FUNCTIONAL AND MORPHOLOGICAL CHANGES PRODUCED BY PROFOUND GENERAL REFRIGERATION IN THE CENTRAL NERVOUS SYSTEM AFTER THE HEART HAS BEEN EXCLUDED FROM THE GENERAL CIRCULATION

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For successful intracardiac surgery it is essential to develop safe methods permitting exclusion of the heart from the circulation so that its interior can be operated on under direct vision in a dry field. However, when this is done, blood no longer reaches the tissues and, unless special precautions are undertaken, within 5-7 minutes irreversible changes occur in the central nervous system.

An enormous aid in maintaining tissue stability during oxygen starvation is a general cooling of the body below temperatures of 28-30°. This procedure has been employed lately during intracardiac operations both experimentally and in the clinic [2,3].

However, the method of general refrigeration and exclusion of the heart has not been well-developed in the clinic and is by no means a safe procedure. The pathological and physiological changes which occur in the nervous system (which is most sensitive to anoxic interference) have not as yet been investigated adequately. There is as yet no absolute answer as to how long the heart may be excluded from the circulation while the patient is in the refrigerated state. The aim of the present study, undertaken jointly by a pathological physiologist, surgeon and neuropathologist, was to outline the precise procedures of generalized refrigeration to be used in a surgical clinic.

EXPERIMENTAL METHODS

All experiments were done on dogs. The animals were always cooled while narcotized (morphine, penthotal, ether and curare– like drugs– diplatsin, paramion*). The best results were obtained under ether anesthesia with oxygen combined with morphine and curare-like drugs. To cool the animals either cloth-covered bags filled with ice or ice baths (water temp. 2-4°) were used. Cooling was stopped when the body temperatures fell to 28-26°. During surgery, the temperature was usually lowered another 2-3°. Cooling was maintained from 40 minutes to 2 hours. The temperature was depressed most rapidly when the animal was immersed in water. To exclude the heart from the circulation the superior and inferior vena cava were clamped off, the unpaired vein being ligated.

EXPERIMENTAL RESULTS

6 control experiments were done with cardiac exclusion at normal temperatures. In 3 animals where the heart was excluded for 4 $^1/_2$ to 6 $^1/_2$ minutes, on the day following surgery, when the effect of the anesthesia

* Russian trade name.

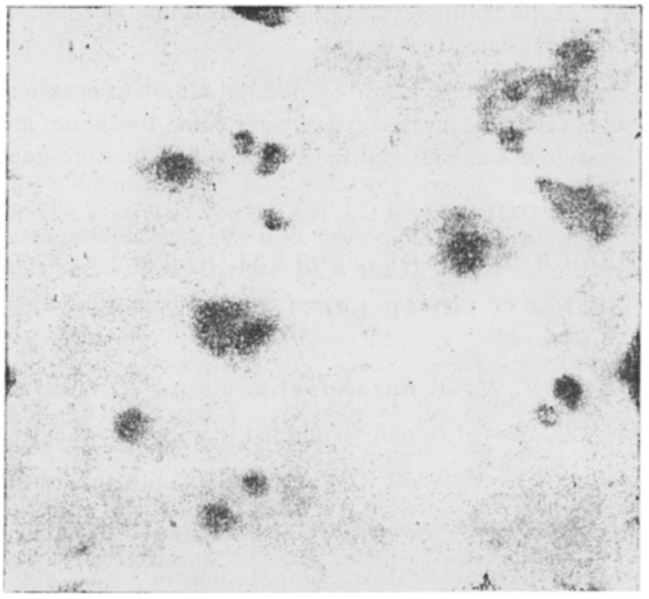

Figure 1. Severe alterations in cortical cells of dog cerebral hemisphere when animal had been subjected (without refrigeration) to the heart being excluded from the circulation for 7 $^{1}/_{2}$ minutes. Thionin stain (after Nissl). Ocular 12, obj. 40.

had worn off, the first severe changes in the nervous system could be seen to proceed, the behavior of the animals could not be distinguished from the normal. When the heart had been excluded from the circulation for from 7 to 7 minutes 45 seconds (3 experiments) 2 dogs perished; one – from cardiac failure during the circulatory exclusion period, the second – 5 hours after the exclusion, the animal never emerging from a deep comatose state. The surviving dog for 2 days was fearful, aggressive, permitted no approach and bit the individual feeding it. By the 3d day these disturbances subsided and on the 4th day it was sacrificed for histologic studies. The data obtained on cardiac exclusion is comparable with that obtained by I. P. Petrov [1].

The results of the refrigeration experiments are shown in the table.

Experimental Results When the Heart is Excluded from the Circulation During General Cooling.

Length of time of cardiac exclusion from the circulation in minutes	Survived			Perished				Total
	Observed 7 days to 6 months	Sacrificed within first 7 days in good condition	Total	During cardiac exclusion	Within 1st day after surgery	Later	Total	
To 10	1	—	1	2	1	—	3	4
10—14	2	—	2	3	3	—	6	8
15—19 $^{1}/_{4}$	4	8	12	2	7	2	11	23
21—26	—	—	—	—	3	—	3	3
Total	7	8	15	7	14	2	23	38

The high mortality was due to various complications, principally disturbances of the cardiovascular system. During the course of our experiments, we discovered effective prophylactic and therapeutic measures which markedly reduced the mortality. Out of the first 15 dogs, 12 perished, while in the last 7, in spite of

prolonged cardiac exclusion, only 2 animals died.

Up to the moment of cardiac exclusion the refrigerated animals were, as a rule, in a state of inhibition whose depth was about equal to the usual narcotized level.

During cardiac exclusion the severe hemodynamic alterations were most conspicuous. The arterial pressure dropped precipitately but not to zero, in most experiments being 10-20 mm mercury, this being apparently associated with preservation of some arterial tone. The venous pressure rose soon reaching the arterial level.

In the central nervous system there could be observed an increasing inhibitory state. The vessel tone diminished and the arterial pressure fell, the pupil in most instances dilated, respiration in many instances ceased although sometimes they assumed an agonal character which would subside when the clamps on the caval arteries were released. If, before clamping, corneal, pupillary and spinal reflexes were present, within the first few minutes they would disappear.

When vessel tone was preserved, removal of the vein clamps would quickly restore the arterial blood pressure. However, more often special measures were required to restore vessel tone and cardiac activity.

It must be remarked that in some experiments, on the background of restored reflex activity, the blood pressure remained at 40-50 mm mercury pressure, the medication for restoring tone gave only a transient effect and the animal would perish 5-8 hours after the operation. At autopsy, there would be usually found a large hemorrhagic pleural exudate or a secondary pneumothorax. It may be assumed that in some instances there must have occurred a special type of shock stage produced by the profound inhibition of the central nervous system after the cardiac exclusion, as well as the influence of the cooling, besides, possibly, ether overdosage as its blood solubility increases with decreasing temperature.

As the nervous system would resume functioning after the operation, first of all it was vessel tone that was restored, then spontaneous respiration, pupillary reaction to light and corneal reflexes, increased tone of the muscles of the extremities, reappearance of the tendon reflexes, sometimes manifestations of plastic tonus, shivering of the extremities, then the animal would raise its head, response to sound, light and pain, would become manifest and, finally, the functions of standing and walking would return. The day following surgery the animals would behave normally.

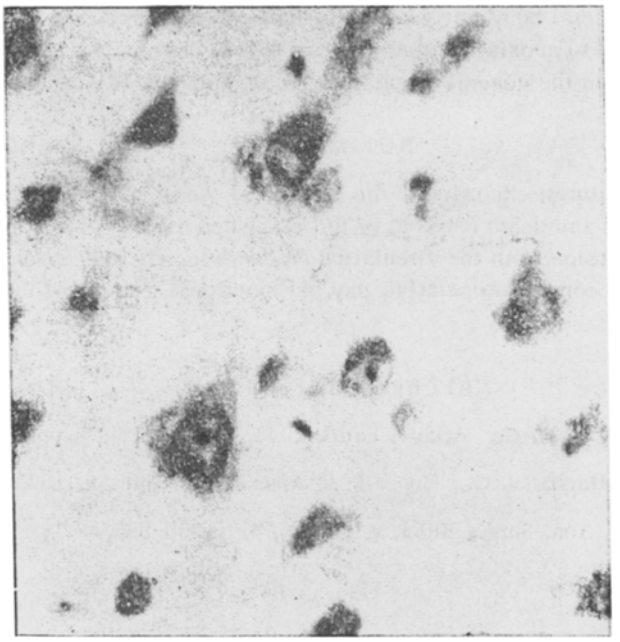

Figure 2. Reversible changes in nerve cells (honeycombed structures in the protoplasm) of the cerebral cortex observed after the heart had been excluded from the circulation for 19 minutes after the animal had been refrigerated. Thionin stain (after Nissl). ocular 12, obj. 40.

Thus restoration, as a rule, would occur within the first day and would be complete.

In a whole series of instances some functions would not return by following the "ladder" switching in procedure of including the various divisions of the nervous system according to their phylogenetic age. Thus, usually the first reflex to be restored was the pupillary reaction to light (midbrain) and only later the corneal reflexes (medulla oblongata), spinal reflexes, etc..

The morphology of the nervous system was examined in 20 animals. In the control animals, whose heart had been excluded from the circulation for 6 $^{1}/_{2}$ - 7 minutes while the body was at normal temperature, there were marked circulatory disturbances (leukostasis, erythrostasis in the vessels, fragmentation of the vessel walls), brain edema, hemorrhages, nerve cell alterations characteristic of severe disease (Fig. 1) up to transformation into "ghost-cells", ischemic cells, hydropic nerce cells and disappearance of entire groups of nerve cells. There could be observed swelling and wrinkling with chromatolysis and hyperchromatism of the chromatophilic substance and appearance of honeycombed and basophilic structures within the bodies of the nerve cells.

The refrigerated dogs, even when subjected to much longer cardiac exclusion (up to 19 minutes), showed many fewer alterations. Basically, the changes seemed to be of a reversible type: scattering of the chromatophilic substance, its redistribution within the bodies of the nerve cells, honeycombing of the protoplasmic structure (Fig. 2), manifestations of a moderate hyperchromatosis, moderate edema of the nerve cell bodies and their outgrowths and some circulatory upsets. There were also irreversible changes: severely altered nerve cells, "ghost cells", ischemic nerve cells and nerve cells which had disappeared.

In all instances studied the severest alterations were seen in the cerebral cortex of both hemispheres, less in the hippocampus, cerebellum, and still less in the subcortical ganglia, the lower olives, nuclei of the cranial nerves and spinal cord. The nerve fibers and their endings were altered less than the cell bodies. In the early stages, the neurologist could see only some degenerative changes in the astrocytes. In the later stages (several days and later) there could be observed an increase in the glia with an overgrowth of its protoplasm.

The neurological data and the pathological-morphological investigations show that, after cardiac exclusion, the functional alterations in many instances were less than the morphologic changes. This might be due to the great plasticity of the nervous system, this allowing functional restoration even after such severe damage that some nerve cells actually become destroyed. Restoration is also accomplished by the reversibility of many of the changes.

Our results show that general body refrigeration combined with narcosis increases the stability of the nervous system when subjected to anoxia and thus prevents severe irreversible functional disturbances even when the heart is excluded from the general circulation for as long as 15-19 minutes.

SUMMARY

At normal body temperatures, exclusion of the heart from the circulation for as long as 7 minutes is apt to lead to irreversible changes and death (two out of three). When the body temperature is lowered to 24-28°, even 19 minutes of heart exclusion from the circulation produces mostly only reversible central nervous system alterations. Usually, by the second postoperative day, no functional changes of the nervous system could be observed.

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