DEFINITIONS

Portal hypertension is defined as an increase in the portal venous pressure gradient (i.e., portal pressure–inferior vena cava pressure), which is a function of portal venous blood flow and intrahepatic and portal collateral resistance.

Portal hypertension results in collateral formation between systemic and portal circulation. Common sites of collateral circulation have been shown in the table below. Portal hypertension results in development of varices at these sites with subsequent rupture and gastrointestinal bleeding. Esophageal variceal rupture is the most common cause of portal hypertension-related GI bleeding.

Table: Sites of Collateral Formation in Portal Hypertension

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<table>
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<td>1.</td>
<td>Distal esophagus</td>
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<td>2.</td>
<td>Stomach</td>
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<td>3.</td>
<td>Rectum</td>
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<td>4.</td>
<td>Umbilicus</td>
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<td>5.</td>
<td>Retroperitoneum</td>
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PRESSURE

Portal venous pressure is directly related to blood flow and resistance through the liver as described by Ohm’s law, i.e., \( P = Q \times R \), where \( P \) is the pressure along a vessel, \( Q \) is the flow, and \( R \) is the resistance to the flow.

Portal hypertension may result from both the increased in flow and in resistance. Resistance is due to architectural distortion and regenerating nodules which cause resistance to the portal blood flow. There is an active intrahepatic vasoconstriction that accounts for 20–30% of the increased intrahepatic resistance, which is mostly due to a decrease in the endogenous production of nitric oxide. Endothelin-I also contributes to increased intrahepatic vasoconstriction in portal hypertension by enhancing hepatic stellate cell contractility. Vasoconstrictive mediators are angiotensin, thromboxane, and leukotrienes.

In addition to resistance, increase in flow is also responsible for portal hypertension. There is hyperdynamic circulation characterized by splanchnic vasodilatation, reduced mean arterial pressure, and increased cardiac output. The hyperdynamic circulatory state of cirrhosis is well-known, but it is not widely appreciated that the heart itself can be affected in patients with cirrhosis.

Vasodilatation is mainly in splanchnic bed resulting in increased portal blood flow. In the liver, increased intrahepatic resistance is due to decreased production of vasodilatory nitric oxide, but in splanchnic circulation increased resistance is due to increased blood flow.

HEMODYNAMIC MEASURES OF PORTAL HYPERTENSION

Wedged Hepatic Venous Pressure

It is obtained by placing a catheter in the hepatic vein and wedging it into a small branch or, better still, by inflating a balloon and occluding a larger branch of the hepatic vein. The wedged hepatic venous pressure (WHVP) has been shown to correlate very closely with portal pressure in cirrhosis.

Hepatic Vein Pressure Gradient

It is the difference between WHVP and free hepatic venous pressure. The normal hepatic vein pressure gradient (HVPG) is 3–5 mmHg. HVPG is normal in presinusoidal cause of hypertension, i.e., extraportal venous hypertension (EHV). Esophageal varices do not develop unless HPG increases to ≥10 mm. Variceal bleeding and ascites occur when the value reaches ≥12 mm. Studies have demonstrated that if HVPG falls to ≤12 mm either with drug treatment or spontaneously, variceal bleeding is totally prevented. It has been seen that more than 20% decrease in HVPG from baseline offers total protection from variceal bleeding.

In addition, a good hemodynamic response is independently associated with a decreased risk of ascites and spontaneous bacterial peritonitis on follow-up and is an independent predictor of survival. HVPG is helpful in determining the cause of portal hypertension like presinusoidal, sinusoidal, or postsinusoidal, and to monitor patients in prevention of variceal bleeding. Other measures of portal pressure are splenic pulp pressure, portal vein pressure, and endoscopic variceal pressure. HVPG is a safe
procedure in cirrhosis of liver, and its levels are higher among those with ascites large esophageal varices and poorer Child Pugh class. It is however used as a clinical tool in very few centers in India due to the fact that it is an invasive procedure and need for repetitive measurement.

Classification of portal hypertension

Prehepatic

- Portal vein thrombosis
- Splenic vein thrombosis

Hepatic

- Presinusoidal
  - Schistosomiasis
  - Primary biliary cirrhosis
  - Idiopathic portal hypertension
- Noncirrhotic portal fibrosis

Sinusoidal

- Alcoholic cirrhosis
- Cryptogenic cirrhosis
- Post necrotic cirrhosis
- Alcoholic hepatitis

Postsinusoidal

- Veno-occlusive disease
- Posthepatic
- Budd Chiari syndrome
- IVC obstruction
- Constrictive pericarditis

Portal blood flow

Portal hemodynamics can be measured non-invasively using color Doppler. In patients with cirrhosis, there is decreased portal venous blood flow (PVBF) and portal flow velocity (PFV). This decrease correlated with severity of liver disease as measured by Child-Pugh score. There is significant decrease in PVBF and PFV in patients with ascites. The association between low PVBF and PFV in patients with PHG probably reflects occurrence of PHG in patients with more severe liver disease.

However, one must keep in mind that absolute values of PVBF, PFV and GMBF may vary in different studies because of variations in Doppler measurement, observer variability and differences in collateral flow.

The congestion index (CI) is defined as the ratio of cross-sectional area of the portal vein (cm²) and the blood flow velocity (cm/sec). The vessel size increases and the flow velocity decreases in chronic liver disease, so the ratio decreases with PHT. The pathophysiology of variceal rupture is based on Laplace's law. Laplace's law states that variceal wall tension is directly related to transmural pressure and varix radius and inversely related to variceal wall thickness, thus combining all three of these variables.

The three key variables that are predictive of variceal bleeding are Child-Pugh class, variceal size, and the presence and severity of red wale markings. The capacity to predict variceal bleeding is especially important when considering prophylactic therapy.

Portal Hypertensive Gastropathy (PHG)

PHG is the term used to describe the endoscopic appearance of gastric mucosa, with a characteristic mosaic-like pattern with or without red spots, seen in patients with cirrhotic or noncirrhotic portal hypertension. Body and the fundus of the stomach are the predominant sites of PHG distribution, rarely present in the gastric antrum. Similar changes are seen in small intestine and colon also, which are termed portal hypertensive enteropathy and colopathy, respectively.

Endoscopically, PHG is classified into mild and severe grade. In mild PHG, gastric mucosa is reddened, edematous with a snake skin or mosaic pattern. When it has discrete cherry red spots, fine pink speckling, or scarlatina type rash, collectively called red marks, PHG is severe. PHG occurs in up to 65% of all patients with cirrhosis and portal hypertension. Mild PHG is seen in 65–90% of patients, whereas 10–25% patients have severe PHG.

The etiopathogenesis of the condition is controversial. Most consistent findings appear to be changes in NO production, tumor necrosis factor-alpha (TNF-α) synthesis, and sensitivity to prostaglandin inhibition.

There are definite alterations in gastric blood flow in PHG. Duration of cirrhosis, but not the degree of liver dysfunction, correlates with the development of PHG.

Gastric mucosal blood flow in PHG

Portal hypertension leads to altered blood flow in the gastric microcirculation. This altered hemodynamics may be responsible for marked sensitivity to gastric mucosal damage in cirrhotic subjects. Gastric mucosal lesions are frequently observed in patients with liver cirrhosis and portal hypertension.

Measurement of gastric mucosal blood flow (GMBF) on laser Doppler velocimetry (LDV) is based on the principle of scattering of light by movements of red blood cells as they course through the mucosa.

In our study comparing gastric mucosal blood flow (GMBF) and hepatic perfusion index in normal subjects with that in patients with portal hypertension with or without portal hypertensive gastropathy, patients with portal hypertension are found to have significantly reduced GMBF and significantly attenuated vasomotor reflex in the gastric vascular bed as compared to normal subjects.

Endoscopic laser Doppler velocimetry was performed in 30 patients with portal hypertensive gastropathy due to cirrhosis.
Portal Hypertension Dynamics - Pressure, Portal Flow, Progress & Prognosis

of the liver (8 class A, 13 class B, 9 class C, according to Child-Pugh classification) and 6 normal subjects. GMBF was found to be inversely related with hepatic perfusion index. Hepatic perfusion index decreased with increase in severity of cirrhosis.

Other studies have shown increased GMBF; and advocate the use of propranolol which reduces GMBF. It has been hypothesized that in PHG, there is less mucosal blood flow and increased blood flow in submucosal, muscular, and serosal layers.

Progression

Portal hypertension as the major complication of liver cirrhosis is associated with severe consequences including bleeding of esophageal varices, gastric varices, portal hypertensive gastropathy (PHG), ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome.

An increase in the portacaval pressure gradient leads to the formation of portosystemic venous collaterals spontaneously to decompress the system. Esophageal varices, drained predominantly by the azygos vein, are clinically the most important collaterals because of their propensity to bleed. Varices develop when pressure exceeds a threshold pressure gradient.

Liver cirrhosis is characterized by complex changes in portal and renal circulation. Splanchnic vasodilatation along with increase resistance to arteriolar flow leads to congestion. In the kidney resistance to arteriolar flow increases and organ perfusion decreases. Portal venous blood flow (PVBF) has been found to be significantly lower in patients with responsive and refractory ascites, as compared to those without ascites.

Renal artery resistance index (RARI) decreases from hilum towards the cortical renal parenchyma in cirrhotics with no ascites and responsive ascites but not in refractory ascites. RARI is inversely related to organ perfusion. High cortical RARI in patients with refractory ascites may indicate a failure of intra-renal regulatory mechanisms that preserve the cortical blood flow. This may lead to cortical ischemia and renal failure.

Prognosis

Portal hypertension secondary to intrahepatic disease has a poor prognosis. In this subset, portal hypertension is usually progressive and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for hepatopulmonary syndrome and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction.

End stage liver disease and advanced portal hypertension result in blood from splanchnic circulation, not adequately detoxified by liver entering systemic circulation. The damaged liver also produces abnormal mediators, the lungs and brain get exposed to this altered milieu resulting in hepatic encephalopathy, hepatopulmonary syndrome and portal pulmonary hypertension. The other major manifestation of advanced liver disease include variceal bleeding, ascites and hepato renal syndrome. Thus there is deterioration of the quality of life and increasing morbidity and mortality.

In patients with portal vein obstruction, episodes of bleeding may become less frequent and severe with age as a collateral circulation develops. Most patients can be treated conservatively with endoscopic methods like banding or sclerotherapy when necessary. Children may continue to experience significant bleeding during adolescence, however, and may eventually require a portosystemic shunting procedure. The outcome of cirrhosis depends on the patient’s stage. Patients with compensated cirrhosis die of liver disease only after transition to a decompensated stage. The 10-year survival rate of patients who remain in a compensated stage is approximately 90%, whereas their likelihood of decomposition is 50% at 10 years.

Predictors of survival are different in compensated and decompensated patients, with parameters of portal hypertension (varices, splenomegaly, platelet count, gamma globulin) assuming greater importance in compensated patients, whereas renal dysfunction, bleeding, and hepatocellular carcinoma are important predictive factors in patients with decompensated cirrhosis. In clinical practice, the Child-Pugh score is applicable to all cirrhotic patients, and the MELD score is used in decompensated patients to determine priority for liver transplantation. Onset of renal failure in patients with cirrhosis carries a poor prognosis. The plasma renin activity, plasma concentration of antidiuretic hormone, and serum sodium concentration have some value as predictors of survival, but in the absence of a clearly reversible cause of renal failure, treatment is largely supportive.

Liver transplantation remains the ultimate treatment for HRS. When transplantation is successful, full recovery from functional renal failure can be expected. Delaying transplantation until the onset of renal failure imposes great risks.

Medical therapy often delays progression of various complications of advanced liver disease, however liver transplant is considered the only definitive care.

REFERENCES


