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MARKERS OF MYOCARDIAL DYSFUNCTION: THEIR ROLE IN THE PATHOGENESIS OF FUNCTIONAL DISORDERS OF THE CARDIOVASCULAR SYSTEM IN NEWBORNS

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Summary. *The article is devoted to the establishment of the role of indicators of the biochemical spectrum of blood, a complex of indicators of the system of free radical oxidation and antioxidant defense of the body in the development of the pathogenesis of hypoxic lesions of the cardiovascular system. The method of multivariate correlation analysis of the results of the study of additional paraclinical methods was used. The severity of the revealed changes in the cardiovascular system is in direct proportion to the severity of the general condition of the newborn under conditions of perinatal pathology.*

Key words*: newborns; markers; cardiovascular system; hypoxia; pathogenesis; metabolic disorders; antioxidant system; multivariate correlation analysis.*

Introduction.

Cardiac injury biomarkers are very sensitive markers for the detection of myocardial injury and have been studied in healthy newborns, after tocolysis, intrauterine growth restriction, respiratory distress and asphyxia. The proportion of newborns with elevated troponin was higher than that in ill infants, children, and adolescents and in healthy adults, suggesting that myocardial injury, although clinically occult, is common in this young age group. Results suggest that significant elevation of cord troponin is an excellent early predictor of severity of hypoxic-ischaemic encephalopathy and mortality in term infants. Cardiac biomarkers may also benefit centres without on-site echocardiography with evidence showing good correlation with echo-derived markers of myocardial function.

Oxygen deficiency is an important factor in the functioning and damage of the fetus cells and tissues. It is considered as a general energy distress which means an organism syndrome that causes the development of clinical manifestations of chronic fetal hypoxia. The main links of the hypoxia pathogenesis are energy deficiency in the cells, metabolic disorders, changes in the internal organ blood flow. Oxygen plays a key role in the energy supply of cells and the synthesis of adenosine triphosphoric acid (ATA) in oxidative phosphorylation. There are two ways of utilization oxygen in the body: the first one is associated with the oxidation of energy substrates and is implemented by cytochrome oxidase, the second is the oxygenase way, which involves the inclusion of one, two or three atoms of oxygen into the substrate molecule and is characterized by the formation of highly toxic products of oxidative stress.

The hypoxia pathogenesis is characterized by a complex dynamic flow, a wide spectrum of polyorganic and functional metabolic lesions at the molecular, cellular and organ level. Heavy and prolonged hypoxia causes a breakdown of compensatory mechanisms, which manifests itself, first of all, in the exhaustion of the sympathic – adrenal system and adrenal cortex, bradycardia, arterial hypotension and collapse. Continuation of the hypoxia duration causes activation of anaerobic glycolysis.

As the lack of oxygen influences on the nature of the compensatory and adaptive mechanisms of the child's organism, the search of cell damage mechanisms and their microstructures with hypoxia is being to continue, in particular, the attention of the researches is paid to oxidative stress (OS), the questions of the body's ability to withstand the influence of hypoxia and its consequences are being studied.

Material and methods.

To achieve the goal, an analysis of paraclinical parameters was conducted, namely: general and biochemical blood tests (total protein level, bilirubin and its fractions; glucose, urea, creatinine; activity of alanine aminotransferase (ALT), aspartate amino transferase (AST), lactic dehydrogenase (LDH), Creatinphosphokinase (CPK), creatinkinase - MB (CK-MB), troponin- I); indicators of the free radical oxidation system (FRO) (level of malonic aldehyde (MA) in erythrocytes), oxidative modification of proteins (OMP) in blood plasma and antioxidant defense system (ADS) indicators of an organism (activity of glucose-6-phosphate dehydrogenase (G6PD), glutathione peroxidase (GP) and glutathione reductase (GR) in erythrocytes, the level of ceruloplasmin (CP), HS-groups, as well as the activity of catalase (CT), glutathione-S-transferase (GST), g-glutamyltransferase (GGT) in blood plasma) in children during the first days of life with the subsequent multi - factor correlation analysis of 30 paraclinical indices in newborn infants.

At the same time, the manifestations of hypoxic lesions of the central nervous system were clinically marked in 10 children in the background of different forms of perinatal pathology, the manifestations in 10 children were respectively severe, and 10 newborns were referred to a group of conditionally healthy newborns in the control group.

Results and discussion.

Three main factors of the examined children were identified as a result of multi - factor correlation analysis of paraclinical indices, the determination of which allowed to identify possible pathogenetic links of hypoxic lesions of cardiovascular system (CVS) in newborns in the early neonatal period (probability 79.8%).

The first factor (r = 24.0) reflected significant violations of metabolic processes in newborns under the conditions of the leading factor in perinatal pathology-hypoxia, indicating a violation a of the protein metabolism, namely, a decrease in albumin level (r = -0.78746), an increase in total bilirubin levels (r = 0.81304) and indirect bilirubin level (r = 0.79294), the level of triglyserides (r = 0.82168) and uric acid (r = 0.97419), a decrease in calcium (r = -0.87353) and glucose levels (r = -0.84934), an increase in urea level (r = 0, 81245); an increase in the enzymatic activity of the blood, in particular: an increase in the level of KFK (r = 0.97651), lactate dehydrogenase (LDH) (r = 0.96883), troponin I (r = 0.96987),

Creatinphosphokinase CPK (r = 0.96933), ALT (r = 0.98870), aspartate aminotransferase AST (AAST) (r = 0.90694), which accompanied the destructive processes in cardiomyocytes. Also, the first factor reflected the character of the free radical oxidation (FRO) processes in the body, which indicated an increase in the level of malonic dialdehyde MD (r = 0.95614), an increase in the intensity of oxidation modification of proteins (OMP) (r = 0.98797) with a simultaneous decrease in the level of SH- plasma groups (r = -0, 90002) and increased serum of catalase activity (r = 0.93372) and (GGT) (r = 0.778774).

The second factor (r = 6,2) to a greater extent reflected the nature of the antioxidant defense system response of the of children's body with the signs of functional disorders of the cardio vascular system (CVS), which indicated an increase in the level of ceruloplasmin (CP) (r = 0.8888845), glucose-6-phosphate dehydrogenase (G6PD) erythrocytes (r = 0.933610)), glutathione-S-transferase (GTS) plasma (r = 0.871212), GR (r = 0.800696), and glutathione peroxidase GP (r = 0.8882624).

Our studies indicate that the dynamics of antioxidant system activity is characterized by an initial increase in the analyzed parameters in the general condition of newborns moderate severity, which is probably due to the compensatory reaction of the organism to the effect of oxidative stress due to hypoxia.

The high content of this enzyme may result in the rapid exhaustion of the energy reserves of cells.

However, when there was a severe condition in newborns, a decrease in the activity of GST, glutathione reductase (GR), glutathione peroxidase (GP), Gl-6-FDH was observed, which may be due to the exhaustion of the enzyme activity of the glutathione linkage of the antioxidant defense system due to damage to their active forms of oxygen .

The third factor (r=0,47) – included an average volume of erythrocyte (MCV) (r = 0.787922). This erythrocyte index is calculated as a measure that allows finding out the volume occupied by one erythrocyte. According to the analyzed literature, an increase in the level of this indicator above the norm may indicate hypotonic dehydration.

The studies showed a slight increase of MCV in newborns with moderate and severe general conditions compared with the controls, which is likely to indicate hypoxia and acidosis associated with bone loss, blood clotting, and microcirculation.

Thus, according to the multifactor correlation analysis, a mathematical model that characterizes the possible mechanisms of CVS hypoxic lesions in full - termed infants in the early neonatal period has such a form as (looks like):

$$Y = 24{,}0.f1 + 6{,}2.f\,2 + 0{,}47.f\,3$$

Adhering to the final result interpretation rules, taking into account the laws of normal distribution, the value of the value of "Yst" in a group of children who have a dysmetabolic disorder in the early neonatal period of moderate severity, the amount of points taking into account the direction of the vectors will correspond to the value that is within the range -1 -1 <Yst <+1 "; the value "Yst> +1" will correspond to a violation of the metabolism of a severe degree; the value of "Yst < -1" - a group of newborns with a satisfactory level of metabolic adaptation.

The absolute coefficients values of the mathematical model factors testify, that the most important factors in the formation of post-hypoxic myocardial changes in newborns are the Ist and the IInd factors, since they are characterized by the highest correlation coefficients with the value of "Y".

Factor III has coefficients of average strength correlation, indicating a moderate diagnostic value of the indicators that are the part of their composition. According to the literature, the factor of acute hypoxia leads to functional and organic disorders of the fetus organs, in the first place the brain and CVS. This leads to disorders of metabolic processes in the body of newborns, which create unfavorable conditions for the functioning of the central nervous system and the myocardium with insufficient oxygen supply during the perinatal period.

Changes in hemodynamic system, centralization of blood circulation, activation of anaerobic glycolysis with the accumulation of lactate contributes to the development of metabolic acidosis. Increase in metabolic acidosis contributes to the activation of plasma proteases, pro - inflammatory factors, electrolyte disturbances, which lead to cellular membranes damage with the release of enzymes in the blood. Increasing of the vascular wall permeability causes the sludge of erythrocytes, the formation of intravascular blood clots and hemorrhages, and the output of a liquid part of the blood from the vascular bloodstream promotes the development of hypovolemia and edema. Thus, dysmetabolic changes due to hypoxia in newborns are a predictor of multiple organ inconsistencies, CVS dysfunction. The results of the research confirm the opinion that one of the leading places in the hypoxic heart damage pathogenesis in newborns is significant metabolic disorders with clinical manifestations of dysadaptation.

The supply of myocardium with energy is ensured by the high rate of oxygen consumption, the exchange of fatty acids and carbohydrates. The energy released by these processes turns into adenosine triphosphate (ATP) and creatine phosphate (CP) and enters the contractile elements of cardiomyocyte, where it provides the process of reducing the myocardium and the work of a calcium pump, which, in turn, is involved in diastolic relaxation. According to physiological conditions, the main part (60-90%) of all adenosine triphosphoric acid (ATA) is synthesized due to the oxidation process in mitochondria of free fatty acids (FFA**s**), and the rest of ATA - as a result of mitochondrial oxidation of pyruvic acid, the formation of which is the result of anaerobic decomposition of glucose in the cytoplasm of cardiomyocyte.

Any pathological process has the violation of the structural and functional organization of the cell in its basis, its cell membrane and receptor apparatus. The state of cell membranes is one of the main key indicators of the newborn's state under hypoxic conditions.

Lack of oxygen, causing severe malfunctioning of cell membranes for a long time, reduces the reserve adaptive capacity of the child. In the development of perinatal hypoxic lesions, the determining role is given to increasing the level of intracellular calcium, the level of which is controlled by the enzymes of the transmembrane transport of (Na + -K + -Ca2 + -ATPase). It was established that the activity of enzymes in newborns that had acute hypoxia is characterized by an initial increase in the activity of enzymes, which changes with their stabilization by the end

of the neonatal period. In addition, severe form of hypoxia leads to the development of energy - deficient state of cardiomyocytes due to the intensive usage of glucose in the processes of anaerobic glycolysis, inadequate activation of glycogenolysis process and violation of glucose utilization mechanisms that are caused by functional immaturity of enzyme systems in the newborns.

At the same time, as a result of reducing the glucose utilization by tissues and damaging to mitochondria, energy insufficiency and disturbance of plastic processes develop, the degree changes of which is in directly dependent on the severity of intrauterine hypoxia and gestational age of the child.

Power exchange is a complex of processes providing the vital functions of living matter at the level of the whole organism and a single cell. An important link of this complex is mitochondria – the structures that are inherent in the cytoplasm of all eukaryotic cells and perform vital functions for each cell. Numerous environmental factors can cause pathological changes in mitochondria. Such factors in the neonatal period can be the action of medications, hydroxyl radicals, etc. Changes in cellular energy metabolism, based on mitochondrial insufficiency, lead to a large number of clinical manifestations.

The transformation of the main metabolic pathways in newborns with the activation of gluconeogenesis processes, primarily from the protein source, is determined by the need to maintain the sustainability of energy homeostasis under hypoxia conditions. Activation of the hypothalamic-pituitary-adrenal system under stress leads to an increase in catabolic processes, manifested by hypoproteinemia and hyperazotemia. At the same time, the level of albumin decreases much more than the level of globulins.

Increased protein catabolism leads to significant violations of the corresponding functions: catalytic, receptor, transport, and oncotic balance and so on. Plasma proteins determine the viscosity of blood and, therefore, play an important role in the hemodynamics of the circulatory system. Reducing the level of total protein and albumin in newborns is also due to insufficient activity of the protein synthesizing function of the liver and as a result of increased protein intake in the body against the background of hypoxia. A certain role in the development of hypoproteinemia in newborn plays and increases the intensity of OMP. With excessive destruction of protein molecules, the increase in urea content is also associated.

Increased bilirubin in blood serum effect the protein biosynthesis, changes the activity of enzymes, and regulates the processes of oxidative phosphorylation and the transportation of electrons in isolated mitochondria. Indirect bilirubin, being a lipotropic substance, at high concentrations in the blood has a toxic tissue effect on the heart, kidneys, and pancreas, changes the rheological properties of the blood.

It is known that as a result of the indirect bilirubin interaction with lipids of the intracellular membrane, the activity of membrane binding enzymes is disturbed, which leads to a decrease in the oxidative processes and the rate of oxygen utilization by the cell that results in gemic hypoxia of the myocardium.

As a result of the cell membranes violation integrity and the apoptosis process in conditions of severe oxygen deficiency, cytolytic syndrome develops, with which the enzyme cascade is associated with an increase in the level of enzymes in the blood of

newborns: KFK, KFK-MB, Tn I, lactate dehydrogenase (LDH), aspartate aminotransferase (AsAT), alanine aminotransferase (ALT) and increased cholesterol levels. The development of ultrastructural, metabolic, electrophysiological and a number of other disorders can lead to death of cells.

Thus, significant dysmetabolic changes in conditions of the pathological maternal oxidative stress, one of the causes of which is a functional violation state of the CVS on the background of vascular insufficiency, cause disorders of homeostasis processes in newborn, which, in their turn, are accompanied by clinical manifestations of dysadaptation syndromes and nosological pathology of any etiology in the early neonatal period. The severity degree of the detected changes in the cardiovascular system, as a rule, has a direct correlation with the severity of the general condition of the newborn.

The results of our studies have shown that along with the activation of peroxide oxidation of lipids under conditions of oxygen lack in newborns there is an increase in the intensity of OMP, magnification in the concentration of MA and violation of the functions of the ion channels.

An increase in OMP indicates the presence of cellular membrane destruction and tension of metabolic metabolism. According to modern ideas, the carbonyl protein derivatives are an early indicator of tissues damage by active oxygen metabolites. There is an increase in the antioxidant activity of the glutathione system enzymes with an average severity degree of the newborn's condition with subsequent progressive decrease in accordance with the increase in the severity of perinatal pathology. Similar changes arise as a result of lowering the level of SH-groups in blood plasma and erythrocytes, a decrease in r-glutamyltransferase GGT activity**.** Reducing the activity of antioxidant defense system (ADS) components in hypoxia conditions that accompanies severe cases of perinatal pathology causes the intensification processes of oxidative destruction of cell membrane structures. In our opinion, this is one of the leading causes of hypoxic myocardial damage. In response to maternal stress in the body, the arteries spasm of the small blood circulation flow occurs, resulting in increased pressure in the pulmonary artery system maintains blood flow through fetal communication, which leads to neonatal pulmonary hypertension.

Long term functioning of the open arterial duct (OAD) can lead to hemodynamic disorders, which, in combination with energy imbalance, leads to the development of heart failure (HF).

Consequently, the dynamic imbalance between the need for myocardium in oxygen and its actual provision in the newborn leads to hypoxia of the cardiac muscle, which is accompanied by two leading pathological disturbances of intracellular metabolism: a decrease in the production of the main energy substrate of the cell - adenosine triphosphoric acid (ATA) molecules and the activation of the free radical oxidation (FRO), resulting in damage to myocardial cell membranes.

Conclusions.

In our opinion, the basis of post-hypoxic lesions of CVS in newborns in the early neonatal period is energy deficiency in cells, significant dysmetabolic processes and violation of the physiological interaction of the prooxidant and antioxidant

systems of the body, which leads to a decrease in the functional activity of cardiomyocytes and, without timely therapeutic correction, to the destruction of cellular structures. The severity degree of detected changes on the part of the CVS, as a rule, has a direct correlation with the severity of the general condition of the newborn. Therefore, in order to predict CVS dysfunction in dysadaptation syndromes in newborns, a comprehensive diagnosis should be performed, which enables the timely prevention and correction of homeostatic disorders and the possibility of adapting the child's body to the background of hypoxia.

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