



## Research paper

# Invasive measurement of portal hypertension in the hemodynamics laboratory as an important element of qualification for the treatment of esophageal varices: A single-center experience

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## ABSTRACT

**Introduction:** The measurement of hepatic venous pressure gradient (HVPG) is an essential prognostic factor in subjects with chronic liver disorders.

**Aim:** The present study aimed to present the feasibility and applicability of HVPG in the modern hemodynamics laboratory in patients with liver cirrhosis as a stage for qualification in variceal band ligation (VBL).

**Material and methods:** We included 78 patients with liver cirrhosis and esophageal varices, who had HVPG measurements taken at the hemodynamics laboratory between January 2015 and January 2019.

**Results and discussion:** The mean age was  $55.5 \pm 10.9$  years, and 66.7% were males. The most common cause of liver cirrhosis was alcohol abuse (65.4%), and the most common varices stage was 3 (83.3%). The mean HVPG was  $16.3 \pm 6.2$  mm Hg. In total, 67 (85.9%) patients had HVPG over 10 mm Hg and underwent VBL. No perioperative complications were observed. At 12 months, recurrent hospitalizations were observed in 67 (85.9%), 5 (6.4%) had cirrhosis-related bleeding episodes, and 4 (5.1%) patients died.

**Conclusions:** HVPG measurement is a feasible, safe and reproducible procedure that provides valuable diagnostic/prognostic information and helps make therapeutic decisions. This procedure can be done quickly in the modern hemodynamics laboratory.

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## 1. INTRODUCTION

The measurement of hepatic venous pressure gradient (HVPG) is an essential prognostic factor in subjects with chronic liver disorders.<sup>1</sup> HVPG alterations characterize a predictive value in subjects at the beginning of the disease (HVPG 6–10 mm Hg) as well as in subjects in whom hemodynamically significant portal hypertension has developed (HVPG  $\geq$  10 mm Hg). In various scenarios, HVPG values are strictly linked to clinical outcomes.<sup>2</sup> The course of esophageal varices, the risk of ascites and encephalopathy as well as the risk of hepatocellular carcinoma development are associated with HVPG in subjects with liver cirrhosis.<sup>3–6</sup>

Additionally, subjects responding to pharmacotherapy of portal hypertension (e.g., decrease in values of HVPG more than 20% or up to 12 mm Hg) characterized a clear risk drop of portal hypertensive complications. They also exhibited a better prognosis.<sup>7</sup> Moreover, early HVPG assessment is a useful marker when used in the course of acute variceal bleeding.<sup>8</sup>

## 2. AIM

The present study aimed to present the feasibility and applicability of HVPG in the modern hemodynamics laboratory in patients with liver cirrhosis as a stage for qualification in variceal band ligation (VBL).

## 3. MATERIAL AND METHODS

### 3.1. Study population

We included subjects with liver cirrhosis and esophageal varices, who had HVPG measurements taken at the hemodynamics laboratory. We included only patients with medium to large varicose veins without prior variceal bleeding.

Esophageal varices were classified according to Organisation Mondiale d'Endoscopie Digestive (OMED).<sup>9</sup>

Between January 2015 and January 2019, 84 patients were referred for HVPG measurement. Unfortunately, in 6 patients, measurements were not successfully performed due to: very small diameter of the hepatic vein ( $n = 4$ ), critically stenosed hepatic vein at the ostium ( $n = 1$ ), and impossibility to identify hepatic vein ( $n = 1$ ). Therefore, in further analysis, 78 patients were analyzed.

### 3.2. Procedure

HVPG is a parameter obtained using the invasive method of measuring the venous hepatic pressure gradient, which elevated values confirm the indication for endoscopic banding of esophageal varices in patients with portal hypertension. By puncturing the right femoral vein, the Swan-Ganz catheter is inserted through the inferior vena cava (IVC), and the pressures are measured successively in the right atrium (RA), IVC, and free hepatic vein (FHV). The catheter is then wedged in the hepatic vein (WHV), indirectly measuring the portal circulation pressures. Based on the pressure difference in the portal and hepatic circulation, the HVPG value is calculated (Figures 1 and 2). Subjects with HVPG of more than 10 mm Hg were qualified for VBL.

### 3.3. Statistics

Continuous variables were shown as the mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR) based on the normality check with the Shapiro–Wilk test. Categorical data were shown as numbers and percentages. The Kaplan–Meier estimator was used to analyze the time to event data and prepare survival curves. The Pearson correlation method was applied to determine the relationship between continuous variables, and the Spearman correlation – in the remaining analyses.

The threshold of statistical significance was 0.05, and we performed two-sided tests. Formal sample size calculation

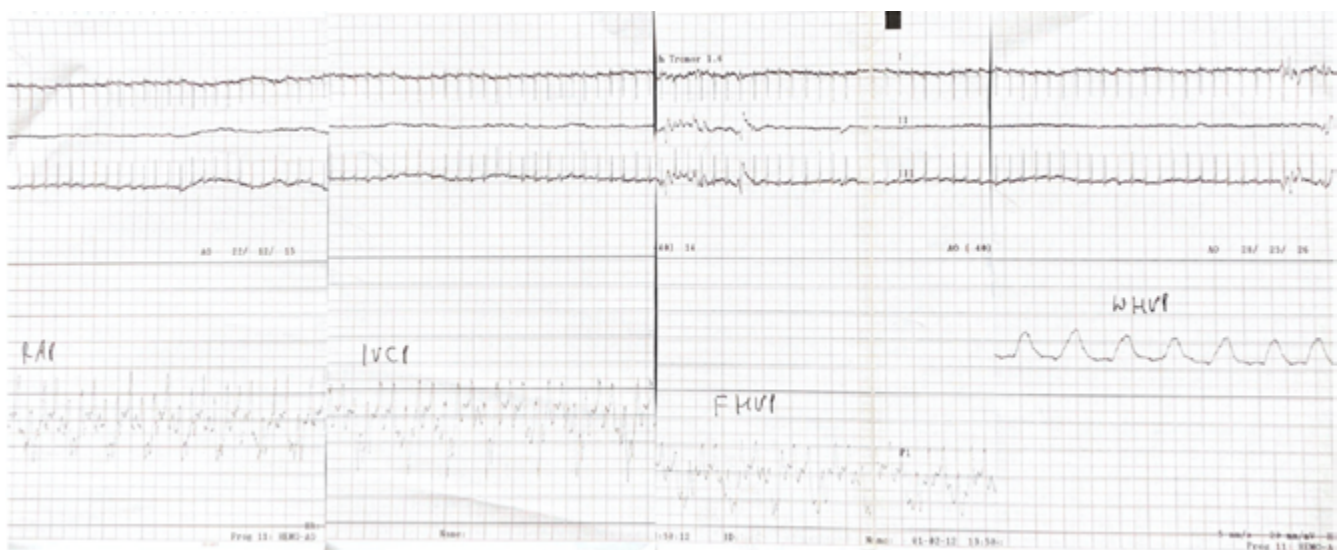
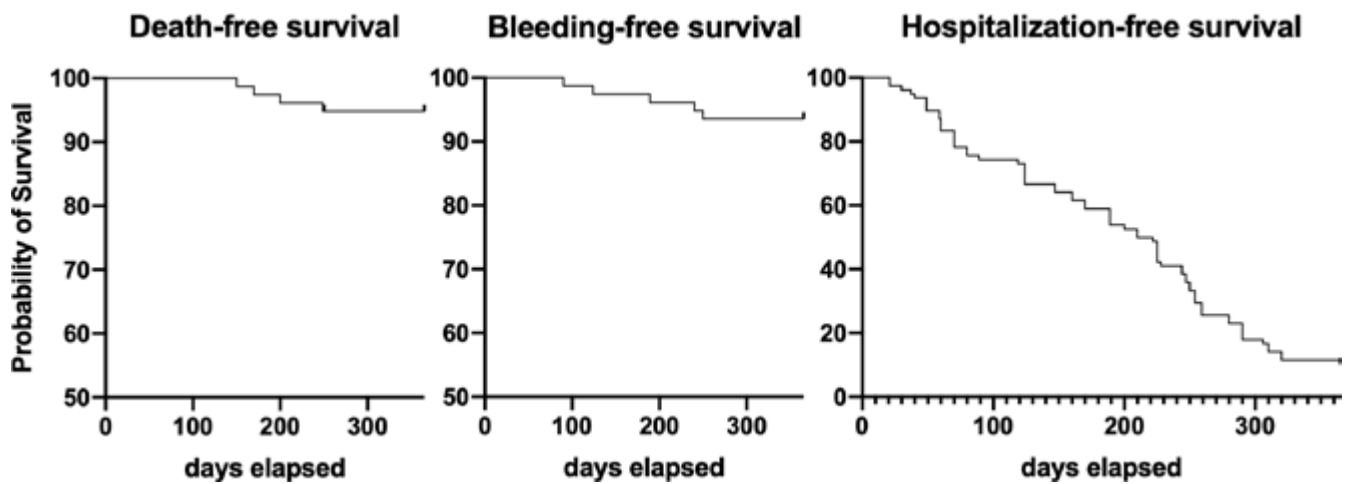


Figure 1. HVPG measurements: Example of a pressure curve recording and hepatic vein cannulation.



**Figure 2. HVPG measurements: Kaplan–Meier curves for bleeding, death, and recurrent hospitalization in the study population.**

was not performed, as the study had explorative character. The study population was restricted by the number of subjects referred for HVPG measurement, and the enrollment's period. We performed statistical analyses using R 3.0.2 for OS (R Foundation, Vienna, Austria).

## 4. RESULTS

### 4.1. Baseline characteristics

The mean age was  $55.5 \pm 10.9$  years, and 66.7% were males. The most common cause of liver cirrhosis was alcohol abuse (65.4%), and the most common varices stage was 3 (83.3%) (Table).

### 4.2. Measurements

The mean HVPG was  $16.3 \pm 6.2$  mm Hg (Table). In total, 67 (85.9%) patients had HVPG over 10 mm Hg and underwent VBL. No periprocedural complications were observed.

The HVPG value did not correlated with any liver test (ALT, AST, GGTP, INR). However, free hepatic vein pressure correlated significantly with AST ( $r = 0.33$ ,  $P = 0.003$ ), and wedged hepatic vein pressure significantly correlated with ALT ( $r = 0.23$ ,  $P = 0.04$ ) and AST ( $r = 0.30$ ,  $P = 0.008$ ), but not with GGTP or INR.

### 4.3. 12-month observation

At 12 months, recurrent hospitalizations were observed in 67 (85.9%), 5 (6.4%) had cirrhosis-related bleeding episodes, and 4 (5.1%) patients died (Figure). We observed no significant correlation between HVPG values and recurrent hospitalizations ( $\rho = 0.19$ ,  $P = 0.08$ ), bleeding episodes ( $\rho = 0.20$ ,  $P = 0.07$ ) or death ( $\rho = 0.03$ ,  $P = 0.77$ ).

However, as mentioned earlier, in 11 patients at baseline HVPG was below 10 mm Hg. In those patients at 12 months no bleeding episodes or death were recorded.

**Table. Baseline characteristics and measurement results.**

Parameter	Value
Age, mean $\pm$ SD	$55.5 \pm 10.9$
Males, $n(\%)$	52(66.7)
Reasons for liver failure, $n(\%)$	
HBV,	4(5.1)
HCV	17(21.8)
Alcohol abuse	51(65.4)
Thrombosis	4(5.1)
Autoimmune	6(7.7)
Others	6(7.7)
Varices stage, $n(\%)$	
0	2(2.6)
1	2(2.6)
2	9(11.5)
3	65(83.3)
Measurements, mean $\pm$ SD, mm Hg	
IVCP	$10.9 \pm 4.8$
RAP	$10.7 \pm 4.7$
HVPG	$16.3 \pm 6.2$
FHVP	$13.8 \pm 4.8$
WHVP	$30.2 \pm 8.2$
Laboratory results	
Hemoglobin, mean $\pm$ SD, g/dL	$12.5 \pm 2.1$
Platelets, median (IQR), $\times 10^3/\mu\text{L}$	94 (66–144)
ALT, median (IQR), U/L	33 (24–51)
AST median (IQR), U/L,	46 (35–82)
GGTP, median (IQR), U/L	56 (38–167)
INR, mean $\pm$ SD	$1.37 \pm 0.3$

Comments: ALT – alanine aminotransferase; AST – aspartate aminotransferase; FHVP – free hepatic venous pressure; GGTP – gamma-glutamyltransferase; HVPG – hepatic venous pressure gradient; INR – international normalized ratio; IVCP – inferior vena cava pressure; RAP – right atrium pressure; WHVP – wedged hepatic venous pressure.

## 5. DISCUSSION

We have shown that HVPG measurement is feasible and applicable in the modern hemodynamics laboratory in patients with liver cirrhosis as a stage for qualification in VBL. This patient population characterizes an elevated risk of long-term complications, with a staggeringly high risk of recurrent hospitalizations.

Invasive HVPG measurement is available only in reference centers with extensive experience in hemodynamic flow measurements other than those routinely assessed in invasive cardiology. It is, as demonstrated in this paper, a useful and safe tool for qualifying for endoscopic treatment of esophageal varices. In our center candidates for invasive evaluation of the clinical significance of portal hypertension are selected in the course of routine endoscopic surveillance, guided by the Baveno VI Consensus Workshop guidelines, and the assessment of tolerability of routinely used beta-blockers.<sup>10</sup> Patient compliance and comorbidities play a major role.

In the observed group of patients undergoing invasive intrahepatic flow measurement, it was assumed, following the guidelines of the Baveno VI Consensus Workshop, that an HVPG value less than 10 mmHg indicated a low risk of size progression and bleeding from varices. This allowed further clinical, endoscopic, and ultrasound surveillance of this group of patients without qualifying for sequential invasive endoscopic procedures. Indeed, in our study 11 patients at baseline had HVPG below 10 mmHg. In those patients at 12 months no bleeding episodes or death were recorded.

What is important, in all patients without contraindications and not reporting intolerance, non-selective beta-blockers were continued. The role of beta-blockers in the prevention of portal hypertension has been evaluated in several meta-analyses and they have a well-established role in the primary and secondary prevention of esophageal variceal bleeding.<sup>11</sup> The problem is often in achieving a tolerated dose that produces the intended hemodynamic effects, often coexisting with liver disease contraindications or intolerance to beta-blockers. In our study all patients received at least the smallest doses of betablockers.

If, despite their use, progression of variceal size and/or the appearance of symptoms threatening hemorrhage is observed already without remeasurement of invasive HVPG, patients are qualified for VBL as primary prophylaxis of bleeding. As has been proven earlier such strategy is associated with reduced mortality.<sup>12</sup>

Only minor periprocedural complications during VBL were reported in the literature, e.g., temporary cardiac arrhythmias, focal pain, or vasovagal response, with frequency less than 1%. It is also worth stressing that HVPG measurements can proceed in less than 15 minutes with a trans-jugular approach with simultaneous liver biopsy. Despite many benefits (favorable safety profile, repeatability), this method remains invasive. And many subjects with chronic liver disorders do not accept it. Also, HVPG measuring demands high-level expertise mainly available only in tertiary healthcare facilities.<sup>13</sup>

In case of acute variceal bleeding, HVPG measuring

characterizes prognostic value on the evolution of the bleeding event. Most papers indicated that subjects with variceal bleeding almost always characterized HVPG above 12 mmHg. It was also shown that short-term prognosis in subjects with alcoholic cirrhosis and variceal bleeding was associated with HVPG obtained within the first 48 h.<sup>14</sup> In another research paper, baseline HVPG value above 20 mmHg was linked with a substantially more extended hospital stay, more transfusions, and poor prognosis (1-year mortality: 64% vs. 20%,  $P < 0.01$ ).<sup>15</sup> Whereas Kim et al. disclosed that HVPG values more than 11 mmHg characterize a prognostic value in predicting the first episode of variceal bleeding (92.4 % sensitivity; 27.7% specificity).<sup>16</sup>

The early impact of endoscopic injection sclerotherapy, as well as endoscopic VBL on HVPG values during acute bleeding, were investigated as well. Endoscopic injection sclerotherapy was associated with a persistent rise in HVPG values compared with endoscopic VBL. In research with 50 subjects with liver cirrhosis, HVPG was recorded before and just after the endoscopic procedure (endoscopic VBL and endoscopic injection sclerotherapy) and later every 24 h for 5 days. A marked rise (18.1 mmHg to 20.7 mmHg and 18.1 mmHg to 21.5 mmHg,  $P < 0.01$ ) was recorded in the mean portal pressure value in the endoscopic VBL and endoscopic injection sclerotherapy groups just after the procedure compared with baseline values. Notwithstanding, HVPG values reverted to baseline values within 48 h in subjects with endoscopic VBL, and in subjects with endoscopic sclerotherapy these values maintained high during the 5-day monitoring.<sup>13</sup>

However, in the end, one must also mention the study by Rossle et al., who systematically evaluated FVHP measurement accuracy.<sup>17</sup> The study showed that, due to the hepatic vein's conical shape, pressure recordings in the free hepatic vein are substantially affected by the catheter's location. Repeatability may be skewed by various positions of the catheter's tip and are succumb to manipulation. The authors showed that discrepancies between two positions might overtop the pharmacologic intervention's expected effects (10%–25% reduction in the HVPG value), questioning credibility of the procedure using FHVP as an internal standpoint for HVPG. Therefore, it was advised to obtain at the same time pressures in the IVC at the level of the hepatic veins' orifice and to apply this recording when the discrepancy among these two values is above 2 mmHg.<sup>18</sup>

## 6. CONCLUSIONS

HVPG measurement is a feasible, safe and reproducible procedure that provides valuable diagnostic/prognostic information and helps make therapeutic decisions. This procedure can be done quickly in the modern hemodynamics laboratory.

### Conflict of interest

None declared.



## Funding

None declared.

## Ethics

It was a retrospective study hence no institutional ethics committee's approval was required as well as no written informed consent was obtained.

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