	0
2	1	Asphyxia	6	0
	2	"	6	0
	3	"	6	17,4
	4	Fibrillation	5	0
	5	"	6	0
3	6	Asphyxia	8	55,9
	7	"	8	62
	8	"	8	58
	9	"	8	21,5
	10	"	8	21,6
	11	Fibrillation	7	23,3
	12	"	7	20,5
	13	"	8	12,2
	14	"	8	39,9
		Mean		35,2±6,45
4	15	Asphyxia	12	0,75
	16	"	12	1,2
	17	"	12	4,2
	18	"	20	2,5
	19	"	20	9,5
	20	"	20	8,0
	21	Fibrillation	10	0
	22	"	10	0
	23	"	10	0
	24	"	13	2,2
	25	"	20	2,7
	26	"	20	23
	27	"	20	9,4
		Mean		4,8±4,0

sess the no-reflow phenomenon quantitatively, the area of the brain zones filled and unfilled with ink was measured on the surface of all the sections described above by means of a platimeter with a magnification of 10 times.

EXPERIMENTAL RESULTS AND DISCUSSION

The experimental results are given in Table 1, and they are distributed in four groups. In group 1 (control) a uniform filling of the brain vessels with ink was observed, and there were no areas in which the ink did not penetrate into the intracerebral vascular network. In group 2, with ABF for 5-6 min, the no-reflow phenomenon was not observed, except in one case with ABF for 6 min produced by asphyxia. The third group consisted of experiments with ABF for 7-8 min produced by asphyxia and electric shock. In these cases extensive areas unfilled with ink appeared both in the cortex and in the subcortical formations, white matter, and cerebellum of the experimental animals. The fourth group consisted of experiments with ABF lasting 10-20 min. The picture of incomplete filling observed in the animals of these experiments was completely different both quantitatively and qualitatively. The areas unfilled with ink were smaller (after ABF for 10 min produced by electric shock no no-reflow phenomenon was generally observed), and the white zones in this case were arranged differently from their appearance in animals in the experiments of group 3: most frequently they were found in the subcortical formations and the white matter, and only very rarely were they seen in the cortex. The mechanism of incomplete filling after ischemia lasting 7-8 and 12-20 min is evidently very different. A statistically significant difference was found between the mean values of the unfilled area in the principal groups (3 and 4; $t = 4.0$; $P < 0.01$).

In the experiments of Ames et al., [2] on rabbits the number and area of the regions with vessels unfilled with ink was greater the longer the duration of ABF. The greatest area of the zones with the no-reflow phenomenon in the experiments of Ames et al. (up to 95%) was obtained after ABF lasting 15 min. The unfilled zones were located mainly in the subcortical formations and only rarely in the cortex. The main cause of occlusion of the vessels, in their opinion, was compression of the capillaries by swollen processes of the astrocytic glia and the appearance of microemboli in the blood. However, the investigation of Ames et al. did not rule out the possibility of arterial spasm, which could explain the exclusion of large territories of the brain from the blood flow, as observed after ABF for 15 min. From the point of view of the capillary hypothesis, these investigators found it difficult to explain the gradual disappearance of the no-reflow phenomenon in the postischemic period, especially considering the large size of the unfilled zones.

Ginsberg and Myers [5] demonstrated the presence of the no-reflow phenomenon in monkeys in which, unlike in rabbits, extensive unfilled zones were observed not only in the subcortical formations, but also in the cerebral cortex. The no-reflow phenomenon reached a maximum after ABF for 30 min, and with a longer duration of the ABF (50-70 min) the unfilled area decreased. Like Ginsberg and Myers [5], the present writers observed the spontaneous disappearance of the no-reflow phenomenon, but on a much larger scale than in monkeys. In addition, the zones with no reflow reached their largest size in the present experiments after ABF lasting 8 min.

The main result of this investigation was the establishment of two forms of no reflow. The primary no-reflow phenomenon can hardly be explained by compression of the capillaries by the swollen processes of the astrocytes or by their thrombosis, for these changes could not disappear during continued ABF [1].

In addition, the results of the experiments on heparinized dogs were identical with the results obtained in experiments on other animals.

Without denying the possibility of a mechanism of compression of the capillaries by swollen astrocytes, as described by Ames et al., [2], the writers consider that another pathophysiological mechanism of temporary occlusion of small blood vessels may exist – for example, myogenic arterial spasm.

The fact will be noted that the method of inducing ABF in the present experiments did not affect the no-reflow phenomenon. A primary no-reflow phenomenon appeared at the same times whether after fibrillation or after asphyxia. Since the structure of the pathogenic factors in these two types of ABF differed somewhat (hypercapnia combined with hypoxemia, followed by circulatory hypoxia in the case of mechanical asphyxia, and circulatory hypoxia alone after ventricular fibrillation), it can be postulated that the decisive factor for the no-reflow phenomenon is the arrest of the blood flow, and the preceding hypercapnia and hypoxemia were not of significant importance.

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