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STUDY OF COAGULATION HEMOSTASIS IN RATS UNDER CONDITIONS OF INDUCED GENERAL MODERATE HYPOTHERMIA

The use of induced hypothermia in clinical practice can lead to coagulopathy, increasing the risk of peri- and postoperative bleeding. The aim of this study was to investigate the effect of cooling the body to moderate hypothermia on the hemostatic system in rats. Activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT) were determined upon reaching a rectal temperature of 32°C and after prolonged two-hour hypothermia while maintaining the animal's temperature at the same level. It was shown that cooling the animals to moderate hypothermia resulted in an increase in activated partial thromboplastin time, thrombin time, and prothrombin time, indicating the development of hypocoagulation shifts and impairment of the secondary hemostasis. With prolonged hypothermic exposure, a decrease in APTT, TT, and PT parameters from the achieved values was observed, which probably indicates some suppression of coagulation reactions with prolonged exposure to moderate hypothermia. It is suggested that impaired thrombin generation may be a key factor in hypothermia-induced coagulopathy.

Keywords: moderate hypothermia; hemostatic system; rats.

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Introduction. All organs and tissues are involved in the formation of an urgent response to general hypothermia. However, under conditions of general hypothermia, the state of the cardiovascular system is key to ensuring the adequate functioning of other organs and systems [10; 18; 26]. Maintaining adequate tissue perfusion relies heavily on the hemostatic system [2;19].

Numerous studies have shown that maintaining the body in a state of mild hypothermia can have a protective effect on damaged brain tissue [14; 25; 28; 29]. However, hypothermia used in surgical practice to protect against ischemic damage, for example, during aortic surgery with circulatory arrest, often leads to coagulopathy, which is one of the main life-threatening complications [12]. Low body temperature alters platelet aggregation and reduces the activity of enzymes in the coagulation cascade [22; 23], these changes inevitably increase the risk of perioperative bleeding.

It is considered [26; 27] that in a hypothermic state, blood clotting is reduced, primary and secondary hemostasis are impaired, and platelet function is decreased. A number of animal studies confirm the weakening of hemostasis markers during hypothermia [20; 23; 33], however, some studies [17; 24] using hypothermia in experimental models of trauma and/or hemorrhagic shock did not show this. Other researchers show [9] that increased bleeding at moderately reduced temperatures (33°–37°C) is primarily the result of a platelet adhesion defect, rather than reduced enzyme activity or platelet activation. However, at temperatures below 33°C, both reduced platelet function and reduced enzyme activity likely contribute to coagulopathy.

It is noted [7] that hypothermia leads to a decrease in circulating blood volume, causing hemoconcentration, manifested by an increase in blood viscosity and hematocrit, and prolonged vasoconstriction (small venous vessels are most affected) leads to frostbite and thrombus formation. The risk of thrombosis also increases in the presence of postoperative hypothermia in a patient who has undergone prolonged surgery accompanied by blood loss [31].

Studies of blood drawn at normal body temperature and then incubated at various temperatures have yielded conflicting results [1; 21]. These studies showed that temperature has an ambiguous effect on the activating and inhibiting reversible reactions of hemostasis. Thus, hypothermia reduces the rate of the platelet shape change reaction from discoid to spherical, however, activation of human platelets by various agonists leads to acceleration of their aggregation.

Thromboelastography, as a method determining the dynamics of interaction of all components of hemostasis, revealed [13; 30; 34] a decrease in coagulation with delayed thrombus formation during hypothermia. In healthy subjects, progressive delay in thrombus formation began only when the temperature dropped below 30°C [16]. It was confirmed [11] that blood clotting disorders during hypothermia were associated with a decreased clot formation rate, reduced clot strength, and impaired fibrinolysis.

In-depth studies of the hemostatic system under various environmental conditions, including hypothermic states, are conducted in our country by Barnaul researchers, who have demonstrated a stereotypical stress response of the hemostatic system in response to a single threshold stressor [8]. Furthermore, it was found [5] that during sequential cooling with immersion hypothermia, changes in the hemostatic system are phased, transitioning from hypocoagulation (in mild hypothermia) to thrombinemia (in moderate and deep hypothermia), with subsequent disappearance of signs of coagulation activation at ultra-deep hypothermia. With immersion cooling of rats to a rectal temperature of 30°C, an increase in platelet aggregation ability and the concentration of soluble fibrin-monomer complexes was registered [4], with a decrease in their polymerization time, which characterizes a shift in the hemostatic potential of blood towards hypercoagulation. When cooling animals in air to a rectal temperature of 30°C, platelet aggregation ability significantly decreased relative to normothermia.

The contradictory conclusions of researchers regarding the effect of hypothermia on hemostasis can be explained by the methods of achieving hypothermia, its duration, and the degree of temperature reduction. The use of hypothermia in the clinic unequivocally indicates [29] that very mild hypothermia (up to 35°C) does not affect coagulation, and at lower temperatures, moderate platelet dysfunction may begin.

The aim of this study was to investigate the effect of cooling the body to moderate hypothermia on the hemostatic system. The objectives included determining hemostasis parameters (APTT – activated partial thromboplastin time, TT – thrombin time, PT – prothrombin time) upon reaching a rectal temperature of 32°C and after prolonged two-hour hypothermia while maintaining the rectal temperature at the same level.

Materials and Methods. Experiments were performed on male Wistar rats weighing 300-320 g from the biocollection “Collection of laboratory mammals of different taxonomic affiliations” of the I.P. Pavlov Institute of Physiology of the Russian Academy of Sciences. All procedures performed in this study complied with ethical standards approved by the legal acts of the Russian Federation, the principles of the Basel Declaration, and the recommendations of the Commission for the Control over the Keeping and Use of Laboratory Animals at the I.P. Pavlov Institute of Physiology of the Russian Academy of Sciences (Protocol No. 12/19 of December 19, 2022).

Anesthetized rats (urethane, i.v., 1000 mg/kg) were cooled using ice packs. The time to reach the target Tr was 30 min, after which the ice packs were removed, and the animals were kept at room temperature on a thermostatically controlled mat to maintain the required Tr. To assess hemostasis parameters (APTT, PT, TT), blood was collected from the hepatic sinus in the norm (group 1, control, n=7), upon reaching a rectal temperature (Tr) of 32°C (group 2, n=8), and after 2 hours of maintaining Tr at 32°C (group 3, n=8).

As additional criteria for platelet functional activity, PDW (platelet distribution width) and MPV (mean platelet volume) were measured. Platelet count, PDW, and MPV were determined using an automated hematology analyzer Mindray BC-30 Vet (Mindray Animal Care, China). Blood for hematological analysis was stabilized with EDTA solution at a concentration of 2 mg/ml of whole blood.

For the study of the coagulation link of hemostasis, 5 ml of blood was collected into a tube containing 0.11 M (3.8%) sodium citrate solution (blood-to-citrate ratio 9:1) and centrifuged for 10 min at 3000 rpm. PT, TT, and APTT were determined using a CoaTest-4 coagulometer (NPC “Astra”, Ufa, Russia) with standard DDS reagents from Diakon (Pushchino, Russia).

For statistical data processing, the STATISTICA 6.0 software package was used; the Mann-Whitney non-parametric test was used to identify differences between groups. The critical significance level p for testing statistical hypotheses was taken as 0.05. All experimental data are presented as mean ± standard error of the mean (M ± SE).

Results and discussion. Coagulopathy, often observed in accidental hypothermia and acidosis, can be caused by a decrease in the number and/or function

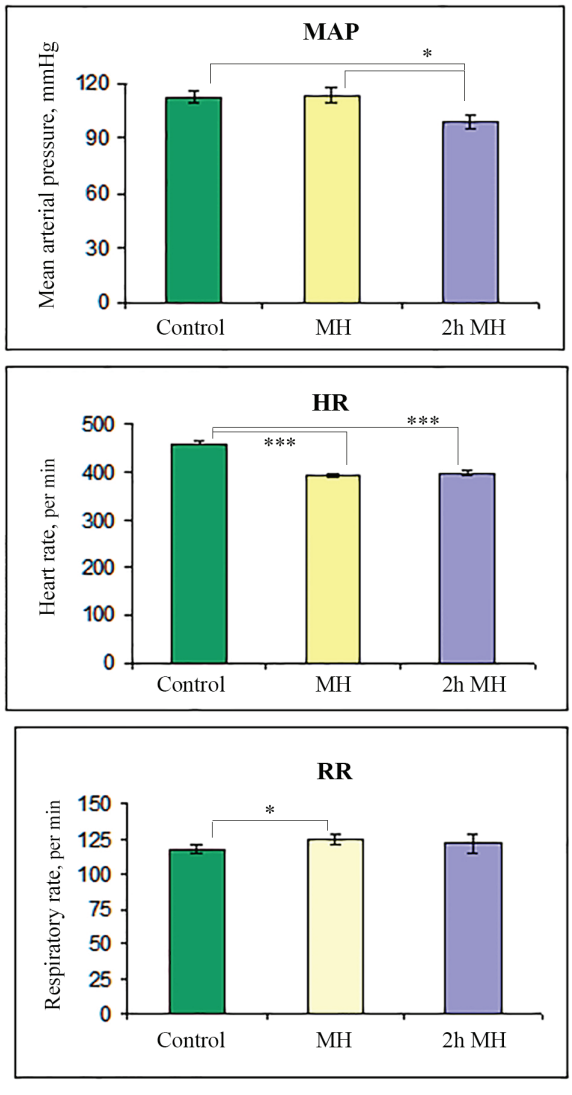

Fig. 1. Effect of moderate hypothermia on SAP, HR, and RR.
Note: MH – moderate hypothermia upon reaching Tr 32°C; 2h MH – prolongation of moderate hypothermia at Tr 32°C for 2 hours.

of platelets, thrombin and fibrinogen synthesis/degradation, and also by a specific effect on various blood clotting factors [20]. We developed our experimental hypothermia model to investigate whether, compared to normothermia, induced general hypothermia alters the coagulation link of hemostasis, which could lead to increased bleeding when using body cooling in the clinic.

Unlike mild hypothermia [32], moderate hypothermia significantly suppresses hemodynamic responses, especially when using general anesthesia. In our experiment, when cooling anesthetized rats to a rectal temperature (Tr) of 32°C (Fig. 1), a 15% decrease in heart rate (HR) ($p<0.001$) compared to the norm and a 14% increase in respiratory rate (RR) ($p<0.05$) were noted, while systolic arterial pressure (SAP) did not change. Prolonging hypothermia at Tr 32°C for two hours led to a 13% decrease in SAP ($p<0.05$), while no further changes in HR and RR occurred.

In this study, we determined a number of parameters of the coagulation link of hemostasis (APTT, TT, PT). Thrombin time (TT) reflects the interaction of thrombin with fibrinogen – the final stage of blood clotting. Prothrombin time (PT) measures the time required for clot formation in the presence of a thromboplastin-calcium mixture, which ensures the functioning of the extrinsic pathway of fibrin formation. Activated partial thromboplastin time (APTT) measures the time required for clot formation in the presence of an activator of the intrinsic pathway of blood coagulation and calcium, and assesses the ability to form fibrin through the sequential interaction of a number of blood clotting factors [3].

The results of this study allow us to conclude that lowering body temperature to moderate hypothermia significantly affects the activity of the extrinsic and intrinsic pathways of blood coagulation in rats. When assessing coagulation hemostasis parameters in rats cooled to Tr 32°C (group 2), it was established (Fig. 2) that APTT was prolonged by 29%, TT by 41%, and PT by 17% ($p<0.001$). With the prolongation of moderate hypothermia (group 3), APTT and PT returned to normal, while TT remained elevated (by 30% above normal).

The study [4] showed a phased nature of changes in the hemostatic system depending on the duration of a single cold exposure necessary to achieve a particular degree of hypothermia. The hypocoagulation shifts recorded in the initial stages of hypothermia are replaced

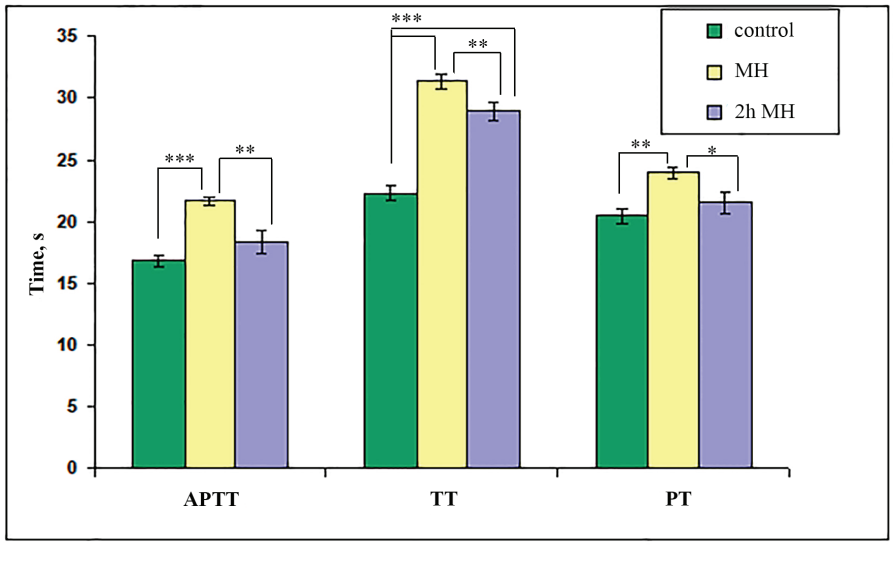

Fig. 2. Changes in activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time (PT) during moderate hypothermia in rats

by the development of a thrombotic readiness state as body temperature decreases. In our experiment, when Tr decreased and was maintained at 32°C, we observed similar changes in APTT, TT, and PT, indicating hypocoagulation shifts at moderate hypothermia.

A study investigating coagulation hemostasis at a higher Tr in rabbits [32] showed that short-term mild hypothermia affects the blood clotting mechanism to a clinically insignificant extent. With the use of mild hypothermia [15] in patients with traumatic brain injury over two days, prolongation of PT and APTT was observed, and when the duration of temperature exposure was increased to five days, PT and APTT decreased significantly (more than 35%), which likely indicates a dependence of the coagulation link of hemostasis on the duration of induced hypothermia. Our study at a lower Tr also showed a dependence of APTT and TT on the duration of hypothermic exposure.

Hypothermia reduces the activity of enzymes in the coagulation cascade reactions [18]. Enzymes, like all biochemical reactions, slow down with decreasing temperature. In general, impaired thrombin generation is one of the main factors contributing to coagulopathy during hypothermia. The slowing of this key enzyme's activity leads to disruption of the entire blood coagulation cascade, increased clotting time, and increased bleeding risk. Analysis of kinetic curves characterizing thrombin generation and the formation of the thrombin-antithrombin complex [22] showed that hypothermia in the temperature range from 36°C to 31°C gradually slowed thrombin generation, as evidenced by clotting time, time to reach the thrombin peak, and prothrombin time, which increased in all subjects. Our work also supports the idea that impaired thrombin generation may be a key factor in hypothermia-induced coagulopathy, since the maximum changes in the coagulation link of hemostasis during hypothermia concerned the increase in thrombin time both upon reaching Tr 32°C and with the prolongation of moderate hypothermia at Tr 32°C for 2 hours.

Results obtained in vitro in isolated hypothermic platelets [35] showed a temperature-dependent decrease in thrombin generation: in hypothermic platelet samples, thrombin generation was 25% (33°C) and 68% (23°C) lower compared to normothermic platelet samples. These results lead to the conclusion that with hypothermia, proper microvascular hemostasis may be initially delayed due to a delay in the thrombin initiation phase, i.e., moderate hypothermia leads to a delay in thrombin generation in the initial stage. Our study confirmed that induced hypothermia primarily affects the rate of thrombin formation; these changes are likely temporary.

Hypothermia significantly affects both blood clotting and hemorheology. According to [18], the increase in blood viscosity with decreasing body temperature leads to hematological concentration and increased hematocrit. In our study, we also obtained an 8% increase in hematocrit upon reaching Tr 32°C (group 2), and a 15% increase with prolonged hypothermia (group 3).

Cold stress, stimulating the release of catecholamines such as adrenaline and noradrenaline, can lead to increased vascular resistance and reduced blood flow in peripheral vessels [6]. As a result, platelets may be retained in the vessels, which can contribute to their destruction and a decrease in their number in the blood. In addition, thrombocytopenia during hypothermia can occur due to platelet sequestration [18], and this, in turn, can lead to uneven distribution of platelets in the vessels. In our work, we recorded a significant decrease in the number of platelets (by 80% in group 2 and by 92% in group 3, $p<0.001$). Accordingly, the risk of bleeding in the cold may increase due to a decrease in the number of platelets themselves, and, consequently, the ability of platelets to adhere and form thrombi. It should be noted that the values of the mean platelet volume and platelet distribution width by volume with hypothermic exposure differed insignificantly from the initial values (within 5-9%).

Thus, it has been shown that a number of enzymatic reactions of the coagulation cascade are inhibited by induced general moderate hypothermia, as evidenced by the significant prolongation of PT, APTT, and TT with a decrease in Tr in rats to 32°C and the preservation of the increased TT value with the prolongation of moderate hypothermia at Tr 32°C for 2 hours. We believe that when diagnosing and managing patients with reduced body temperature, the prolongation of blood clotting time and the risks of perioperative bleeding should be taken into account.

Conclusions:

1. With single, short-term cooling of anesthetized rats to Tr 32°C (to the stage of moderate hypothermia), an increase in activated partial thromboplastin time, thrombin time, and prothrombin time occurs, indicating the development of hypocoagulation shifts and impairment of secondary hemostasis.

2. During maintenance of Tr at 32°C for two hours, a decrease in APTT, TT, and PT parameters from the achieved values is observed, which probably indicates some alteration of coagulation reactions with prolonged exposure to moderate hypothermia.

3. Upon reaching the boundary of moderate hypothermia, the main changes may be associated with impaired thrombin generation, which may be a key factor in hypothermia-induced coagulopathy.

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