MICROSURGICAL MODEL OF CEREBRAL ISCHEMIA

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UDC 616.831-005.4-089:57.086.2].001.57

KEY WORDS: brain; ischemia; model.

Cerebral ischemia remains a fundamental problem in modern medicine. To study it, dogs, cats, and rabbits are most frequently used, and a model of cerebral ischemia is produced in them by compression of the cervico-cerebral vessels [3, 6, 9]. It is difficult, however, to create vascular isolation of the brain in these animals because of their well-developed collateral circulation [5]. It is most powerful in dogs, less so in cats and rabbits, and weakest of all in rats [4, 8]. Moreover rats tolerate the operations well, and they are economical animals, convenient for care and maintenance [2]. Depsite this, models of ischemia of all parts of the brain have not been obtained in rats because of the small diameter of the vessels and difficulty of access to them. At present, as a result of the invention of the operating microscope and the development of microsurgical techniques, it has become possible to produce the most complete vascular isolation of the rat brain.

The aim of this investigation was to develop a model of cerebral ischemia in rats in order to study the after-effects of disturbance of the cerebral circulation.

EXPERIMENTAL METHOD

Altogether 102 experiments were carried out on noninbred rats of both sexes weighing 150-250 g. Anesthesia was induced by intraperitoneal injection of 1 mg of 1% solution of hexobarbital/100 g body weight. Operations were performed under an operating microscope, using a microsurgical technique. Through a midline incision in the lower third of the neck and upper third of the chest extrapleural access was gained to the mediastinum, where the common carotid and subclavian arteries were isolated from surrounding tissues and clamped distally to the origin of the intrathoracic arteries and proximally to the origin of the vertebral arteries (Fig. 1). During cerebral ischemia and in postischemic period artificial ventilation of the lungs was instituted until spontaneous breathing was restored.

To determine the adequacy of the model as a means of studying the aftereffects of disturbances of the circulation in all parts of the brain, angiography was performed: In the first minutes of cerebral ischemia 2-3 ml of 60% verografin was injected via the abdominal aorta towards the heart, and roentgenograms were taken at the height of injection of the contrast substance; the vessels were infused at the 10th minute of cerebral ischemia by injection of 20 ml methylene blue via the abdominal aorta toward the heart, the blood pressure (BP) was measured in the carotid arteries distally to the site of their occlusion, EEG changes were recorded, and brain-stem functions were analyzed by studying activity of the respiratory and cardiovascular systems.

In all experiments the EEG was recorded on a Polygraph RM-150 (from Nihon Kohden, Japan), for which purpose the cranial bones were exposed in the frontal and occipital regions and electrodes were fixed to them for recording the EEG [9]. The ECG, BP, and respiration were recorded on a Biograph (from Harvard Apparatus, USA). The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

During the first few seconds of cerebral ischemia BP in the carotid arteries distal to their site of occlusion fell to zero. During infusion of the vessels and angiography no

Academic Group of Academician of the Academy of Medical Sciences of the USSR V. V. Kovanov, affiliated with the All-Union Scientific Center for Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kovanov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 2, pp. 140-142, February, 1985. Original article submitted June 15, 1984.

0007-4888/85/9902-0159$09.50

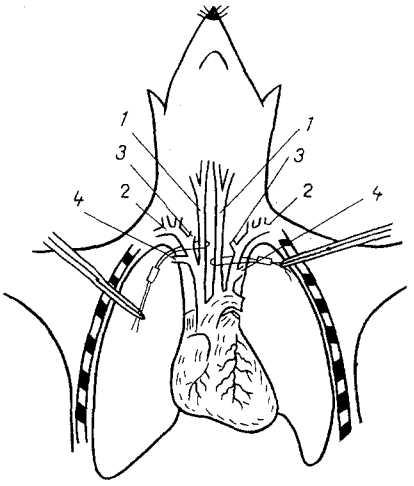

Fig. 1. Scheme of cerebral ischemia. 1) Common carotid arteries; 2) subclavian arteries; 3) vertebral arteries; 4) intrathoracic arteries.

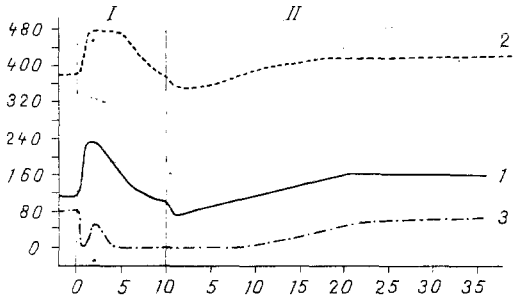

Fig. 2

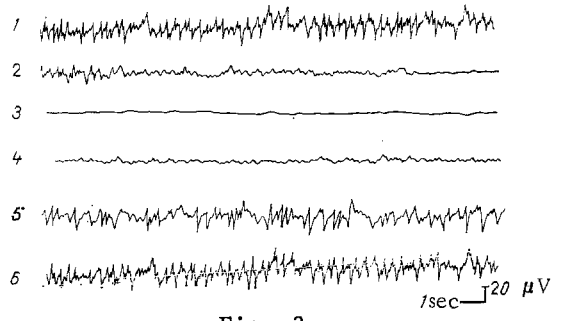

Fig. 3

Fig. 2. Changes in systolic BP (1), HR (2), and respiration rate (3) during and after cerebral ischemia for 10 min. Abscissa, time (in min); ordinate, BP (in mm Hg), HR (beats/min), and respiration rate (cycles/min). I) Period of cerebral ischemia; II) postischemic period.

Fig. 3. EEG during cerebral ischemia for 10 min and in postischemic period. 1) Background EEG; 2, 3) EEG after 23 sec and 10 min of cerebral ischemia respectively; 4, 5, 6) EEG after 19, 60, and 90 min of postischemic period respectively.

contrast material could be detected in the soft tissues of the head, neck, forelimbs, or brain, either in the cortex or deep brain regions. EEG changes during cerebral ischemia appeared after 5 ± 1.3 sec as an increase in amplitude of α- and β-waves. This was followed by slowing of the EEG rhythm with extinction of the β- and α-bands, after which θ-waves and, later, δ-waves began to predominate. The amplitude of the waves fell rapidly, and by 23 ± 5 sec brain electrical activity ceased completely to be recorded. After 6 ± 1.5 sec of cerebral ischemia, apnea developed and continued until the second minute, but breathing gradually weakened and, after 4 ± 0.3 min it ceased. The cardiovascular system responded to cerebral ischemia by a sharp rise of BP (by 93%; $P < 0.01$) and in the heart rate (HR; by 24%; $P < 0.05$). With an increase in the duration of cerebral ischemia BP gradually fell, and after 10 min it amounted to 80% ($P < 0.05$) of its initial value; HR became slower (Fig. 2). After restoration of the cerebral circulation, BP and HR both fell. For instance, after I0 min of ischemia, at the first minute of the postischemic period BP fell by 22% ($P < 0.05$) and HR by 4.5% ($P < 0.05$). BP then gradually rose, and reached its initial level after 18 ± 1.4 min. Normalization of the ECG occurred at the same time. Respiration was restored after 10 ± 1.2 min; the EEG reappeared 19 ± 3 min after ischemia lasting 10 min, in the form of a gradual increase in amplitude of the slow waves, and it returned to normal by 1.5 h of the postischemic period (Fig. 3). After cessation of the circulation in the brain for 10 min none of the animals died from causes connected with ischemic damage to brain tissues. After 11 min of cerebral ischemia, 57% of the animals recovered from coma, but only 33% after 12

min of ischemia. However, all animals subjected to vascular isolation of the brain for 11 and 12 min died during the first 5-7 days of the postischemic period. After 13 min of cerebral ischemia the EEG, ECG, BP, and respiration were not restored and all the animals died on the day of the operation without reviving from coma.

The model of vascular isolation of the brain described above, with compression of the common carotid and subclavian arteries distally to the point of origin of the intrathoracic and proximally to the origin of the vertebral arteries, thus sharply reduces the cerebral circulation. Combined studies of the adequacy of this model, when used to study ischemia in all parts of the brain, showed: 1) absence of a collateral circulation in the brain and soft tissues of the head, neck, and forelimbs as shown by angiography and by injection of the blood vessels; 2) BP in the carotid arteries distally to the site of their occlusion falls to zero; 3) brain electrical activity ceases after 23 ± 5 sec of cerebral ischemia; 4) brain stem functions are inhibited, leading to respiratory arrest after 4 ± 0.3 min and to disturbance of central regulation of activity of the cardiovascular system; 5) all animals surviving cerebral ischemia for a period longer than 10 min die in the early postischemic period.

Times of disappearance of the EEG after sudden cardiac arrest in dogs described in the literature [1], namely 15-30 sec, correspond to the times of cessation of brain electrical activity in the period of ischemia observed in the present experiments. The times of respiratory arrest during cerebral ischemia in the rats in the present experiments also agreed with those in dogs after sudden cardiac arrest [7]. All these facts are evidence that the cerebral circulation was inhibited in the present experiments to such a degree that it did not support the vital activity of the cortex and deep brain formations.

Resumption of the cerebral circulation after 10 min of ischemia led to recovery of the electrophysiological parameters of activity of the CNS and cardiovascular system during the first 20 min of the postischemic period. BP began to rise after 5 ± 0.8 min and reached its initial values after 18 ± 1.4 min. The ECG recovered at the same time. Spontaneous breathing appeared after 10 ± 1.2 min of the postischemic period. After normalization of BP, at 19 ± 3 min, the EEG reappeared, and its frequency and amplitude characteristics were restored after 1.5 h of the postischemic period.

LITERATURE CITED

1. A. M. Gurvich, Electrical Activity of the Dying and Reviving Brain [in Russian], Leningrad (1966).
2. I. D. Kirpatovskii and É. D. Smirnova, Principles of Microsurgical Technique [in Russian], Moscow (1978).
3. E. F. Lunets, A. F. Smeyanovich, and P. A. Vlasyuk, in: Efficiency Studies in the Health Service of the Belorussian SSR [in Russian], Minsk (1974), p. 123.
4. I. R. Petrov, Cerebral Hypoxia [in Russian], Leningrad (1949).
5. I. A. Ponomareva, V. P. Vakhov, and M. V. Solov'ev, in: Acute Ischemica of Organs and Early Postischemic Disorders [in Russian], Moscow (1978), p. 167.
6. E. E. Radomskaya, Tr. Volgograd. Med. Inst., 24, 303 (1971).
7. S. V. Tolova, in: Principles of Resuscitation [in Russian], Tashkent (1977), p. 65.
8. V. P. Shafranova and T. V. Ryasina, in: Laboratory Animals in Medical Research [in Russian], Moscow (1974), p. 208.
9. P. Niaussat, H. Labori, B. Weber, et al., Presse Med., 42, 1578 (1959).