Mechanisms of Endothelial Dysfunction in Pathologies of Various Genesis

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Abstract – Studies in the experiment and the clinic demonstrated the nature of changes in the system of POL – AOC, nitric oxide homeostasis and cholesterol as factors contributing to dysfunction of the vascular endothelium. In metabolic syndrome in pregnant women and in patients with myocardial ischemia, as well as in intoxication syndrome (cobalt chloride), the induction of the lipid peroxidation process according to malonic aldehyde and impaired AODS cells was detected. A deficit of nitric oxide (NO), a violation of its bioavailability and vasoconstriction develops. Consequently, lipid peroxidation-triggering factors: elevated blood glucose, impaired oxygen supply to the myocardium (ischemia), and exposure to cobalt chloride play an important role in disrupting the formation of nitric oxide and adaptive mechanisms from reactive oxygen species (ROS). Disruption of nitric oxide homeostasis (eNOS/NO) plays a decisive role in the genesis of vascular complications and can be considered a biochemical marker for the development and progression of various pathologies. Based on these data, it is possible to develop a methodology for correcting the pathogenetic orientation.

Key words – endothelial dysfunction, pathologies, biomedicine, vascular endoteleum

I. INTRODUCTION

Modern biomedical science pays special attention to the study of the role of endothelial dysfunction in the pathogenesis of vascular complications in many pathologies: toxic effects, coronary artery disease, metabolic syndrome in pregnant women, etc. Summarizing the literature data, it should be noted that endothelialocytes under physiological conditions produce vasoactive substances: nitrogen oxide, angiotensin I and II, prostacyclin, endothelin and thromboxane [1, 2]; participate in hemocoagulation and activation of fibrinolysis; in reactions of innate and acquired immunity; perform an enzymatic function – the expression of angiotensin converting enzyme (ACE); regulate the proliferative processes of smooth
Atherosclerosis – hypercholesterolemia (GHS), leading to the development of endothelial dysfunction (DE), is a key factor initiating atherogenesis and contributing to its progression [4, 5]. Oxidized, modified LDL contribute to the disruption of NO synthesis and a decrease in the expression level of the NOS-3 gene and the enzyme endothelial NO synthase itself [6]. From the position of free radical theory, one can substantiate the main mechanisms of atherogenesis: the formation of foam cells and the development of aortic lipoidosis, the migration of smooth muscle cells from media to intima, the increase in their proliferation and the occurrence of complications of atherosclerosis with subsequent vascular thrombosis. Many different substances are involved in the course of free radical reactions, and an even greater number of components participate in the process of their regulation. Violation of any link in this system can lead to oxidative stress. The ratio of the main links of this system prooxidants and antioxidants, determines the development and progression of oxidative stress and, as a result, the development of free radical pathology [7].

II. STATEMENT OF THE PROBLEM

Study of the involvement of lipid metabolism changes in the development of endothelial dysfunction in various angiopathies: against the background of heavy metal salts, coronary heart disease (CHD) and metabolic syndrome.

III. MATERIALS AND METHODS

Experimental studies were carried out on Wistar male rats, with chronic intoxication with cobalt chloride for 1 month. At the end of the experiment, samples were analyzed in rats. The intensity of lipid peroxidation was judged by the concentration of malonic acid dialdehyde (MDA) [8], as well as the activity of catalase enzymes [9], SOD [10], and the concentration of ceruloplasmin [11]. The concentration of the final metabolites of nitric oxide (total content of nitrates and nitrites (NOX)) was determined by the method of Metelskaya V.A. [12]. Studies were conducted on the background of pharmacological agents that affect the reproduction of eNOS – the substrate itself and the L-NAME inhibitor. Lipid metabolism was judged by the content of total cholesterol and its fractions.

In clinical studies, the state of oxidative stress, antioxidation protection was determined according to the functioning of SOD, catalase, and the concentration of ceruloplasmin. In patients with coronary artery disease and in pregnant women with metabolic syndrome, violations of biochemical parameters were determined, including changes in lipid and carbohydrate metabolism, as well as blood pressure values, as an indicator of endothelial dysfunction.

A survey of 24 pregnant women, 14 – with metabolic syndrome. Conditions for the inclusion of patients in the survey were: singleton pregnancy, age over 18 years, no indication of diabetes and severe somatic pathology. The control group consisted of 20 relatively healthy individuals, with normal blood levels of cholesterol (4.3 mmol/l), triglycerides – 1.23 mmol/l, LDL-C – 1.46 mmol/l, LDL-C – 2.68 mmol/l.

For typing of dyslipoproteinemia (DLP), A.N. Klimov and N.G. Nikulcheva (1984). The total cholesterol (cholesterol), triglycerides (TG), high-density lipoprotein cholesterol (cholesterol HDL) cholesterol were determined, the cholesterol atherogenic coefficient (cholesterol coefficient) according to A. Klimov (1984) was calculated using the Fredewald equation.

IV. DISCUSSION OF THE RESULTS

Experimental and clinical data showed that toxic angiopathies and vascular complications caused by heavy metal intoxication (cobalt chloride) are characterized by the formation of reactive oxygen species (ROS) and activation of free radical oxidation (FRO), as evidenced by a statistically significant increase in MDA concentration in hemolysate red blood cells. In patients with coronary artery disease and in pregnant women with metabolic syndrome, activation of free radical oxidation in erythrocytes was also detected. Analysis of AOS data showed that, in toxic pathologies in serum, SOD activity decreases, while catalase activity and ceruloplasmin concentration increase. Regarding clinical material, it should be noted a decrease in the activity of all AOS enzymes. In all pathologies under conditions of oxidative stress, the NO-producing function of the endothelium is disturbed, as evidenced by the concentration of NOx.

When intoxicated with cobalt chloride in rats against the background of developed oxidative stress, a decrease in the concentration of total NO metabolites was found by 19.7 % (p <0.001) and an increase in the concentration of MDA – POL product by 10.9 % (figure 1).

The study of the relationship between these indicators revealed the presence of a strong inverse relationship (r = – 0.72).

Administration of L-arginine to rats with cobalt intoxication showed an increase in NO with inhibition of lipid peroxidation. At the same time, there is an increase in the level of SOD functioning. Unlike L-arginine, the eNOS inhibitor L-NAME showed opposite results, i.e., the ability of the enzyme instead of NO to produce ROS.
In patients with coronary artery disease and in pregnant women with metabolic syndrome, a stable significant increase in plasma lipoperoxidation products was found according to MDA data. The concentration of MDA significantly increased, which amounted to 83.2% in relation to the data of the control group (table 1).
Therefore, under conditions of oxidative stress, apo-β 100 structure changes, as a result of which this LDL protein loses its affinity for receptors of LP particles. Modified LDL phagocytosis by macrophages in the subendothelial space and they are accumulated in areas of atherosclerotic vascular lesion [14].

Intensification of lipid peroxidation processes in the liver in atherosclerosis is accompanied by suppression of the enzymatic catabolism of cholesterol (cholesterol) in hepatocytes, which in turn helps to maintain elevated levels of cholesterol in blood plasma [7].

The dyslipoproteinemia (DLP) revealed by us was manifested by increased blood levels of total cholesterol, high levels of cholesterol-LDL, and decreased cholesterol-free cholesterol. According to the characteristics of the lipid spectrum by the World Health Organization (1992), such DLP is classified as type II, subtype II-a.

Consequently, the accumulation of products of metabolic disorders of lipid peroxidation products, atherogenic lipoproteins and a decrease in the content of nitric oxide induces ischemia, and this pathological cascade can progress and become a risk factor for worsening IHD and the development of myocardial infarction. Adequate pathogenetic therapy is necessary to prevent this.

V. CONCLUSION

Thus, the pathogenetic link of endothelial dysfunction in chronic toxic angiopathies is the intensification of POL, caused by reactive oxygen species (ROS) and the inhibition of antioxidant protection of cells (AOD). Under conditions of oxidative stress, the expression of eNOS is disturbed, the production and bioavailability of nitric oxide – the main vasodilating factor, which is accompanied by impaired tissue metabolism. In patients with coronary artery disease and metabolic syndrome under conditions of oxidative stress, impaired nitric oxide production and cholesterol metabolism is accompanied by endothelial dysfunction, increased blood pressure during the day and hemodynamic changes in the myocardium. The change in the nitrooxide synthase system – NOX is an indicator of vascular disorders.

References