CHANGES IN THE REACTION OF ANIMALS TO INTRAVENOUS INJECTION OF CAFFEINE AND STROPHANTHIN AFTER RESUSCITATION FROM CLINICAL DEATH

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Restoration of the vital activity of the body after clinical death by means of V. A. Negovskii's [6] method is being increasingly used in Soviet medical practice. The restoration of the action of the heart and of spontaneous respiration are decisive stages in the program of resuscitation of an animal in an agonal state. The appearance of the heart beat and of respiration, however, still does not imply normalization of the basic functions, and still less, restoration of normal health [1, 5, 6, 7].

The work of G. L. Lyuban and his co-workers [2, 3, 4, 5 and others] showed that the reactivity of the animal in the period of restoration of the vital functions after clinical death shows certain essential changes, which are evidently of importance to the effect of both pathogenic and therapeutic agents on the body. Their findings are in agreement with the observations of other authors [6, 8, 9 and others].

It must be mentioned that the reaction of animals which survive clinical death to the administration of certain drugs has not yet been adequately studied. At the same time the investigation of the reaction of the body to different stimuli and in different periods of resuscitation is important in another direction: it assists in explaining the mechanism of action of the etiological factor.

The aim of the present investigations was to study the reaction of animals, which had survived clinical death, to caffeine and strophanthin.

Many factors are known which suggest the importance of the functional state of the body to the character of the action of a particular drug. Drugs such as caffeine and strophanthin may have different effects on the same function, depending not only on the dose of the drug but also on the state of the animal and of its central nervous system. It may be supposed that after the profound anoxia which accompanies clinical death, changes be found in the action of the drugs tested.

EXPERIMENTAL METHOD

Experiments were carried out on 98 cats. Clinical death was induced by exsanguination from the femoral artery, the animals being under light ether anesthesia.

Resuscitation was started after 3-5 minutes of clinical death, by means of intra-arterial injection of blood toward the heart and artifical (mechanical) respiration. Heparin was given preliminarily, and a few ml of physiological saline was added to the blood used for the infusion.

Caffeine or strophanthin were injected intravenously in the first 10 minutes after the appearance of spontaneous respiration.

TABLE 1

Time of Appearance of Convulsions after Injection of Caffeine (6-8 mg/kg of a 10% solution)

Animals	Time after 1st spontaneous inspiration to caffeine inject., in min	Number of animals	Time of appearance of convulsions				
			1 minute	1-5 min	5-10 min	over 10 min	none
Resuscitated	1—4	6	1	1	—	2	2
	4—6	6	1	4	—	1	—
	6—10	8	4	—	2	2	—
All resuscitated		20	6	5	2	5	2
Control		10	9	1	—	—	—

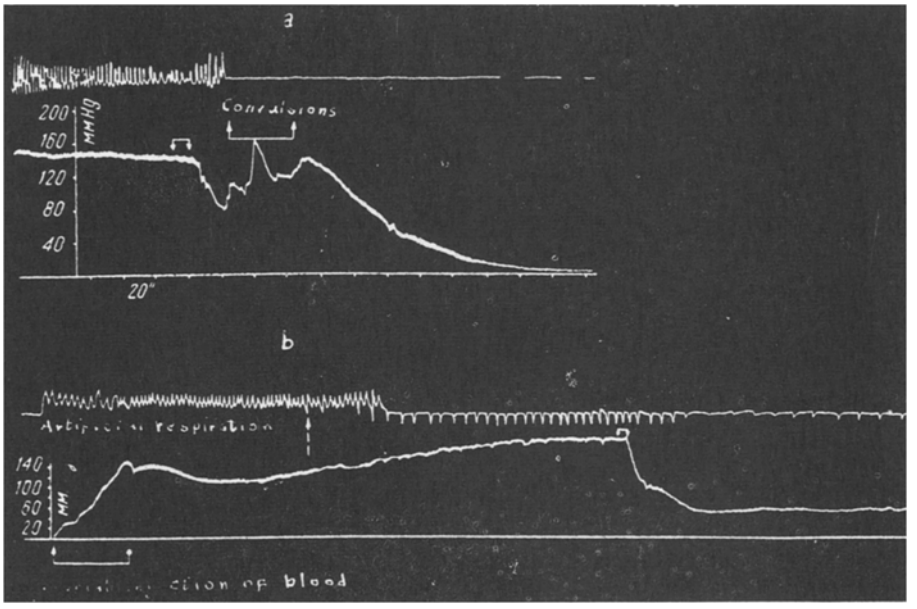

Fig. 1. Reaction to injection of 8 ml/kg of 10% caffeine solution: (a) in a control and (b) a resuscitated animal.

EXPERIMENTAL RESULTS

After injection of a toxic dose — 6-8 ml/kg of a 10% solution of caffeine — to 10 control animals, they all died in the first 10 minutes. Of 20 resuscitated animals, only 3 died at this period; 2 cats died after 10 and 15 minutes; the remainder survived for the 40-60 minutes of observation.

After receiving injections of caffeine the animals developed convulsions, but in the resuscitated animals these appeared later and were less intensive in character.

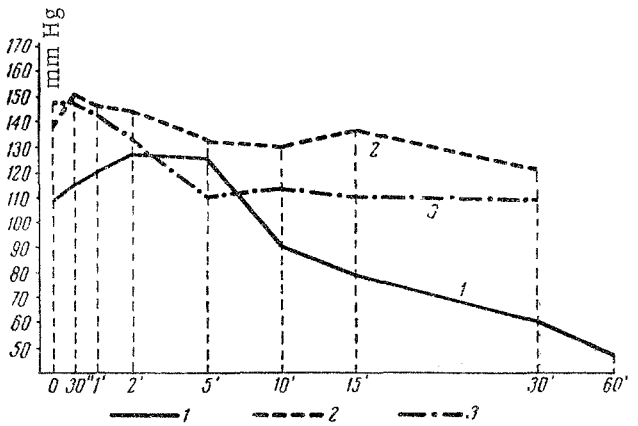

Fig. 2. Changes in the arterial pressure after injection of 1.5 ml/kg of 1% tincture of strophanthin to (1) resuscitated and (2) control animals; resuscitated animals not receiving strophanthin (3).

The longer the animal remained moribund, the longer the period of clinical death and the later spontaneous respiration was restored, the weaker were convulsions.

The time elapsing from the moment of resuscitation was very important: the sooner after the appearance of spontaneous respiration that the caffeine was injected, the less severe were the convulsions (Table 1).

After injection of caffeine the action currents of the heart were severely disturbed. As a rule paroxysmal tachycardia developed and the impulses acquired a polytopic character. In control animals this was followed immediately by a gradual extinction of electrical activity. In the resuscitated animals the heart usually continued working. Cases occurred in which sinus rhythm was restored.

The arterial pressure of the resuscitated animals fell after the injection to 40-50 mm Hg and respiration was temporarily slowed and became more superficial, whereas in control cats respiration ceased at once and the pressure fell to zero (Fig. 1).

In some experiments when, until injection of caffeine into resuscitated animals, their respiration succeeded in acquiring a periodic character, it was found that it returned to an agonal type.

After injection of 1 ml/kg of a 10% solution (larger than the therapeutic dose but not lethal) the difference in the reactions of the resuscitated animals took the form, in the first place, of delay and slight intensity of the convulsions, and secondly, of a considerable reaction of the respiration. After the injection of this dose of caffeine, however, in the resuscitated animals the process of changeover of respiration from an agonal to a periodic type was speeded up slightly.

In control experiments, after injection of 1 ml/kg of 10% caffeine, the arterial pressure fell by 40-50 mm Hg, but rapidly returned to normal, whereas in the resuscitated animals the return to normal was somewhat protracted.

In both the control and the resuscitation animals, after injection of this dose of caffeine a temporary disturbance took place in the work of the heart: the rate was changed, atrioventricular conduction was prolonged the T wave was reduced in amplitude, heart block and paroxysmal tachycardia sometimes developed.

Tincture of strophanthin, like other glucosides, has a selective action on the heart, but has the distinct advantage of rapidity of action and of not causing vasoconstriction. This may be important in the selection of a cardiac glucoside for patients surviving clinical death. In contrast to caffeine, at an early period an increase was observed in the sensitivity to toxic doses of strophanthin (Table 2, Fig. 2).

The more prolonged the course of the agonal state, the clinical death and the resuscitation, the more sensitive the resuscitated animal was to strophanthin. It was interesting to observe that after receiving injections which would be lethal to controls, animals surviving clinical death usually died within a shorter time. There

TABLE 2

Sensitivity of Resuscitated Animals to Tincture of Strophanthin

Dose of 1% solution	Animals	Number of animals	Of which	
			lived	died
1 ml/kg	Resuscitated	10	8	2
	Control	10	10	—
1.5 ml/kg	Resuscitated	10	3	7
	Control	10	8	2
2.5 ml/kg	Resuscitated	9	—	9
	Control	7	—	7

were differences also in the character of the changes in the action currents of the heart, in the respiration and the arterial pressure of the resuscitated animals.

At the moment of injection of 1.0-1.5 ml/kg of tincture of strophanthin, the control animals usually showed an insignificant (within limits of 10-15 mm Hg) and transient fall in the arterial pressure, preceding a subsequent rise. In the resuscitated animals this fall was usually absent, which probably indicated the participation of a reflex component in this reaction.

In contrast to the resuscitated animals, the respiration of the control animals was usually slightly more excited after injection of strophanthin.

After injection of a toxic or lethal dose of strophanthin characteristic changes were observed in the electrocardiogram: the rate and rhythm were disturbed and complete block sometimes developed; the ventricular complex was lengthened; after a certain interval of time ventricular flutter developed. The changes in the electrocardiogram of animals surviving clinical death were usually more pronounced and developed more quickly than in control animals. These investigations showed that the sensitivity of animals, resuscitated after clinical death, to caffeine and strophanthin was altered. In particular, in the initial period of restoration of the vital functions, a lowering of the sensitivity to caffeine and an increase in that to strophanthin were observed.

A direct relationship was revealed between the changes in sensitivity and the degree of recovery of the function of the body and the degree of involvement of the central nervous system. In this respect, as the convulsive reaction to caffeine showed, even the few minutes from the beginning of recovery of respiration to the injection of the drug are important.

In a previous paper [8] we showed that 30-40 minutes after resuscitation, animals become more sensitive to caffeine than control animals.

The decrease in the sensitivity of the resuscitated animal to large doses of caffeine at the beginning of the restoration of the vital functions may probably be accounted for by the state of severe depression of the central nervous system, and it corresponds to the views of other authors of a diminution of the reaction of the body to toxic substances during profound inhibition of the central nervous system [10].

The enhanced toxic action of strophanthin in the first minutes after resuscitation may be associated with the anoxia to which the animals have been exposed, for this is known to bring about an increase in the sensitivity of the body to cardiac glucosides. A decrease in the gap between the therapeutic and toxic doses of tincture of strophanthin after resuscitation must be taken into consideration when this drug is used.

The results obtained may be important in answering the question of what the prospects may be from the use of caffeine and strophanthin in the treatment of the resuscitated patient, and also in judging the mechanism of action of these drugs. At the same time they add weight to the opinion that the dosage of drugs used in the treatment of patients surviving the terminal state must be reexamined.

SUMMARY

There is a sharp change in the sensitivity to caffeine and strophanthin in cats revived after clinical death by V. A. Negovskii's method. In the first minutes following their revival the sensitivity of cats to caffeine decreases and that to strophanthin increases.

The varied reaction of these substances, differing in their mechanism of action, is consequent upon changed body reactivity after deep anoxia; this should be taken account of in therapy.

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