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# Pulmonary Oedema: Physiology of Lung Circulation, Pathophysiology of Pulmonary Oedema

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**ABSTRACT**

In modern medical practice, there are several clinical forms of pulmonary edema: cardiogenic and non-cardiogenic pulmonary edema, acute lung injury, acute respiratory distress syndrome, neurogenic pulmonary edema. Blood transport is facilitated by low pressure in the circulatory system and relatively low vascular resistance to blood flow. In an extremely short time, which does not exceed 1 s, the diffusion of oxygen and carbon dioxide occurs, i.e. one of the main functions of the lungs is realized — gas exchange. Another important function of pulmonary circulation is the release and metabolism of a large group of mediators involved in the most diverse processes of the human body.

***KEYWORDS:*** *The morphological organization of lung tissue and pulmonary circulation play an important role in the regulation of water and electrolyte balance*

These three functions of pulmonary circulation: gas exchange, regulation of electrolyte and water metabolism, as well as participation in the metabolism of biologically active substances are closely interrelated and complement each other. The pressure in the extraalveolar vessels is also affected by hyperinflation of the lung tissue and changes in the elastic traction of the lungs. Alveolar vessels are mainly capillaries; anatomically they are located in the interalveolar septa. They are surrounded by alveoli, and the pressure in them has a hemodynamically significant effect on capillary perfusion. Increased pressure in the alveoli leads to the effect of capillary compression. Corner vessels are part of the thickened part of the interalveolar septum and are located between 3 alveoli. This type of capillaries is not affected by the pressure in the alveoli, thus, the perfusion of the capillary network is preserved, even if the pressure in the alveolar space is increased. It should be emphasized that with the development of emphysema, which is accompanied by an increase in dead space, there is a significant increase in resistance in alveolar vessels, while resistance decreases in extraalveolar vessels. The resistance in the pulmonary vessels is influenced by the viscosity of the blood flowing through the small circulation. Viscosity also affects the ability of erythrocytes to deform (deformability), which is of great importance in the mechanisms of gas diffusion. Thus, blood viscosity is a factor influencing the pressure in the pulmonary artery, the formation of resistance in the pulmonary vessels, the diffusion capacity of the lungs. Compliance of the vessels of the small circulatory circle is characterized as very high. About 10% of the circulating blood in the human body falls on the small circle of blood circulation. Blood is distributed between the arteries, capillaries and veins. There are about 75 ml of blood in the capillaries, which is from 10 to 20% of the blood that is currently in the small circle of blood circulation. However, the amount of blood in the capillaries can increase to 200 ml or more. The relationship between pressure and blood volume in the vessels of the lungs is linear, but this nature of the relationship changes with increasing pressure, and it already becomes nonlinear. Small diameter vessels play a leading role in the formation of pulmonary circulation compliance. This physiological process is controlled by sympathetic activity. With an increase in sympathetic activity, compliance decreases. The filling of blood vessels and its circulation depends on the anatomical location in the lungs. Thus, in the upper apical parts of the lungs, with an increase in transmural pressure, blood circulation occurs, while in the basal parts of the lungs, blood vessels are filled with blood. Wet remote wheezing is initially localized in the upper parts of the lungs, and subsequently, when the clinical picture of pulmonary edema is expanded, they spread to the middle and lower parts of the lungs. The tone of the pulmonary vessels is very sensitive to oxygen tension. In alveolar hypoxia, when the oxygen tension in the alveoli is below 70 mmHg, a typical vasoconstrictor reaction is caused. An increase in resistance in the vascular system of the lungs is associated with constriction of precapillary vessels. This is the difference between the vessels of the small circle of blood circulation from the vessels of the large circle, which respond to hypoxia with the effect of dilation. The constrictor reaction of the precapillary vessels of the lungs is a phenotypic property of the smooth muscles of these vessels. An attempt to explain this reaction from the perspective of the role of peptidergic nerves or the axon reflex did not yield results. The role of a large group of biologically active substances is being actively studied: catecholamines, histamine, serotonin, angiotensin II, thromboxane, leukotriene C4, platelet activation factor, and the role of nitric oxide is also being investigated. In clinical practice, it has been shown that the vasoconstrictor reaction decreases with the appointment of nitroglycerin and inhalations of nitric oxide. However, it was not possible to find a mediator or isolate the leading mechanism of stimulation of nervous activity. Currently, the main explanation is the hypothesis of the direct effect of hypoxia on the function of muscle fibers through inhibition of potassium and calcium channels. Calcium channels open under conditions of hypoxia, and calcium accumulates in the muscle fibers of the arteries of the small circulatory circle. The calcium theory is based on its increased concentration in vascular smooth muscles. Calcium leads to phosphorylation of myosin and vasospastic reactions. Pulmonary edema is defined as a condition for which a characteristic feature is the process of accumulation of water in the extravasal space of the lungs. When water fills the alveoli (alveolar phase of pulmonary edema), pulmonary edema is accompanied by severe arterial hypoxemia. A gravimetric method was used to study the water content in the lung tissue. It exceeds 80% of the total weight of the lungs. With pulmonary edema, water initially accumulates in the interstitial lung tissue, and in cases of further disruption

of water-electrolyte metabolism in the lungs, water is soaked to the surface of the alveoli. The formalization of water exchange in lung tissue is achieved using the law described by Starling, known as the Starling hypothesis. According to the modified Starling formula, the accumulation of fluid in the intervascular space will occur in the event of an increase in hydrostatic pressure inside the capillaries. However, this mechanism will be implemented provided that there is no compensated increase in hydrostatic pressure in the interstitial tissue. In cases of deterioration of the integrity of the endothelial capillary cover, as occurs with the development of respiratory distress syndrome, fluid, electrolytes and proteins will flow into the alveolar space. These pathological changes lead to gross violations of the gas exchange function of the lungs, which is the cause of the development of acute hypoxemia. Recently, much attention has been paid to the study of the mechanisms of protein impregnation into the alveolar space. Oncotic pressure plays an important role in the passage of proteins through the semipermeable basement membrane of the alveoli. With an increase in the permeability of the membrane, albumin in large quantities will enter the alveolar space. Lipid-insoluble molecules (which are proteins) are retained by the pores of endothelial cells. The molecular weight above 60 kDa prevents the passage of molecules through the pores. An electric charge plays an important role. The endothelial cells of the pulmonary capillaries are negatively charged, which affects the diffusion of compounds with the opposite charge. It should be emphasized that endothelial cells represent a vast surface and are the place where filtration and diffusion are carried out. Several ways through which water and electrolytes are transported are described: vesicles, interendothelial connections, transendothelial channels. Compounds with low molecular weight are lipid-soluble (lipophilic), and their diffusion with water is carried out directly through endothelial cells (the transcellular diffusion pathway). Lipophilic molecules such as oxygen and carbon dioxide diffuse directly across the entire surface of capillary endothelial cells. Most lipid-insoluble molecules cannot penetrate the barrier of epithelial cells. Water and ions can pass through this barrier in a limited amount, while lipid-soluble molecules, such as oxygen and carbon dioxide, freely diffuse through this barrier. Fundamentally new information was obtained on the study of the role of the epithelium of the distal respiratory tract in the active transport of ions and water of the alveolar space. In experimental models of pulmonary edema, it was shown how epithelial cells of the distal respiratory tract regulate the movement of salt and water ions (Matthay and Folkesson) [4]. The main mechanism of movement of electrolytes through the epithelial cover is carried out due to osmotic transport of water. Changes in the hydrostatic and oncotic pressure of blood vessels do not affect the level of active ion transport carried out by epithelial cells. The transport of electrolytes is influenced by pharmacological substances that inhibit the transport of sodium through the membrane of epithelial cells. On an isolated culture of epithelial cells of the distal part, their role in osmotic water transport was shown. The clearance of electrolytes and proteins is not carried out simultaneously. With pulmonary edema, the reabsorption process begins with water and salt solution ions, so the protein concentration increases. Clearance of albumin from the respiratory tract is considered as a prognostic sign of acute lung injury. Ware and Matthay [5] showed that the average clearance of the alveolar fluid is 6 hours. The same authors have shown that endogenous and exogenous catecholamines do not affect the clearance rate of the alveolar fluid. Pulmonary lymphatic vessels are represented by a dense network. They perform the function of a drainage system that specialized in the removal of fluid, electrolytes; through the system of lymphatic vessels, the traffic of lymphocytes and other shaped blood elements is carried out. Terminal sections of the lymphatic system can be found in the tissue surrounding the pulmonary vessels, as well as in the thickened part of the interalveolar septa. The fluid enters the lymphatic vessels from the interstitium due to the concentration gradient of soluble compounds. The pulmonary lymph flow increases with an increase in fluid in the interstitial tissue, i.e. with an increase in hydrostatic pressure in the intercellular space (modified Starling's law). However, it should be emphasized that there is no linear relationship between the lymph flow and the pressure level in the interstitial tissue. With the development of pulmonary edema, the insufficiency of the drainage function of the lymphatic system plays a pathogenetic role in the fact that it is not possible to compensate for the hydrostatic pressure of the interstitial tissue. An increase in compliance occurs when the hydrostatic pressure of the interstitial tissue increases, which can be considered as a certain mechanism for protecting the alveolar space from possible accumulation of water on its surface. The main mechanism through which albumin is transported is associated with specific receptors located on the surface of endothelial cells. Albumin binds to the receptor and is transported in dissolved form through endothelial cells by means of a transcytotic mechanism. When albumin binds to the receptor, tyrosine kinase is activated, which activates the formation of vesicles and its further transport through the cell. Albumin clearance, which is determined in the lumen of the respiratory tract in pulmonary edema, has a prognostic value in assessing the severity and outcomes of this syndrome. Many mechanisms are involved in vascular permeability. It is necessary to emphasize the morphological changes that occur with acute lung damage and the subsequent development of pulmonary edema. They relate primarily to the occurrence of rupture sites of endothelial cells. These changes indicate deep confirmation changes in the endothelial cover of the alveolar capillaries. The appearance of these morphological changes is considered as a cardinal sign of the inflammatory process leading to the development of a shock lung. The organization of the basement membrane and extracellular matrix surrounding the endothelial cells of the alveolar capillaries plays an important role in regulating the movement of electrolytes, as well as albumin. Albumin transport is reduced primarily because glucosaminoglycan has a negative charge. In vivo studies have shown that the interstitial matrix reduces the diffusion transport of albumin by 14 times (Fox and Way land). Integrins play an important role in the permeability of the basement membrane, which are associated with local adhesion effects of various molecules. This process can lead to disruption of the barrier function of the basement membrane, which, in particular, is observed in acute lung damage. Despite the progress made in the study of molecular and cellular mechanisms, the violation of which is associated with increased vascular permeability and the development of pulmonary edema, the process of restoring the barrier function of endothelial cells of alveolar capillaries remains an area of little study. Mechanical stress of the lung tissue caused under experimental conditions leads to an increase in vascular permeability. The breakdown of the

permeability of the pulmonary vascular barrier occurred when stretched by a force of 1 to 10 din / cm2. The compensatory reaction was manifested in an increase in the intracellular concentration of cyclic AMP, which is able to inhibit the effects of thrombin and histamine. With an increase in the concentration of cyclic AMP in the endothelial cells of the alveolar capillaries, its barrier function increased, and the degree of edema severity decreased. The surfactant plays a pathogenic role in the mechanisms of pulmonary edema; its degradation occurs with acute lung injury; it can be considered as a medicinal agent in the treatment of patients with acute respiratory distress syndrome. There is a certain sequence in the development of pulmonary edema. At the first stages, the area of the lung roots is involved in the pathological process of pulmonary edema development, subsequently interstitial tissue and, finally, water, electrolytes and proteins fill the alveolar surface. The pressure gradient in pulmonary circulation has a vertical dependence. In this regard, the small circle of blood circulation differs from other organs and systems of the human body. Thus, indicators of hydrostatic pressure of vessels and interstitial tissue, pressure in the pleural cavity and pulmonary volumes in different parts of the lungs have different indicators. The distribution of water in the lung tissue is also differentiated depending on the characteristics of regional hemodynamics and ventilation. The pressure gradient in the alveolar-septal region of the adventitia microvessels is greatest in the apical part of the lungs, so the accumulation of water in this part of the lungs is greatest. This has clinical significance: for example, wet wheezing, which appears with the development of pulmonary edema, initially appears in the upper parts of the lungs. The appearance of wet wheezing in this part of the lungs indicates that the interstitial phase of pulmonary edema has passed into the alveolar one, which is more unfavorable. The fluid that has accumulated in the interstitial tissue cannot be removed by lymphatic vessels that perform a drainage function. Small diameter lymphatic vessels surround the microvascular system of the lungs and bronchioles. If the lymphatic vessels are not able to provide fluid transport from the interstitial tissue, then the phenomenon of "cuffs" appears around the vessels. In the initial stages, the accumulation of fluid by the lung tissue leads to a picture of focal changes, which is manifested during X-ray methods of lung examination. When fluid accumulates in the interstitial tissue from 35 to 50%, the fluid begins to penetrate the surface of the alveoli, alveolar pulmonary edema is formed. At this stage, there are significant disturbances in the diffusion of oxygen and carbon dioxide, which affects the increase in shortness of breath and a drop in oxygen saturation < 90%. The exact mechanism of the transition of the interstitial phase of pulmonary edema to the alveolar is unknown. However, great importance is attached to the transmission mechanisms. The pores open for the passage of water and electrolytes, the function of the channels is disrupted: the inhibition of potassium channels and the entry of calcium into the cytosol of the smooth muscles of the vascular wall. The manifestation of acute lung damage is interepithelial ruptures, which indicates gross violations in the barrier function of epithelial cells. A universal mechanism in the development of pulmonary edema is an increase in hydrostatic pressure in the capillaries of the alveoli (Starling's law). A certain hemodynamic dependence has been established. An increase in pressure in the left atrium (which can be extrapolated to jamming pressure) > 20-25 mmHg is considered critical: the probability of developing pulmonary edema is high. The mechanisms of protection that resist the development of pulmonary edema are: drainage function of the lymphatic system, resorption of water into vessels, drainage into mediastinal vessels, drainage into the pleural cavity, increased barrier function of the alveolar epithelium, reduction of surfactant tension forces, increased active transport of water and electrolytes from the distal respiratory tract. All of these mechanisms can counteract the release of water from the circulating blood in cases of increased pressure in the left atrium. A decrease in oncotic pressure is also one of the pathogenetic mechanisms of the development of pulmonary edema. A decrease in the concentration of proteins in plasma, which is observed with hypoalbuminemia, is accompanied by a reduction in absorption oncotic pressure in interstitial tissue. This mechanism leads to an increase in transcapillary fluid filtration, thus forming edematous syndrome. The appearance in the edematous fluid that collects during pulmonary edema on the surface of alveoli, macromolecules, leukocytes indicates profound pathological changes in the permeability of epithelial and endothelial cells. The morphological marker of these profound changes is the appearance of breaks in cellular connections. A complex of inflammatory mediators, reactive oxygen species, and increased proteolytic activity lead to these morphological processes. Such changes are accompanied by the development of acute pulmonary edema. Lymphatic vessels are able to remove a significant amount of fluid from the interstitial space, the pleural cavity. The propulsive activity of lymphatic vessels is determined by the inspiratory and expiratory acts of the respiratory cycle, as well as the functional activity of the valves of the vessels. It should be emphasized that there is no linear relationship between lymph flow and hydrostatic pressure in interstitial tissue. However, it should be stated that the insufficiency of the lymphatic system is one of the leading pathogenetic factors in the transition from the interstitial phase of pulmonary edema to the alveolar one. Thus, pulmonary circulation is designed to provide both respiratory and non-respiratory lung function. Evolutionarily, this system is designed to ensure the diffusion of acid into circulating red blood cells and eliminate carbon dioxide from the human body. Low pressure, low vascular resistance are unique properties of pulmonary circulation, and this is why it differs significantly from systemic circulation. The gravitational effect in the distribution of blood is more characteristic of lung tissue than it can be stated in relation to other organs and systems of the human body. Another unique feature of pulmonary circulation is the reaction of precapillaries to hypoxia, which manifests itself as a vasospastic effect, while in systemic circulation hypoxia leads to a vasodilation effect. With the development of pulmonary edema, the pulmonary microvessels are the primary place where water and electrolytes go beyond the vascular wall. Fluid filtration refers to physiological processes, but in the case of pulmonary edema, the balance of fluid entering the extravascular space exceeds the ability of the lungs to eliminate it. Pathological changes occur, in which inflammatory reaction mediators, reactive oxygen species, enzymes with proteolytic activity participate, which influence the formation of hydrostatic pressure and changes in vascular permeability. In recent years, attention has been paid to the study of intercellular interactions and their disorders in the development of acute lung injury. These

pathological processes also affect the transepithelial and transendothelial transports, the functional state of the basement membrane. In the final phase of the development of pulmonary edema, abnormal accumulation of proteins, primarily albumins, occurs in the alveolar fluid.

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