Pathogenesis of Portal Hypertension and Esophageal Varices

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Abstract

Esophageal varices are the major complication of portal hypertension. It is detected in about 50% of cirrhosis patients. Portal hypertensionis associated with both increased portal inflow and increased intrahepatic vascular resistance. Intrahepatic vascular resistance is caused by the architectural distortion of the liver resulting from fibrosis and by increased sinusoidal tone. Portal venous inflow results from a combination of ahyperdynamic circulatory state and increased plasma volume. In response to the increased portal pressure, collateral circulation develops by the opening of preexisting vascular channels. Esophagogastric varices are the most important collateral vessels: they tend to increase in size with the increase of portal pressure and rupture when wall tension exceeds a critical value.

Introduction

Portal hypertensionis a progressive condition of chronic liver disease and is a major cause of complications and death in patients with liver cirrhosis**[1]**.It is defined as hepatic venous pressure gradient (HVPG) of more than 5 mmHg **[2]**.It indicates increased pressure in portal venous system. Normal portal venous pressure is 10 mmHg [3]..Portal hypertension is associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastro-esophageal varices[4].

Esophageal variceal hemorrhage is a major complication of portal hypertension. Initial mortality approximates 30% and 1 year after an index hemorrhage only 34% of patients are a1ive **[5,6]**. Both initial and long-term survival rates are inversely related to the severity of the underlying liver disease **[6,7]**.

Treatment of esophageal varices requires a clear understanding of the pathophysiology of portal hypertension. In this paper, we outline the current knowledge in the pathogenesis of portal hypertension andesophageal varices.

Pathogenesis of portal hypertension and esophageal varices

Increased intrahepatic vascular resistance:

Intrahepatic endothelial dysfunction

Cirrhosis is associated with evidence of endothelial dysfunction, both in the systemic circulation and within the liver [8,9]. The endothelium under normal condition has a function to produce vasodilators. Abnormality in the endothelium related vascular reaction occurs in several pathologic conditions, that is, endothelial dysfunction [10], and have been attributed to a diminished NO bioavailability or to an increased production of endothelial-derived contracting factors, such as prostaglandin H2[11]**.** Recent studies have shown the possibilities of additional treatments as statins which decreases intrahepatic vascular resistance and improve flow mediated vasodilation of hepatic vasculature in liver cirrhosis, due to increase of NO production and improvement of hepatic endothelial dysfunction **[12,13]**.

Imbalance between hepatic vasodilators and vasoconstrictors:

The imbalance between endogenous vasoconstrictors and vasodilators in

cirrhotic liver is thought to be implicated in the pathogenesis of the dynamic component of the increased intrahepatic resistance of the cirrhotic liver **[14]**.

1. Hepatic Vasodilators

1.1, Nitric Oxide:

Nitric oxide (NO) is a powerful endogenous vasodilator, and it modulates the intrahepatic vascular tone. In the cirrhotic liver, the synthesis of NO is insufficient to compensate for the activation of vasoconstrictor systems frequently associated with cirrhosis**[15]**.Also, there isdecreased NO availability because of its utilization for nitrosylation reactions secondary to oxidative stress **[16]**, decreased endothelial nitric oxide synthetase (eNOS) activity and nitric oxide(NO) production. The net effect in the liver is intrahepatic vasoconstriction**[11,17]**.

1.2, Carbon Monoxide:

Carbon monoxide (CO), a byproduct of heme group oxidation by hemeoxygenases (HOs), is considered as an important modulator of intrahepatic vascular resistance **[18]**. CO activates guanylatecyclase and thereby promotes smooth muscle relaxation so the inhibition of CO production increases portal resistance in normal livers, and HOs/CO system is activated in patients with liver cirrhosis**[19]**.

2. Hepatic Vasoconstrictors:

During the course of cirrhosis excess of vasoconstrictors with respect to vasodilators does progressively occur. The main vasoconstrictors are COX1-derived prostanoids, thromboxane, endothelin, angiotensin, vasopressin, and norepinephrine **[14,20,21]**.

Increased resistance to portal blood flow

It is initially caused by distortion of the hepatic vascular bed, as a consequence of both the architectural disturbances caused by the cirrhotic process and of an active contraction of several cellular elements. Contractile elements influencing the hepatic vascular bed include vascular smooth muscle cells of the intra-hepatic vasculature, activated hepatic stellate cells (HSCs) and hepatic myofibroblasts, that may compress the regenerating nodules or venous shunts within the fibrous septa **[21]**.

Increased Portal Venous Inflow:

Portal hypertension is maintained, at least in part, by an increased portal blood flow. Splanchnic hemodynamics was predominately altered in cirrhotic liver. Primarily, portal venous inflow was increased and total splanchnic arterial resistance was reduced. This provides further support for the cardinal role of increased splanchnic blood flow in maintaining chronic portal hypertension**[22]**.Mesenteric arterial vasodilation is a hallmark ofcirrhosis and contributes to both increased portal venous inflow and a systemichyperdynamic circulatory state (low systemic vascular resistance and mean arterial pressure with high cardiac output)**[23]**.

Splanchnic vasodilatation

Splanchnic blood flow tends to increase in cirrhosis, particularly in advanced stages of portal hypertension, due to the vasodilatation of arterial splanchnic vessels, both in splenic and mesenteric vascular beds and this can be initially caused by increased resistance to portal blood flowandother possible mechanisms which account for the portal hemodynamic abnormalities; neurogenic, humoral, and local mechanism**[24]**. Numerous vasodilators in the systemic circulation have been proposed as possible mediators: glucagon**[25-27]**, prostacyclin (PGI2), intestinal vasoactive peptide, histamine, substance P, estrogens, colecystokinin, ammonia, endotoxins, adenosine, biliary acids**[25]**,NO**[28-30]**, endogenous cannabinoids **[25,29]**and

carbon monoxide**[31]**.The levels of these substances increase because of impaired hepatic function or development of portosystemic collaterals, as most of them underwent hepatic metabolisms**[24]**.

Hyperdynamic Circulation:

Hyperdynamic circulation is characterized by increased cardiac output and heart rate, and decreased systemic vascular resistance with low arterial blood pressure. The condition mainly attributed to systemic and splanchnic vasodilatation**[32]**. Peripheral vasodilatation activates endogenous neurohumoral systems that cause sodium retention, which leads to expansion of the plasma volume, followed by an increase in the cardiac index which in turn aggravates portal hypertension **[33]**.Portal venous inflow is affected by hyperdynamic circulation, which is characterized by low systemic resistance, plasma volume expansion, and high cardiac index**[34]**.

Portosystemic Collateral Circulation:

In patients with portal hypertension, a large network of portal-systemic collateral veins develops. Frequent and significant pathways of collaterals consist of esophageal collateral which includes esophageal varices and veins outside the esophageal wall extending from the left and short gastric veins**[35-37]**.

Morphologic pattern of esophageal varices

Esophageal varices can be divided into two main topographical groups:

1- Internal varices: Include dilated interepithelial, subepithelial and submucosal venous plexuses buging into the esophageal lumen **[38]**. The submucosal or deep intrinsic veins become massively enlarged and develop into tortousvariceal columns **[39]**.

2- External varices: External varices are embeded in the outer fibrous coat of the esophagus **[38]**.

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