REVERSIBLE WHOLE-BODY DEEP HYPOTHERMIA IN RATS

P. V. Shcherbakov, V. I. Ter'pukhov, and A. V. Khokhlov

UDC 612.014.46:615.832.9].08

KEY WORDS: deep hypothermia; whole body; restoration of functions

Whole-body hypothermia is attractive as a means of lowering the metabolic rate [4] (especially in brain tissue) for the solution of problems in neurosurgery and cardiovascular surgery. There are two methods of inducing hypothermia [8]: external cooling of the body and extracorporeal cooling of the blood (a combination of both is possible). Although with even an average degree of hypothermia it is possible to lengthen the safe period from the beginning of cerebral ischemia to the appearance of irreversible changes in the brain, the possibility of lowering the temperature to 0°C or below remains an open question [3, 5]. To achieve reversible deep hypothermia (to 0°C), hypercapnic hypoxia is used at the present time in conjunction with cooling in order to inhibit the CNS, or heat-blocking preparations may be used with extracorporeal cooling of the perfused blood [2, 6]. To restore functions of the deeply hypothermic organism, reheating is required, but its rate has not been determined [1].

The aim of this investigation was to achieve a maximal depth of hypothermia by the use of external whole-body cooling with ice-cold water (0°C) in rats without the use of hypercapnic hypoxia or drugs, and also to determine the optimal rate of reheating the body to enable resuscitation and subsequent restoration of specific functions to take place.

EXPERIMENTAL METHOD

There were four series of experiments on 35 mature male Wistar rats weighing 300-400 g. The technique of forced cooling to the lowest possible depth of hypothermia was developed in experiments on a series of ten animals. In series II, III, and IV, on 10, 10, and 5 animals respectively, the possibility of their resuscitation was studied by the use of forced, moderate, and slow reheating with water. The rate of reheating was 0.6, 0.4, and 0.2°C/min respectively. Under open ether anesthesia the right subclavian artery was catheterized and the animal incubated with a special tube with a device to prevent water from entering the lungs, and fixed to the chest. The catheter in the subclavian artery was connected to a pressure transducer and electrodes for recording the ECG were applied, a rectal temperature transducer inserted, and a mercury thermometer placed in the external auditory meatus. The rat was cooled in ice-cold water until the minimal body temperature was reached, after which reheating began with a power of 1200, 800, or 400 W. Reheating the animal continued until the rectal temperature was 28°C, and no special resuscitation measures were used except maintaining artificial ventilation of the lungs through an open circuit. Final reheating was then carried out with the aid of an air heater. The catheter was removed and the operation wound sutured. The animals remained under observation for 4 months. An EPM-2 apparatus (USSR) was used for artificial ventilation of the lungs and a PST-01 air heater (USSR) was used for final reheating and drying of the animal. The ECG and blood pressure (PB) were recorded on a biograph (Harvard Apparatus, USA) and the rectal temperature was measured by means of a TEM-2-5 electrothermometer (USSR). The results were subjected to statistical analysis [7].

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. 107, No. 5, pp. 543-545, May, 1989. Original article submitted April 20, 1988.

0007-4888/89/0005-0617$12.50

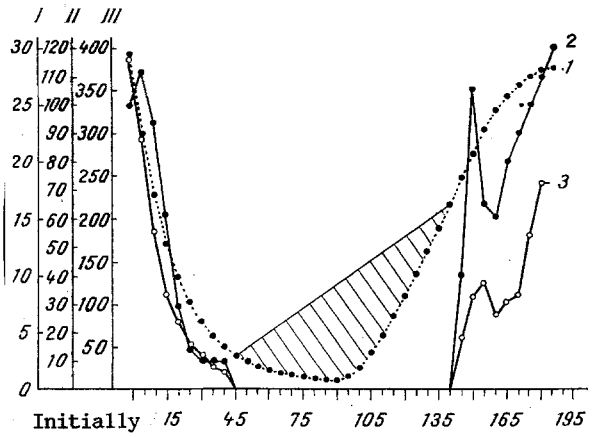

Fig. 1. Changes in temperature (1), BP (2), and HR (3) during cooling and reheating of animal (period of clinical death is shaded). Abscissa, time (in min); ordinate: I) rectal temperature (in °C), II) BP (in mm Hg), III) HR (beats/min).

EXPERIMENTAL RESULTS

Before the beginning of cooling the animal's temperature was 29.4°C. During forced cooling, a maximal depth of hypothermia of 0.5°C was achieved 90 min after the beginning of the experiment. Prolonging cooling longer than 90 min did not produce any further fall of temperature. The 90th minute was therefore chosen as the initial point for subsequent reheating. During forced reheating spontaneous restoration of cardiac activity and resuscitation were observed in only half of the animals, but they all died in the next 6 days. With slow reheating, cardiac contractility was restored but BP could not be determined. With an average rate of reheating, the survival rate of the animals was 100%.

The cooling period was divided into two stages: stage I from 29.4°C to cold-induced asystole, stage II from cold asystole to the minimal temperature. The rectal temperature fell during stage I of cooling to 3°C in the course of 45 min, in stage II it fell to 0.5°C, also in 45 min. Subsequent reheating also was divided into two stages: stage I from 0.5°C until the appearance of the first cardiac contractions, stage II from the beginning of cardiac contractions until the temperature reached 28°C. The rectal temperature rose during stage I of reheating to 10.1°C in the course of 35 min, and in stage II to 28°C to 60 min. The appearance of the temperature curve of cooling and reheating of the animals with 100% survival we described by the term "hypothermic pit" (Fig. 1).

Before the beginning of cooling the mean BP was 100 mm Hg and the heart rate (HR) at that time was 390 beats/min. At the beginning of stage I of cooling BP rose, to reach 112 mm Hg at 22.5°C, but by the end of stage I it had fallen gradually to 10 mm Hg at 6°C. At 3°C the pressure fell to zero. In the initial stage of cooling bradycardia developed (down to 296 beats/min), and by the end of stage I, there were only single cardiac contractions. Neither arrhythmias nor fibrillation were observed until total cardiac arrest, which took place at 3°C. By the end of stage I of reheating, when the temperature was 10.1°C, single cardiac contractions appeared and created a pressure of up to 10 mm Hg. At 16.2°C the pressure rose slowly, and at 18.6°C it jumped up to 40 mm Hg. This indicated restoration of the natural color of the iris. During further reheating BP rose to 105 mm Hg at 20.7°C, after which it fell again to 60 mm Hg at 24.4°C. Toward the end of reheating of the animal BP rose to 120 mm Hg. In the course of stage II of reheating HR increased to 240 beats/min. Arrhythmias of bigeminy and trigeminy types were observed, but they disappeared before the end of stage II. Clinical death lasted 95 min.

During reheating and restoration of the vital functions, movements of the head and neck were the first to appear. Considerable swelling of the eyes were observed during reheating to 28°C, but after the final reheating with air it disappeared, to be followed by the appearance of limb movements, shivering, and attempts to move about. The pupillary

reflex and nociceptive response of the fore- and hind limbs to pinching were restored in all the animals completely by the time of ending of final reheating. After 1-3 h the rats adopted a normal posture, and after 5-12 h they could move about unaided. During the first few days transient hyperesthesia was observed. After 2-3 months, the rats gave birth to healthy offspring.

As the experiments showed, rapid reheating prejudices survival. Rapid reheating can be considered to trigger many specific functions before an adequately compensated energy metabolism has been restored. This phenomenon evidently leads to rapid exhaustion of the residual substrates and accumulation of incompletely oxidized products, leading ultimately to irreversible changes and death of the animals. Thus in the case of forced reheating the rapid rise of temperature is a factor limiting survival. Reheating at a slower rate revealed the second temporary limiting factor. Optimal reheating thus ought not, first, to cause the too early recovery of specific functions, and second, to extend the period of ischemia outside the limit of the safe time interval.

We found that single cardiac contractions, observable down to 3°C, can maintain a pulse wave of 10/0 mm Hg.

The fact that recovery of specific functions takes place in phases will be noted. Rapid growth is followed by quite rapid inhibition, possibly due to exhaustion of residual substrates and delayed activation of the energy systems of the cell. Nevertheless, secondary inhibition does not develop to the irreversible level, as during too rapid reheating. It is very quickly replaced by secondary growth and normalization. The optimal rate of reheating is evidently a compromise between the intensity of restoration and its stability.

The investigation thus showed that it is possible to achieve deep hypothermia of 0.5°C by surface cooling. Cessation of cardiac activity is observed on average at 3°C. Reheating at the rate of 0.6 and 0.2°C/min is followed by death. Forced cooling followed by reheating at the rate of 0.4°C/min are followed by full and complete recovery of the vital functions of animals exposed to clinical death for 95 min under conditions of deep hypothermia.

LITERATURE CITED

L. G. A. Akimov, N. V. Alishev, V. A. Bernshtein, and V. A. Bukov, General Cooling of the Body [in Russian], Leningrad (1977).
2. N. V. Korostovtseva, Artificial Hypothermia [in Russian], No. 3, Tashkent (1961), p. 163.
3. A. Labori, Regulation of Metabolic Processes [Russian translation], Moscow (1970).
4. E. N. Meshalkin and I. P. Vereshchagin, Occlusion under Superficial Hypothermic Protection [in Russian], Novosibirsk (1985).
5. V. A. Negovskii, Essays on Resuscitation [in Russian], Moscow (1986).
6. V. A. Negovskii, V. I. Soboleva, N. L. Gurvich, and K. S. Kisileva, Vest. Akad. Med. Nauk SSSR, No. 10, 40 (1960).
7. N. A. Plokhinskii, Algorithms of Biometrics [in Russian], Moscow (1980).
8. A. M. Khil'kin and V. A. Svetlov, Experimental Modeling of Cardiac and Vascular Lesions [in Russian], Moscow (1979).