ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

ORIGINAL STUDY

DOI:10.23888/PAVLOVJ2019272160-171

СОСТОЯНИЕ СИСТЕМ МИКРОЦИРКУЛЯЦИИ И ГЕМОСТАЗА В РАЗЛИЧНЫЕ ПЕРИОДЫ ПОСЛЕ УМЕРЕННОЙ ГИПОТЕРМИИ У КРЫС

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Гипотермия оказывает генерализованное воздействие на организм, с вовлечением в ответную реакцию всех органов и систем. Показано, что действие гипотермии способствует развитию полиорганной недостаточности, что делает важным и актуальным проблему изучения действия гипотермии на состояние системы гемостаза и микроциркуляторного русла (МЦР). ***Цель.*** Изучить состояние системы гемостаза и МЦР в различные периоды действия умеренной гипотермии у крыс. ***Материалы и методы.*** Исследование выполнено на 50 крысах-самцах линии Wistar. У животных исследовалось состояние МЦР с помощью лазерной допплеровской флоуметрии, состояние системы гемостаза – с помощью рутинных методик и тромбоэластографии. Статистический анализ выполнен с использованием пакета прикладных статистических программ Statistica 6.0 (StatSoft, США); рассчитывался непараметрический критерий Манна-Уитни. ***Результаты.*** Сразу по достижении умеренной степени гипотермии наблюдалось развитие вазодилатации, свидетельствующее о декомпенсаторном состоянии экспериментальных животных. Наибольший риск развития гемодинамических расстройств наблюдается через 5 дней после прекращения охлаждения и характеризуется массивным снижением тонуса сосудов с интенсификацией гемодинамики, на фоне появления в кровотоке маркеров тромбинемии и выраженном угнетении фибринолиза. Усиление гемодинамики в нутритивном бассейне на фоне прогрессирования состояния тромботической готовности является мощнейшим фактором развития тромбоза и полиорганной недостаточности. По истечении 2 недель с момента восстановления температуры тела наблюдается вазоспазм, что свидетельствует о глубокой модуляции сосудистого русла и сохранении симпатической импульсации на высоком уровне, а также о повышении жесткости сосудистой стенки. Прогрессирование воспалительной реакции подтверждается нарастающей концентрацией фибриногена. ***Заключение.*** Достижение умеренной степени гипотермии оказывает выраженное модулирующее влияние на систему микроциркуляции. Установленные закономерности позволяют сформировать четкое представление о течение и развитии патологической реакции в организме пострадавших и дать рекомендации по применению фармакологических препаратов для проведения превентивной терапии. Так, установлен период, в котором развитие состояния тромботической готовности максимально, и требуется применение антикоагулянтных и антиагрегантных препаратов, а также средств, улучшающих реологию крови.

Ключевые слова*: гипотермия; гемостаз; тромбоз; микроциркуляция; крысы.*

DOI:10.23888/PAVLOVJ2019272160-171

CONDITION OF MICROCIRCULATORY AND HEMOSTASIS SYSTEMS IN RATS AFTER MODERATE HYPOTHERMIA

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Hypothermia produces a generalized impact on an organism, with involvement of all organs and systems into the response. It was shown that hypothermia promotes multi-organ dysfunction syndrome, which makes it important to study the influence of hypothermia on condition of hemostasis and microcirculatory systems. ***Aim.*** To study the condition of the hemostasis system and the microcirculatory bed in different periods of moderate hypothermia in rats. ***Materials and Methods.*** The current study was performed on 50 male Wistar rats. Condition of microcirculatory blood stream in all animals was assessed with laser Doppler flowmetry. Condition of hemostasis system was studied according to routine protocols and an integrated method of examination – thromboelastography. Statistical analysis was performed using Statistica 6.0 software package (StatSoft, USA) with calculation of Mann-Whitney nonparametric test. ***Results.*** Analysis of the experimental data showed that moderate hypothermia produced a pronounced modulating influence on the microcirculatory system. Vasodilatation occurred immediately after reaching the stage of hypothermia, suggesting the beginning of decompensation in the experimental animals. The highest risk for hemodynamic pathologies was observed 5 days after cessation of cooling and was characterized by a massive reduction in the vascular tone, intensification of hemodynamics against the background appearance of thrombinemia markers in the blood stream and pronounced inhibition of fibrinolysis. Enhanced hemodynamics of the nutritional vascular bed with the underlying progressive prothrombotic condition is a potent risk factor for thrombosis and multiple organ dysfunction syndrome. Vasospasm that developed 2 weeks after recovery of the body temperature, indicated a profound modulation of vasculature and preservation of high-level sympathetic input, as well as increasing rigidity of blood vessel walls. Rising fibrinogen concentrations confirm a progressive inflammatory reaction. ***Conclusion.*** A moderate degree of hypothermia produces a pronounced modulating effect on the microcirculation. The established regularities make it possible to form a clear understanding of the course and development of the pathological reaction in the body of victims and to give recommendations on the use of pharmacological medicine for preventive therapy. Thus, a period has been established when thrombotic readiness is maximal, and use of anticoagulant and antiplatelet drugs is required, together with drugs that improve rheological properties of blood.

Keywords*: hypothermia; hemostasis; thrombosis; microcirculation; rats.*

Hypothermia produces a generalized effect of an organism not only in the natural, but also in the artificial environment used in practical medicine. Action of cold temperature may be a damaging factor causing destructive processes of different extent of severity in tissues. In practical medicine hypothermia is an obligatory condition for performing operations on an open heart and an important component of complex therapy of some urgent conditions including craniocerebral injuries, ischemic and hemorrhagic lesions of the brain [4,5]. An acute response of an organism to cooling involves all organs and systems. With this, the main components responsible for adequate trophism of tissues

DOI:10.23888/PAVLOVJ2019272160-171

are microvasculature (MV) and the system of hemostasis.

The systemic non-intentional hypothermia includes the following periods: period of *compensation* characterized by activation of heat production processes with sufficient intensity for to keep the body temperature at the constant level; period of *hypothermia* as such with development of irreversible alterations leading to loss of heat by the body; *posthypothermal* period that lasts from stoppage of cooling to 2 days; period of *recovery* characterized by recovery of the blood flow in the damaged areas, and period of *delayed consequences* with modification and compensational changes of organ systems. Hypothermia was shown to promote multi-organ failure [1].

An important task is to study the condition of MV and the system of hemostasis in the posthypothermal period characterized by development and manifestations of traumatic consequences of general overcooling of an organism [5-7]. Forecasting probable disorders in the MV and the system of hemostasis that develop after stoppage of cooling, will permit to minimize the consequences of the damaging effect of hypothermia on an organism.

Aim – to study the condition of the system of hemostasis and of microvasculature in different periods of moderate hypothermia in rats.

Materials and Methods

The work was performed on 50 male Wistar rats of 300±15 g. The systemic controlled immersion hypothermia was modelled by cooling the animals in water of 5°C temperature at air temperature 7°C with preliminary narcotization. The criteria of stoppage of exposure was reaching rectal temperature 27-30°C in the experimental animals. The time of exposure was individual in the range 5±3 minutes.

The control was blood of 25 animals taken after placement of them in individual cages into water of 30°C temperature at the temperature of air 22-25°C after preliminary narcotization. The time of exposure corresponded to the time of cooling of animals of the experimental group.

The animals were narcotized by intraperitoneal introduction of zoletil solution at a dose of 0.05 ml/kg, after which in all animals the condition of MV was analyzed. Then animals were cooled to the mentioned temperature, after which MV parameters were recorded again.

Further on all animals were divided into groups. In animals of the first group (n=10) blood was taken and the condition of MV was analyzed immediately after achievement of moderate hypothermia. In the second group (n=10) – in 2 days, in the third group (n=10) – in 5 days, in the fourth group (n=10) – in 10 days, in the fifth group (n=10) – in 14 days after stoppage of cooling.

In all animals parameters of platelet and coagulation hemostasis and also anticoagulant and fibrinolytic activity of the blood plasma were studied using test kits of Tekhnologia-Standart (company, Russia). Platelet aggregation was induced on Биола aggregometer (OOO Biola, Russia) according to G.V.R. Born (1962) with adenosine phosphate (ADP) solution of 10 μg/ml concentration as an inductor. Thromboelastometry was performed on Rotem device (Pentapharm GmbH, Germany) with use of diplosystems, reagents and control materials offered by the manufacturer. For the test, Natem reagent was used that included calcium chloride. Blood for test in the amount of 5 ml was taken from hepatic sinus into polystyrol syringe containing 0.11 M (3.8%) sodium citrate solution (proportion between blood and citrate was 9:1).

The condition of MV was studied with use of laser Doppler flowmetry (LDF) on LAKK-02 apparatus (NPO Lazma, Russia), with record of the main parameters of microcirculation and with the analysis of amplitude-frequency spectrum of variations of the blood flow. The head of the optic probe was fixed at the base of the tail of an experimen-

DOI:10.23888/PAVLOVJ2019272160-171

tal animal. Duration of LDF-gram record was 7 minutes.

Within the period of adaptation to the conditions of vivarium before the experiment (1 week) rats were kept in standard conditions meeting the requirements of Rules of Good Laboratory Practice – GLP. The rats were used in the experiment in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes, and with 86/609/EEC Directives [8]. Narcotization and mortification were conducted in compliance with the Rules of Conduction of Works with Use of Experimental Animals.

Comparison of the results was performed by calculation of median (Me) and percentiles (25 and 75%). Statistical analysis was conducted using nonparametric Mann-Whitney test on a personal computer with use of application program package Statistica 6.0 (StatSoft Inc., USA). The critical level of significance in verification of hypotheses was taken to be 0.05.

Results and Discussion

The results of study of the parameters of the system of hemostasis in animals of control and experimental groups are given in Table 1.

Table 1

Parameters of Hemostasis System in Rats Taken Initially and in Different Posthypothermal Periods

Parameter	Control	1st Group	2nd Group	3d Group	4th Group	5th Group
Platelets, 10^9/l	511 [502÷554]	715 [704÷719]*	459 [402÷469]#	459 [279÷623]	586 [518÷654]	737 [704÷751]*
ADP-induced aggregation rel. un.	10.2 [6.7÷12.3]	1.26 [1.0÷5.12]*	23.8 [20.3÷24.9]*#	17.9 [13.1÷25.1]*	26.6 [21.2÷33.1]*	8.48 [5.3÷12.4]#
Fibrinogen, g/l	2.1 [2.1÷2.2]	2.3 [1.8÷2.3]	2.6 [2.5÷2.7]*	2.5 [2.3÷2.5]*	2.45 [2.3÷2.5]*	2.8 [2.8÷2.9]*#
SFC, mg/100 ml	3.0 [3.0÷3.0]	3.0 [3.0÷3.0]	3.0 [3.0÷5.3]*#	28 [15.5÷28]*#	3.0 [3.0÷3.0]#	3.0 [3.0÷3.5]
SFCPT, r	1.8 [1.6÷2.1]	1.2 [1.1÷1.3]*	0.89 [0.8÷1.1]*#	0.77 [0.63÷0.79]*#	1.095 [0.9÷1,2]*	0.94 [0.8÷0.9]*
Antithrombin III, %	116.5 [114.0÷117.0]	70.0 [47.3÷100.0]*	103.2 [97.5÷115.4]#	90.0 [82.4÷97.1]	82.1 [70.4÷89.1]*	75.4 [70.4÷78.1]*#
Euglobulin fibrinolysis, min	558.0 [360.0÷558.0]	1248 [1212.0÷1248.0]*	454.0 [400.0÷512.0]#	700.0 [670.1÷785.2]*#	815.0 [782.4÷870.1]*	870.0 [890.4÷910.1]*#
CT, s	259.0 [227.0÷279.0]	218.0 [207.0÷236.0]*	179.5 [171.0÷181.0]*#	127.0 [71.0÷166.0]*#	187.5 [132.7÷208.7]*	233.0 [196.0÷267.0]*
CFT, s	98.0 [82.0÷118.0]	102.0 [70.0÷103.0]	69.0 [60.0÷71.0]*#	49.0 [46.0÷56.0]*#	51.0 [49.0÷58.0]*	91.0 [86.0÷111.0]
ML, %	15.0 [0.0÷20.0]	5.0 [1.0÷9.0]*	15.0 [3.0÷24.0]#	1.0 [1.0÷5.5]*#	2.0 [2.0÷2.1]*	2.0 [0.9÷3.1]*

Note: the data are given in the form of Me – median of sample […÷…] – 25 and 75 percentiles of sample; * – statistically significant differences between the studied and control groups ($p<0.05$); # – statistically significant differences between the studied group and preceding experimental groups ($p<0.05$); SFC – soluble fibrin complexes, SFCPT – soluble fibrin complexes polymerization time, r – ratio of SFCPT in plasma of experimental animals to SFCPT in plasma of intact animals, CT – coagulation time, CFT – clot formation time, ML – maximal lysis

DOI:10.23888/PAVLOVJ2019272160-171

As it follows from the data of the table, immediately after cessation of cooling, 39% ($p<0.05$) increase in platelets was recorded, with 8 times reduction of their aggregation capacity ($p<0.01$). Besides, achievement of the moderate degree of hypothermia was accompanied by hypercoagulation that was confirmed by both thromboelastogram (16% of CT parameter, $p<0.05$), and by 35% shortening of time of polymerization of fibrin complexes ($p<0.05$). The recorded hypercoagulation was worsened by evident reduction (by 40%, $p<0.05$) of the activity of antithrombin III against the background 2-fold suppression of fibrinolytic activity of blood plasma ($p<0.01$).

In 48 hours after cessation of cooling, 35% ($p<0.05$), reduction of platelet count was recorded in animals' blood with 18-fold increase in their aggregation capacity against the parameter recorded immediately after cessation of cooling ($p<0.05$). Hypercoagulation recorded in experimental animals of the 1st group, persisted. Besides, increase in the amount of fibrinogen was recorded accompanied by increase in the concentration of soluble fibrin complexes (SFC). The condition of animals was aggravated by a significant shortening of the time of clot formation (by 31%, $p<0.05$) and of the time of polymerization of fibrin complexes (by 30%, $p<0.05$).

After 5 days in blood of the 3d group of animals the condition of thrombotic readiness was recorded characterized by persistence of a high aggregation capacity of platelets, by sharply increased concentration of SFC (9-fold, $p<0,01$) with the progressing shortening of their polymerization time. Besides, progression in hypercoagulation was seen characterized by reduction of coagulation time (according to thromboelastogram – 1.5-fold against the parameter recorded in the 2nd experimental group, $p<0.01$). Concentration of fibrinogen also stayed at a high level. The condition of experimental animals was aggravated by an evident suppression of the activity of fibrinolytic system (4 times, according to thromboelastogram, $p<0.01$).

Assessment of the condition of the system of hemostasis in 10 days showed persistence of hyperaggregation, hypercoagulation and reduction of clot formation time confirmed by thromboelastogram data (reduction in coagulation time and clot formation time by 30% and 50%, respectively, $p<0.05$) and by 40% reduction of polymerization of fibrin complexes ($p<0,01$). Besides, concentration of fibrinogen remained high ($p<0,05$). Activity of fibrinolytic system was suppressed ($p<0.05$). At the same time, concentration of markers of thrombinemia was returning to the initial values.

Assessment of condition of the system of hemostasis in 14 days after cessation of exposure showed increase in the amount of platelets by 44% ($p<0.05$), with decline of their aggregation activity and returning of the parameter to the initial values. At the same time 15% increase in the concentration of fibrinogen was recorded ($p<0.05$). Tension in the system of hemostasis was confirmed by preserved twice shortened time of polymerization of fibrin complexes ($p<0,01$). Besides, suppression of the activity of anticoagulation and of fibrinolytic system of blood plasma was observed by 36% ($p<0.05$) and 55% ($p<0.05$) respectively

The results of study of parameters of microcirculatory vasculature recorded in the mentioned periods of hypothermia and post-hypothermia in rats, are given in Table 2.

In assessment of the condition of MV immediately after cessation of cooling, 2-fold increase ($p<0.01$) in parameters of microcirculation and σf MQD was recorded. On the part of active mechanisms of control of microcirculation, 1.5-fold ($p<0.01$) increase in the amplitudes of endothelial waves and an insignificant increase in the amplitudes of vasomotor waves (25%, $p<0.05$) were found. Besides, 23% ($p<0.05$) increase in respiratory waves was recorded.

In 2 days after cessation of cooling, a sharp reduction of microcirculation index was recorded (3.5 times, $p<0.01$). Besides, the amplitude of endothelial and vasomotor waves decreased 50 and 40% ($p<0.05$), re-

DOI:10.23888/PAVLOVJ2019272160-171

Table 2

MV Parameters in Rats Taken Initially and in Different Periods of Hypothermia

Parameter	Initial	1st Group	2nd Group	3d Group	4th Group	5th Group
MI, pf. un.	6.6 [4.2÷8.5]	11.6 [10.7÷13.5]*	1.9 [1.8÷3.6]*#	7.1 [6.5÷7.4]#	1.1 [0.8÷1.6]*#	1.8 [1.5÷6.6]*
MQD (σ), pf. un.	3.1 [2.1÷4.2]	6.54 [4.6÷9.1]*	1.8 [1.4÷3.1]*	2.3 [1.7÷4.0]*#	0.9 [0.7÷1.9]*#	0.9 [0.5÷1.3]*
Endothelial waves, pf. un.	9.01 [4.5÷18.1]	14.9 [10.1÷22.1]*	8.09 [2.1÷8.5]#	14.9 [5.5÷28.8]*#	3.1 [2.6÷8.0]*#	2.76 [1.6÷3.3]*
Vasomotor waves, pf. un.	10.04 [3.5÷17.1]	12.7 [10.6÷20.5]*	7.5 [2.1÷8.09]#	9.5 [4.4÷29.9]#	2.3 [2.1÷5.9]*#	2.3 [1.5÷2.4]*
Respiratory waves, pf. un.	7.2 [2.7÷11.2]	8.89 [5.1÷15.3]*	1.74 [1.1÷3.9]*#	6.5 [3.0÷12.3]*#	1.24 [1.1÷3.06]*#	0.7 [0.7÷1.0]*
Pulse waves, pf. un.	3.25 [1.4÷4.7]	4.3 [2.7÷5.6]	0.71 [0.6÷1.6]*#	1.89 [0.8÷6.5]#	0.48 [0.4÷0.7]*#	0.43 [0.4÷0.5]*

Note: the data are given in the form of Me – median of sample […÷…] – 25 and 75 percentiles of sample; * – statistically significant differences between the studied and control groups ($p<0.05$); # -statistically significant differences between the studied group and preceding experimental groups ($p<0.05$); MI – microcirculation index; MQD (σ) – mean root square deviation of amplitudes of fluctuation of the blood flow; pf. un. – perfusion units

spectively. Reduction of the amplitude of respiratory and pulse waves decreased 5 and 6 times, respectively ($p<0.01$).

After 5 days (3d experimental group) we recorded 3.7-fold ($p<0.01$) increase in perfusion index relative to the value recorded in the 2nd group. Increase in the microcirculation index was accompanied by insignificant increase in MQD (27%, $p<0.05$). Besides, 1.8-fold increase in the amplitudes of endothelial waves ($p<0.01$) and 26% increase in the amplitude of vasomotor waves ($p<0.05$) was recorded. From the part of passive mechanisms of control of microcirculation, 3.7-fold and 2.5-fold increase in amplitudes of respiratory and pulse waves, respectively, was recorded ($p<0.01$). After 10 days (4th experimental group) we again noted reduction of microcirculation index and of MQD 6.5 and 2.5 times, respectively ($p<0,01$). Besides, amplitude of endothelial and vasomotor waves decreased 5 and 4 times, respectively ($p<0.01$). Besides, a concomitant reduction of the amplitude of respiratory (5 times, $p<0.01$) and pulse waves (4 times, $p<0.01$) was present.

After 2 weeks (5th experimental group), the microcirculation index and CQD remained low. Amplitudes of endothelial and vasomotor waves also remained low. The amplitudes of respiratory and pulse waves stayed at the previous low level.

Thus, it was demonstrated that under anesthesia active thermoregulatory mechanisms lose their controlling functions. The initial phase of hypothermia runs with the reduction of the temperature threshold in the hypothalamus, in response to which the thermoregulatory center increases peripheral blood flow (mechanism of protection against overcooling in normal conditions) [9,10]. Besides, a direct action of an anesthetic on precapillaries increases the blood flow to superficial tissues inducing redistribution of heat from internal organs to peripheral tissues [2,11]. In clinical practice hypothermia is controlled and is accompanied by a medical support with use of respective medical drugs, whereas un-

DOI:10.23888/PAVLOVJ2019272160-171

controlled hypothermia results in decompensation with a progressive decrease in temperature [6,12].

In achievement of a moderate degree of hypothermia animals developed vasodilatation resulting from both a probable primary effect of narcosis on capillaries, and relase of nitric oxide into the blood flow in result of intensification of the blood circulation and increase in the shear stresses on the vessel wall [10,13]. Release of nitric oxide accounts for increase in the amplitude of endothelial waves and reduction of the aggregation activity of platelets. With the underlying vasodilatation the volume of blood in microcirculation increased which was accompanied by increase in the microcirculation index. Increase in MQD was due to a more intensive functioning of active mechanisms of control of microcirculation and evidenced a deep modulation of the blood flow [5,9,14]. Increase in MQD parameter was also promoted by increase in the amplitude of respiratory waves which was in turn induced by increase in the microcirculation pressure and by developed vasodilatation. Increase in the amplitude of respiratory waves with the underlying increase in microcirculation index evidences a decline in the tone of venules, impairment of the outflow of blood and development of congestive events in the microcirculation [15,16]. Development of unfavorable hemodynamic shifts in experimental animals in this period was aggravated by hypercoagulation changes in the hemostasis system. Many clinical works characterize hypothermia as a factor of thrombosis in victims [10,12,17]. Thus, in examination of people exposed to hypothermia, polycythemia and hypercoagulation shifts were noted conditioned by hemoconcentration due to increase in the permeability of vessels [18]. In rats who reached rectal temperature +28...+32°C, an increase in the concentration of inhibitor of I type plasminogen activator (PAI-I) producing prothrombotic effect was recorded which reached maximum at +31°C [16]. Similar changes were found in experiments on mice with cooling to +31ºC. In the experiment a significant increase in the concentration of PAI-I was found that was interpreted as increased risk for development of thrombosis in experimental animals [16,17]. Besides, in systemic undeliberate hypothermia in humans exposed to +30°C within 30 minutes, suppression of the activity of tissue plasminogen activator (t-PA) was noted that was accompanied by depression of fibrinolysis [6]. At the same time, the described prothrombotic changes in the system of hemostasis were a reasonable reaction of an organism. Thus, in hypothermia «physiological amputation» takes place with subsequent development of ischemic damages in the overcooled limbs, while a high coagulation status and depression of fibrinolysis restricts the damaged area and hypoaggregation promotes preservation of rheological properties of blood in developed hemoconcentration.

In the clinical course of hypothermia a posthypothermal period is distinguished that is characterized by development and manifestation of traumatic consequences of the systemic overcooling of an organism [18]. According to statistical data, the highest amount of lethal outcomes is recorded within the first 48 hours after normalization of the body temperature [1].

After 2 days from the moment of stoppage of cooling we recorded an evident reduction of the amplitude of waves in all frequency ranges that indicates development of a massive vasospasm [10]. With the preliminary cooling, vasospasm reduces a mismatch between a demand for oxygen and the amount of oxygen delivered to tissues which is shown in research conducted on dogs and humans [5]. Increase in the vessel tone and development of vessel spasm is explained by increased sympathetic activation in the posthypothermal period induced by activation of stress response which increased tension in smooth muscle cells of vessel wall. Developed spasm impaired the nutritive blood flow, led to ischemia and to reduction of the perfusion index [19]. The primary disorder in circulation caused by vasospasm, increased resistance to the blood flow and led to second-

DOI:10.23888/PAVLOVJ2019272160-171

ary changes in the system of hemostasis. Vasospasm, ischemic events and a direct action of hypothermia on the body stimulated release of antiinflammatory cytokines into blood possessing a potent procoagulation effect [18]. Thus in the first 24-48 hours, maximal possible levels of tumor necrosis factor (TNFα), interleukins 6 and 18 (IL-6, IL-18), possessing a powerful procoaculation effect, were recorded [16]. An additional stimulator of blood coagulation is acidosis that develops in posthypothermal period [5]. In our study, activation of coagulation system was confirmed by development in experimental animals of the condition of thrombotic readiness characterized by hyperaggregation, hypercoagulation, appearance of soluble fibrin complexes in the blood stream and by shortening of the time of their self-assembly. Besides, the data of thromboelastogram showed shortening of the time of clot formation. Suggestion about development of acute phase of inflammatory reaction is further evidenced by initial rise of the concentration of fibrinogen.

After 5 days a critical condition of the system of microcirculation in experimental animals was recorded. Thus, we observed increase in the microcirculation index against the background increase in the amplitude of waves of the entire frequency range. A concomitant increase in the amplitudes of pulse and respiratory waves indicated intensification of circulation, and increase in the amplitudes of endothelial and vasomotor waves spoke for development of vasodilatation [5]. At the same time, in the system of hemostasis a more expressed hypercoagulation was recorded and a complete block of fibrinolysis, according to thromboelastogram. A significant (9-fold) increase in concentration of soluble fibrin complexes in blood, reduction of the time of their polymerization against the preserved high level of fibrinogen, considerably increased the risk of thrombosis in experimental animals. The model of hypothermia reproduced by us was characterized by a sharp cooling of an experimental animal with a full contact of the body with cooling media which excluded formation of local damages and areas of necrosis, but led to circulation of cold blood in the body and promoted development of ischemic events in tissues [12]. Development of thrombotic hypothermia can be probably assigned to by a systematic build-up of inflammatory reaction and progressing damage to the endothelium [10]. Besides, in the given period of time a reduction of the activity of protein C was found that functions as anticoagulant [17]. Besides, some authors recorded increase in the concentration of vascular cell adhesion molecules (VCAM-1) and of intercellular adhesion molecules (ICAM), and also of monocytic chemotoxic factor with simultaneous reduction of the concentration of interleukin 10 (IL-10) [16].

Absence of compensatory changes on the part of fibrinolytic system indicates a deep modification of microcirculatory bed and a mismatch between the balance of pro- and anticoagulant systems of an organism [20].

Enhancement of hemodynamics in the nutritive vascular bed with the underlying progression of the thrombotic readiness condition is a potent factor for development of thrombosis and multi-organ failure.

After 10 days a reduction of perfusion of tissues with blood due to vasospasm was again recorded. In the system of hemostasis shifts toward hypercoagulation persisted and were characterized by hyperaggregation with the underlying shortening of time of thrombosis and suppression of fibrinolysis which confirmed the danger of development of thrombotic complications. According to the data presented in literature, the specified time interval corresponds to the period of recovery after a cold trauma, and with the absence of significant damages is characterized by restoration of the blood supply [5,14]. Analysis of experimental data indicates development of destructive changes in the microcirculatory bed against the background achievement of the moderate degree of hypothermia. [11]. Preservation of vasospasm was probably associated with a high level of sympathetic activation [1]. According to some authors, a triggering mechanism of hemostatic disorders in the given period is appearance and further

DOI:10.23888/PAVLOVJ2019272160-171

persistence in the blood flow of desquamated endotheliocytes [14,18].

In 2 weeks after cessation of cooling, both the general condition of the microcirculation and the amplitude-frequency spectrum of microcirculatory bed did not show changes. Analysis of literature data shows that a long-term reduction of perfusion of tissues with the underlying reduction of the amplitude of waves of all frequency ranges indicates increase in the rigidity of the vessels wall [4]. This agrees with the data of histological studies indicating thickening of intima-media in the muscular type vessels [7]. At the same time, a probability of development of the hemostatic disorders not only persisted but increased due to an increased concentration of fibrinogen and reduction in the activity of anticoagulation system [16].

Conclusion

Analysis of the obtained experimental data showed that a moderate hypothermia produces a modulating influence on the microcirculatory system. Immediately after achievement of moderate hypothermia, vasodilatation was observed indicating the condition of decompensation in the experimental animals.

The highest risk of development of hemodynamic disorders forming the basis of multi-organ failure was observed 5 days after recovery of the body temperature (heating) and was characterized by a massive reduction of the vessel tone with intensification of hemodynamics, with appearance in blood of markers of thrombinemia and a pronounced suppression of fibrinolysis. Increase in the hemodynamics in the nutritional vascular bed with the underlying progression of thrombotic readiness condition is a highly potent factor of development of thrombosis and multi-organ failure.

In 2 weeks from the moment of recovery of the body temperature, a vasospasm was seen that evidenced a profound modulation of the vascular bed, preservation of high sympathetic input and a high rigidity of the vessel wall. A progression of the inflammatory reaction was confirmed by increasing concentration of fibrinogen.

The established regularities permit to obtain a clear understanding of the course and development of a pathological reaction in an organism of a victim and to give recommendations on preventive therapy. Thus, a period is established with the maximal thrombotic readiness, which requires application of anticoagulant and antiaggregant medical drugs as well as drugs that improve rheological properties of blood.

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Дополнительная информация [Additional Info]

Источник финансирования. Исследование выполнено при финансовой поддержке Российского фонда фундаментальных исследований в рамках научного проекта №16-34-60054/15 мол_а_дк. [**Financing of study.** The study was performed with financial support Russian Foundation for Basic Research, Research project No. 16-34-60054/15 mol_a_dk.]

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить в связи с публикацией данной статьи. [**Conflict of interests.** The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

Участие авторов. Лычева Н.А. – концепция и дизайн исследования, Шахматов И.И. -редактирование, Седов А.В., Макушкина Д.А.- сбор и обработка материала, Вдовин В.М. – статистическая обработка, написание текста. [**Participation of authors.** N.A. Lycheva – concept and design of the study, I.I. Shakhmatov – editing, A.V. Sedov, D.A. Makushkina – collection and processing of the material, V.M. Vdovin – statistical processing, writing the text.]

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DOI:10.23888/PAVLOVJ2019272160-171

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Цитировать: Лычева Н.А., Шахматов И.И., Седов А.В., Макушкина Д.А., Вдовин В.М. Состояние систем микроциркуляции и гемостаза в различные периоды после умеренной гипотермии у крыс // Российский медико-биологический вестник имени академика И.П. Павлова. 2019. Т. 27, №2. С. 160-171. doi:10.23888/PAVLOVJ 2019272160-171

To cite this article: Lycheva NA, Shakhmatov II, Sedov AV, Makushkina DA, Vdovin VM. Condition of microcirculatory and hemostasis systems in rats after moderate hypothermia. *I.P. Pavlov Russian Medical Biological Herald.* 2019;27(2):160-71. doi:10.23888/PAVLOVJ 2019272160-171

Поступила/Received: 30.11.2018
Принята в печать/Accepted: 17.06.2019