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Classification of cirrhosis: The clinical use of HVPG measurements

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Abstract. The modern paradigm considers cirrhosis as a dynamic and potentially reversible disease. It consists of two different entities, compensated and decompensated cirrhosis, each with a distinct prognosis and different predictors of survival. The development of portal hypertension is a hallmark in the history of cirrhosis, and its progression parallels that of the disease. In consequence, portal pressure measurement by means of HVPG allows stratifying cirrhosis in stages with defined outcomes, prognosis, and management strategies.

Keywords: Compensated cirrhosis, decompensated cirrhosis, portal pressure

1. Introduction

The term cirrhosis has been used for decades to define a pathological and a clinical entity, which is the final pathway of many types of chronic liver injury. The term was considered sufficient to connote a broad spectrum of clinical manifestations and an overall prognosis. Additionally, this paradigm of cirrhosis also established that once settled, the process was static, irreversible and inevitably progressive to death. Our general perception of cirrhosis has changed in the last two decades. i) The advent of effective therapies, specifically antivirals, has shown that cirrhosis can be dynamic and reversible. ii) The development of clinical complications secondary to portal hypertension and associated circulatory abnormalities differentiates two distinct phases of cirrhosis with a distinct prognosis and different predictors of survival. iii) The search of therapies directed to correct the etiology (i.e. antivirals), to prevent or treat complications or to replace the failing liver has fostered the stratification of the disease in stages with defined outcomes and prognosis for which different management strategies are warranted. The development of portal hypertension has been increasingly recognized as a hallmark in the history of cirrhosis: its presence identifies the start point of the disease, and its worsening (or improvement) is associated with the development (or the resolution) of the related complications and prognosis. This article describes the prognostic relevance of portal hypertension in cirrhosis, the reasons behind considering portal pressure measurement as a validated surrogate outcome measure in cirrhosis, and the proposal to stage cirrhosis based on the degree of portal hypertension and the presence of the related complications.

2. Portal hypertension in cirrhosis

Portal hypertension is the initial consequence of cirrhosis. Portal hypertension is defined as a pathologic increase in the portal venous pressure, specifically an increase in portal pressure gradient (the gradient between the portal vein and the inferior vena cava) to levels greater than 5 mmHg [1].

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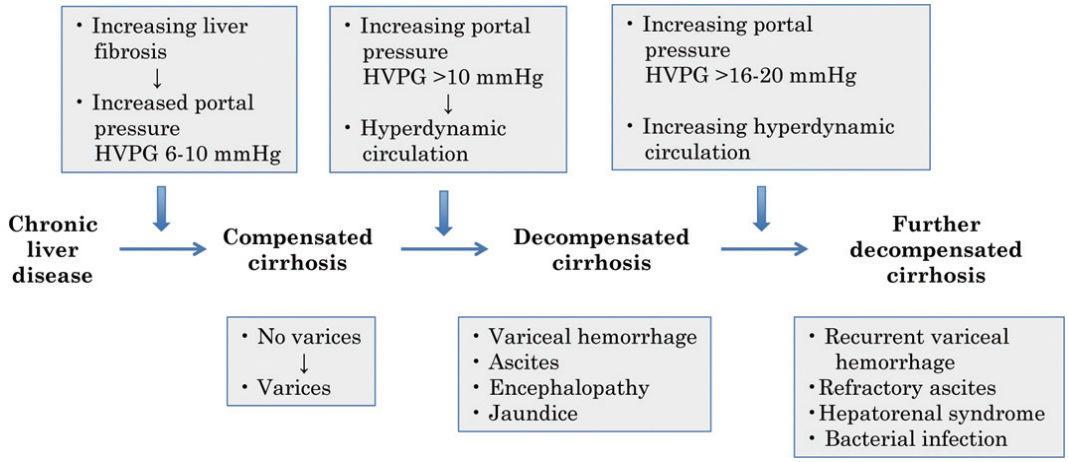

Fig. 1. Natural history of cirrhosis: relationship with increasing portal pressure.

The hepatic venous pressure gradient (HVPG) summarizes in a single measurement the interplay of factors that determine sinusoidal pressure: hepatic resistance to portal flow and portal venous (and hepatic arterial) blood flow. HVPG accurately estimates portal pressure in diseases in which the resistance to portal flow is located at the sinusoids, such as the most common etiologies of liver cirrhosis, alcoholic and viral-related [2]. In chronic liver disease, the increased intrahepatic resistance results from architectural distortion, due to fibrous tissue deposition and formation of regenerative nodules, endothelial dysfunction leading to intrahepatic vasoconstriction, thrombosis of small portal and hepatic veins, and intrahepatic vascular shunts between afferent and efferent vessels of the liver.

The initial mechanism leading to portal hypertension is an increase in intrahepatic vascular resistance to portal flow. One of the initial consequences of portal hypertension is the formation of portal-systemic collaterals, despite which portal hypertension persists because of a concomitant increase in portal venous inflow secondary to splanchnic vasodilatation [3], and because the resistance of the collaterals themselves is higher than that of the normal liver [4]. Thus, in advanced cirrhosis the rise in portal pressure is determined by hepatic and extrahepatic factors, such as splanchnic hyperemia and the resistance that portal-systemic collaterals oppose to portal blood flow.

Portal hypertension directly or indirectly leads to all the complications of cirrhosis, except for jaundice (Fig. 1). Whereas varices formation is a direct consequence of increasing portal pressure, other complications of cirrhosis (ascites, encephalopathy) result from the systemic circulatory abnormalities of cirrhosis and/or portosystemic shunting, which in turn are triggered by portal hypertension. In this regard, worsening of portal hypertension is coupled with progressive systemic and splanchnic vasodilation, arterial hypotension, activation of the neurohumoral systems, renal sodium and water retention, and development of the hyperdynamic circulatory state [3,5]. Extreme vasodilation is associated with further decompensation of cirrhosis (i.e., refractory ascites, hyponatremia and hepatorenal syndrome). Splanchnic and systemic vasodilation is mainly due to an increased production of nitric oxide [5].

Increasing fibrogenesis characterizes the progression of chronic liver disease from a purely inflammatory state to cirrhosis, and seems to be the most important contributor to an increased HVPG as has been shown in studies of chronic alcoholic and non-alcoholic liver disease [6,7]. This contention is well supported by studies in posttransplant recurrent hepatitis C correlating fibrosis stage in liver biopsies with concurrent HVPG measurements. In this setting, collagen content quantified by computer-assisted digital image analysis strongly correlates with increased HVPG [8]. Patients with posttransplant recurrent hepatitis C and severe fibrosis assessed semiquantitatively (METAVIR fibrosis stages 3 or 4, Ishak stage $\geqslant 4$, Scheuer stage $\geqslant 2$) almost uniformly have portal hypertension (HVPG > 5 mm Hg) [9,10]. In fact, it has been shown that even in well-established cirrhosis, septal thickness and the amount of fibrosis are predictors of the presence of clinically significant portal hypertension (HVPG $\geqslant 10$ mmHg), the pressure associated with the development of complications [11].

Table 1
Staging of cirrhosis based on hemodynamic and clinical parameters

	Non-cirrhotic	Cirrhosis				
		Compensated cirrhosis			Decompensated cirrhosis	
		Stage 1	Stage 2	Stage 3	Stage 1	Stage 2
HVPG (mmHg)	<6	6–10	>10	>10	>12	>16 >20 in acute variceal bleeding
Clinical manifestation	None	No esophageal varices No ascites		Esophageal varices No ascites	Ascites Variceal hemorrhage Hepatic encephalopathy	Refractory ascites Bacterial infection Hepatorenal syndrome Recurrent variceal hemorrhage
% reduction in HVPG associated with reduced risk of outcome		Reduction of $\geqslant$ 10% from baseline: reduces risk of varices formation or clinical decompensation (ascites, hemorrhage)		Reduction to $\leqslant$ 12 mmHg: eliminates the risk of first variceal hemorrhage Reduction of $\geqslant$ 10–12% from baseline: reduces risk of first variceal hemorrhage and ascites	Reduction to $\leqslant$ 12 mmHg: eliminates the risk of recurrent variceal hemorrhage Reduction of $\geqslant$ 20% from baseline: reduces the risk of recurrent variceal hemorrhage, ascites, and death	Normalization of portal pressure (via TIPS) reduces mortality
Best prognostic assessment	Liver biopsy	HVPG (prediction of varices formation or clinical decompensation)		Endoscopy (variceal size) MELD, Child-Pugh	MELD, Child-Pugh	
Mortality (% at 1-yr)		1%		3%	10% after variceal bleeding alone, 20% after ascites alone, 30% after ascites and hemorrhage	> 60% overall, 100% in hepatorenal syndrome, 66% after bacterial infection

HVPG > 10 mm Hg, clinically significant portal hypertension.

3. HVPG to assess the severity and prognosis of chronic liver disease

HVPG measurement has evolved from being mainly used with diagnostic purposes to be considered a useful tool to assess the severity and prognosis of chronic liver disease and cirrhosis, and the risk of the associated complications:

3.1. Evaluation of fibrosis in chronic hepatitis

As mentioned above, portal hypertension correlates with fibrosis stage. An HVPG $\geqslant$ 6 mmHg indicates the presence of cirrhosis more accurately than liver histology, as it is a better predictor of clinical decompensation [9]. Therefore, identification of portal hypertension through measurements of HVPG becomes more relevant than of other parameters of disease severity, such as histological stage and can be used as a quantitative tool to address disease severity.

HVPG measurement has several advantages over liver biopsy to stage fibrosis: i) HVPG is a quantitative dynamic marker of disease progression, ii) HVPG addresses a larger area of hepatic parenchyma than liver biopsy since the pressure obtained is the average pressure of many sinusoids, which reduces the possibility of sampling error due to heterogeneity in disease progression of different areas of the liver, and iii) serial HVPG measurements can be a good tool to monitor the response to antiviral therapy in patients with advanced chronic viral hepatitis. Indeed, two recent studies have shown a significant reduction in HVPG in patients with HCV-related severe fibrosis or cirrhosis who achieve a sustained virological response to treatment [12,13].

3.2. Cirrhosis

Portal hypertension is the earliest and most important consequence of cirrhosis and plays a critical role in the development of most of the complications of the disease. In consequence, mounting evidence in the last decade has demonstrated a close relationship between the presence and degree of portal hypertension, as mea-

sured by the HVPG, and clinical events in cirrhosis (Fig. 1, Table 1).

Gastroesophageal varices do not develop until a minimal threshold HVPG of 10–12 mmHg is reached [14]. Importantly variceal hemorrhage does not occur with HVPG levels of 12 mmHg or below [14,15]. An HVPG $\geqslant$ 10 mmHg is the best predictor of the development of varices, clinical decompensation and hepatocellular carcinoma [16–18]. Therefore, an HVPG $\geqslant$ 10 mmHg has been termed "clinically significant portal hypertension". Indeed, the risk of varices formation or clinical decompensation is negligible in patients with compensated cirrhosis with an HVPG $<$ 10 mm Hg, whereas it reaches 40% at 4 years in patients with an HVPG $\geqslant$ 10 mmHg [16,17].

Clinically decompensated cirrhosis is defined by the presence of complications of portal hypertension (ascites, variceal hemorrhage, encephalopathy) or liver insufficiency (jaundice). Although each of the individual complications of portal hypertension has a definitive impact on survival in different studies [19–24], measurement of HVPG adds valuable information to the survival prediction rate in decompensated disease. In this regard, HVPG has been shown to have an independent effect on survival in addition to the MELD score in a series of patients with cirrhosis, most of them with decompensated disease [24]. In this study, each 1-mmHg increase in HVPG contributed to increase the death risk by 3%.

In decompensated cirrhosis, an HVPG $\geqslant$ 16 mmHg is an important predictor of poor outcome [26,27]. In acute variceal bleeding, an initial HVPG $\geqslant$ 20 mmHg identifies patients with greater probabilities of poor evolution and of actuarial probability of mortality at 1 year (64% vs. 20%) [28]. In this setting, normalization of portal pressure by TIPS reduces mortality [29].

3.3. Response to therapy for portal hypertension

Portal hypertension causes the development of esophageal varices, first and recurrent variceal bleeding, ascites and spontaneous bacterial peritonitis. Different thresholds of HVPG reduction have been linked to a decreased development of the complications of portal hypertension, and even with an improvement in survival. Such reductions in HVPG can be the result of drug therapy, of TIPS insertion, or of spontaneous improvement in liver disease.

A reduction of HVPG of $\geqslant$ 10% decreases the risk of varices formation in patients with compensated cirrhosis [16]. Two independent meta-analyses that summarize the available information of the relationship between changes in HVPG and complications of portal hypertension showed that a good hemodynamic response, defined by a decrease in HVPG of $\geqslant$ 20% from baseline or to $\leqslant$ 12 mmHg, markedly reduce the risk of first or subsequent episodes of variceal bleeding and also that of other complications of portal hypertension, such as ascites and spontaneous bacterial peritonitis [30,31]. Moreover, in these studies having a good hemodynamic response is associated with lower mortality. In patients with varices and no previous hemorrhage (a "healthier" population) a mere reduction of only $\geqslant$ 10–12% is associated with a reduction in first variceal hemorrhage [32–34].

The above data have several relevant implications. First, the prognosis of patients with cirrhosis can be improved if we are able to decrease HVPG at the target end-point values. Thus, to achieve the target reductions in HVPG is a therapeutic aim in cirrhosis. Secondly, portal pressure estimated by the HVPG is a validated surrogate outcome measure in the management of patients with cirrhosis, since there is a strong association between changes in the surrogate measure (HVPG) and clinical outcomes (complications of portal hypertension and survival) [35].

4. Stratification of patients with cirrhosis

The prognosis of cirrhosis is marked by the development of complications, the absence or presence of which broadly divides the disease in two distinct entities, compensated and decompensated cirrhosis, respectively. They are distinct entities because a) they have entirely different prognoses; b) predictors of death that are different and, c) for those predictors that are common to both, their hazard ratio is significantly different between entities. Within compensated and decompensated cirrhosis, one can identify subgroups that are also distinct since they have a different prognosis and probably different predictors of outcome [36].

At the non-cirrhotic stage of chronic liver disease (METAVIR F1-F3) there is no histological or clinical evidence of cirrhosis, and portal pressure is within normal range (1–5 mm Hg).

Compensated cirrhosis is defined by the absence of the clinical complications that define decompensation (specifically, ascites, variceal hemorrhage, encephalopathy and jaundice). Compensated cirrhosis can be classified based on the absence or the presence of esophagogastric varices. Although the risk of death

in patients with compensated cirrhosis is low (median survival time $>$ 12 years), patients without varices have a significantly lower mortality than those with varices [37] and these patients should be thus stratified. In patients with compensated cirrhosis it is more useful to look at predictors of decompensation and, as mentioned previously patients with an HVPG above 10 mmHg are at a significantly higher risk of developing varices and decompensation [16,17]. Since the presence of varices assumes an HVPG $\geqslant$ 10 mmHg, it is patients without varices that should be stratified by HVPG. In this patient population with very early cirrhosis, liver insufficiency is minimal or absent and portal hypertension is the predominant consequence of cirrhosis. HVPG $\geqslant$ 10 mmHg is the strongest predictor of varices formation: patients with an HVPG $<$ 10 mmHg have a 90% chance of remaining free of varices and clinical decompensation (variceal hemorrhage, ascites) at 4 years [16,17], whereas patients with an HVPG $\geqslant$ 10 mmHg develop varices at a rate of 28% at 2 years, clinical decompensation at a rate of 22% at 2 years, and have a 6-fold greater risk of hepatocellular carcinoma [16–18]. Moreover, the risk of varices formation is lower in patients that achieve an HVPG reduction $\geqslant$ 10% [16]. It is also likely that splanchnic vasodilation does not begin to develop and splanchnic hyperemia does not contribute to portal hypertension until HVPG reaches 10 mmHg [38].

Clinical decompensation occurs at a rate of 5–7% per year [37]. HVPG at these stages is above 12 mmHg. The subclassification of decompensated cirrhosis is not as well-defined as compensated cirrhosis. The risk of death in this entity is influenced not only by the degree of portal hypertension, but also by liver insufficiency and circulatory dysfunction. In fact, worsening of portal hypertension and of circulatory dysfunction result in further decompensation (refractory ascites, bacterial infection, hepatorenal syndrome) and liver-related deaths. Thus, appearance of this "further" decompensation represents a more severe stage of the decompensated cirrhosis. Indeed, the median survival time of patients with decompensated cirrhosis is of 2 years [37], sharply lower than in patients with compensated cirrhosis, and of 1 and 6.7 months in patients with hepatorenal syndrome type 1 and 2, respectively [39]. Bacterial infection increases mortality in cirrhosis by 4-fold to 66% at 1 year [40]. Although in a recent systematic review of prognosis studies HVPG was an independent predictor of death in six out of nine studies [37], the influence on prognosis of factors other than portal hypertension explains why inclusion of HVPG in addition to MELD barely increases the discriminative ability of the MELD model alone in patients with decompensated cirrhosis [25].

5. Technique to measure portal pressure

The current preferred technique to determine portal pressure is to measure the HVPG, the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP) or the inferior vena cava pressure, by hepatic vein catheterization [1,41]. The WHVP is the most common procedure used to indirectly evaluate portal pressure. The concept is the same as using the wedged pulmonary arterial pressure as a surrogate measurement of pulmonary capillary and left atrial pressure [41]. To measure the WHVP, a branch of the hepatic vein is catheterized under fluoroscopic control via a transfemoral or transjugular approach using a balloon-tipped catheter. The balloon is then inflated to completely occlude a branch of hepatic vein and the pressure, WHVP, is recorded. The fluid in the wedged or occluded hepatic venous catheter forms a continuous column with the blood in the hepatic sinusoids of a large area of the liver. At that moment, the pressure measurement represents that of the next point of free communication with the hepatic circulation, that is, the sinusoidal pressure. After recording the WHVP, the balloon is deflated and the FHVP is recorded. The latter represents the abdominal venous pressure, and is used as an internal reference point to correct for extraportal, intra-abdominal contributions to portal pressure elevation, such as by the presence of ascites. Normally, the HVPG ranges from 1 to 5 mm Hg, and pressures above this limit define the presence of portal hypertension.

In the normal liver, the low-resistance, interconnected sinusoidal network partially dissipates the pressure backup from the wedged catheter, and the WHVP is slightly lower (about 1 mm Hg) than directly-measured portal pressure. In liver cirrhosis, the intersinusoidal communications are blocked by fibrous tissue, dissipation of pressure in the wedged vessels is insignificant and the WHVP accurately estimates portal pressure [42]. It is important to note that the use of a balloon catheter instead of a straight one allows occluding a large hepatic vein branch at the lobar and sublobar level [41,43]. Thus, the WHVP pressure obtained averages the pressure of several segments of the liver and represents an accurate estimation of portal pressure.

6. Portal pressure assessment and cirrhosis staging by liver stiffness measurement

HVPG measurement has the drawbacks of being invasive and not widely available. The existence of a non-invasive method to assess portal pressure would facilitate the process of the subclassification of cirrhosis, particularly useful in compensated cirrhosis. The most promising of the non-invasive tools to monitor fibrosis progression and associated portal hypertension is liver stiffness measurement (LSM) by transient elastography [44]. The reliable and quantitative measurements of liver stiffness provided by transient elastography can be correlated with advanced fibrosis, which in turn appears to correlate with portal hypertension. The correlation between liver stiffness and HVPG is excellent in patients with HVPG values below 10 mmHg, when portal hypertension is entirely due to increased intrahepatic resistance [45], but less accurate in patients with an HVPG $>$ 10 mmHg or in those with decompensated cirrhosis in whom portal hypertension is also due to increased portal venous flow.

Several recent studies have evaluated the relationship between liver stiffness values and HVPG in patients with cirrhosis, and specifically whether liver stiffness can identify patients with significant portal hypertension. The AUROC for prediction of HVPG 10–12 mmHg ranges from 0.76 to 0.99 with a cutoff of 13.6 to 34.9 kPa [45–47]. Presence of portal hypertension (HVPG $\geqslant$ 6 mmHg) was predicted by a 8.7 kPa cutoff [48]. Interestingly, in a series of 100 patients with cirrhosis the ability to predict decompensation of a liver stiffness of $\geqslant$ 21 kPa or an HVPG $\geqslant$ 10 mmHg was similar (AUROC of 0.83 and 0.84, respectively) [49].

7. Summary

The modern paradigm considers cirrhosis as a dynamic and potentially reversible disease. It consists of two different entities, compensated and decompensated cirrhosis, each with a distinct prognosis and different predictors of survival. The development of portal hypertension is a hallmark in the history of cirrhosis, and its progression parallels that of the disease. In consequence, portal pressure measurement by means of HVPG allows stratifying cirrhosis in stages with defined outcomes, prognosis, and management strategies.

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