MECHANISM OF THE HYPERCOAGULANT EFFECT OF HYPEROXIA

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Inhalation of 100% O_2 at normal atmospheric pressure for 30 min is accompanied by an increase in the clotting power of the blood and a sharp decrease in the number of platelets, with changes in their structure, in man and rabbits. The trigger mechanism of this hypercoagulant effect is probably viscous metamorphosis of the platelets, developing under the influence of activation of Hageman's factor by oxygen.

KEY WORDS: *normobaric hyperoxia; platelets; hypercoagulation syndrome.*

Hyperoxia induces a protective reaction manifested as a decrease in the respiration and heart rates, slowing of the blood flow, increased peripheral resistance, a reduced circulating blood volume, and a decrease in the number of circulating erythrocytes [2, 6]. However, the state of the clotting and platelet systems of the blood in hyperoxia have been the subject of few investigations, in which a reduction in the number and changes in the size of the platelets were observed [1, 3].

The object of this investigation was to study the mechanism of the hypercoagulant effect of hyperoxia.

EXPERIMENTAL METHOD

The state of blood coagulation was studied electrocoagulographically and biochemically in 20 healthy humans and 40 sexually mature rabbits. To determine the state of the megakaryocytes—platelets system the number of platelets was counted and their structure and dynamic function determined by the adhesion to glass fabric and ADP-aggregation tests. A differential megakaryocyte count was carried out on bone marrow films from the rabbits and the peroxidase activity and glycogen concentration were determined. Pure O_2 was inhaled through a mask by means of a reconstructed Narkon-2 apparatus with humidifier at a temperature of 20-22°C and under a pressure of 690-695 mm Hg (the conditions in the city of Frunze). Tests were carried out after the subjects had been suitably trained; blood samples were taken at rest, before inhalation of O_2 and after inhalation for 5, 10, and 30 min. The blood O_2 saturation was monitored by oxyhemography (the 057M apparatus) and with a micro-Astrup apparatus.

EXPERIMENTAL RESULTS

During inhalation of O_2 for 30 min its partial pressure in the rabbits' blood was increased threefold, in agreement with data in the literature [5]; the pH of the blood was 7.38-7.41. The clotting time of the blood was considerably shortened (Fig. 1). The platelet count fell sharply, to correlate with the increase in the plasma heparin tolerance ($r = 0.83$) and the shortening of the recalcification time ($r = 0.71$). This suggests that the hypercoagulation changes begin with destruction of platelets. The earliest changes include activation of the Hageman factor and an increase in the adhesive and aggregating properties of the platelets (from 36.2 ± 4 to 61 ± 5 and from 36 ± 2.4 to 50 ± 2.7% respectively; $P < 0.01$). The decrease in the number of platelets by the end of the period of observation was accompanied by an increase in their size and by degenerative changes — discharge of granules and vacuolation.

The thrombocytopenia caused by normobaric hyperoxia for 30 min lasted for only a short time. After 1 h the platelet count was already 23% higher than initially. During this pe-

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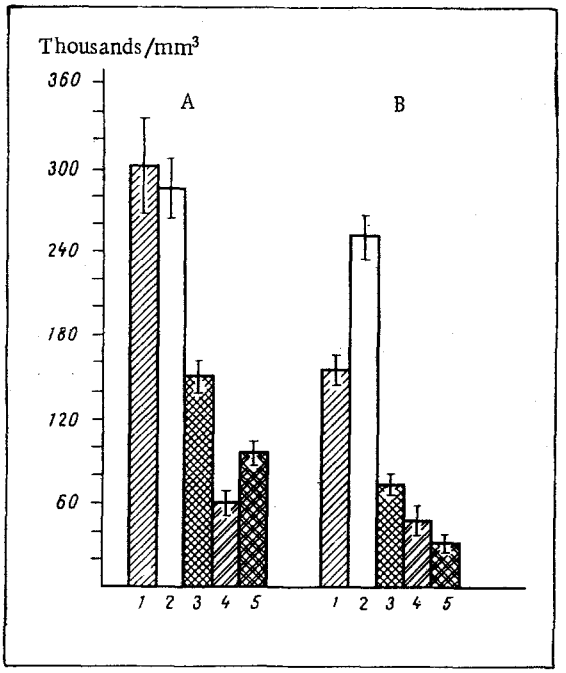

Fig. 1. Changes in blood coagulation in rabbits under the influence of hyperoxia. A) Before; B) during inhalation of O_2; 1) platelet count (in thousands/mm^3); 2) end of blood clotting (in sec); 3) plasma heparin tolerance (in sec); 4) recalcification time (in sec); 5) Hageman factor (in sec).

riod the number of megakaryocytic cells in the bone marrow increased from 0.2 ± 0.097 to 0,77± 0.058% ($P < 0.01$). The number of bare nuclei of megakaryocytes increased considerably (Fig. 2), but fragments of cytoplasm could be seen on most of them, indicating the "explosive" destruction of these cells. The relative percentage of juvenile and mature forms was reduced. In the mature megakaryocytes the glycogen content was increased (before inhalation of O_2 glycogen was detected in 99.5% of megakaryocytes, with a cytochemical coefficient of 2.97 ± 0.04; after inhalation it was detected in 100% of cells with a cytochemical coefficient of 3,34 ± 0,09; $P < 0,01$); the peroxidase also was increased (before inhalation of oxygen peroxidase was found in 91% of megakaryocytes, with a cytochemical coefficient for the number of granules of 14.4 ± 0.32, after inhalation in 99% of cells, with a cytochemical coefficient of 27.2 ± 0.25; $P < 0.01$). The morphological and cytochemical features of the megakaryocytes described above are evidence of activation of their function.

In additional experiments O_2 was perfused through platelet-enriched donors' plasma. After 10 min the partial pressure of O_2 in the plasma reached 657.8 ± 7.6 mm Hg. At this time the activity of Hageman's factor was increased significantly ($P < 0.01$). This can be regarded as the mechanism of activation of the dynamic fraction of the platelets. The adhesive and aggregating functions of the platelets were activated ($P < 0.01$); a process of viscous metamorphosis with release of the platelet plug, and the platelet count fell ($P < 0.01$). Meanwhile the viscosity of the plasma increased from 2 ± 0.08 to 3 ± 0,22 ($P < 0.01$).

The passage of N_2 through the same plasma caused virtually no change in the indices of the state of the plasma and platelets. Passage of O_2 through platelet-deprived plasma likewise did not change the coagulability and viscosity of the plasma. Comparison of the results suggests that the hypercoagulation effect is based on the influence of the oxygen on the platelets, and that it is probably effected through activation of the Hageman factor.

In healthy human subjects aged from 18 to 30 years normobaric hyperoxia for 30 min likewise caused a decrease in the platelet count from 30.65 ± 1,1 to 20.1 ± $1.3 \cdot 10^4/\mu l$ ($P < 0,01$), with changes in their size and structure. A marked hypercoagulation syndrome appeared in four subjects, whereas in the rest the changes in the rate of blood clotting were less marked. Investigation of patients during hyperoxia revealed considerable changes in the

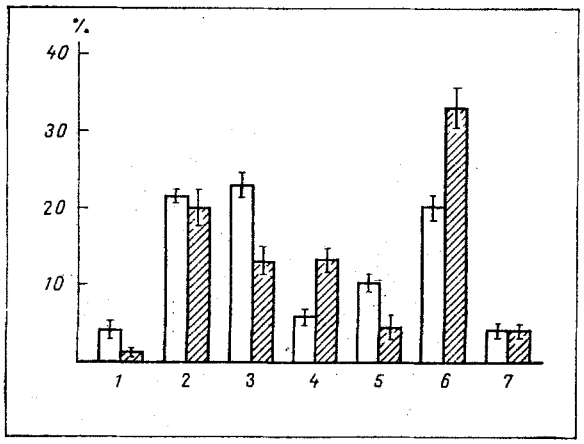

Fig. 2. Changes in differential megakaryocyte count of rabbits after hyperoxia. Unshaded columns — before, shaded columns — after inhalation of O_2; 1) megakaryoblasts; 2) promegakaryocytes; 3) polychromatophilic megakaryocytes; 4) orthochromic megakaryocytes; 5) involution forms of megakaryocytes; 6) bare nuclei; 7) degenerated megakaryocytes.

blood clotting system, amounting in some cases to a thrombohemorrhagic syndrome [4].

The mechanism of the hypercoagulant effect arising in normobaric hyperoxia can be represented as follows: with an increase in the O^2 concentration Hageman factor is activated and, under its influence, viscous metamorphosis of the platelets begins and this is the trigger factor for development of the hypercoagulation syndrome. These changes lead to an increase in the viscosity of the blood, which is one stage of the reaction aimed at preventing oversaturation of the tissues with oxygen.

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