Low and paramedian values of IL-6 / TNFa in venous blood were detected in a significant majority of women (77%) of the main group, whose children were diagnosed with aspiration pneumonia. Five women (23%; N = 22) showed high values of the coefficient ($\chi 2 = 11.0$; $p = 0.0009$), they also had children with aspiration pneumonia.

IL-6 / TNFa ratio was lower in umbilical cord blood in children with sepsis 0.11 (0.09; 1.39), in comparison with children without signs of perinatal infections 1.59 (0.66; 52.53); $U = 54$, $p = 0.038$. When constructing the ROC curve, the threshold value of the ratio of IL-6 / TNFa in cord blood for the development of sepsis in the neonatal period was less than 1.40 (Se = 85.7%, Sp = 63.6%, AUC = 0.71, 95% CI 0.61-0.80, $p = 0.02$).

As a result, it was found that in patients of the main group, lower values of the IL-6 / TNFa coefficient were observed in venous blood (Me = 2.50; $p = 0.0002$). Coefficient of IL-6 / TNFa in a woman's blood serum was lower in group with labor resistant to tocolytics (Me = 3.37; $p = 0.02$). In newborns who had aspiration pneumonia IL-6 / TNFa ratio was assigned to the 1st and paramedian quartile (77.3%; $p = 0,0009$). Lower IL-6 / TNFa index in umbilical cord blood was diagnosed in newborns with sepsis (Me = 0.11; $p = 0.038$). The threshold value for the development of neonatal sepsis was the value of IL-6 / TNFa less than 1.40 ($p = 0.02$).

Conclusion: Low values of the ratio in the placental and fetal stages of perinatal infections were found. IL-6 / TNFa ratio has shown importance as the earliest marker of perinatal infections.

***Key words:*** *gestational pathology, cytokines, perinatal infections.*

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## DYNAMICS OF MARKERS OF INFLAMMATORY ENDOTHELIUM ACTIVATION IN PATIENTS WITH ISCHEMIC HEART DISEASE IN COMBINATION WITH NON-ALCOHOL FATTY LIVER DISEASE AFTER INFLUENCE BETARGIN AND QUERTSETIN

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Coronary heart disease (CHD) is ranked first place among the causes of mortality in the world according to WHO [1]. Functional disorders of the liver cause dyslipidemia, which is a significant pathogenetic component of the CHD. Therefore, according to modern notions, nonalcoholic fatty liver disease (NAFLD) is considered as a risk factor of cardiovascular diseases (CVD) [2]. Recent scientific studies have shown that endothelial dysfunction (ED) is one of the most important links in the pathogenesis of atherosclerosis – the morphological basis of CHD. The disturbance of endothelial properties resulting from damage of the cell membrane by free radicals, modified low density lipoprotein, antigenic complexes, monocytes-macrophages, and cytokines leads to the activation of endothelial cells with subsequent apoptosis and the formation of a stable imbalance of all endothelial-dependent functions [3]. A leading role in the formation of ED and, accordingly, the development of atherosclerosis, plays a chronic systemic inflammation, which is also an important pathogenetic component of NAFLD [4]. The state of the problem with the incidence of CHD, the frequency of comorbid cases with NAFLD causes the necessity to find new effective therapeutic approaches with an impact on the common links of the pathogenesis of these diseases. The purpose of the study was to investigate parameters of inflammatory activation and endothelial dysfunction in patients with stable ischemic heart disease

in combination with nonalcoholic fatty liver disease and the effect of complex therapy with the addition of betaine, arginine and quercetin to detected violations.

**Materials and Methods**. The study included 75 patients of both sexes aged 40-69 years with diagnosis of CHD: stable angina pectoris, FC II, HF 0-I, NAFLD. Patients were randomized into 2 groups: 27 patients were included into the study group and 48 patients – to comparison group. To achieve the goal of investigation, the number of circulating endothelial microparticles (CEM) in peripheral blood was determined with molecular markers of inflammatory activation of ET CD32 and CD40 by flow cytometry and measured the velocity values of blood flow in the hepatic and portal veins using ultrasound pulsed wave doppler (PWD) [ 5, 6, 7]. All patients were prescribed standard therapy for stable CHD (β-blockers, statins, aspirin) and silymarin 90 mg per day with 1200 mg lecithin per day for NAFLD correction. Patients in the study group were additionally assigned to betargin in a dose of 2 grams of arginine citrate and 2 grams of betaine daily per os and quercetin in a dose of 120 mg per os per os. After 2 months of treatment examination of patients in the aforementioned volume was performed.

**Results.** In patients with CHD, associated with NAFLD, quantity of CD32 + CD40 + was 2.77 ± 1.94 x 107 / l. The value of this indicator in healthy persones was within (1,05-2,11) x 107 / l. Speed of the blood flow in the portal vein of the studied patients exceeded the data of healthy persons by 39.5% and amounted to 0.38 m / s. Speed of the blood flow in the liver veins reached 0.19 ± 0.06 m / s, while the indicators of healthy persons are within the range of 0,14-0,16 m / s [6].

The content of CD32 + CD40 + in blood had direct correlation with velocity of blood flow in the liver veins ($r = 0,517$, $p<0,01$), which demonstrates the dependence of the functional state of vessels on inflammatory endothelial activation. After the therapy, quantity of CD32 + CD40 + cells significantly reduced in the study group ($p = 0.046$), in contradistinction to the data of the comparison group, where the dynamics of CEM CD32 + CD40 + was not reliable ($p> 0.05$). The study of blood flow velocity in the hepatic veins while administration of Betargin and quercetin revealed a significant decrease in this index in 1,3 times ($p <0,01$) - the value was 0,30 ± 0,08 m / s versus 0,35 ± 0,05 m / s in the comparison group, in which the differences in values before and after treatment were not statistically significant ($p> 0,05$).

Conclusion. Thus, the obtained results demonstrate the importance of chronic systemic inflammation in the development of endothelial dysfunction, as well as the relationship between inflammatory activation of the endothelium and the functional state of the liver vessels, which manifests itself as an increase in the speed of blood flow. The obtained data, also, highlights the common features and mechanisms of the violation of the structural and functional state of the vascular bed in conditions of comorbidity - CHD and NAFLD.

Adding to the therapy of CHD and NAFLD Betargin and quercetin positively affected the state of vascular blood flow, in particular regarding the hepatic and portal veins, reduced level of inflammatory activation and vascular endothelial dysfunction, which underlined influence of these agents on clinical course of the studied comorbidity.

Prospects for further research. These studies suggest the necessity for further investigation of the possible effects and mechanisms of the Betargin and quercetin influence in conditions of CHD, NAFLD and other pathological conditions based on endothelial dysfunction and chronic systemic inflammation.

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***Key words:*** *coronary heart disease, non-alcoholic fatty liver disease, endothelial dysfunction, chronic systemic inflammation, quercetin, betargin.*

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# ASSOCIATION OF THE *EPHA1* AND *PARP1* GENES POLYMORPHISMS WITH ALZHEIMER'S DISEASE

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Relevance. Alzheimer's disease (AD) is the most common cause of dementia. AD neurodegeneration damages the brain and leads to disruption of the memory functioning, cognitive and behavior impairment. At the present time, early diagnostics and identification of presymptomatic individuals who are at higher risk of developing AD represent the global public health priority. Numerous studies demonstrate that genetic factors have important role in development of AD and can serve as markers for its diagnosis and prognosis. Studies of poly(ADP-ribose) polymerase-1 (*PARP1*) gene polymorphisms were documented in a numerous studies to be associated with late onset Alzheimer's disease (LOAD) [1, 2]. *PARP1* is thought to have an important role in the initiation of the DNA repair pathway in the response to cellular injuries such as DNA breaks, excitotoxicity, oxidative stress and also involved in microglia-mediated inflammation and apoptosis regulation [3]. Furthermore, *EPHA1* (erythropoietin-producing hepatocellular receptor A1) gene polymorphisms rs11767557 and rs11771145 were documented in recent genome wide association studies to be strongly associated with LOAD [4, 5]. *EPHA1* is also an important gene for immune response involved in regulation of cell morphology and motility, neurogenesis, synaptic plasticity and neuroinflammation [6]. However, it is unknown whether *EPHA1*and *PARP1* genetic variants combinations are associated with LOAD.

The presented study aimed to clarify role of *PARP1* (rs3219023) and *EPHA1* (rs11767557 and rs11771145) polymorphisms and its combinations as genetic factors of LOAD pathogenesis.

**Materials and Methods.** Assays for the detection of *PARP1* rs3219023 and *EPHA1*rs11767557 and rs11771145 SNVs based on PCR followed by RFLP analysis were developed. Specific oligonucleotides that were used as primers designed and synthesized in accordance to corresponding sequences of *EPHA1* and *PARP1* genes. The comparative analysis of genotypes distribution was performed in the LOAD patients group, consisted of81 individuals including 31 (38.3%) males and 50 (61.7%) females and control group, consisted of 87 age-matched cognitively normal unrelated volunteers