# INVOLVEMENT OF THE LUNGS IN THE HEMOSTATIC SYSTEM AND ITS DISORDERS IN ACUTE RESPIRATORY DISEASES

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The lungs perform not only a respiratory function, but also participate in maintaining homeostasis in the body. None дыхательным функциям-respiratory functions of the lungs include:protective (90% of90% aeropollutants are neutralized in the lungsby pulmonaryslugs,immunoglobulins and alveolar macrophages), filtration (purificationofение bloodand mechanical impurities), фибринолитическаяfibrinolytic and anticoagulant (maintenance of hemostasis), participation in lipid metabolism (лlipolysis of fats, blood), синтез surfactantsynthesisп, water balance maintenance (removal of up to 500 ml of water per day with exhaled air),hormone and neurotransmitter synthesis (exchange of serotonin, histamine, angiotensin, acetylcholine, norepinephrine), detoxification (neutralization of xenobiotics),hemodynamic (blood reservoir, shunt between the right and left sides halves of the heart), t-thermoregulation, b-suction (andthe inhalation route of drugadministration), c-secretory (isolation fromerosive-mucosaloro secreta), and others. The synthetic function consists in the synthesis , of heparin, phospholipidsincluded in the surfactant, activation of angiotensin I, prostaglandins, and thromboxanes. In the microcirculatory bed of the lungs, kinins, angiotensin-1, prostaglandins, serotonin, and catecholamines are metabolized, and this function depends on the blood flow rate and the microcirculatory units included in the enzymatic function. When venous blood passes through the lungs, about 80% of bradykinin, 60-98% of serotonin, 40% of norepinephrine, a significant amount of acetylcholine, up to 60%of endo - and exogenous kallikrein are inactivated, protecting the body from endogenous intoxication and from the action of vasoactive substances, whileaminalin, dopamineамин and isoproterenol do not change.

The lungs are actively involved in the processes of coagulation and fibrinolysis. In particular, thelung tissue is a rich source of blood clotting and anticoagulant factors. Thromboplastin, heparin, tissue plasminogen activator, prostacyclines, thromboxane Aa2 , etc. are synthesized in the lungs. In the lungs, fibrinolysis is carriedout, with the formation of fibrin degradation products (PDF). The lungs are able to extract not only fibrin from the bloodstream,but also its degradation products, which are excessively formed in DIC. The consequences of overloading or insufficiency of this function can be thromboembolic complications of the pulmonary artery), and excessive PDF formation leads to damage to

the ACM and the development of infiltrative-inflammatory disorders in the lungs, impaired gas diffusion [1].

In various lung diseases, not only the respiratory function of the lungs will naturally be disrupted, but also внедыхательныеits non-respiratory functions, in particular the role of the lungs in maintaining homeostasis. A vivid confirmation of this is the COVID-19 pandemic, which was manifested not only by the development of acute respiratory distresssyndrome, interstitial pneumonia, but also by hypercoagulation with vascular endothelial damage and the development of vasculitis. In the pathogenesis of these lesions, the leading role belongs to damage to organs and tissues by immune system cells and the development of a systemic inflammatory response [2]. Cytokines such as interleukin-1b (IL-1b) and tumor necrosis factor-α (TNF-α) are intensively synthesized in activated alveolar macrophages of damaged lungsTNF. They induce the synthesis of IL-6, IL-8, and monocyte chemotactic factor [3]. According tothe authors, such a systemic lesion of the vascular endothelium increases the risk of developing cardiovascular catastrophes and фиброзированиялung fibrosis. Similar changes were observed in fibrosing alveolites. Thus, the main cells responsible for the development of lung fibrotic rearrangement are myofibroblasts and their precursors [4]. They are mediated by the production of a large number of inflammatory mediators: cytokines, chemokines, fibrogenic factors, coagulation proteins, oxidants, and apoptosis regulators [5]. They determine changes in the hemostatic parameters of the lungs. Indeed, morphological studies of the lungs in the initial stages of the disease showed the presence of extensivex necrosis of pneumocytes, swelling of endothelial cells with expansion of intercellularoro spacesa, and the formation of hyaline membranes from fibrin in the alveolar ducts and air spaces. At later stagesвыявляется, massive neutrophil infiltration and the formation offibrin x thrombiin the pulmonary arteries and alveolar capillaries are detected [6]. Under these conditions, there is a shift in the alveolar hemostatic balance, which is manifested by an increase in the procoagulant activity of the bronchoalveolar content, against the background of a noticeable decrease inой fibrinolyticactivity and due to a highой concentration of fibrinolysis inhibitors in the lungs [6,7,8]. Cytokines are the main binding factors between inflammation, blood clotting changes, and fibrinolysis. A similar mediating role of cytokines in endotoxin-induced changes in bronchoalveolar coagulation and fibrinolysis was established in experiments [9]. The introduction of monoclonal antibodies against interleukin-6 (IL-6) completely eliminated the endotoxin-induced activation of bronchoalveolar thrombin formation, which indicates that the activation of bronchoalveolar coagulation depends on IL-6. It should be said that the activation of coagulation in inflammation is a physiological process that helps to restrain inflammatory activity or even infection at the site of injury. However, coagulopathy, caused by pneumonia can worsen lung damage and thus contribute to the progression of the disease. According to the literature, NF-kB dysregulation as a result of direct stimulation of TF activation, it causes inflammation and autoimmune diseases [10]. On the other hand, coagulation itself can affect bronchoalveolar inflammation. 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 complex increases inflammation directly or indirectly through the formation of PCa, thrombin, and fibrin. Along with this, the productionя of chemokines and vascular endothelial growth factor increases, causing иchanges in vascular permeability [12]. It should be noted that thrombin and thromboxanea2 synthesized by the lung tissue2activate platelets, which leads to a wide range of cellular responses, contributing to the development of lung damage [13].

Therefore, platelet-neutrophil interactions play an important role in attracting neutrophils to the lungs during lung damage and ARDS. The physiological role of fibrin is to regulate the inflammatory response, restore the structure and function of damaged tissues. At the same time, a significant accumulation of it in the lungs has a direct pro-inflammatory effect. According to the published data,binding of fibrin to monocytes activates фактор transcription factorи and activator protein 1,which regulate cytokine production [14], and the interaction of fibrin with monocytes and fibroblastsstimulates cell migration, enhances the inflammatory response и, andleads to lung fibrosis [1]. Studies by several authorshave shown that fentrin directly impairs lung functionет , inactivates surfactant and leads to loss of lung elasticity, as well as atelectasis [15].

Activation of coagulation in the lungs is initiated by an increased release of TF, which is constantly and in large quantities present in the lungs [16].

Proinflammatory cytokines and activated macrophages are also sources of tissue factor [17]. Increased destruction of lung tissue leads to activation of alveolar thrombin and coagulation factor VII (CVII) свертывания крови [18]. TF-induced thrombin formation is poorly controlled by physiological anticoagulant mechanisms in the lungs, since LHегкие в незначительных количествах can synthesize protein C in small amounts. протеин CIt is a physiologicallyactive anticoagulant and its active form is capablea of binding to protein S and cleaving coagulation factors Va and VIIIa. Activated protein C provides not only physiological antithrombotic activity of the blood, but also has a pronounced anti-inflammatory and anti-apoptotic activity [19]. In conditions of lung damage, the ability to produce APS is significantly reduced, on the other hand, it can be intensively cleaved under the action of activated neutrophil elastase, determining its insufficiency

[20]. Another important mechanism for reducing protein C is an increase in the level of soluble thrombomodulin. Normally, it is located on the membrane of endothelial cells, captures thrombin from the circulating blood and binds it, thereby accelerating the activation of protein C. Along with this в норме в легких , the antithrombin content in the lungs is normally low, and its increased consumption during inflammation leads to an even greater deficit [7].

PAI-1 is knownтором to be an inhibitor of the plasminogen activator urokinase, whichcleaves plasminogen to form plasmin. Thelatter, together with matrix metalloproteinases, participates in the degradation ofthe extracellular matrix. In patients

with pneumonia, a high concentration of PAI-1 is observed in BA, which leads to inhibition of fibrinolytic activity,despite the increased production of bronchoalveolar fibrin [1].

Analysis of BA in patients with pneumonia and ARDS shows increased activation of coagulation and inhibition of fibrinolysis, which correlate with the severity of inflammation [21].Higher PAI-1 levels are also associated with higher mortality in patients with ARDS [7].

Thus, in inflammatory lungdiseases, fibrin deposition is inherent in lung damage for various reasons, including ARDS in COVID-19, and possibly as a secondarye повреждениelung injury, in relation to systemic inflammation. Activation of coagulation mediated by TF-FVIIa, which is insufficiently counteracted by local natural coagulation inhibitors and simultaneous suppression of fibrinolysis, leads to abnormal fibrin exchange. Lung damage can be aggravated by various mechanisms, such as blood clotting proteases interacting with specific cellular receptors, as well as direct опосредованныеand indirect effects of TF-FVIIa, PCa, thrombin and fibrin, which leads to a massive influx of biologically active substances, activated clotting factors, coagulation and fibrinolysis products, microthrombi, etc. into the arterial bloodstream. cellular aggregates. And the whole process stimulates иммунореактивныйthe body's immunoreactive response (a "cytokine" storm that activates macrophages, platelets, and endothelial cells). The process is generalized with the development of a systemic inflammatory response and multiple organ failure. Given the above, the use of anticoagulant therapy, in addition to having an anti-inflammatory effect, may be one of the therapeutic targets for coronavirus infection. The difficulty here is that it seems appropriate to study the effect of anticoagulant interventions on clinically significant cardio-respiratory parameters.

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