Epidemiology and pathogenesis of portal vein thrombosis in adults

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INTRODUCTION

The portal vein is formed by the confluence of the splenic and superior mesenteric veins, which drain the spleen and small intestine, respectively (figure 1). Portal hypertension develops as a result of obstruction to flow within the portal venous system. It can be categorized as prehepatic, intrahepatic, or posthepatic based upon the site of obstruction to flow (table 1). The intrahepatic causes of portal hypertension have been further subdivided as presinusoidal, sinusoidal, or postsinusoidal based on the location of the obstruction to portal blood flow within the liver. Causes of extrahepatic portal vein obstruction include thrombosis and invasion or constriction by a malignant tumor.

This topic will review portal vein thrombosis (PVT), the most common cause of extrahepatic portal vein obstruction. Other important causes of noncirrhotic portal hypertension (including noncirrhotic portal fibrosis and schistosomiasis) and the clinical manifestations, diagnosis, and treatment of acute and chronic PVT are discussed separately. (See "Noncirrhotic portal hypertension" and "Acute portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management" and "Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management".)

EPIDEMIOLOGY

The incidence of PVT among patients without cirrhosis is unclear. It is thought to account for 5 to 10 percent of patients with portal hypertension in developed countries and up to a third of patients in developing countries (because of an increased frequency of infectious complications that predispose to PVT) [1,2]. Among patients with cirrhosis, PVT is common and is associated with the severity of the patient's liver disease [3,4]. Autopsy studies have reported prevalences of 6 to 64 percent, whereas studies that used ultrasonography to diagnose PVT reported prevalences of 5 to 24 percent [5]. The prevalence of PVT is estimated to be less than 1 percent in patients with compensated cirrhosis, but is 8 to 25 percent in patients who are candidates for liver transplantation [6,7].

In a study of almost 24,000 autopsies in Sweden performed between 1970 and 1982, the prevalence of PVT was 1 percent [8]. The most common predisposing conditions for PVT were cirrhosis (28 percent), primary or secondary hepatobiliary malignancy (23 and 44 percent, respectively), major infectious or inflammatory abdominal disease (10 percent), or a myeloproliferative disorder (3 percent). However, no predisposing factors were identified in 14 percent.

PATHOGENESIS

Portal vein thrombosis (PVT) in patients with a previously healthy liver is thought to be due to inherited or acquired prothrombotic states [9] (table 2). However, no apparent cause for PVT is identified in more than 25 percent of patients [10-12]. Among patients with cirrhosis, the pathogenesis is likely related to unbalanced hemostasis and slowing of portal flow [13]. (See "Overview of the causes of venous thrombosis" and "Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors".)

Inherited conditions associated with PVT include [3,14-20]:

- Factor V Leiden
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Increased factor VIII levels

The relative frequency of prothrombotic disorders in patients with PVT is illustrated by observations from two series:

- In a case-control study of patients with cirrhosis, prothrombotic states were more common in the 23 patients with PVT than in the 40 patients without PVT, including mutations in factor V Leiden (13 versus 7.5 percent), the prothrombin gene (35 versus 2.5 percent), and the *MTHFR* gene (44 versus 5 percent) [14]. Overall, a thrombophilic genotype was detected in 70 percent of patients.

- The second study compared 65 patients with PVT without overt neoplastic disease or cirrhosis with 500 patients with lower limb deep vein thrombosis (DVT) and 700 healthy controls [18]. At least one thrombophilic abnormality was detected in 40 percent of patients with PVT or DVT, compared with only 13 percent of controls. PVT was associated with the prothrombin gene mutation and deficiencies of antithrombin, protein C, and protein S. Prothrombin gene mutations were more likely in those with PVT than in those with DVT. (See "Prothrombin G20210A".)

Acquired conditions associated with PVT include [15,18,21-28]:

- Cirrhosis
- Hepatocellular carcinoma
- Philadelphia-chromosome negative chronic myeloproliferative disorders (polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis, unclassifiable myeloproliferative disorders) (see "Overview of the myeloproliferative neoplasms")
- Antiphospholipid syndrome
- Paroxysmal nocturnal hemoglobinuria
- Behçet syndrome
- Recent pregnancy or oral contraceptive use
- Abdominal inflammatory lesions including infection, pancreatitis, and inflammatory bowel disease
- Trauma

Procedures that have been associated with PVT include [15,23,26,29-32]:

- Abdominal surgery or surgical injury of the portal vein axis
- Endoscopic sclerotherapy
- Transjugular intrahepatic portosystemic shunt
- Splenectomy
- Hepatic resection
- Pancreatic islet cell transplantation

Patients often have multiple risk factors for PVT, so in general, PVT should not be attributed to a single etiology without first evaluating for other predisposing conditions [15,18,21]. In a study

of 92 patients with portal vein thrombosis, zero, one, two, three, or four simultaneous acquired or inherited risk factors were seen in 16, 47, 24, 10, and 3 percent of patients, respectively [15]. Among patients with cirrhosis, patients with PVT are more likely than patients without PVT to have mutations associated with prothrombotic states (factor V Leiden, *MTHFR*, and prothrombin gene mutations) [3,14,33].

COMPLICATIONS

Portal vein thrombosis can lead to complications such as intestinal ischemia, portal hypertension, and portal cholangiopathy.

Intestinal ischemia — Extensive thrombosis involving the mesenteric venous arches may lead to intestinal ischemia and eventually infarction [34,35]. This is typically seen in acute PVT because collaterals have not yet developed. The ischemia is likely related to obstruction of mesenteric venous outflow and reflex arterial constriction and occlusion. (See "Mesenteric venous thrombosis in adults" and "Acute portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management", section on 'Prognosis'.)

Septic portal vein thrombosis — Septic portal vein thrombosis (acute pylephlebitis) occurs when PVT develops in a patient with an abdominal focus of infection, though the source of the infection may be difficult to find. Typically, the infection is with *Bacteroides fragilis* or *Escherichia coli,* though other pathogens have also been found. (See "Pylephlebitis", section on 'Pathogenesis' and "Pylephlebitis", section on 'Microbiology'.)

Portal hypertension — Portal hypertension is responsible for the majority of the complications seen in patients with chronic PVT. It also leads to the formation of collaterals around the obstructed portal vein, known as a cavernous transformation of the portal vein or portal cavernoma.

Portal hemodynamics — Portal venous pressure is determined by the product of portal venous flow and the resistance to outflow from the portal venous system:

- Portal pressure = portal venous flow x portal venous outflow resistance

Portal hypertension is defined by a hepatic venous pressure gradient (HVPG) greater than 5 mmHg. It is usually caused by an increase in resistance in the portal-hepatic vascular bed due to obstruction to flow. In patients with PVT, it occurs because of obstruction to flow in the portal vein. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Complications of portal hypertension'.)

Differences in portal hemodynamics in the settings of acute and chronic portal vein occlusion have been studied in animal models. One model involved acutely clamping the portal vein [36]. This produced a reflex increase in splanchnic arteriolar tone that decreased flow into the portal vein and tended to nullify the effects of increased portal venous resistance from the clamp [36]. On the other hand, in an animal model of chronic portal vein stenosis, there was a paradoxical decrease in splanchnic arteriolar tone leading to increased portal flow, which compounded and perpetuated the portal hypertensive state and contributed to the hyperdynamic circulation associated with portal hypertension [37].

The hyperdynamic circulation in the portal vein stenosis model was less prominent than that seen in cirrhosis, a setting in which increased production of nitric oxide also contributes [38]. The reasons for this difference are not well understood. While it has been hypothesized that impaired hepatic reticuloendothelial function allows bacteria and endotoxins to reach the systemic circulation and activate nitric oxide production, experimental models do not support a role of endotoxin in prehepatic portal hypertension [39]. Rather than an endotoxin-induced increase in iNOS (the inducible form of NO synthetase), it is the constitutively expressed NO synthetase (eNOS) that is increased [38,40,41].

Varices — Patients with PVT frequently form varices [42]. When only a segment of the portal venous bed is obstructed, varices develop only in areas that decompress the corresponding segment. As an example, segmental portal hypertension within the splenic vein (splenic vein thrombosis) is associated with the formation of isolated gastric varices in the fundus of the stomach (picture 1). On the other hand, patients with portal vein thrombosis commonly form varices in sites other than the esophagus and stomach (ectopic varices) [43].

Ascites — Sinusoidal portal hypertension (portal pressure >12 mmHg) is usually required for the formation of ascites. Thus, patients with isolated presinusoidal or prehepatic portal hypertension (as is seen with PVT) typically do not have significant ascites unless they develop acute dilutional hypoalbuminemia during fluid resuscitation for a variceal bleed or have associated cirrhosis. By contrast, ascites more readily forms in postsinusoidal and posthepatic portal hypertension (eg, from Budd-Chiari syndrome), even in the absence of well-established cirrhosis. (See "Pathogenesis of ascites in patients with cirrhosis".)

Portal cholangiopathy — Portal cholangiopathy (also referred to as portal biliopathy) is a complication that may be seen in patients with longstanding PVT. Portal cholangiopathy develops when the venous collaterals that form in the setting of portal hypertension compress and deform the large bile ducts [44,45]. It has been hypothesized that this may lead to stricture formation, fibrous scarring of the porta hepatis, and ischemic injury to the bile ducts resulting in stricture formation and caliber irregularity. Patients with portal cholangiopathy may develop

biliary complications including pruritus, obstructive jaundice, cholecystitis, and cholangitis [44-50]. (See "Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management", section on 'Clinical manifestations'.)

SUMMARY

- Portal hypertension develops as a result of obstruction to flow within the portal venous system. It can be categorized as prehepatic, intrahepatic, or posthepatic based upon the site of obstruction to flow (table 1). As a general rule, the clinical consequences of portal hypertension are similar regardless of the cause or site of obstruction. Portal vein thrombosis (PVT) is the most common cause of extrahepatic portal vein obstruction. (See 'Introduction' above.)

- The incidence of PVT among patients without cirrhosis is unclear. It is thought to account for 5 to 10 percent of patients with portal hypertension in developed countries and up to a third of patients in developing countries. (See 'Epidemiology' above.)

- Among patients with cirrhosis, PVT is common and is associated with the severity of the patient's liver disease. The prevalence of PVT is estimated to be less than 1 percent in patients with compensated cirrhosis, but it is 8 to 25 percent in patients who are candidates for liver transplantation. (See 'Epidemiology' above.)

- PVT in a patient with a previously healthy liver is thought to be due to inherited or acquired prothrombotic states (table 2). However, no apparent cause for PVT is identified in more than 25 percent of patients. (See 'Pathogenesis' above and "Overview of the causes of venous thrombosis" and "Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors".)

- Among patients with cirrhosis, the pathogenesis of PVT is likely related to unbalanced hemostasis and slowing of portal flow.

- PVT can lead to complications such as intestinal ischemia, portal hypertension, and portal cholangiopathy. (See 'Complications' above.)

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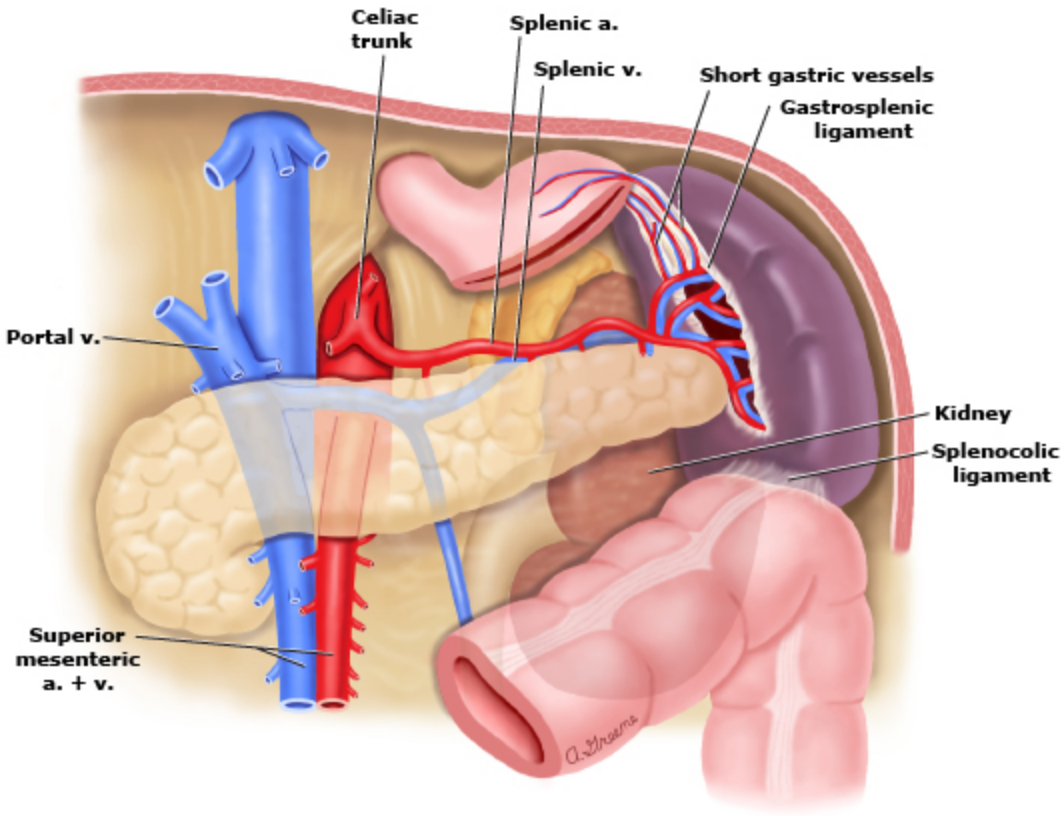
Topic 88016 Version 23.0

GRAPHICS

Vascular supply of the spleen



The splenic artery is a branch of the celiac trunk. It traverses along the superior margin of the pancreas toward the spleen, branching to form up to six major arteries before entering the spleen. The splenic vein joins the superior mesenteric vein to form the portal vein.

Graphic 68680 Version 4.0

Classification of noncirrhotic portal hypertension

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Splenomegaly (eg, from lymphoma, Gaucher's disease*)
Intrahepatic
Presinusoidal
Schistosomiasis*
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis
Sarcoidosis*
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Hepatic arteriopetal fistula
Adult polycystic liver disease
Arteriovenous fistulas
Autoimmune cholangiopathy
Vinyl chloride toxicity*
Neoplastic occlusion of the intrahepatic portal vein
Mineral oil granuloma*
Sinusoidal
Arsenic poisoning
Vinyl chloride toxicity*
Drugs (eg, amiodarone, methotrexate)
Alcoholic liver disease*
Nonalcoholic fatty liver disease
Gaucher's disease*
Zellweger syndrome
Viral hepatitis

Chronic Q fever
Schistosomiasis*
Amyloid or light-chain deposition in the space of Disse
Acute hepatic injury
Mastocytosis
Agnogenic myeloid metaplasia
Acute fatty liver of pregnancy
Postsinusoidal
Sinusoidal obstruction syndrome (venoocclusive disease)
Budd-Chiari syndrome*
Alcoholic liver disease*
Chronic radiation injury
Vitamin A toxicity
Epithelioid hemangioendothelioma
Angiosarcoma
Sarcoidosis*
Mycobacterium avium or *M. intracellulare* infection
Mineral oil granuloma*
Posthepatic
IVC obstruction (eg, Budd-Chiari syndrome*)
Cardiac disease (constrictive pericarditis, restrictive cardiomyopathy)

IVC: inferior vena cava.

* May cause noncirrhotic portal hypertension via several mechanisms.

Schouten JN, Garcia-Pagan JC, Valla DC, Janssen HL. Idiopathic noncirrhotic portal hypertension. Hepatology 2011; 54:1071.

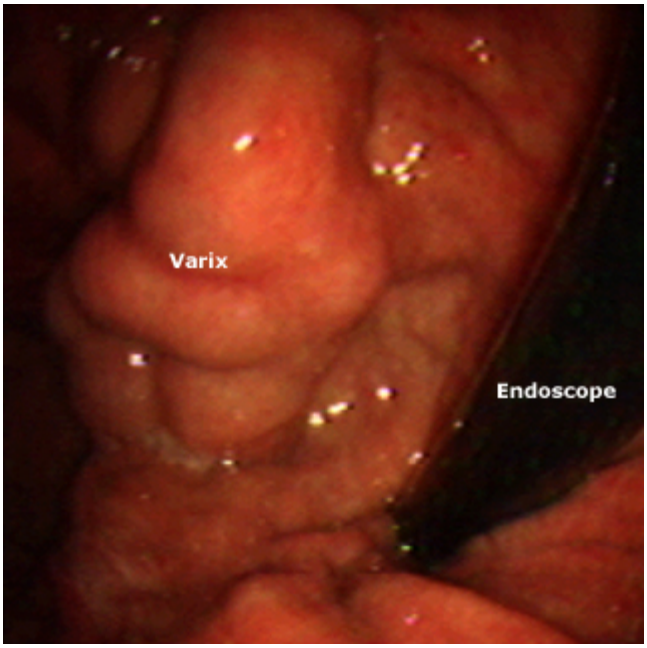
Graphic 76516 Version 4.0

Causes of portal vein thrombosis

Abdominal sepsis
Abdominal surgery
Behçet's syndrome
Cirrhosis
Collagen vascular diseases (eg, lupus)
Compression or invasion of the portal vein by tumor (eg, pancreatic cancer)
Endoscopic sclerotherapy
Hepatocellular carcinoma
Inflammatory bowel disease
Inherited thrombophilias
Myeloproliferative syndromes
Omphalitis
Oral contraceptives
Pancreatic islet cell transplantation
Pancreatitis
Paroxysmal nocturnal hemoglobinuria
Pregnancy
Retroperitoneal fibrosis
Transjugular intrahepatic portosystemic shunt
Trauma

Graphic 73799 Version 5.0

Gastric varix



Upper endoscopy of a gastric varix in the fundus of the stomach. Gastric varices can arise in conjunction with esophageal varices. They can also be isolated when they result from segmental portal hypertension due to obstruction of the splenic vein by pancreatic carcinoma or chronic pancreatitis.

Courtesy of Rome Jutabha, MD, and Dennis M Jensen, MD.

Graphic 58644 Version 1.0

Contributor Disclosures

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