

Pathophysiology of variceal bleeding in cirrhotics

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SUMMARY

Liver cirrhosis is frequently complicated by the development of portal hypertension. This syndrome is characterised by a pathological increase of the portal venous pressure, which leads to the formation of portal-systemic collaterals. Among these, gastroesophageal varices are of special interest, since are responsible for the main complication of portal hypertension, massive gastrointestinal bleeding. The development of collaterals is due to different factors, including the dilation of pre-existing vessels and the action of angiogenic factors. Once formed, varices tend to dilate as a function of time, persistence of portal hypertension, and repeated physiological stimuli such as meals, ethanol consumption, exercise, and increased intrabdominal pressure which cause abrupt rises in portal pressure and/or blood flow. The concept of variceal wall tension, which combines variceal size, variceal wall thickness, and variceal pressure correlates well with the clinical observation that increased variceal pressure, increased variceal size and presence of red colour signs are independent predictors of the risk of variceal bleeding. Tension in the variceal wall is probably the decisive factor determining variceal bleeding, as when exceeding the elastic limit of the vessel, the varix ruptures. Endoscopic and endosonographic examinations may allow a better assessment of variceal pressure, size and wall thickness, and thus a more accurate evaluation of the individual risk of variceal bleeding in cirrhotic patients.

Key Words: Liver Cirrhosis, Portal hypertension, Gastroesophageal varices, Variceal size, Variceal wall tension, Variceal bleeding.

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INTRODUCTION

Cirrhosis of the liver is a highly prevalent disease worldwide, accompanied by profound disturbances in the splanchnic hemodynamics. These are not limited to the intrahepatic circulation, but involve also the splanchnic and systemic circulatory beds. These hemodynamic disorders cause the development of portal hypertension, which appears in the majority of patients with cirrhosis and is responsible for its most frequent clinical features: ascites, renal dysfunction, hepatic encephalopathy and massive gastrointestinal bleeding from ruptured gastroesophageal varices and other portal hypertension-related lesions.

Varices are present in about 50% of cirrhotics at diagnosis, but the incidence increases to up to 90% of patients on long-term follow up, with a yearly incidence of 6%.¹ Bleeding from ruptured varices is the most severe complication of portal hypertension, and represents a common cause of death in patients with cirrhosis. Despite the advances in diagnosis and therapy, mortality from acute variceal bleeding is still very high, averaging 25-35% in recent series.^{1,2}

Variceal bleeding is the last step of a chain which is initiated by an increased portal pressure, followed by the development and progressive dilation of varices, until they finally bleed (Figure 1). Therefore, to understand the mechanism of bleeding, we must understand the mechanisms leading to an increase in portal pressure and to the formation of the varices.

Haemodynamic factors in the development of portal-systemic collateral circulation

The pressure gradient in any vascular system depends on the relationship between the flow within this vascular system and the resistance that impedes that flow. According to Ohm's law the portal pressure gradient (PPG) can be defined as: $PPG = \text{Blood flow} \times \text{Resistance}$. Changes in portal pressure are therefore related to chang-

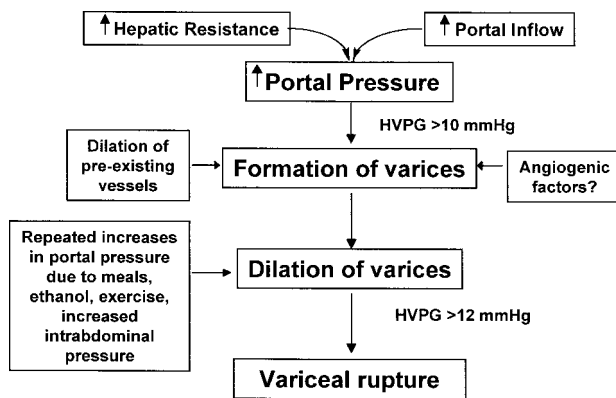


Figure 1. Pathophysiology of portal hypertension and variceal bleeding.

es in flow and resistance in the portal venous system, which includes the portal vein, the portocollateral circulation and the intrahepatic circulation. Many studies have shown that portal hypertension is initiated by increased resistance to portal blood flow. When collaterals begin to develop, the portal venous inflow increases because of splanchnic vasodilatation. The increased portal venous inflow (which is equivalent to the sum of the portal and the collateral blood flow) represents an important factor contributing to the maintenance and worsening of the portal pressure elevation.^{3,4} When collateralisation is extensive, factors modulating the collateral resistance become important determinants of portal pressure.

Increased portal pressure

Increased portal pressure is the initial and most important factor leading to the development of portal-systemic collaterals. Gastroesophageal varices represent the most common and clinically relevant part of these collaterals. A threshold increase in the portal pressure gradient (most commonly evaluated in clinical practice by its equivalent, the hepatic venous pressure gradient or HVPG) has been established for the development and rupture of esophageal varices. This is of 10-12 mmHg.⁵⁻⁸ However, above this threshold, there is no close correlation between the portal pressure elevation and the formation/rupture of esophageal varices.^{6,8} Therefore, a high pressure gradient is necessary but not sufficient for the development and rupture of esophageal varices.

Increased blood flow

The amount of blood flow diverted from portal to systemic circulation through the gastroesophageal collaterals is thought to be another important factor in the formation and progressive dilatation of varices.⁹ This is

suggested by studies evaluating azygos blood flow, an index of blood flow through gastroesophageal collaterals, including esophageal varices, in portal hypertensive patients. These studies show a close and exponential relationship between portal pressure and azygos blood flow as well as a parallelism between the presence and size of the varices and the increase in azygos blood flow.¹⁰ However, about 5% of patients with high azygos blood flow and increased portal pressure, do not have gastroesophageal varices illustrating that formation of collaterals is not always associated with development of varices.¹⁰ Conversely, other patients may have varices and a normal azygos blood flow, since in about 15% of patients gastroesophageal collaterals do not drain into the azygos vein, but into other thoracic vessels.²⁸

Factors modulating collateral resistance

The vascular resistance of the collateral vessels, although lower than that of the obstructed portal system, is nevertheless higher than normal portal resistance.^{4,11,12} Because of this, the development of portal-systemic collaterals does not lead to normalization of portal pressure, even in the extreme situation in which virtually all portal flow is diverted to the systemic circulation. Changes in vascular resistance (R) mainly depend on variations in the size (radius) of the vessel, as expressed by Poiseuille's: $R = 8\eta l / \pi r^4$ (where η is the viscosity of blood, r is the radius of the vessel, and l is the length of the system).

The collateral vessels indeed have a vascular smooth muscle layer, which, by contraction or relaxation, is able to modify vessel diameter. Different vasoactive stimuli modify collateral resistance, including nitric oxide, β - and α -adrenergic stimulation/blockade, vasopressin, endothelin and 5-hydroxytryptamine.^{13,14}

The importance of this active component modulating the development and dilation of portal-systemic collaterals is illustrated by experimental studies showing that the early administration of propranolol,¹⁵ or clonidine, an α_2 -adrenergic agonist, decreases the development of collaterals.

Increased blood volume

An increased blood volume is a constant finding in portal hypertension. This plays a key role in allowing the maintenance of the hyperkinetic circulation.¹⁶ Sequential studies have shown that increased blood volume precedes the increase in cardiac index. Low sodium diet and spironolactone reverse the increase in blood volume and significantly reduce portal pressure.^{16,17} Interestingly,

portal hypertensive animals maintained on a low sodium diet had a diminished formation of collaterals compared to animals kept on normal sodium intake.¹⁶ These results suggest that an increased blood volume may contribute to the formation of collaterals.

Anatomical factors and neoangiogenesis

Whenever portal pressure rises above normal values, collateral circulation begins to develop in an attempt to decompress the portal system. In man, different anastomotic venous systems between portal and systemic circulation have been described.¹⁸

Two mechanisms have been involved in the development of portal-systemic collateral circulation, which includes the gastroesophageal varices: dilatation of pre-existent embryonic channels connecting the portal and the systemic circulation and angiogenesis.¹⁸ Available evidence indicates that the most important factor in the formation of the portal-systemic collaterals is the dilatation of pre-existent embryonic channels triggered by the increase in portal venous pressure.¹⁹ A role for angiogenesis is suggested by the fact that portal-systemic collaterals are not merely dilated vessels, but vessels that have a marked hyperplasia and hypertrophy of their walls, which requires the activation of specific cell factors to develop.

Varices are a part of cephalad collaterals, formed through the dilatation of the left gastric (coronary) vein and the short gastric veins. The left gastric vein arises from the portal vein and is what is mainly responsible for the development of esophageal varices. The short gastric veins, arising from the splenic vein, are responsible for the dilatation of fundal and gastroesophageal varices, in association with the polar gastric vein when present.

Esophageal varices

According to the normal venous drainage of the esophagus, this organ is divided in four zones.¹⁸ These zones are (from distal to proximal esophagus): I: the gastric zone; II: the palisade zone; III: the perforating¹⁸ or transitional¹⁹ zone (which begins 2 to 3 cm above the gastroesophageal junction extending superiorly for 2 cm); and IV: the truncal zone.

Noda¹⁹ identified the transitional or perforating zone as the "critical area" for variceal rupture, the highest risk corresponding to the area of transition from palisade to perforating zone.

The palisade zone appears to be a key point in the development of esophageal varices, due to its physiological role as spontaneous communication between the

portal and the systemic circulation, through the azygos venous system.¹⁸ In normal conditions, this zone is characterized by a uniform distribution of vessels running parallel and longitudinally in the lamina propria (four to five groups of vessels also called "sudare-like" veins) as well as a venous plexus of extrinsic veins situated in the submucosa.^{18,19} Both plexuses run independently in order to protect the intrinsic vessels from the high pressure zone represented by the lower esophageal sphincter. In chronic portal hypertension, the significant increase in pressure and blood flow, causes a marked dilatation of the submucosal veins which is associated with a high congestion of the "sudare-like" veins that become superficial and visible at endoscopy as varices at this location.¹⁹ These changes are also responsible for the progressive decrease in esophageal wall thickness.

It has been hypothesized that decreases in the lower esophageal sphincter (LES) pressure may play a role in the development of varices.²⁴ Some studies suggest beneficial effects of drugs such as metoclopramide, domperidone and pentagastrin, which act increasing the LES pressure, causing a significant reduction of variceal blood flow, and variceal pressure.²⁵

Incompetent perforating veins allow retrograde blood flow from the paraesophageal to the submucosal veins and may represent an important mechanism for the dilatation of varices.²⁴

Endosonographic studies allow the *in vivo* evaluation of perforating veins by the identification of communicating vessels between paraesophageal and submucosal vessels.²⁷

The blood flow in the perforating zone has special characteristics because of its particular position separating two luminal structures with opposite cavitory pressures, and also because of the continuous variations in pressure that it has to support depending on the respiratory cycle, coughing and stretching. This may reverse the direction of blood flow and cause turbulence, which has been hypothesized to contribute to variceal dilatation and rupture.²⁴

Paraesophageal varices

Paraesophageal varices may be very large and carry most of the collateral blood flow draining into the azygos system.¹⁰

Endosonography allows the objective and accurate visualization of paraesophageal varices.^{21,22,27} The size of these vessels usually varies in parallel with that of the esophageal varices.⁸ In addition, recent studies have sug-

gested a close relationship between the presence of patent paraesophageal vessels and the recurrence of esophageal varices after eradication by sclerotherapy.²⁷

Gastric varices

The reported prevalence of fundal varices varies greatly, mainly due to its difficult diagnosis, the method used for diagnosis and the stage of portal hypertension.²⁰ There are two types of gastric varices. Type I are gastric varices that continue above the cardias as esophageal varices. Type II are isolated gastric varices, most commonly in the fundus of the stomach. While pathologic studies have found fundal varices in 40% of cirrhotic patients,¹⁸ endoscopy allows diagnosis of gastric varices in 15% to 35% of these patients.^{21,22} Endosonography has increased the number of patients in whom fundal varices are diagnosed, the published prevalences range from 55% to 78%.^{21,22} It is not yet known whether fundal varices observed at endosonography, but not at endoscopy, have a potential bleeding risk.

Clinical studies suggest that fundal varices bleed less frequently but more severely than esophageal varices.²⁰ The incidence of bleeding from fundal varices was of 15% in prospective studies.²³

In 20% of patients, varices in the fundus of the stomach flow into the left renal vein, and are part of large spontaneous spleno-renal shunts. Compared to esophageal varices, these varices are frequently observed with a lower portal pressure.

MECHANISM OF VARICEAL BLEEDING

Two theories have been proposed to explain variceal

bleeding (Figure 2). The **erosion** hypothesis proposed that variceal hemorrhage resulted from an external trauma eroding the thin and fragile wall of the varices. Esophagitis and subsequent ulceration were the most commonly suggested erosives, although some other factors, such as deglutition of solid food, were also implicated. However, this theory has been abandoned because of lack of objective supporting evidence.²⁸ At present, most authors accept the **explosion** hypothesis, that suggests that the main factor leading to rupture of the varices is the increased hydrostatic pressure inside the varix and its ensuing consequences, increasing variceal size and decreasing the thickness of its wall.^{9,28}

Role of hemodynamic factors determining variceal hemorrhage

Increased portal pressure

Many studies have shown that variceal bleeding does not occur if the PPG is not greater than 12 mmHg. Conversely if the PPG is reduced to below 12 mmHg - by means of pharmacological therapy.^{29,30} TIPS³¹ or spontaneously - there is total protection from the risk of bleeding, the varices decrease in size and may even disappear.²⁹ Also patients decreasing the HVPG substantially (i.e. more than 20% from baseline values) have a very low risk of further variceal bleeding, even if their final HVPG still greater than 12 mmHg.^{30,34}

However, above this threshold value there is no clear relationship between the magnitude of the portal pressure elevation and the risk of hemorrhage.^{9,32} This may be due to different factors, including the chronological dissociation between portal pressure measurements and bleeding, and difference in portal and variceal pressure.³²

It has been suggested that the magnitude of variceal bleeding may be defined by the equation:

$$\text{Severity of Bleeding} = (P_1 - P_2) \cdot \text{Area of variceal rent} / \text{blood viscosity}$$

in which P_1 is the intravariceal pressure (which is a function of the increased portal pressure) and P_2 is the oesophageal luminal pressure. Indeed, studies assessing portal/variceal pressure during variceal bleeding support the concept that the higher the portal pressure elevation, the worse the prognosis of the variceal bleeding episode is. Moitinho et al³³ showed in a large series of patients that the outcome of the bleeding episode, in terms of lack of control of bleeding and development of early rebleeding, was accurately predicted by the early measurement of HVPG. Patients with an admission HVPG equal or greater than 20 mmHg (40% of the to-

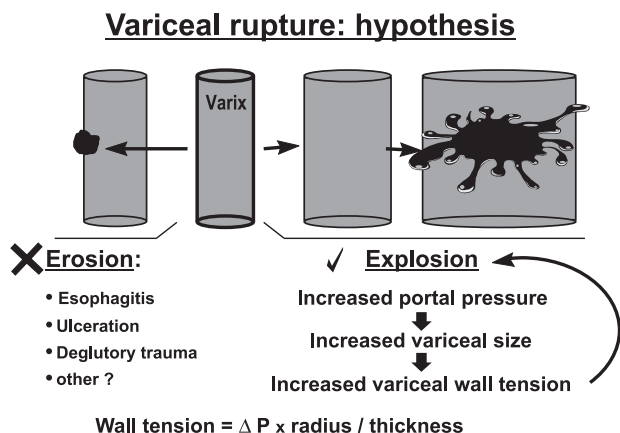


Figure 2. Theories explaining the mechanism of variceal rupture.

tal population) had a much worse outcome than patients with HVPG < 20 mmHg, as shown by a significantly higher frequency of lack of control of bleeding, early rebleeding, 1-year mortality, transfusion requirements and ICU and total hospital stay.³³ This finding may have practical implications, since it is conceivable that patients with an admission HVPG > 20 mmHg will fare better if treated aggressively (i.e., by using early TIPS), while those at low risk may not require intensive care and/or invasive therapies. Experimental studies also support the role of an increased portal pressure determining the severity of variceal hemorrhage. Preliminary data suggests that endoscopic variceal pressure measurements may have a similar prognostic value,⁴⁸ but these measurements are difficult to obtain.

On the other hand, it has been suggested that changes in portal pressure, associated with physiological circumstances, could be as important as the absolute value of HVPG determining a progressive dilation of the varices and variceal rupture.⁹ Physiological stimuli modifying portal pressure include meals, that cause a significant increase in HVPG because of the concomitant postprandial hyperemia,³⁵ ethanol consumption³⁶ and physical exercise.³⁷

It has also been shown that HVPG in patients with cirrhosis follows circadian variations, increasing at night and decreasing during afternoon/evening.³⁸ Interestingly, similar variations are also observed in the moment of presentation of variceal bleeding.³⁸

Portal hypertension may be worsened by iatrogenic factors, which may precipitate bleeding. These are well exemplified by the increase in HVPG and in the risk of bleeding following splanchnic angiography, or after the development of hepatic artery to portal vein fistulae as a complication of liver biopsy. Marked increases in portal pressure are also known to occur during alcoholic hepatitis and in patients with hepatocellular carcinoma (due to arteriovenous fistulae within the tumour or to associated portal vein thrombosis).³⁹

Variceal pressure

The introduction and validation of methods for the measurement of variceal pressure has allowed interesting observations in patients with portal hypertension. The use of a pressure-sensitive gauge allows an accurate, reproducible measurement of variceal pressure at endoscopy.^{7,40,41} Previous studies from our laboratory using this technique show that, in spite of being significantly correlated, variceal pressure is significantly lower than portal pressure, probably because of a significant resistance

along the collaterals feeding the varices, which causes a pressure drop from the portal vein to the varix.^{7,41} These results suggest that collateral circulation (and resistance to blood flow in collaterals) is an important factor modulating variceal pressure.

Patients who have bled from varices have significantly higher variceal pressure than those who have never bled despite having similar portal pressures,^{7,41} indicating that the pressure gradient between the portal vein and the varices was lower in bleeders than in non-bleeders. Resistance in the collaterals feeding the varices may be modified. Drugs contracting the LES increase the inflow resistance into the varices resulting in reduced variceal pressure and azygos blood flow, despite having no effect on portal pressure.^{25,26} Drugs used in the treatment of portal hypertension, such as β -blockers, in addition to its effects on portal venous pressure, may modify collateral resistance and thereby cause greater falls in variceal pressure than in portal pressure.⁴¹ Blood volume restitution after a hemorrhage may worsen the increase in portal pressure (even without actually expanding the intravascular volume as compared to the pre-hemorrhage values).

Changes in intra-abdominal pressure (such as those caused by ascites and paracentesis) lead to hemodynamic modifications that may have implications in variceal hemorrhage. Thus, increased intra-abdominal pressure increases portal pressure, collateral (azygos) blood flow⁴³ and variceal pressure. Conversely, total paracentesis decreases portal pressure, azygos blood flow and variceal pressure.⁴⁴

Variceal pressure is greater in patients with large varices compared to those with small varices, who are known to have a lower risk of bleeding,⁷ suggesting that a high variceal pressure is contributing to increase the size of the varices. Indeed, variceal pressure has been shown to correlate with the risk of bleeding, with the severity of the hemorrhage, and with the response to drug therapy.^{45-47,53}

Variceal size

Patients who have bled from varices have larger varices than those who have not.^{6,7,23,45,48} In addition, the risk of bleeding is directly related with the size of the varices.^{23,45,48-50} However, about 20% of patients with variceal hemorrhage have "small" varices (of less than 5 mm in estimated diameter).^{6,49} However, endoscopy is not the best method for measuring variceal size. Endosonography allows more objective and accurate measurements of variceal size.^{27,51,52}

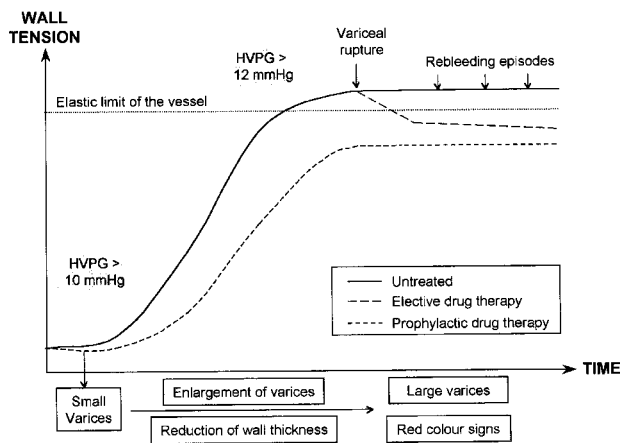


Figure 3. Natural history of esophageal varices as a function of variceal wall tension.

Variceal wall tension

Variceal bleeding is thought to occur when the tension exerted over the thin wall of the varices goes beyond a critical value determined by the elastic limit of the vessel. In other words, the progressive vessel distension generates an increasing resistance to further distension (wall tension).⁹ When reaching the elastic limit of the vessel, the variceal wall cannot increase its resistance to further dilatation, leading to variceal rupture⁹ (Figure 3).

Tension in the wall of the varix may be the decisive factor determining variceal rupture.^{7,9} According to Frank's modification of the Laplace's law,⁹ variceal wall tension is directly proportional to the transmural variceal pressure (the gradient between variceal and intraesophageal pressures) and the radius of the varix, and inversely proportional to the thickness of the variceal wall.

This pathophysiological concept fits perfectly with clinical observations showing that increased variceal pressure, increased variceal size and presence of red colour signs (markers of reduced wall thickness) are independent predictors of the risk of variceal bleeding.^{7,23,45,48-50}

The combination of the measurements of variceal pressure, variceal size and thickness of variceal wall at endoscopic and endosonographic examinations⁵¹⁻⁵³ may allow a better assessment of the variceal wall tension, which is likely to reflect the bleeding risk in patients with portal hypertension.

REFERENCES

1. Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Trai-

- na M, Madonia S, Luca A, Guerrera D, Puleo A, D'Antoni A. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ (eds). Portal hypertension: pathophysiology and treatment. Blackwell Scientific Publications. Oxford, 1994; pp.72-92
- Pascal JP, Calès P, Desmorat H. Natural history of esophageal varices. In: Bosch J, Rodés J (eds). Recent advances in the pathophysiology and therapy of portal hypertension. Serno Symposia Review No.22. Rome,1989; pp. 127-142.
 - Vorobioff J, Bredfeldt JE, Groszmann RJ. Hyperdynamic circulation in portal-hypertensive rat model: a primary factor for maintenance of chronic portal hypertension. *Am J Physiol* 1983; 244:G52-G57.
 - Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. *Gastroenterology* 1984; 87:1120-1126.
 - Viallet A, Marleau D, Huet PM, Martin F, Farley A, Villeneuve JP, Lavoie P. Hemodynamic evaluation of patients with intrahepatic portal hypertension. Relationship between bleeding varices and the portohepatic gradient. *Gastroenterology* 1975; 69:1297-1300.
 - García-Tsao G, Groszmann RJ, Fisher RI, Conn HO, Atterbuty CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985; 5:419-424.
 - Rigau J, Bosch J, Bordas JM, Navasa M, Mastai R, Kravetz D, Bruix J, Feu F, Rodés J. Endoscopic measurement of variceal pressure in cirrhosis: correlation with portal pressure and variceal hemorrhage. *Gastroenterology* 1989; 96:873-880.
 - Escorsell A, Ferayorni L, Bosch J, García-Pagán JC, García-Tsao G, Grace ND, Rodés J, Groszmann RJ. The portal pressure response to β -blockade is greater in cirrhotic patients without varices than in those with varices. *Gastroenterology* 1997; 112:2012-2016.
 - Polio J, Groszmann RJ. Hemodynamic factors involved in the development and rupture of esophageal varices: a pathophysiologic approach to treatment. *Semin Liver Dis* 1986; 6:318-331.
 - Bosch J, Mastai R, Kravetz D, Bruix J, Rigau J, Rodés J. Measurement of azygos venous blood flow in the evaluation of portal hypertension in patients with cirrhosis: clinical and hemodynamic correlations in 100 patients. *J Hepatol* 1985; 1:125-139.
 - Kroeger RJ, Groszmann RJ. Increased portal venous resistance hinders portal pressure reduction during the administration of beta-adrenergic blocking agents in a portal hypertensive model. *Hepatology* 1985; 5:97-101.
 - Blei AT, Gottstein J. Isosorbide dinitrate in experimental portal hypertension. A study of factors that modulate the hemodynamic response. *Hepatology* 1986; 6:107-111.
 - Liao JF, Yu PC, Lin HC, Lee FY, Kuo JS, Yang MC. Study on the vascular reactivity and α_1 -adrenoceptors of portal-hypertensive rats. *Br J Pharmacol* 1994; 111:439-444.
 - Cummings SA, Groszmann RJ, Kaumann AJ. Hypersensitivity of mesenteric veins to 5-hydroxytryptamine and

- ketanserine-induced reduction of portal pressure in portal-hypertensive rats. *Br J Pharmacol* 1986; 89:501-513.
15. Lin HC, Soubrane O, Cailmail S, Lebrec D. Early chronic administration of propranolol reduces the severity of portal hypertension and portal-systemic shunting in conscious portal-vein stenosed rats. *J Hepatol* 1991; 13:213-219.
 16. Genecin P, Polio J, Groszmann RJ. Na restriction blunts expansion of plasma volume and ameliorates hyperdynamic circulation in portal hypertension. *Am J Physiol* 1990; 259:G498-G503.
 17. García-Pagán JC, Salmerón JM, Feu F, Luca A, Ginès P, Pizcueta P, Clària J, Píera C, Arroyo V, Bosch J, Rodés J. Effects of low sodium diet and spironolactone on portal pressure in patients with compensated cirrhosis. *Hepatology* 1994; 19:1095-1099.
 18. Vianna A. Anatomy of the portal venous system in portal hypertension. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodés J (eds).
 19. Noda T. Angioarchitectural study of esophageal varices (with special reference to variceal rupture). *Virchows Arch A* 1984; 404:381-392.
 20. Sarin SK. Diagnostic issues: portal hypertensive gastropathy and gastric varices. In: De Franchis R (ed). *Portal hypertension II (proceedings of the second Baveno International Consensus Workshop)*. Blackwell Science. Oxford, 1996; pp.30-55.
 21. Caletti G, Brocchi E, Baraldini M, Ferrari A, Gibilaro M, Barbara L. Assessment of portal hypertension by endoscopic ultrasonography. *Gastrointest Endosc* 1990; 36:S21-S27.
 22. Boustière C, Dumas O, Jouffre C, Letard JC, Patouillard B, Etaix JP, Barthelemy C, Audigier JC. Endoscopic ultrasonography classification of gastric varices in patients with cirrhosis. Comparison with endoscopic findings. *J Hepatol* 1993; 19:268-272.
 23. Kim T, Shijo H, Kokawa H, Tokimitsu H, Kubara K, Ota K, Akiyoshi N, Iida T, Yokoyama M, Okumura M. Risk factors for hemorrhage from gastric fundal varices. *Hepatology* 1997; 25:307-312.
 24. McCormack TT, Rose JD, Smith PM, Johnson AG. Perforating veins and blood flow in esophageal varices. *Lancet* 1983; 2:1442-1444.
 25. Mastai R, Grande L, Bosch J, Bruix J, Rigau J, Kravetz D, Navasa M, Pera C, Rodés J. Effects of metoclopramide and domperidone on azygos venous blood flow in patients with cirrhosis and portal hypertension. *Hepatology* 1986; 6:1244-1247.
 26. Saraya A, Sarin SK. Effects of intravenous nitroglycerin and metoclopramide on intravariceal pressure: a double-blind, randomized study. *Am J Gastroenterol* 1993; 88:1850-1853.
 27. Liu JB, Miller LS, Feld RI, Barbarevech CA, Needleman L, Goldberg BB. Gastric and esophageal varices: 20-MHz transnasal endoluminal ultrasonography. *Radiology* 1993; 187:363-366.
 28. Bosch J. ¿Porqué sangran las varices? *Med Clin (Barc)* 1984; 82:401-403.
 29. Groszmann RJ, Bosch J, Grace N, Conn HO, García-Tsao G, Navasa M, Fisher R, Bermann R, Rofe S, Patrick M, Rodés J. Hemodynamic events in a prospective randomized trial of propranolol vs placebo in the prevention of the first variceal hemorrhage. *Gastroenterology* 1990; 99:1401-1407.
 30. Feu F, García-Pagán JC, Bosch J, Luca A, Terés J, Escorsell A, Rodés J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal hemorrhage in patients with cirrhosis. *Lancet* 1995; 346:1056-1059.
 31. Casado M, Bosch J, García-Pagán JC, Bru C, Bañares R, Bandi JC, Escorsell A, Rodríguez-Laiz JM, Gilabert R, Feu F, Schorlemer C, Echenagusia A, Rodés J. Clinical events following TIPS: correlation with hemodynamic findings. *Gastroenterology* 1998; 114:1296-1303.
 32. Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis? *Hepatology* 1997; 25:245-248.
 33. Moitinho E, Escorsell A, Bandi JC, Salmeron JM, Garcia-Pagan JC, Rodes J et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; 117:626-631.
 34. Vorobioff J, Groszmann RJ, Picabea E, Gamen M, Villavicencio R, Bordato J, Morel I, Audano M, Tanno H, Lerner E, Passamonti M. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. *Gastroenterology* 1996; 111:701-709.
 35. Lee SS, Hadengue A, Moreau R, Sayegh R, Hillon P, Lebrec D. Postprandial hemodynamic responses in patients with cirrhosis. *Hepatology* 1988; 8:647-651.
 36. Luca A, García-Pagán JC, Bosch J, Feu F, Caballería J, Groszmann RJ, Rodés J. Effects of ethanol consumption on hepatic hemodynamics in patients with alcoholic cirrhosis. *Gastroenterology* 1997; 112:1291-1296.
 37. García-Pagán JC, Santos C, Barberá JA, Luca A, Roca J, Rodríguez-Roisin R, Bosch J, Rodés J. Physical exercise increases portal pressure in patients with cirrhosis and portal hypertension. *Gastroenterology* 1996; 111:1300-1306.
 38. García-Pagán JC, Feu F, Castells A, Luca A, Hermida RC, Rivera F, Bosch J, Rodés J. Circadian variations of portal pressure and variceal hemorrhage in patients with cirrhosis. *Hepatology* 1994; 19:595-601.
 39. Yeo W, Sung JY, Ward SC, Chung SC, Lee WY, Li AK, Johnson PJ. A prospective study of upper gastrointestinal hemorrhage in patients with hepatocellular carcinoma. *Dig Dis Sci* 1995; 40:2516-2521.
 40. Bosch J, Bordas JM, Rigau J, Rigau J, Viola C, Mastai R, Kravetz D, Navasa M, Rodés J. Noninvasive measurement of the pressure of esophageal varices using an endoscopic gauge: comparison with measurements by variceal puncture in patients undergoing endoscopic sclerotherapy. *Hepatology* 1986; 6:667-672.
 41. Feu F, Bordas JM, Luca A, García-Pagán JC, Escorsell A, Bosch J, Rodés J. Reduction of variceal pressure by propranolol: comparison of the effects on portal pressure

- and azygos blood flow in patients with cirrhosis. *Hepatology* 1993; 18:1082-1089.
42. Kravetz D, Bosch J, Arderiu M, Pizcueta MP, Rodés J. Hemodynamic effects of blood volume restitution following a hemorrhage in rats with portal hypertension due to cirrhosis of the liver: influence of the extent of portal-systemic shunting. *Hepatology* 1989; 9:808-814.
 43. Luca A, Cirera I, García-Pagán JC, Feu F, Pizcueta P, Bosch J, Rodés J. Hemodynamic effects of acute changes in intra-abdominal pressure in patients with cirrhosis. *Gastroenterology* 1993; 104:222-227.
 44. Luca A, Feu F, García-Pagán JC, Jiménez W, Arroyo V, Bosch J, Rodés J. Favorable effects of total paracentesis on splanchnic hemodynamics in cirrhotic patients with tense ascites. *Hepatology* 1994; 20:30-33.
 45. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1988; 13:983-989.
 46. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: An evidence-based approach. *Semin Liver Dis*, 1999; 19:475-505
 47. Merkel C, Bolognesi M, Sacerdoti D, Bombonato G, Bellini B, Bighin R, Gatta A. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000; 32:930-934.
 48. Siringo S, Bolondi L, Gaiani S, Sofia S, Zironi G, Rigamonti A, Di Febo G, Miglioli M, Cavalli G, Barbara L. Timing of the first variceal hemorrhage in cirrhotic patients: prospective evaluation of Doppler flowmetry, endoscopy and clinical parameters. *Hepatology* 1994; 20:66-73.
 49. Lebrech D, De Fleuty P, Rueff B, Nahum H, Benhamou JP. Portal hypertension, size of the varices and risk of gastrointestinal bleeding in alcoholic cirrhosis. *Gastroenterology* 1980; 79:1139-1144.
 50. Zoli M, Merkel C, Magalotti D, Marchesini G, Gatta A, Pisi E. Evaluation of a new endoscopic index to predict first bleeding from the upper gastrointestinal tract in patients with cirrhosis. *Hepatology* 1996; 24:1047-1052.
 51. Schiano TD, Adrain AL, Cassidy MJ, McCray W, Liu JB, Baranowski RJ, Bellary SV, Miller LS. Use of high-resolution endoluminal sonography to measure the radius and wall thickness of esophageal varices. *Gastrointest Endosc* 1996; 44:425-428.
 52. Escorsell A, Bordas JM, Feu F, García-Pagán JC, Gines A, Bosch J, Rodés J. Endoscopic assessment of variceal volume and wall tension in cirrhotic patients: effects of pharmacologic therapy. *Gastroenterology* 1997; 113:1640-1646.
 53. Escorsell A, Bordas JM, Castaneda B, Llach J, Garcia-Pagan JC, Rodes J et al. Predictive value of the variceal pressure response to continued pharmacological therapy in patients with cirrhosis and portal hypertension. *Hepatology* 2000; 31:1061-1067.