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EFFECT OF VARIABLE HYDROSTATIC PRESSURE ON THE PLATELET–VESSEL WALL SYSTEM

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The important role of disturbances of platelet-vascular hemostasis in the pathogenesis of circulatory disorders can be taken as established [6], although many apsects of regulation of the functional state of the platelet–vessel wall system remain unexplained, and this is an obstacle in the way of the development of methods of adequate correction of its disorders. The mechanism of regulation of the functional state of rabbit platelets has been described [5]: essentially exposure of a platelet suspension to variable hydrostatic pressure (VHP) on an apparatus simulating the conditions which exist in the real blood flow leads to increased ability of the platelets to aggregate and to release ADP. A new approach is thus obtained to the understanding of the mechanisms of development of disorders of hemostasis, especially during fluctuations of the general arterial pressure (AP). It also seemed important to study the problem of whether such a control mechanism also extends to the hemostatic function of the vessel wall, especially in the light of data on the ability of the vascular endothelium to produce substances effectively influencing platelet aggregation and blood coagulation [1, 8].

This paper gives the results of a study of the effect of VHP on various parameters of the functional state of human platelets and the hemostatic function of the vascular wall.

EXPERIMENTAL METHOD

Platelet-rich plasma was obtained from fresh citrate-stabilized blood from clinically healthy blood donors. Platelet aggregation was tested as described previously [2]. Adhesion of platelets to glass was tested by the method in [4]. Blood vessels for investigation were obtained from 15 human cadavers during the first 8 h after death, which was from various causes unconnected with cardiovascular diseases. In the course of the investigations the antiaggregating activity of the vessel wall [7] and the effect of an extract of vascular endothelium on the blood recalcification time, which reflects the blood concentration of thromboplastic factor [1], were estimated. The platelet suspension was exposed to VHP by the method in [5]. During investigation of the effect of VHP on the vessel wall, the same apparatus was used, but the segment of vessel (0.5-0.7 cm) was connected to a syringe, to the plunger of which pressure pulses were applied. The results were subjected to statistical analysis, using the nonparametric Wilcoxon–Mann–Whitney criterion.

EXPERIMENTAL RESULTS

VHP over 100 mm Hg, with a maximum at 180-220 mm Hg, significantly increases the aggregating activity of platelets induced by ADP, serotonin, and adrenalin (Fig. 1). The fact that the effect obtained on human platelets was similar to that obtained on rabbit platelets [5] and that it was independent of the type of aggregant used demonstrates the

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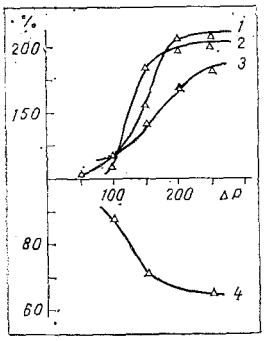

Fig. 1. Effect of VHP on platelet aggregation induced by ADP (1), adrenalin (2), and serotonin (3), and on intracellular serotonin concentration of platelets (4). Abscissa, pressure pulses (in mm Hg); ordinate, effect (in percent of initial value).

universal character of the mechanism regulating the state of the platelets described above.

Simultaneously with increased ability of the platelets to aggregate under the influence of VHP the intracellular serotonin concentration of the platelets also decreased (Fig. 1), evidence of the development of a release reaction. Meanwhile exposure of the platelet suspension to VHP led to increased adhesiveness of the platelets; whereas the index of adhesiveness without exposure to VHP was 37.8 ± 6.4%, after exposure to a pressure of 180 mm Hg it increased to 75.5 ± 7.9% ($P < 0.05$). The physical mechanism of regulation of platelet function tested by these experiments thus covers a very wide range of different parameters, so that great physiological importance can be ascribed to it.

The pattern of the effect of VHP on the hemostatic function of the vessel wall was very complex. Under the influence of VHP within the pressure range 60-180 mm Hg the antiaggregating activity of the vessel wall was observed to decrease, but the degree of these changes differed during exposure to pressure pulses of different magnitude. An averaged graph of the change in antiaggregating activity under the influence of VHP, obtained by the use of 20 specimens from the basilar and carotid arteries, is shown in Fig. 2. The graph in Fig. 2 shows that VHP of between 60 and 100 mm Hg caused a significant decrease in the antiaggregating activity of the blood vessels, but on increasing the pressure to 140 mm Hg this effect weakened. With a further increase of pressure to 180 mm Hg a marked effect reappeared, in the form of depression of the antiaggregating activity of the vessel wall. Incidentally the shape of the graph was very variable for different specimens of blood vessels. In three cases, under the influence of a pressure of 140 mm Hg an increase in the antiaggregating activity of the vessel wall was observed, not a decrease. Meanwhile in some cases [4] the maximal inhibitory action on antiaggregating activity of the vessel was exhibited under a pressure of 60 mm Hg.

The character of the action of VHP on thromboplastic activity of the basilar artery was rather different. Exposure to VHP within the range 60-180 mm Hg led to increased ability of endothelial cell extract to reduce the blood recalcification time; the effect of VHP increased, moreover, with an increase in amplitude of the pressure pulses (Fig. 2). The different shapes of the graphs of changes in antiaggregating and thromboplastic activity evidently indicate that the mechanisms responsible for realization of these two properties of the vessel wall are independent.

VHP also had a complex action on these two parameters, depending on the time of its application. After exposure of a specimen from the basilar artery for 1 min to VHP (80 mm Hg) an increase in the antiaggregating activity of the vessel wall was observed, and its degree differed considerably on different specimens. The picture observed after exposure for 5 min was not clear, for the parameter tested could be either strengthened or weakened. After an exposure of 10 min the effect was a clear decrease in antiaggregating activity, and this also continued after exposure for 20 min, with a very small increase.

A study of the thromboplastic activity showed it to be clearly increased only after exposure of the vessels for 10 min to VHP (180 mm Hg), but it was rather weaker after 20 min.

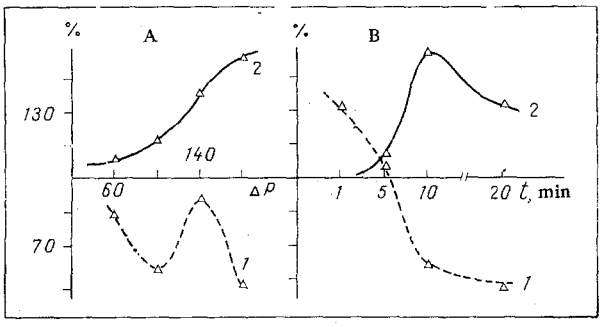

Fig. 2. Effect of VHP on antiaggregating (1) and thromboplastic (2) activity of vessel wall depending on magnitude (A) and time of application (B) of pressure pulses.

The results thus indicate that VHP has a significant effect on the functional state of the vessel wall—platelet system: the effect of VHP on this system may be exhibited as increased adhesiveness of the platelets and their increased ability to aggregate, accompanied by a simultaneous decrease in the antiaggregating activity of the vessel wall and an increase in its concentration of thromboplastin factors. This may evidently lead to displacement of the hemostatic potential toward increased risk of intravascular thrombus formation. The results suggest that pressure gradients arising in the body, especially during hypertensive crises, may be the direct cause of hemostatic disorders. This suggestion is confirmed by data showing normalization of the parameters of hemostasis in patients with arterial hypertension when their blood pressure is stabilized. Meanwhile changes arising under the influence of the hydrostatic factor and a change in the concentration of so powerful a vasodilator as prostacycline in the vessel wall may be the causes of changes in vascular tone associated with fluctuations in the general AP. Finally, a decrease in prostacycline synthesis and the increase in the content of thromboplastic factors under the influence of VHP, especially in the case of long exposure of the vessel, may probably reveal one cause of the increased intensity of atherosclerotic changes in the blood vessels in patients with arterial hypertension.

It is an interesting fact that analysis of the effect of VHP on the antiaggregating activity of different parts of the vascular system revealed that changes taking place in specimens taken from different cadavers were by no means identical (Fig. 3). VHP (100 mm Hg) reduced the antiaggregating activity of the carotid, basilar, and coronary arteries taken from different cadavers by no means equally. The results of three observations are given in Fig. 3. In the first case exposure to VHP led to sharp inhibition of the antiaggregating activity of the coronary artery, and had much less effect on the basilar and carotid arteries. In the second case the maximal effect was observed in the basilar and left

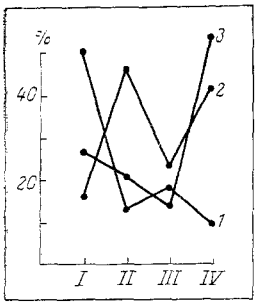

Fig. 3. Effect of VHP (100 mm Hg) on antiaggregating activity of coronary (I), basilar (II), and right (III) and left (IV) carotid arteries taken from three different cadavers.

carotid arteries, and in the third case in the left carotid artery. The effect of fluctuations in the general AP is probably manifested unequally in different parts of the vascular system, in agreement with the concept of the mosaic pattern of hemostatic potentials [3]. It can be postulated that those regions of the vascular system in which the effect of VHP is strongest are zones of increased risk from the point of view of development of intravascular thrombosis.

The presence of a phenomenon due to the effect of VHP on the functional state of the platelet–vessel wall system, simulating conditions which arise in the body during fluctuations of general AP, highlights the problem of pharmacologic correction of this mechanism of development of disorders of hemostasis. When the effect of dipyridamole, aspirin, aminophylline, pentoxifylline, and kavinton on the ability of VHP to induce platelet hyperaggregation was studied, only in the case of aspirin was ability to depress the aggregation-promoting activity of pressure treatment observed ($P < 0.05$). A similar, but not significant effect was given by preliminary incubation of the segment of blood vessel with aspirin on the ability of VHP to suppress its antiaggregating activity.

These results suggests that the effect of VHP on the parameters of platelet and vascular wall function studied in these experiments is realized to some extent with the participation of the prostaglandin system. Meanwhile the effect which aspirin has been shown to give, especially in the case of platelets, indicates a new aspect of the action of this drug, namely that of a unique kind of "buffer" preventing the development of severe platelet hyperaggregation during fluctuations in the general AP.

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