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Changes in Hemostasis in Ischemic Heart Disease and Innovative Methods of Its Treatment

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Abstract: The article examines and compares the dynamics of hemostasis system parameters in patients with acute coronary syndrome (ACS) and chronic coronary heart disease (CHD) who underwent myocardial surgical revascularization under EC conditions. In patients with chronic ischemic heart disease (CHD) and acute coronary syndrome (ACS) who underwent surgical myocardial revascularization under cardiopulmonary bypass, 11 indicators of the hemostasis system were determined in the 3Q stages of the preoperative study, during the first postoperative day. surgery, and before discharge from the hospital.

Keywords: hemostasis system, chronic ischemic heart disease, stages of treatment, cardiopulmonary bypass, circulation

Introduction

Achievements in world and domestic clinical medicine show that in order to improve the results of treatment of patients with coronary artery disease, it is necessary to take into account some fundamentally important trends in the development of cardiology, cardiac surgery, anesthesiology and resuscitation. One of these trends is the timely diagnosis and correction of disorders in the hemostasis system at all stages of treatment. In patients, in the process of progression of diseases of the cardiovascular system, pronounced disturbances in the hemostasis system are aggravated during surgical intervention.

Literary review, materials and methods

This is of particular importance for patients undergoing myocardial revascularization under cardiopulmonary bypass (EC) [2]. Thus, in the perioperative period, the coagulation and anticoagulation systems of the body are repeatedly exposed to aggressive pharmacological and physicochemical effects: the use of antiplatelet agents and anticoagulants in the preoperative period, complete heparinization in order to implement extracorporeal circulation, significant intraoperative and postoperative blood loss, severe artificial hemodilution, the use of whole blood components

(donor or autoerythrocytes, fresh frozen plasma), the use of aprotinin, protamine sulfate, infusion solutions [3].

In the practice of surgical treatment of coronary artery disease, it is fundamentally important to single out the two most critical periods: a) immediate postperfusion period, in which the development of significant hypocoagulation and, consequently, postoperative bleeding is dangerous; b) delayed postoperative, in which there is a high probability of the formation of hypercoagulable syndrome and thrombosis in the revascularized coronary arteries, which leads to the resumption of the clinic of severe angina pectoris or AMI.

Traditional preventive therapy with antiplatelet agents, anticoagulants in some cases is insufficient, or excessive and dangerous. In this case, dynamic control of the state of the hemostasis system in the perioperative period should be considered an important diagnostic procedure aimed at improving the results of surgical myocardial revascularization in patients with various forms of coronary artery disease. To study and compare the dynamics of hemostasis system parameters in patients with chronic coronary heart disease (CHD) and acute coronary syndrome (ACS) who underwent surgical myocardial revascularization under cardiopulmonary bypass (EC).

The study included 43 patients (men — 36, women — 7) who had angina pectoris II—III functional class according to the Canadian classification of stable angina pectoris, postinfarction atherosclerotic coronary cardiosclerosis, and hypertension II—III degree. This study was performed on specially selected groups of patients, which does not reflect all the conditions encountered in clinical practice. Patients, depending on the clinical course of the disease, were divided into two groups. Group A consisted of 20 patients with chronic coronary heart disease (CHD) admitted to the cardiosurgical department for planned myocardial revascularization. Group B consisted of 23 patients with acute coronary syndrome (ACS) who needed urgent myocardial revascularization due to a sharp destabilization of the course of coronary artery disease and a high likelihood of developing acute myocardial infarction (MI). As a control group (group C), we used the data of a comprehensive hemostasiological examination of practically healthy male donors in the amount of 12 people. The studied patients were comparable in age, anthropometric data, volume of intraoperative blood loss, time of cardiopulmonary bypass and myocardial ischemia. The study included patients in whom the number of coronary arteries with hemodynamically significant stenoses of the left ventricle ranged from 1 to 5, and the ejection fraction according to cardiac ventriculography was 54.5±7.6%.

The study excluded patients with clinical and hemodynamic signs of acute circulatory failure (arterial hypotension, pulmonary edema, oliguria), with pathology of the thyroid gland, adrenal glands, diabetes mellitus and other diseases that affect the state of the vascular wall, as well as patients admitted for treatment in cardiac surgery department for repeated surgical treatment.

The goal of treating this category of patients was to improve the prognosis by eliminating myocardial ischemia and its complications, preventing the development of myocardial necrosis (or its further spread), improving and stabilizing coronary blood flow.

Considering that at all stages of the study, the examined patients had activation of the vascular-platelet link of hemostasis, they, depending on the number of platelets and the severity of disorders, received antiplatelet agents: mainly cyclooxygenase inhibitors - Thrombo ACC, ADP-receptor blockers - ticlopidine, Plavix and others. Basic therapy for stable angina pectoris included: long-acting organic nitrates, β-blockers, calcium antagonists. In the presence of circulatory failure, diuretics, cardiac glycosides, and ACE inhibitors were connected to the therapy. Acute coronary syndrome includes a heterogeneous group of patients who have their own characteristics in the prevalence and severity of underlying coronary atherosclerosis [4].

In this regard, the basic therapy for ACS included: limitation of physical activity; anti-ischemic drugs (β-blockers, nitrates, calcium antagonists); anticoagulants (unfractionated heparin, low molecular weight heparin); antiplatelet agents (aspirin, ticlopidine); analgesics (agonists, agonists-antagonists of opioid receptors), non-steroidal anti-inflammatory drugs. Anticoagulants and antithrombotic drugs were canceled 24 hours before surgery.

Results and discussion

According to the data of various researchers, when analyzing disorders in the hemostasis system in patients with cardiac surgery, special attention should be paid to laboratory methods for detecting hypercoagulation, which is a predictor of thrombosis [7–10]. When comparing the parameters of the hemostasis system in the group of patients with CIHD (group A) and the control group before surgery, an acceleration of platelet aggregation was revealed ($p<0.05$) (Table 1). In the coagulation link of hemostasis, the disturbances were more significant. There was a shortening of APTT ($p<0.05$) and INR ($p<0.05$) - activation of external and internal coagulation mechanisms, indicating that a large number of activated factors are present in the bloodstream. An increase in the level of D-dimers ($p<0.05$), correlation of RKPM ($p<0.05$) with APTT ($p<0.05$), ($r=-0.65$) — we regarded it as a manifestation of intravascular coagulation. A high level of D-dimers indicates the formation of fibrin (a predictor of coronary thrombosis) and the consistency of fibrinolysis ($p<0.05$) in patients of this group [11, 12]. Correlation of RKFM with ABP ($r=-0.7$), thrombin time with ABP ($r=-0.6$) and time of Hageman-dependent fibrinolysis ($r=+0.55$), INR with AT-III ($r=+ 0.6$), indicating the activation of the external and internal coagulation pathways and the reserve capabilities of the anticoagulant and fibrinolytic systems due to the functional load. The activity of the protein C system ($p<0.05$) was close to the lower limit of normal due to the large number of activated factors of the general and internal pathways of activation - V, VIII - (correlation of APTT and RKFM), of which it is an inhibitor.

The reserve capacity of the hemostasis system due to the functional load in this group was high, probably due to the absence of a deficiency of individual coagulation factors and higher reserve capacity of the activity of AT-III and the fibrinolytic system, therefore, it was extended due to an increase in the substrate for plasmin and the accumulation of fibrinolysis inhibitors, in including pathological ones. In patients with CIHD, these disorders can be detected using screening tests - APTT, INR.

When comparing the parameters of the hemostasis system of the group of patients with ACS (group B) and the control group before surgery, the activation of coagulation is indicated by a large amount of soluble fibrin-monomer complexes in the bloodstream ($p<0.05$), a high level of D-dimers ($p=0.06$) and increased platelet aggregation ($p<0.05$). The platelet aggregation time in ACS patients was significantly shorter than in the control group with normal platelet count in both groups. A tendency to elongation of the ABP, APTT was revealed, which may be due to a lack of factors of the internal coagulation pathway due to prolonged activation. AVR correlated with APTT ($r=+0.6$) and thrombin time ($r=+0.8$), thrombin time with the activity of the protein C system ($r=+0.6$). The trend towards a decrease in the overall coagulation activity is due to a deficiency of some factors of the internal coagulation mechanism and the activity of the protein C system. The reserve capabilities of the anticoagulant and fibrinolytic systems are within the reference values, as evidenced by the correlation between the fibrinogen level and the time of Hageman-dependent fibrinolysis ($r=+0$,5).

The platelet component of hemostasis ensures the rapid formation of platelet clots at the site of vessel injury. In addition, platelets secrete vasoconstrictor substances, and their membranes provide a surface and phospholipid components for the formation of enzyme-cofactor complexes at the next stage of coagulation. The interaction of plasma coagulation factors leads to the completion of thrombus formation by reinforcing it with fibrin strands. Acute coronary syndrome - NS / MI - have a common morphological basis. Rupture of an atherosclerotic plaque, hemorrhage into the plaque, or, less commonly, disruption of the integrity of the endothelium overlying the plaque, combined with increased blood clotting activity (hypercoagulability and increased platelet aggregation), leads to thrombus formation at the rupture or defect in the endothelium of the coronary artery [13]. Fragile platelet thrombi can be a source of microembolism of the distal parts of the coronary vessels, necrosis is formed in the corresponding parts of the myocardium. Circulating platelets adhere to the area of damaged endothelium, which leads to the release of powerful vascular and proaggregant substances, activation of platelet glycoprotein IIb/IIIa receptors. Activated receptors bind a number of substances, especially fibrinogen, which causes the formation of a blood clot.

A significantly higher level of RKFM indicates the activation of coagulation, the presence of a large amount of thrombin and other non-specific proteolytic enzymes in the bloodstream, and the potential danger of thrombosis. Before surgery, there were no adequate changes in the prothrombin complex, APTT (p=0.6) (although some patients with ACS had a slight prolongation of APTT), thrombin time was not detected (Table 1). Thus, to detect disorders in the hemostasis system in patients with ACS, a wider range of tests is needed: platelet aggregation, APTT, INR, determination of the activity of the protein C system, the time of Hageman-dependent fibrinolysis, the amount of fibrinogen, RKPM and D-dimers.

The identified disorders according to the classification are not DIC, since the activity of physiological anticoagulants (in particular, the activity of the protein C system) and fibrinolysis were significantly within the normal range. However, these disorders seem to contribute to the development of DIC in the critically ill. The hemostatic status is only additional information for predicting the risk of coronary disease and confirms the opinion of the authors that in some patients with unstable angina and myocardial infarction there are no adequate changes in the prothrombin complex, APTT, thrombin time [14, 15].

When comparing hemostasis parameters before surgery in groups A and B (Table 2), activation of the external and internal coagulation pathways was revealed in group A - APTT ($p<0.05$), INR ($p<0.05$) - significantly relative to group B These facts indicate the presence in the bloodstream of a large number of activated coagulation factors, as a result of which the activity of the protein C system has decreased ($p<0.05$).

In group B before surgery, in contrast to group A, we did not detect activation of external, internal coagulation pathways, although a high level of RKPM, D-dimers, and platelet hyperaggregation indicated activation of coagulation. APTT and INR were significantly within the physiological norm, although the APTT values in some patients were at the upper limits of the norm and even slightly exceeded it. Correlation of ABP with thrombin time (r=+0.8) and c APTT (r=+0.6), as well as correlation of thrombin time and activity of the protein C system (r=+0.6), with normal readings of prothrombin and thrombin time, reflects the state of the initial stage of the internal mechanism of coagulation and indicates a deficiency in the bloodstream of activated factors - XII, XI, IX or VIII, or the presence of their inhibitors (heparin and others). The activity of physiological anticoagulants was also within the physiological norm, although the activity of AT-III was lower in this group (decrease in activity due to prolonged activation of coagulation, the presence of thrombin and other factors that are the substrate for inactivation), and the activity of the protein C system was higher, which may also be due to factor VIII deficiency (the amount of substrate for inhibition is negligible).

On the first day after the operation, in group A, an increased tendency of blood to coagulate also remained, although some changes occurred. Surgical intervention, the entry into the bloodstream of a large number of biologically active substances, enhance the cascade of coagulation and fibrinolysis. Stabilization of the wound surface by fibrin, accumulation of fibrinogen/fibrin degradation products lead to a decrease in the overall coagulation activity. In the CIHD group, a significant decrease in the total coagulation activity of blood plasma was observed, as evidenced by the prolongation of AVR (apparently due to the accumulation of a large number of clotting inhibitors and paracoagulation products). An increase in thrombin in the bloodstream led to an increase in the activity of the protein C system and a decrease in the activity of AT-III (AT-III is a thrombin inhibitor), as evidenced by the correlation of protein C activity and AT-III activity (r=+0.65). When combined with thrombomodulin, thrombin loses its substrate specificity (activation of factors V, VIII, XI, fibrinogen and platelets), but activates protein C. As a result, activation of the plasma link of hemostasis is interrupted and the formation of thrombin is inhibited. In connection with an increase in the activity of the protein C system, there was a slight decrease in activated factors of internal and general coagulation mechanisms, which is also evidenced by the correlation of APTT with the activity of the protein C system (r = +0.8) and a decrease in overall coagulation activity - the correlation of APTT with APTT (r =+0.7), protein C and thrombin time systems (r=+0.82), AVR with thrombin time (r=+0.64), APTT with thrombin time (r=+0.71).

Platelet aggregation remained elevated, the extrinsic and intrinsic coagulation pathways remained activated. The amount of coagulation products increased, the time of fibrinolysis lengthened.

Conclusion

The results of the studies indicate that in all examined patients at all stages of the study, an increased tendency of blood to intravascular thrombosis prevailed, but the degree of impairment and the causes of its occurrence in the groups are probably different [19]. In group A (CIHD), before discharge, these disorders were more pronounced, since not only an increased ability of blood to platelet aggregation was observed, but also activation of the external and internal coagulation pathways. The reserve capacity of the hemostasis system in this group was higher, probably due to the absence of a deficiency of individual coagulation factors and higher reserve capacity of the fibrinolytic system — the time of Hageman-dependent fibrinolysis was prolonged due to an increase in the substrate for plasmin and the accumulation of fibrinolysis inhibitors. The consistency of fibrinolysis is evidenced by an adequate level of D-dimers and a correlation between the time of fibrinolysis, the level of RKFM, fibrinogen and D-dimers. The data obtained indicate the presence of a pre-thrombotic state, i.e. on the potential thrombosis, which, with the presence of other risk factors, can most likely be realized in thrombosis.

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