Hemodynamic assessment in clinical practice in portal hypertensive cirrhotics

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SUMMARY

With the advent of the balloon catheter technique for the measurement of HVPG, portal hemodynamics can be studied safely, conveniently and accurately. Evaluation of portal hemodynamics not only provides information in diagnosing the etiologies of portal hypertension, it is also essential in evaluating efficacy of various treatments for this devastating syndrome. Furthermore, HVPG has also been shown to correlate with survival prognosis in patients with end-stage liver disease. In light of the current shortage of donor organs, the role of HVPG in classification of liver transplantation candidates should be worth future investigation. In addition, although HVPG by itself is not a reliable predictor of variceal hemorrhage, it has been suggested that serial measurements of HVPGs may be a better risk prognosticator. This issue also deserves further investigation. Recently, HVPG has assumed an importance in the pre-operative assessment in cirrhotics, even though this prognostic value was derived from a specific situation, hepatic resection in early HCC. Before a definite recommendation can be made regarding other types of surgery, future studies should compare HVPG with conventional tools such as Child/Pugh classification score. Lastly, non-invasive methods of quantitative portal hemodynamic measurement should be compared directly with HVPG in order to further define their roles in the evaluation of portal hypertension.

Key Words: portal hypertension, hepatic venous pressure gradient, esophageal varices, variceal hemorrhage, hepatocellular carcinoma, cirrhosis

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INTRODUCTION

Without doubt, HVPG is a valuable tool in clinical management of cirrhotic patients. Whether or not HVPG should be a routine evaluation depends upon whether it dictates treatment strategies that are beneficial to patient care. With mounting evidence that HVPG may be a better prognostic marker than other currently available parameters, further studies will hopefully strengthen the role of HVPG measurement as an integral management of portal hypertensive cirrhosis. Many of the clinical complications of cirrhosis are the direct consequences of elevation of portal venous pressure (PVP). Portal hypertension is defined as a PVP of greater than the normal 5-10 mmHg. The degree of portal hypertension has been shown to correlate with the severity of liver disease, both functionally[1]and histologically.[2,3] However, direct portal venous pressure measurement is invasive and cannot be routinely performed. As a surrogate, hepatic venous pressure gradient (HVPG) has been widely accepted as a measurement for portal venous pressure. The ease and safety of HVPG measurement has made it a valuable tool not only in the research arena, but more and more in clinical practice as well. In addition, non-invasive techniques such as duplex-doppler ultrasonography have also been investigated as a tool to assess portal hemodynamics. In this article, we will first review the techniques used in evaluating PVP and its surrogate, HVPG. We will then review how this hemodynamic as-

sessment is currently utilized in various clinical settings.

Portal Venous Pressure Measurement

Portal venous pressure was first measured in humans in 1937 by directly inserting a needle catheter into a branch of portal vein.[4] This procedure was performed during abdominal surgery and therefore not practical for wide-scale usage. Furthermore, the splanchnic hemodynamics are affected by the use of general anesthesia and thus the PVP obtained during surgery may not reflect the true pressure. Other direct measurement techniques that have been used include threading the catheters into portal venous branches via transhepatic approach,[5] or via umbilical vein catheterisation.[6] These techniques are nonetheless invasive, technically difficult and associated with appreciable risk of procedural complications.

Indirect measurement of portal venous pressure was first described in 1951 by Myers and Taylor.[7] By advancing a small catheter into a hepatic venule until it could go no further, the authors were able to demonstrate that this 'wedged hepatic venous pressure (WHVP)' was closely correlated with the directly measured portal venous pressure. The difference between the pressure in the wedged position (WHVP) and the free position (FHVP) constitutes the hepatic venous pressure gradient (HVPG) which represents the gradient between portal vein and intra-abdominal vena caval pressure. Because both WHVP and FHVP are affected equally by intra-abdominal pressure, their gradient, HVPG is not. In other words, unlike PVP which can be falsely elevated in the presence of ascites and elevated intra-abdominal pressure, the measurement of HVPG incorporates its own zero reference point and is not affected.

Currently, the most widely used technique in evaluating HVPG is a modification of Myer's method.[8] Under fluoroscopic guidance, a fluid-filled balloon catheter is advanced into a branch of hepatic vein. FHVP is the pressure measured with the balloon deflated and the catheter floating freely within the vein. The balloon is then inflated until that branch of hepatic vein is completely occluded. In this position, the hepatic venous pressure is equalized to the sinusoidal pressure via a static column of blood connecting the sinusoid to the balloon tip (Figure 1). The advantage of balloon catheter is that serial measurements of free and wedged hepatic venous pressure can be obtained with ease using the same catheter, inflated and deflated as needed. In addition, the catheter can be left safely in place for hours and hence the effects of pharmacological agents on portal hemodynamics can be studied over time. Furthermore, unlike the conventional catheter where WHVP is measured in a small hepatic venule, the balloon catheter allows measurement in the hepatic veins at the lobar and sublobar levels. Therefore, the pressure obtained, an average pressure of several segments of the liver, is more likely to represent the true portal venous pressure.

HVPG measurement nonetheless is not without its drawbacks. It is important to recognize that WHVP is a measurement of sinusoidal pressure and not of portal venous pressure per se. Consequently, WHVP will be an underestimation of PVP if a pre-sinusoidal resistance is present. For example, WHVP (and hence HVPG) was found to correlate very well in alcoholic cirrhosis where the sites of increased hepatic vascular resistance are within the sinusoid as well as post-sinusoidal area. Yet, WHVP was found to be less than PVP in non-alcoholic cirrhosis where pre-sinusoidal resistance is increased.[5, 9] Nevertheless, in other studies there was no significant difference when PVP and WHVP were compared in cirrhotic patients with hepatitis B and hepatitis C infection.[10,11] However, since the majority of cirrhosis in the western world is caused by alcoholism and viral hepatitis, one should still be able to use HVPG with confidence as a surrogate measurement for PPV in most cirrhotic patients.

Clinical Applications of Portal Hemodynamics Assessment

Because of the safety and convenience of HVPG measurement, it has found many applications in clinical practice as well as in the research field. In the next section, the current usage of HVPG will be reviewed. We will see that HVPG measurement is a valuable tool in diagnosing the etiologies of liver disease, in determining the prognosis, in evaluating the efficacy of various treatments of portal hypertension and more recently, in predicting the outcome of hepatic resection for hepatocellular carcinoma.

Hepatic Venous Pressure Gradient as a Diagnostic Tool

A normal liver is a low-resistance system. Portal pressure is readily dissipated throughout the hepatic sinusoid. Portal hypertension develops when there is an increase in resistance to portal venous flow. The sites of increased resistance can be pre-hepatic, intra-hepatic or post-hepatic. Portal hypertension from intrahepatic causes can be conceptually subdivided into pre-sinusoidal, sinusoidal and post-sinusoidal portal hypertension. Yet, it is worth noting that a disease process can involve more than one anatomical site. For example, in alcoholic cir-

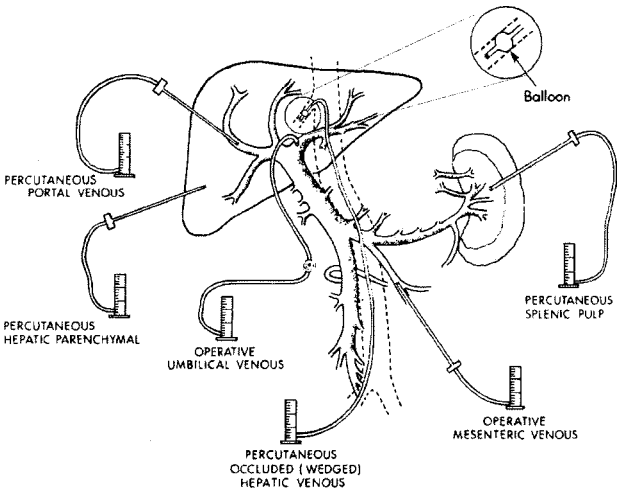

Figure 1. Site and methods of portal hemodynamics evaluation. (Modified and reproduced with permission from Lippincott Williams & Wilkins: Conn HO and Groszmann RJ. The Pathophysiology of Portal Hypertension. Arias I, Popper H, Schachter D, and Shafritz DA, eds. The Liver: Biology and Pathophysiology, 1982, pp 821-848).

rhosis, fibrin and collagen deposition in the space of Disse give rise to the sinusoidal component while terminal hepatic vein fibrosis contributes to the post-sinusoidal component of portal hypertension. Schistosomiasis, on the other hand, involves the pre-sinusoidal area initially, but the sinusoid becomes involved as the disease progresses.

Keeping the classification scheme above in mind, patterns of PPV, WHVP and FHVP can be used to delineate the types of portal hypertension as well as its possible etiologies. For instance, in patients who have clinical syndrome of portal hypertension but have normal WHVP, a pre-hepatic cause of portal hypertension should be suspected. This is illustrated in cases of patients who develop gastroesophageal hemorrhage but have normal WHVP. They are likely to have pre-hepatic etiologies such as splenic vein thrombosis, portal vein thrombosis or splanchnic arteriovenous fistula. On the other hand, a post-hepatic cause such as right heart failure will give rise to elevation in both WHVP and FHVP while HVPG remains normal. Examples of etiologies of portal hypertension and their respective patterns of portal hemodynamic parameters are given in Table 1. Moreover, a significant heterogeneous pressure gradient from one branch of the hepatic vein to another may signify a presence of hepatocellular carcinoma and an appropriate work up should be commenced.[12]

Hepatic Venous Pressure Gradient as a Clinical Prognosticator

In addition to aiding in diagnosing the etiologies of portal hypertension, HVPG has also been used to assess prognosis of cirrhotic patients. In the present days of organ donor shortage, a reliable prognostic tool will undoubtedly facilitate organ allocation. HVPG has been shown to correlate with severity of liver disease and Child-

Table 1. Examples of etiologies of portal hypertension and their patterns of portal hemodynamic parameters

Causes of portal hypertension	WHVP	FHVP	HVPG
Pre-hepatic portal hypertensive syndrome	Normal	Normal	Normal
1. Portal vein thrombosis			
2. Splenic vein thrombosis			
Intrahepatic portal hypertensive syndromes			
Predominantly pre-sinusoidal involvement	Normal or	Normal	Normal or
1. Schistosomiasis, Primary biliary cirrhosis, Idiopathic portal hypertension (early stage)	slightly elevated		slightly elevated
2. Nodular regenerative hyperplasia			
Predominantly sinusoidal and/or post-sinusoidal involvement	Elevated	Normal	Elevated
1. Hepatic cirrhosis			
2. Schistosomiasis, Primary biliary cirrhosis, Idiopathic portal hypertension (advanced stage)			
3. Acute alcoholic hepatitis			
Post-hepatic portal hypertensive syndromes	Elevated	Elevated	Normal
1. Budd-Chiari syndrome			
2. Right heart failure			
3. Constrictive pericarditis			

Pugh classification,[1-3] a traditional tool used to predict survival in patients with end-stage liver disease.[13] In this section, we will review trials investigating HVPG as a predictor of both survival as well as development of variceal hemorrhage.

HVPG as a Predictor of Survival

There are several studies that assess the relationship between HVPG and survival prognosis. Many of these trials indeed show that HVPG measurement is valuable in predicting survival in cirrhotic patients.[14-23] Furthermore Gluud, et al[17] and Merkel, et al[20] found in their respective studies that, by including HVPG in the Child-Pugh score, survival prediction was significantly better than analysis using Child-Pugh classification alone.

One study however failed to demonstrate the relationship between HVPG and survival. In this study, the prognostic significance of HVPG was compared to that of aminopyrine breath test.[24] It was found that the higher level of aminopyrine correlated significantly with survival while HVPG did not. However, in this study, the authors did not specify if any of the test subjects had history of previous variceal hemorrhage or when such hemorrhage occurred. Since HVPG has been shown to decrease spontaneously shortly after the acute bleeding episodes,[25] such lack of information makes the interpretation of the studies difficult.

With respect to the timing of HVPG measurement in patients who develop variceal hemorrhage, some authors have suggested that HVPG obtained close to the bleeding episode may have a higher predictive value with regards to survival. In one study where HVPG was measured within 48 hours of the bleeding episode, Vinel et al. showed that patients who survived after the first month had significantly lower HVPG than patients who expired ($19.\pm7.9$ mmHg versus 23.9 ± 8 mmHg; $P<0.25$).[16] In another study, Patch et al. advocated that a single HVPG measurement within the first 2 weeks of the index bleed may have a better predictive value than measurement obtained after the sixteenth day.[23]

HVPG as a predictor of Variceal Hemmorhage

While it is widely accepted that HVPG is a good prognostic indicator of survival, it is less clear if HVPG is a good predictor of variceal hemorrhage. Several studies have been published on this subject with conflicting results. The early studies were retrospective and included HVPG measurements at varying time points after the index bleeding episodes.[26-29] Since HVPG has been shown to change spontaneously after an acute hemorrhage.[25] it is important to establish a standardized time frame in portal hemodynamic evaluation. Nevertheless, an HVPG of 12 mmHg was shown by several authors to be a minimal threshold below which variceal rupture was unlikely.[26-28]

Among the recent prospective studies involving patients who never bled or had no recent bleeding, there are again conflicting results with regards to the relationship between risks of variceal bleed and HVPG. Four studies (two published papers and two abstracts), using Cox regression analysis, demonstrated that HVPG is an independent predictor of variceal hemorrhage.[17, 20, 30, 31] One study by Lebrec, et al., on the other hand, failed to show a significant correlation.[32]

In studies examining the relationship between HVPG and recurrent variceal hemorrhage after a recent bleeding episode, the results of the studies are again onflicting. Adamson, et al. first suggested that the height of HVPG influenced whether the acute hemorrhage would or would not resolve with non-operative treatment.[33] This correlation was later confirmed by Ready, et al, who further suggested that HVPG of 16 mmHg or above was associated with 50% risk of uncontrolled bleeding.[34] Nevertheless, two other studies by Westaby, et al,[35] and Patch, et al[23] failed to find a significant correlation between HVPG and the risk of recurrent hemorrhage.

Perhaps, instead of using one measurement of HVPG as a prognostic indicator of recurrent variceal hemorrhage, it has been suggested that a change in HVPG from baseline during serial measurements may represent a more accurate predictor of rebleeding. In 1996 Vorobioff et al reported that recurrent hemorrhage was much less common in patients who had a spontaneous reduction of HVPG by 15% or more after the index bleed.[21] In the above study from Westaby, et al, on the other hand, the reduction of HVPG after 1 month of oral propanolol was only 11% (from 17.4 ± 0.8 to 15.4 ± 0.9 mmHg). This small degree of HVPG reduction, therefore, may not be sufficient to protect patients against recurrent hemorrhage.

Hepatic Venous Pressure Gradient as an Assessment of efficacy of Therapy

The two most devastating consequences of portal hypertension are ascites and esophageal varices, both of which can lead to lethal complications including spontaneous bacterial peritonitis, hepatorenal syndrome and variceal hemorrhage. Therapeutic trials for portal hypertension should therefore aim at eliminating these complications. Studies have shown that there appear to be

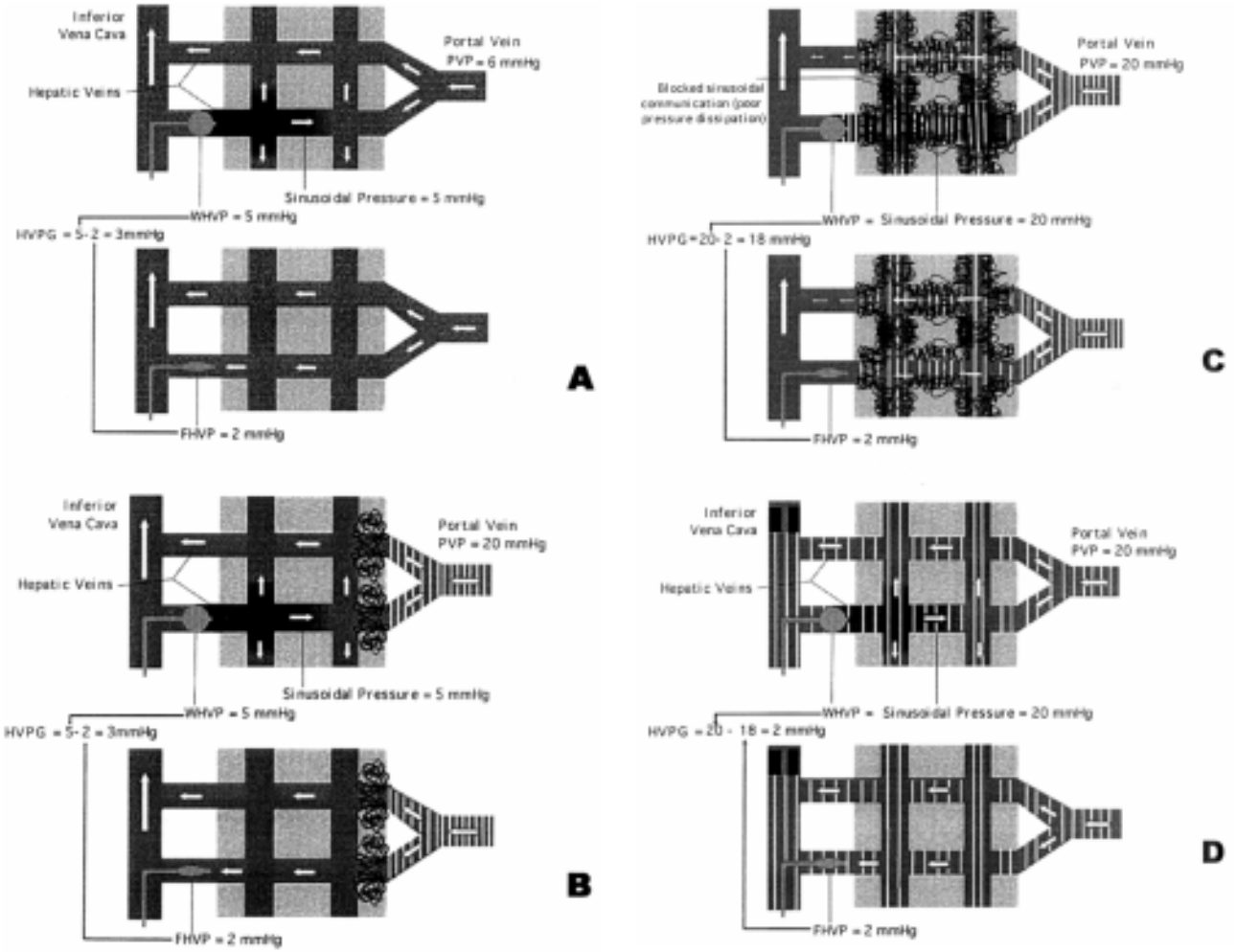

Figure 2. Principles involved in measuring hepatic vein pressure (pressure levels are provided as examples). Stripes indicate hypertensive area; dark area indicate stasis.

(A) The normal liver: Due to normal dissipation of pressure through the sinusoids when the hepatic vein is occluded (top), the measured pressure in the hepatic vein is slightly lower than the normal portal venous pressure (PVP). The difference is usually insignificant.

(B) Presinusoidal portal hypertension: Wedged hepatic venous pressure (WHVP) and hepatic venous pressure gradient (HVPG) are normal in sinusoidal portal hypertension because the intersinusoidal communications are normal and permit decompression of the static column of blood formed by the occluding balloon (top). The site of the obstruction is depicted with dark twisted lines.

(C) Portal Hypertension in cirrhosis: The PVP and WHVP are elevated equally in sinusoidal portal hypertension; effective decompression of the static column of blood created by the occluded balloon (top) cannot occur at the sinusoidal level due to disruption of the normal intersinusoidal architecture. In this situation wedged hepatic venous pressure gives an excellent approximation of the actual portal venous pressure.

(D) Post-hepatic portal hypertension: WHVP is elevated, but HVPG is normal in syndromes such as right-sided carciac failure. The normal HVPG reflects the normal liver architecture present in these syndromes unless permanent liver injury supervenes. (Modified and Reprinted by permission from Lippincott-Raven Publication: Groszmann RJ and de Francis R. Portal Hypertension. Schiff ER, Sorrell MF, Maddrey WC, eds. Diseases of the Liver, 8th ed., vol. 1, 1999, pp 387-442).

threshold HVPGs necessary for the formation of ascites and gastroesophageal varices which are 8 mmHg.[36,37] and 10-12 mmHg[38] respectively. Furthermore, there also appears to be a threshold HVPG for variceal rupture since it has been shown that variceal hemorrhage is unlikely if HVPG is less than 12 mmHg.[19] In current practice, the optimal goal for HVPG is between 10-12 mmHg, but this extent of reduction can only be achieved in a small per-

centage of patients undergoing pharmacologic therapy. Feu et al has subsequently reported that even a 20% reduction in HVPG from baseline can incur a significant secondary prophylaxis against recurrent variceal hemorrhage[39] even though the post-treatment HVPG is still higher than 12 mmHg. In this study, cumulative probability of rebleeding at 1, 2, and 3 years was 4%, 9%, and 9% in patients who achieved a decrease in HVPG = 20%. In other patients, however, the probability of recurrent hemorrhage were 28%, 39%, and 66% at 1, 2 and 3 years respectively.

In addition to pharmacotherapy, portosystemic shunts, such as TIPS (transjugular intrahepatic portosystemic shunt), have also been used to alleviate portal hypertension. As with patients treated with pharmacologic therapy, it was shown that recurrence of variceal bleed as well as ascites occurred only when the portosystemic gradient rose above 12 mmHg.[40]

In recognition of the value of HVPG in clinical practice, experts in the field have recently reached a consensus during the Baveno III conference, defining 'clinically significant portal hypertension' as HVPG of 10 mmHg or more.[41] Future trials should therefore consider incorporating measurement of HVPG as a means of assessing efficacy of any novel therapeutic modalities.

HVPG as a Tool for Pre-operative Assessment in Cirrhotic Patients

It is generally accepted that cirrhotics carry a much higher operative risks than non-cirrhotic patients and elective surgery is best avoided. For intra-abdominal surgery, the mortality rate was found to range from 5-67% and morbidity rate 7-39%[42]. Traditionally operative risks are stratified using Child-Pugh classification score.[42,43] More recently it has been shown that HVPG is associated with surgical outcome after hepatic resection for early hepatocellular carcinoma (HCC).[44,45] HVPG has since been adopted by clinicians as a pre-operative assessment tool for other types of surgery as well.

Bruix, et al first reported in 1996 that, by multivariate analysis, an elevated HVPG was the only parameter significantly associated with unresolved decompensation at 3 months after hepatic resection for HCC.[44] Subsequently, using intention-to-treat model, the same group of investigators demonstrated that clinically significant portal hypertension as well as serum bilirubin were independent predictors of survival after hepatic resection.[45] In this study, patients were selected to undergo hepatic resection (as opposed to liver transplantation) if a single tumor of less than 5 cm was present and if the patients' Child/Pugh scores were less than 6 (Child class A). Among these patients, the 5-year survival probability was drastically better when bilirubin was less than1mg/dL and HVPG less than 10mmHg (74% versus 25%). In fact, the survival rate after resection for a 'good' candidate is comparable to the survival outcome of patients undergoing liver transplantation for early HCC.[46-48]

Several specialized centers have now adopted the practice of measuring HVPG in cirrhotics as a part of pre-operative risk assessment. Nevertheless, it is worth bearing in mind that the above trial was conducted for a specific surgical indication, namely hepatic resection for early HCC. Before a definite recommendation can be made, further studies are necessary to investigate HVPG as a general operative risk prognosticator.

Non-invasive Assessment of Portal Hemodynamics

Although the current technique of measuring HVPG is safe and only minimally invasive, it is still not widely available outside major institutions. Efforts have been made to correlate HVPG to non-invasive methods of portal hemodynamic evaluation. Duplex-Doppler Ultrasonography (DDUS) is safe, economical and widely available. Unfortunately, studies have shown that there can be a significant inter- and intra-observer variability in measurements of DDUS parameters,[49,50] making this study a non-reliable means for quantitative evaluation of portal hypertension. CT scan, while useful in providing qualitative information, is severely limited as a quantitive study. MRI, like CT studies, provides useful qualitative data. Yet, unlike CT, MRI can also be useful in quantitative measurement of vascular flow. In one study, azygos flow was found to be elevated in cirrhotic patients who had esophageal varices, but not for those in whom varices were absent,[51] suggesting usefulness of MR angiography in detecting clinically significant portal hypertension. Nevertheless, direct correlation to HVPG measurement needs to be investigated further.

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