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PATHOPHYSIOLOGY OF HEMOSTASIS (LECTURE)

© Mikhail M. Zabezhinsky, Lev D. Balashov, Sarng S. Purveev, Anna N. Kosova

Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Mikhail M. Zabezhinsky — Candidate of Medical Sciences, Assistant Professor of the Department of Pathological Physiology with the course of Immunopathology. E-mail: mih.zabezhinsky@yandex.ru ORCID: https://orcid.org/0000-0003-4028-5197 SPIN: 7052-4730

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Abstract. The mechanisms of development of many very common diseases (myocardial infarction, stroke, tumors, infectious pathology, and others) are associated with pathological changes in the hemostasis system. Understanding the pathophysiology of these changes is at the heart of proper diagnosis and effective treatment. This lecture, intended for medical students and doctors of various specialties, briefly summarizes the basic ideas about the structural components and mechanisms of the hemostasis system, presents the main groups of hemostasiopathies, describes the types, causes and mechanisms of the development of hemorrhagic diathesis, thrombophilic syndromes, thrombohemorrhagic syndrome.

Keywords: hemostasis, hemorrhagic syndrome, thrombophilic syndrome, thrombohemorrhagic syndrome

ПАТОФИЗИОЛОГИЯ СИСТЕМЫ ГЕМОСТАЗА (ЛЕКЦИЯ)

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Сарнг Саналович Пюрвеев, Анна Николаевна Косова

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Михаил Маркович Забежинский — к.м.н., доцент кафедры патологической физиологии с курсом иммунопатологии. E-mail: mih.zabezhinsky@yandex.ru ORCID: https://orcid.org/0000-0003-4028-5197 SPIN: 7052-4730

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Резюме. Механизмы развития многих весьма распространенных заболеваний (инфаркт миокарда, инсульт, опухоли, инфекционная патология и др.) связаны с патологическими изменениями в системе гемостаза. Понимание патофизиологии этих нарушений лежит в основе правильной диагностики и эффективного лечения. В данной лекции, предназначенной для студентов медицинских вузов и врачей различных специальностей, кратко изложены базовые представления о структурных компонентах и механизмах функционирования системы гемостаза, представлены основные группы гемостазопатий, описаны виды, причины и механизмы развития геморрагических диатезов, тромбофилических синдромов, тромбогеморрагического синдрома.

Ключевые слова: гемостаз, геморрагический синдром, тромбофилический синдром, тромбогеморрагический синдром

Hemostasis pathology plays an important role in mechanisms of development of many common diseases, including those that are the most common causes of death worldwide, such as coronary heart disease (CHD), stroke, diabetes mellitus, tumors, infectious diseases, injuries, obstetric and gynecological pathology, autoimmune diseases, hemorrhagic diathesis, etc. All types of shock also inevitably cause disturbances in hemostatic system. Thromboembolic complications, one of the severe consequences of hemostasopathies, are the direct causes of death in 25% of fatal

outcomes worldwide [30, 31]. The prevalence and significance of hemostasopathies creates the need to develop in medical students and doctors of various clinical specialties correct, based on modern scientific data, basic knowledge about structural components, functions, possible pathologies of hemostasis, the causes and mechanisms of their development and consequences.

BRIEF DESCRIPTION OF HEMOSTASIS PHYSIOLOGY

It is possible to understand the pathology of hemostasis only on the basis of knowledge about its normal physiology. According to modern concepts, the hemostatic system is a set of structural components (so-called links) and finely balanced, partially antagonistic mechanisms that ensure the cessation of bleeding when the vascular wall is damaged, the local and reversible nature of thrombosis and the liquid state of blood and the integrity of blood vessels outside the damage [17, 18, 22, 23, 40]. By ensuring blood fluidity and integrity of bloodstream, regulating the aggregate state of blood [14], the hemostatic system forms dynamic space of internal environment of the body, largely determining homeostasis. When the vascular wall is damaged, blood composition changes, or the nature of blood flow is disrupted (the classic Virchow triad, which determines the conditions for thrombus formation), thrombus formation mechanisms are activated in the hemostatic system, aimed at stopping bleeding and localizing the pathological process. These mechanisms ensure the formation of a barrier around the site of inflammation, and also participate in non-specific defense reactions and in the mechanisms of restoration of damaged tissue. Insufficiency or excess of these mechanisms in pathological conditions can lead to the development of hemorrhagic and thrombophilic syndromes, respectively.

The main structural components of the hemostatic system are three links: vascular, cellular and plasma. All three links interact closely with each other, ensuring a balance between the mechanisms of thromboresistance and the processes of thrombus formation. In the vascular link, the key role is played by endothelial cells, lining the bloodstream from the inside and representing, due to the wide range of biologically active substances synthesized by them, a giant endocrine, paracrine and autocrine organ of the human body. Such an organ regulates the activity of platelets and leukocytes, tone and permeability of blood vessels, and activity of coagulation, anticoagulation and fibrinolytic systems [2, 18]. Physiologically, intact endothelium provides so-called thromboresistance by producing antiplatelet agents — NO, PgI_2 (prostacyclin), ERF (endothelial relaxing factor); anticoagulants — glycosaminoglycans (heparan sulfate, dermatan sulfate, etc.), thrombomodulin, TFPI (tissue factor pathway inhibitor); fibrinolysis activators — t-PA (tissue plasminogen activator) and u-PA (urokinase plasminogen activator). When the vascular wall is damaged by exogenous and endogenous factors, it reacts with immediate spasm and turns into a powerful thrombogenic surface that activates platelets and coagulation cascade. The damaged endothelium begins to produce vasoconstrictors — endothelin-1; aggregators — PAF (platelet activating factor); VWF (von Willebrand factor) — an adapter of platelet adhesion to subendothelial collagen exposed as a result of damage; TF (tissue factor), which triggers coagulation cascade (produced primarily by subendothelial smooth muscle cells and fibroblasts); TFPI-1 and TFPI-2 (tissue plasminogen activator inhibitors), limiting fibrinolytic activity at the site of hemostatic plug formation [1, 10, 11, 40].

Platelets are a key component of cellular link of hemostasis. They are the smallest, with a diameter of about 3 μm, anuclear cellular elements of blood, formed during fragmentation of megakaryocytes localized in bone marrow and, as has been shown in modern studies, in microvessels of lungs [19, 20, 29]. The number of platelets in peripheral blood ranges from 180 to 400×10^9 per liter. The lifespan of platelets in the bloodstream is 7–10 days. Despite the absence of a nucleus and small size, the structure of platelets is very complex and surprisingly flexible. These are quite consistent with their diverse functions, which include not only hemostatic, but also trophic (primarily in relation to the vascular wall), participation in immune reactions, angiogenesis and regeneration [7, 19, 20, 25, 29, 32].

On the surface of platelets there is a wide range of receptors, the entire spectrum of which cannot be characterized within the framework of this lecture. Some of these receptors are expressed and activated when the vascular wall is damaged and cause adhesion and aggregation, that is, platelets sticking to the site of damage to the vascular wall and sticking together, respectively. Of particular importance among these receptors, in light of the subsequent discussion of hemostatic defects, is transmembrane receptor complex GPIb-V-IX. On average, 25,000 such complexes are present on the platelet membrane. The complex interacts with a von Willebrand factor. This factor acts as an adapter of platelet adhesion to subendothelial collagen exposed as a result of damage. Also it is involved in activation of platelets and their interaction with coagulation factors FXI, FXII, high-molecular-weight kininogen (HMWK), and FVIIa. The role of glycoprotein receptor GPVI is also important, causing direct interaction of platelets with collagen (without intermediaries) at later stages of adhesion. In mechanisms of platelet aggregation, the key role is played by integrin receptors GPIIb/IIIa ($\alpha_{II}b\beta_{III}$). These receptors are present on the

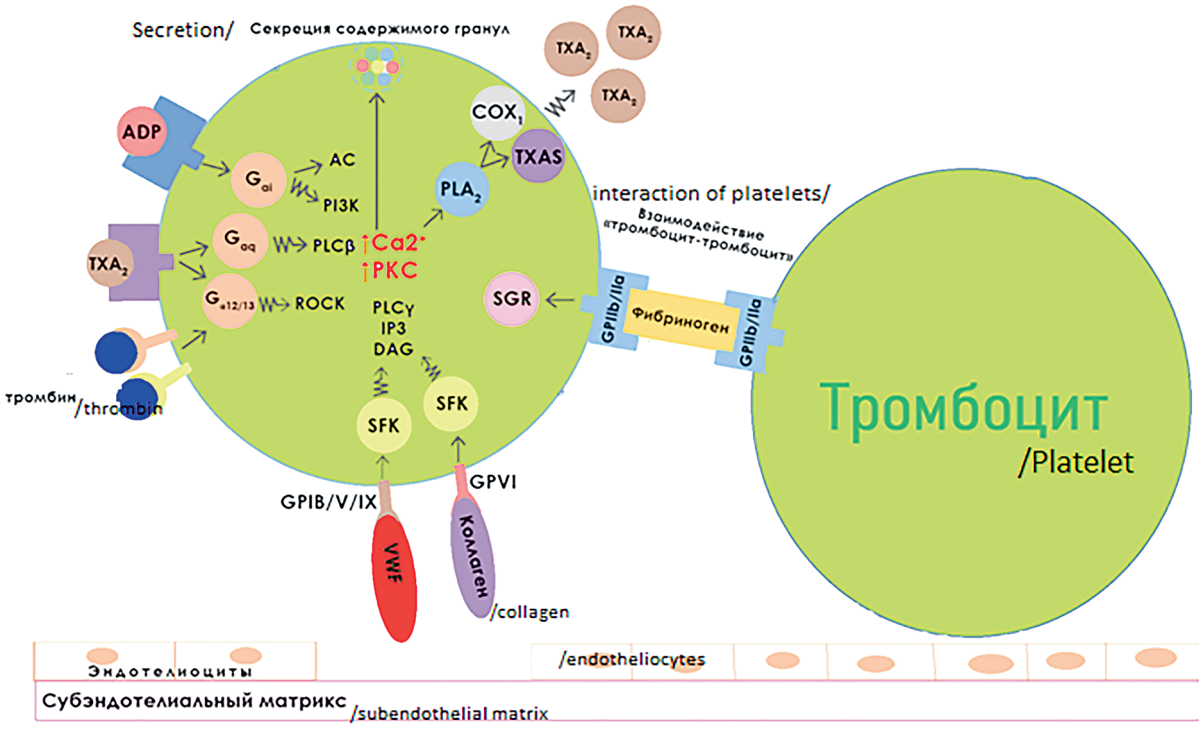

Fig. 1. Mechanisms of platelet involvement in primary hemostasis [12]

Примечания/notes: ADP — аденозиндифосфат/adenosine diphosphate; TXA2 — тромбоксан А2/thromboxane A2; Gai — α-субъединица G-белка/the G-protein subunit; Gaq — αq-субъединица G-белка/the G-protein subunit; Gα12/13 — α12/13-субъединицы G-белка/the G-protein subunits; AC — аденилатциклаза/adenylate cyclase; PI3K — фосфоинозитид-3-киназа/phosphoinositide 3-kinase; PLCβ — фосфолипаза Cβ/phospholipase Cβ; PLCγ — фосфолипаза C γ/phospholipase C γ; PLA2 — фосфолипаза А2/ phospholipase A2; ROCK — Rho-ассоциированная протеинкиназа/Rho-associated protein kinase; IP3 — инозитол-3-фосфат/inositol-3-phosphate; DAG — диацилглицерол/diacylglycerol; SFK — Src семейство киназ/Src family kinases; GP (IB, IIa, IIb V, VI, IX) — гликопротеины/glycoproteins; VWF — фактор фон Виллебранда/the von Willebrand factor; SGR — малый регулятор G-белка/small G-protein regulator; COX1 — циклооксигеназа 1/cyclooxygenase 1; TXAS — тромбоксан А2-синтаза/thromboxane A2 synthase

Рис. 1. Механизмы участия тромбоцитов в первичном гемостазе [12]

surface of platelets in the greatest numbers. On average, there are about 80,000 receptors per platelet, with about 40,000 copies stored in the α-granules and in the open canalicular system. In the absence of vascular wall damage, they are located on platelet membranes in an inactive conformation. They can be activated by collagen, podoplanin, thrombin, thromboxane A_2, ADP, and epinephrine. In an active open conformation, they interact with bivalent ligands: fibrinogen, VWF, fibronectin, vitronectin, which bind platelets to each other [29, 32] (Fig. 1).

Platelets contain three types of granules in cytoplasm: α-granules, dense granules, and lysosomal granules. Their total number is about 70 per platelet. α-Granules are the most numerous (50–60 per platelet) and largest. These granules contain about 300 different proteins involved in coagulation, adhesion and aggregation of platelets, acting as receptors and growth factors, in particular fibrinogen, FV, P-selectin, platelet-derived growth factor, etc. Dense granules contain smaller molecules: ADP, ATP, serotonin, calcium. Hydrolytic enzymes are present in lysosomal granules [19, 20].

At rest, in the absence of effects that threaten homeostasis, platelets have a disc-shaped form. They are pushed by axial blood flow, represented by erythrocytes, to endothelium, where platelets perform a trophic function, participate in microcoagulation, maintaining thromboresistance. However, when damage occurs, platelets not only adhere to the site of vascular wall defect, but they are also activated. This is accompanied by a change in shape from discoid to process-like. A reaction of platelet release occurs in the form of secretion of granules content through an open canalicular system into blood and onto the platelet membrane. This enhances both platelet aggregation and activation and coagulation cascade by the positive feedback mechanism. The production of thromboxane A_2 (TxA_2) in platelets, an important stimulator of aggregation, also increases. The conformation of receptors changes. Phosphatidylserine is transferred from the inner bilayer of phospholipid membrane to the outer one, which causes a procoagulant surface formation on platelet membrane [16, 29, 39] (Fig. 1).

In addition to platelets, other blood cells also play a significant role in hemostasis. In particular, neutrophils participate

in thrombus formation by interacting with platelet aggregates via P-selectin receptors on the platelet surface. Neutrophils adhere to damaged endothelium and are capable of releasing nuclear chromatin into extracellular space, forming so-called neutrophil extracellular traps (NETs), which activate coagulation. In 2004, this interesting phenomenon was discovered by Brinkman et al. and named NETosis [34].

Erythrocytes are also important participants in the cellular link of hemostasis, largely determining hemorheological properties of blood. They can form aggregates with platelets, participating in the formation of red thrombi, releasing ADP and TxA_2, which stimulate platelet adhesion and aggregation, and suppressing fibrinolysis activity [41]. Mechanisms of participation of cellular and vascular links in stopping bleeding are conventionally called primary (vascular-platelet) hemostasis.

The plasma link of hemostasis includes components of coagulation, anticoagulation and fibrinolysis. Components of the coagulation system are represented by so-called coagulation factors: serine proteases that cascade-activate each other, and their cofactors. Since the work of Morawitz (1905), a number of key stages have been identified in coagulation process: the release of tissue factor (in past terminology, tissue thromboplastin), conversion of prothrombin (fII) by activated thromboplastin into thrombin (fII_a) in the presence of calcium, and the conversion of fibrinogen (fI) into fibrin (fI_a) under the action of thrombin. Formed in the 1960s the cascade model of coagulation characterizes stages of this process in more detail and distinguishes between the so-called internal, all components of which are present in the bloodstream, and external, which is activated by TF coming from outside, pathways for the formation of prothrombinase complex (Fig. 2). This model is quite suitable for describing the process of blood clotting *in vitro*, in particular during laboratory tests such as PT (prothrombin

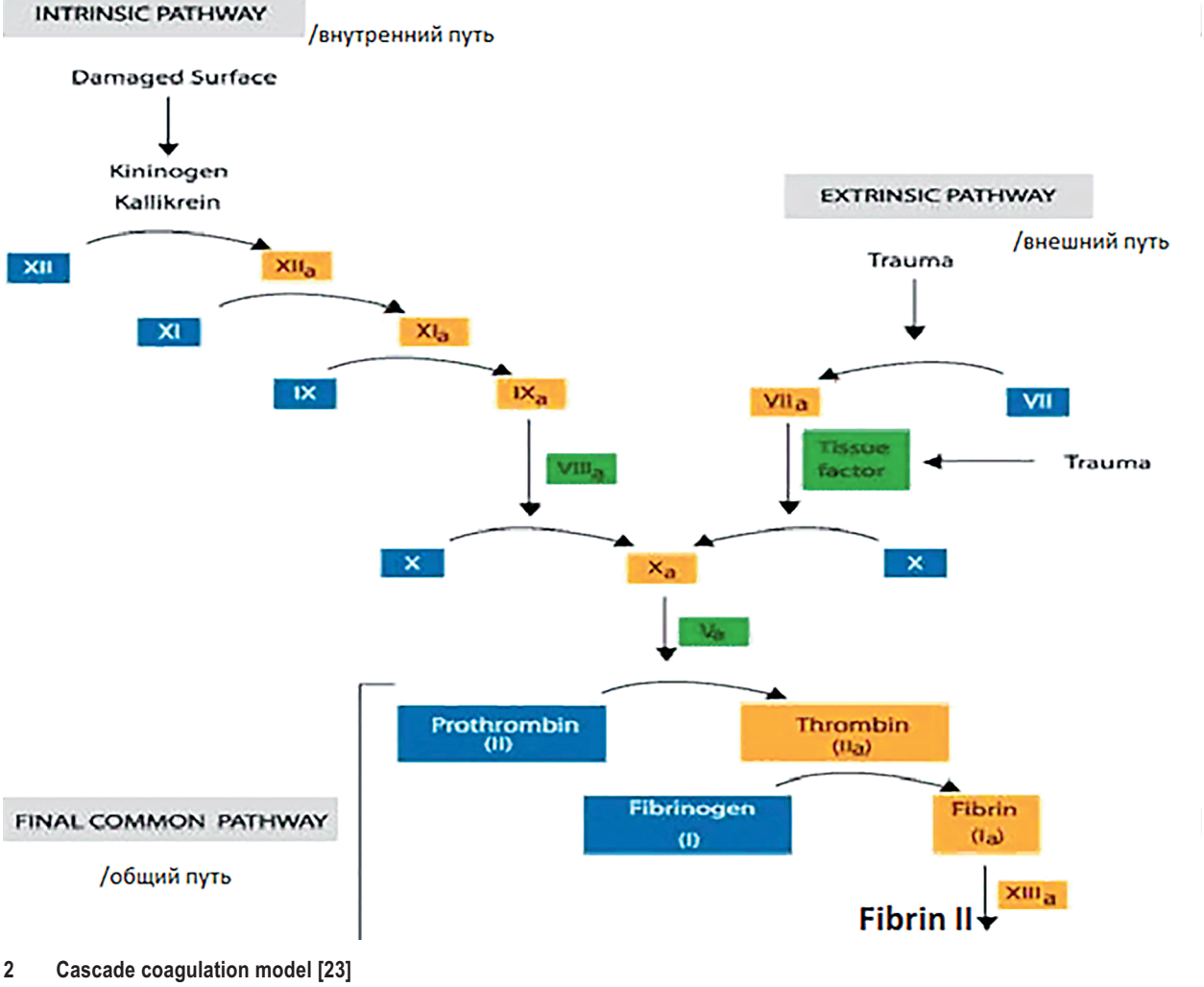

Fig. 2 Cascade coagulation model [23]
Рис. 2. Каскадная модель коагуляции [23]

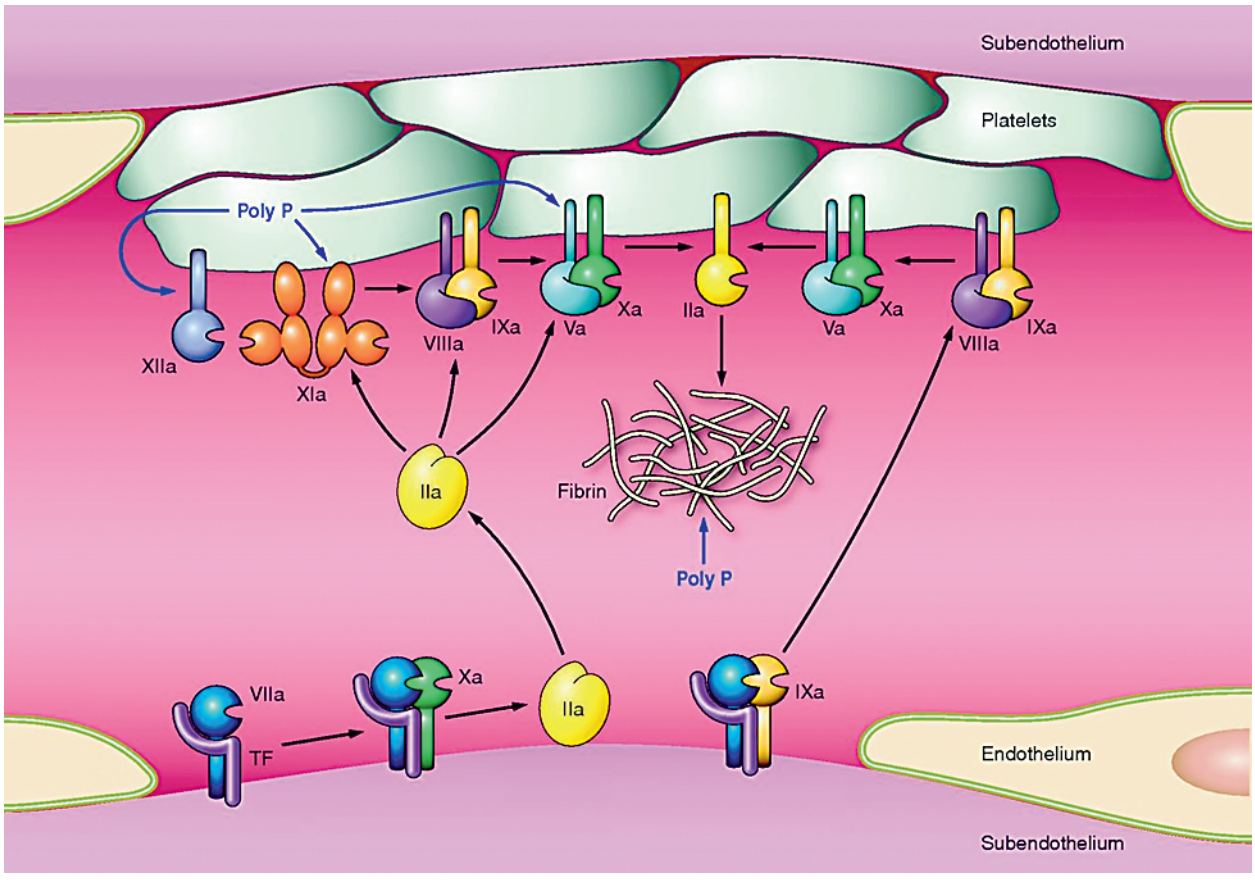

Fig. 3. Cellular model of coagulation (figure taken from [40])
Рис. 3. Клеточная модель коагуляции (рисунок взят из [40]). TF — тканевой фактор; IIa — тромбин; Poly P — полифосфаты; Platelets — тромбоциты; Subendothelium — субэндотелий; Endotyelium — эндотелий

time) and APTT (activated partial thromboplastin time), and is therefore still relevant.

However, in the XXI century, ideas about mechanisms of blood coagulation *in vivo* have undergone serious revision, and a cell biological model of coagulation has been formed [21, 33, 38]. This model distinguishes three stages: initiation, amplification, and propagation. During initiation, smooth muscle cells and fibroblasts exposed as a result of damage to the vascular wall endothelium express tissue factor, which binds to factor VII and activates it. The TF/VIIa complex proteolytically activates small amounts of factors IX and X. FXa binds to FVa on the surface of TF-expressing cells to form a prothrombinase complex, which converts prothrombin to thrombin. During the amplification stage, a small amount of thrombin formed in the previous phase activates platelets adhered to the site of vascular wall damage, and also activates FV, FVIII, and FXI. This closes the positive feedback loop, i.e., enhances thrombin formation. The propagation stage occurs on a procoagulant surface of activated platelets, rich in phosphatidylserine. Activated FXI activates FIX, which then activates FVIII on the platelet surface, forming the fIXa/fVIIIa tenase complex, which catalyzes formation of fXa. The prothrombinase complex fXa/fVa then converts prothrombin to thrombin, which in turn catalyzes fibrin formation. In parallel, polyphosphates (Poly P) released by activated platelets can further stimulate activation of factor XII, factor V, and factor XI and inhibit thrombus lysis (Fig. 3).

According to the cell biological model, the so-called intrinsic pathway serves to amplify extrinsic pathways. Three physiological triggers of intrinsic pathway have been identified, namely collagen, linear phosphate polymers (polyphosphates), and neutrophil extracellular traps (NETs) [40]. The involvement of the coagulation system in stopping bleeding is conventionally called secondary coagulation hemostasis.

Coagulation is restrained by the anticoagulation system. It is represented by a whole set of protease inhibitor proteins found in plasma and causing a limited, localized nature of thrombus formation. These primarily include antithrombin, heparin cofactor II, tissue factor pathway inhibitor (TFPI), C1 inhibitor, proteins C and S. Interestingly, thrombomodulin plays an important role in protein C activation.

It is a transmembrane protein found on endothelial cells. Thrombomodulin forms a complex with thrombin, which activates protein C bound to a corresponding receptor on endothelium. Thus, thrombin is used in this case as an activator of one of the important components of the anticoagulant system [40].

The reversibility of thrombosis is ensured by the fibrinolytic system. The key component of this system is plasmin (fibrinolysin), formed from plasminogen. The conversion of plasminogen to plasmin is catalyzed by plasminogen activators, among which the greatest importance is given to tissue plasminogen activators (t-PA, u-PA) produced by endothelium, monocytes, and megakaryocytes. Plasmin breaks down fibrin and fibrinogen. As a result, FDPs (fibrin and fibrinogen degradation products) are formed, some of which have properties of secondary anticoagulants and antithrombotics. For example, fragment Y competitively inhibits thrombin, fragments D and E inhibit platelet aggregation. Plasmin is also capable of breaking down a number of coagulation factors: V, VIII, XI, XII, XIII, FV. The process of plasmin formation is balanced by a number of inhibitors. These include plasminogen activator inhibitors (PAI-1, PAI-2, PAI-3), formed in endothelium, smooth muscle cells, platelets, and inhibitors of plasmin itself, the most important of which is α_2-antiplasmin, produced by the liver [23].

PATHOGENESIS OF HEMOSTASOPATHIES. GENERAL CONCEPTS. MAIN GROUPS OF HEMOSTASOPATHIES

Hemostatic system, thanks to the mechanisms of checks and balances under physiological conditions, a dynamic balance is maintained between mechanisms involved in stopping bleeding (primary and secondary hemostasis) and mechanisms causing thromboresistance (let's call them antihemostasis). Violation of this balance is the basis of hemostasopathies. In principle, three variants of imbalance in the hemostatic system can be distinguished. The first variant is represented by conditions in which the mechanisms of stopping bleeding for various reasons are insufficient in relation to the mechanisms of thromboresistance. The result of such imbalance is a tendency to increased bleeding (hemorrhagic diathesis — group I of hemostasopathies). The second variant is represented by a large group of hereditary and acquired disorders, in which mechanisms of thrombus formation prevail over mechanisms of thrombus resistance. Such conditions, characterized by an increased tendency to thrombus formation, are called thrombophilic syndromes. If the hemostatic system was static, then variants of hemostasopathies would be limited to this. However, in a dynamic system, a third variant of imbalance is possible, a kind of "swing". In this case, in the first phase, the balance is pathologically shifted towards mechanisms of thrombus formation with excessive uncontrolled generalized thrombus formation in vessels of various areas. During the second phase, a shift in the balance in the opposite direction is observed with the development of pathological deficiency of platelets and coagulation factors as a result of their excessive consumption. Because of this, a patient experiences increased bleeding (Fig. 3). The general name for group III of hemostasopathies is thrombohemorrhagic syndrome. The most common example of this variant is DIC — disseminated intravascular coagulation syndrome.

Let's take a closer look at each of the above three main groups of hemostasis.

BRIEF GENERAL CHARACTERISTICS OF HEMORRHAGIC DIATHESIS

Hemorrhagic diathesis is characterized by an increased tendency to bleeding and can develop as a result of pathological defects in various parts of the hemostasis system: vascular, cellular and plasma. Hemorrhagic diathesis caused by defects of the vascular link is called vasopathy, of the cellular link — thrombocytopathy and thrombocytopenia, of the plasma link — coagulopathy. According to etiology, the three above-mentioned types of hemorrhagic diathesis can be hereditary and acquired. It is impossible to describe in detail the causes and mechanisms of all diseases characterized by increased bleeding in one lecture. It remains possible to characterize some of the most relevant mechanisms of damage to blood vessels, platelets, and the coagulation system.

Among mechanisms that damage the vascular wall and underlie hemorrhagic vasculitis, immunopathological ones are common. As a result of provoking factors' actions (bacterial, viral, drug antigens) immune complexes are formed in predisposed patients, deposited in skin microvessels, kidneys, gastrointestinal tract and other areas. Immune complexes are capable of activating the complement system and causing inflammation of the vascular wall with the development of bleeding. These mechanisms are the basis of Henoch–Schönlein purpura (infectious-allergic capillary toxicosis), which is very common in children and clinically manifests as purpura in the form of diffuse, fine-point, hemorrhagic rash. Along with skin vessels, microvasculature of kidneys, gastrointestinal tract, and periarticular areas can be affected [28].

In addition to immunopathological mechanisms, a number of other factors can also lead to vascular wall damage: increased blood pressure, metabolic disorders, direct damaging effects of toxins, infectious agents, drugs, vitamin deficiency, in particular vitamin C deficiency (scurvy). Vitamin C

is necessary for the post-translational modification of collagen (hydroxylation of proline and lysine). Collagen plays an important role in the interaction of platelets with the vascular wall during so-called vascular-platelet hemostasis. Collagen defect leads to increased bleeding.

Hereditary collagen defects in Ehlers-Danlos syndrome and Marfan syndrome may also be accompanied by bleeding tendency. The most common hereditary vasopathy accompanied by hemorrhagic syndrome is Rendu–Osler–Weber disease (hereditary hemorrhagic telangiectasia) [23, 27]. In the vast majority of cases, the disease is based on a defect in genes located on chromosomes 9 and 12, encoding endothelial membrane glycoprotein endoglin (type 1) and ACVR1 protein (formerly ALK-1) (type 2), which are involved in interaction with TGFβ (transforming growth factor β). As a result, patients experience vascular wall defects with dilation of capillaries and venules, formation of telangiectasias, arteriovenous shunts, and a high risk of vascular wall rupture and bleeding. Most patients (90% of cases) experience nosebleeds from pathologically dilated defective vessels of nasal mucosa. In addition, vessels of skin (75%), lungs (33–50%), liver (30%), gastrointestinal tract (15%), and the central nervous system (5–23%) may be affected [24].

Deficiency in the quantity (thrombocytopenia) and defects in the quality (thrombocytopathy) of platelets underlie most hemorrhagic diathesis (up to 80%, according to Barkagan Z.S.) [3]. Fundamentally, thrombocytopenia can result from increased destruction of platelets and/or their precursors — megakaryocytes, increased consumption of platelets during thrombus formation, decreased production of platelets in bone marrow (for example, in aplastic anemia), blood loss, sequestration of platelets in spleen [23].

The most common are destructive thrombocytopenias caused by immunopathological mechanisms. In adults, the most typical form of immunopathological thrombocytopenia is Werlhof's disease (chronic immune thrombocytopenic purpura), which most often affects women aged 20–30. In essence, Werlhof's disease is an autoimmune disease, when, for reasons not entirely clear, antibodies to normal antigens on the surface of platelets, in particular to GPIIb/IIIa aggregation receptors, are formed. Platelets labeled with antibodies are eliminated in spleen, severe thrombocytopenia (less than $10–20\times10_9$/l) occurs, accompanied by nasal and gastrointestinal bleeding, menorrhagia, petechiae, and ecchymosis on skin.

Immune thrombocytopenia is also common in children, often occurring after viral infections (rubella, chicken pox, influenza), vaccination, or taking medications (quinine, quinidine, drugs with gold content, heparin). Unlike Werlhof's disease, in this case the body of a sick child produces antibodies against viral and other heteroantigens adsorbed on the surface of platelets. Since viral antigens are eliminated over time, immune thrombocytopenic purpura in children in 80% of cases passes spontaneously within 2 months [23]. Immune thrombocytopenia can also occur in utero in a child with antigenic incompatibility of maternal and fetal platelets (isoimmune variant) or a mother with Werlhof's disease (transimmune variant).

Important mechanisms of thrombocytopathies are hereditary defects of various structural components involved in platelet hemostasis. Considering the complexity of the structure of platelets, a fairly wide variety of hereditary defects is observed. The most common hereditary disease leading to a disorder of not only platelet but also coagulation hemostasis is von Willebrand disease. This disease is based on defects in a gene located in chromosome 12 and encoding VWF. VWF is synthesized in endothelium and megakaryocytes, has a complex multimeric structure and is involved in processes of initial adhesion of platelets to subendothelial collagen, playing the role of an adapter and interacting, on the one hand, with collagen, on the other hand, with GPIb-V-IX receptors on the platelet surface. In addition, VWF binds to circulating factor VIII, stabilizing it and localizing it at the site of activation of bleeding arrest mechanisms. In different forms of von Willebrand disease, a decrease in the total amount of VWF (occurs in 70%) or qualitative defects of various VWF domains are possible, causing various ratios of platelet and coagulation hemostasis disorders. In essence, this variant of hemorrhagic diathesis is combined with elements of vasopathy, thrombocytopathy, and coagulopathy [3, 6, 22, 23].

Interesting hereditary thrombocytopathies include Bernard–Soulier syndrome, characterized by a defect in adhesion receptors GPIb-V-IX, and Glanzmann thrombasthenia, caused by a defect in aggregation receptors GPIIb/IIIa. Hereditary defects and deficiency of α-granules (gray platelet syndrome), deficiency of dense granules (Hermansky–Pudlak, Chediak-Higashi, Griscelli syndromes), defects in the phospholipids of the platelet membrane (Scott syndrome), etc. have been described [26, 35].

Acquired thrombocytopathy may occur against the background of uremia, paraproteinemia, and medication. A classic example is thrombocytopathy caused by aspirin. Aspirin blocks COX (cyclooxygenase), which reduces the synthesis of TxA_2 in platelets, which in turn leads to a decrease in secretion of platelet granule contents and a decrease in aggregation.

Blood coagulation disorders (coagulopathies) are caused primarily by hereditary and acquired coagulation factor deficiencies or impaired activity. Among hereditary coagulopathies, the most common, along with the above-mentioned von Willebrand disease, are hemophilia A and B, characterized by a deficiency and/or impaired activity of coagulation

factors VIII and IX, respectively. Both hemophilias are inherited in a recessive X-linked manner and are clinically manifested by a very characteristic hematoma type of bleeding with a predominance of hemorrhages into large joints of the extremities (hematoses), under skin, and in muscles [3].

One of the most common causes of acquired coagulopathies is vitamin K deficiency. This vitamin is fat-soluble, enters the body with food (greens, vegetables, beef liver, chicken meat), and is also formed by normal intestinal microflora. It is necessary for the formation of active coagulation factors X, IX, VII, II, as well as the activation of anticoagulants proteins C and S. The mechanism of vitamin K-dependent activation consists of Y-carboxylation of glutamic acid residues of these proteins. It is necessary for their binding to Ca2+ and phospholipids of platelet and endothelial membranes. Vitamin K deficiency in the patient's body can be associated with enteropathies and intestinal dysbacteriosis, impaired bile secretion and diseases of liver and pancreas, treatment with indirect anticoagulants [22].

Liver damage is the second most significant cause of acquired coagulopathies. Since the liver synthesizes most coagulation factors, liver disorders can lead to a deficiency of not only vitamin K-dependent factors, but also a number of others — V, I, XI, XIII.

Along with damage to coagulation system, increased bleeding can be caused by hereditary and acquired defects of fibrinolytic system, for example, hereditary deficiency of α_2-antiplasmin, excessive formation of plasminogen activators, and insufficient inactivation of plasminogen activators [23].

GENERAL CHARACTERISTICS OF THROMBOPHILIC SYNDROMES

Thrombophilias are hereditary and acquired disorders of hemostatic system, characterized by a predisposition to excessive, recurrent thrombus formation. It can be complicated by vascular obstruction with the development of ischemia and infarction (thrombosis in arteries) and venous congestion (thrombosis in veins), as well as thromboembolism, including its most formidable variant — pulmonary embolism (PE). In the 19th century, for understanding the mechanisms of thrombophilia, the so-called Virchow triad was formed. This triad is of enduring importance. According to the triad, to trigger the process of thrombus formation, the presence of at least one of three conditions is necessary: damage to the vascular wall, change in blood composition, and change in blood flow nature. Mechanisms of thrombophilia are always based on the action of one or more factors from this triad. The prominent Russian scientist Z.S. Barkagan, depending on causes and mechanisms, identified 10 groups of thrombophilic syndromes [4].

The first group includes so-called hemorheological forms, in which the tendency to thrombus formation is caused by blood thickening, as happens, for example, with true polycythemia.

The second group includes thrombophilias caused by an increase in the number of platelets and/or an increase in their adhesive and aggregation abilities. An increase in the number of platelets (thrombocytosis) can be primary (essential thrombocytosis) and secondary reactive, for example, in acute and chronic infections. An increase in adhesive and aggregation properties of platelets can be hereditary (syndrome of "viscous" platelets) and acquired (in diabetes mellitus). Adhesion and aggregation of platelets can also increase due to hyperproduction or insufficient degradation of VWF [8].

The third group included forms caused by hereditary and acquired deficiency of anticoagulants: AT (antithrombin), proteins C and S, and TFPI.

The fourth group includes forms caused by hyperproduction and anomalies of coagulation factors. Among these types of pathology, the most common is so-called Leiden mutation — a hereditary anomaly of factor V. It becomes resistant to the inhibitory action of protein C, as a result of which coagulation cascade is pathologically enhanced [27]. In the second place in frequency is hereditarily caused excess synthesis of coagulation factor II — prothrombin.

In the fifth group of thrombophilias, Z.S. Barkagan included pathologies of the hemostatic system caused by hereditary and acquired decrease in fibrinolysis caused by insufficient production of tPA by endothelium or increased production of TFPI.

The sixth group includes metabolic thrombophilias that occur in atherosclerosis, diabetes mellitus, and hyperhomocysteinemia. The leading mechanism is endothelial dysfunction, accompanied by a decrease in its thromboresistance [5, 18].

The seventh group includes autoimmune thrombophilias, among which the leading place is occupied by antiphospholipid syndrome. This syndrome occurs in systemic lupus erythematosus, chronic viral infections, lymphomas and is characterized by the formation of a large number of autoantibodies to phospholipids of endothelial cell membranes, activated platelets, monocytes. As a result, an imbalance in the hemostasis system occurs, in 75% of cases manifested by thrombophilia, in 25% — increased bleeding.

The eighth group includes paraneoplastic thrombophilias accompanying oncological diseases. In pathogenesis of paraneoplastic thrombophilias, an important role is played by mechanisms associated with the disruption of structural and functional integrity of the endothelium by tumor cells; activation of platelets by tumor cells; increased synthesis of procoagulants and fibrinolysis inhibitors by tumor cells;

and procoagulant activity of macrophages present in a tumor area [13].

The ninth group includes iatrogenic thrombophilia, for example, caused by taking hormonal contraceptives. Estrogens included in these drugs increase the synthesis of the number of coagulation factors (II, V, VII, IX, X, XI) [15].

The tenth group included thrombophilias that arose from a combination of several of the above-mentioned disorders. For example, the use of hormonal contraceptives by a patient with Leiden mutation increases the risk of venous thrombosis by 30–35 times, while the Leiden mutation itself increases the risk of thrombosis by 3–7 times [15, 27].

GENERAL CHARACTERISTICS OF THROMBOHEMORRHAGIC SYNDROME

In the study of thrombohemorrhagic syndrome, priority belongs to domestic researchers. In the first place are M.S. Machabeli, his colleagues and followers, who, since the 60s of the 20th century, have done a great deal of work to decipher its mechanisms and fully appreciate the general biological and general medical significance of this pathological process [3, 14].

Thrombohemorrhagic syndrome is represented in clinical practice by a number of pathologies. First of all, it is represented by DIC, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombotic thrombocytopenia, etc. Some diseases, referred to in this lecture as other types of hemostasopathies, for example, Henoch–Schönlein purpura and paraneoplastic thrombophilia, also gravitate towards thrombohemorrhagic syndrome in their pathogenesis [22, 27].

Thrombohemorrhagic syndrome is characterized by a phased total dynamic imbalance in all links of hemostatic system, which can be likened to the rocking the swing (pendulum), when all attempts of the body (and sometimes the attending physician) to stabilize the situation in most cases lead to even greater amplitude of deviations (Fig. 4).

The trigger mechanism of thrombohemorrhagic syndrome is hyperactivation of one of the links of the hemostasis system (coagulation, platelet, vascular) by exogenous and endogenous factors, leading to widespread, non-local, uncontrolled thrombus formation. In this case, natural endogenous mechanisms (thromboresistance of vascular wall, coagulation inhibitors, fibrinolytic system), providing local and reversible thrombosis, prove ineffective. Excessive widespread thrombus formation leads to characteristic consequences — ischemic damage to various organs, multiple organ failure. Subsequently, mechanisms of thrombus formation are depleted, the so-called consumption coagulopathy occurs, characterized by thrombocytopenia, deficiency of coagulation factors, activation of fibrinolytic system and clinically manifested by bleeding. This is the general picture of thrombohemorrhagic syndrome [3].

From the point of view of clinical practice, the most relevant and widespread variant of thrombohemorrhagic syndrome is DIC. It is always secondary and can develop as a complication of a wide range of diseases: sepsis (primarily

Рис. 4. Дисбаланс в системе гемостаза при тромбогеморрагическом синдроме
Fig. 4. Imbalance in the hemostasis system in thrombohemorrhagic syndrome

caused by gram-negative bacteria), a number of viral infections (including COVID-19), injuries, burns, surgeries, crush syndrome, massive hemolysis, pancreatitis, solid tumors, acute promyelocytic leukemia, obstetric pathology (premature placental abruption, amniotic fluid embolism, intrauterine fetal death), all types of shock, and poisonous snake bites. All of the above diseases are characterized by the release of a large number of procoagulants into blood, primarily TF. This leads to hypercoagulation with the generation of excess amounts of thrombin, activation of platelets, production of fibrin and the formation of a large number of thrombi in the vessels of the microvasculature of various areas [3, 9, 36, 37]. Conventionally, four stages of DIC syndrome are distinguished: Stage I — hypercoagulation and platelet activation; Stage II — transient with increasing coagulopathy and thrombocytopenia; Stage III — deep hypocoagulation caused by the consumption of coagulation factors and platelets; IV — recovery (or, in case of unfavorable course, the phase of outcomes and complications) [3, 14]. The course of DIC syndrome is quite diverse and can be both acute and chronic recurrent. The consequences are mainly reduced to the development of severe multiple organ failure (respiratory, renal, adrenal, hepatic) with a predominance of damage to various organs depending on characteristics of an underlying disease.

Treatment of DIC syndrome is one of the most complex and still not fully resolved problems. It is very important for a clinician to understand the dynamic, staged nature of thrombohemorrhagic syndrome. Just as when swinging a swing, the same impact in magnitude and direction, produced at different times, can either increase the amplitude of swinging or decrease it, so in treatment of DIC, the introduction of the same drug can have a beneficial effect if used in a timely manner and a harmful destructive effect if used untimely.

CONCLUSION

In conclusion, it is necessary to emphasize that with a high probability, almost every clinician will have to face the need to diagnose and treat hemostasis disorders. Success of treatment will largely depend on the doctor's understanding of pathophysiology of hemostasopathies.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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REFERENCES

1. Alekseev V.V., Alipov A.N., Andreev V.A. i dr. Medicinskie laboratornye tehnologii. [Medical laboratory technologies]. Tom 2. Moskva: GEOTAR-Media Publ.; 2013. (in Russian).
2. Babichev A.V. Rol' endoteliya v mekhanizmakh gemostaza. [The role of endothelium in the mechanisms of hemostasis]. Pediatr. Pediatrician. 2013;1:122–127. (in Russian). URL: https://cyberleninka.ru/article/n/rol-endoteliya-v-mehanizmah-gemostaza.
3. Barkagan Z.S. Gemorragicheskiye zabolevaniya i sindromy. [Hemorrhagic diseases and syndromes]. 2-ye izd., pererab. i dop. Moskva: Meditsina Publ.; 1988. (in Russian).
4. Barkagan Z.S. Kliniko-patogeneticheskiye varianty, nomenklatura i osnovy diagnostiki gematogennykh trombofiliy. [Clinical and pathogenetic variants, nomenclature and basics of diagnosis of hematogenous thrombophilias]. Problemy gematologii i perelivaniya krovi. 1996;3:5–15. (in Russian).
5. Vasil'yev A.G., Morozova K.V., Brus T.V., Zabezhinskiy M.M., Kravtsova A.A., Balashov L.D., Vasil'yeva A.V., Pyurveyev S.S., Kosova A.N. Rol' narusheniy obmena gomotsisteina v patologicheskikh protsessakh. [The role of homocysteine metabolism disorders in pathological processes]. Rossiyskiye biomeditsinskiye issledovaniya. 2022;1:44–59. (in Russian). URL: https://cyberleninka.ru/article/n/rol-narusheniy-obmena-gomotsisteina-v-patologicheskih-protsessah.
6. Grin D., Ladlem K.A. Gemorragicheskiye zabolevaniya i sindromy. [Hemorrhagic diseases and syndromes]. Perevod s angliyskogo pod red. O.V. Somonovoy. Prakticheskaya meditsina; 2014. (in Russian).
7. Gorbacheva I., Sycheva Yu. Patologiya parodonta i arterial'naya gipertenziya. [Periodontal pathology and arterial hypertension]. Universitetskiy terapevticheskiy vestnik. 2023;5(3):59–68. DOI: 10.56871/UTJ.2023.14.31.006. (in Russian).
8. Domina I.A., Kumskova M.A., Panteleyev M.A. Trombotsitopatii. [Thrombocytopathies]. Rossiyskiy zhurnal detskoy gematologii i

onkologii. 2015;1:54–60. URL: https://cyberleninka.ru/article/n/trombotsitopatii. URL: https://cyberleninka.ru/article/n/trombotsitopatii. (in Russian).
9. Dondurej E.A., Pshenichnaja K.I., Ivanova I.A. Sostojanie sistemy gemostaza u detej s COVID-19. [The state of the hemostasis system in children with COVID-19]. Pediatr. 2023;14(1):35–43. DOI: 10.17816/PED14135-43. (in Russian).
10. Dorofiyenko N.N. Rol' sosudistogo endoteliya v organizme i universal'nyye mekhanizmy izmeneniya yego aktivnosti (obzor literatury). [The role of the vascular endothelium in the body and the universal mechanisms of changes in its activity (literature review)]. Byul. fiz. i pat. dykh. 2018;68:107–116. URL: https://cyberleninka.ru/article/n/rol-sosudistogo-endoteliya-v-organizme-i-universalnye-mehanizmy-izmeneniya-ego-aktivnosti-obzor-literatury. (in Russian).
11. Kade A.Kh., Zanin S.A., Gubareva Ye.A., Turovaya A.Yu., Bogdanova Yu.A., Apsalyamova S.O., Merzlyakova S.N. Fiziologicheskiye funktsii sosudistogo endoteliya. [Physiological functions of the vascular endothelium]. Fundamental'nyye issledovaniya. 2011;11(3):611–617. URL: https://fundamental-research.ru/ru/article/view?id=29285. (in Russian).
12. Latypov I., Pyurveyev S., Nekrasov M., Dedanishvili N., Tagirov N. Sovremennyye predstavleniya o mekhanizmakh arterial'nogo tromboza. arterial'nyy tromboz pri novoy koronavirusnoy infektsii. [Modern ideas about the mechanisms of arterial thrombosis]. Russian Biomedical Research. 2024;8(3):61–68. DOI: 10.56871/RBR.2023.85.16.008. (in Russian).
13. Makatsariya A.D., Vorob'yev A.V., Karapetyan L.G., Solopova A.G. Trombofiliya i problemy profilaktiki trombozov u onkologicheskikh bol'nykh. [Thrombophilia and problems of thrombosis prevention in cancer patients]. Zh. akush. i zhen. bolezn. 2012;6:3–17. URL: https://cyberleninka.ru/article/n/trombofiliya-i-problemy-profilaktiki-trombozov-u-onkologicheskih-bolnyh. (in Russian).
14. Machabeli M.S. Trombogemorragicheskiy sindrom. [Thrombohemorrhagic syndrome]. Zh. Problemy gematologii i perelivaniya krovi. 1981;1:48–54.(in Russian).
15. Momot A.P., Nikolayeva M.G., Serdyuk G.V., Grigor'yeva Ye.Ye., Akker L.V. Rol' trombogennykh DNK-polimorfizmov v vybore metoda kontratseptsii. [The role of thrombogenic DNA polymorphisms in the choice of contraceptive method]. Vestnik RUDN. Seriya: Meditsina. 2009;7:239–248. URL: https://cyberleninka.ru/article/n/rol-trombogennyh-dnk-polimorfizmov-v-vybore-metoda-kontratseptsii. (in Russian).
16. Panteleyev M.A., Sveshnikova A.N. Trombotsity i gemostaz. [Platelets and hemostasis]. Onkogematologiya. 2014;2:65–73. URL: https://cyberleninka.ru/article/n/trombotsity-i-gemostaz. (in Russian).
17. Patofiziologiya. [Pathophysiology]. Uchebnik: v 2 t. Pod red. V.V. Novitskogo, Ye.D. Gol'dberga, O.I. Urazovoy. 4-ye izd., pererab. i dop. Moskva.: GEOTAR-Media Publ. 2009;2. (in Russian)
18. Vasil'yev A.G., Vlasov T.D., Galagudza M.M.red. Patofiziologiya. Tipovyye patologicheskiye protsessy i sostoyaniya. [Pathophysiology. Typical pathological processes and conditions]. Uchebnik dlya studentov meditsinskikh vuzov. Sankt-Peterburg: SPbGPMU Publ.;2023. (in Russian).
19. Serebryanaya N.B., Shanin S.N., Fomicheva Ye.Ye., Yakutseni P.P. Trombotsity kak aktivatory i regulyatory vospalitel'nykh i immunnykh reaktsiy. Chast' 1. Osnovnyye kharakteristiki trombotsitov kak vospalitel'nykh kletok. [Platelets as activators and regulators of inflammatory and immune reactions. Part 1. Basic characteristics of platelets as inflammatory cells]. Meditsinskaya immunologiya. 2018;6:785–796. URL: https://cyberleninka.ru/article/n/trombotsity-kak-aktivatory-i-regulyatory-vospalitelnyh-i-immunnyh-reaktsiy-chast-1-osnovnye-harakteristiki-trombotsitov-kak. (in Russian).
20. Serebryanaya N.B., Shanin S.N., Fomicheva Ye.Ye., Yakutseni P.P. Trombotsity kak aktivatory i regulyatory vospalitel'nykh i immunnykh reaktsiy. Chast' 2. Trombotsity kak uchastniki immunnykh reaktsiy. [Platelets as activators and regulators of inflammatory and immune reactions. Part 2. Platelets as participants in immune reactions]. Meditsinskaya immunologiya. 2019;1:9–20. URL: https://cyberleninka.ru/article/n/trombotsity-kak-aktivatory-i-regulyatory-vospalitelnyh-i-immunnyh-reaktsiy-chast-2-trombotsity-kak-uchastniki-immunnyh-reaktsiy. (in Russian).
21. Schastlivtsev I.V., Lobastov K.V., Tsaplin S.N., Mkrtychev D.S. Sovremennyy vzglyad na sistemu gemostaza: kletochnaya teoriya. [Modern view of the hemostasis system: cellular theory]. Meditsinskiy Sovet. 2019;16:66–71. URL: https://cyberleninka.ru/article/n/sovremennyy-vzglyad-na-sistemu-gemostaza-kletochnaya-teoriya. (in Russian).
22. Churilov L.P. Obshchaya patofiziologiya (s osnovami immunopatologii). [General pathophysiology (with the basics of immunopathology)]. Uchebnik dlya studentov medVUZov. Izdaniye 5-ye. Sankt-Peterburg: ELBI-SPb Publ.; 2015. (in Russian).
23. Shiffman F.Dzh. Patofiziologiya krovi. [Pathophysiology of blood]. Per. s angl. N.B.Serebryanaya, V.I.Solov'yev. Moskva: BINOM Publ.; 2020. (in Russian).
24. Shcheglov D.V., Nosenko N.N., Konotopchik S.V., Chebanyuk S.V. Nasledstvennaya gemorragicheskaya teleangiektaziya, ili bolezn' Oslera-Rendyu-Vebera. [Hereditary hemorrhagic telangiectasia, or Osler-Rendu-Weber disease]. Ukraíns'ka ínterventsíyna neyroradíologíya ta khírurgíya. 2016;1(15):73–86. URL: https://cyberleninka.ru/article/n/nasledstvennaya-gemorragicheskaya-teleangiektaziya-ili-bolezn-oslera-rendyu-vebera. (in Russian).
25. Yakimenko A.O., Sveshnikova A.N., Artemenko Ye.O., Panteleyev M.A. Etot zagadochnyy trombotsit. [This mysterious platelet]. Priroda. 2014;2:3–9. (in Russian).
26. Aliotta A., Bertaggia Calderara D., Zermatten M.G., Marchetti M., Alberio L. Thrombocytopathies: Not Just Aggregation Defects-The Clinical Relevance of Procoagulant Platelets. J Clin Med. 2021;10(5):894. DOI: 10.3390/jcm10050894.
27. Bick R.L. Hereditary and acquired thrombophilic disorders. Clin Appl Thromb Hemost. 2006;12(2):125–35. DOI: 10.1177/107602960601200201.
28. Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. Clin Appl Thromb Hemost. 2001;7(3):178–94. DOI: 10.1177/107602960100700302.

29. Holinstat M. Normal platelet function. Cancer Metastasis Rev. 2017;36(2):195–198. DOI: 10.1007/s10555-017-9677-x.
30. Hsu C., Hutt E., Bloomfield D.M., Gailani D., Weitz J.I. Factor XI Inhibition to Uncouple Thrombosis From Hemostasis: JACC Review Topic of the Week. J Am Coll Cardiol. 2021;78(6):625–631. DOI: 10.1016/j.jacc.2021.06.010.
31. Lozano R., Naghavi M., Foreman K., Lim S., Shibuya K., Aboyans V., Abraham J., Adair T., Aggarwal R. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128. DOI: 10.1016/S0140-6736(12)61728-0. Erratum in: Lancet. 2013;381(9867):628.
32. Michelson A.D. Platelets. 3rd ed. San Diego: Elsevier/Academic Press; 2013.
33. Monroe D.M, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol. 2006;26:41–48.
34. Noubouossie D.F., Reeves B.N., Strahl B.D., Key N.S. Neutrophils: back in the thrombosis spotlight. Blood. 2019;133(20):2186–2197. DOI: 10.1182/blood-2018-10-862243.
35. Nurden A., Nurden P. Advances in our understanding of the molecular basis of disorders of platelet function. J Thromb Haemost. 2011;9(1):76–91. DOI: 10.1111/j.1538-7836.2011.04274.x.
36. Papageorgiou C., Jourdi G., Adjambri E., Walborn A., Patel P., Fareed J., Elalamy I., Hoppensteadt D., Gerotziafas G.T. Disseminated Intravascular Coagulation: An Update on Pathogenesis, Diagnosis, and Therapeutic Strategies. Clin Appl Thromb Hemost. 2018;24(9):8S–28S. DOI: 10.1177/1076029618806424.
37. Popescu N.I., Lupu C., Lupu F. Disseminated intravascular coagulation and its immune mechanisms. Blood. 2022;139(13):1973–1986. DOI: 10.1182/blood.2020007208.
38. Riddel J.P. Jr., Aouizerat B.E., Miaskowski C., Lillicrap D.P. Theories of blood coagulation. J Pediatr Oncol Nurs. 2007;24(3):123–31. DOI: 10.1177/1043454206298693.
39. Sang Y., Roest M., de Laat B., de Groot P.G., Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021;46:100733. DOI: 10.1016/j.blre.2020.100733.
40. Versteeg H.H., Heemskerk J.W., Levi M., Reitsma P.H. New fundamentals in hemostasis. Physiol Rev. 2013;93(1):327–58. DOI: 10.1152/physrev.00016.2011.
41. Weisel J.W., Litvinov R.I. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost. 2019;17(2):271–282. DOI: 10.1111/jth.14360.

ЛИТЕРАТУРА

1. Алексеев В.В., Алипов А.Н., Андреев В.А. и др. Медицинские лабораторные технологии. Том 2. М.: ГЭОТАР-Медиа; 2013.
2. Бабичев А.В. Роль эндотелия в механизмах гемостаза. Педиатр. 2013;1:122–127. URL: https://cyberleninka.ru/article/n/rol-endoteliya-v-mehanizmah-gemostaza.
3. Баркаган З.С. Геморрагические заболевания и синдромы. 2-е изд., перераб. и доп. М.: Медицина; 1988.
4. Баркаган З.С. Клинико-патогенетические варианты, номенклатура и основы диагностики гематогенных тромбофилий. Проблемы гематологии и переливания крови. 1996;3:5–15.
5. Васильев А.Г., Морозова К.В., Брус Т.В., Забежинский М.М., Кравцова А.А., Балашов Л.Д., Васильева А.В., Пюрвеев С.С., Косова А.Н. Роль нарушений обмена гомоцистеина в патологических процессах. Российские биомедицинские исследования. 2022;1:44–59. URL: https://cyberleninka.ru/article/n/rol-narusheniy-obmena-gomotsisteina-v-patologicheskih-protsessah.
6. Грин Д., Ладлем К.А. Геморрагические заболевания и синдромы. Перевод с английского под ред. О.В. Сомоновой. Практическая медицина; 2014.
7. Горбачева И., Сычева Ю. Патология пародонта и артериальная гипертензия. Университетский терапевтический вестник. 2023;5(3):59–68. DOI: 10.56871/UTJ.2023.14.31.006.
8. Дёмина И.А., Кумскова М.А., Пантелеев М.А. Тромбоцитопатии. Российский журнал детской гематологии и онкологии. 2015;1:54–60. URL: https://cyberleninka.ru/article/n/trombotsitopatii.
9. Дондурей Е.А., Пшеничная К.И., Иванова И.А. Состояние системы гемостаза у детей с COVID-19. Педиатр. 2023;14(1):35–43. DOI: 10.17816/PED14135-43.
10. Дорофиенко Н.Н. Роль сосудистого эндотелия в организме и универсальные механизмы изменения его активности (обзор литературы). Бюл. физ. и пат. дых. 2018;68:107–116. URL: https://cyberleninka.ru/article/n/rol-sosudistogo-endoteliya-v-organizme-i-universalnye-mehanizmy-izmeneniya-ego-aktivnosti-obzor-literatury.
11. Каде А.Х., Занин С.А., Губарева Е.А., Туровая А.Ю., Богданова Ю.А., Апсалямова С.О., Мерзлякова С.Н. Физиологические функции сосудистого эндотелия. Фундаментальные исследования. 2011;11(3):611–617. URL: https://fundamental-research.ru/ru/article/view?id=29285.
12. Латыпов И., Пюрвеев С., Некрасов М., Деданишвили Н., Тагиров Н. Современные представления о механизмах артериального тромбоза. артериальный тромбоз при новой коронавирусной инфекции. Russian Biomedical Research. 2024;8(3):61–68. DOI: 10.56871/RBR.2023.85.16.008.
13. Макацария А.Д., Воробьев А.В., Карапетян Л.Г., Солопова А.Г. Тромбофилия и проблемы профилактики тромбозов у онкологических больных. Ж. акуш. и жен. болезн. 2012;6:3–17. URL: https://cyberleninka.ru/article/n/trombofiliya-i-problemy-profilaktiki-trombozov-u-onkologicheskih-bolnyh.
14. Мачабели М.С. Тромбогеморрагический синдром. Ж. Проблемы гематологии и переливания крови. 1981;1:48–54.
15. Момот А.П., Николаева М.Г., Сердюк Г.В., Григорьева Е.Е., Аккер Л.В. Роль тромбогенных ДНК-полиморфизмов в выборе метода контрацепции. Вестник РУДН. Серия: Медицина. 2009;7:239–248. URL: https://cyberleninka.ru/article/n/rol-trombogennyh-dnk-polimorfizmov-v-vybore-metoda-kontratseptsii.
16. Пантелеев М.А., Свешникова А.Н. Тромбоциты и гемостаз. Онкогематология. 2014;2:65–73. URL: https://cyberleninka.ru/article/n/trombotsity-i-gemostaz.

17. Патофизиология. Учебник: в 2 т. Под ред. В.В. Новицкого, Е.Д. Гольдберга, О.И. Уразовой. 4-е изд., перераб. и доп. М.: ГЭОТАР-Медиа. 2009;2.
18. Васильев А.Г., Власов Т.Д., Галагудза М.М., ред. Патофизиология. Типовые патологические процессы и состояния. Учебник для студентов медицинских вузов. СПб.: СПбГПМУ;2023.
19. Серебряная Н.Б., Шанин С.Н., Фомичева Е.Е., Якуцени П.П. Тромбоциты как активаторы и регуляторы воспалительных и иммунных реакций. Часть 1. Основные характеристики тромбоцитов как воспалительных клеток. Медицинская иммунология. 2018;6:785–796. URL: https://cyberleninka.ru/article/n/trombotsity-kak-aktivatory-i-regulyatory-vospalitelnyh-i-immunnyh-reaktsiy-chast-1-osnovnye-harakteristiki-trombotsitov-kak.
20. Серебряная Н.Б., Шанин С.Н., Фомичева Е.Е., Якуцени П.П. Тромбоциты как активаторы и регуляторы воспалительных и иммунных реакций. Часть 2. Тромбоциты как участники иммунных реакций. Медицинская иммунология. 2019;1:9–20. URL: https://cyberleninka.ru/article/n/trombotsity-kak-aktivatory-i-regulyatory-vospalitelnyh-i-immunnyh-reaktsiy-chast-2-trombotsity-kak-uchastniki-immunnyh-reaktsiy.
21. Счастливцев И.В., Лобастов К.В., Цаплин С.Н., Мкртычев Д.С. Современный взгляд на систему гемостаза: клеточная теория. Медицинский Совет. 2019;16:66–71. URL: https://cyberleninka.ru/article/n/sovremennyy-vzglyad-na-sistemu-gemostaza-kletochnaya-teoriya.
22. Чурилов Л.П. Общая патофизиология (с основами иммунопатологии). Учебник для студентов медвузов. Издание 5-е. СПб.: ЭЛБИ-СПб; 2015.
23. Шиффман Ф.Дж. Патофизиология крови. Пер. с англ. Н.Б. Серебряная, В.И.Соловьев. М.: БИНОМ; 2020.
24. Щеглов Д.В., Носенко Н.Н., Конотопчик С.В., Чебанюк С.В. Наследственная геморрагическая телеангиэктазия, или болезнь Ослера-Рендю-Вебера. Українська інтервенційна нейрорадіологія та хірургія. 2016;1(15):73–86. URL: https://cyberleninka.ru/article/n/nasledstvennaya-gemorragicheskaya-teleangiektaziya-ili-bolezn-oslera-rendyu-vebera.
25. Якименко А.О., Свешникова А.Н., Артеменко Е.О., Пантелеев М.А. Этот загадочный тромбоцит. Природа. 2014;2:3–9.
26. Aliotta A., Bertaggia Calderara D., Zermatten M.G., Marchetti M., Alberio L. Thrombocytopathies: Not Just Aggregation Defects-The Clinical Relevance of Procoagulant Platelets. J Clin Med. 2021;10(5):894. DOI: 10.3390/jcm10050894.
27. Bick R.L. Hereditary and acquired thrombophilic disorders. Clin Appl Thromb Hemost. 2006;12(2):125–35. DOI: 10.1177/107602960601200201.
28. Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. Clin Appl Thromb Hemost. 2001;7(3):178–94. DOI: 10.1177/107602960100700302.
29. Holinstat M. Normal platelet function. Cancer Metastasis Rev. 2017;36(2):195–198. DOI: 10.1007/s10555-017-9677-x.
30. Hsu C., Hutt E., Bloomfield D.M., Gailani D., Weitz J.I. Factor XI Inhibition to Uncouple Thrombosis From Hemostasis: JACC Review Topic of the Week. J Am Coll Cardiol. 2021;78(6):625–631. DOI: 10.1016/j.jacc.2021.06.010.
31. Lozano R., Naghavi M., Foreman K., Lim S., Shibuya K., Aboyans V., Abraham J., Adair T., Aggarwal R. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128. DOI: 10.1016/S0140-6736(12)61728-0. Erratum in: Lancet. 2013;381(9867):628.
32. Michelson A.D. Platelets. 3rd ed. San Diego: Elsevier/Academic Press; 2013.
33. Monroe D.M, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol. 2006;26:41–48.
34. Noubouossie D.F., Reeves B.N., Strahl B.D., Key N.S. Neutrophils: back in the thrombosis spotlight. Blood. 2019;133(20):2186–2197. DOI: 10.1182/blood-2018-10-862243.
35. Nurden A., Nurden P. Advances in our understanding of the molecular basis of disorders of platelet function. J Thromb Haemost. 2011;9(1):76–91. DOI: 10.1111/j.1538-7836.2011.04274.x.
36. Papageorgiou C., Jourdi G., Adjambri E., Walborn A., Patel P., Fareed J., Elalamy I., Hoppensteadt D., Gerotziafas G.T. Disseminated Intravascular Coagulation: An Update on Pathogenesis, Diagnosis, and Therapeutic Strategies. Clin Appl Thromb Hemost. 2018;24(9):8S–28S. DOI: 10.1177/1076029618806424.
37. Popescu N.I., Lupu C., Lupu F. Disseminated intravascular coagulation and its immune mechanisms. Blood. 2022;139(13):1973–1986. DOI: 10.1182/blood.2020007208.
38. Riddel J.P. Jr., Aouizerat B.E., Miaskowski C., Lillicrap D.P. Theories of blood coagulation. J Pediatr Oncol Nurs. 2007;24(3):123–31. DOI: 10.1177/1043454206298693.
39. Sang Y., Roest M., de Laat B., de Groot P.G., Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021;46:100733. DOI: 10.1016/j.blre.2020.100733.
40. Versteeg H.H., Heemskerk J.W., Levi M., Reitsma P.H. New fundamentals in hemostasis. Physiol Rev. 2013;93(1):327–58. DOI: 10.1152/physrev.00016.2011.
41. Weisel J.W., Litvinov R.I. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost. 2019;17(2):271–282. DOI: 10.1111/jth.14360.