PATHOPHYSIOLOGY OF VARICEAL HEMORRHAGE

Part of "11 - PORTAL HYPERTENSION"

Two theories have been proposed to explain variceal bleeding (Fig. 11.4). The *erosion theory* suggested that varices bleed when external trauma to their thin and fragile walls is caused by the deglutition of solid food or by gastroesophageal reflux. This theory has been abandoned because of a lack of objective evidence. No relationship between eating and bleeding has been proved, nor is the incidence of reflux and esophagitis greater in patients with bleeding varices than in those without (5,60).

FIGURE 11.4. Proposed theories on the mechanism of variceal hemorrhage. Variceal bleeding occurs when the thin wall of a varix leaks. The erosion theory proposed that leaks were caused by external injury. On the contrary, today's accepted “explosion” theory proposes that variceal rupture is mainly a consequence of increased hydrostatic pressure inside a varix, which causes an increase in the tension of the variceal wall to above its elastic limit.

On the contrary, the so-called *explosion hypothesis* suggests that the main cause of bleeding is excessive hydrostatic pressure inside the varices, which is a consequence of increased portal pressure (Fig. 11.4). In support of this hypothesis, many studies have shown that variceal bleeding does not occur before the HVPG reaches a threshold value of 12 mm Hg (1,2,4) (Fig. 11.5). In addition, since the introduction of endoscopic techniques to measure variceal pressure (see below), new observations have been made to support the role of increased intravariceal pressure in variceal rupture.

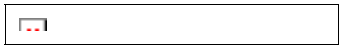
FIGURE 11.5. Variceal bleeding occurs only in patients with a hepatic venous pressure gradient above 12 mm Hg (the threshold value for variceal bleeding). (From Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985;5:419–424, with permission.)

Measurements of variceal pressure are higher in patients with previous bleeding than in nonbleeders; also, variceal pressure is a better indicator of the risk for bleeding than is the HVPG. Furthermore, longitudinal studies have shown that variceal pressure is a good prognostic indicator of the risk for bleeding and the likely response to pharmacologic therapy. Interestingly, higher variceal pressures have been documented in patients with large varices and in those with red color signs, which are more prone to bleeding.

Variceal pressure, size, and wall thickness can be integrated in the concept of *wall tension,* the inwardly directed force exerted by the variceal wall to oppose an outwardly directed force that causes further distention (Fig. 11.6). Variceal bleeding occurs when the tension exerted by the thin wall of a varix is beyond a critical value, determined by the elastic limit of the vessel. At this point, the variceal wall cannot resist further dilation, and variceal

rupture occurs. According to Frank's modification of Laplace's law, variceal wall tension (*WT*) can be defined by the following equation:

FIGURE 11.6. The factors determining variceal wall tension are interrelated. An increase in variceal pressure increases wall tension directly; it also increases the size (radius) of the varix and decreases the thickness of its wall. As indicated, repeated increases in portal pressure caused by several factors contribute to accelerate this process.



in which P_i is the intravariceal pressure, P_e the pressure in the esophageal lumen, *r* the radius of the varix, and *w* the thickness of its wall (5,60).

This equation indicates that a large variceal size exaggerates the deleterious effects of a high intravariceal pressure, so that the tension exerted on the wall of the varix is increased; the wall tension (and risk for bleeding) of a big varix with thin walls will be high at a much lower variceal pressure than will that of a small varix with thick walls.

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This may explain why large gastric fundal varices bleed at relatively low portal pressures. Similarly, the equation explains the prognostic value of the red color signs (which indicate areas where the wall of a varix is especially thin) (61,62).

The concept of variceal wall tension explains why esophageal varices are more likely to bleed than other collaterals, either in the thorax (e.g., the periesophageal veins), gut, or other abdominal organs (ectopic varices). The transmural pressure is higher in esophageal varices than in varices at other locations because negative esophageal luminal pressure occurs during inspiration. Furthermore, the lack of external tissue support of esophageal varices decreases their elastic limit. The factors determining variceal wall tension are interrelated. Increased variceal pressure increases wall tension directly; it also increases the size (radius) of a varix and, by the same mechanism, decreases wall thickness (Fig. 11.6).

Accordingly, the natural history of portal hypertension can be described as a function of variceal wall tension. Once wall tension increases to values exceeding the elastic limit of a varix, the patient experiences a first episode of bleeding. After this, the patient remains at a high risk for rebleeding unless wall tension is decreased. Similarly, primary prophylaxis protects the patient from bleeding by preventing or delaying variceal wall tension from reaching the rupture point by decreasing portal pressure and portal collateral blood flow.

The sequence of events leading to variceal hemorrhage is therefore initiated by a high portal pressure, which promotes the formation of collaterals and varices. An increase in intravascular pressure, together with a high rate of collateral blood flow, causes varices to dilatate, and as they dilate, their walls become thinner (Fig. 11.6). At this point, any further increase in variceal pressure or size or any defect in the variceal wall causes rupture and clinical hemorrhage.

In this regard, it should be remembered that portal pressure and blood flow are not static parameters; on the contrary, they vary markedly in response to physiologic stimuli. It is

well-known that portal pressure increases transiently after a meal in relation to the postprandial hyperemic response. Alcohol intake, physical exercise, and conditions that increase intraabdominal pressure can increase portal pressure abruptly (Fig. 11.6). In all these circumstances, repeated abrupt increases in portal pressure cause a progressive dilation of varices and therefore increase the risk for variceal bleeding. These observations are relevant because they suggest important new therapeutic targets to reduce the risk for variceal hemorrhage. Moreover, we have observed circadian variations in portal pressure; pressure increases during the night and decreases during the afternoon and evening. These physiologic variations in portal pressure may affect the onset of bleeding in patients at risk (those with a high variceal tension in resting conditions); a circadian pattern has been observed in variceal hemorrhage, which is more frequent at midnight, when portal pressure generally is increasing. Finally, portal pressure increases with worsening liver function and in complications such as alcoholic hepatitis, situations that are known to increase the risk for bleeding.