The Hepatic Venous Pressure Gradient: Anything Worth Doing Should Be Done Right

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Over the last two decades, our understanding of the treatment and prognosis of portal hypertension has continued to improve.[1,2] The use of techniques to measure the wedged hepatic venous pressure (WHVP), developed more than 50 years ago, has played a major role in elucidating the pathophysiology of the syndrome[3] and, consequently, in developing currently available pharmacologic therapy. Recently, a role for measurements of WHVP has also been proposed in evaluating the progression of chronic liver diseases.[4] This measurement has been shown to be the best predictor of the development of complications of portal hypertension in patients with early cirrhosis.[5] Investigators in this area of research need not be convinced about the importance of the WHVP technique in advancing our knowledge of portal hypertension from the experimental arena[3] to current clinical applications.[6–8] However, there is an unanswered question that has lingered with us for more than 20 years: Should measurement of WHVP be incorporated into clinical practice?

To begin to answer this question, we must assure ourselves that the technique is executed properly. In a recent study performed to evaluate a new pharmaceutical agent, one of us (R.J.G.) was asked to be a blind reviewer of WHVP tracings performed by centers experienced in the measurement of WHVP. Even though minimal criteria for acceptable measurements have been established (Table 1), approximately 30% of studies% had to be rejected as the tracings obtained were uninterpretable. Our experience is not unique (Jaime Bosch, personal communication). We cannot draw conclusions about the usefulness of this technique in a clinical setting if investigational studies designed to answer the question do not themselves comply with minimal criteria for technical adequacy. To achieve results that are consistent and comparable from center to center, meticulous attention to detail is required (Table 1).

Direct measurement of portal venous pressure (PVP) is invasive and inconvenient. In 1951, Myers and Taylor[9] first described WHVP, which is the measurement of the sinusoidal pressure, an indirect measurement of PVP. Since then, WHVP has been shown to be very safe and the rate of successful hepatic vein catheterization is greater than 95%. By threading a small catheter into a hepatic vein until it cannot be advanced further, a "wedged" hepatic venous pressure is obtained. As the hepatic vein is occluded, a continuous column of fluid between the catheter and the sinusoid is formed, resulting in a pressure reading that is equal to the sinusoidal pressure (Fig. 1). In normal livers, the low-resistant sinusoidal network dissipates most of the pressure back up from the wedged catheter. As there is no direct connection, via a static column of fluid, between the catheter and the portal tributaries, the pressure reading of the transducer reflects sinusoidal pressure (in normal livers is slightly lower than portal pressure). This is also observed in presinusoidal causes of portal hypertension such as schistosomiasis or early primary biliary cirrhosis. Because the catheter in these cases is not in continuity with the area of increased resistance, the recorded pressure will be that of the normal sinusoids and not of the increased pressure in the portal vein. In these cases, WHVP will be an underestimation of the PVP.[11,12] Conversely, in alcoholic cirrhosis and in most cases of hepatitis C and B virus-induced cirrhosis, connections between sinusoids are decreased because of narrowing of the sinusoidal vascular bed (caused by collagen deposition in the space of Disse, compression by regenerative nodules, and microthrombosis). As there is little dissipation of pressure in the narrowed sinusoids, the static column of blood extends from the catheter to the portal vein and the WHVP is virtually equal to the PVP (Fig. 1).[3,11–14]

Currently, the most commonly utilized parameter is not the WHVP, but hepatic venous pressure gradient (HVPG), the difference between WHVP and free hepatic venous pressure (FHVP). HVPG represents the gradient between the portal vein and the intraabdominal vena caval pressure. Whereas both the WHVP and FHVP are affected equally by intraabdominal pressure, their gradi-

Abbreviations: WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; PVP, portal venous pressure.

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Table 1. Obtaining Accurate and Reliable HVPG Measurements

Required equipment
1. A recorder capable of producing a permanent tracing of pressure values.
2. A quartz pressure transducer that can detect changes in venous pressure (not arterial!).
3. An occlusion balloon catheter.

Adequate calibration and recording
1. Use an appropriate scale. Venous pressures have an upper range of approximately 30–40 mm Hg. Therefore, scales used for arterial pressure measurements are not adequate. To be able to detect small changes, the scale should be set at 1 mm Hg = 1 mm on the scale (or more, e.g., 1 mm Hg = 2.5 mm on the scale; Fig. 2).
2. Use slow recording speed. Stabilization of venous pressures should be evaluated over a period of approximately 1 min for WHVP or 15 s for FHVP. The appropriate speed is <5 mm/s, optimally 1–2 mm/s. Note that in a "normal" ECG with a speed of 25 mm/s, one page of tracing includes approximately 10 s of measurement and this is not adequate for accurate interpretation of the tracing.
3. Check the accuracy of the transducer calibration by obtaining tracings of a known external pressure (e.g., a column of water of 13.6 cm should read 10 mm Hg and 27.2 cm H_2O should read 20 mm Hg). If a transducer does not calibrate exactly against a known external pressure, replace it.
4. Place the transducer at the level of the right atrium (midaxillary line). The intravascular pressures will read higher if the transducer is lowered, but they will decrease if the transducer is raised. Record the IVC pressure on the tracing at the level of the liver (hepatic veins) before catheterizing the hepatic vein. Catheterize preferably the main right hepatic vein.

Actual measurement
1. Do not advance the catheter too far into the hepatic vein when measuring the free pressure (or FHVP). The FHVP should not be more than 1 mm Hg greater than the IVC pressure. Greater differences require withdrawal of the catheter closer to the IVC for an accurate measurement of FHVP.
2. Record the tracing for 45–60 s to allow the measure to stabilize. Some patients may require a longer time! Also, continue recording when deflating the balloon to recheck the FHVP.
3. Obtain a mean pressure.
4. Repeat measurements at least three times to make sure that values obtained are reproducible. If they are not, check the wedged position of the catheter.
5. Check the inflated balloon for total occlusion of the hepatic vein (Fig. 1). If it is not (e.g., venous-to-venous shunts, insufficient inflation of the balloon), the measurements should be repeated either by moving the balloon catheter distal to the venous-to-venous shunts, or, when the drainage is to another hepatic vein, by changing the position of the catheter to another hepatic vein without venous-to-venous shunts. A hepatic vein that drains into another hepatic vein or distal to the balloon occlusion will underestimate the WHVP. In rare cases, the measurement cannot be accomplished. Checking for total occlusion of the balloon (wedged position) should be performed at the end of the measurement by slowly injecting 5 mL of contrast into the hepatic vein while the balloon is inflated. This should show the typical wedged (sinusoidal) pattern and no communication with other hepatic veins. After deflating the balloon the dye should wash out quickly. Do this consistently (i.e., do not check for balloon occlusion before measurements on one procedure and after the measurements in another).
6. If the patient is premedicated, for comparative purposes, subsequent measurements should be performed under the same conditions.
7. Register on tracing ongoing events. For example, cough or slight movements cause artifacts that may give inaccurate readings. *Any* such changes that affect the measurement should be noted on the tracing.
8. Never rely on digital readings on the screen! These are instantaneous readings and may not be representative (because of cough, movement) of the correct measurement. Digital readings should not be accepted owing to the lack of a hard copy that can be reviewed.

Abbreviations: HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; ECG, electrocardiogram; IVC, inferior vena cava.

ent, HVPG, is not. Unlike PVP or WHVP, which can be elevated falsely in the presence of ascites and elevated intraabdominal pressure, the measurement of HVPG incorporates its own zero reference point and is not affected by increases in intraabdominal pressure. Furthermore, the use of the HVPG eliminates another very important source of error, the external zero reference point, which may vary from center to center.

A recent study indicates differences in the values obtained when the catheter is wedged in different hepatic veins, which is a cause of concern.[15] These differences probably may be due to the heterogeneity of sinusoidal involvement by the disease process affecting the liver. The smaller the vein where the catheter is wedged, the greater the potential discrepancy with a subsequent measurement in a different hepatic vein. This observation reflects the finding that cirrhosis is not a homogeneous disease.[16,17]

The use of a balloon-tipped catheter[18] (Fig. 1) versus a straight catheter provides both theoretical and practical advantages. The balloon catheter occludes a larger hepatic venous branch and can, theoretically, measure WHVP over a wider vascular territory of the liver compared with the straight catheter. The use of balloon catheter also provides a practical advantage as it allows repeated measurements from the same hepatic vein and avoids the decompressive effect of venous-to-venous shunts that are proximal to the balloon. Conversely, a straight catheter has to be advanced and withdrawn for each WHVP and FHVP measurement, making it difficult to wedge the same venule with each successive pressure determination.

Having experience with this procedure for more than 25 years, we are confident that properly executed, the balloon catheter technique produces HVPG values that are accurate and reproducible. Adherence to guidelines suggested in Table 1 is extremely important. Further-

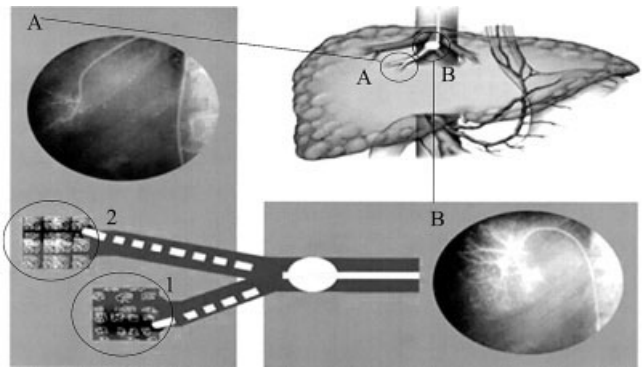

Fig. 1. (A) The pressure transducer on the straight catheter is wedged into a small hepatic vein. Because there is a regional variability of fibrosis, the WHVP of the more fibrotic area (**inset 1**) is higher than that of the relatively normal parenchyma (**inset 2**). (B) The balloon catheter eliminates this inconsistency by averaging WHVP over a wider segment of the liver.

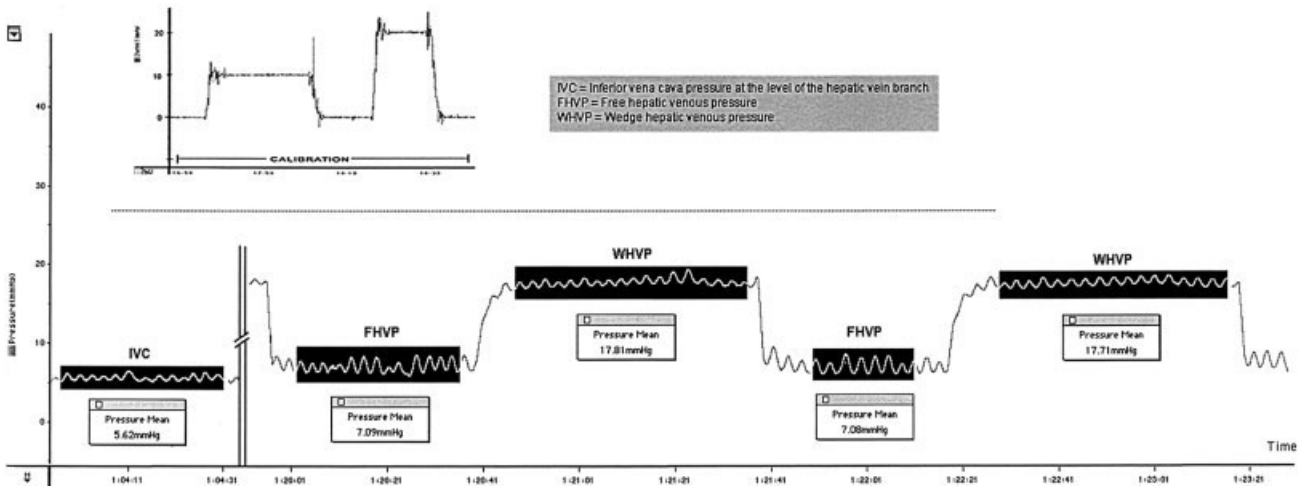

Fig. 2. The pressure transducer needs to be calibrated carefully against known external pressure. (**Top**), a 13.6-cm and a 27.2-cm column of water are used to calibrate the transducer to 10 and 20 mm Hg, respectively. Pressure readings are obtained by averaging values of stable tracings as shown in the highlighted area. We use the arithmetic function built into the tracing recorder to calculate the mean pressures for the inferior vena cava (IVC), FHVP, and WHVP. A stable tracing of 45 to 60 seconds is necessary for WHVP measurement whereas a tracing of 15 to 20 seconds is adequate for IVC and FHVP measurement.

more, pressure tracings should be annotated and recorded so that they can be reviewed subsequently by an independent observer (Fig. 2).

In summary, we do not believe that proponents of HVPG measurement have overemphasized its importance. Even if this method does not achieve the clinical utility that many of us believe it should, we have no doubt of the importance that it played and is still playing in advancing our knowledge of the portal hypertensive syndrome. What is also clear to us is that to reach any conclusion about this technique, one must first ensure that the technique is performed properly.

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Changing Clinical Practice With Measurements of Portal Pressure

Thomas D. Boyer

The technique for determining the portal vein pressure by measuring the wedged hepatic vein pressure (WHVP) was developed in the 1950s.[1] Although the technique was shown to be relatively easy to perform, and it gave accurate estimates of portal pressure in most situations, measurement of WHVP is considered a research tool and it is used in a limited number of clinical situations.[2,3] Three developments have lead to a reevaluation of the utility of WHVP measurement in the management of patients with portal hypertension. The first development is the widespread use of the transjugular intrahepatic portal systemic shunt (TIPS) for the treatment of complications of portal hypertension.[4] The experience gained by interventional radiologists in the measurement of portal pressure during the performance of a TIPS has provided training of a large group of individuals in the measurement of portal pressure and its clinical applications. Secondly, and perhaps most importantly, has been the recent observations that the hemodynamic response to pharmacologic therapy correlates with risk of bleeding. If the hepatic venous pressure gradient (HVPG) falls to less than 12 mm Hg or by more than 20%, the risk of bleeding in the responders is significantly less than in the patients who failed to have a meaningful decline in the HVPG.[5] Lastly, a number of studies have shown that the higher the level of the HVPG, especially following an acute bleed, the greater the risk of recurrent bleeding.[6] Given these developments it is now reasonable to ask whether measurement of the response of the HVPG to therapy or following an episode of variceal bleeding should be used in clinical practice. This is not a trivial issue, as death from bleeding varices remains a significant problem for patients with cirrhosis.[7]

Abbreviations: WHVP , wedged hepatic vein pressure; HVPG, hepatic venous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt; VBL, variceal band ligation.

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Primary Prophylaxis

Primary prophylaxis is the prevention of bleeding from varices in patients who have never bled. Options for the treatment of these patients include pharmacologic and endoscopic therapies.[5,8,9] Treatment of patients with cirrhosis and varices with pharmacologic therapy reduces the risk of bleeding by about 50% to an incidence of approximately15% over two years. Treatment of patients with large varices increases the benefits of pharmacologic therapy. These observations have led to recommendations that all patients with cirrhosis undergo a screening endoscopy and that patients with large varices be treated with beta-blockers ± nitrates, or with variceal band ligation (VBL) if intolerant of beta-blockers.[10,11] Recently, this approach has been questioned on the basis of cost-effectiveness analysis.[12,13] In the two analyses using the Markov approach, no screening paradigm was found to be cost-effective when compared with treatment of all cirrhotic patients with beta-blockers irrespective of the presence or absence of varices. Only if the risk of bleeding over two years could be reduced to about 5% was the screening approach followed by VBL found to be cost-effective.[13]

Pharmacologic therapy is not as effective as expected, because approximately half of the patients fail to have a hemodynamic response to therapy. If therapy could be based on hemodynamic response, then efficacy should be improved, and perhaps bleeding rates of 5% or less could be achieved. Merkel et al.[14] administered a beta-blocker ± nitrates to 49 cirrhotic patients with varices. They measured the HVPG before and 1 and 3 months after initiation of therapy and followed the patients for up to 5 years. Sixty-one percent of the patients had a hemodynamic response, and the three-year risk of bleeding was 7%. In contrast, the risk of bleeding for the nonresponders was 41%. In a second study, none of 21 patients who achieved a HVPG of < 12 mm Hg bled from varices.[15] Most recently Bureau and colleagues,[16] treated 20 patients with beta-blockers ± nitrates to prevent variceal bleeding. About 60% of the patients had a hemodynamic response to therapy and none bled whereas one-third of the nonresponders bled during follow-up.

The data on using pressure measurements during primary prophylaxis are quite consistent. If the patients

achieve a hemodynamic response to pharmacologic therapy, their risk of bleeding during the next 2– 3 years falls to about 5%. If the HVPG falls to < 12 mm Hg (about one-third of patients), then the risk of bleeding is close to zero. In contrast, in those who fail to respond, the risk of bleeding is 30–40% over the same period of time.[14–16] Two of the studies used beta-blockers initially, and if they failed to have a hemodynamic response, nitrates were added. About 40–55% of patients achieve a hemodynamic response with beta-blockers alone, and another 20–30% with the addition of nitrates.[14,16,17] Despite the apparent advantage of nitrates on the hemodynamic response, the benefit of the addition of nitrates in preventing bleeding is unclear.[18,19]

Secondary Prophylaxis

Pharmacologic therapy has also been used in the prevention of rebleeding in patients with varices. The likelihood of rebleeding in untreated patients is 55–67%. Use of pharmacologic or endoscopic therapy or TIPS or other shunts all reduce the risk of bleeding significantly.[5,8,20] As with primary prophylaxis, the major cause for failure of pharmacologic therapy is the lack of a hemodynamic response. The likelihood of a failure to have a hemodynamic response varies from 45 to 63%. Bleeding rates in individuals who fail to respond to pharmacologic treatment varies from 46 to 65%, whereas in responders the bleeding rates are 7–13%. As with primary prophylaxis, the risk of bleeding in those whose HVPG falls to < 12 mm Hg is nearly zero.[5]

Clinical Usefulness of Measurement of HVPG

From the above discussion it is clear that the response of the HVPG to pharmacologic therapy may be predictive of bleeding. Achieving a HVPG of <12 mm Hg virtually assures that bleeding will not occur or recur, and a > 20% fall in pressure also greatly reduces the risk of bleeding. Unfortunately, all but one[16] of the aforementioned studies analyzed the data on pressure measurement retrospectively; *i.e.* the findings were not used to make therapeutic decisions. Thus, it is unknown whether or not the use of the hemodynamic response to make therapeutic decisions will have a positive effect on bleeding rates. This is not a trivial question, as in the study of Bureau et al.,[16] treating patients who failed to respond to pharmacologic therapy with VBL had no impact on rebleeding.

The situation with secondary prophylaxis is complicated, because the risk of rebleeding is greatest during the first six months following the index bleed.[21] Thus, if the measurement of the repeat WHVP is delayed, then many of the patients will bleed before their response to therapy can be determined. For example, in the study by Villanueva et al.,[22] only 49 of the 72 patients who received drug therapy had repeat pressure measurements (1–3 months following the initial procedure). The failure to have the second measurement was either because of rebleeding or failure to consent to the second procedure. Thus, if the response to pharmacologic therapy is to be used to determine efficacy, repeat measurements must be obtained as soon as the maximum dose of drug is achieved (2–4 weeks following index measurement). The alternative for this group of patients is to use both pharmacologic and endoscopic therapy and forgo pressure measurements altogether.[23]

Measuring the HVPG following an acute episode of variceal bleeding may also be useful, as it may predict which patients are likely to rebleed in hospital and therefore should be managed with more definitive therapy such as a TIPS.[6,24] As most patients with an acute variceal bleed are placed in an intensive-care-unit setting where the technology required for obtaining a WHVP is frequently present, this use of pressure measurements is possible. However, controlled trials in which pressure measurements are used to determine therapy need to be performed before this approach can be taken.

The most likely situation in which measurement of portal pressure will find the greatest use is in the primary prevention of variceal bleeding. The appeal of determining the response in this group is that the timing of the repeat pressure measurement is not as critical. In addition, many patients will remain on the medication for a prolonged period of time, and therefore one would like to be certain that the therapy is effective, and if not, to apply another form of treatment, the so-called "A La Carte" approach.[16] It seems likely that bleeding rates of 5% over two years can be achieved if pharmacologic therapy is limited to those with a hemodynamic response and the nonresponders undergo VBL.[14,25] However, randomized controlled trials are required before this approach can be taken. It is unlikely that the use of WHVP measurements will be cost-effective.[26] However, the purpose of the controlled trials will be to establish whether or not this "A La Carte" approach is significantly more effective than the current approach of treating everyone with large varices with beta-blockers ± nitrates.[11] Once it has been proven that the "A La Carte" approach is significantly better than the current approach, then the next step is to develop accurate, noninvasive techniques to measure portal vein pressure.

Conclusions

Measurement of WHVP is safe and relatively simple. The information obtained may be predictive of new or recurrent bleeding and potentially can help in determining whether or not pharmacologic therapy is effective. However, controlled trials are required before measurement of portal pressure can be used to make decisions in clinical practice. Although new agents are likely to be developed that also reduce portal pressure in a predictive manner,[9] it is unlikely that one drug or combination of drugs will be effective in all patients. As with systemic hypertension, we need a safe and accurate noninvasive method for the measurement of portal pressure. Once we can measure portal pressure easily, the management of patients with portal hypertension will be much more straightforward. Until that goal is achieved, the WHVP measurement remains the only way to assess responses to pharmacologic therapy and to develop a tailored approach to prevent variceal bleeding in patients with portal hypertension.

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Targeting Portal Pressure Measurements: A Critical Reappraisal

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Many of the complications of cirrhosis reflect the presence of portal hypertension, which is commonly expressed as the hepatic venous pressure gradient (HVPG). Baseline and repeat measurements of HVPG have been recommended for the management of patients with cirrhosis in the setting of pharmacologic prophylaxis of variceal bleeding and for gaining information about prognosis. However, published studies have demonstrated problems with the interpretation of the data on HVPG monitoring, making its use controversial. We view the current data as insufficient evidence to support the monitoring of a targeted reduction of HVPG as routine clinical practice. We recommend the performance of new prospective studies to establish the clinical importance of HVPG measurements. (HEPATOLOGY 2004;39: 286–290.)

Portal hypertension develops during the natural history of cirrhosis and is responsible for the development of gastroesophageal varices and bleeding, ascites, hepatorenal syndrome, and hepatic encephalopathy. These complications worsen a patient's prognosis and are a major cause of death. For many years, the degree of portal hypertension has been recognized as an independent factor for survival among patients with cirrhosis.[1] Conversely, improvement in liver function in alcohol-abstinent subjects with cirrhosis has been associated with a reduction in portal pressure.[2] A reduction in portal pressure has been shown to result in a reduction of the complications of cirrhosis and in improved survival, although it is unclear if a concomitant improvement in liver function occurred.[3] Measurement of the hepatic venous pressure gradient (HVPG) is a common and indirect way of assessing the portal pressure gradient. Wedge hepatic venous pressure reflects the values of portal pressure in cirrhotic patients with a predominantly sinusoidal site of resistance.[4–6]

Clinically significant portal hypertension is defined by a portal pressure gradient greater than 12 mm Hg,[7] as the development of ascites and variceal bleeding usually occur above this threshold. Monitoring of HVPG is being used increasingly to assess target reductions of portal pressure during secondary and primary pharmacologic prophylaxis of variceal bleeding. A decrease in HVPG of ≥20% from baseline[8–10] or to ≤12 mm Hg[8–11] is a favorable hemodynamic response to treatment because it correlates with a significant reduction in bleeding. In addition, studies have shown that cirrhotic patients who bleed have an HVPG of ≥12 mm Hg.[12–14]

Secondary Prevention of Variceal Bleeding

In five major studies[8–10,15,16] and one smaller series,[17] published as correspondence, HVPG was measured at baseline and at a subsequent time point. Three of these studies were randomized, controlled trials[9,10,16] that compared pharmacologic prophylaxis of variceal bleeding with sclerotherapy[9] or with endoscopic banding ligation.[10,16] Two studies[8,15] evaluated the prognostic value of HVPG monitoring in the setting of medical therapy for the secondary prevention of variceal hemorrhage. Three studies[8–10] justified the routine practice of HVPG monitoring during pharmacologic prevention of recurrent variceal bleeding. Two other studies[18,19] considered the importance of hemodynamic response to drug therapy for the prevention of variceal bleeding. However, the study populations in these two studies combined both patients with and without a history of previous variceal bleeding. Therefore, interpretation of these study results were difficult due to the different response rates to pharmacologic prevention and bleeding risks[19,20] in primary and secondary prophylaxis. Tables 1 to 3 summarize these five studies.

Abbreviation: HVPG, hepatic venous pressure gradient.

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Table 1. The Key Studies of Repeated HVPG Measurement in the Prevention of Variceal Rebleeding: Total Populations and Hemodynamic Responders

Author (reference)	Feu et al.[8]	Villanueva et al.[9]	McCormick et al.[15]	Villanueva et al.[10]	Patch et al.[16]
Total patients	83	43*	63	72†	51‡
Patients with baseline HVPG measured	83% (69)	100% (43)	89% (56)	100% (72)	78% (40)
Patients with remeasurement of HVPG	83% (69)	72% (31)	71% (45)§	68% (49)	35% (18)
Hemodynamic responders	36% (25)	45% (14)	64% (28)	51% (25)	50% (9)
Patients with repeat HVPG ≤12 mm Hg	12% (8)	29% (9)	48% (21)	14% (7)	9% (2)
Mortality in patients with baseline HVPG measurement	13% (9)	9% (4)	n/a	32% (23)	33% (17)

NOTE. Absolute number of patients is shown in parentheses.
Abbreviation: HVPG, hepatic venous pressure gradient.
*Initial cohort comprised 121 patients, 86 of whom were included (43 patients in each treatment arm).
†Initial cohort comprised 233 patients, 144 of whom were included (72 patients in each treatment arm).
‡Initial cohort comprised 205 patients, 102 of whom were included (51 patients in each treatment arm).
§Only 44 patients were included in the study (1 patient was excluded because of low initial and repeat HVPG [7 mm Hg]).

Initially, the five studies appeared similar, but there are marked differences between them, making the hemodynamic data difficult to interpret. As a result, questions arise regarding their value as evidence to justify the clinical performance of HVPG monitoring.[21]

The studies varied with regard to treatment used (only beta-blockers were used in one sudy and combination therapy with nitrates was used in the remaining four studies), percentage of patients with alcoholic liver disease (range, 50%-70%), time of follow-up (range, 8-28 months), percentage of patients in Child class C (range, 6%-47 %), and especially in the interval of time after which the second HVPG measurement was performed (Table 2). This time interval varied as widely as a mean of 57 days[16] to 5.3 months[15] (Table 2). Furthermore, several specific factors complicate the interpretation of the hemodynamic data.

First, the hemodynamic response in these studies is defined as either an HVPG decrease of ≥20% from baseline or a decrease to ≤12 mm Hg. However, there is overlap so that some patients who achieved a ≥20% decrease from baseline also had a final HVPG of ≤12 mm Hg. Patients with such an overlap had a lower baseline HVPG. In the only studies that report the data, 32%[8] to 57%[9] of hemodynamic responders achieved both criteria and 62% of patients with a ≥20% decrease also decreased their HVPG to ≤12 mm Hg.[9] Therefore, it is unclear whether the ≥20 % decrease, if an absolute reduction to ≤12 mm Hg is not achieved, is a valid therapeutic target *per se*. Unfortunately, these data cannot be derived from the published studies.

Second, the determination of the prognostic value of HVPG monitoring is flawed. The responder/nonresponder status could not be assessed in 17%[8] to 65%[16] of patients as the HVPG was not measured and/or remeasured (Table 3). One would expect this group to be composed of both potential responders and nonresponders and to have a rebleeding rate intermediate to both groups. However, the rebleeding rate among these patients varies widely, from 17%[9,10] to 64%[8] (Table 3). Therefore, the rebleeding rate when HVPG was not measured or remeasured was similar to the responder group in Villanueva et al.'s second study[10] (17% vs. 16 %) and is higher than the rate in the nonresponder group in the Feu et al.[8] study (64% vs. 52 %). This omission represents an important source of bias and

Table 2. Key Studies of Repeated HVPG Measurement in the Prevention of Variceal Rebleeding: Baseline Characteristics, Time to Remeasurement, and Length of Follow-up

Author (reference)	Feu et al.[8]	Villanueva et al.[9]	McCormick et al.[15]	Villanueva et al.[10]	Patch et al.[16]
Time of, or mean interval to, remeasurement (mo)	3	3-4	5.3	1-3	2
Child class C	6% (4)	16% (7)	6% (4)	19% (14)	47% (24)
Alcoholic etiology	59% (41)	51% (25)	70% (31)	50% (43)	63% (32)
Follow-up (mo) (range)	28† (1-69)	18* (4-36)	22 responders†, 26 nonresponders† (0.1-60)	20* (1-65)	8* (0.25-46)
Patients with nitrates	0	100% (43)	68% (30)	100% (72)	41% (22)
Baseline HVPG (mm Hg, mean ± SD)	18.3 ± 3.6	17.7 ± 3.4	17.5 ± 0.6 responders, 18 ± 1.0 nonresponders	19.9 ± 3.5	18.3 ± 4.9

Abbreviation: HVPG, hepatic venous pressure agent.
*Median value.
†Mean value.

Table 3. Patients Rebleeding in the Key Study Populations of Repeated HVPG Measurement in the Pharmacologic Prevention of Variceal Rebleeding

Author (reference)	Feu et al.[8]	Villanueva et al.[9]	McCormick et al.[15]	Villanueva et al.[10]	Patch et al.[16]
Total patients	83	43*	63	72†	51‡
HVPG not measured	17% (14)	0%	11% (7)	0%	22% (11)
HVPG not remeasured	17% (14)	28% (12)	17% (11)§	33% (23)	65% (33)
Rebleeding is not remeasured	64% (9/14)	17% (2/12)	28% (5/18)‖	17% (4/23)	33% (11/33)
Rebleeding (patient groups)					
Total	36% (25/69)	26% (11/43)	37% (16/44)	33% (24/72)	37% (19/51)
Hemodynamic responders	8% (2/25)	7% (1/14)	43% (12/28)	16% (4/25)	11% (1/9)
Hemodynamic nonresponders	52% (23/44)	47% (8/17)	25% (4/16)	67% (16/24)	22% (2/9)
Repeat HVPG ≤12 mm Hg	0% (0/8)	0% (0/9)	30% (7/23)	? (?/7)	50% (1/2)
Rebleeding before remeasurement	7% (5/69)	Some¶	16% (7/44)	Some¶	22% (5/23)

NOTE. Absolute numbers are shown in parentheses.

Abbreviation: HVPG, hepatic venous pressure gradient.

*Initial cohort comprised 121 patients, 86 of whom were included (43 patients in each treatment arm).

†Initial cohort comprised 233 patients, 144 of whom were included (72 patients in each treatment arm).

‡Initial cohort comprised 205 patients, 102 of whom were included (51 patients in each treatment arm).

§Only 44 patients were included in the study (1 patient was excluded because of low initial and repeat HVPG [7 mm Hg]).

‖Rebleeding rate in both nonmeasured and nonremeasured patients (rebleeding occurred in two of seven patients who did not have their baseline HVPG measured and in 3 of 11 patients who did not have a repeat HVPG measurement).

¶Number not stated (in the second study[4] it can be derived that this number must be between 1 and 4).

explains the heterogeneity of the results among the studies.

Third, HVPG was not remeasured in some patients because they rebled before the scheduled repeated measurement. This proportion of patients varied from 7%[8] to 22%.[16] In the cohort studied by Feu et al.,[8] remeasurement was performed at 3 months. The rebleeding rate was low during this interval, suggesting a selection of patients with better risk in terms of rebleeding. Conversely, the highest percentage of rebleeding before remeasurement, probably due to the high percentage of Child class C patients, occurred in the Patch et al.[16] study in which HVPG was remeasured after a median of 49 days. As Child class C patients are at the greatest risk of experiencing rebleeding. If they are excluded from HVPG monitoring, then the value of this approach is greatly reduced and is less applicable. The influence of the timing of remeasurement in now accepted as being clinically relevant. Whereas the initial interval to HVPG remeasurement was 3 months[8] (with only 7% of patients experiencing rebleeding in this interval), the same group now suggests 2 weeks.[22] However, this recommendation has not been tested prospectively. Furthermore, the interval to remeasurement influences the proportion of patients who rebleed before a second HVPG measurement and who experience a spontaneous reduction of HVPG.[2,11]

Primary Prevention of Variceal Bleeding

In contrast to secondary prevention, few data exist for HVPG monitoring in the primary prophylaxis of variceal hemorrhage.[11,23] Merkel et al.[23] reported that the cumulative probability of variceal bleeding was significantly higher among hemodynamic nonresponders. Variceal bleeding did not occur among responders who were compliant and who did not have portal vein thrombosis. In the study by Groszmann et al.,[11] none of the patients who achieved an HVPG of ≤12 mm Hg during subsequent measurements experienced a hemorrhage. The prognostic value of a 20% decrease from baseline was not assessed in that study.

However, in primary prevention, the low bleeding rate (≤20%) and the protection afforded by nonselective beta-blockers do not justify HVPG monitoring, particularly with an invasive procedure, albeit one with a low risk. Moreover, the cost-effectiveness of this approach has been questioned.[24]

Other Considerations Concerning HVPG Monitoring

The ability of pressure measurements to predict the response to medical treatment for the prevention of variceal rebleeding might be better with baseline HVPG values versus the hemodynamic response.[16] This possibility was not commented upon in the other studies. A decrease of HVPG by ≥20% or to ≤12 mm Hg may be an expression of a lower baseline HVPG value. This could be especially true if patients who rebleed early, and thus cannot have a remeasurement, have a higher baseline HVPG.

The five studies show a better correlation between the absence of rebleeding and the absolute reduction of HVPG to ≤12 mm Hg than with the ≥20 % reduction.[21] The validity of a 20% HVPG decrease from base-

line as a therapeutic target is difficult to determine. For instance, if a 3-mm Hg difference in HVPG is considered when the baseline HVPG is 15 mm Hg, then a 20% change will be produced. As the intraindividual variability in HVPG measurement in specialized centers is approximately 8% (a coefficient of variation of 1 mm Hg),[1] this finding could make a significant difference in defining whether a patient has achieved a decrease by more or less than 20% from baseline or a value below or above 12 mm Hg (thereby changing the responder status). Therefore, defining a hemodynamic response by an HVPG decrease of 20% when the baseline HVPG is low may inherently introduce an error due to the variability in measurement.

Thresholds in HVPG reduction represent a surrogate for hemodynamic changes at the level of the varix. Variceal wall tension decreases with the use of a nonselective beta-blockade. However, due to the influence of the collateral resistance, there is variability in the decrease in variceal pressure, which can be greater than the decrease in portal pressure.[25] A decrease in variceal wall tension associated with a ≥20% HVPG reduction, independent of basal HVPG, has been proposed as the mechanism for protection against bleeding.[26] However, it is noteworthy that no difference in variceal pressure reduction was found between hemodynamic responders and nonresponders (defined by a ≥10 % decrease in HVPG from baseline).[25] A less than 10% decrease in HVPG, or even more so a 10% to 20% reduction in HVPG, can lead to a decrease in variceal pressure (and, thus, wall tension), which may be sufficient to prevent rebleeding. Therefore, other factors may be important for rebleeding. The degree of liver cell dysfunction may change the risk of bleeding as much as the degree of portal pressure reduction. The risk of first bleeding in patients with small varices and Child C disease is higher than that of patients with large varices and Child grade A disease,[27] supporting this concept.

The impairment of liver function, as expressed by the Child-Pugh score, is an important predictive factor for variceal hemorrhage.[10,27–30] An improvement in the Child-Pugh score is associated with a decrease in HVPG.[2,11] In some studies, the hemodynamic response to drug therapy is linked to an improvement in liver function.[10,19,31] In both studies by Villanueva et al.,[9,10] there was a higher Child-Pugh score at 3 months in the endoscopic therapy group, which subsequently showed a higher rebleeding rate. This observation may be especially important in patients with alcoholic cirrhosis because abstinence can improve liver function[32] and reduce portal pressure.[33] In a recent study,[3] both the lack of hemodynamic response to pharmacologic therapy and the severity of liver disease, as expressed by a lower serum albumin concentration, were independently associated with the development of variceal rebleeding.

Nonselective beta-blockers reduce bleeding risk, yet the protection afforded may not be solely related to the degree of HVPG response. The risk of rebleeding with drug therapy is remarkably similar in four of the five studies cited (range, 33%-37%) and was 26% in one,[9] which may be due to a shorter follow-up. This similar rebleeding rate is despite having different hemodynamic response rates, different proportions of patients whose HVPG was not measured and/or remeasured, and different percentages of patients bleeding in the not measured/remeasured group (Tables 1–3).

Conclusions

There is no doubt that pharmacologic therapy of portal hypertension using non-selective beta-blockers is effective in reducing bleeding rates and is at least equivalent to banding ligation for secondary prevention of variceal bleeding.[10,16] Although we concur that an absolute reduction of HVPG to 12 mm Hg confers near complete protection against bleeding, this is a rare event. Absolute reduction of HVPG occurred in only a median of 14% of the patients in whom HVPG was measured in the five studies (Table 1). When considering the target of ≥20% reduction, there are too many difficulties in interpreting its clinical validity from published work.

Monitoring target HVPG reductions instead of the empirical use of propranolol (which is an extremely cheap generic drug) increases the cost of therapy. Therefore, this approach needs to be substantiated by solid evidence that demonstrates better therapeutic efficacy and clinical applicability. Monitoring of HVPG used as a splanchnic sphygmomanometer[1] needs to be assessed in a new prospective study of secondary prophylaxis. This new study should remeasure HVPG at 2 weeks from bleeding and should randomize patients to a change of therapy or no modification if target reductions of HVPG have not been achieved. In addition, changes in liver function need to be assessed during follow-up to explore the interaction of liver function with HVPG.

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