Hepatic blood flow in patients with alcoholic liver cirrhosis

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Paper received : Revised : Accepted for publication .

Abstract. This research is devoted to studying of hepatic blood flow in patients with alcoholic liver cirrhosis (ALC). The presence of endothelial dysfunction (ED) in cirrhotic patients directly corre ates with the diameter of portal vein ($r = 0.673$) ($p < 0.05$) and with the level of nitrogen monoxide ($r = -0.821$) ($p < 0.05$) and the indicator endothelium dependent vasodilation (EDVD) ($r = -0.657$). So, ED is an additional independent predictor of portal hypertension (PH) forming in patients with ALC, as the expression of nitrogen monoxide in ED patients is significantly reduced, which creates prerequisites for the growth of resistance in the portal vein system and forming PH.

Keywords: *alcoholic liver cirrhosis; portal hypertension; hepatic blood flow.*

Background. Alcoholic liver cirrhosis (ALC) is widely spread now days. Complications of this disease cause a high death rate, and one of such complications is portal hypertension (PH).

Progress in understanding of mechanisms that hinder a free hepatic blood flow, opens new perspectives for the development of more effective therapeutic strategies. Due to the modern vision of the pathogenesis of PH the level of pressure in portal vein is determined by three factors: the size of portal blood flow (increases not only because of splanhnic vasodilatation, but also because of increased angiogenesis in the liver and formation of arterio-venous anastomoses between the branches of hepatic artery and portal vein in the fibrous septum), vascular tone of the branches of portal vessels, and general intrahepatic vascular resistance [6]. From the above it follows that the pathogenesis of PH can't be reduced only to the difficulties of intrahepatic venous blood flow due to mechanical barriers, changes of liver architectonics and other local factors. The hemodynamic factors are also very important, and their reversibility determines the priority of this trend in the development of methods for therapeutic correction of PH.

Until now it was thought that the main cause of PH is a mechanical obstruction of blood flow in the portal vein due to proliferation of connective tissue in the liver parenchyma (irreversible factor). The role of reversible factors remained underestimated. These include the following components: tone of the blood vessels, blood rheology, micro thrombosis, swelling of the liver parenchyma. The tone of hepatic blood vessels is provided by a number of factors, among which the most important is nitrogen monoxide (NO) – natural vasorelaxsing substance, produced by vascular endothelium [2]. The impact of endothelial dysfunction (ED) on the pathogenesis of PH is extensively studied for today [5].

Aim & Objectives. The aim of our research was to examine the condition of hepatic blood flow in patients with alcoholic liver cirrhosis.

Material & methods. The research was carried out at the Gastroenterological Department of Emergency Hospital in Chernivtsi. The study involved 63 patients with ALC, complicated with I-II stage of PH (study group). As controls 37 apparently healthy persons were examined (control group). Exclusion criteria in study group were: old age, the presence of cardiac failure, kidney failure and other diseases in decompensated stage.

For the verification of the diagnosis liver biopsy, esophagogastroduodenoscopy, Doppler study of hepatic blood flow (using ultrasound and Doppler diagnostic system "En Visor HD" (Philips, USA)) were performed. We've measured lumen diameters of portal vein in it's broad segment, vena lienalis diameters, hepatic veins diameters 2-3 cm above the place of their confluence in the vena cava inferior. We've performed the calculation of the linear (Vlin.) and volume (Q) velocity of blood flow in vena lienalis, portal vein, vena cava inferior using pulse-wave sensor 2.5 MHz. Also we've calculated congestive (CI), portal-spleen venous (PSVI), spleen-vascular (SVI) and hepatic-vascular (HVI) indexes [3].

The presence of endothelial dysfunction was evaluated for content in the blood of stable metabolites of NO (nitrites, nitrates) (using Griss reagent) and by index of the endothelium-dependent vasodilation (EDVD) according to Celermajer-Sorensen test(1992) using duplex Doppler ultrasound of brachial artery at rest and at the condition of reactive hyperemia [1].

The study started after patient stay in a horizontal position for 10 minutes. The diameter of brachial artery was measured by 10 MHz transducer in longitudinal section on 2-1,5 cm above the elbow bend before and after tests with reactive hyperemia through 30-90 seconds. The cuff of sphygmomanometer was imposed to patient's arm and pumped to 50 mm Hg more than his systolic blood pressure. The duration of occlusion phase was 5 minutes. The normal reaction of brachial artery was dilatation to 10% or more of the initial diameter on the reactive hyperemia background, smaller indicators or vasoconstriction regarded as abnormal.

Studies were performed in compliance with the Council of Europe Convention on Human Rights and Biomedicine and recommendations of the Committee on Bioethics at the Presidium of Academy of Medical Sciences of Ukraine. Statistical data processing was implemented in the application of "STATISTICA 6.0". After checking the normality of distribution and equality of variances in the samples we've calculated arithmetic average and its error ($M \pm m$). When checking the statistical hypotheses, null hypothesis was rejected at significance level less than 0.05. The reliability of differences of averages of independent samples was evaluated using Student's t-test by U. Gosset. The degree of correlation between pairs of independent signs was evaluated by Pearson's coefficient of correlation – r.

which reliability was determined by comparing the calculated value of r with critical ones.

Results. Assessment of Doppler examination data revealed that in patients of the study group Vlin parameters of portal vein were increased for 16,6% with increase in its diameter compared with controls ($p<0.05$). Q in portal vein was higher than normal value for 27,4 %. Q and the diameter of vena lienalis where in the upper limit of normal. CI was slightly increased, but the difference with control was not significant statistically ($p>0,05$). PSVI was decreased for 13 %, but HVI and SVI where increased for 14,2 % and 18,7 % correspondently ($p<0.05$). Besides, ultrasound examination visualized such additional signs of portal hypertension: porto-systemic collaterals in 9 (33,3 %) patients; thickening of gallbladder wall – in 20 (74 %); moderate spleenomegaly – in 11 (40,7 %) patients. In 100% of examined patients porto-systemic and spleen-renal collaterals have been visualized in 32,5% cases we've observed a steady thickening of vascular walls of portal vein branches.

The level of plasma NO in the subgroup 1 was significantly reduced (11,63±0.82 mmol/l) (while in the subgroup 2 it was 15,32±0.77 mmol/l ($p<0,05$)) which conforms to the severe stage of ED.

Doppler examination of the brachial artery patients of the 1-st subgroup have revealed decreased EDVD – 7,3±0,18% (against 12,9±0,22% in 2nd subgroup) ($p<0,05$).

The analysis of the data determined the availability of reverse correlation between the degree of portal hypertension and the level of NO in blood ($r=0,87$) and between the diameter of portal vein and EDVD index ($r=0,54$) with a high degree of probability, indicating the important pathogenetic role of endothelial dysfunction in the development and progression of portal hypertension.

Discussion. The reasons for the endothelial dysfunction progression in patients with chronic hepatitis are: systemic inflammatory reaction, dysbiosis and endotoxemia, violation of metabolic liver function. They form a closed pathological system, the main target of which is vascular endothelium, including sinusoids of liver reticuloendothelial system.

Thus, ED accompanied with NO deficiency is characterized by violation of endothelium-dependent relaxation of blood vessels and by increasing of endothelium adhesivity, what ultimately leads to spasm, thrombosis, formation of liver tissue hypoxia and progression of fibrosis, increased pressure in the portal vein system [7].

ED may be an independent cause of poor circulation in the tissue as often provokes angiospasm or thrombosis of blood vessels (that, in fact, observed in some forms of ischemic heart disease). And ED is a risk factor for the early development of PH in patients with ALC. That is why results of our research could be used like background for modern screening of this pathology, using Doppler methods.

Conclusion. This study shows that the ED is an independent determinant of the PH development in patients with ALC. The imbalance of endothelium-dependent vasoactive substances is an important part of potentiating of hepatic hemodynamic failure and formation of high pressure in the portal vein system in such patients.

Prospects for further investigations is the search for medications to correct endothelial dysfunction in order to improve results of treatment of patients with alcoholic liver cirrhosis, complicated with portal hypertension.

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Печеночный кровоток у пациентов с алкогольным циррозом печени

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Аннотация. Данное исследование посвящено изучению печеночного кровотока у пациентов с алкогольным циррозом печени (АЦП). Наличие у них эндотелиальной дисфункции (ЭД) прямо коррелирует с диаметром воротной вены ($r=0,673$) ($p<0.05$) и с уровнем монооксида нитрогена ($r=-0.821$) ($p<0.05$), а также с показателем эндотелий-зависимой вазодилятации (ЭЗВД) ($r=-0,657$). Таким образом, ЭД является дополнительным независимым предиктором развития портальной гипертензии (ПГ) у пациентов с АЦП, поскольку продукция монооксида нитрогена у таких пациентов сильно понижена, что обусловливает повышение давления в системе воротной вены и формирование ПГ.

Ключевые слова: *алкогольный цирроз печени; портальная гипертензия; печеночный кровоток.*