

# Hepatic Venous Pressure Gradient Does Not Correlate with the Presence and the Severity of Portal Hypertensive Gastropathy in Patients with Liver Cirrhosis

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## Abstract

**Background and aims.** To evaluate whether the hepatic venous pressure gradient (HVPG) differs between cirrhotic patients with severe portal hypertensive gastropathy (PHG) and those with mild or absent PHG. **Methods.** 59 cirrhotic patients with portal hypertension underwent hepatic vein catheterisation. 44 patients (76%) had PHG (16 mild and 28 severe). **Setting:** tertiary care setting (Liver Unit, Internal Medicine). **Results.** HVPG values did not differ between the patients without PHG ( $21.6 \pm 10.1$  mmHg) and those with PHG ( $18.6 \pm 9.1$  mmHg), nor between those with mild ( $19.3 \pm 4.3$  mmHg) or severe PHG ( $17.7 \pm 4.6$  mmHg;  $p = 0.26$ ). The overall prevalence of PHG and the proportion of patients with severe PHG did not differ regarding the Child Pugh classification. The etiology of the cirrhosis did not influence the HVPG. No correlations were found between HVPG values and Child Pugh score, age, platelet count, prothrombin time, bilirubin levels and ALT values. The HVPG did not differ between patients with small, medium or large esophageal varices, nor between subjects with or without gastric varices. **Conclusions.** Our data show that PHG does not correlate with the degree of portal pressure, and that the prevalence and the severity of this condition are not influenced by the severity of underlying liver disease or by the size of varices.

## Key words

Cirrhosis – gastropathy – HVPG - portal pressure – oesophageal varices

## Introduction

Portal hypertensive gastropathy (PHG) is a rather common finding in patients with liver cirrhosis and portal

hypertension, which in recent years has been recognized as a cause of acute or insidious gastrointestinal bleeding in these subjects (1). Several controversies exist concerning the incidence of PHG, its relevance as a cause of upper gastrointestinal bleeding, the evolution of the disease after endoscopic sclerotherapy of esophageal varices and the mortality rates of patients bleeding from PHG.

The pathophysiology of this condition is not clearly understood. The correlation between PHG and the severity of liver disease seems to be fairly weak (1). Conflicting results exist regarding the alterations of gastric mucosal hemodynamics and permeability (2-4). It has been suggested that PHG is a dynamic condition, which may not only worsen from mild to severe, but also improve and even disappear completely (1). This finding suggests that although portal hypertension remains the crucial trigger for the development of PHG, other factors should be considered in the progression of this condition.

Despite these uncertainties, the relationship between portal hypertension and PHG has not been widely investigated. Given the scarcity of data and the consistent discrepancies between different studies, we decided to measure the hepatic venous pressure gradient (HVPG) in a group of patients with liver cirrhosis and portal hypertension. Our aim was to evaluate whether the HVPG differs between cirrhotic patients with severe PHG and those with mild or absent PHG, and to correlate the results with clinical parameters.

## Patients and methods

### Patients

Fifty-nine consecutive cirrhotic patients with portal hypertension (47 males, mean age  $61.2 \pm 9.2$  years) referred to our Liver Unit between June and December 2006 were prospectively included in this study. Cirrhosis and portal hypertension were diagnosed and scored by clinical, biochemical, endoscopic, histologic or sonographic criteria (5,6).

Patients with: portal vein thrombosis, treatment with beta blockers or nitrates, previous endoscopic treatment of

varices (sclerotherapy or endoscopic band ligation), multifocal hepatocellular carcinoma (HCC), severe clotting defects, hepatic encephalopathy grade III and IV, non-cirrhotic portal hypertension, previous surgical portosystemic shunts or TIPS were excluded from the study. None of the patients had had previous bleeding. The severity of cirrhosis was classified according to the Child Pugh criteria (5). The degree of PHG was assessed according to the Third Baveno International Consensus Workshop (6), and classified as mild when mosaic-like pattern (MLP) without redness of the areola was present, and severe when the MLP was superimposed by red signs or if any other red sign was present.

Esophageal varices (EV) were classified according to the North Italian Endoscopic Club (7). Gastric varices (GV) were assessed according to Sarin et al (8). All endoscopic studies were performed by the same investigator (C.P.). The study protocol conformed to the Helsinki Declaration. Informed written consent was obtained from all participants.

### Hemodynamic procedures

Hemodynamic studies were performed after endoscopic procedures, and within one week from endoscopic investigations. After an overnight fast, the patients were transferred to the Hepatic Hemodynamic Laboratory of our Department. With the patients under local anaesthesia, a venous introducer was placed in the right internal jugular vein by the Seldinger technique, and a balloon catheter (MediTech, Cooper Scientific Corp., MA, USA) was advanced under fluoroscopic control into the main right hepatic vein, where it was kept for the whole study allowing the determination of the wedged hepatic venous pressure (WHVP) and of the free hepatic venous pressure (FHVP). Hepatic venous pressure was measured in the occluded position, filling the balloon with air, and then in the free position, after balloon deflation and after checking that the catheter tip was floating in the middle of the hepatic vein. Adequacy of occlusion was always checked by distal injection of a small amount of radiographic contrast medium. The hepatic venous pressure gradient (HVPG) was calculated by subtracting the FHVP from the WHVP. These pressure measurements were performed by triplicate in each case. Results were given as arithmetic means of the three determinations. Permanent tracings were always maintained. Heart rate and ECG were continuously monitored during the whole procedure. Transjugular liver biopsy was performed in each patient at the end of the hemodynamic procedures. All procedures were performed according to previously reported methodology (9). At the time of the hemodynamic study, hemodynamists were not aware of the endoscopic status of the patients.

### Statistical analysis

Statistical significance was assessed by  $\chi^2$  test with Yates' and Bonferroni's correction and 95% confidence intervals (CIs), analysis of variance (ANOVA), multivariate analysis of variance (MANOVA) and two-sample  $t$  test for independent data. Relationships between the variables were

examined using simple linear regression and correlation models. A  $p$  value of less than 0.05 was considered significant. Data were expressed as means  $\pm$  S.D.

## Results

### Clinical features

The main clinical and biochemical characteristics of the 59 patients are reported in Table I. Thirty-six patients belonged to Child Pugh class A, 19 to class B and 4 to class C. The etiology of cirrhosis was virus-related in 34 cases and alcoholic in 25. None of the patients had active alcohol intake at the time of the study. The mean age did not differ with regards to the etiology or Child Pugh class ( $p = 0.97$  and  $p = 0.63$ , respectively).

**Table I** Main clinical and biochemical features in the 59 patients

|                              |                              |
|------------------------------|------------------------------|
| Age (range)                  | 61.2 $\pm$ 9.2 years (28-74) |
| Males (%)                    | 47 (80%)                     |
| Etiology                     |                              |
| Virus                        | 34                           |
| Alcohol                      | 25                           |
| Child Pugh Class (A/B/C)     | 36/19/4                      |
| Child Pugh score             | 7.4 $\pm$ 1.6                |
| Platelet count $\times 10^3$ | 85 $\pm$ 46                  |
| Bilirubin (mg/dL)            | 2.4 $\pm$ 1.9                |
| ALT (IU/L)                   | 53 $\pm$ 40                  |
| Albumin (g/L)                | 3.0 $\pm$ 0.5                |
| GGT (IU/L)                   | 94 $\pm$ 78                  |
| Prothrombin activity (%)     | 66 $\pm$ 14                  |
| PHG (absent/mild/severe)     | 15/16/28                     |
| EV (small/medium/large)      | 10/25/18                     |
| GV                           | 16                           |

PHG=portal hypertensive gastropathy; EV=esophageal varices; GV=gastric veins

### Correlation between PHG and clinical and endoscopic features

Features of PHG (Table I) were found in 44 out of the 59 patients (75%), EV in 53/59 (90%) and GV in 16/59 (27%). None of the patients showed endoscopic features of gastric vascular ectasia (GVE). The proportion of subjects with EV and GV did not differ between the three classes of Child Pugh ( $\chi^2 = 9.3$ ,  $p = 0.15$ , and  $\chi^2 = 1.70$ ,  $p = 0.42$ , respectively). According to the presence and the severity of PHG, patients were categorized into three groups: no endoscopic features of PHG, mild PHG, severe PHG. As shown in Table II, clinical and biochemical features did not differ between the three groups of patients. The overall prevalence of PHG and the proportion of patients with severe PHG did not differ with regard to the Child Pugh classification. PHG was present in 72% of patients from Child Pugh class A, 79% of patients from class B, and 75% of those from class C (NS), and severe forms were present in 47%, 42% and 75%, respectively (NS). The prevalence of PHG did not differ between patients with EV and those without varices, and among patients with EV it did not differ between subjects with large varices and those with medium or small varices (Table III), nor between subjects with or without GV ( $\chi^2 = 0.72$ ,  $p = 0.69$ ).

**Table II** Clinical and biochemical features of patients with and without PHG

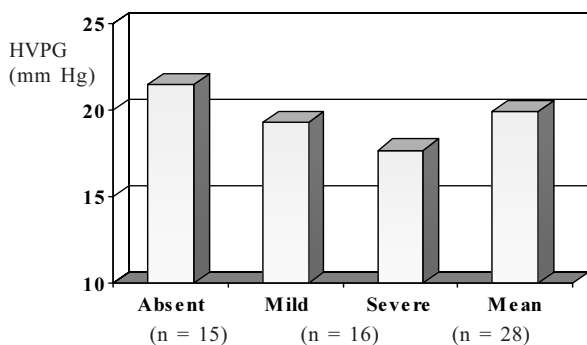
|                                  | Absent   | Mild     | Severe   | p    |
|----------------------------------|----------|----------|----------|------|
| N.                               | 15       | 16       | 28       |      |
| Age (years)                      | 64.9±9.4 | 62.1±7.3 | 59.5±9.5 | 0.24 |
| Males (%)                        | 13 (87)  | 13 (81)  | 21 (75)  | 0.94 |
| Etiology                         |          |          |          |      |
| Virus                            | 9        | 11       | 14       | 0.66 |
| Alcohol                          | 6        | 5        | 14       | 0.37 |
| Child Pugh Class (A/B/C)         | 10/4/1   | 9/7/0    | 17/8/3   | 0.19 |
| Child Pugh score                 | 7.5±1.6  | 7.4±0.7  | 7.3±1.9  | 0.96 |
| Platelet count x 10 <sup>3</sup> | 72±22    | 81± 31   | 91±54    | 0.56 |
| Bilirubin (mg/dL)                | 1.7±0.8  | 1.7±0.4  | 2.9±2.3  | 0.15 |
| ALT (IU/L)                       | 60±65    | 44±27    | 53±34    | 0.72 |
| Albumin (g/L)                    | 2.9±0.3  | 3.1±0.6  | 2.9±0.5  | 0.73 |
| GGT (IU/L)                       | 99±39    | 89±122   | 95±72    | 0.97 |
| Prothrombin activity (%)         | 64±12    | 69±5     | 66±16    | 0.74 |
| EV (small/medium/large)          | 4/6/ 2   | 4/6/5    | 2/13/11  | 0.37 |
| GV                               | 7        | 4        | 5        | 0.70 |

**Table III** Prevalence of PHG among patients with and without esophageal varices

|            | Esophageal varices |    |    |    | p  |
|------------|--------------------|----|----|----|----|
|            | Absent             | F1 | F2 | F3 |    |
| <b>PHG</b> |                    |    |    |    |    |
| Absent     | 3                  | 4  | 6  | 2  | NS |
| Mild       | 1                  | 4  | 6  | 5  | NS |
| Severe     | 2                  | 2  | 13 | 11 | NS |

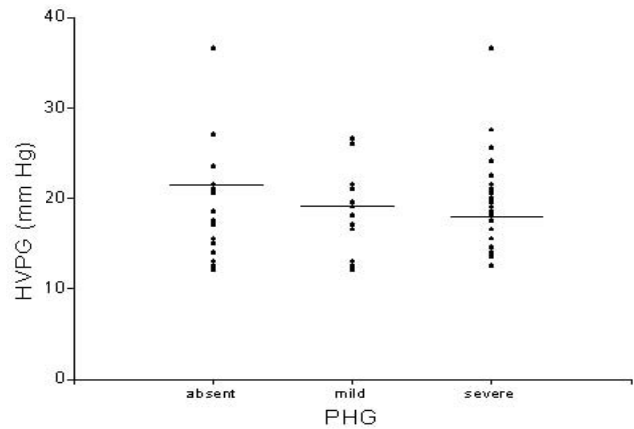
**Hepatic hemodynamics**

The results are shown in Fig.1. The mean HVPG was 19.9 ± 6.1 mmHg (range 11.5–36.5 mmHg). HVPG values did not differ between the 15 patients without PHG (21.6 ± 10.1 mmHg) and those showing the endoscopic presence of PHG (18.6 ± 9.1 mmHg). No HVPG differences were found between the 16 subjects with mild PHG (19.3 ± 4.3 mmHg) and the 28 cases with severe PHG (17.7 ± 4.6 mmHg; p=0.26). Individual HVPG values are shown in Fig.2. A wide overlap between the three groups was seen.

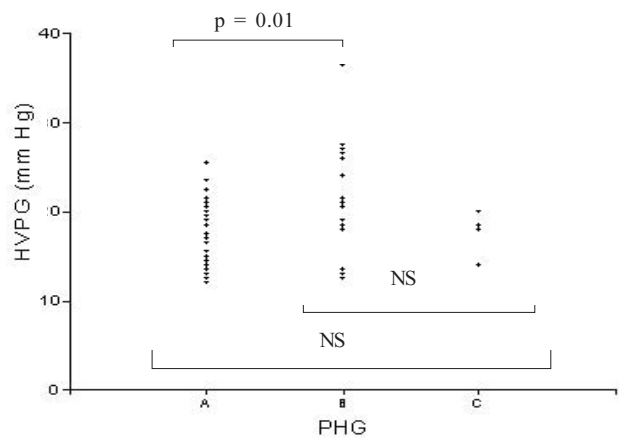


**Fig.1** HVPG levels according to the presence and the degree of PHG.

The etiology of the cirrhosis did not influence the HVPG. No correlations were found between HVPG values and Child Pugh class (Fig.3), age, platelet count, prothrombin time, bilirubin levels and ALT values. The HVPG did not differ between patients with small (21.1 ± 9.4 mm Hg), medium



**Fig.2** Individual HVPG values in the three groups of patients.



**Fig.3** HVPG values according to Child Pugh class.

(17.3 ± 3.3 mm Hg) or large EV (20.3 ± 5.9 mm Hg; p=0.49), nor between subjects with or without GV (19.2 ± 5.7 vs 18.1 ± 7.7 mm Hg, p=0.24).

**Discussion**

PHG has been recently recognized as an important complication of cirrhosis with portal hypertension, which might give rise to acute upper hemorrhage or chronic bleeding

in these patients (1, 6). Attempts to assess the relevance of PHG as a cause of bleeding and to define the prognosis of patients bleeding from PHG have given conflicting results. Further, the pathophysiology of this condition is far from being clarified. Despite the relevance of this issue, only a few studies have addressed the relationship between the degree of portal hypertension and the presence and the severity of PHG, although such information may have important clinical and therapeutic implications. For example, while the existence of an HVPG threshold level for the development and growth of EV has been clearly shown (6), at present it is not yet known whether a similar HVPG minimal threshold also exists for the development of severe PHG, and whether the risk of bleeding from PHG correlates with the levels of HVPG.

Existing data are scarce and conflicting, as very few studies have directly evaluated the degree of portal hypertension. Iwao et al (10) found that patients with severe gastropathy had higher HVPG than those with mild forms or without PHG. In contrast, in the study of Quintero et al (11) no differences in HVPG levels were seen between cirrhotics with and without GVE. Sarin et al (12) reported that development of PHG was not directly correlated with intravariceal pressure, and in the study of Ohta et al (13) portal venous pressure did not differ between patients with and without PHG. Primignani et al (1) suggested that a correlation exists between PHG and the severity of portal hypertension, as the prevalence of gastropathy was higher in patients with large EV than in those with small varices. However, in this study no data about portal pressure values were given.

The main goal of our study was to determine whether the HVPG, expression of portal pressure in sinusoidal and post-sinusoidal outflow block as in cirrhosis, correlates with the presence and the severity of PHG.

The overall prevalence of PHG in our series of patients (76%) is similar to that reported (80%) by Primignani et al (1). It was mild in 20% and severe in 57% of patients. Prevalence of PHG did not differ between the three Child classes nor was the Child Pugh score different between patients with absent, mild or severe PHG. It has been previously shown that the overall prevalence of PHG was higher in patients in Child Pugh class B than in patients in class A and C, and that the prevalence of severe gastropathy was lowest in patients in class C (1, 6). In contrast, others found that the prevalence and the severity of PHG did correlate with the severity of cirrhosis (12, 14). In accordance with other reports (13), the presence of PHG seemed to be independent of age, sex, cause of cirrhosis in our study. It should be stressed that in our study the distinction between mild and severe PHG and between severe PHG and GVE was done on a subjective basis because no histological examination was performed.

Furthermore, our study seems to indicate that no relationship exists between PHG and the degree of portal hypertension. The prevalence of PHG in our study was not different between patients with EV and those without varices,

and among patients with EV it did not differ between subjects with large varices and patients with medium or small varices. Moreover, we did not find differences in the prevalence of gastropathy between patients with and without GV. This is in contrast with previous reports showing higher prevalence of PHG in patients with GV than in subjects without (1), and in patients with gastroesophageal varices than in those with EV alone (12, 15).

More important, we had the possibility to directly evaluate the degree of portal hypertension through HVPG assessment. In our series of patients, HVPG levels were not different in the three groups of patients. These findings suggest that although portal hypertension remains the crucial trigger for the development of PHG, other factors should be considered in the progression of this condition, such as increased gastric mucosal perfusion (11,16) and increased gastric sucrose permeability (3). However, Kamath et al showed that PHG, but not GVE, often improves after portal decompression by TIPS, thus suggesting that the dominant pathogenetic mechanism in PHG is probably high portal pressure (17).

The etiology of cirrhosis did not influence the HVPG (18) or the prevalence of PHG. HVPG values did not parallel the severity of liver disease (19, 20). Moreover, when the patients were stratified by Child Pugh classes and PHG, no differences in HVPG values were seen, thus confirming that the relationship between portal pressure, PHG and severity of cirrhosis is probably weak (1). Controversially, others found that the degree of liver dysfunction is correlated with the severity of PHG in patients with cirrhosis (10, 21).

Interestingly, when the relationship between the HVPG and both the severity of PHG and the size of EV was examined, no significant differences were found. Similarly, no differences in HVPG values were seen according to presence of both PHG and GV. It means that the severity of endoscopic features and the degree of portal hypertension do not strictly correlate (22).

In conclusion, this is one of the few studies evaluating the relationship between portal hypertension and PHG through assessment of HVPG. Our data show that the presence and the severity of PHG does not correlate with the degree of HVPG, and that the prevalence and the severity of this condition are not influenced by the severity of underlying liver disease or by the presence and the size of varices. Further prospective studies are required to better understand the pathogenesis of the gastric lesions in patients with portal hypertension, and to evaluate whether HVPG might be considered a predictor of the risk of bleeding from PHG (23-26).

### Conflicts of interest

None to declare.

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