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Hepatic venous pressure gradient measurement in pre-primary and primary prophylaxis of variceal hemorrhage

Julio D. Vorobioff,* Roberto J Groszmann**

* University of Rosario Medical School, Rosario, Argentina.
** Yale University School of Medicine, New Haven, CT, U.S.A.

ABSTRACT

Pharmacological therapy of portal hypertensión can be accomplished according to different objectives. Among them, pre-primary prophylaxis aims to avoid / delay esophageal varices development while the target of primary prophylaxis is protection against first variceal bleeding. Hepatic venous pressure gradient (HVPG) measurement closely reflects portal pressure in most liver diseases whith predominant sinusoidal network involvement. Clinical-hemodynamic correlations have been demonstrated in both pre-primary and primary prophylatic therapy, allowing to establish HVPG measurement as a predictive parameter, not only regarding variceal growth and bled but also of liver disease evolution and other portal hypertensive related complications.

Key words. Portal pressure. Liver cirrhosis. Portal hypertension. Esophageal varices.

BACKGROUND

Hepatic venous pressure gradient (HVPG) measurement should be considered one of the main prognostic parameters in chronic liver diseases.[1] Even at early stages (HVPG: 6 to 10 mmHg) or once clinically significant portal hypertension (HVPG ≥ 10 mmHg) is present, either spontaneous or therapeutically induced changes in HVPG have significant predictive value.[2-9]

At different scenarios the HVPG is closely related to clinical outcomes. Therefore, esophageal varices development/growth/regression, the development of ascites and encephalopathy and also the risk of hepatocellular carcinoma (HCC) have been related to HVPG in compensated cirrhotic patients.[2-5,9] Once esophageal varices have developed, HVPG cut-off values are a reliable target aimed at therapeutic outcomes, such as a decrease in both first and recurrent variceal bleeding risk.[6,8,10,11] Moreover, during chronic treatment of portal hypertension, responders (e.g. patients in whom HVPG decreases ≥ 20% from baseline value or to ≤ 12 mmHg) have a significant reduction of portal hypertensive related complications[6,12-14] and improved survival.[6,13,14] Additionally, during acute variceal bleeding, early HVPG measurement is a helpful prognostic and decision-making parameter.[15-18] Besides, HVPG is useful in the preoperative assessment of patients with HCC.[19] and also in monitoring the evolution of viral infections and their therapy.[20,21]

In summary, HVPG measurement is a safe and accurate procedure, providing valuable diagnostic/prognostic information and help for making therapeutic decisions. Portal pressure measured by the HVPG may be as close as we can come to a validated surrogate outcome in hepatology.[22]

THE TECHNIQUE

This technique was originally developed in 1951 by Myers and Taylor, who used a straight catheter to wedge it in the hepatic vein.[23] In 1979, Groszmann, *et al*. introduced a technique that was based in using a ballon catheter to wedge (occlude) the hepatic vein. With minor differences from the original

Correspondence and reprint request: Julio D. Vorobioff, M.D. Professor of Medicine.
University of Rosario Medical School
Morrison 8750, 2000 Rosario, Argentina.
Tel.: +54 341 4514087. Fax: + 54 341 4513191
E-mail: vorodiez@fibertel.com.ar

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description this is the technique that is being used today.[24] There are several advantages of using a balloon catheter to perform the HVPG, including that unlike conventional catheters where the Wedged Hepatic Vein Pressure (WHVP) is measured in a small hepatic venule, the balloon catheter allows measurement in the hepatic veins at the lobar and sublobar levels. This allows the investigator to obtain pressures in several segments of the liver and then to average them in order to more closely represent the true Portal Venous Pressure (PVP). Also, and perhaps the most important feature of this technique, is that serial measurements of free hepatic venous pressure (FHVP) and WHVP can be obtained using the same catheter, inflated and deflated as needed. This is very important in the study of the effects of drugs, because it is necessary to have a catheter that could be left in place for 1 or 2 h and that could be used to obtain several determinations of HVPG without having to advance or withdraw the catheter to obtain measurements. Withdrawing and advancing the catheter could lead to catheter contamination and loss of reproducibility. The procedure of measuring HVPG has proven extremely safe and the rate of successful hepatic catheterization is greater than 95%.[25] It took many years for this technique to come into widespread use, but it is now used by most of the centers that perform these hepatic hemodynamic measurements worldwide.

Recently, the theoretical advantages of the balloon catheter have been clearly established. The results of this controlled study significantly favour balloon catheter versus straight catheter, both in accuracy and reliability terms.[26] In summary, strictly following accepted guidelines will allow obtaining reliable and reproducible measurements.[27]

HVPG MEASUREMENT IN PRE-PRIMARY PROPHYLAXIS

According to previously accepted definitions/recommendations,[28,29] 3 studies have been published in the area of pre-primary prophylaxis.[2,3,30] HVPG measurement being performed in 2 of them.[2,3] The earliest one[3] included 161 patients with small esophageal varices, that were randomized to nadolol (n: 83) or placebo. Variceal growth was the main endpoint evaluated. Nadolol was superior to placebo for the prevention variceal growth. HVPG was measured at baseline and after 2 years in 19 patients (10 of them on nadolol). It decreased from 12.2 ± 1.1 to 11.0 ± 1.5 mmHg ($p < 0.009$) in patients receiving the drug while it changed non-significantly (12.3 ± 1.3 to 12.5 ± 1.1 mmHg) in patients on placebo. At 2 years HVPG was lower in patients on nadolol than in those on placebo ($p < 0.03$).

In the other study,[2] 213 cirrhotic patients without esophageal varices were included. After a baseline evaluation, HVPG measurements were repeated yearly, while patients were on timolol (n:108) or placebo (n:105). Neither the main end-points (development of esophageal varices/variceal hemorrhage) nor HVPG changes differed between patients on drug or placebo. Nevertheless, clear clinical-hemodynamic correlations were established, that may be useful in future studies and also clinical practice. One of the most relevant is the definition of clinically significant portal hypertension, manometrically defined (i.e. a HVPG ≥ 10 mmHg), is by itself a powerful prognostic predictor of portal hypertensive related complications. Another important observation was that the incidence of primary and secondary endpoints was lower in patients whose HVPG decreased > 10% during follow-up, regardless being on timolol or placebo.

A recent *post-hoc* analysis of this study[31] may help in understanding the hemodynamic results. Although the global HVPG response to timolol was not significant, this was not so when patients were analyzed according to the absence/presence of clinically significant portal hypertension at inclusion. In fact, the absence of baseline CSPH (n:30 pts) implied a hemodynamic non-response (HVPG: 7.5 ± 0.2 to 7.5 ± 0.5 mmHg; $p < 0.56$) while its presence (n:42 pts) allowed to observe a significant response (HVPG: 14.5 ± 0.6 to 12.5 ± 0.6 mmHg; $p < 0.002$) at one year. These results may suggest that baseline HVPG levels may be a guide for considering different therapeutic strategies (specially those vasoactive related) in pre-primary prophylaxis of esophageal varices.

HVPG MEASUREMENT IN PRIMARY PROPHYLAXIS

Clinical-hemodynamic correlations

HVPG measurement has been recommended for the assessment of pharmacological prophylactic treatment in portal hypertension.[32,33] Accordingly, a baseline and a long-term evaluation study must be performed. Time interval between these 2 studies is relevant. Previous studies, including more than 200 patients in whom 2 hemodynamic evaluations were performed, reported a wide variability for this period mean range: 19-120 days.[11,34-36] Nevertheless, it

seems reasonable that time elapsing between both HVPG measurements should be as short as possible, 3 to 4 weeks when feasible. This interval is necessary enough to reach the highest stable drug/s dose/s necessary for long-term treatment and to reduce the proportion of patients in whom bleeding may occur before the second hemodynamic investigation.[11]

In the above mentioned studies, treatment assigned was single drug based in 2 (β-blockers)[6,35] and combined (β-blockers + nitrates) in the others.[14,34,36] HVPG changes allowed the definition of 2 different populations: "responders" and "non-responders", both closely related to clinical outcomes. Responders are patients in whom HVPG decreases to ≤ 12 mmHg or at least 20% from baseline (regardless their final value is ≤ or > 12 mmHg). Bleeding risk is nearly abolished when the HVPG is ≤ 12 mmHg and significantly reduced when a 20% reduction is obtained. On the other side, non-responders are patients in whom neither of these hemodynamic targets are reached, and therefore maintain their bleeding risk.[11] A remarkable issue is that the responder status assures long-term protection for first variceal bleeding,[14] provided drug intake is not discontinued.[37] Moreover, on the same long-term basis, responders are significantly protected from other portal hypertension related complications, such as SBP and bacteremia.[14]

In summary, monitoring HVPG response to therapy is crucial in predicting therapy efficacy. Patients achieving a reduction in the HVPG of ≥ 20% have a very low bleeding risk during the next 2 to 3 years (~5%). If the HVPG is reduced to ≤ 12 mmHg the risk of bleeding is close to zero.

Is there a hypothetical explanation for the protective effects of decreasing HVPG at least 20% or to ≤ 12 mmHg?

As mentioned before, after "responder" status achievement, bleeding risk is substantially diminished (a reduction in HVPG of ≥ 20%) or virtually abolished (a reduction in HVPG to ≤ 12 mmHg).[6,8,10-14] Nevertheless, reasons for these arbitrary seeming cut-off levels derived benefits remain unknown. Why should a ≥ 20% reduction may be such highly protective? A guide to an hypothetical answer may be the portal pressure response to certain specific stimulus. It is well known that under some circumstances (such as physical excercise, alcohol intake and/or eating) portal pressure may increase up to 20%. These sudden increases, in an already hypertensive territory, could be involved in esophageal variceal rupture and bleeding by increasing variceal wall tension.[38-41] Accordingly, 30 to 60 min after a meal, a baseline HVPG of 20 mmHg may increase up to 24 mmHg. In this specific case, after a successful 20% reduction, the new baseline would be 16 mmHg and then, a similar stimulus will rise the HVPG to 19.2 mmHg. At least mathematically speaking, as long as the 20% reduction is sustained, the HVPG wont ever reach even the pre-treatment baseline level, and this rules for any considered portal pressure value.

And why is protection almost complete when HVPG is ≤ 12 mmHg? Is this level accomplishment exclusively dependent of vasoactive effects on splanchnic circulation, or an intra-hepatic effect (sometimes including liver disease improvement) may be involved? The increased amount of responders seen when beta-blockers are combined with drugs reducing porto-collateral/intrahepatic resistance would support this contemption.[42-44] Another intrahepatic contributing mechanism to be considered is the hepatic artery.[45] The influence of hepatic arterial flow on sinusoidal resistance after beta-blocker administration could be another potential player in the degree of the HVPG response. And finally, which level of sinusoidal resistance determines the dissapearance of the physiological porto-sinusoidal gradient? In other words, which is the cut-off level at which both sinusoidal and portal pressure equalize? Are patients protected as this gradient is maintained? Although measurement of hepatic vein occluded (wedged) pressure in liver cirrhosis closely reflects portal vein pressure,[46,47] it is not known if this is so during "clinically non-significant or mild portal hypertension" (a HVPG > 6 mmHg but ≤ 10 mmHg) period. Interestingly, both HVPG cut-off levels for complication/decompensation development in chronic liver disease (> 10 mmHg) and variceal bleeding protection (< 12 mmHg) are within a narrow boundary area which may be hypothetically close to that equalizing point.

Is HVPG response to acute drug administration predictive of a sustained hemodynamic response?

HVPG measurement is invasive, costly and not always available. If therapeutic outcomes could be predicted from a single HVPG evaluation, acceptability and feasibility may increase.

In a recent study, HVPG response was assessed 20' after propranolol (0.15 mg/Kg I.V.) in 166 patients (78 of them without previous bleeding).

A ≥ 12% HVPG reduction was the best cut-off value for predicting first variceal bleeding (65% sensitivity and 64% specificity). Accordingly, 54/78 (69%) patients were responders and 24 (31%) were not. Probability of developing a portal hypertensive-related bleeding was half in responders than in non-responders. A cut-off value in HVPG reduction to ≤ 12 mmHg or ≥ 20% would have underestimated the number of acute responders. A second HVPG measurement was performed in 51/166 patients and response was sustained in 30/51 (59%). However, a separate analysis for patients on primary prophylaxis in this group was not reported.[48]

Another recent study, evaluated HVPG response 20' after propranolol (0.15 mg/Kg I.V.) in 105 patients (all previous non-bleeders). A ≥ 10% HVPG reduction was the best cut-off value for predicting variceal bleeding (81% sensitivity and 80% specificity). At baseline study, 75/105 (71%) patients were responders and 30 (29%) were not. Sixteen patients (15%) bled during follow-up. Acute responders had a lower probability of bleeding than non-responders (4% *vs.* 46%, respectively; $p < 0.001$) at 24 months. Patients decreasing their HVPG ≥ 20% at the baseline study had also a lower probability of bleeding than those decreasing ≤ 20% (5% *vs.* 22% at 2 years; $p < 0.003$). However, having used this standard criteria would have underestimated responders (35% *vs.* 71% when using the 10% decrease; $p < 0.001$). A second HVPG measurement was performed in 73/105 patients. Response was sustained in 45/53 (83%) acute responders while it was not in 8 (15%). On the other hand, baseline non-response was maintained in 18/20 (90%) patients while 2 (10%) baseline non-responders became responders. A significant correlation between acute and chronic changes in HVPG was shown (r: 0.61; $p < 0.01$). It is suggested that a reduction in HVPG of ≥ 10% from baseline is a better cut-off level to define response than a reduction of ≥ 20%.[49]

Agreement/disagreement between acute and chronic HVPG response to β-blockers has been previously reported. In the earliest publication, including 18 cirrhotic patients (12 of them previous bleeders), HVPG was assessed 60' after propranolol (40 mg, orally) and after long-term treatment (mean daily dose: 158 ± 63 mg). Nine (50%) patients were acute and 12/17 (71%) were long-term responders (HVPG decrease of ≥ 10%). Acute response was sustained in 7/9 (78%) responders and in 3/8 (38%) baseline non-responders. Two acute responders became non-responders and 5 acute non-responders became responders.[50]

More recently, HVPG response was assessed in 24 cirrhotic patients, 60' to 90' after nadolol (80 mg, orally) and after long-term treatment (mean daily dose: 72 mg). Eleven (46%) and 13 (54%) patients were acute and long-term responders (≥ 20% HVPG reduction or to ≤ 12 mmHg); respectively. Acute response was sustained in 5/11 (46%) and in 7/13 (54%) acute non-responders. Six acute responders became non-responders and 6 acute non-responders became responders.[51]

In summary, conventional criteria of HVPG response (a ≥ 20% reduction from baseline or to ≤ 12 mmHg) may not be a strictly required target for prevention of first variceal bleeding, as smaller reductions may be also protective. Nevertheless, assumption of a sustained or even greater HVPG reduction during long-term treatment may not rely exclusively on an acute (albeit favorable) hemodynamic response, but also on variables reflecting liver disease evolution that may influence portal pressure, beyond the effect.[4,8,52]

SUMMARY

Almost 15 years ago, HVPG measurement was recommended for monitoring cirrhotic patients, who needed to be treated in order to prevent first variceal bleeding.[28,29] At the 2005 Baveno Consensus Meeting it was agreed that "Hepatic venous pressure gradient (HVPG) monitoring identifies patients with cirrhosis who will benefit from non-selective β-blocker therapy in primary prophylaxis.[53] This recommendation has not only been sustained but also widened at the last Baveno Meeting.[54]

Patient identification itself may be an easy task, but HVPG measurement is not widely available in clinical practice, as invasiveness and limited feasibility are important conditioning factors. Although this inconvenience may be partially overcome by performing a single drug-response assessment, the acute challenge strategy needs adequate validation before standardizing new clinical-hemodynamic correlations.[55] Another issue to consider is that to non-selective beta blockers benefitial effects may be mediated through vasoactive mechanisms not predicted by HVPG measurement. It has been shown that propranolol induces significant reductions in azygos blood flow and variceal pressure, even in patients conventionally characterized as non-responders.[56] Moreover, non-selective beta-blockers effect on intestinal motility may decrease bacterial translocation, ameliorating the systemic hemodynamic profile that negatively influences portal pressure in

cirrhotic patients.[57] Therefore, prophylactic effects of beta-blockers on variceal bleeding may not be solely correlated with the degree of portal pressure reduction but on other mechanisms, also observed in patients not reaching a HVPG reduction of ≥ 20% or to ≤ 12 mmHg.[58] This multifactorial background for beta-blockers influence on splanchnic hemodynamics may explain why some "responders" bleed and why many "non responders" do not. So, there's a "grey zone" between both groups, where HVPG measurement may under-estimate other beta-blockers' induced vasoactive effects and therefore, may not be as predictable as needed.[59] Therefore, answers (clinical outcomes) in primary prophylaxis may exceed nowadays adjusted hemodynamic definitions.

In summary, HVPG measurement for primary prophylaxis is a rational but not a *sine quanom* recommendation for daily clinical practice. More strict criteria should prevail in the context of clinical studies, according to the recommendations of both the AASLD-EASL Meeting and Baveno V Consensus Workshop.[59,54]

Regarding pre-primary prophylaxis, at the recent Baveno V Consensus Workshop it was stated that "pre-primary prophylaxis should only include patients without gastro-esophageal varices".[54] This redefinition was eagerly needed in order to unify methodology and outcomes in this kind of trials.

Manometrically speaking, patients to be considered for pre-primary prophylaxis may have "sub-clinical portal hypertension" (a HVPG > 6 mmHg but < 10 mmHg) or "clinically significant portal hypertension" (a HVPG > 10 mmHg).[6] Regardless sharing a common treatment end-point, prognosis of both groups is clearly different.[4,6] Then, main inmediate end-points may also differ. For patients with "sub-clinical portal hypertension" the more rational objective would be to avoid/delay the development of clinically significant portal hypertension. Once clinically significant portal hypertension is established, HVPG itself is a strong predictive parameter for variceal formation/clinical decompensation.[7,9] At the aforementioned Meeting it was also stated that "HVPG measurement in pre-primary prophylaxis may be reccomended only in the context of clinical trials" and that these studies may stratifie populations according to different risks (e.g. patients with HVPG between 6-10 mmHg and those with HVPG > 10 mmHg).[54]

Diagnosis at this stage of liver disease is a challenging issue. Subclinical/clinically significant portal hypertension may be assessed by a non-invasive methodology, such as transient elastography, which seems reliable and may be a complementary tool at both stages.[60-63] Nevertheless, dynamic changes induced by treatment and/or disease evolution may only be accurately evaluated by HVPG measurement. So, at this time, HVPG may still be the most reliable and predictive parameter to assess diagnosis, to establish prognosis and to evaluate therapy results.[7,9,10] Finally, up to date, pre-primary prophylaxis has been limited to the administration of non-selective beta blockers.[7,8,51] Given the lack of responsiveness to these drugs in patients with clinically non-significant portal hypertension,[52] new therapeutic strategies, based on the combination of ethiology-related treatments, other vasoactive agents and drugs targeting specific mechanisms involved in liver damage and disease evolution may be investigated at this early stage.[64-67]

ABBREVIATIONS

- **HVPG:** Hepatic venous pressure gradient
- **HCC:** Hepatocellular carcinoma
- **WHVP:** Wedge hepatic vein pressure
- **PVP:** Portal vein pressure
- **FHVP:** Free hepatic vein pressure

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