

The Hepatic Venous Pressure Gradient: “Remixed and Revisited”

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The hepatic venous pressure gradient (HVPG).¹ HVPG is more than 50 years old!² But what has it taught us regarding the pathophysiology of portal hypertension? A lot, yet it is still not part of the routine investigation of this deadly complication of chronic liver disease. It has never been incorporated in various prognostic indices (Child-Turcotte, Child-Pugh, or model for end-stage liver disease [MELD] scores) and is still not a direct factor in decisions to perform liver transplantation.

We know that the HVPG is an acceptable indirect measurement of portal hypertension, because wedged hepatic venous pressure is very close to portal venous pressure (PVP) in most chronic liver diseases, particularly in alcoholic and viral (B and C) cirrhosis.^{3–6} It is also accepted that changes in portal venous pressure induced by drugs are similarly reflected in wedged hepatic venous pressure, and therefore the HVPG is an adequate measure of drug effects on portal pressure.⁶

A first important step in demonstrating its usefulness was the threshold value of 12 mmHg above which serious complications of portal hypertension can arise, particularly bleeding gastroesophageal varices.^{7–9}

In the early 1980s, the first demonstration that portal hypertension could be modified by a drug was the decrease in the HVPG after acute or chronic propranolol administration.^{8,10,11} Subsequently, the ability to prevent bleeding from gastroesophageal varices was associated with an effect on portal pressure.¹² HVPG measurement also allowed the identification of responders and nonresponders to β -blockers, which explains why protection

from gastroesophageal variceal bleeding is not seen in all treated patients.^{13,14}

Now it is generally accepted that decreasing the HVPG below a threshold value of 12 mmHg by any drug or combination of drugs almost completely reduces the risk of first or recurrent bleeding from varices.^{15,16} Unfortunately, with currently available drugs, this threshold is not frequently attained, except in patients with mild to moderately elevated HVPG and possibly less at risk. In certain patients, a small reduction of the HVPG is associated with a real decline in the risk of first or recurrent bleeding, and it has been proposed that a 20% HVPG decrease should be considered as evidence of a significant response to therapy.^{16,17}

HVPG measurement is a safe technique. No reports of serious complications have been published in the medical literature, and our unit's experience has been positive after more than 4,000 such procedures. In addition, hepatic vein catheterization offers the possibility of performing liver biopsies in patients with poor coagulation, contraindications for transthoracic liver biopsies, or both.

Finally, there is no other less invasive way to estimate the severity of portal hypertension reliably, particularly its changes under medical therapy. No other “splanchnic sphygmomanometer” allows repeated pressure measurements as is the case with arterial sphygmomanometers in the control of high arterial blood pressure.¹⁸

So, why is there such resistance to adopt HVPG measurement in clinical practice? The “Perspective in Clinical Hepatology,” written by three expert groups in the field and reported in the present issue of *HEPATOLOGY*,^{18–20} may explain why such a procedure still is performed mainly in specialized centers, particularly those involved in clinical trials searching for the best way to prevent first or recurrent bleeding from gastroesophageal varices in patients with chronic liver diseases.

Although HVPG measurement is safe and relatively simple, it represents the difference between two pressure readings, doubling the sources of error. In this context, the technical note provided by Groszman and Wongcharatrawee²⁰ is well taken: Any study evaluating the diagnostic or prognostic value of the HVPG must rely on pressure measurements with several technical requirements. Quality control is needed for every hemodynamic evaluation, and it is likely that the criteria for reliable assessments are not always fulfilled in many liver units. Boyer¹⁹ suggested that “performing TIPS procedures pro-

Abbreviations: HVPG, hepatic venous pressure gradient; PVP, portal venous pressure.

From the ¹Fédération d'Hépatogastroentérologie, Centre Hospitalier Universitaire de Nice-Hôpital l'Archet 2, Faculté de Médecine, Nice, France; and ²Centre de Recherche, Centre Hospitalier de l'Université de Montréal - Hôpital Saint-Luc, and Département de Médecine, Université de Montréal, Montréal, Québec, Canada.

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Address reprint requests to: Pierre-Michel Huet, M.D., Ph.D., Fédération d'Hépatogastroentérologie, Centre Hospitalier Universitaire de Nice-Hôpital l'Archet 2, 151 Route de Saint-Antoine de Ginestière (BP 3079), 06202 Nice Cedex 3, France. E-mail: pierre-michel.huet@wanadoo.fr; fax: +04-92-03-65-77.

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vided training to a large group of interventional radiologists in portal pressure measurements.” However, the procedure often is undertaken on an emergency basis, and time limitations are always an important factor in patient turnover from angiographic suites, which may explain why HVPG measurements are inaccurate in many cases. For example, it would be interesting to know how many centers use pressure tracings systematically instead of instant pressure readings on the screen.

In addition, HVPG calculation must be standardized; inferior vena cava pressure (above the liver) rather than free hepatic venous pressure should be recorded. Portal hypertension is defined by an increased pressure gradient between the portal vein and the inferior vena cava, which represents real perfusion pressure within the portal and hepatic circulation. Therefore, pressure measurement in a free hepatic vein should be avoided, because it may give false gradient values, being generally higher than inferior vena cava pressure (1 to 3 mmHg)²⁰ resulting from partial obstruction by the catheter of a narrow, flattened hepatic vein. This is not a trivial issue because the expected changes in HVPG after drug therapy are of a slightly higher magnitude (2 to 6 mmHg).

Although HVPG measurement is useful for the diagnosis of portal hypertension, its prognostic value is still debated. Recently, HVPG has been proposed as a prognostic indicator together with other parameters such as the Child-Pugh and MELD scores. This approach seems logical because the level of portal hypertension has been correlated with histologic damage,²¹ as with the degree of liver failure.²² Other studies have indicated that HVPG may predict early rebleeding after a first variceal bleeding episode.^{23–25} It has been suggested that the risk of rebleeding is higher in patients with HVPG more than 16 mmHg²³ or 20 mmHg.²⁴

The prognostic value of HVPG for survival is another controversial matter. Some authors have proposed that HVPG measured after bleeding^{23,26} or sequential HVPG recordings²⁷ may predict survival, whereas others (even from the same group) have not found any predictive value of HVPG for survival.^{25,28}

The pharmacologic treatment of portal hypertension now is recognized as an important therapeutic option for primary or secondary prophylaxis of variceal bleeding.¹ Vasoactive drugs, mainly nonselective β -blockers and nitrates, have been found to decrease HVPG in a significant number of cirrhotic patients. However, as clearly summarized by Boyer¹⁹ and Thalheimer et al.,¹⁸ there is no consensus on the need for repeat HVPG measurements during treatment or on the target percent reduction of the HVPG for the assessment of treatment efficacy. Many reports note the risk of first bleeding or rebleeding is much

lower in cirrhotic patients with a good response to treatment, defined by a 20% decrease of the HVPG from baseline.^{15,16,29–32} However, this observation has been challenged by other studies that did not demonstrate the predictive value of a 20% HVPG reduction for rebleeding.³³ Fortunately, it is generally agreed that HVPG measurements of less than 12 mmHg offer almost complete protection against variceal bleeding, but this target is achieved only in a minority of patients.

It would be logical to assume that any decrease in the variceal bleeding or rebleeding rates would translate into improved survival. Such a relationship between the hemodynamic response to pharmacotherapy and survival has been reported in some trials,^{15,17} but the issue is still controversial.^{16,31}

As pointed out by Thalheimer et al.,¹⁸ interpretation of the published data is difficult owing to many sources of bias: Certain studies have evaluated patients for primary prophylaxis, and others for secondary prophylaxis, with some including both of them. The proportion of active alcoholism is heterogeneous in different investigations, and it is well known that HVPG may decrease with alcohol abstinence. In addition, the concept of a target HVPG may be questionable; bleeding is the result of increased variceal tension, which is related to variceal pressure and variceal size, both of which are not evaluated by HVPG measurement. The timing of the second measurement is highly variable (1–6 months), and this is crucial because a long interval excludes patients with early rebleeding. In this respect, the acute hemodynamic effect of vasoactive drugs seems to be a promising approach as long as the strategy can predict the likelihood of first bleeding or rebleeding.^{27,34} In addition, such strategy could avoid the need for a second HVPG measurement. The final argument for not measuring HVPG during pharmacological treatment is that this approach may not be cost effective.³⁵

Clearly, there is a need for further clinical trials to evaluate prospectively the prognostic value of HVPG changes for the risk of bleeding; for secondary prophylaxis, the second measurement must be performed as early as possible to avoid the premature exclusion of patients because of rebleeding. In the meantime, it seems reasonable to evaluate the effects of treatment on HVPG only in patients enrolled in controlled clinical trials. However, in such trials, HVPG should be measured according to a rigid protocol such as the one proposed by Groszmann and Wongcharatrawee,²⁰ preferably by experienced hepatologists, well-trained radiologists with a specific interest in hepatology, or both.

Sequential HVPG measurements may be useful not only to assess the efficacy of vasoactive drugs, but also to evaluate the effects of the treatment of various liver dis-

eases used in conjunction with liver biopsy and Child-Pugh score. It is well accepted now that cirrhosis secondary to both hepatitis B virus and hepatitis C virus can improve dramatically with lamivudine or interferon or ribavirin treatment. Indeed, Burroughs et al.³⁶ suggested recently that HVPG measurement could serve as a marker for disease progression or could monitor treatment efficacy in patients with chronic hepatitis C. In addition, most drugs accepted for the treatment of portal hypertension only address the increased portal blood flow component of the syndrome, whereas the intrahepatic resistance component has yet to be explored with new drugs. For this purpose, repeated HVPG measurements will be necessary until less invasive methods of evaluating portal hypertension become available.

To summarize, all three manuscripts published in the present issue of HEPATOLOGY are correct: "Changing clinical practice with measurements of portal pressure" is underway; however, if performed, HVPG assessment "should be done right" and still needs "critical reappraisal."¹⁸⁻²⁰

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PIERRE-MICHEL HUET¹ AND GILLES POMIER-LAYRARGUES²
*¹Fédération d'Hépatogastroentérologie
Centre Hospitalier Universitaire de Nice
Faculté de Médecine
Nice, France
²Centre de Recherche
Centre Hospitalier de l'Université de Montréal-Hôpital
Saint-Luc, and Département de Médecine
Université de Montréal
Montréal, Canada*

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