Chapter 9

Resuscitation of Overcooled Mammals without Rewarming

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Additional information is available at the end of the chapter

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Abstract

Cold is a deadly danger for man. If the temperature of the surrounding air is +1°C, it is death for a naked man, owing to the arrest of respiration at the body temperature 25–28°C. After the heart is arrested, the death occurs at 23–24°C. Our aim was to prolong life at an absolutely deadly body temperature. This problem is important nowadays owing to a lot of sea catastrophes, the investigations in Arctic and Antarctic areas, and so on.

Keywords: rewarming, potassium ions, calcium ions, artificial ventilation

1. Introduction

Temperature is the most important criterion of life. As it increases, the limit is achieved quickly. For homoeothermic organisms, the body temperature between 42 and 45°C is practically incompatible with life. The cold diapason is substantially wider. Humans and mammals can decrease their body temperature to 32–33°C and then restore it without any pathological after effect. At lower temperature, rewarming becomes dangerous. A too intensive external rewarming results in increased oxygen consumption by various, almost indifferent, tissues, so that the brain and heart are subjected to a deficit in the energy material. In such a case, a deterioration of their functions occurs, which can result in the death of an organism. Generally speaking, the resistance to cold in living organisms is essentially higher than the resistance to heat. This is associated with the fact that a high temperature disrupts the tissues, whereas low temperature, to the contrary, favors the conservation of the tissue structure. According to the old data of Andjus [1], a rat frozen at 0 to −1°C revived for a short time if its heart was rewarmed by a special thermode, and thus its circulation was partially restored. However, rewarming a man at a very deep cooling is very dangerous since the distribution of temperature fields may appear unfavorable for the most important organs of a living organism: brain and heart. This can result in the death of deeply cooled organisms. But, let us consider the possibilities of resuscitation of overcooled organism by rewarming.

Rewarming is a conventional method of resuscitation of a frozen man or animal. However, this seemingly irreproachable procedure appears to require compliance with certain rules. First of all, the effect of rewarming the whole organism depends on the state of respiration and circulation. If these functions still operate at the temperature in the rectum 26–28°C, the rescue team has a hope to restore the organism's life. If a man's respiration is arrested upon deep cooling, but a weak circulation is still preserved, there is a hope for recovery of life, but it is very weak, since after arrest of respiration the heart operates briefly, by common opinion only for 15–30 min. Unfortunately, this period of time has not been adequately explored, and it is impossible to say something strictly definite about it. Burton and Edholm [2] described a case when a victim of cold lied in a cold morgue for several hours without respiration. He was supposed to have an extremely weak heart activity and eventually survived. It is supposed that only separate heart impulses remained in him, which resulted in a very weak circulation. It is conceivable that such cases are of frequent occurrences. In this instance, the absence of visual respiration is not the reason for sending a victim of overcooling to a morgue.

There is one more rule. During rewarming, if the brain is warmed more quickly than the heart, the supply of the blood to the brain may appear to be insufficient for the brain life and consequently for the life of the whole organism. At any rate, from the practical point of view, upon the arrest of respiration, the main emphasis must be placed on rewarming the heart. The attention must be focused on the problem that upon rewarming the whole organism, the brain was not rewarmed well before the heart [2–6].

Now we shall consider other methods, which can be used upon resuscitation of overcooled organism without general rewarming.

2. Materials and methods

The studies on the influence of the decrease in the content of potassium ions in the blood were performed on the isolated rat hearts. They were perfused by Krebs-Ginzelite solution with various concentrations of potassium, and the heart activity was studied at normal and decreased temperatures.

The experiments on the influence of calcium ion concentration in the blood on thermoregulation were carried out on white male Wistar rats 280–310 g in mass. After narcotization (125 mg of urethane per 100 g of weight intraperitoneally), the animals were fixed in a special stand. Polyethylene catheters were inserted into the femoral vein and artery for injections and for measuring the blood pressure. The temperature in the rectum (at a depth of 4.5 cm) and in the region of medulla oblongata was measured with the help of copper-constantan thermocouples. One hour after the beginning of narcotization and inserting catheters and thermocouples, the rat on a special stand was immersed into water with the temperature ~+8°C. In this case, the head and nostrils of the animal were located above the water level. The temperature of the animal body decreased gradually at a rate of about 0.35–0.40°C per minute. During the experiments, we periodically recorded the pneumogram (a carbon sensor on the animal breast) and electrocardiogram (ECG), and also measured the blood pressure in the femoral artery and the body temperature in the rectum and brain. The control animals were observed after the respiration arrest and immediately after injection of 1 ml of physiological solution as a placebo up to the moment of the heart arrest and the decrease in the arterial blood flow to zero. Another group of animals was injected with 1 ml of 0.5% solution of ethylenediaminetetraacetate (EDTA) into the femoral vein 8–10 min after the arrest of respiration.

Calcium ion concentration in the whole blood was determined by the method of direct potentiometry with film calcium selective electrodes. The method of determining Ca^{2+} concentration in the blood is described in detail in our previous work [5]. The blood samples for the determination of Ca^{2+} content had the volume not more than 0.3 ml.

We carried out the statistical treatment of the results with the help of Statistica program. We calculated the average values (M) and the error (m); the reliability of the differences was determined by Wilcoxson criteria (p_w).

Artificial ventilation was carried out with the help of special small self-made apparatus for the rats. The maximal power of the apparatus was 13–15 inhales per min. Each inhale contained 1.5 ml of air.

3. Results and discussion

3.1. Decrease in potassium ion concentration in the blood

A comparatively small increase in potassium ion concentration in the rat blood has no distinct effect on the thermal reactions of the animals. However, a decrease in the concentration of these ions in the blood upon its dilution results in a pronounced increase in the resistance to cold.

When an isolated heart of a rat is perfused with the blood with normal concentration of potassium ions (K^+ 5.9 mM), it terminates contractions as the temperature of the heart tissues decreases to 14–12°C. But if the content of K^+ in the blood with which the heart is perfused is 3.6 mM, the heart is arrested at lower temperature of about 10–8°C. If the K^+ content is reduced to 2.5 mM, a complete arrest of the heart will occur at 6–5°C (**Figure 1A–C**; **Table 1**) [7].

Therefore, a decrease in the concentration of potassium ions distinctly increases the heart's resistance to cold and, consequently, decreases the danger of disrupting the circulation. True enough, it is hardly possible to save the victim of overcooling at such low body temperatures with the help of decreasing potassium concentration in the blood. However, a dilution of the blood with the aim of decreasing K^+ concentration along with other procedures may be useful.

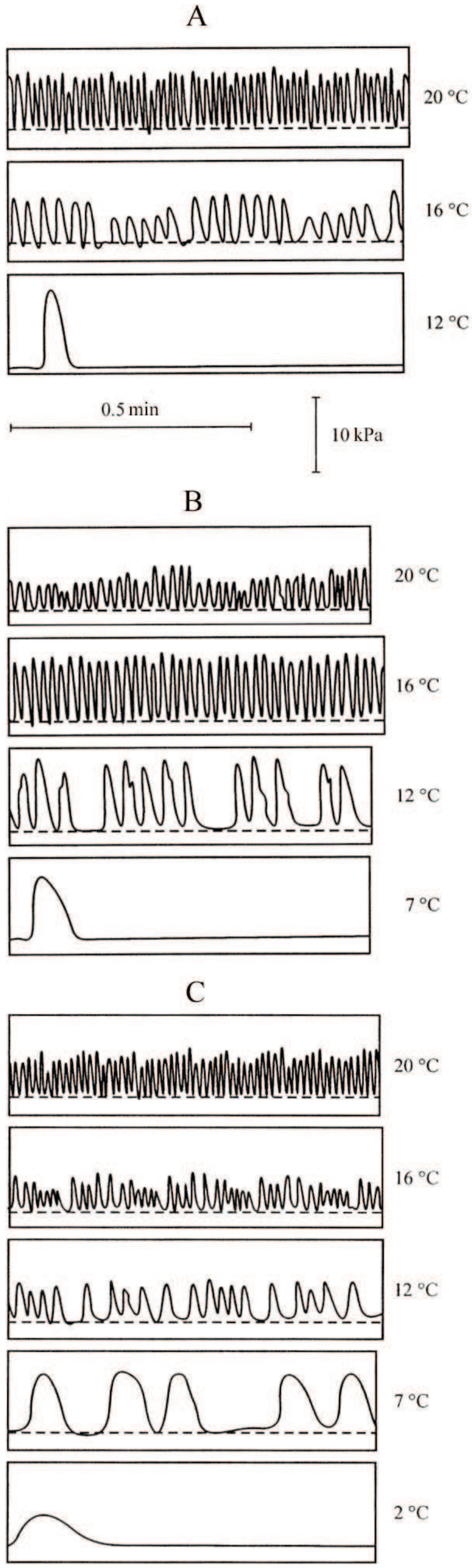

Figure 1. Mechanograms of the heart cooled and perfused with physiologic salt solution with K^+ content: (A) 5.9 mM; (B) 3.6 mM; (C) 2.48 mM.

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Temperature of the hearts arrest, °C	
Perfusion with the solution with potassium content 5.9 mM	**After restoration of contractions by perfusing with potassium concentration 3.6 mM and further cooling**
14.2	9.8
12.0	7.5
12.9	10.2
15.0	12.0
11.7	8.3
13.2 ± 0.6	**9.5 ± 0.7**

Note: $P < 0.001$.

Table 1. Restoration of the contractions of cold paralyzed isolated hearts [6].

It appears difficult to find the data on the effect of ionic composition of the blood on their resistance to cold in the current literature. We were able to find a very interesting paper in Federation Proceedings [8], which supports our data about the role of potassium in this process. Furthermore, the effect of a decrease in potassium concentration on the increase in the heart tissues resistance to cold is very interesting and important from theoretical point of view. We emphasize that this fact opens the way to the studies of a number of other ions with the same purpose. The mechanisms of such action of ions are very interesting; however, such investigations seem to be scarce in the current literature.

3.2. Decrease in calcium ion concentration in the blood

As far back as in 1986, Hochachka [9] reported that in an overcooled organism, the cells die owing to the excess of calcium ions resulting from disrupting metabolism. These extra calcium ions must be removed from the intercellular fluids, but this process requires energy. The matter is that the concentration of calcium ions in the cells is about 10^{-8} M and in the intercellular fluids it is 10^{-3} M, thus we have the diffusion against a great concentration gradient, and the energy deficit in an overcooled organism prevents it.

We decided to examine the effect of calcium ion concentration in the blood on resuscitation of the functions of an overcooled organism.

We did not find any essential changes in the thermoregulation upon a small increase in the Ca^{2+} concentration in the blood. However, when the most important thermoregulation reaction—the cold shivering—is completely oppressed upon deep cooling of an organism, a comparatively small decrease in calcium ion concentration restores this most important muscle reaction in a short period of time (**Figure 2**) [5]. At a low body temperature of an animal, it is recommenced if a solution of ethylenediaminetetraacetate (EDTA) is introduced into the blood. EDTA decreases the calcium ion concentration since it reacts with them to give a complex compound, thus practically removing them from the blood. The introduction of 1 ml of 0.5% solution of EDTA into the blood of a rat 210–240 g in mass results in a decrease in calcium ion concentration by 15–25%. We emphasize that EDTA is a pharmacological preparation which is in wide use in medicine, and we inserted it in the relationships never exceeding those recommended for animals and humans.

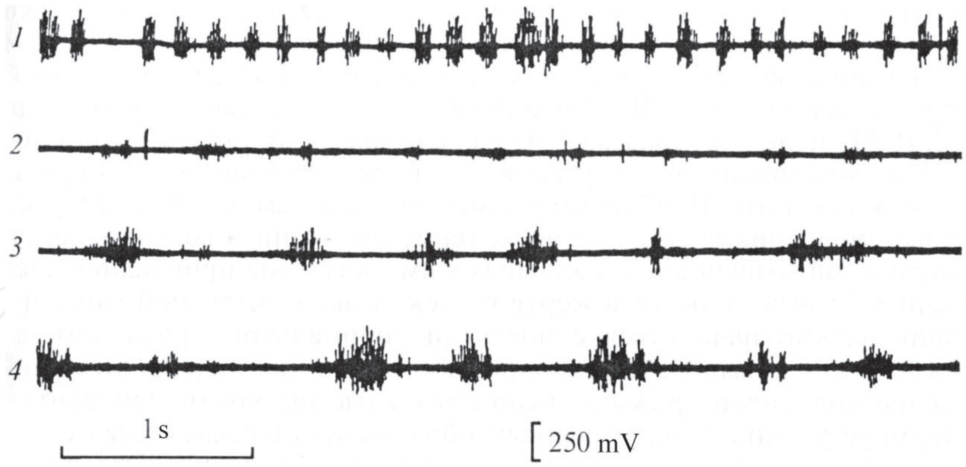

Figure 2. Arrest of cold shivering and thermoregulation tone in rats during cooling of the body and restoration of these physiological functions without rewarming the body after inserting 0.016 mmol of EDTA into the blood. (1) Brain temperature (Tb)—28°C; rectum temperature (Tr)—25°C; maximal intensity of the cold shivering and of the thermoregulation muscle tone. (2) Tb—20°C; Tr—17.2°C; retardation of the functions of thermoregulation center and an almost complete oppression of shivering. (3) Five min after inserting 0.016 mmol of EDTA into the blood: Tb—18.9°C, Tr—17.2°C. (4) Ten min after a repeated insertion of the same dose of EDTA (0.016 mmol): Tb—18.7°C, Tr—17.2°C.

If a decrease in calcium ion concentration exhibits such a distinct positive effect on the most important thermoregulation reaction, the question arises inevitably about how such an action will influence respiration, heart activity, and blood pressure at a low body temperature.

Tables 2 and **3** [10] answer this question. According to these data, EDTA excites the cold paralyzed respiration center and makes it work at a temperature, which under normal conditions results in its cold paralysis. Moreover, a partial restoration of the work of respiration center after EDTA insertion not only restores the cold shivering but also increases the frequency of the heart contractions and the blood pressure. Even though all these functions appear in an abruptly slowed down rhythm, this effect may continue for 1–1.5 h. Only gradually, it tapers down to nothing. If the cooling is stopped, and the animals are removed from water, dried, and left at room temperature, in this case the animal is warmed up on its own during 2.5–3 h

Temperature in the rectum, °C	Temperature in the brain, °C	Arterial blood pressure, mm Hg	Respiration frequency, cycles/min	Frequency of the heart contractions, imp/min
13.5	13.9	20	0	25
11.4	13.4	10	0	10
12.8	14.0	18	0	25
14.0	15.0	10	0	10
13.2	15.7	18	0	20
14.3	16.1	10	0	19
14.8	15.8	24	0	16
13.4 ± 0.6	**14.8 ± 0.2**	**16 ± 6.1**	**0**	**21 ± 5.0**

Table 2. Physiological parameters of the rats in 15 min after the arrest of respiration.

Temperature in the rectum, °C	Temperature in the brain, °C	Arterial blood pressure, mm Hg	Respiration frequency, cycles/min	Frequency of the heart contractions, imp/min
11.6	13.8	36	6	41
12.3	13.8	48	8	84
13.2	15.6	66	24	63
14.1	15.6	50	18	66
9.5	14.9	24	6	36
12.7	15.4	36	12	52
12.2 ± 0.7	**14.9 ± 0.3**	**43 ± 6**.	**12 ± 6**	**57 ± 7**

Table 3. Physiological parameters of these very animals after the arrest of respiration and immediate insertion of 1 ml of 0.5% EDTA solution into the blood.

and later does not differ from other control rats by its behavior. In this case, the insertion of EDTA saves the animal from death.

If a comparatively small decrease in calcium ion concentration exerts such an effect on an animal, it is necessary to reveal the action of this factor on the whole thermoregulation system, that is, on peripheral and central thermosensors. First, we tried to reveal the effect of a decrease in calcium ion concentration by 15–20–25% on the skin thermoreceptors. These experiments were carried out on the skin thermoreceptors of the nose and back skin of a rabbit. They were rather complicated since we have not always met with success trying to keep the even pulsation of the cold thermoreceptors for 1–2 h in the starting state before cooling and then for a sufficiently long time after cooling and EDTA insertion. In **Table 4**, we demonstrate five experiments which distinctly show the restoration of receptor pulsation after their cold paralysis in several minutes after insertion of EDTA solution into the blood [10]. The restored pulsation after its complete or partial oppression with cold continues variously from 20 to 30 min and even more. The secondary paralysis may result from restoration of calcium ion concentration in the blood to the norm.

Number of receptor	Skin temperature at the site of receptor location, °C	Pulsing frequency before EDTA insertion, imp/s	Maximal pulsing frequency after EDTA insertion, imp/s	Skin temperature in the same site of receptor location, °C
1	5.0	0	18	5.0
2	3.0	3	18	3.0
3	0	0	16	0
4	4.8	0	20	4.0
5	0	3	11	0
Mean ± SEM	**2.6 ± 3**	**1 ± 1**	**17 ± 2**	**2.4 ± 3**

Table 4. Pulsing frequency of thermoreceptors in 5–10 min after EDTA insertion at the skin temperature at the site of their location from 0 to +5°C.

Of course, it was of great interest and importance from theoretical and practical point of view to learn how a decrease in calcium ion concentration affects the center of thermoregulation apparatus immediately. The neurons taking part in thermoregulation are known to be located in various parts of the central nervous system, in the hypothalamus among them. Hence, in order to put the central nervous thermoregulation as a whole to a test, we decided to insert EDTA immediately into the brain ventricles of the animals. We selected a minimal dose of 10–15 mmoles for the whole rate 210–240 g in mass. This dose is many times less than the dose that had been inserted into the blood of these animals. As has been found earlier, respiration is completely paralyzed at the rat body temperature 17–18°C. The insertion of this dose of EDTA into the brain ventricles restored the respiration in its frequency and amplitude in 10–15 min, though still far from the norm, that is, the respiration center acquired a certain resistance to cold. Later, we carried out many experiments and confirmed all the results [6]. That means an inhibiting effect of cold on thermoregulation, respiration, and circulation and removal of the cold paralysis from these functions at the expense of activation of peripheral and central thermosensors.

3.3. Artificial ventilation

This is another method of saving a man from death during hypothermia.

Usually, artificial ventilation is considered as a help for the lungs in supplying an organism with oxygen. This is so indeed. A conventional artificial ventilation by manual operation without a special device may appear low efficient and give no expected result for 1 or even 2 h of its use even if there is a weak circulation.

It is seen from **Tables 5** and **6** that the lung respiration disappeared in the animals at the temperatures in the rectum 15.4°C, in the esophagus 16.6°C, in the brain 17.9°C (**Table 5**). In 12–15 min, when the temperature decreased by 1.5–2.0°C more, we switched on the artificial

Temperature in the rectum, °C	Temperature in the esophagus, °C	Temperature in the brain, °C	Respiration frequency, cycles/min	Frequency of the heart contractions, imp/min	Arterial blood pressure, mm Hg
15	16	17.6	0	17	25
17.2	18.4	19.7	0	21	20
14	15	16.3	0	17	30
14.5	15.3	16.6	0	23	10
15.5	17.4	18.7	0	24	24
14.5	15.8	17.1	0	28	18
17	18.4	19.3	0	19	14
15.4 ± 0.5	**16.6 ± 0.5**	**17.9 ± 0.5**	**0**	**21.3 ± 1.5**	**20.4 ± 2.6**

Table 5. Arrest of respiration and an abrupt decrease in the arterial blood pressure and in the frequency of the heart contractions after the animals stay in water with the temperature 8–9°C.

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Temperature in the rectum, °C	Temperature in the esophagus, °C	Temperature in the brain, °C	Respiration frequency, cycles/min	Frequency of the heart contractions, imp/min	Arterial blood pressure, mm Hg
13.7	14.9	16.4	13	58	40
14	15.2	17	13	45	30
13	14.4	15.6	12	55	46
13.9	14.8	15.8	12	58	28
13.9	15.9	17.6	12	72	42
12.5	14.4	15.6	12	44	36
14.5	15.6	17.0	12	70	40
13.6 ± 0.2	**15.0 ± 0.2**	**16.4 ± 0.3**	**12.3 ± 0.2**	**57.4 ± 4.1**	**37.4 ± 2.5**

Table 6. Test rats 2 min after starting artificial respiration of 12–13 inhales per min.

ventilation. Two min after switching on the artificial ventilation, as is seen from **Table 6**, a distinct increase in the frequency of the heart contractions and in the blood pressure occurred, which is necessary for increasing the muscle heat production. If at this point we stopped cooling the animal, that is, removed it from cold water, artificial ventilation resulted in further increase in the frequency of the heart contractions and in the blood pressure, and in 2.5–3.5 h the animal restored completely the normal frequency of the heart contractions and the normal frequency of respiration and arterial blood pressure. But if the artificial ventilation was absent, at this low body temperature, the heart work gradually slowed down, oxygen consumption decreased, and the blood pressure decreased to zero. The animal died.

3.4. The last reserve for saving a homoeothermic organism from cold

Up to 0°C cold does not destroy the construction of the tissues. Consequently, no mechanical destructions of the tissues occur in the death from cold. In a complete physiological rest, the organism tissues consume a physiological minimum of energy. In a man of average weight and age, the energy consumption on the level of normal metabolism is about 1860 kcal per day. This is the required level of energy for maintaining all the living processes in various organs and tissues of a man at a relative rest. If a man is cooled and his average body temperature decreases, the energy consumption also decreases naturally. If a decrease in the energy supply of the tissues appears to be lower than the required quantity, under specific conditions, the tissues die. The last reserve for maintaining the living ability of the tissue is the limit of its temperature decrease (up to 0°C) and the limit of the decrease in the oxygen consumption. With the aim of preventing the animal brain from being devoid of the blood influx and of the minimum of oxygen, we slightly warmed up the heart to 19–20°C. Under these conditions, the heart retained its living ability and provided the brain with a minimum of oxygen and energy at its temperature of about 0°C. This means that under a sufficiently slow and careful rewarming, the heart, the brain, and the organism as a whole can still return to life. **Figure 3** shows one of the experiments of this series. As can be seen from the figure, the brain, after the

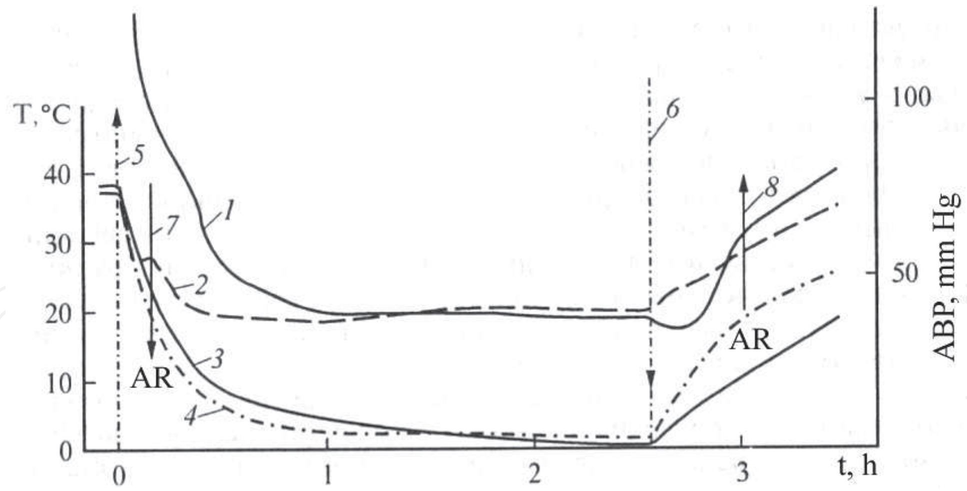

Figure 3. Cooling the rat brain to 1°C under artificial respiration, and local warming the heart retaining the arterial blood pressure at the level 40–45 mm Hg. *X*-axis—the time, h. *Y*-axis to the left—the temperature in the brain and in the rectum; to the right—arterial blood pressure, mm Hg. (1) Arterial blood pressure; (2) t° of the heart; (3) t° in the rectum; (4) t° in the brain; (5) the beginning of cooling the animal; (6) the beginning of warming up; (7) switching on the artificial respiration; (8) switching off the artificial respiration.

beginning of cooling, retained the temperature close to 0°C for a period of about 1.5 h. After the beginning of a careful rewarming, the brain temperature started to increase rapidly, and so did the arterial blood pressure. This experiment showed that the brain retained its living ability and still could exert control over the circulation being at a temperature close to 0°C for about an hour and a half. These animals after a complete resuscitation did not differ in anything from the control rats. This is a very important fact both for the theory of living activity of various animals and from the point of view of practical medicine. This supports the old observations of Andjus on overcooled rats [1]. Now we know that a severe minimum of metabolism is retained up to the lowest temperatures of about −100 or −130°C [11]. At such temperatures, the tissues acquire a complete independence from further decreases in temperature, since they have no need in energy anymore and pass into "eternal" existence without energy.

4. Conclusions

In this short chapter, we gave several sufficiently impressive remarks about the physiological mechanisms of the death and physiological mechanisms of resuscitation of mammals and humans during deathly hypothermia. As has been noted, cold does not destroy the construction of tissues. Ultimately, it only denudes the tissues of oxygen. According to a known axiom, only oxygen releases energy necessary for the living activity of all the organs and tissues as the result of oxidation reactions with carbohydrates, fats, and proteins. There is no alternative to oxygen. Therefore, hypoxia and cold are almost to the same extent responsible for the result and for resuscitation during hypothermia. This is an important reasoning. We hope that medicine will estimate it highly enough and will use it.

In practical medicine, the arrest of respiration and an abrupt decrease in the body temperature are the reasons for sending the "corps" to a morgue. Our experiments show that there are many prerequisites for resuscitation of the victim of overcooling. We suggest that this property of a living material to retain the living ability during a complete loss of the main life symptoms will make possible for the future science the creation of a living creature, which would lose life for centuries and recover after this great period of time. Broadly speaking, the conservation of life with cold is a large and badly developed problem. Of course, for the complete success of this act, a hard and long work is necessary, in the first place the study of the mechanisms of heat production in mammals and the reasons for its decrease up to a complete arrest. The latter is the main trend of our studies.

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