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The epidemiology and pathogenesis of gastrointestinal varices

Aliya F. Gulamhusein, MD[a], Patrick S. Kamath, MD[b,*]

[a] Division of Gastroenterology and Hepatology, Toronto Center for Liver Disease, University of Toronto, Toronto, Ontario, Canada
[b] Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, Minnesota 55905

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ABSTRACT

Gastrointestinal varices are a consequence of portal hypertension that can occur in the setting of cirrhosis or extrahepatic portal vein obstruction. Increased intrahepatic vascular resistance, a hyperdynamic circulation, and increased flow through the portal and collateral venous system lead to persistently elevated portal pressures that result in angiogenesis and formation of collaterals between the portal and systemic circulation. Despite this physiological attempt at decompression, portal hypertension persists as collateral vessels have higher resistance than the normal liver. Variceal wall tension is the main factor that determines vessel rupture and bleeding occurs when tension in the wall exceeds the limit of elasticity of the vessel. Progressive distension leads to increasing resistance to flow and hemorrhage ensues when the limits of resistance to further dilation are surpassed. Gastroesophageal varices are present in 50% of patients with cirrhosis and progress in size at a rate of 8%-10% per year. Hemorrhage occurs at a rate of approximately 12% per year and large esophageal varices carry a higher risk of rupture. Gastric varices occur in 20% of patients with portal hypertension and bleed less frequently, but more severely. Cardiofundal varices have a complex vascular anatomy that is important to consider as it pertains to the effectiveness of strategies used for management. Ectopic varices make up 2%-5% of all variceal bleeding, occur more frequently in patients with extrahepatic portal hypertension, and their identification should prompt assessment of the intra-abdominal vasculature. Varices in the setting of splenic vein thrombosis should be considered a distinct entity owing to their disparate etiologic basis and treatment approach.

1. Introduction

Cirrhosis has traditionally been conceptualized as a discrete rather than dynamic disease associated with advanced degrees of histologic fibrosis. Liver injury from a variety of causes, including viral, autoimmune, metabolic, or cholestatic, lead to progressive fibrosis on liver biopsies, which are often staged using semi-quantitative systems such as METAVIR or Ishak. These staging systems report degree of fibrosis ranging from none to the pathologic "end-stage" of cirrhosis [1-3]. Although a clinical distinction between compensated and decompensated cirrhosis is often made, there is an increasing evidence that cirrhosis, both histologically and clinically, is a much more dynamic phenotype, and that classification systems ought to be more granular to better reflect the natural history and prognosis of patients with advanced liver disease [1,4]. Characterizing cirrhosis as it relates to degree of underlying portal hypertension and associated circulatory dynamics likely more accurately reflects risk of progression to clinically relevant endpoints.

Portal hypertension is a critical consequence of cirrhosis and causes many of the clinical manifestations of advanced liver disease. Though indirect, the wedged hepatic venous pressure is the preferred method for assessing portal pressure [5]. It is obtained by wedging a catheter into a small branch of the hepatic vein and has been shown to closely correlate with portal pressures [6]. The free hepatic vein pressure is then subtracted from the wedged hepatic venous pressure (to correct for increases in intra-abdominal pressure) resulting in the hepatic venous pressure gradient (HVPG). Importantly, this value is a measure of sinusoidal pressure and as such will be elevated in intrahepatic causes of portal hypertension but will be notably normal in prehepatic causes such as portal vein thrombosis (PVT) [5]. The HVPG is an important predictor of varices and clinical decompensation, including ascites, variceal hemorrhage, and hepatic encephalopathy [7-9]. A normal HVPG is 3-5 mm Hg, whereas an HVPG $>$ 10 mm Hg has been termed "clinically significant portal hypertension (CSPH)," that is, the threshold that defines risk of developing varices or clinical complications, or both [1,10]. Patients without CSPH by definition do not have varices and are at a low

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* Corresponding author.
E-mail address: Kamath.Patrick@mayo.edu (P.S. Kamath).

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5-year risk of developing them [10]. Recurrent variceal hemorrhage and ascites do not occur when the HVPG is <12 mm Hg, making this an important threshold to consider in understanding a patient's risk for decompensating events [11-13]. On the contrary, an HVPG >20 mm Hg is an important negative prognostic indicator of poor outcome in the setting of variceal hemorrhage [14].

Considering cirrhosis in terms of degree of portal hypertension allows for a more granular classification system that more closely reflects a patient's risk of liver-related outcomes. One such proposed system breaks down compensated cirrhosis into the following: (1) without portal hypertension (ie, HVPG $<$ 6 mm Hg); (2) portal hypertension that is not clinically significant (ie, HVPG between 6 and 10 mm Hg); and (3) CSPH (ie, HVPG $=$ 10 mm Hg or with the presence of collaterals) [1]. Although such a system is physiologically rational, several inherent limitations to the use of HVPG exist, including its invasive nature, lack of local expertise, variable adherence to guidelines ensuring reliability and reproducibility of measurements, and cost [5,15]. Noninvasive approaches, such as liver stiffness measurement (LSM) using transient elastography (TE), are important advancements in monitoring for fibrosis progression and worsening of portal hypertension in patients with chronic liver disease, and their increasing use is likely to have implications on the role of endoscopy in screening for gastrointestinal (GI) varices [1,10]. Although HVPG measurement remains the gold standard to assess for the presence of CSPH, LSM shows excellent correlation with HVPG values below a threshold of 10-12 mm Hg [16,17]. In fact, the recent Baveno VI consensus document suggests that in patients with virus-related chronic liver disease, noninvasive methods are sufficient to rule in CSPH, with patients with an LSM measurement by TE $>$20-25 kPa being at risk of having endoscopic signs of portal hypertension and thus warranting endoscopic assessment [10]. In contrast, a liver stiffness <20 kPa and a platelet count of $>150{,}000$ in those with virus-related chronic liver disease are at very low-risk of having varices and can avoid screening endoscopy [10]. Importantly, the diagnostic value of TE for other etiologies of liver disease remains to be clarified.

2. Diagnosis of varices

Endoscopy is the gold standard in diagnosis of GI varices. Varices identified endoscopically should simply be classified as either small or large with the suggested cutoff diameter being 5 mm [5]. Recommendations for management of medium sized varices are equivalent to those for large varices making this distinction clinically unnecessary. Although a selected subset of patients may possibly be able to avoid screening endoscopy as indicated earlier (ie, patients with viral hepatitis, LSM <20 kPa, and platelets $>150{,}000$), patients with a diagnosis of cirrhosis should undergo endoscopy to screen for the presence of GI varices. In patients with compensated cirrhosis and no varices at baseline, the interval for repeat screening should be 2-3 years. In patients with compensated cirrhosis and small varices at baseline, repeat endoscopy in 1-2 years is appropriate, with the shorter end of the interval being used particularly for patients with ongoing liver injury (eg, active alcohol use or untreated viral hepatitis). In patients with decompensated liver disease, yearly endoscopy for variceal screening is recommended [10].

3. Pathogenesis of GI varices

3.1. Mechanisms of portal hypertension

From a pathophysiologic perspective, GI varices are a consequence of portal hypertension that develops and persists as a result of increased intrahepatic vascular resistance and increased flow through the portal and collateral venous systems [18,19]. Increased vascular resistance is the inciting factor and occurs primarily owing to vascular obliteration with regenerative nodules and scar tissue compressing and occluding the intrahepatic vasculature [19-21]. This is further aggravated by endothelial dysfunction at the level of the sinusoids that occurs due to an imbalance between local vasoconstrictors, which are increased in number, and potent vasodilators, such as nitric oxide, which have been demonstrated to have reduced bioavailability in cirrhosis [18,20]. At the same time, increased blood flow through the splanchnic circulation occurs as a result of overproduction of endogenous vasodilators, such as nitric oxide, and from increased cardiac output [18,22]. Collateral vessels form between the portal and systemic circulation when the HVPG increases beyond a threshold level both through dilation of preexisting embryonic channels connecting these circulatory systems and via angiogenesis likely driven by angiogenic factors, such as vascular endothelial growth factor (VEGF) and VEGFR-2, which have been observed in splanchnic organs of animal models of portal hypertension [20,21,23]. Despite the development of these collaterals, portal hypertension persists because of the increased portal venous inflow as well as inadequate decompression by the collaterals, which have higher resistance than that of the normal liver [21,22]. Gastroesophageal varices (GOV) are the most clinically relevant of these collaterals because of their risk of growth and rupture as a result of increased pressure and flow through them (Figure).

Many of these mechanisms have been used as pharmacologic targets for clinical intervention. Splanchnic vasoconstriction can be achieved through use of vasoactive agents, such as vasopressin and somatostatin or its analogs, which decrease portal pressure through a decline in portal venous flow [18,22]. Nonselective beta-adrenergic blockade decreases portal flow both through a decline in cardiac output via its beta-1 action and splanchnic vasoconstriction via beta-2 blockade [24]. Attempts to target endothelial dysfunction and intrahepatic vascular resistance have included transfection of nitric oxide synthase genes into cirrhotic livers [20]. An increase in nitric oxide synthesis and reduced portal pressures have been observed after transfer of endothelial nitric oxide synthase and neuronal nitric oxide synthesis in in vivo models [20]. Interestingly, simvastatin has been shown to increase endothelial nitric oxide synthase expression and phosphorylation in liver tissue, which may drive declines in portal pressures observed in patients treated with this agent [20]. Finally, inhibition of angiogenesis through action at the VEGF signaling pathway has also been shown to improve portal pressures, the hyperdynamic circulation, and splanchnic neovascularization in experimental models [20].

3.2. Mechanisms of bleeding

The most accepted theory explaining the mechanism behind variceal bleeding suggests that the main factor leading to rupture is increased hydrostatic pressure inside the varix causing an increase in variceal size and decrease in wall thickness, ultimately resulting in rupture [25]. This fits with Laplace's law that suggests that wall tension is directly proportional to transmural pressure and radius and inversely proportional to wall thickness [25]. The risk of bleeding from esophageal varices (EV) is directly related to variceal size, and it has been shown that the presence of large varices is an important predictor of first hemorrhage [5]. That said, variceal wall tension is likely the main factor that determines variceal rupture. Bleeding occurs when the tension exerted over the thin wall of the varix exceeds the limit of elasticity of the vessel [26]. Tension within the wall is generated when progressive distention of the vessel leads to increasing resistance. When this