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DISORDERS OF THE HEMOSTASIS SYSTEM IN ACUTE RESPIRATORY DISEASES OF THE LUNG.

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Omonov A.A. Axmedova S.N.
Tashkent Medical Academy

The lungs actively participate in the processes of coagulation and fibrinolysis. In particular, lung tissue is a rich source of factors for the coagulation and anti-coagulation systems of the blood. Thromboplastin, heparin, tissue plasminogen activator, prostacyclins, thromboxane A2, are synthesized in the lungs. Fibrinolysis occurs in the lungs, with the formation of fibrin degradation products (FDP). The lungs are capable of extracting from the bloodstream not only fibrin, but also its degradation products, which are excessively formed during DIC. Therefore, platelet-neutrophil interactions play an important role in recruiting neutrophils to the lungs during lung injury and ARDS.

Key words
Lungs, respiratory function, blood coagulation and fibrinolysis, bronchoalveolar thrombin, homeostasis.

НАРУШЕНИЯ СИСТЕМЫ ГЕМОСТАЗА ПРИ ОСТРЫХ ЗАБОЛЕВАНИЯХ ДЫХАНИЯ ЛЕГКИХ.

Omonov.A.A. Axmedova S.N.

Легкие активно участвуют в процессах коагуляции и фибринолиза. В частности, легочная ткань является богатым источником факторов свертывающей и противосвёртывающей систем крови. В легких синтезируются тромбопластин, гепарин, тканевой активатор плазминогена, простациклины, тромбоксан А2 и др. В легких осуществляется фибринолиз, с образованием продуктов деградации фибрина (ПДФ). Легкие способны извлекать из кровотока не только фибрин, но и продукты его деградации, избыточно образующиеся при ДВС-синдроме. Следовательно, взаимодействия тромбоцитов и нейтрофилов играют важную роль в привлечении нейтрофилов в легкие во время повреждения легких и ОРДС.

Ключевые слова

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Легкие, респираторная функция, кровь коагуляции и фибринолиза, бронхоальвеолярный тромбин, гомеостаз

The lungs perform not only the respiratory function but also participate in maintaining homeostasis in the body. In addition to the respiratory function of the lungs, it includes the following tasks: protection (90% of air pollutants are neutralized in the lungs - by the mucous membrane of the lungs, immunoglobulins, and alveolar macrophages), filtration (purification of blood from mechanical impurities), fibrinolytic and anticoagulation (maintaining hemostasis), participation in lipid metabolism (lipolysis of blood fats), synthesis of surfactants, maintaining water balance (removal of up to 500 ml of water per day through exhalation), synthesis of hormones and mediators (metabolism of serotonin, histamine, angiotensin, acetylcholine, norepinephrine), during detoxification (detoxification of xenobiotics), hemodynamics (blood storage, shunt between the right and left half of the heart), thermoregulation, absorption (inhalation route of drug administration), secretory function (secretion of serous mucous secretion) and others. The synthetic function activates the synthesis of heparin, as well as phospholipids, angiotensin-I, prostaglandins, and thromboxanes contained in the surfactant, which is part of the surfactant.

In the microcirculatory flow, the lungs metabolize kinins, angiotensin-1, prostaglandins, serotonin, and catecholamines, and also include an enzymatic function according to the speed of blood flow, depending on this function. Venous blood, passing through the lungs in the form of microcirculatory flow units, inactivates 80% of bradykinin, 60-98% of serotonin, 40% of norepinephrine, a significant amount of acetylcholine, up to 60% of endo- and exogenous kallikrein, protects the body from endogenous intoxication and vasoactive substances. Consequently, adrenaline, dopamine, and isoproterenol do not change, since they protect the body from endogenous intoxication.

The lungs take an active part in the processes of coagulation and fibrinolysis. In particular, lung tissue is a rich source of factors for the blood coagulation and anticoagulation systems. Thromboplastin, heparin, tissue plasminogen activators prostacyclins, thromboxane A2, etc. are synthesized in the lungs; fibrinolysis occurs in the lungs with the formation of fibrin degradation products (FDP).

Not only fibrin is removed from the pulmonary bloodstream, but its excess products of dissociated intravascular coagulation, consumptive coagulopathy, and thrombohemorrhagic syndrome (TICICTS syndrome) are also able to be separated.

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The consequences of overload or disruption of this function can be thromboembolic complications of the pulmonary artery and this can lead to excessive formation of fibrin degradation products (FDP) and damage to alveolar soft tissue sarcoma in the lungs (as a result of ASMT), resulting in the development of infiltrative inflammation and gas diffusion disorders [1].

In various lung diseases, not only the respiratory function of the lung is disrupted, but also its non-respiratory functions, in particular, the role of the lung in maintaining homeostasis. A clear confirmation of this is the COVID-19 pandemic, which manifested itself not only in acute respiratory distress syndrome and interstitial pneumonia but also in the development of hypercoagulable vasculitis with damage to the vascular endothelium. The leading role in the pathogenesis of these processes is due to a decrease in the corresponding immunity, damage to cells of organs and tissues the development of a systemic inflammatory reaction [2].

In the alveoli of the damaged lung, macrophages are activated and intensively synthesize cytokines such as interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), the latter induce the synthesis of IL-6, IL-8 and the chemotactic agent of monocytes. [3].

According to the authors, such systemic damage to the vascular endothelium increases the risk of developing cardiovascular diseases and pulmonary fibrosis. Thus, the main cells responsible for the development of fibrotic remodeling of the lung are myofibroblasts and their precursors [4]. They are carried out due to the production of a large number of inflammatory mediators: cytokines, chemokines, fibrogenic factors, blood coagulation proteins, oxidants, and regulators of apoptosis [5]. They determine changes in the hemostatic parameters of the lungs. Indeed, in the early stages of the disease, morphological studies of the lungs showed the presence of extensive necrosis of pneumocytes, swelling of endothelial cells, expansion of the intercellular space, and the formation of hyaline membranes from fibrin in the alveolar canals and air spaces. At later stages, massive infiltration of neutrophils and the formation of fibrin thrombi in the pulmonary arteries and alveolar capillaries are determined [6].

Under such conditions, a shift in the alveolar hemostatic balance occurs, which is manifested by an increase in procoagulant activity and bronchoalveolar contents against the background of a significant decrease in fibrinolytic activity due to the high concentration of fibrinolysis inhibitors in the lungs [6,7,8]. Cytokines are the main linking factors between changes in inflammation, blood coagulation, and fibrinolysis. Experiments have established that changes in endotoxin during

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bronchoalveolar coagulation and fibrinolysis are mediated by cytokines [9]. Administration of monoclonal antibodies against interleukin-6 (IL-6) completely abolished the activation of bronchoalveolar thrombin formation caused by endotoxins, indicating that the activation of bronchoalveolar coagulation is dependent on IL-6.

It should be noted that the activation of coagulation during pneumonia is a physiological process that involves inflammatory activity or even infection of the site of injury. However, coagulopathy caused by pulmonary inflammation may worsen lung damage and thus lead to disease progression. According to the literature, dysregulation of NF-κB (transcription factor NF-κB is a universal transcription factor that controls the expression of immune response, apoptosis, and cell cycle genes) as a result of direct stimulation of tissue factor (TF) activation and inflammation causes autoimmune diseases [10]. On the other hand, coagulation of bronchoalveolar inflammation can have a negative impact. In particular, coagulation leads to the formation of proteases, their interaction with specific cellular receptors, and activation of intracellular signaling pathways [11].

The resulting TF-FVIIa (TF binds to FVII and forms the TF/FVIIa complex. This complex activates FX and FIX locally on the surface of cells bearing TF) directly activates the inflammatory process or indirectly through factor-Xa (O-Xa), increases thrombin formation, and fibrin. At the same time, the production of chemokines and vascular endothelial growth factor increases, which leads to changes in vascular permeability [12].

It should be noted that thrombin and thromboxane A2, synthesized in lung tissue, activate platelets, which leads to a wide range of cellular reactions that contribute to the development of lung damage [13]. Therefore, the interaction of platelets and neutrophils is important in lung injury and acute respiratory distress syndrome (ARDS), as well as in adult respiratory distress syndrome (ARDS) (a type of respiratory failure. Neutrophils in ARDS play an important role in lung recruitment). The physiological role of fibrin is to regulate the inflammatory response and restore the structure and function of damaged tissues. However, its significant accumulation has a direct anti-inflammatory effect on the lungs. According to the literature, the binding of fibrin to monocytes activates the transcription factor and activates protein-I, which regulates the production of cytokines [14], and the interaction of fibrin with monocytes and fibroblasts stimulates cell migration, enhances the inflammatory response, and causes pulmonary fibrosis. [1].

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Studies by several authors have shown that fibrin directly impairs lung function, inactivates surfactant reduces the elasticity of the lungs, and also causes atelectasis [15]. Activation of coagulation in the lungs begins with an increase in TF, which is constantly and abundantly present in the lungs [16]. Proinflammatory cytokines and activated macrophages also become sources of tissue factor [17]. Increased lung tissue damage leads to alveolar activation of thrombin and coagulation factor VII (FVII) [18]. Thrombin generation induced by TF is poorly controlled by physiological anticoagulant mechanisms in the lungs because little protein C is synthesized in the lungs. It is a physiological anticoagulant, its active form can bind to protein C and release coagulation factors Va and VIIIa. Activated protein C not only increases the physiological antithrombotic activity of the blood but also has pronounced anti-inflammatory and anti-apoptotic activity [19]. Autoimmune polyglandular syndromes (APS) against the background of lung damage (primary damage to 2 or more peripheral endocrine glands by an autoimmune process, usually leading to their failure, often combined with various organ-specific non-endocrine diseases) production capacity is significantly reduced. On the other hand, activated neutrophils can intensively decompose, detecting their deficiency under the action of elastase. [20].

Another important mechanism of C protein reduction is an increase in soluble thrombomodulin levels. Normally, it is located in the membrane of endothelial cells, captures thrombin circulating in the blood, and binds it, thereby accelerating the activation of protein C. At the same time, normally the amount of antithrombin in the lungs is low, and its increase during inflammation leads to an even greater deficiency [7].

Plasminogen activator inhibitor-1 (PAI-1). The polymorphism is associated with the presence of a DNA region containing 4G or 5G in the promoter region of the PAI-1 gene, which is known to be an inhibitor of urokinase plasminogen activator, which cleaves plasminogen to plasmin. As a result, it participates in the breakdown of the extracellular matrix together with matrix metalloproteinases. In patients with pneumonia, a high concentration of PAI-1 was noted in bronchoalveolar lavage (BAL) (Bronchoalveolar lavage (BAL)), which leads to inhibition and increased fibrinolytic activity, despite an increase in the production of bronchoalveolar fibrin [1].

Analysis (BAY) in patients with pneumonia and acute respiratory distress syndrome (ARDS) shows activation of coagulation and inhibition of fibrinolysis, which is associated with the severity of inflammation [21]. Elevated levels of PAI-1 are also associated with higher mortality in patients with ARDS [7].

Thus, fibrin deposition in inflammatory lung diseases is characteristic of lung injury from a variety of causes, including ARDS in COVID-19 and possibly lung injury secondary to systemic inflammation. TF-FVIIa-mediated activation of blood coagulation is insufficiently counteracted by local natural inhibitors of blood coagulation and simultaneous suppression of fibrinolysis, resulting in an abnormal state of fibrin metabolism. Lung damage can be aggravated by various mechanisms, such as the interaction of proteases with specific cells, and receptors, as well as direct activation of TF-FVIIa, FXa, thrombin, and fibrin, and indirectly this leads to a massive flow of biologically active substances into the lungs. Substances, activated blood coagulation factors, coagulation and fibrinolysis products, microthrombi, and cellular aggregates enter the arterial bloodstream. In this case, the entire process stimulates the body's immunoreactive response ("cytokine" storm, activating macrophages, platelets, and endothelial cells); generalization occurs; the process is observed with the development of multiple organ failure as a result of a systemic inflammatory reaction. In therapy, taking into account the use of the above anticoagulant, in addition to providing an anti-inflammatory effect, it can be one of the therapeutic targets for coronavirus infection. The challenge in this situation is that it would be worthwhile to study the effect of anticoagulant interventions on clinically relevant cardiorespiratory parameters.

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