In last years significant progress in recognizing mechanisms of portal hypertension pathophysiology was done. However, some unclear topics in this disease still exist. Portal hypertension is primarily caused by the increase in resistance to portal outflow and secondly by an increase in splanchnic blood flow. Portal hypertension is associated with changes in the intrahepatic, systemic, and portosystemic collateral circulation. Alterations in vasoreactivity (vasodilation and vasoconstriction) play a central role in the pathophysiology of portal hypertension by contributing to increased intrahepatic resistance, hyperdynamic circulation, and expansion of the collateral circulation. Among vasoactive substances which are activated in portal hypertension nitric oxide (NO) is considered as the most important vasodilator. Endothelin-1 and cyclooxygenase-derived prostaglandins are the main vasoconstrictor factors. The imbalance between the hyperresponsiveness and overproduction of vasoconstrictors and the hyporesponsiveness and impaired production of vasodilators are the mechanisms responsible of the increased vascular tone in the sinusoidal area of the liver. New concepts in the pathophysiology of portal hypertension find the significant role of hepatic stellate cells activated by endothelial factors which cause vascular remodeling as an adaptive response of the portal vessels wall. The most frequent causes of portal hypertension include portal vein thrombosis, storage diseases of the liver, hepatic cirrhosis (independent of etiology), hepatic veins thrombosis and schistosomiasis. Understanding the pathophysiology of portal hypertension could be of great utility in preventing and curing the complications of portal hypertension, such as esophageal varices, hepatic encephalopathy, ascites.

**Key words:** portal hypertension, pathophysiology, etiology.

**INTRODUCTION**

Recent years have brought much progress in understanding etiopathogenesis and pathophysiology of portal hypertension mechanism. Nevertheless many
issues involved remain unclear. Clinicians and investigators have learned and applied new concepts of the pathophysiology of portal hypertension.

Attention should be paid to a peculiarity of hepatic portal system. It is the unique circulatory system, which connects two systems of capillary beds; one in the wall of the small intestine and spleen and the second in sinusoidal area of the liver. The portal venous system is responsible for directing blood from parts of the gastrointestinal tract to the liver (Fig. 1). The portal venous system includes all veins which carry blood from subphrenic part of digestive tract: from pancreas, gallbladder and spleen to the liver. The hepatic portal vein is formed by the splenic vein, superior mesenteric vein and inferior mesenteric vein and devides into a right and a left branch immediately before entering the liver and then into tiny channels that run through the liver. The inferior mesenteric vein usually does not directly connect to the hepatic portal vein; it drains into the splenic vein. The left gastric vein is the significant branch of the portal vein which plays an important role in pathophysiology of portal hypertension and in formation of esophageal varices. Blood flow to the liver is unique in that it receives both oxygenated and deoxygenated blood. As a result, the partial pressure of oxygen ($pO_2$) and perfusion pressure of portal blood are lower than in other organs of the body. Blood passes from branches of the portal vein through sinusoids of the liver. Blood also flows from branches of the hepatic artery and mixes in the sinusoids to supply the hepatocytes with oxygen. This mixture percolates through the sinusoids and collects in a central vein which drains into the hepatic vein. The hepatic vein subsequently drains into the inferior vena cava. The hepatic artery originates 20% of vascular supply of the liver while the portal vein does remaining 80%.

![Fig. 1. Portal venous system](image-url)
Portal hypertension is a pathology within the scope of interest of many fields of medicine, e.g. internal medicine, gastroenterology, hepatology, surgery, radiology, ultrasonography and pediatrics. It is defined as a clinical syndrome manifested by hemodynamic changes due to difficult blood outflow from the portal bed (1, 2).

Normal portal pressure is 5-10 mmHg. Portal pressure > 12 mm Hg with concomitantly increased wedged hepatic vein pressure (WHVP) gradient between the pressure in the portal vein and inferior jejunal vein > 2-6 mm Hg diagnose portal hypertension (3, 4). Portal pressure is measured by angiography as hepatic vein pressure gradient (HVPG) which is a difference between wedged hepatic venous pressure – WHVP (pressure in the venous sinuses) and free hepatic venous pressure – FHVP. Determined difference > 5-12 mm Hg is considered as portal hypertension. Clinically it is diagnosed by catheterization of portal veins which is one of basic methods to detect portal hypertension (5).

Recent research has influenced the opinions on the pathophysiology of portal hypertension. They explicitly suggest several causative mechanisms contributing to hypertension developing in the portal circulation. It was observed that formation of collateral circulation that decompresses portal venous system does not decrease portal pressure. Those facts undoubtedly suggest other mechanisms besides anatomical occlusion are involved in developing portal hypertension (6).

From the point of view of physics blood pressure determined in the vascular bed is defined by a simple formula:

\[ \text{pressure} = \text{vascular resistance} \times \text{blood flow} \]

Thus etiopathogenetic pressure is a resultant from increased vascular resistance and/or increased volume of blood flowing through the portal vascular bed. Vascular resistance increases due to difficult outflow of the blood from the portal bed to the hepatic veins and inferior vena cava mainly as a consequence of mechanical occlusion. Its location and size depend on the cause and hemodynamic efficiency of the portal-systemic circulation (6).

Another significant factor decisive of portal pressure is increased blood flow in the portal circulation. It is connected with so called hyperkinetic circulation, which is manifested as cardiac output volume and generalized vasodilation of the vascular bed, including visceral (increased volume of systemic circulation) (6, 7). Increased portal flow in turn increases further changes within blood vessels thus enhances vascular resistance. The mechanism of enlarged visceral bed has not been described yet. Portal hypertension is associated with changes in the intrahepatic, systemic, and portosystemic collateral circulation. Alterations in vasoreactivity (vasodilation and vasoconstriction) play a central role in the pathogenesis of portal hypertension by contributing to increased intrahepatic resistance, hyperdynamic circulation, and expansion of the collateral circulation. Portal hypertension is also importantly characterized by changes in vascular structure; termed vascular remodeling, which is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment such as shear stress. These complementary processes of vasoreactivity and vascular remodeling
contribute importantly to increased intrahepatic resistance and represent important targets in the treatment of portal hypertension (8).

Biologically active vasodilators that increase portal flow seem to play an important role. They include nitric oxide (NO), glucagons, prostaglandins, bile acids, TNF-\(\alpha\), and carbon monoxide. It is their dysfunction that differentiates the response of the vascular bed in the form of vasodilation or vasoconstriction (9-13). Thus, the imbalance between the hyperresponsiveness and overproduction of vasoconstrictors (mainly endothelin-1 and cyclooxygenase-derived prostaglandins) and the hyporesponsiveness and impaired production of vasodilators (mainly NO) are the mechanisms responsible of the increased vascular tone in the sinusoidal/postsinusoidal area. Recent investigations have found different availabilities of NO in the intrahepatic circulation with preserved production in the presinusoidal area and impaired production in the sinusoidal/postsinusoidal area. Decreased vascular resistance in the presinusoidal area of the liver is caused by increased concentrations of NO and adenosine. In case of portal hypertension however NO is not produced in the presinusoidal system and its production is disturbed or substantially decreased in the sinusoidal/postsinusoidal area (11,12,14,15). Thus altered vascular vasoreactivity has to be considered an important pathogenetic factor of portal hypertension which produces vasoconstriction or vasodilation that cause increased vascular resistance, hyperkinetic circulation and formation of collateral portal circulation (8, 13).

Subsequent research has found other factors that determine the flow of blood within the portal bed responsible for increased portal pressure. Vitamin A-rich hepatic stellate cells (HSC) seem to be very important (16, 17). They make up 13-15% all hepatic cells and once activated they play the role of miofibroblasts and are considered to be the main source of collagen, fibronectin and other components of extracellular matrix (ECM). HSCs, also called Ito cells, are found in perisinusoidal spaces of the liver and significantly modulate blood flow through the hepatic sinuses. Their activity is regulated by endothelial factors: endothelin (the activation of its receptor constricts muscular cells in the portal vascular bed wall) and NO (18-24).

Portal hypertension results in blood retention in the portal area and formation of collateral circulation that directly connect the portal blood vessels to the general circulation, bypassing the liver. Because of this bypass, substances (such as toxins) that are normally removed from the blood by the liver can pass into the general circulation. It is the latter that provides an architectural picture of portal hypertension. It develops at specific places, in the area where the portal system meets systemic circulation. Adaptative capacity of the portal circulation is individual-specific and mainly depends on the size of intra- and extrhepatic collateral vascular juncture between the portal and systemic circulation. The common sites of collateral formation are: between mesenteric and rectal veins which accounts for hemorrhoids formation,
- within the abdominal wall around the umbilicus between the umbilical and superficial epigastric vein with caput medusae or less regular vascularisation within the abdominal wall,
- From the clinical and hemodynamic point of view the most important are collaterals formed in the gastro-esophageal cardial area which results in esophageal varices and varices of the gastric fundus; they affect 80-90% patients. These engorged vessels are fragile and prone to bleeding, sometimes seriously and occasionally with fatal results (6).

Considering the pathophysiology of portal hypertension these collaterals decompress the portal system. In practice it means that the larger collateral circulation has formed, the better compensation of the portal circulation. The most essential for the portal circulation is blood retention in vascular system in the portal bed. Increased portal pressure alone, without collateral circulation formed, especially without esophageal varices, does not bear any clinical significance (6, 25, 26).

Portal hypertension is a consequence generally of chronic, more rarely acute diseases affecting hepatic parenchyma or hepatic veins and as a disease it is usually concomitant with progressive impairment of liver functions. Table 1 presents etiological classification of portal hypertension including prehepatic, intrahepatic and posthepatic forms. In majority of cases prehepatic portal

Table 1. Classification of portal hypertension according Petruff (30)

<table>
<thead>
<tr>
<th>1. Prehepatic</th>
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<tbody>
<tr>
<td>Portal vein thrombosis – independent of cause, splenic vein thrombosis, cavernous transformation of the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly</td>
<td></td>
</tr>
<tr>
<td>2. Intrahepatic</td>
<td></td>
</tr>
<tr>
<td>a) presinusoidal</td>
<td></td>
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<tr>
<td>Schistosomiasis, chronic viral hepatitis HBV, HCV, cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson’s disease, hemochromatosis, amyloidosis, remaining storing diseases, polycystic liver disease, infiltration of liver hilus - independent of cause, benign and malignant neoplasms</td>
<td></td>
</tr>
<tr>
<td>b) sinusoidal</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis - independent of etiology, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy</td>
<td></td>
</tr>
<tr>
<td>c) postsinusoidal</td>
<td></td>
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<tr>
<td>Venous-occlusion disease, alcoholic hyaline sclerosis of central veins</td>
<td></td>
</tr>
<tr>
<td>3. Extrahepatic</td>
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<tr>
<td>Hepatic veins thrombosis (Budd- Chiari disease), inflammatory/neoplastic infiltration covering hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency</td>
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hypertension is caused by thrombosis of portal vein whereas tumors infiltrating portal vein are most frequent causes of posthepatic portal hypertension. In North America and Europe, intrahepatic portal hypertension is usually the result of cirrhosis of the liver. However, in less industrialized parts of the world, climate permitting, the major cause is schistosomiasis.

Clinically portal hypertension is diagnosed when portal bed stoppage has been found, with manifestations like varices formed in the esophagus, fundus of the stomach, portal gastropathy, splenomegaly with secondary hypersplenism, ascites, edema of the lower limbs; the symptoms may occur in various constellation. In case of intrahepatic hypertension due to hepatic cirrhosis esophageal varices form very soon and the symptoms of hypertension add to the clinical signs of hepatic failure. In prehepatic hypertension without impaired functions of the liver ascites is very uncommon, moderate and is easily managed by diuretics. Posthepatic hypertension is manifested by ascites extremely intense and resistant to treatment (26-29).

Concluding, portal hypertension is primarily caused by the increase in resistance to portal outflow and secondly by an increase in splanchnic blood flow, which worsens and maintains the increased portal pressure. Increased portal inflow plays a role in the hyperdynamic circulatory syndrome, a characteristic feature of portal hypertensive patients. Almost all the known vasoactive systems/substances are activated in portal hypertension, but most authors stress the pathogenetic role of endothelial factors, such as COX-derivatives, NO, carbon monoxide. Endothelial dysfunction is differentially involved in different vascular beds and consists of alteration in response both to vasodilators and to vasoconstrictors. Understanding the pathogenesis of portal hypertension could be of great utility in preventing and curing the complications of portal hypertension, such as esophageal varices, hepatic encephalopathy, ascites. Despite enormous advances in research on pathophysiology of portal hypertension unclear are the mechanisms that would clarify precisely the processes in the portal circulation leading to increased portal pressure. The syndrome is complex and needs to be thoroughly investigated.

Conflict of interest statement: None declared.

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