DEEP HYPOTHERMIA AS A METHOD OF PROLONGING CLINICAL DEATH

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The foundations of the study of deep hypothermia in mammals were laid by investigations conducted on small animals (marmots, hamsters, rats). Their results demonstrated convincingly that the body temperature of these animals could be lowered artificially to 0-5° and even to below zero for a period of 1-2 h, after which all their vital functions could be restored merely by warming [5, 7, 8, 14, 15]. Reports were first published in 1952 [10] showing that the heart could be excluded from the circulation during deep hypothermia in higher, warm-blooded animals. Various authors [11, 12] have succeeded by the use of an extracorporeal circulation incorporation a perfusion apparatus and a special temperature-regulating device, in lowering the body temperature of dogs to 1-3° and, after excluding the heart for 45-60 min, restoring the animals to life. Other workers have described their experimental and clinical observations in this direction [1, 3, 4, 6, 9, 13, 18].

The object of the present investigation was to attempt to restore the vital functions of dogs after long periods of clinical death from acute blood loss under deep hypothermia and to evaluate the factors hindering and facilitating this process.

EXPERIMENTAL METHOD

Experiments were conducted on 31 dogs. Before the experiments the animals received a subcutaneous injection of 2% pantopon solution in a dose of 0.1 mg/kg body weight. Heparin was used as blood stabilizer. Before the beginning of cooling, a 0.2% solution of nembutal was given at intervals by intravenous drip until "cold anesthesia" supervened. The animals were cooled in a bath of ice. As the body temperature fell and breathing was disturbed, artificial respiration was applied; should fibrillation arise it was controlled by single electric pulses; electrical stimulation of the heart was used in case of asystole. When the rectal temperature reached 20-23° bleeding was started from the femoral artery, and continued until the onset of clinical death. Clinical death lasted 2 h. Resuscitation was carried out by means of intra-arterial blood transfusion in conjunction with mechanica artificial respiration, defibrillation, and electrical stimulation of the heart. To bring the animals out of the state of hypothermia, besides the general application of heat, an artificial circulation was provided by injecting warm, acerated blood centripetally into the femoral artery and withdrawing blood at the same time from the femoral or jugular vein. Active heating was discontinued when the body temperature reached 32°. The blood for injection was oxygenated by means of the oxygenator of a perfusion apparatus. In some experiments venous blood obtained from the experimental animal was injected into a donor for the purpose of oxygenation. In the recovery period exchange transfusion was performed on some of the animals by the method of O. S. Glozman and A. P. Kasatkina [2]. The ECG was recorded throughout the experiment.

EXPERIMENTAL RESULTS

As the body temperature fell the functions of the respiration and circulation were considerably modified. Besides a slowing of respiration, a gradual slowing of atrioventricular conduction took place, accompanied by a corresponding slowing of the heart rate. In some animals a disturbance of the shape of the ventricular complexes took place at 28-26°, as shown by the appearance of Osborne's waves, depression of the S-T segment, and enlargement

(or less frequently, lowering) of the T wave on the ECG. At a body temperature of 26-21° single or grouped extrasystoles developed in 12 of the 31 animals, changing to ventricular fibrillation. The fibrillation during cooling lasted for between 30 sec and 25 min. At a low body temperature, if ventricular fibrillation arose it was difficult to control by treatment. For instance, in 8 of 12 dogs permanent control of fibrillation could not be maintained during cooling and bleeding was started in association with periodic bouts of ventricular fibrillation. In 16 dogs fibrillation did not develop during cooling, and in 4 it was observed during exsanguination. In 2 of the 16 dogs asystole was recorded during exsanguination.

With anesthesia of adequate depth, cooling took place more rapidly and fibrillation was less common. Of the 20 dogs whose body temperature was lowered to 23-21° over a period of 1-2 h, only 6 developed fibrillation. When the body temperature was lowered more slowly – over 2-5 h – 6 of the 11 animals developed fibrillation.

The onset of fibrillation was accompanied by respiratory disturbances, and artificial respiration had to be applied. This was also done in connection with some of the animals which did not fibrillate, but which developed respiratory disturbances during cooling. The timely application of artificial respiration prevented the development of ventricular fibrillation during cooling. This agrees with observations made by several other workers [16, 17].

At the beginning of bleeding the body temperature of the animals fell to 23-20°. The period of development of clinical death lasted for between 4 and 42 min. As bleeding continued and the temperature fell, the disturbances of automatism and conduction in the heart progressed. The terminal activity of the heart usually ended in fibrillation. In rarer cases slow, monophasic complexes of low amplitude could be observed for an hour after the onset of clinical death. At the beginning of the period of active resuscitation the body temperature of the animals was 7.5-13°.

Because of differences in the technique of restoration of the cardiac activity, for the part of the experiment covering the resuscitation period the animals were divided into two groups.

In the first group (23 dogs) the venous system was drained during perfusion from the femoral vein and the first intra-arterial transfusion consisted of the blood taken from the animal during exsanguination. In the animals of the second group (8 dogs) continuous perfusion was maintained by intra-arterial injection of fresh donor's blood from 2 bottles, and blood was withdrawn during perfusion from the jugular vein. Blood, taken from the experimental animals during exsanguination, was not subsequently reinjected.

In the animals of both groups, intra-arterial blood transfusion led after 2-6 min to reappearance of the electrical activity of the heart, in the form of fibrillary low-amplitude oscillations of slow rhythm. An increase in the frequency of the fibrillary oscillations to 300-400/min and an increase in their amplitude to 0.5 mV were signs of the restoration of myocardial function and of the possibility of effective defibrillation. The first cardiac contractions in 13 of the 23 dogs of the first group appeared after intervals of 2.5-12 min at 12-18°. Periodic interruptions of the cardiac activity observed after restoration of the first contractions were caused either by the onset of fibrillation or the development of partial or complete atrioventricular block, for which defibrillation or electrical stimulation of the heart was necessary.

At this period delay in the initial part of the ventricular complex was observed, together with distortions of its shape as a result of a transverse block of the right or left branch of the bundle of His. Conduction in the terminal branches of the conducting system was usually disturbed.

Stable cardiac activity was restored quickly (after 150 sec) in only one dog, and in the other animals this took place later (after 12-72 min), after repeated defibrillation and electrical stimulation, while in two cases direct cardiac massage had to be used. Complete restoration of pacemaker activity took place in most animals when the body temperature had risen to 26-29° at the 40th-70th minute of cooling. For a long period after restoration of pacemaker activity disturbances of conduction were observed in the myocardium of the right ventricle (a deep, wide S wave).

During resuscitation and recovery from deep hypothermia the animals received adrenalin to strengthen the existing fibrillation and to change it from weak into active. In most of the reviving dogs the vascular tone was extremely unstable during the recovery period, and sharp fluctuations of arterial pressure were observed, while some dogs developed atrioventricular block. These animals were given intra-arterial or intravenous injections of small volumes of blood, glucose, or polyglucin with adrenalin, noradrenalin, and ephedrine periodically for a long period of time (for 2-3 h), and in one case for about 24 h). When necessary the heart was stimulated electrically.

In the remaining 10 dogs of the first group the cardiac activity could not be restored on account of acute dilatation of the heart from faulty perfusion, and weak ventricular fibrillation persisted. In the later stages of resuscitation, besides intra-arterial injections, all these dogs received direct or indirect cardiac massage. It must be pointed out that in some of the animals of this group difficulty in stopping fibrillation was caused not only be acute dilatation of the heart, but also be the fact that overheated blood was used for perfusion, and this caused a thermal contracture of the heart muscle and thrombosis of the auricles of the atria. The resuscitated animals recovered their respiration after intervals of 20-57 min at 18-27°; in some dogs breathing returned while the heart was still fibrillating. The corneal reflexes were restored after intervals of between 57 min and 3 h 32 min at 26-33.2°. Of the 13 resuscitated dogs, 5 remained alive, of which three outwardly appeared to have recovered completely after periods varying from 12 days to 3 months, and two showed cerebellar disorders before sacrifice 4-5 months and 1 year 3 months 10 days respectively after clinical death. Seven of the remaining 8 resuscitated dogs died 1-2 days after the beginning of resuscitation. At necropsy of these animals marked engorgement of the venous system was observed, with multiple and, in some cases, extensive hemorrhages into the heart muscle and other organs. Some animals showed pulmonary edema and degenerative changes in the liver and kidneys (N. P. Romanova).

The experiments with the first group of animals disclosed a number of factors hindering resuscitation. These included prolonged cooling of the animals and faulty anesthesia, leading to the more frequent development of ventricular fibrillation; acute dilatation of the heart, maintaining weak ventricular fibrillation, difficult to control; and in some cases asystole, which developed at the beginning of resuscitation when the venous outflow was insufficient during perfusion; the use of inadequately aerated, overheated, or too cold blood for perfusion of the heart during resuscitation; or faulty perfusion technique during resuscitation, leading to long periods of depression of the arterial pressure below the critical level (60 mm).

Severe hemodynamic disturbances in the scitated dogs during the recovery period, and severe metabolic acidosis continuing for several hours (according to O. N. Bulanova) during recovery from hypothermia also delayed the subsequent course of resuscitation and led to serious abnormalities of the internal organs and brain.

The object of the experiments with the animals of the second group was to overcome these factors by the more active withdrawal of blood from the venous system during resuscitation, the provision of continuous transfusion, the intra-arterial injection of fresh donor's blood, and the use of exchange transfusion in the later stages.

In all 8 dogs of this group, as in the animals of the first group, at the beginning of resuscitation ventricular fibrillation developed. In 7 dogs the first active contractions appeared after intervals of between 4 and 9 min at 13.5-16°. In these animals, in contrast to the animals of the first group, brisk fibrillation developed, and this was easily and quickly removed. In 3 of the 7 dogs electrical stimulation was used together with defibrillation. The arterial pressure in 5 of the 7 animals of this group was maintained above the critical level during perfusion, i.e., until the cardia activity had been permanently restored, which took place after 8-35 min. Indirect cardiac massage had to be applied to one of these dogs. The vascular tone in most of the animals was stable after permanent restoration of the cardiac activity 40-60 min after the beginning of resuscitation. The general course of the ECG changes in the recovery period was similar to that observed in the animals of the first group, although the normal ECG was restored sooner and at a lower temperature.

Respiration was restored in 7 of the 8 dogs of this group after 17-38 min at 18-23.5°, and in one dog of the 98th minute of resuscitation at 33.2°. The corneal reflexes were restored after 36-76 min at 21.5-32.4°.

In order to speed up the subsequent resuscitation of the animals, after their normal vascular tone had become restored 70-80 min after the beginning of resuscitation exchange transfusion was performed in 6 of the 8 dogs. Complete recovery of the vital functions took place in 5 of the 8 dogs after intervals of between 4 days and 1 month 7 days; in all these animals resuscitation began with perfusion of fresh donor's blood and in 3 animals exchange transfusion was also performed.

Three of the resuscitated dogs died on the 1st and 2nd days: one from hemothorax and two from cardiac weakness. Death of 2 animals of the second group was evidently caused by severe hypoxia, arising during the first 40 min of resuscitation as a result of a faulty perfusion technique, in association with the rising temperature. The low level of the arterial pressure, alternation of fibrillation with periods of asystole, and disturbances of the cardiac rhythm in the later stages of resuscitation led to severe, irreversible changes in the heart, which were the immediate cause of death of the animals as a result of massive hemorrhages into the internal organs.

Comparison of the results of the experiments with the two groups of animals shows that the better the perfusion technique in the initial stages of resuscitation, the more easily the cardiac activity is restored.

Exchange blood transfusion hastens the subsequent course of recovery. It may be assumed that a faster cooling technique, the correct choice of anesthetic, and perfection of the perfusion technique during resuscitation will contribute towards the prevention of the complications arising during resuscitation and the recovery period, and thereby enable resuscitation to be successful even after periods of clinical death exceeding 2 h in duration.

SUMMARY

The body temperature was reduced in dogs to 7-13°C by general cooling of the body. The first experimental series demonstrated that with the aid of deep hypothermia in a number of animals (in 5 of 23) it was possible to prolong to 2 hours the period of clinical death from acute blood loss with subsequent complete restoration of the vital functions. However, the majority of the animals of this group either could not be revived at all or died 1 to 2 days after the experiment.

Imperfect perfusion during revival, leading to actue dilatation of the heart, marked hemodynamic disturbances occurring during the restoration period in the revived dogs, and severe metabolic acidoses, lasting hours during the period of recovery from hypothermia, inhibited subsequent restitution, leading to severe changes in the internal organs and the brain.

Control of the aforementioned factors, as well as intra-arterial infusion of fresh donor's blood and exchange transfusion, employed during the later stages of revival, promoted a more rapid and complete restoration of the vital functions in the 2nd group of animals. All 8 dogs of this group were revived, complete restoration of the vital functions being achieved in 5 animals.

LITERATURE CITED

1. S.S. Vail', V. M. Pinchuk, and V. G. Petrukhin, Proceedings of the 1st Congress of Surgeons of the Russian Federation [in Russian], p. 390, Leningrad (1959).
2. O. S. Glozman and A. P. Kasatkina, Complete and Partial Exchange Transfusion [in Russian], Moscow (1950).
3. E. V. Gubler, N. V. Alishev, and N. I. Lassi, Pat. fiziol., 5, 41 (1959).
4. I. S. Kolesnikov, B. M. Kostyuchenok, and V. N. Sheinis, Khirurgiya, 4, 65 (1956).
5. N. V. Korostovtseva, Arkh. pat., 8, 54 (1959).
6. I. R. Petrov, Pat. fiziol., 6, 8 (1958).
7. R. K. Andjus and J. E. Lovelock, J. Physiol. (London) (1955), 128, p. 541.
8. R. K. Andjus, Ibid, p. 547.
9. C. E. Drew, G. Keen, and D. B. Benazon, Lancet (1959), 1, p. 745.
10. F. Gollan, P. Blos, and H. Schuman, J. appl. Physiol. (1952), 5, p. 180.
11. F. Gollan et al., Am. J. Physiol. (1955), 181, p. 297.
12. F. Gollan, Fed. Proc. (1954), 13, Pt. 1, p. 57.
13. F. Gollan, R. Phillips, J. T. Grace et al., J. thor. Surg. (1955), 30, p. 626.
14. S. A. Niazi and F. J. Lewis, Surgery (1954), 36, p. 25.
15. A. U. Smith, Proc. roy. Soc. B. (1956), 145, p. 391.
16. H. Stone, C. Donnelly, and A. Frobese, Surg. Gynec. Obstet. (1956), 103, p. 313.
17. H. Swan, J. Zeavin, and J. Holmes, Ann. Surg., (1953), 138, p. 360.
18. M. Weiss, A. Piwnica, C. Lenfant et al., Rev. franc. Et. Clin. biol. (1960), 5, p. 65.