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ROLE OF ACIDOSIS IN THE MECHANISMS OF FORMATION OF MULTIPLE ORGAN FAILURE

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Abstract.

The authors carry out the analysis of review of literature about the influence of lactate acidosis in the development of multiple organ failure at the patients being in critical state. Hyperlactatemia is one of the most wide-spread metabolic disturbances at patients in critical state. It accompanies the most difficult phase of systemic inflammatory response, i.e. multiple organ failure (MOF). During emergency state at patients the precursors of multiple organ failure (MOF) are often aggravating metabolic disturbances in organs, systems and tissues with the development of syndrome hypermetabolic hypoxemia. In these conditions mitochondria becomes more sensitive to acidosis, incompletely oxidized metabolic products launch the mechanism of “mitochondrial dysfunction” and close the vicious circle of metabolic disturbances by increasing hypoxemia. Such changes occur in the myocardial metabolism and they lead it to structural changes. Myocardial infarction (MI) is the corollary of them. Because of it, the working of theoretical principles of the development of multiple organ failure (MOF) and its pathogenetically proved prophylaxis and treatment are at the centre of attention of scientists.

Keywords: lactate acidosis, mitochondrial dysfunction, multiple organ failure (MOF), critical states, hypoxemia, systemic inflammatory response (SIRS).

POLIORGAN YETISHMOVCHILIKNI SHAKLLANTIRISH MEXANIZMLARIDA ATSIDOZNING O’RNI

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Annotatsiya

Maqolada og'ir holatdagi bemorlarda poliorgan yetishmovchiligining rivojlanishida laktat atsidozning roli bo'yicha adabiyotlar tahlil qilinadi. Giperlaktatemiya og'ir holatdagi bemorlarda eng ko'p uchraydigan metabolik kasalliklardan biridir. Bu tizimli yallig'lanish reaktsiyasining eng og'ir bosqichi - poliorgan yetishmovchilik bilan birga keladi. Bemorlarda favqulodda vaziyatlarda POYe (poliorgan yetishmovchilik) ning prediktorlari ko'pincha organlar, tizimlar va to'qimalarda

ularning gipermetabolik gipoksiya sindromi rivojlanishi bilan progressiv metabolik kasalliklar ekanligi ko'rsatilgan. Ta'riflanishicha, bunday sharoitlarda mitoxondriyalar atsidozga eng sezgir bo'lib qoladilar, kam oksidlangan metabolik mahsulotlar "mitoxondriyal disfunktsiya" mexanizmini ishga tushiradi, bu esa gipoksiyani kuchaytiradi va metabolik kasalliklarning ayanchli doirasini yopadi. Xuddi shunday o'zgarishlar miyokard metabolizmida sodir bo'ladi va uning tarkibiy o'zgarishlariga olib keladi, bu esa miokard infarktiga olib keladi. Shuning uchun ham POYe rivojlanishining nazariy asoslarini ishlab chiqish va uning patogenetik jihatdan asoslangan oldini olish va davolash tadqiqotchilarning diqqat markazida bo'lib qolmoqda.

Kalit so'zlar: laktat atsidoz, mitoxondrial disfunktsiya, POYe (poliorgan yetishmovchilik)*, kritik holatlar, gipoksiya, tizimli yallig'lanish reaktsiyasi.*

РОЛЬ АЦИДОЗА В МЕХАНИЗМАХ ФОРМИРОВАНИЯ ПОЛИОРГАННОЙ НЕДОСТАТОЧНОСТИ

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Аннотация.

В статье проведён анализ литературы о роли лактат-ацидоза в развитии полиорганной недостаточности у больных, находящихся в критических состояниях. Гиперлактатемия - одно из самых распространённых метаболических нарушений у больных, находящихся в критическом состоянии. Она сопровождает наиболее тяжёлую фазу системной воспалительной реакции - полиорганную недостаточность. Показано, что при неотложных состояниях у больных нередко предшественниками ПОН (полиорганной недостаточности) являются прогрессирующие нарушения метаболизма в органах, системах и тканях с развитием синдрома их гиперметаболической гипоксии. Описано, что в этих условиях митохондрии становятся наиболее чувствительны к ацидозу, недоокисленные продукты обмена запускают механизм «митохондриальной дисфункции», усиливающей гипоксию, и замыкают порочный круг метаболических нарушений. Подобные изменения происходят в метаболизме миокарда и приводят к его структурным изменениям, следствием которых является инфаркт миокарда. Именно поэтому разработка теоретических основ развития ПОН и патогенетически оправданной её профилактики и лечения остаётся в центре внимания исследователей.

Ключевые слова: лактат-ацидоз, митохондриальная дисфункция, ПОН (полиорганная недостаточность), критические состояния, гипоксия, системный воспалительный ответ.

In modern medicine of critical states, anesthesiology and intensive therapy occupy the main place, since, directly interfering in the activity of the body, most significant affects various functions, and, consequently, on the

state of homeostasis [9]. A critical state is an extreme degree of any, including a phenomenon of pathology, which requires support for the vital functions of the body. The concept of insufficiency of the function of vital organs - multiple -organized insufficiency (PON) - is based on the unperture of the mechanisms of its occurrence and a close relationship with the severity of the injury, the period and quality of specialized assistance. That is why the development of the theoretical foundations of the development of pathogenetically justified its prevention and treatment remains at the center of attention of researchers.

Polyorgan failure is the most severe phase of the development of a systemic inflammatory reaction and is the consequences of a non-specific stress of the body of a high degree of severity. These phenomena are due to progressive metabolic disorders in organs, systems and tissues with the development of their hypermetabolic hypoxia syndrome [11]. One of the most common metabolic disorders in patients in critical condition is hyperlactamia. The level of lactate in the blood and/or lactate clearance is a diagnostic, therapeutic and projection marker of tissue hypoxia for circulatory shock [18]. For the pathogenic compensation of acute blood loss, it is necessary to take into account not only the state of hemodynamics, but also the parameters characterizing the tissue metabolism using transport and oxygen consumption indicators, the acid-main state of the venous blood and a number of metabolites, including lactate and pyruvate [12]. According to V. X. Timirbaev, E. S. Vladimirov [2], lactate monitoring is required in patients in a state of shock. A direct dependence between the nature of the dynamics of blood lactate against the background of the on -shock therapy and death was revealed. At the same time, the pieron coefficient is 0.68, and the probability of a fatal outcome is higher in the victims, in which the lactate level at the end of the operation, despite the intensive tenders, increases.

The occurrence of multiple organ failure syndrome after adopted mass blood loss, which is a common cause of death of patients, is also associated with the development of lactate ancidosis. Violation of microcirculation, tissue hypoxia and acidosis, which compose the basis of the development of Pont, lead to vicious activation of the immune system, which defends further progression of the pathological state. Oxygen deficiency on the periphery of 3 to 24 hours leads to the appearance of a systemic inflammatory pollutant characterized by hyperproduction of endogenous vasoactive mediators. The cascading reactions of the acute phase of inflammation lead to a sharp increase in oxygen deficiency, an increase in lactate, acidosis and the

progression of PON [19]. Hyperlactacidemia and lactate -acidosis is an important feature of cardiogenic and other types of shock. An increase in lactate concentration from 2.1 to 8.0 Meq % reduces the possibility of survival from 90 % to 10 %. The value of lactate, exceeding 7-8 Meq %, is always critical [9].

In states such as peritonitis, political trauma, sepsis, pancreatic, shocks of prize etiology, an extensive complex of pathological syndromes is observed, which, if not corrected, ultimately lead to death [8, 15]. These syndromes include metabolic disorders, and the leading pathogenetic factors are: hypoxia, hypoergosis, endotoxemia, metabolic acidosis, and out of the processes of lipid peroxidation, pronounced disorders in the hemostasis system [16].

The state of prolonged hypoxia of organs becomes a factor in the progressive trafficking of all energy -dependent processes responsible for the structural support of intracellular reactions. Forming tissue hypoxia leads to an increase in them of lactic acid content, which instantly decomposes into hydrogen ions and lactate and thereby leads to the development of lactate ancidosis [14]. An increase in lactate can be due to both enhanced products and a reduced consumption. Normally, the lactate is mainly utilized in the liver, kidneys and heart muscle, where it is used for energy purposes and glucose synthesis (gluconeogenesis), only is only excreted in the urine. Against the background of oxygen deficiency and consistently developing polyorgana, the role of these organs in reducing the concentration of lactate is significantly weakened and in some cases does not manifest itself at all. In particular, in the late stages of shock, there is insufficient use of lactic acid by the liver (due to reduced perfusion), and the measles cycle becomes invalid [9].

The situation is also aggravated by the fact that the carbohydrate metabolism is suffering first of all, as a result of which hyperglycemia develops as one of the components of hypermetabolic syndrome. However, the supply of carbohydrates is small, if not replenished, they are enough for only 6 hours, and fats are 40 days [11]. In this regard, there is a restructuring of energy metabolism from carbohydrate to fat, and since at this time a lack of glucose and oxygen is already developing in the body, oxidation of fatty acids is inhibited at the stage of the formation of acetone, acetocus and p-oxyx acids [1] .

Under the current conditions of hypoxia, the function of all systems of the body suffers, but the nervous system is more sensitive to it: with the complete cessation of blood flow, the recognition of damage to the cerebral

cortex is found after a few minutes. A decrease in oxygen consumption by 20 % structures of the brain causes loss of consciousness. After 5-6 minutes of brain anoxia, deep structural changes in neurons and an oblong brain occur- after 10-15 minutes. In the heart muscle, the small foci of necrosis are 3-5 minutes from the moment of ischemia, and a large-focal heart attack is formed after 20-30 minutes [3]. The transition of acidosis to an uncompensated phase leads to alteration of myocardial structures. In the zone of acidosis, the processes of membrane spheres, electromechanical conjugation are violated, anomalous electrical activity is formed and the processes of cellular aliteration are activated. The consequence of this is the decrease and complete loss of contractile activity of the heart, the occurrence of arrhythmias and myocardial infarction [1, 10].

In parallel, the development of endogenous intoxication as a non - specific syndrome of non-compliance between the formation and excretion of products of normal obstacle and impaired metabolism occurs. In conditions of endo- and exogenous intoxication, tissue macrophages activated by tissue decay products and microbial antibodies are cleaned to produce a number of pro-inflammatory cytokines. This mechanism is universal in nature controlled by the immune system, which prevents the uncontrolled release of cytokines and other inflammation mediators, ensuring an adequate reaction of the body to inflammation [13]. But a significant number of traumatic damage does not obey the general laws, due to which the conditions for continuous (multiple) intake of antigenic structures in the tissue are created. This leads to the predominance of pro -inflammatory stimulation of the body, which triggers the pathological mechanism of the systemic inflammatory reaction. Prospective cytokines, according to many authors [6, 12], strengthen the expression of the Villebrand factor, the tissue factor and fibrinolysis inhibitors, as well as chemokin. All this leads to the appearance of new portions of thrombin and contributes to the occurrence of DIC and thrombosis. At the same time, the permeability of blood vessels and the transmigration of leukocytes in the extra -vascular space increases, which leads to the development of blankets and edema. A considerable role in this process belongs to the endothelium of blood vessels containing interferons receptors. As a result of the excitation of R-Afna, the proliferation of endothelial cells is inhibited, but their apoptosis is enhanced. The stimulation of the R-Finy leads to increased expression on the endothelium of the antigens of the main histocompatibility complex of the 2nd class, as well as IL-1ß and ICAM-1 products, which is accompanied by the

involvement of endotheliocytes in the reaction of cellular and humoral immunity [6]. The accumulation of excessive concentration in the blood flow system of pro-inflammatory mediators entails a change in the organs and systems of a person and the development of multiple organ failure [15].

One of the mechanisms of the occurrence of the gender is the development of mitochondrial dysfunction against the background of metabolic acidosis [2, 5]. Violation of the structure of mitochons with lactatat-acydosis leads to a sharp increase in calcium ions in the cytosol. With an excess of intracellular calcium, the processes of swelling of mitochondria are aggravated, ATP deficiency is intended and all energy -dependent reactions in the cell are suppressed [26].

An increase in the concentration of lactate is several times compared to the physiological level, regardless of the size of the pH, can cause swelling of the mitochondria, which is accompanied by activation of breathing, and the division of oxidative phosphoriling [17]. Even a short -term change in the concentration of hydrogen ions (protons) in liquid media leads to a change in enzymes and the treatment of physiological processes. A decrease in the level of creatine phosphate (CF) in the development of metabolic disorders in the nervous tissue and myocardium occurs after a few seconds, while the brain tissue loses about 70 % of the CF, and after 40-45 with the CF completely exhausts [5]. Thus, with ischemia, the content of adenine nucleotides in cardiomyocytes (CMC) decreases, which further complicates the synthesis of ATP. The degree of decrease in the level of ATP depends on the rate of the occurrence of ischemia and its severity.

Using the direct measurement method of intramicocardial pH during heart-tank resuscitation, F. Kette et al. [17] showed that even a short period of cardiac arrest caused by fibrillation is characterized by a deep myocardial acidosis - after 5 minutes of cardiac arrest, when the pH of arterial blood still remains normal, and mixed venous is 7.26, the intramicocardial pH is reduced to 6.95 . In turn, the excessive accumulation of hydrogen ions and biologically active compounds leads to a sharp increase in the permeability of biological membranes due to structural transitions in proteins and lipids and the activation processes of free radical oxidation [7].

Therefore, in conditions of hypoxia and acidosis of various genes, oxidation of fatty acids in tissues are blocked, acidic products accumulate in excess, metabolic acidosis is formed and, accordingly, ATP deficiency develops, and all energy -dependent reactions are suppressed. Violation of

bioenergy caused by hypoxia, high level of catecholamines in the blood and metabolic acidosis can be carried out to the processes of the floor in critical conditions, which ultimately leads to a massive formation of free radicals and toxic peroxide compounds [3, 14]. Oxidizing stress leads to damage to the vascular wall, an increase in the pro -cargulant activity of plasma and platelets, which is one of the leading moments in the development of atherosclerosis [4], and damage to platelet membranes, erythrocytes and endothelia is the trigger mechanism for the development of acute myocard infarction, as well as violations cerebral circulation. Strengthening lipoperoxidation reduces the stability of the lipid layer, which can lead to electrical breakdown of cardiomyocytes with its own membrane potential [10]. The above mechanisms primarily lead to electrophysiological disorders, to diastolic, and then to systolic myocardial dysfunction and only then to the occurrence of pain in the chest. This sequence of changes is called the "ischemic state." Obviously, the angianous attack is its final stage, in fact the “tip of the iceberg”, at the basis of which are the changes in myocardial metabolism that have arisen due to perfusion disorders and, above all, mitochondrial dysfunction, which in this case is secondary, acquired in nature.

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