

PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

THE EFFECT OF TEMPORARY EXCLUSION OF THE HEART FROM THE CIRCULATION ON THE HIGHER NERVOUS ACTIVITY OF DOGS IN A STATE OF HYPOTHERMIA

V. F. Novikov

Department of Normal Physiology (Head—Prof. P. M. Starkov)

Kuban Medical Institute, Krasnodar

(Presented by Active Member AMN SSSR, V. V. Parin)

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 50, No. 12,

pp. 28-33, December, 1960

Original article submitted November 18, 1959

The further development of cardiac surgery requires the urgent widening of the scope of possible surgical intervention in a "dry field" [3, 7, 13, 14]. Hypothermia is used for this purpose, as a method of increasing the resistance of the body and, in particular, of the central nervous system to temporary interruption of the blood flow [4, 5, 12]. The character of the functional changes developing in the cerebral cortex as a result of the temporary exclusion of the heart from the circulation under the conditions of hypothermia has not been discussed in the literature; its importance at the present time is obvious, for the study of this question will furnish more detailed and accurate information on the permissible periods of interruption of the circulation of the blood.

We have investigated the recovery of conditioned reflexes in dogs after exclusion of the heart from the circulation for 15 min during hypothermia.

METHODS

Experiments were carried out on 3 dogs. The animals had firmly established conditioned reflexes, produced experimentally and involving various analyzers of the cerebral cortex. The dog Sil'va had protective respiratory reflexes, reinforced by ammonia, to a bell, to a light and touch stimulus, with differentiation to a bell of another pitch. The dogs Mirnyi and Valetka had food conditioned reflexes (with a delay of 10 sec) to a metronome, a light and touch stimulus and differentiation to each in turn, the complete sequence forming a stereotype. Hypothermia was induced in the animals by means of a cold pack under general intubation anesthesia with ether and oxygen on a basis of morphine (0.5 ml/kg of 1% solution) until the rectal temperature was 24°. A right-sided thoracotomy was then performed and the heart excluded from the circulation by ligation of the azygos vein and clamping of the vena cava; fibrillation was prevented by the method of V. M. Pokrovskii and V. M. Bensman [10]. After restoration of the circulation the chest was closed without drainage and warming of the animals to a temperature of 32° commenced. The dogs were then taken from the operating table and subsequent experiments were carried out in the conditioned reflex chamber. We made 55 investigations of the conditioned reflexes in the three dogs after exclusion of the heart from the circulation on one occasion.

RESULTS

Immediately after its removal from the operating table the animal persistently held its head crown uppermost, reacted to a loud noise by turning its head, and made attempts to get up on to its legs, making haphazard movements with its paws. Tests of the protective respiratory reflexes in the dog Sil'va at this time showed that they were completely absent to all stimuli (see figure, a, b). Twelve hours after operation the dogs

TABLE 1.

Recovery of Conditioned Reflexes in the Dog Mirnyi after Exclusion of the Heart from the Circulation for 15 Minutes during Hypothermia

Conditioned stimulus		June 10, 1957 initial values		June 11, 1957		June 12, 1957		June 13, 1957		July 14, 1957	
		day after operation		first		second		third		fourth	
				latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex
Metronome +240	3	9	—	—	0	12	2	—	0	—	0
Light	2	8	—	—	0	—	0	—	0	—	0
Metronome -60	3	4	—	—	0	3	6	—	0	9	2
Touch stimulus	9	3	—	—	0	—	0	—	0	—	0
Total		24			0		8		0		2

* The magnitude of the conditioned reflex is given in drops of saliva during the action of the conditioned stimulus alone for 30 seconds.

tried to walk; in so doing they staggered, collided with objects in their way and fell. The reaction to a summons by name was inconstant, and the animals did not recognize the experimenter. Conditioned reflexes were absent. After 24 hours the dogs walked with difficulty and staggered. The reaction to a summons was stabilized and a positive reaction to the experimenter also appeared. The animals, however, could not stand up on the bench, but hung on their straps. Tests of the conditioned protective reflexes in Sil'va showed them to be completely absent. Conditioned salivatory reflexes were found only in Valetka. Their magnitude in response to all positive stimuli was equal to one drop of saliva. The differential reaction was disinhibited to 5 drops. The higher response to the differential stimulus than to the positive led to a state closely resembling an ultraparadoxical phase in the cerebral cortex. This fact bore witness to the profound limiting inhibition of the cells of the cerebral cortex.

After 48 hours the animals' condition deteriorated. The body temperature reached 39-40°, and tachycardia and dyspnea were observed. Tests of the conditioned reflexes in the dog Sil'va were not carried out because of its poor general condition. The salivatory conditioned reflexes in Valetka were absent. In the dog Mirnyi, 2 drops of saliva were secreted in response to a strong stimulus--metronome; subsequent positive stimuli did not evoke reflexes, and the differential reaction was disinhibited to 6 drops.

After three days the conditioned reflexes were absent. The animals did not react to the offer of food, nor did they take food. An unconditioned reflex reaction to the odor of ammonia could now be observed in Sil'va. On the fourth day no respiratory conditioned reflexes were seen (see figure, c). Positive food reflexes were also absent; at this stage disinhibition of the differential reaction to 2 drops was observed in Mirnyi (Table 1).

Recovery of the respiratory conditioned reflexes began on the fifth day, when the conditioned reflex to the bell first appeared. Differentiation was retained at this stage (see figure, d). Tests of the salivatory conditioned reflexes in Valetka showed them to be absent to the metronome and light; meanwhile the effect of the weak touch stimulus was equal to the initial response (3 drops). The dog Mirnyi died on the fifth day from secondary hemorrhage from the femoral artery.

The next tests of the conditioned reflexes were made on the seventh day. The characteristic

TABLE 2.

Recovery of Conditioned Reflexes in the Dog Valetka after Exclusion of the Heart from the Circulation for 15 Minutes during Hypothermia

Conditioned stimulus	June 26, 1957	June 27, 1957	July 1, 1957	July 3, 1957	July 4, 1957	July 6, 1957	July 8, 1957	July 10, 1957	July 15, 1957							
	day after operation															
	initial values	first		fifth		seventh		eighth		tenth		twelfth		fourteenth		nineteenth
	latent period (sec)	magnitude of conditioned reflex*	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex	latent period (sec)	magnitude of conditioned reflex
Metronome +240 . . .	7	5	29	1	0	2	12	3	16	3	4	2	7	3	5	6
Light	9	3	4	1	0	0	1	0	1	0	0	1	0	8	7	4
Metronome -60. . . .	-	0	3	5	0	0	1	3	10	3	0	0	0	15	17	1
Touch stimulus	16	2	2	1	3	0	1	0	1	0	0	15	1	6	11	3
Total		10		8	3	2		6		4		8		12		14

* The magnitude of the conditioned reflex is given everywhere in drops of saliva during the action of the conditioned stimulus alone for 30 sec.

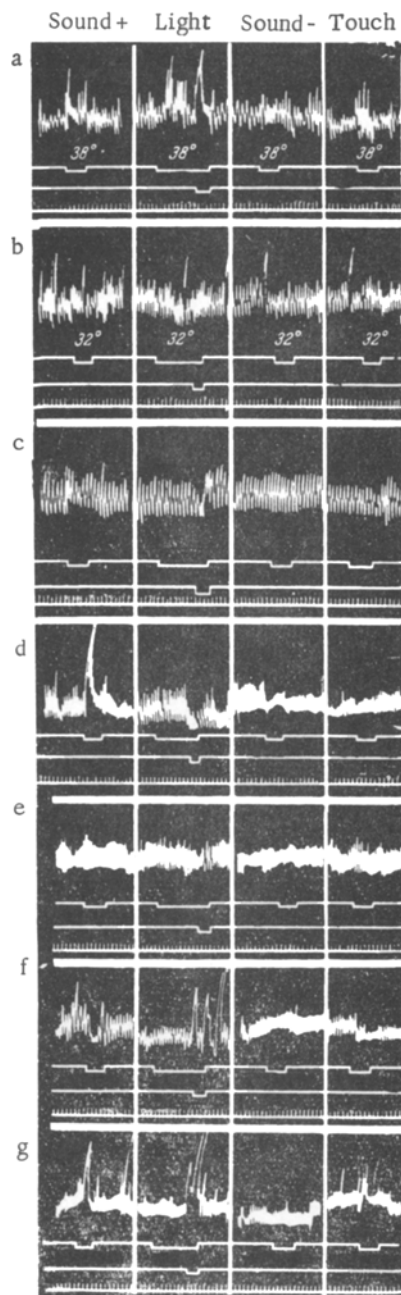


Fig. 1. Changes in the protective conditioned respiratory reflexes after exclusion of the heart from the circulation for 16.5 min at a body temperature of 24° , in the dog Sil'va. a) Initial level of the reflexes; b) after exclusion of the heart, on the day of operation; c) on the 4th day after operation; d) on the 5th day; e) on the 7th day; f) on the 8th day; g) on the 10th day after operation. Significance of the curves (from above down): tracing of the respiration, application of the conditioned stimulus, application of the unconditioned stimulus, time marker (3 sec).

findings on that day were, that in Valetka a natural conditioned reflex to the sight and smell of meat-biscuit powder appeared simultaneously with the conditioned reflex to the metronome (2 drops). This was the first dog to take food from the basin after reinforcement of the conditioned stimulus. Respiratory reflexes were absent in Sil'va (see figure, e).

On the eighth day, together with the conditioned reflex to the bell, recovery of the conditioned reflex to light took place with well marked delay. The reaction to the touch stimulus was hardly perceptible, and differentiation was retained. Complete recovery of the protective respiratory reflexes took place on the tenth day (see figure f, g). Later investigations of the conditioned respiratory reflexes showed them to be normal.

Tests of the food conditioned reflexes in Valetka on the eighth day revealed a conditioned reflex to the metronome (3 drops of saliva). Disinhibition of differentiation to 3 drops was also observed at the same time. On the ninth day, investigation showed the absence of conditioned reflexes to all the stimuli in this dog.

During tests of the stereotype in Valetka nine days after operation a response reaction was observed only to the first strong stimulus—the metronome (4 drops of saliva). This can be regarded as an indication that the process of excitation in the cerebral cortex was rapidly exhausted, revealing the low limit of functional capacity of the cortical cells. Differentiation was not disinhibited. Starting at this time, the conditioned reflex to the metronome appeared persistently in all the subsequent experiments (Table 2).

On the 12th day, together with the conditioned reflex to the metronome a conditioned reflex to the touch stimulus appeared (7 drops and 1 drop of saliva respectively). This was the first animal to eat food after the operation with all forms of reinforcement. On the 14th day after operation artificial conditioned reflexes to all stimuli were found. Their magnitude, however, was not yet equal to their initial level; the latent period was appreciably shortened and the strength relationships between the individual stimuli were abnormal. Only on the 19th day did the conditioned salivatory reflexes revert to their initial values. The insignificant disinhibition of differentiation (1 drop) was evidence of some degree of weakness of the internal inhibition.

After exclusion of the heart from the circulation for 15 min in conditions of hypothermia, recovery of the conditioned protective respiratory reflexes thus began on the fifth day and was complete on the tenth day. Recovery of the salivatory conditioned reflexes after this operative procedure began on the seventh day and was complete on the 19th day after operation. In the course of recovery, all the animals showed transitional hypnotic phases, indicating the development of limiting protective inhibition in the cerebral cortex;

these were particularly noticeable during the first five days after operation. It should be pointed out that the process of recovery of the higher nervous activity showed a characteristic fluctuation, with the development of cycles of cortical activity; this also was evidence of the low limit of the functional capacity of the cortical cells.

Analysis of the rate of recovery of the different conditioned reflexes shows that it is dependent upon the type and strength of the conditioned stimuli. Quickest of all was the recovery of the conditioned reflexes from the auditory analyzer (bell, metronome), next—from the optic analyzer (light) and then—from the cutaneous analyzer (the touch stimulus). The rate of recovery is also dependent on the form of the reflexes; this is seen particularly clearly when the results obtained are compared with those of our previous experiments on the study of the effect of general anesthesia and hypothermia on the conditioned reflex activity of dogs. First to recover were the protective conditioned respiratory reflexes, and then the food reflexes [1, 9].

Test of the conditioned reflexes 2-3 months after exclusion of the heart from the circulation during hypothermia revealed no changes in the behavior and the character of the conditioned reflexes to artificial stimuli.

The interruption of the blood flow to the brain by exclusion of the heart from the circulation for 15 min during hypothermia thus causes well marked disturbances of the function of the cerebral cortex. These disturbances are reversible in character.

The production of cerebral anemia for this length of time (16 min) at the ordinary body temperature leads to irreversible changes in the cortical cells. Electrical defensive reflexes do not recover under these circumstances [11]. Normalization of the conditioned reflexes as a result of the subsequent exclusion of the anterior cerebral arteries (after an interval of 10-40 min) takes place on the 15th-19th day [6]. According to G. A. Akimov [2], the function of the cerebral cortex in man after arrest of the heart for 5-6 min at the ordinary body temperature is restored later than the activity of the lower divisions of the central nervous system; irritability and loss of memory are subsequently noticed. In patients who die, pathomorphological changes are found in the cells of the cerebral cortex.

The findings described show that the increased resistance of the cells of the cerebral cortex in dogs as a result of hypothermia leads to a prolongation of the period of exclusion of the heart from the circulation to 15 min. Under these circumstances the signal activity of the cerebral hemispheres is fully restored. The time of recovery of the conditioned reflex activity observed in our experiments agrees with that found by L. I. Murskii and V. I. Soboleva [8]. These authors showed that in animals surviving clinical death (for 30 min) under conditions of hypothermia, recovery of the higher nervous activity takes place within 13 to 23 days. In view of these findings it may be postulated that, in dogs, exclusion of the heart from the circulation for 15 min at a body temperature of 24-25° is not an upper limit. It is possible that this period may be extended to 20-25 minutes. A special study of this problem is required.

SUMMARY

The conditioned reflexes are completely restored after the exclusion of the heart from the circulation for a period of 15 min during hypothermia. Restoration of protective conditional respiratory reflexes begins on the 5th day and they normalize completely on the 10th day. Normalization of the salivary conditioned reflexes starts on the 7th day and is completed by the 19th day. The process of restoration fluctuates with the development of hypnotic phases of cerebral cortex activity.

LITERATURE CITED

1. E. V. Aganyants and V. F. Novikov, Abstracts of Proceedings of the Twelfth Conference of the Southern RSFSR Branch of the All-Union Society of Physiologists, Biochemists and Pharmacologists [in Russian] (Voronezh, 1958) p. 7.
2. G. A. Akimov, *Vestnik Khir. im. Grekova*, 78, 5, 80 (1957).
3. A. A. Vishnevskii and V. I. Burakovskii, *Grudnaya Khirurgiya*, 1, 5 (1959).
4. E. V. Gukevich, *Novyi Khirurg. Arkh.*, 3, 16 (1956).
5. A. M. Gurvich, *Fiziol. Zhur. SSSR* 44, 5, 424 (1958).
6. A. S. Kuklina, *Voprosy Neirokhir.* 2, 46 (1957).
7. P. A. Kupriyanov, *Vestnik Khir. im. Grekova* 76, 9, 3 (1955).
8. L. I. Murskii and V. I. Soboleva, *Byull. Eksp. Biol. Med.* 44, 8, 43 (1957).*

*Original Russian pagination. See C.B. translation.

9. V. F. Novikov, in : Anesthesia and Disturbance of the Circulation during Surgical Operations [in Russian] (Krasnodar, 1958) p. 226.
10. V. M. Pokrovskii and V. M. Bensman, *Eksp. Khir.* 4, 15 (1956).
11. G. T. Sakhiulina, *Zhur. Vysshei Nerv. Deyatel.* 5, 1, 76 (1955).
12. P. M. Starkov, et al., Abstracts of Proceedings of the Eighth All-Union Congress of Physiologists, Biochemists and Pharmacologists [in Russian] (Moscow, 1955) p. 586.
13. F. Lewis and M. Taufic, *Surgery* 33, 52 (1953).
14. H. Swan, R. H. Wilkinson, and S. G. Blount, *J. Thoracic Surg.* 35, 139 (1958).