DYNAMICS OF SOME PARAMETERS OF HEMOSTASIS IN TRANSIENT CORONARY INSUFFICIENCY DEPENDING ON THE DURATION OF MYOCARDIAL ISCHEMIA

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Transient coronary insufficiency (TCI) is a combination of two syndromes — ischemic and reperfusion [4, 8, 9]. The writers showed previously that development of both syndromes is based on pathogenetic mechanisms some of which are common to both whereas others are characteristic of each separately [4, 5, 7-9]. In our view, in the course of development of both the ischemic and the reperfusion syndromes of TCI, factors changing the state of the clotting and anticlotting systems of the blood are initiated and (or) activated. An important argument in support of this view is given by experimental and clinical data on significant deviations of the parameters of hemostasis in animals with myocardial ischemia (MI) and also in patients with different forms of coronary insufficiency — angina pectoris, preinfarction, and myocardial infarction [2, 9, 10, 14]. However, the results of these investigations demonstrate deviations in the hemostasis system mainly in MI and they do not allow their changes to be judged at different stages of postischemic resumption of the coronary blood flow. At the same time, we know that the initial period of reperfusion (RP) often is not accompanied by resumption of microcirculation in various parts of the previously ischemized zone of the heart. This phenomenon has been called the postischemic "no reflow phenomenon." One possible cause of this phenomenon could be intravascular thrombosis or aggregation of blood cells.

The aim of this investigation was to study the dynamics of parameters characterizing contact activity of the platelets and the state of the clotting and fibrinolytic systems of the blood during the period of ischemia and reperfusion of the myocardium in TCI.

EXPERIMENTAL METHOD

Experiments were carried out on 93 noninbred male albino rats weighing 200 ± 10 g. The animals were kept under vivarium conditions on an ordinary diet. TCI was produced by the method described previously [4, 9]. All manipulations were carried out under urethane anesthesia (1200 mg/kg) with artificial ventilation of the lungs with atmospheric air. The duration of MI was 10, 40, and 120 min. During RP the parameters of hemostasis were tested at the 10th and 40th minutes. This experimental schedule was chosen because the electrophysiological, biochemical, and structural changes in the heart in experimental TCI in which the duration of MI is up to 10-20 min are similar to those in the different forms of angina, in TCI with MI lasting up to 25-60 min they are similar to the intermediate coronary syndrome (focal myocardial degeneration), and in TCI with MI lasting more than 60-300 min, they are similar to the state after surgical revascularization of the zone of ischemia of the heart in the acute period of infarction [1, 3, 5, 8, 9]. The state of the hemostasis system was evaluated from the results of coagulography and thrombodynamotachography. In addition, the concentration of fibrinogen [11], platelet factor 4 [15], and of soluble fibrin-monomer complexes [16], the adhesive-aggregation properties of the platelets [12], and the retractile and fibronolytic characteristics of the fibrin-platelet structure (FPS) of the blood clot [13], were determined.

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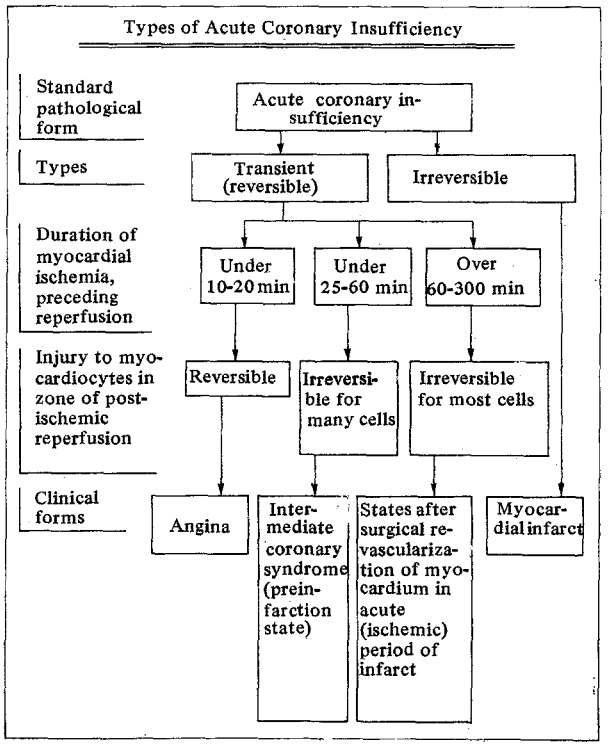

EXPERIMENTAL RESULTS

Local MI was characterized by successive stages of changes in adhesive activity of the platelets, the rate of fibrin formation, and FPS of the blood clot and also by a fall in the degree and rate of its lysis (Table 1).

In the early stage of MI (the first 10 min) the adhesive power of the platelets increased. This was shown by acceleration of their adhesion to a foreign surface (metal, fibrin threads), and also the platelet liberation reaction (in particular, factor 4 from α-granules). The latter observation is particularly important because release of components of platelet granules outside the cell not only potentiates the contact activity of the blood cells, but also initiates the blood clotting process. The basis for this conclusion is formed by two facts: acceleration of fibrin formation and the FPS of the blood clot. The retraction time of FPS of the clot is reduced at the same time, whereas its retractile forces and density increase.

More prolonged MI (40 and 120 min) was accompanied by a decrease in contact activity of the platelets, in the rate of their release reaction, and also in the rate of fibrin formation, but these parameters were still higher than their background values. Parallel with this, the formation of FPS of the blood clot was slowed, and its retractile forces and density were reduced.

Hypercatecholaminemia, the development of acidosis, a disturbance of the systemic hemodynamics and microcirculation, increased ATP breakdown and liberation of ADP from the tissues into the blood, which as we showed previously [3-9] is characteristic of the ischemic period of TCI, can be identified as the leading causes of activation of the cellular and humoral components of hemostasis in MI.

Significant changes in MI also were observed in the fibrinolysis system. The rate and degree of lysis of FPS of the blood clot were reduced as early as by the 10th minute of MI, and they still remained at a low level after 40 and 120 min. The concentration of soluble fibrin–monomer complexes was very slightly reduced by the 10th minute of MI, but thereafter it rose progressively until the 40th and 120th minutes. This fact, and also data on slowing of the formation and retraction of FPS, form the basis for the assumption that the transformation of fibrin monomer into insoluble fibrin is disturbed.

The shifts mentioned above: potentiation of the adhesive-aggregation properties of the platelets, acceleration of fibrin formation, the phasic time course of formation of

TABLE 1. Dynamics of Parameters of Hemostasis in TCI with Different Durations of MI (M ± m)

Parameter	Background	MI for 10 min	Postischemic RP for 40 min	MI for 40 min	Postischemic RP for 40 min	MI for 120 min	Postischemic RP for 40 min
Total platelet adhesion time, min	21,0±1,4	16,0±2,3	20,0±1,8	19,0±1,3	25,0±1,6	16,0±2,6	18,0±1,9
Platelet factor 4 liberation time, sec	7,4±2,0	3,0±0,4*	6,0±1,1	5,0±0,8	4,0±0,6*	4,0±1,0	4,0±0,3
Fibrin formation time, min	1,3±0,4	0,9±0,02	2,4±0,6*	1,2±0,5	1,8±0,03*	0,5±0,02*	0,9±0,001*
FPS formation time, min	4,0±0,4	3,5±0,03	4,5±0,9	3,8±0,6	5,2±0,03*	4,0±0,06	3,9±0,04
Fibrinogen concentration, mg/ml	8,2±0,7	11,4±1,1	10,4±1,8	12,6±1,5	10,2±0,9	9,1±1,2	9,8±0,7
FPS retraction time, min	19,0±1,4	15,0±2,3	18,0±2,6	15,0±1,3	22,0±1,3	15,0±2,4	15,2±0,7*
Retractile forces, mg/mm^2	310±5,0	325±4,5*	250±10,2*	275±2,6*	330±6,6*	300±4,5	325±0,6*
Density of FPS, %	99,3±0,005	99,5±0,004*	99,2±0,01	99,3±0,002	99,4±0,006*	99,5±0,004*	99,4±0,006*
FPS lysis time, min	8,9±1,3	10,2±0,7	4,5±0,6*	9,3±0.9	7,6±1,2	12,0±0,7*	8,0±0,6
Degree of FPS lysis, %	6,6±0,04	3,4±0,03*	9,7±0,2*	3,2±0,007*	2,4±0,005*	2,3±0,004*	3,6±0,004*
Content of soluble fibrin–monomer complexes, extinction units	0,37±0,03	0,35±0,02	0,67±0,09*	0,61±0,07*	1,1±0,09*	0,77±0,09*	0,71±0,16*

*Differences from background significant at $P < 0.05$ level ($n = 8$).

FPS of the blood clot, the decrease in the rate and degree of its lysis, and inhibition of polymerization of fibrin–monomer, are evidence of substantial deviations in the hemostasis system in MI. Taken as a whole the results given above suggest activation of the cellular (platelet) and humoral (coagulation of blood proteins) components of hemostasis, and also a decrease in the activity of finrinolysis factors in the ischemic period of TCI.

The period of postischemic resumption of the local coronary blood flow was characterized by a complex and phasic reorganization of the hemostasis system. The character of this reorganization depended essentially on the duration of MI (Table 1). On reperfusion after short-term (10 min) MI a further increase in contact activity of the platelets and acceleration of fibrin and FPS formation, combined with a fall in the degree and rate of lysis of the FPS formation, combined with a fall in the degree and rate of lysis of the FPC of the blood clot were observed initially (during the first 10 min). Temporary activation of hemocoagulation in the initial stage of postischemic resumption of the coronary blood flow was evidently due to an increase in the activity and concentration of procoagulants liberated from blood cells and myocardial and endothelial cells as a result of their ischemic and also reperfusion injury and washed out by the blood from pathologically altered regions of the heart. By 40 min of RP many of the parameters studied had almost returned to their background levels. Meanwhile, considerable slowing of fibrin formation, an increase in the rate and degree of lysis of FPS, and an increase in the content of soluble complexes of fibrin–monomer were observed. These facts are evidence that RP after short-term MI is accompanied by transient activation of the cellular and hemocoagulation components of hemostasis, and also by increased fibrinolysis.

RP after MI lasting 40 min was characterized by a steady fall in the contact properties of the platelets, delayed formation of fibrin and FPS, and a marked decrease in the degree of its lysis, especially toward the end of the 40-min period. These changes are evidence of a reduction in the activity of most factors of the clotting and, more especially, the fibrinolytic systems of the blood, suggesting exhaustion and(or) suppression of the activity of these systems as a result of substantial changes in the structure of cardiac activity and the hemodynamics, and also of metabolic changes in the blood and tissues, which are observed, as the writers showed previously [4, 6, 7, 9], in this type of TCI.

Resumption of the coronary blood flow after 120 min of MI also was accompanied by a temporary (toward the 10th minute of RP), but considerable decrease in contact activity of the platelets, delay in the formation of fibrin and FPS, and delay in its retraction. Later the changes in these parameters were reduced by different amounts, but toward the 40th minute of RP, they were still significantly higher than their background values. Meanwhile sharp

changes were observed in the rate and degree of lysis of FPS. These facts are evidence of considerable changes, in different directions, in the parameters of the hemostasis system during the period of RP after prolonged (120 min) MI, and they suggest reorganization of the mechanisms of regulation of this system. This reorganization may be due to disturbances of the circulation, of metabolism and (what is particularly important) of the sympathetic and cholinergic mechanisms of regulation characteristic of this particular type of TCI [6-9].

On the whole the results of this investigation indicate a substantial reorganization of the clotting and fibrinolytic systems of the blood in TCI. Local ischemia of the heart is characterized by increased adhesive activity of the platelets, acceleration of fibrinogenesis, a sequence of stages (acceleration in the early and delay in the later stage of MI) of formation of FPS of the blood clot, depression of the rate and degree of its lysis, and also depression of fibrin polymerization. Postischemic resumption of the coronary blood flow is not accompanied by normalization of all parameters of the hemostasis system (within the period of the investigation) even during RP after short-term (10 min) MI. RP after a longer period (40 min) of MI leads to suppression of activity of the clotting and fibrinolytic systems, but after an even longer period (120 min) of MI it led to discordant changes in the parameters of hemostasis.

Considering that TCI with periods of MI of different duration, reproduced in animals, is an experimental model of various forms of ischemic heart disease in man (angina pectoris, the intermediate coronary syndrome, states after revascularization of the zone of MI in the acute period of infarction), it can be tentatively suggested that similar changes in the hemostasis system are also observed in patients with coronary heart disease.

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