Hepatic venous pressure gradient measurement in patients with liver cirrhosis: a correlation with disease severity and variceal bleeding

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Key words: *hepatic venous pressure gradient; portal hypertension; variceal bleeding; Child-Turcotte-Pugh score.*

Summary. *The aim of present study was to evaluate relationships between degree of portal hypertension, severity of the disease, and bleeding status in patients with liver cirrhosis.*

Patients and methods. All study patients with liver cirrhosis underwent hepatic venous pressure gradient measurements, endoscopy, clinical and biochemical evaluation. Liver function was evaluated according to Child-Turcotte-Pugh (Child's) scoring system. Patients with decompensated cirrhosis (presence of severe ascites, acute variceal bleeding occurring within 14 days, hepatorenal syndrome, cardiopulmonary disorders, transaminase levels >10 times higher the upper normal limit), active alcohol intake, use of antiviral therapy and/or beta-blockers were excluded from the study.

Results. One hundred twenty-eight patients with liver cirrhosis (male/female, 67/61; mean age, 53.8±12.7 years) were included into the study. Etiology of cirrhosis was viral hepatitis, alcoholic liver disease, cryptogenic and miscellaneous reasons in 57, 49, 14, and 8 patients, respectively. Child's stages A, B, and C of liver cirrhosis were established in 28 (21.9%), 70 (54.9%), and 30 (23.4%) patients, respectively. The mean hepatic venous pressure gradient significantly differed among patients with different Child's classes: 13.8±5.3 mm Hg, 17.3±4.6 mm Hg, and 17.7±5.05 mm Hg in Child's A, B, and C classes, respectively (P=0.003). The mean hepatic venous pressure gradient in patients with grade I, II, and III varices was 14.8±4.5, 16.1±4.3, and 19.3±4.7 mm Hg, respectively (P=0.0001). Since nonbleeders had both small and large esophageal varices, patients with large varices were analyzed separately. The mean hepatic venous pressure gradient in patients with large (grade II and III) varices was significantly higher than that in patients with small (grade I) varices (17.8±4.8 mm Hg vs 14.6±4.8 mm Hg, P=0.007). Thirty-four (26.6%) patients had a history of previous variceal bleeding; all of them had large (20.6% – grade II, and 79.4% – grade III) varices. In patients with large varices, the mean hepatic venous pressure gradient was significantly higher in bleeders than in nonbleeders (18.7±4.7 mm Hg vs 15.9±4.7 mm Hg, P=0.006).

Conclusions. Hepatic venous pressure gradient correlates with severity of liver disease, size of varices, and bleeding status. Among cirrhotics with large esophageal varices, bleeders have a significantly higher hepatic venous pressure gradient than nonbleeders. Hepatic venous pressure gradient measurement is useful in clinical practice selecting cirrhotic patients at the highest risk of variceal bleeding and guiding to specific therapy.

Introduction

Portal hypertension is one of the main consequences of cirrhosis. It results from a combination of increased intrahepatic vascular resistance and increased blood flow through the portal venous system. Increased cardiac output and decreased systemic vascular resistance (1) result a hyperdynamic circulatory state with splanchnic and systemic arterial vasodilation. Splanchnic arterial vasodilation leads to increased portal blood flow, which in turn leads to more severe portal hypertension. Splanchnic arterial vasodilation results from an excessive release of endogenous vasodilators such as nitric oxide, glucagon, and active vasointestinal peptide.

The direct measurement of portal pressure is an invasive procedure associated with significant morbi-

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dity. Measurement of the hepatic venous pressure gradient (HVPG; the difference between wedged and free hepatic venous pressure) is a simple, safe procedure, and it accurately reflects the portal pressure in patients with liver cirrhosis (2–4). It is now well established that portal pressure must increase above a threshold value of 12 mm Hg for variceal bleeding to occur (5, 6). In addition, there is conclusive evidence that a fall in HVPG to values below 12 mm Hg, or by more than 20%, significantly reduces the risk of first variceal bleeding as well as rebleeding (7–10).

The impairment of liver function as determined by the Child-Turcotte-Pugh (Child's) score is an important predictive factor for variceal hemorrhage (11). An improvement in Child's score is associated with a decrease in HVPG (8, 9). However, the relationship between Child's status and HVPG is not well investigated. It has been observed that the risk of first bleeding in patients with small varices and Child's class C disease is higher than that of patients with large varices and Child's class A disease (11). These studies, however, were not supported by the HVPG measurements.

In fact, there is a paucity of large studies evaluating portal pressure parameters and their correlation with clinical and endoscopic signs of portal hypertension. We carried out this study in order to evaluate the relationship of baseline HVPG to Child's status, size of esophageal varices, and presence of episodes of variceal bleeding in cirrhotic patients.

Patients and methods

The patients admitted to the Department of Gastroenterology, Hospital of Kaunas University of Medicine, between 2006 and 2008 were included into the study. Diagnosis of liver cirrhosis was confirmed by biopsy. The exclusion criteria were as follows: presence or a history of hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma (diagnosed with an α-fetoprotein level of >400 ng/mL with a lesion in the liver detected using an imaging technique or by histology); underlying severe cardiac, respiratory, or psychiatric illness, or a Child's score of >12. Patients with noncirrhotic portal hypertension and patients receiving β-blockers, nitrates, or any other pharmacotherapy for prevention of variceal bleeding were also excluded from the study.

HVPG measurement

HVPG was measured by introducing a 5-Fr transfemoral sheath into a major hepatic vein through the right femoral vein. The catheter was advanced until it was wedged into the hepatic vein. The criteria of Groszmann and Bosch (12, 13) were used to confirm adequate wedging. The occluded position of the catheter was checked by the absence of reflux after the injection of 2 mL of contrast medium and appearance of a sinusoidogram. A mean of three readings was taken for further analysis. If there was a difference of more than 1 mm Hg between the readings, all the recordings were discarded and fresh readings were taken. An attempt was made to cannulate the right hepatic vein for all pressure measurements.

Definitions

Esophageal varices were classified at endoscopy according to commonly employed system of classification: F1, small straight varices; F2, enlarged tortuous varices that occupy less than one-third of the lumen; and F3, large coil-shaped varices that occupy more than one-third of the lumen (11). A history of variceal bleeding was established from previous medical records and defined according to BAVENO IV criteria (6) as active bleeding, "white nipple," or a clot seen at endoscopy, or blood in the stomach in a patient with esophageal varices and no other potential bleeding source.

Statistical analysis

Quantitative data were expressed as mean±SD and were compared using Mann-Whitney test. Qualitative data were analyzed by the chi-square test or Fisher's exact test. Statistical analysis was done using SPSS 12 software package. Statistical significance was set at $P \leq 0.05$.

Results

Demographic profile of the patients studied is presented in Table. One hundred twenty-eight patients with liver cirrhosis were included into the study. One hundred (78.1%) of them had advanced Child's class B or C liver disease. In the majority of the patients, cirrhosis of the liver was caused by chronic hepatitis B or C infection (44.5%) and alcohol (38.3%). Ninety-four (73.4%) patients were nonbleeders, while the remaining had bleeding from the varices in the past. Ascites was present in 70 (54.7%) patients.

Hepatic venous pressure gradient and Child's status

Baseline HVPG was evaluated in all study patients and was correlated with Child's status of the patients. The mean HVPG in patients with Child's class A cirrhosis was 13.8±5.3 mm Hg, whereas in patients

Table. **Demographic profile of the study population**

Total number of patients	128
M:F	67:61
Mean age (yr)	53.8±12.7
Etiology	
Viral	57 (44.5%)
Alcohol	49 (38.3%)
Cryptogenic	14 (10.9%)
Miscellaneous	8 (6.3%)
Child's classes	
A	28 (21.87%)
B	70 (54.69%)
C	30 (23.44%)
Nonbleeders	94 (73.44%)
Bleeders	34 (26.56%)

with Child's class B and C disease, it was 17.3±4.6 and 17.7±5.0 mm Hg, respectively (P=0.003; Fig. 1). HVPG was higher in both Child's B and C patients compared with Child's A cirrhotics (P<0.01). The difference comparing cirrhotic patients with Child's classes B and C disease was not statistically significant (P>0.05).

HVPG and variceal size

Out of the 128 patients, 89 (69.5%) had large esophageal varices. The variceal size showed a good correlation with the HVPG levels (Fig 2): the mean HVPG in patients with grade I, II, and III varices were 14.8±4.5, 16.1±4.3, and 19.3±4.7 mm Hg, respectively (P=0.0001). The mean HVPG in patients with large (grade II and III) varices was significantly higher than that in patients with small (grade I) varices (17.8±4.8 mm Hg vs 14.6±4.8 mm Hg, P=0.007).

HVPG and variceal bleeding status

Thirty-four (26.6%) patients had a history of previous variceal bleeding; all of them had large (20.6% – grade II and 79.4% – grade III) varices. Since nonbleeders had both small and large esophageal varices, patients with large varices were analyzed separately. There were 34 (38.2%) variceal bleeders and 55 (61.8%) nonbleeders in the group of patients with large varices. The mean HVPG in bleeders vs nonbleeders with large varices was 18.7±5.5 mm Hg and 15.9±4.7 mm Hg, respectively (P=0.006).

Discussion

The prognostic value of HVPG has been clearly demonstrated in different clinical situations of chronic liver disease (14, 15). The influence of baseline HVPG values on other important determinants of portal

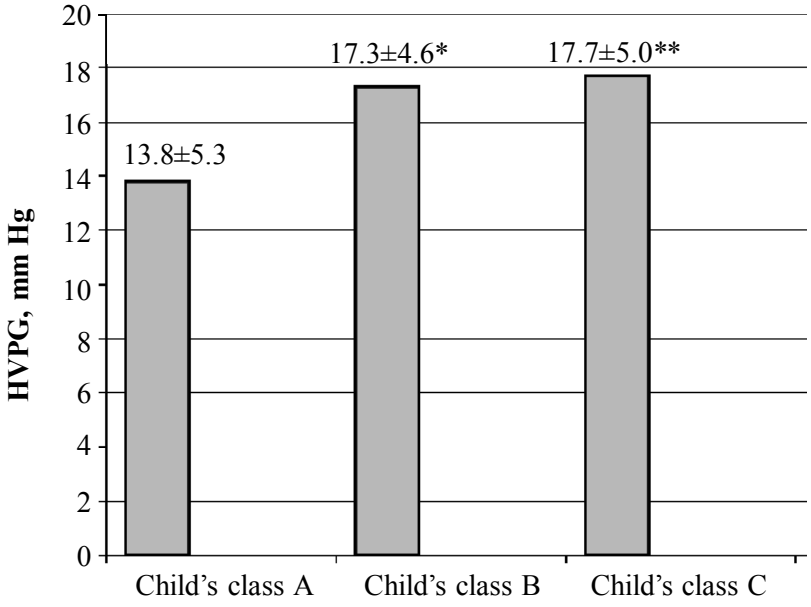

Fig. 1. **Hepatic venous pressure gradient (HVPG) levels according to Child's classes in patients with liver cirrhosis (P=0.003)**

*P=0.002, comparing patients with Child's class A and B disease;
**P=0.003, comparing patients with Child's class A and C disease.

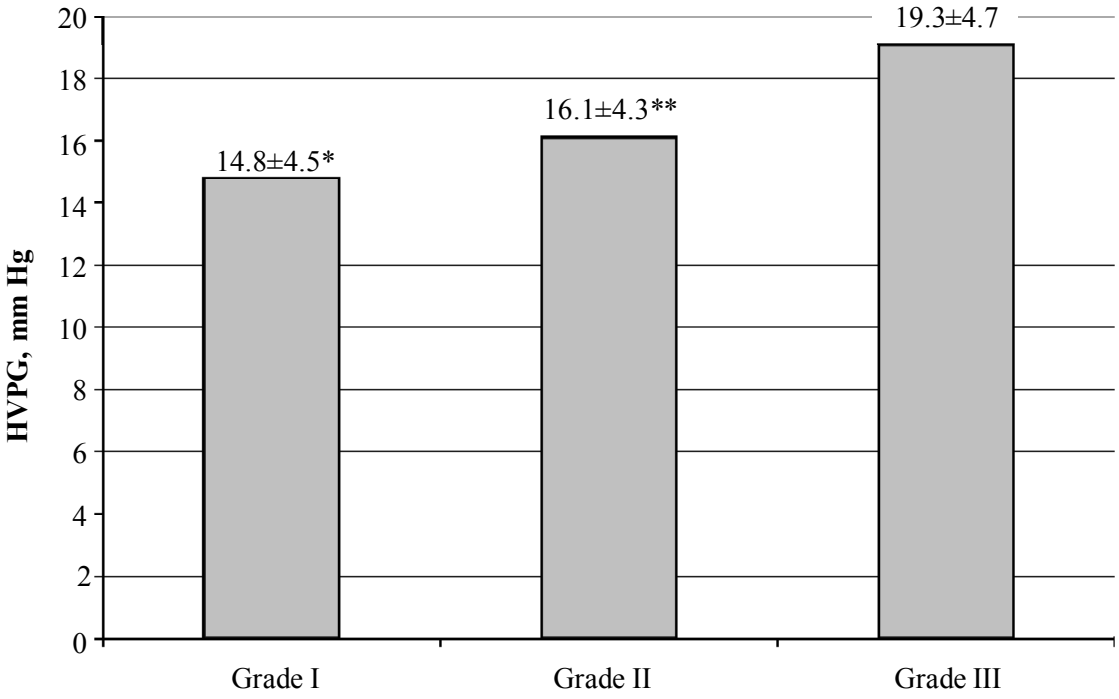

Fig 2. **Hepatic venous pressure gradient (HVPG) levels according to variceal size in cirrhotic patients (*P*=0.0001)**

**P*=0.001, comparing patients with grade I and grade III varices;
***P*=0.002, comparing patients with grade II and grade III varices.

hypertension and chronic liver disease has still not been well studied, especially in a large cohort of cirrhotics with varying etiology.

The results of this study clearly emphasize the clinical relevance of measuring HVPG in patients with cirrhosis of the liver. The HVPG was significantly higher in patients with Child's class B and C diseases compared with Child's A patients. This observation has clinical relevance and indicates that the rise in HVPG correlates with the severity of liver disease. Child's C cirrhotics also had a higher HVPG compared to Child's B but the difference did not reach statistical significance. It needs to be determined whether these elevated pressures influence the outcome of the disease predominantly due to elevated pressure.

Gastroesophageal varices are present in approximately 50% of cirrhotic patients, whereas the lifetime prevalence of varices is 80–90% (16, 17). Variceal hemorrhage occurs in 25–40% of patients with cirrhosis (18). However, there are not many data on the relation between variceal size and baseline HVPG. In the present study, the HVPG was compared between patients with small and those with large varices. The mean HVPG was significantly higher in patients with large varices compared to patients small varices. This is an important observation for clinical applications.

It is known that cirrhotics with an HVPG below 12 mm Hg rarely bleed (5, 6). In addition, there is conclusive evidence that a reduction of HVPG below 12 mm Hg protects the patient from the risk of variceal bleeding (7–10, 19). However, there is controversy whether the mean HVPG is different between bleeders and nonbleeders. While all bleeders had large varices, nonbleeders had both small and large varices, and this may be considered as a confounding variable in the analysis. To eliminate this, we compared the HVPG levels in patients only with large varices with or without variceal bleeding. The HVPG was still significantly higher in bleeders compared with nonbleeders. These observations support the basic concept of a reduction in portal pressure to prevent growth of varices, first and recurrent variceal bleeding in patients with cirrhotic portal hypertension (16). Recurrent variceal bleeding is very frequent after the first variceal hemorrhage, and pharmacological therapy is the first-choice treatment. Recently, baseline and repeat measurements of HVPG have been considered necessary to optimally manage patients receiving pharmacological therapy so as to reduce the frequency of rebleeding.

Thus, clinical relevance and correlations of HVPG in several important aspects of chronic liver diseases still remain to be fully studied. The degree of HVPG

reduction after pharmacological treatment predicts the probability of rebleeding, ascites, peritonitis, hepatorenal syndrome, encephalopathy, and death (2, 20). Finally, there is evidence that HVPG has prognostic value in complications of cirrhosis and survival of patients with alcoholic liver cirrhosis (3, 4). However, the clinical validity and applicability of monitoring for target HVPG reductions is not sufficiently proven and needs to be specifically evaluated in prospective trials.

Conclusions

The severity of portal hypertension correlates with severity of liver disease, size of varices, and bleeding status. Among cirrhotics with large esophageal varices, bleeders have significantly higher hepatic venous pressure gradient than nonbleeders. Hepatic venous pressure gradient measurements are useful in clinical practice selecting cirrhotic patients at the highest risk of variceal bleeding and guiding to specific therapy.

Kepenų venų spaudimo gradiento matavimas kepenų ciroze sergantiems pacientams: ryšys su kepenų ligos sunkumo laipsniu ir varikoziniu kraujavimu

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Raktažodžiai: kepenų venų spaudimo gradientas; vartų venos hipertenzija; varikozinis kraujavimas; Child-Turcotte-Pugh sistema.

Santrauka. *Tyrimo tikslas.* Įvertinti ryšį tarp vartų venos hipertenzijos, kepenų ligos sunkumo laipsnio ir varikozinio kraujavimo sergantiesiems kepenų ciroze.

Metodai. Pacientams išmatuotas kepenų venų spaudimo gradientas (HVSG), atliktas endoskopinis, klinikinis bei biocheminiai tyrimai. Kepenų ligos sunkumo laipsnis vertintas pagal „Child-Turcote-Pugh“ (Child) vertinimo sistemą. Į tyrimą neįtraukti dekompensuota kepenų ciroze sergantys pacientai (didelis ascito kiekis, varikozinis kraujavimas per paskutines 14 dienų, hepatorenalinis sindromas, gretutinės širdies, kvėpavimo ligos, daugiau kaip 10 padidėjusios transaminazės), nesaikingai vartojantys alkoholinius gėrimus, gydomi priešvirusiniais vaistais ir (ar) beta blokatoriais.

Rezultatai. 128 kepenų ciroze sergantys pacientai (67 vyrai ir 61 moteris; amžiaus vidurkis – 53,8±12,7 metų) įtraukti į tyrimą. Kepenų cirozės priežastys: virusinis hepatitas, alkoholinė kepenų liga, kriptogeninė ir kitos priežastys atitinkamai – 57/49/14/8 pacientams. Child A, B ir C klasių kepenų cirozė diagnozuota atitinkamai 28 (21,9 proc.)/70 (54,9 proc.)/30 (23,4 proc.) pacientams. Vidutinis HVSG reikšmingai skyrėsi tarp skirtingų Child klasių pacientų: 13,8±5,3 mmHg; 17,3±4,6 mmHg; 17,7±5,05 mmHg, atitinkamai Child A, B ir C klasėse (p=0.003). Vidutinis HVSG pacientams, kuriems diagnozuota I/II/III laipsnio stemplės varikozė buvo atitinkamai – 14,8±4,5/16,1±4,3/19,3±4,7 mmHg (p=0,0001). Kadangi anksčiau nekraujavusiems pacientams rastos ir mažos, ir didelės stemplės varikozinės venos, pacientai, kuriems nustatyta didelio laipsnio stemplės varikozė, analizuoti atskirai. Vidutinis HVSG pacientams, kuriems nustatyta didelio (II ir III) laipsnio stemplės varikozė, buvo reikšmingai (p=0,007) didesnis nei pacientams, kuriems nustatyta maža (I laipsnio) varikozė (17,8±4,8 mmHg vs 14,6±4,8 mmHg). Buvęs varikozinis kraujavimas dokumentuotas 34 (26,6 proc.) pacientams; visiems rasta didelė (20,6% – II laipsnio ir 79,4 proc. – III laipsnio) stemplės varikozė. Tarp pacientų, kuriems nustatyta didelė stemplės varikozė, vidutinis HVSG buvo reikšmingai didesnis kraujavusiems (18,7±4,7 mmHg vs. 15,9±4,7 mmHg; p=0,006) nei nekraujavusiems pacientams.

Išvados. Kepenų venų spaudimo gradientas koreliuoja su kepenų ligos sunkumo laipsniu, stemplės varikozės dydžiu ir varikoziniu kraujavimu. Tarp kepenų ciroze sergančių pacientų, kuriems nustatyta didelė stemplės varikozė, kraujavusiųjų HVSG reikšmingai didesnis nei nekraujavusiųjų. HVSG matavimas naudingas klinikinėje praktikoje atrenkant kepenų ciroze sergančius pacientus, kuriems yra didžiausia varikozinio kraujavimo rizika, ir taikant jiems specifinį gydymą.

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