Are There any Alternative Methods to Hepatic Venous Pressure Gradient in Portal Hypertension Assessment?

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INTRODUCTION

In chronic liver diseases (CLD) the occurrence of complications is mainly related to portal hypertension (PHT). The best way to diagnose PHT is the direct measurement of portal pressure, as indicated by the first attempts more than 50 years ago [1]. Once the correlation between portal pressure and the wedge hepatic vein pressure (WHVP) was demonstrated [2], this became the standard in portal pressure assessment. Due to the fact that WHVP may be overestimated by an increased intraabdominal pressure, as in ascites, this potential source of error was eliminated by using the difference between WHVP and free hepatic vein pressure (FHVP) that is equally influenced by the abdominal pressure [3]. This difference is called hepatic venous pressure gradient (HVPG) and it is currently the gold standard for diagnosis of intrahepatic PHT.

In healthy persons, HVPG is below 5 mmHg. An HVPG more than 5 mmHg is suggestive for the presence of PHT, but the PHT-related complications, as variceal bleeding or ascites, occur only when HVPG is above 10 mmHg. For this reason, patients with HVPG >10 mmHg are considered to have a clinically significant PHT (CSPHT) [4-6].

HVPG measurement and its complications

The HVPG can be measured with a transjugular or femoral access, using the same materials as transjugular liver biopsy or using a balloon catheter. The patient may be slightly sedated and the vital signs are continuously monitored. Using the transjugular approach, a catheter is descended into one of the hepatic veins. Once the wedge position is reached, the WHVP may be measured. The FHVP is measured at 2-3 cm from
the hepatic vein ostium and the difference between the two pressures represents the HVPG.

Due to the fibrotic changes, the sinusoidal network becomes noncompliant and therefore, the WHVP is equal to the portal pressure [7]. In the normal liver, the WHVP may be slightly inferior to the portal pressure [3].

The HVPG can be measured with a balloon catheter and in this case the WHVP is obtained by inflating the balloon in the hepatic vein until total occlusion. The pressure at the tip of the catheter is similar to the sinusoidal and portal pressure. In this case, the larger sinusoidal area measured makes the HVPG assessment more accurate [8].

There are limited data on the safety of HVPG measurement. Frequently, HVPG is complementary to transjugular liver biopsy and therefore, all safety studies of transjugular liver biopsy may partially apply. There are no severe complications reported after HVPG measurement. The most frequent complications are limited to the jugular access, including local hematomas (especially by accidental carotid puncture), neck pain or Horner syndrome [8]. However, these local complications are reduced by the use of ultrasound guidance [9]. Cardiac arrhythmias may occur, mostly self-limited supraventricular ectopic beats.

Although there are frequently coagulation abnormalities in cirrhosis, there is no need to correct them unless platelets are less than 20,000/mm³ or prothrombin index less than 30% [8].

Recently, we demonstrated that the overall tolerance of transjugular liver biopsy (including here HVPG measurement) is similar to percutaneous liver biopsy [10] and therefore, we may conclude that HVPG is a safe procedure.

Clinical applications of HVPG measurement

At present, the HVPG is considered to be the most accurate method to diagnose PHT, which is defined as HVPG > 5 mmHg [4]. The complications related to PHT, such as variceal bleeding or ascites, tend to appear if HVPG > 10 mmHg [6, 11], therefore this threshold is known as CSPHT.

The HVPG remains unchanged in pre-hepatic PHT, most frequently caused by portal vein thrombosis, and initially in post-hepatic PHT, known as Budd-Chiari syndrome. The PHT is more often caused by intra-parenchymal liver diseases and therefore the HVPG is an important tool for diagnosis.

In chronic viral hepatitis with advanced fibrosis (> F2 Metavir) the HVPG is frequently > 5 mmHg [12]. In the presence of sustained viral response to antiviral therapy, the HVPG significantly decreases [13]. There is strong evidence that HVPG is correlated with the amount of fibrosis, quantified as the thickness of the fibrous septa on the liver biopsy [14, 15]. In this light, the HVPG could be a surrogate marker of treatment response to antiviral therapy. In the post-transplant settings for HCV cirrhosis, HVPG > 6 mmHg is predictive for HCV recurrence [16-18].

In acute alcoholic hepatitis, HVPG > 22 mmHg is an independent risk factor for death [19]. In patients with alcoholic cirrhosis presenting with variceal bleeding, HVPG is a reliable short term survival indicator [20].

In cirrhosis, HVPG > 10 mmHg is associated with a greater risk of esophageal varices (EV) development and bleeding [21, 22], of ascites development [6] or hepatocellular carcinoma occurrence [23]. We prospectively confirmed this threshold in a non-selected CLD population, where no PHT related complications occurred in patients with HVPG < 10 mmHg [24]. The patients with previous decompensation and HVPG > 16 mmHg have an increased risk of death [25] whereas in the acute variceal bleeding HVPG > 20 mmHg demonstrates a five-fold greater risk of failure to control bleeding [26]. Moreover, these patients have a greater mortality, longer intensive care unit (ICU) hospitalization and greater transfusion requirement [27, 28].

HVPG is used as a surrogate marker for evaluation of PHT treatment efficacy. A decrease of HVPG < 10 mmHg induced by beta blockers in patients with cirrhosis but without EV prevents the development of EV over time [11], whereas a HVPG reduction < 12 mmHg or greater than 20% prevents first variceal bleeding or variceal rebleeding [4, 29-31]. The patients who were initially non-responders to propranolol may benefit from other therapeutic options, as the association of isosorbide-5-mononitrate, or carvedilol that may recruit more HVPG responders [32, 33]. Although a decrease of HVPG as response to treatment has a prognostic significance, there are some issues that must be highlighted. Not all patients with HVPG reduction of 20%, except for those with HVPG < 12 mmHg, are protected from bleeding and only 22-67% of non-responders rebleed [34]. Moreover, there is a subgroup of non-responders that are protected from hemorrhage under beta-blocker treatment and the analysis of this subgroup of patients shows that HVPG has a positive predictive value for rebleeding of only 52.1% [35]. The potential benefit of these patients from beta-blockers may lie in other mechanisms such as the reduction of the risk of infections [36]. Finally, despite the clear prognostic significance of the HVPG response, there are not sufficient data for using HVPG measurement in routine management of EV, except in expert centers [37].

Recently, it has been demonstrated that initial responders to beta-blockers may increase HVPG despite treatment continuation and this PHT aggravation goes in parallel with hepatic function worsening [38]. Over a follow-up of 54 months, 40% of responders developed HVPG worsening. These patients had an increased risk of decompensation and greater mortality.

The value of HVPG measurement as a prognostic relevance is represented in Fig. 1.

HVPG has also a prognostic relevance in post-surgical setting in patients with resectable liver tumors. The patients with HVPG > 10 mmHg have an increased risk of persistent decompensation (more than 3 months after surgery) [39, 40]. Alternatively, clinical signs of PHT, such as EV, trombocytopenia or splenomegaly, may be used for the selection of patients with a great risk of post-operative decompensation. However, there is no validation of these surrogate markers [41-43]. Despite this low evidence, the present guidelines for hepatocellular carcinoma treatment recommend the evaluation of PHT before liver surgery [44, 45]. Stermitzer et al found that a HVPG > 5 mmHg predisposes to post-operative complications, suggesting that the 10 mmHg is a cut-off value too high for evaluation of these patients [46]. However, in his study all post-operative complications were recorded, whereas in the study of Bruix et
al [39] only persistent liver related complications were counted. In conclusion, all these data suggest that cirrhotic patients with hepatocellular carcinoma suitable for surgical resection may have an increased risk of post-operative complications if they have PHT (HVPG > 5 mmHg), and a greater risk for persistent decompensation if they have CSPH (HVPG > 10 mmHg). More studies are warranted for validation of these cut-offs.

Alternative non-invasive methods for HVPG measurement

Although HVPG measurement is a safe procedure, it is still considered an invasive method and therefore the development of new non-invasive markers of PHT was encouraged [47].

Given the fact that in the natural history of any CLD the sequence liver injury - fibrosis - PHT is generally present, it was not surprising that markers of liver fibrosis were tested as indicators of PHT.

From the initial report of the new technique of quantifying the amount of liver fibrosis by liver stiffness (LS) measurement using transient elastography [48], there were numerous studies validating this method in the diagnosis of cirrhosis and PHT. Liver stiffness is well correlated with HVPG in many studies [17, 49-52] with good performances, AUROC varying between 0.76 and 0.99. Liver stiffness is able to diagnose CSPH but the problem is that the cut-off value for CSPHT is variable among these studies, between 13.6 kPa and 34.9 kPa (Table I). These differences are probably caused by heterogeneity in studied populations and different etiology. It was demonstrated that LS is more elevated in alcoholic liver disease compared to viral liver disease [51]. Interestingly, the LS is very well correlated with HVPG up to values of 10-12 mmHg, but beyond these values the correlation is lower, proving that PHT is only partially caused by the amount of fibrosis [53].

Liver stiffness was validated in the diagnosis of EV [49, 50, 54-59], but again, with great heterogeneity among the cut-off values. However, it is reasonable that LS has less accuracy regarding EV diagnosis, as CSPHT (HVPG > 10 mmHg) is a necessary but insufficient condition for development of EV [60]. More recently, we and others have demonstrated that LS has prognostic relevance [24, 61]. In our study, LS had a performance similar to HVPG in the prediction of clinical decompensation and PHT related complications in a non-selected population of CLD [24].

Due to the good correlation between LS and HVPG, the potential role of LS in selecting patients with resectable liver tumors suitable for surgery was recently tested [62]. Even if in this study LS was able to classify accurately half of the patients as having or not CSPH, there are some methodological limitations that make the results difficult to interpret. The included patients were classified according to two different cut-off values for CSPHT, priorly published by different teams. Therefore, the discussion about the heterogeneity of the cut-off values among different studies may also apply to this study. Moreover, the correlation between LS and HVPG in this population was only moderate, even after the exclusion of any potential influence from tumor characteristics. Finally, because the surgical indication was mainly based on a HVPG < 10 mmHg, it was impossible to calculate in this population a specific cut-off value for LS which may predict clinical decompensation after surgical resection. More studies are warranted to establish the value of LS for pre-surgical assessment of PHT in patients with cirrhosis.

In routine practice, due to the good correlation of LS with HVPG and to the prognostic relevance of LS in the PHT setting, it is reasonable to use LS in order to select patients with low risk of decompensation in whom the invasive methods (such as HVPG measurement or upper endoscopy) may be avoided or delayed.

Serum bio-markers validated in staging CLD were attractive non-invasive methods for diagnosing PHT but strong evidence is still lacking. Prothrombin index was validated by our group in diagnosing CSPHT with a good performance (AUROC=0.89) and an optimal cut-off value of 82.5% [50].

Table I. The cut-off values validated for clinically significant PHT (HVPG > 10 mmHg)

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<thead>
<tr>
<th>Study (reference)</th>
<th>Cut-off (kPa)</th>
<th>AUROC</th>
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<tbody>
<tr>
<td>Vizzutti et al 2008 [49]</td>
<td>13.6</td>
<td>0.99</td>
</tr>
<tr>
<td>Bureau et al 2008 [50]</td>
<td>21</td>
<td>0.94</td>
</tr>
<tr>
<td>Lemoine et al 2008 [51]</td>
<td>20.5 (viral C cirrhosis)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>34.9 (alcoholic cirrhosis)</td>
<td>0.94</td>
</tr>
<tr>
<td>Sanchez-Conde et al 2010 [52]</td>
<td>14</td>
<td>0.80</td>
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</table>
The only PHT dedicated score is “The Risk Score” [63] which combines bilirubin and platelet count for predicting CSPHT with good performance (AUROC=0.91) at the optimal cut-off of 1.0. This cut-off value has considerable performance in EV detection (AUROC=0.82). Among the fibrosis scores only Fibrotest was validated in CSPHT diagnosis [64]. The problem of all these biomarkers is that the promising results from the initial studies have not been confirmed thereafter and therefore it is still difficult to interpret all the amount of data and replace invasive procedure.

In general, when a non-invasive test is proposed for diagnostic purposes its performance is judged comparatively with the invasive method (liver biopsy or HVPG). The performance of non-invasive test is quantified as Area Under the Receiver Operating Curve (AUROC), which represents the graphical representation of sensibility and 1-specificity. Because the invasive methods are imperfect standards, the AUROC of a non-invasive never reaches 1 (the maximum AUROC value) [65]. Moreover, the AUROC is influenced by the prevalence of different stages of disease in the studied population [66] so that an ideal non-invasive marker should have an AUROC of 0.9 [67].

The main problem of the non-invasive tests is that the performance quantified as AUROC is not always sufficient to replace the invasive methods. In this respect, there were several attempts to combine a few non-invasive tests to increase the overall performance. Kim et al created a model based on LS measurement and spleen diameter/platelet count which demonstrated that the performance of LS in the diagnosis of high risk EV might be improved by the complementary contribution of spleen diameter and platelet count, as other markers of PHT [68]. Another group recently confirmed the superior performance of this model over LS when the study end-point was CSPHT [69]. Moreover, based on the logistic regression method, Berzigotti et al created a new model based on almost the same variables but with better performance than the Kim et al’s model [69]. An interesting aspect of this study is the subgroup analysis of patients with resectable liver tumors, which confirms the applicability of these tests for CSPHT assessment prior to hepatectomy [69]. These studies are clear examples of performance improvement of a single non-invasive test by adding other complementary tests. A step-by-step algorithm using LS and serum markers, rather than a complex formula, as in the studies mentioned above, was recently proven to have an increased accuracy in the diagnosis of EV than LS alone [59].

Even if these models are very attractive for clinical practice, they probably are not useful when there are confounding factors for LS assessment such as acute hepatitis [70, 71], extrahepatic cholestasis [72] or cardiac failure [73, 74]. In these situations spleen stiffness assessment may contribute to PHT quantification, as it was demonstrated that spleen stiffness is increased in patients with CSPHT and EV [75, 76].

Recently, a new non-invasive method using Acoustic Radiation Force Impulse Imaging (ARFI) was developed for the assessment of liver fibrosis [77, 78]. Even if some studies have methodological issues, there is increased evidence that ARFI of the liver and spleen could be useful for PHT diagnosis [79-83]. However, up to now there are no studies that correlate ARFI with HVPG and therefore the large-scale implementation of this technique is still difficult.

Although simple and attractive, non-invasive tests still require an extensive validation before replacing HVPG measurement for CSPHT diagnosis or upper gastrointestinal endoscopy for EV detection.

CONCLUSIONS

HVPG is a very useful tool in both the diagnosis and prognosis of liver diseases. Over a period of time, it has been validated in many studies and consequently now it is the standard for the diagnosis of PHT. Moreover, it could represent a surrogate endpoint for antiviral treatment for advanced fibrosis in viral hepatitis or for surveillance of liver grafts. In cirrhosis it has an important prognostic relevance by accurately predicting decompensation or death. Despite this, there are insufficient data to use HVPG in PHT treatment monitoring or in treatment decision. Lately, the development of non-invasive markers of PHT is encouraged but, ideally, their validation must be done in comparison with the gold standard: the HVPG value.

Conflicts of interest: None to declare.

REFERENCES


