The Role of Hepatic Venous Pressure Gradient in the Management of Cirrhosis

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KEYWORDS

• Portal hypertension • Varices • β-blockers

KEY POINTS

- Liver catheterization with hepatic venous pressure gradient (HVPG) is the standard test for estimating the degree of portal hypertension in patients with cirrhosis.
- Patients with cirrhosis with an HVPG $\geq$ 10 mm Hg have clinically significant portal hypertension and are at risk of complications.
- The assessment of changes in HVPG is the standard for investigating new drugs for the treatment of portal hypertension.

INTRODUCTION

Cirrhosis causes an increased resistance to portal blood flow. This increased resistance results in an increase in portal pressure that subsequently activates several pathophysiologic mechanisms that lead to an increased splanchnic blood inflow, which perpetuates and aggravates portal hypertension despite the development of portal systemic collaterals.[1] Portal hypertension plays a causal mediation role in most complications of cirrhosis, including variceal bleeding, ascites, kidney dysfunction, hepatic encephalopathy, and infections. It is well established that the degree of portal hypertension is closely associated with the risk of these complications.[2] In addition, a decrease in portal pressure, either in response to specific treatments to improve portal hemodynamics or related to an improvement in the cause of cirrhosis, is associated with an improvement in prognosis. Therefore, quantifying the degree of portal hypertension provides useful information to estimate prognosis and to evaluate new therapies for portal hypertension. This article addresses the applications of measuring portal pressure in cirrhosis.

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MEASURING PORTAL PRESSURE GRADIENT IN CLINICAL PRACTICE: THE HEPATIC VENOUS PRESSURE GRADIENT

Technique

The wedge hepatic venous pressure as a readout of portal venous pressure

The portal vein is located between two capillary territories and, therefore direct measurements of the portal vein pressure require the puncture of the portal vein through the liver parenchyma, using percutaneous,[3] transjugular,[4] or, more recently, a transgastric/transduodenal approach (under endoscopic ultrasonography guidance).[5] Direct measurements are seldom used in clinical practice because of their invasiveness. In 1951, Myers and Taylor,[6] first introduced the indirect measurement of portal venous pressure by measuring the wedge hepatic venous pressure (WHVP). The principle of the technique is that if a catheter is introduced, usually through the right femoral or jugular vein into a hepatic venous radicle until it can go no further (**Fig. 1**A), occluding the vein and stopping the blood flow, the static column of blood transmits the pressure that is present in the preceding vascular territory; that is, the hepatic sinusoids. Although this is a measurement of liver sinusoidal pressure, it reflects portal pressure in the absence of pre-sinusoidal obstruction.[3] Note that because WHVP reflects the pressure in the portal vein, it does not solely measure the changes occurring in the section of the liver occluded by the catheter (ie, it does not sample a small portion of the liver). Portal pressure is determined by the structural and functional changes in the whole liver (because the entire liver contributes to hepatic resistance) and by the upstream changes in the splanchnic circulation, and these are all further modulated by the development of collaterals (**Fig. 2**). Therefore, WHVP measurement

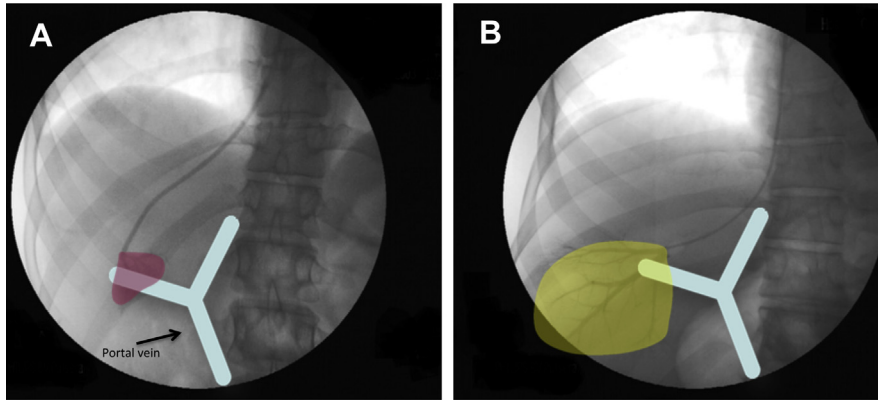
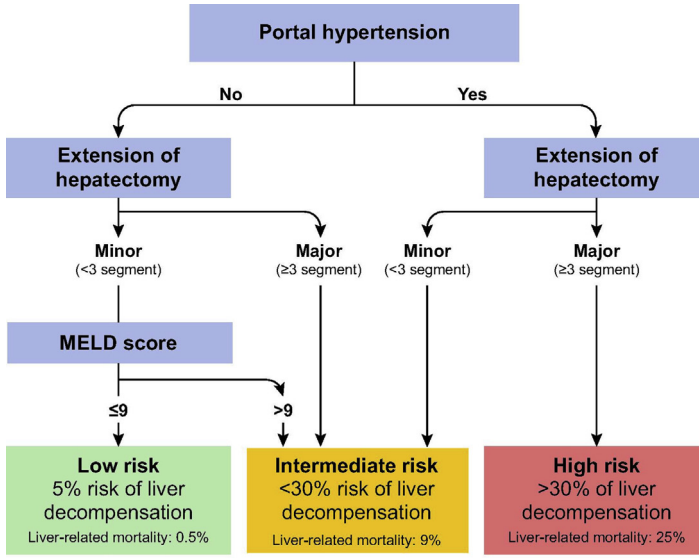


Fig. 1. End-hole catheter (*A*) and balloon catheter (*B*) techniques to measure WHVP. After occluding the hepatic vein, the static column of blood transmits the pressure of the preceding vascular territory: the hepatic sinusoids. In the absence of a presinusoidal obstruction, this equates to the pressure in the portal vein. The volume of liver transmitting pressure, painted in purple in (*A*) and in yellow in (*B*), is much larger (and thus less prone to artifacts) with the balloon catheter than with the end-hole catheter. Note that the WHVP measurement is not sampling the specific area of liver that is coloured in the figure because WHVP is a measure of portal pressure that depends on whole-liver hepatic resistance, portal blood flow, and the degree of collateralization. Once WHVP is measured, the free hepatic venous pressure (FHVP) is measured with the catheter freely floating in the hepatic vein. This FHVP permits the determination of HVPG, which can be calculated with the equation HVPG = WHVP − FHVP.



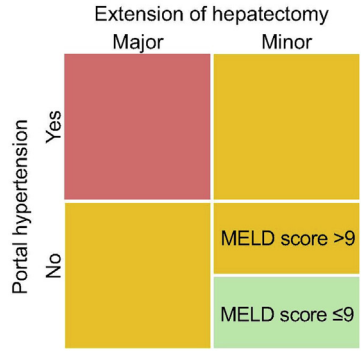


Fig. 2. Role of portal hypertension as a decision tool to select patients with early hepatocellular carcinoma for liver resection. This algorithm from the EASL guidelines for the management of liver cancer[53] is based on the hierarchical model proposed by Citterio and colleagues.[54] European Association for the Study of the Liver (EASL) guidelines define clinically relevant portal hypertension as HVPG > 10 mm Hg, which is equivalent to the concept of clinically significant portal hypertension. In the original publication of this algorithm,[54] portal hypertension was defined by the presence of esophageal varices or the coexistence of low platelet count ($<100 \times 10^3/mm^3$) and splenomegaly (>120 mm in diameter). MELD, Model for End-stage Liver Disease. (Figure reproduced from European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236, with permission. (Figure 4 in original).)

integrates the contribution of all hemodynamic pathophysiologic events occurring in cirrhosis.

WHVP has been shown to accurately reflect portal pressure in alcoholic and viral cirrhosis.[3] However, recent data suggest that, in patients with advanced nonalcoholic fatty liver disease (NAFLD) cirrhosis undergoing transjugular intrahepatic

portosystemic shunt (TIPS), there is lower agreement between WHVP and direct portal pressure than in patients with alcohol/hepatitis C.[7] In addition, WHVP was a mean 1.3 mm Hg lower than portal pressure, suggesting that WHVP tends to underestimate portal pressure in patients with NAFLD.[7] Whether this is the case at earlier stages of NAFLD cirrhosis is still uncertain.

The free hepatic venous pressure and the hepatic venous pressure gradient

Once WHVP is measured, the catheter is withdrawn to measure the free hepatic venous pressure (FHVP), which provides an internal zeroing for portal pressure and allows calculating the portal pressure gradient across the liver. Using this internal zero provides several additional advantages. Because the measurements are expressed as a gradient, the potential variations introduced by the height of the external zero (normally a water column at the level of the midaxillary line of the patient) are neutralized. In addition, it discounts the variation induced by the intra-abdominal pressure, which might be significant in patients with ascites or obesity.[4]

In 1979, Groszmann and colleagues[8] described a variation of the technique in which the FHVP and the WHVP were obtained by deflating and inflating a balloon at the tip of the catheter (**Fig. 1**B). This variation offers several advantages. Firstly, inflation and deflation of a balloon is much simpler than moving the catheter in and out of the wedged position. Secondly, it permits repeated pressure measurements of hepatic venous pressure gradient (HVPG) without moving the catheter, thus decreasing artifacts. Thirdly, the volume of the liver circulation transmitting the portal pressure is much larger than that attained by wedging the catheter, which reduces the variability of the measurements[9] (see **Fig. 1**B). A specifically designed balloon catheter that improves the rate of direct cannulation of the hepatic vein has recently been developed.[10]

Guidelines for reliable HVPG measurements have been published by different research groups,[11–15] and there have been new, recent attempts of standardization with the use of HVPG as a surrogate marker for drug development in NAFLD.[16–19] These studies have shown the feasibility of homogenizing the quality of HVPG measurements in multicenter studies.

The Controversy of Internal Zeroing

In recent years, and especially since the introduction of TIPS, many reports have used the right atrial pressure (RAP) as the internal zero reference to calculate portal pressure gradient (hepatic-atrial pressure gradient [HAPG]),[20] the rationale being that in a small number of patients, the anatomy of the hepatic vein does not allow a free-floating position of the catheter. In addition, because the esophageal varices drain mainly through the azygos vein near the right atrium, it could be hypothesized that the gradient between WHVP and RAP better reflects the hemodynamics of these varices. However, in a large cross-sectional study, La Mura and colleagues[21] showed that the HAPG had a poor agreement with HVPG. More importantly, although HVPG response to pharmacologic therapy showed an excellent predictive value for bleeding risk and survival, the response measured with HAPG did not.[21] This issue is still a source of controversy. A subsequent more recent study showed high variability in FHVP measurement depending on the position of the tip of the catheter and hepatic vein morphology, thereby recommending the use of HAPG.[20] However, until data showing a prognostic value of HAPG become available, HVPG measured with the FHVP should be the standard for diagnosis and prognosis prediction.

Another source of controversy has been the use of inferior vena cava (IVC) pressure rather than FHVP as the internal reference, especially when the difference between the

FHVP and IVC pressure is >2 mm Hg, because this suggests that the catheter is not in a fully free-floating position, or it is causing a partial obstruction of the hepatic vein. This question was addressed in a recent study showing that, even in these cases, HVPG calculated with the FHVP offers a better prognostic estimate than HVPG calculated with IVC.[22]

Complications and Tolerance

Only 1% of patients show major complications at the puncture site, including local bleeding, hematoma, and more rarely arteriovenous fistulae or Horner syndrome in the case of jugular puncture. Because of these risks, ultrasonographic guidance should always be used when available. Supraventricular arrhythmias may also occur because of the passage of the catheter through the right atrium,[13] but they are self-limiting in more than 90% of cases.

Catheterization of the hepatic vein can be performed under light sedation (midazolam, up to 0.02 mg/Kg),[23] and overall is well tolerated, although this can decrease with longer procedures (such as those assessing hemodynamic response to drugs) and is associated with worse tolerance.[24] Higher doses of midazolam or deep sedation significantly alter pressure measurements.[4,23]

APPLICATIONS OF HEPATIC VENOUS PRESSURE GRADIENT IN CIRRHOSIS

Differential Diagnosis of Portal Hypertension

Cirrhosis is the most common cause of portal hypertension in the Western world and is often easily diagnosed with specific clinical history, laboratory data, and imaging findings. However, in certain clinical contexts, alternative differential diagnosis exists.[25] Examples of these are the presence of varices without obvious morphologic changes of cirrhosis, where the main differential is noncirrhotic portal hypertension,[25,26] or ascites of unclear origin. In the latter, HVPG measurement might help differentiate between a cardiac origin (increase in both FHVP and WHVP, with normal HVPG, but, with progression to cardiac cirrhosis, HVPG might increase), tumoural ascites (normal FHVP, WHVP, and HVPG) or ascites caused by portal hypertension in the setting of cirrhosis (increased HVPG).

Table 1 shows how HVPG measurements can aid in classifying portal hypertension according to the cause and the location of the increased resistance to portal flow.

Risk Stratification in Cirrhosis

Compensated cirrhosis

The natural history of liver cirrhosis can be divided into two main phases: a long, compensated phase (median survival of 12 years) and a much shorter decompensated phase (median survival of 2 years).[27] Although there are excellent prognostic models to predict outcomes in patients with decompensated cirrhosis,[28,29] tools for risk stratification in compensated cirrhosis are limited. A major driver for decompensation in patients with cirrhosis is the development of clinically significant portal hypertension (CSPH), defined as an HVPG $\geq$ 10 mm Hg. This definition is based on cross-sectional studies that found that patients with an HVPG < 10 mm Hg did not develop esophageal varices or complications related to portal hypertension.[30] More importantly, longitudinal studies have also shown that the 5-year risk of progression to decompensation is minimal (<10%) in patients without CSPH, whereas, in patients with CSPH, the risk increases to 30-40%.[2] This concept was initially described in series in which the main causes were untreated hepatitis C and alcohol,[2] and has recently been confirmed in patients with nonalcoholic steatohepatitis (NASH)–related cirrhosis.[19] The impact of the degree of portal hypertension showed a remarkable

Table 1
Hepatic vein pressure measurements in the different types of portal hypertension

Type of PH[a]		Hepatic Vein Pressure Measurement: Wedged (WHVP)	Free (FHVP)	Gradient[b] (HVPG)
Prehepatic (portal vein thrombosis)		Normal	Normal	Normal
Presinusoidal (cirrhosis attributed to cholestatic liver disease, schistosomiasis, and idiopathic portal hypertension)[c]		Normal	Normal	Normal
Sinusoidal (cirrhosis attributed to alcohol/HCV/NASH)		↑	Normal	↑
Postsinusoidal	Sinusoidal obstruction syndrome (hepatic veno-occlusive disease)	↑	Normal	↑
	Budd-Chiari syndrome	Unable to catheterize hepatic vein		
Posthepatic	Right heart failure	↑	↑	Normal

Abbreviations: FHVP, free hepatic venous pressure; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PH, portal hypertension.
[a] PH is classified by the site of increased resistance to blood flow.
[b] Gradient or HVPG is calculated by subtracting the FHVP from the WHVP: HVPG = WHVP - FHVP.
[c] In advanced stages of presinusoidal causes of PH, the WHVP and HVPG may increase.

consistency across these studies: for every 1 mm Hg that the baseline HVPG was higher, the risk of decompensation increased by 11%.[2,31]

The development of CSPH also has major therapeutic consequences. Firstly, in patients without CSPH, treatments specifically designed to decrease portal pressure are unlikely to have a role in the management of cirrhosis, thus the main goal is to target its cause. Secondly, and as detailed later in this article, in those patients that have already reached the threshold of CSPH, elimination of the cause of cirrhosis does not always result in a regression of portal hypertension to levels less than 10 mm Hg.[32–35] Therefore, these patients require, in addition to etiologic treatments, specific treatments to decrease portal pressure to prevent decompensation. Thirdly, reaching the threshold of CSPH has an impact on the pathophysiology of portal hypertension. Only after reaching the threshold of CSPH does the increased portal blood inflow become a relevant contributor to increasing portal pressure.[36] Consequently, only patients with CSPH are likely to benefit from treatments to reduce splanchnic blood flow, such as nonselective β-blockers (NSBBs).[36,37] A recent randomized controlled trial (RCT), focused on patients with compensated cirrhosis with CSPH, showed a major decrease in the risk of decompensation with the use of NSBBs.[38] The results of this trial have markedly increased the relevance of identifying patients with CSPH. However, performing HVPG in every patient with compensated cirrhosis is unfeasible, thus highlighting the relevance of non-invasive methods to identify patients with CSPH, who would then benefit from treatment with β-blockers. This topic is covered elsewhere.[39]

Decompensated cirrhosis

HVPG measurements have also been shown to predict prognosis in patients with decompensated cirrhosis.[40–42] An HVPG $\geq$ 16 mm Hg is independently associated

with increased mortality in series of patients with overall decompensated cirrhosis,[40,43–45] and in patients with acute variceal bleeding, an HVPG of $\geq$ 20 mm Hg is an independent predictor of rebleeding and of mortality.[46–48] These findings are relevant to understanding the role of portal pressure causing further decompensation. However, alternative risk prediction models such as Model for End-stage Liver Disease (MELD)[28] or Child-Pugh[29,48] are more commonly used to predict prognosis in different clinical scenarios of decompensated cirrhosis.

Risk of decompensation after liver surgery

Patients with hepatocellular carcinoma (HCC) in the context of compensated cirrhosis and normal liver function are frequently considered for curative surgery if this is technically feasible. However, many of these patients have asymptomatic CSPH. An initial small series identified an HVPG $\geq$ 10 mm Hg as an independent predictor of overt cirrhosis decompensation after liver surgery.[49] Subsequent studies and a recent meta-analysis[50,51] confirmed that the presence of CSPH was a negative prognostic marker in patients undergoing surgery for HCC. The odds of 3-year and 5-year mortality were roughly double in patients with CSPH compared with patients without CSPH, and the odds of clinical decompensation after surgery were increased by approximately three times in patients with CSPH.

However, recent guidelines[52,53] modulate the message of avoiding liver resection in early HCC with CSPH, acknowledging that advances in surgical techniques have allowed for good outcomes in patients with CSPH that have preserved liver function requiring a minor extension hepatectomy (<3 segments).[54] Latest European Association for the Study of the Liver (EASL) recommendations are based on the model proposed by Citterio and colleagues[54] and are summarized in **Fig. 2**.

Surgical risk in extrahepatic surgery

Cirrhosis is associated with increased morbidity and mortality in extrahepatic surgery. These patients have an increased risk of complications, including infections, renal failure, decompensation, blood transfusion, reintervention, and mortality.[55] Because portal hypertension in cirrhosis is associated with marked systemic and splanchnic hemodynamic changes that can contribute to postsurgical complications, it is plausible that measuring portal pressure could help in estimating the surgical risk in cirrhosis. This possibility was tested in a multicenter study including 140 patients with cirrhosis undergoing extrahepatic surgery.[56] HVPG was independently associated with transplant-free survival. An algorithm to predict 30-day, 90-day, and 1-year transplant-free survival was provided (**Fig. 3**), which could help in decision making. This study also sets a conceptual rationale for assessing the role of preemptive TIPS before surgery in patients with severe portal hypertension.

Assessment of the Hemodynamic Response to Drug Therapy for Portal Hypertension

Several cohort studies have shown that, if the HVPG decreases to less than 12 mm Hg, either by pharmacologic therapy[57,58] or spontaneously (because of an improvement in liver disease),[41] esophageal variceal bleeding is markedly reduced. This pressure threshold of 12 mm Hg is less precise for predicting bleeding from fundal gastric varices, and occasionally bleeding may occur below this threshold.[59] In addition, even if this target is not achieved, a decrease in HVPG of at least 20%[58,60,61] from baseline levels offers substantial protection from variceal bleeding in the long-term. In patients surviving a bleeding episode, achievement of these targets (reduction <12 mm Hg or >20% from baseline) constitutes a strong independent predictor of protection from subsequent variceal bleeding, reduces the risk of other portal hypertension–

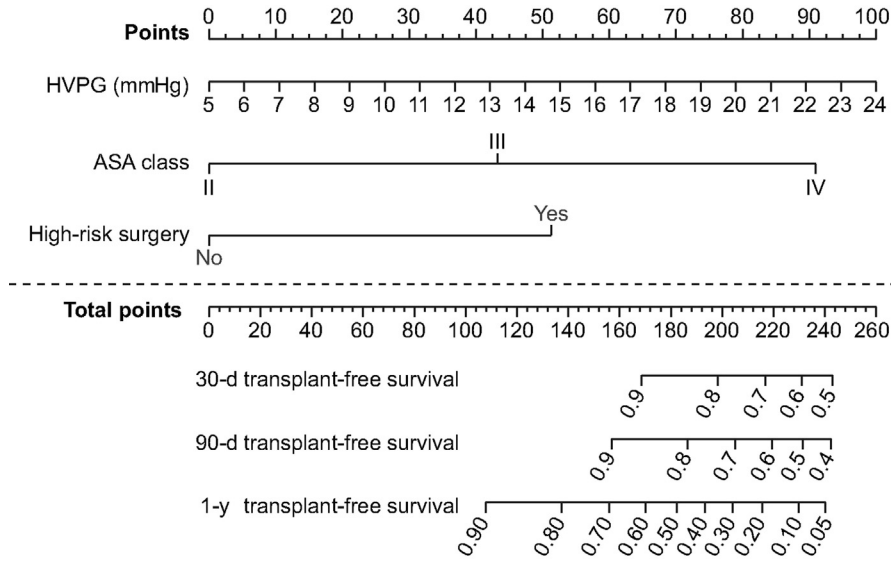


Fig. 3. Nomogram for 30-day, 90-day, and 1-year transplant-free survival predictions in patients with cirrhosis undergoing extrahepatic surgery, according to HVPG, American Society of Anesthesiologists (ASA) class, and low-risk versus high-risk surgery. To calculate the risk score, first estimate the points contributed by each variable using the points scale at the top. Then add all points and bring the total number of points to the second scale, which estimates the transplant-free survival. The high-risk group of surgeries included cardiovascular, thoracic, and open abdominal surgeries, whereas the low-risk group included laparoscopic and abdominal wall surgeries, orthopedic surgeries, and others. (Reproduced from Reverter E, Cirera I, Albillos A, et al. The prognostic role of hepatic venous pressure gradient in cirrhotic patients undergoing elective extrahepatic surgery. *J Hepatol.* 2019;71(5):942-950, with permission. (Figure 2 in original).)

related complications (eg, ascites, spontaneous bacterial peritonitis), and is associated with an improved survival.[60–63] Interestingly, this survival benefit could not be attributed to an improvement in liver function.[64] In compensated patients, a decrease by 10% in HVPG might be enough to achieve protection from complications of cirrhosis.[38,65,66]

The clinical application of the prognostic value of changes in HVPG is hampered by the need for repeated measurements of HVPG, and by the fact that a significant number of patients might bleed before a second HVPG measurement is taken.[67] Two studies have shown that evaluation of the acute HVPG response to intravenous propranolol therapy is a useful tool in predicting the prognosis in patients treated with nonselective β-blockers for the prevention of first bleeding or rebleeding.[65,68] The acute HVPG response to propranolol was independently associated with survival in these patients.[68] The threshold reduction in HVPG that defines a good response (associated with decreased bleeding and mortality) in these studies was a decline of 10-12% from baseline (instead of the 20% decrease that applies when using the chronic response).

Issues in defining what constitutes a clinically relevant decrease in portal pressure

Although the studies mentioned earlier are of capital conceptual relevance because they show that decreasing portal pressure improves prognosis in cirrhosis, there is no biological rationale or clinical evidence to suggest that there is a minimal threshold

of portal pressure decrease that yields a clinical benefit. If the association between the HVPG and prognosis is a continuum,[2,31] then likely the association between a reduction in portal pressure and improved prognosis is also a continuum, and recent data (Ref.[69], published in abstract form) suggest that even reductions in portal pressure of 1 mm Hg could have therapeutic benefit. It has been questioned whether HVPG has enough resolution to detect differences as low as 1 mm Hg (which would be <7% in a patient, for example, with a baseline HVPG of 15 mm Hg). When considering the variation in before and after HVPG measurements in the placebo groups of several recent trials,[17,70,71] such differences, or even substantially greater differences, cannot be detected at the individual level. However, in the context of a randomized clinical trial, in which only the mean group responses (but not individual responses) have an interpretation,[72] differences as small as 1 mm Hg between placebo and treated patients can be detected with only 40-50 patients per treatment arm.

Hepatic venous pressure gradient measurements to guide pharmacologic therapy for portal hypertension

A relevant question is whether there is any benefit in monitoring pharmacologic therapy for portal hypertension with HVPG in day-to-day practice. One of the limitations of this approach is that the relative invasiveness and the cost of HVPG limit the possibility of obtaining several measurements at different time points to assess the response to a drug (such as is done with arterial hypertension, a physiologic variable with wide physiologic variability, where repeated measurements or 24-hour monitoring are used to assess response and escalate therapy).[73]

In the context of trials, it precludes conducting several crossover studies, which would be required to reliably detect individual treatment responses.[72] These considerations require caution over approaches to tailoring pharmacologic therapy according to individual HVPG response or to indicate an escalation of therapy in nonresponders, and emphasizes the notion that these strategies should be extensively validated in RCTs before being implemented in practice. In addition, although the patients achieving a target reduction in portal pressure with β-blockers have much better prognosis than hemodynamic nonresponders, the labeling of these patients as nonresponders led to the (wrong) concept that these patients do not benefit from β-blockers.[74] Randomized trials showing the benefits of β-blockers compared with placebo were conducted without guiding treatment according to HVPG response.[75] Because these were parallel randomized trials, conclusions regarding the benefits of NSBBs apply to the whole group of patients treated in those trials, and it cannot be inferred that the efficacy of NSBBs was limited to hemodynamic responders.

To our knowledge, three RCTs have compared HVPG-guided therapy with alternative treatments, one in patients with compensated cirrhosis and two for the secondary prevention of variceal bleeding.

The 2019 PREDESCI trial compared β-blockers with placebo for the prevention of decompensation in patients with CSPH.[38] During baseline HVPG study, the acute hemodynamic response to propranolol was tested, and those patients that were responders received propranolol (or placebo), and nonresponders received carvedilol (or placebo). This optimization of the use of β-blockers, which would be unfeasible in practice, was likely unnecessary. With current knowledge about the hemodynamic effects of propranolol and carvedilol,[76] hemodynamic response to β-blockers in compensated patients can be optimized by treating all patients with carvedilol.

In a multicenter randomized trial in Germany, TIPS was compared with a medical/endoscopic treatment arm guided by HVPG as first-line therapy for the prevention

of variceal rebleeding.[77] In this treatment arm, patients achieving a good hemodynamic response to β-blockers plus nitrates were treated with drug therapy only, whereas nonresponders were switched to endoscopic variceal ligation only. Rebleeding in the HVPG-guided treatment arm was higher than in the TIPS arm and not relevantly different from the rebleeding risk reported in previous RCTs in the same setting.

Finally, in an open single-center randomized trial,[78] 172 patients were randomized to pharmacologic HVPG-guided therapy (using nadolol alone, nadolol plus nitrates, or nadolol plus prazosin to optimize the response, adding ligation in those nonresponders after the third HVPG measurement) or to empiric treatment with β-blockers plus nitrates plus ligation. Rebleeding and survival were better in the HVPG-guided group. Therefore, the evidence to use HVPG-guided therapy, is very limited and of questionable applicability because of the need for repeated (up to 3) HVPG measurements.

Assessment of New Therapeutic Agents for the Treatment of Portal Hypertension

The rationale for the development of new drugs for the treatment of portal hypertension has been that the patients' disease phenotypes can be modified by decreasing portal pressure. Therefore, the effect of a candidate drug on HVPG has been used to triage new drugs to be subsequently assessed in randomized trials with clinical end points.[79,80] The considerations made earlier to quantify what is a relevant decrease in portal pressure also apply for trial design. Furthermore, additional readouts of potential hemodynamic effects (either beneficial or harmful) such as liver blood flow (with clearance techniques) or azygos blood flow, might contribute in clarifying the potential of the drug for the management of patients with cirrhosis and portal hypertension.[79,80] In addition, although HVPG measurements are still needed for proof-of-concept studies (phase II clinical trials), HVPG reduction is not yet an accepted surrogate for drug approval in phase III trials. For this, more evidence relating changes in HVPG with outcomes at each of the stages and substages of compensated and decompensated cirrhosis would be needed.

Achieving such validation would be relevant in patients with compensated cirrhosis, because the rate of clinical events is low. Having a surrogate end point such as HVPG would facilitate the early completion of trials and faster approval of drugs that can prevent cirrhosis decompensation. This validation is close to being available. In the trial by Groszmann and colleagues[37] comparing timolol versus placebo for the prevention of the development of varices, timolol did not achieve a decrease in portal pressure compared with placebo, and timolol did not provide clinical benefit. However, a spontaneous decrease in portal pressure was associated with improvement in the risk of decompensation.[2] In the trial by Villanueva and colleagues,[38] comparing β-blockers with placebo to prevent decompensation, β-blockers did achieve a moderate decrease in portal pressure (−1.9 mm Hg compared with placebo), and β-blocker treatment was associated with a hazard ratio of 0.6 for decompensation-free survival (∼40% relative reduction), which was within the range of expected benefit observed with a spontaneous decrease in portal pressure in the timolol trial.[69] A reasonable provisional proposal could combine the efficacy of the new drug decreasing portal pressure with the overall profile of the drug (favourable or unfavourable depending on convenience of administration, potential additional benefits, side effects, and costs) to define an area of potential drug approval, as depicted in **Fig. 4**.

In settings such as secondary prophylaxis of bleeding, in which relevant clinical end points are frequent, the relevance of HVPG as a surrogate would be much lower.[79] Therefore, trials in secondary prophylaxis can be efficiently designed and conducted

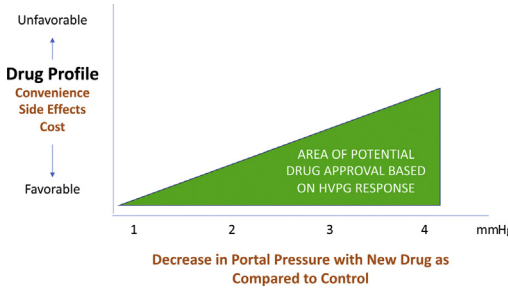


Fig. 4. A proposal for potential drug approval to treat portal hypertension in compensated cirrhosis combining the capacity of the drug to decrease portal pressure with the overall profile in terms of safety, easiness of administration, and costs. Drugs inducing mild decreases in portal pressure but associated with an overall favourable profile could be considered for approval. Drugs with less favourable profile require stronger portal pressure–reducing effects to be considered for approval based on HVPG response.

based on relevant clinical outcomes, without the need for surrogate end points such as HVPG response.[81] However, HVPG studies would obviously be required in trials assessing a therapeutic arm of HVPG-guided therapy and could provide useful additional explanatory information to understand the effects (or lack thereof) of novel drugs on relevant clinical endpoints.

In addition, HVPG has also been proposed as a potential endpoint to assess the effects of etiologic treatments.[82] Because disease progression is reflected as an increase in portal pressure, the assumption for using HVPG as a readout in these trials would be that an improvement in the underlying disease that causes cirrhosis would be associated with a decrease in portal pressure. Although this is a reasonable assumption (as discussed next) changes in HVPG might be slow after removing the causative agent and might not capture in full the potential benefit of suppressing the activity of the underlying liver disease. Therefore, HVPG is probably much better suited to assess hemodynamic drugs, which act through a vasoactive mechanism, rather than to assess the effects of etiologic treatments for cirrhosis.

Assessment of the Regression of Portal Hypertension After Treating the Underlying Liver Disease

Several studies have assessed the effects on portal pressure of treating the underlying liver disease, and how these relate to prognosis. By assessing the liver as a whole, including the potential functional changes in the hepatic microvasculature, the assessment of HVPG changes after therapy might provide a more comprehensive understanding of the effects of therapy rather than histology.[18]

A landmark prospective study by Vorobioff and colleagues[41] conducted in patients with cirrhosis related to alcohol, with esophageal varices but no previous bleeding, showed that alcohol abstinence is followed by a sustained decrease in portal pressure, which was associated with improved outcomes (bleeding and survival). Because none of these patients had received any form of prophylaxis for their first variceal bleeds, the study suggests that this improvement was the result of a reversible component of the disease.

In patients with cirrhosis from viral causes (mainly hepatitis C), several studies have assessed in recent years the impact of curing the viral disease on portal hypertension, initially with interferon-based therapies, in which only a small proportion of patients

achieved sustained viral response (SVR)[34] and more recently with direct antivirals, which achieve SVR in most patients with cirrhosis.[32,33,35,83,84]

Collectively, these studies show consistent results that can be summarized as follows. Patients without CSPH at the time of viral eradication do not progress to CSPH and remain compensated. In patients in whom SVR is achieved when CSPH is already present, even if most patients show some degree of decrease in HVPG, only a fraction (~30%) regress to an HVPG < 10 mm Hg in the short term. The higher the baseline HVPG, the lower the probability of regressing to non-CSPH. Patients remain at risk of decompensation if CSPH persists after SVR, although a decrease in HVPG > 10% after SVR is associated with decreased risk of decompensation. The decrease in portal pressure probably continues over the years, and the proportion of patients regressing to non-CSPH increases with time. This last result is still difficult to interpret, because in these studies only a small subset of patients were assessed for long-term HVPG response, likely representing a selected group of patients not experiencing events in the interim. Altogether, these results suggest that most patients with CSPH at baseline, even if they achieve SVR, require treatment of portal hypertension (nowadays with β-blockers) to prevent decompensation. Again, this suggests the need for noninvasive markers to identify post-SVR patients with persistent CSPH. This topic is covered elsewhere.

SUMMARY

HVPG reflects disease severity and has strong prognostic value with regard to survival and decompensation in patients with cirrhosis. Furthermore, repeated measurements of HVPG provide information on the response to the medical treatment to decrease portal pressure and represent an essential tool for drug development for portal hypertension. Moreover, because changes in HVPG also correlate with the extent of structural changes in the liver, assessing the trajectory of HVPG after etiologic therapies (mainly hepatitis C) has provided new insights into the patterns and clinical consequences of portal hypertension regression after removing the causative agent of cirrhosis. Because of the wide range of applications of this measurement, hepatologists should be familiar with the procedure for assessing HVPG and interpretation of the results.

CLINICS CARE POINTS

- Various methods for measuring or estimating the portal hepatic pressure gradient exist but catheterization remains the gold standard.
- Clinically significant portal hypertension (CSPH) defined as hepatic venous pressure gradient (HVPG) $\geq$ 10mmHg is the threshold above which many of the complications from cirrhosis occur.
- Assessing the trajectory of CSPH after the underlying etiology of cirrhosis has been treated can help predict ongoing occurrences of such complications.

DISCLOSURE

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