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Tolerance and acceptance of hepatic venous pressure gradient measurement in cirrhosis (CHESS1904): An international multicenter study

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Abstract

Aim: To determine the tolerance and acceptance of hepatic venous pressure gradient (HVPG) measurements in patients with liver cirrhosis.

Methods: This prospective international multicenter study included 271 patients with cirrhosis who were scheduled to undergo HVPG measurement between October 2019 and June 2020. Data related to the tolerance and acceptance of HVPG measurements were collected using descriptive questionnaires.

Results: HVPG measurements were technically successful in all 271 patients, with 141 (52.0%) undergoing HVPG measurement alone. The complication rate was 0.4%. Postoperative pain was significantly lower than preoperative expected pain ($p < 0.001$) and intraoperative pain ($p < 0.001$), and intraoperative pain was also significantly lower than preoperative expected pain ($p = 0.036$). No, mild, moderate, severe, and intolerable discomfort scores were reported by 36.9%, 44.6%, 11.1%, 6.3%, and 0.4% of these patients, respectively, during HVPG measurement and by 54.6% 32.5%, 11.4%, 1.5%, and 0%, respectively, after HVPG measurement. Of these patients, 39.5% had little understanding and 10% had no understanding of the value of HVPG measurement, with 35.1% and 4.1% regarding HVPG measurements as being of little or no help, respectively. Most patients reported that they would definitely (15.5%), probably (46.9%), or possibly (29.9%) choose to undergo additional HVPG measurements again, and 62.7% regarded the cost of the procedure as acceptable.

Conclusion: HVPG measurement was safe and well-tolerated in patients with cirrhosis, but patient education and communication are warranted to improve the acceptance of this procedure.

KEYWORDS

design, hypertension, multicenter study, portal, pressure, prospective study, questionnaire, wedge

Key points

Significant findings of the study: This prospective multicenter study showed that HVPG measurement was well-tolerated in patients with cirrhosis, but the acceptance of HVPG measurement was not as high as expected.

What this study adds: Although HVPG measurement was safe and well-tolerated in patients with cirrhosis, more in-depth patient education and communication are warranted to improve the acceptance of the procedure.

1 | INTRODUCTION

Portal hypertension is the main consequence of cirrhosis, with its severity usually determining the development of complications, such as ascites, hepatic encephalopathy, and variceal hemorrhage.[1] Evaluation of portal venous pressure is crucial for predicting patient prognosis and the effect of drugs used to treat cirrhosis. Direct measurement of portal venous pressure is extremely invasive and is associated with high patient risk. In addition, changes in intra-abdominal pressure can affect portal pressure, which can lead to unreliable results.[2] Therefore, direct measurement of portal venous pressure is not recommended in patients with cirrhosis.

Hepatic venous pressure gradient (HVPG), defined as the difference between wedged and free hepatic venous pressure, is an accurate reflection of portal venous pressure and is therefore regarded as the standard method for evaluating portal hypertension.[3,4] This procedure, however, is not that widely performed in clinical practice,[5] due largely to its invasiveness, high cost, and the requirement for operator expertise.[5–7]

Tolerance and acceptance of medical techniques have been considered important factors for their promotion and application.[8–12] A single-center study evaluating parameters related to the tolerance (i.e., pain and duration) of hepatic hemodynamic procedures (i.e., HVPG measurement ± transjugular liver biopsy [TLB] ± Swan–Ganz catheterization) in patients with (62.1%) and without (37.9%) cirrhosis showed that tolerance to these hepatic hemodynamic procedures was good.[13] To our knowledge, however, no international multicenter study has evaluated the tolerance of HVPG measurement in patients with cirrhosis. Moreover, although acceptance of a medical procedure, such as liver transplantation or COVID-19 vaccination, is considered important for its promotion and application, no study to date has evaluated the acceptance of HVPG measurement by patients with cirrhosis.[8,9,14,15] The present study was therefore designed to also assess the tolerance and acceptance of HVPG measurements in patients with cirrhosis.

2 | METHODS

2.1 | Ethical approval

This study was performed in compliance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Hospital of Lanzhou University. All patients who participated in this study provided written informed consent.

2.2 | Study design

This prospective international multicenter observational cohort study (ClinicalTrials.gov, identifier: NCT04121520) enrolled patients with cirrhosis who were scheduled to undergo HVPG measurement at 20 institutions, including 17 in China and 1 each in Turkey, Japan, and Brazil, between October 2019 and June 2020.

2.3 | Inclusion and exclusion criteria

Patients were included if they (1) were aged 18–75 years with no restriction on gender; (2) had been clinically and/or pathologically diagnosed with sinusoidal cirrhosis; (3) provided written informed consent; and (4) were scheduled to undergo HVPG measurement. Patients were excluded if they (1) had contraindications for HVPG measurement; (2) were pregnant or lactating women; (3) had severe coagulopathy (i.e., international normalized ratio >5); or (4) had severe heart, lung, or kidney disease.

2.4 | HVPG measurement

The indications for HVPG measurement included: (1) assessment of the efficacy of primary and secondary prophylactic drugs for gastroesophageal variceal bleeding; (2) prediction of the risk of gastroesophageal variceal bleeding and determination of treatment regimens; (3) prediction of the risks, progression, and clinical outcomes of decompensation events in cirrhosis; (4) evaluation of the efficacy of new drugs; (5) evaluation of the accuracy of new noninvasive techniques; and (6) diagnosis and differential diagnosis of types of portal hypertension. HVPG was measured as described.[16,17]

2.5 | Design of the questionnaires

Tolerance and acceptance of HVPG measurements were determined using descriptive questionnaires prepared based on discussions among the investigators. The questionnaires were subsequently evaluated by an expert panel consisting of three professionals with expertise in hepatology and three professionals with

expertise in interventional radiology before the approval of these questionnaires for use in this study.[18,19] Tolerance of HVPG measurement was evaluated by determining the severity of preoperative anxiety; intraoperative and postoperative pain scores were rated on a scale ranging from 0 (no pain) to 10 (most severe pain); and discomfort level was rated as none, mild, moderate, severe, or intolerable during and after the HVPG procedure. The preoperative expected pain score was also determined after the procedure. In addition, to determine the uncomfortable step during the HVPG measurement procedure, the latter was divided into four steps (i.e., local anesthesia, paracentesis, catheterization, and measurement of HVPG), and the patients were asked to choose the most uncomfortable step during the HVPG measurement. Acceptance of the HVPG measurement procedure was assessed using questions pertaining to four aspects: (1) understanding the value of HVPG measurements; (2) determining whether HVPG measurements were helpful; (3) determining whether the patient would choose to measure HVPG again; and (4) assessing whether the cost of HVPG measurement was acceptable.

2.6 | Data collection

Baseline characteristics, including age, sex, etiology of cirrhosis, Child–Pugh class, complications of cirrhosis, and preoperative treatment, were recorded. Parameters related to the HVPG measurement procedure were recorded during (i.e., value of HVPG, duration of HVPG measurement, venous access, and procedures) and after (i.e., procedure-related complications) HVPG measurements. The value of HVPG in each patient was calculated as the mean value of HVPG measurements in that patient. The duration of HVPG measurement was defined as the time interval between administration of local anesthetic and removal of the catheter from the hepatic vein immediately after HVPG measurement. Data assessing the tolerance and acceptance of HVPG measurement were collected within 24 h after the procedure. Complications were defined as a secondary disease or condition that developed after the HVPG measurement and required additional care, prolonged hospitalization, or therapy.[20,21] Complications experienced within 24 h of the start of HVPG measurement were also recorded.

2.7 | Statistical analyses

Continuous variables were compared using Student's t tests or Mann–Whitney U tests, as appropriate, and categorical variables were compared using χ^2 or Fisher's exact tests, as appropriate. Pairwise comparisons between groups were performed by the one-way analysis of variance using the Bonferroni post hoc tests. Two-sided $p < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS software for Windows (version 21.0; SPSS).

3 | RESULTS

3.1 | Patient characteristics

This study included 271 patients, 166 (61.6%) men and 105 (39.4%) women, with a mean age of 55.3 ± 11.9 years. The characteristics of these patients were shown in Table 1. Hepatitis B virus infection (55.4%) was the most common etiology of cirrhosis, followed by alcohol (12.2%), autoimmune hepatitis (11.8%), hepatitis C virus infection (4.1%), primary biliary cirrhosis (2.2%),

TABLE 1 Baseline characteristics of patients with cirrhosis who were scheduled to undergo HVPG measurement ($n = 271$).

Characteristic	Value
Mean age, years (SD)	55.3 ± 11.9
Sex	
Male	167 (61.6)
Female	104 (38.4)
Etiology of cirrhosis	
Hepatitis B virus infection	150 (55.4)
Alcohol	33 (12.2)
Autoimmune hepatitis	32 (11.8)
Hepatitis C virus infection	11 (4.1)
Primary biliary cirrhosis	6 (2.2)
Nonalcoholic fatty liver disease	5 (1.8)
Others[a]	34 (12.5)
Child–Pugh class	
A	137 (57.8)
B	94 (39.7)
C	40 (16.9)
Complications of cirrhosis	
Variceal hemorrhage	169 (62.4)
Ascites	110 (40.6)
Hypersplenism	107 (39.5)
Hepatic encephalopathy	17 (6.3)
Hepatocellular carcinoma	19 (7.0)
Preoperative treatment	
Nonselective beta-blockers	113 (41.7)
Endoscopic ligation or sclerotherapy	85 (31.4)
Splenectomy	15 (5.5)
PSE	13 (4.8)
Conservative treatment	8 (3.0)
No treatment	58 (21.4)

Note: Data are presented as mean ± standard deviation or as n (%).

Abbreviations: HVPG, hepatic venous pressure gradient; PSE, partial splenic embolization.

[a]Other etiologies included schistosomiasis, drug-induced liver injury, and cryptogenic cirrhosis.

and nonalcoholic fatty liver disease (5.8%). The most common complication of cirrhosis was variceal hemorrhage (62.4%), followed by ascites (40.6%), hypersplenism (39.5%), and hepatic encephalopathy (6.3%). In addition, 7% of these patients were diagnosed with hepatocellular carcinoma. Evaluation of liver function classified 137 (57.8%), 94 (39.7%), and 40 (16.9%) patients as Child–Pugh Classes A, B, and C, respectively. Of these patients, 78.6% had been treated before HVPG measurement, including with nonselective beta-blockers (41.7%), endoscopic ligation or sclerotherapy (31.4%), splenectomy (5.5%), partial splenic embolization (PSE, 4.8%), and conservative treatment (3.0%), such as percutaneous peritoneal drainage or administration of ursodeoxycholic acid. After HPVG measurement, 112 (41.3%) patients were treated with the transjugular intrahepatic portosystemic shunt (TIPS) or PSE, 56 (20.7%) with nonselective beta-blockers, 48 (17.7%) with endoscopic ligation or sclerotherapy, 45 (16.6%) with conservative treatment, and 10 (3.7%) with splenectomy.

3.2 | HVPG measurement

HVPG measurement was technically successful in all patients. Of these patients, 52.0% underwent HVPG alone, with 41.0% undergoing TIPS or PSE, 6.6% undergoing TLB, and 0.4% undergoing TLB and TIPS after HVPG measurement (Table 2). The duration of HVPG measurement was <30 min in 90.4% of patients. HVPG was measured through the jugular vein in 263 patients (97.0%), through the femoral vein in 5 (1.8%), and through the median antebrachial vein in 3 (1.1%). Fever (38.8°C/101.8°F) was observed in one patient 28 h after HVPG measurement, with these symptoms resolved within 3 days after taking cefoperazone. No other complication was observed during this study.

TABLE 2 Characteristics of HVPG measurement in patients with cirrhosis ($n = 271$).

Characteristic	Value
HVPG (mmHg)	17.1 ± 6.9
Duration of HVPG measurement (min)	
≤30	245 (90.4)
>30	26 (9.6)
Complications	
Fever	1 (0.4)
Other complications	0
Venous access	
Jugular vein	263 (97.0)
Femoral vein	5 (1.8)
Median antebrachial vein	3 (1.1)
Procedures	
HVPG measurement alone	141 (52.0)
HVPG measurement followed by TIPS or PSE	111 (41.0)
HVPG measurement followed by TLB	18 (6.6)
HVPG measurement followed by TLB and TIPS	1 (0.4)

Note: Data are presented as mean ± standard deviation or as number (%).
Abbreviations: HVPG, hepatic venous pressure gradient; PSE, partial splenic embolization; TIPS, transjugular intrahepatic portosystemic shunt; TLB, transjugular liver biopsy.

3.3 | Tolerance of HVPG measurement

Twenty-one patients (7.7%) presented with severe preoperative anxiety before HVPG measurement, whereas most patients presented with moderate (24.0%), mild (41.7%), or no (26.6%) anxiety (Table 3). Mean preoperative expected pain scores (2.7 ± 2.1), intraoperative pain scores (2.2 ± 2.3), and postoperative pain scores (1.5 ± 1.8) all differed significantly from each other ($p < 0.001$; Figure 1). The postoperative pain score was significantly lower than the preoperative expected pain score ($p < 0.001$) and intraoperative pain score ($p < 0.001$), and the intraoperative pain score was significantly lower than the preoperative expected pain score ($p = 0.036$). During the HVPG measurement, three patients rated discomfort as intolerable, with two experiencing maximum discomfort during insertion of the catheter and one during the HVPG measurement. No, mild, moderate, and severe discomfort were reported by 36.9%, 44.6%, 11.1%, and 6.3% of patients, respectively, during HVPG measurement and by 54.6%,

TABLE 3 Tolerance of HVPG measurement in patients with cirrhosis ($n = 271$).

Parameter	Value
Severity of preoperative anxiety (none/mild/moderate/severe)	72/113/65/21 (26.6/41.7/24.0/7.7)
Pain scores (range: 0–10)	
Preoperative expected	2.7 ± 2.1
Intraoperative	2.2 ± 2.3
Postoperative	1.5 ± 1.8
Discomfort level (none/mild/moderate/severe/intolerable)	
Intraoperative	100/121/30/17/3 (36.9/44.6/11.1/6.3/1.1)
Postoperative	148/88/31/4/0 (54.6/32.5/11.4/1.5/0)
Uncomfortable step during the procedure	
Paracentesis	83 (30.6)
Local anesthesia	70 (25.8)
Catheterization	61 (22.5)
Measurement	56 (20.7)

Note: Data are presented as mean ± standard deviation or as *n* (%).
Abbreviation: HVPG, hepatic venous pressure gradient.

32.5%, 11.4%, and 1.5%, respectively, after HVPG measurement. Of the 271 patients, 30.6% reported that paracentesis was the most uncomfortable step during HVPG measurement, followed by local anesthesia (25.8%), insertion of balloon catheter (22.5%), and balloon inflation (20.7%).

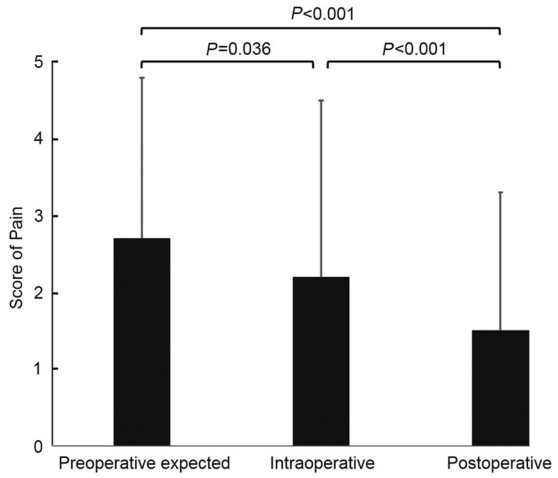

FIGURE 1 Pain scores at different times. Preoperative expected pain (2.7 ± 2.1), intraoperative pain (2.2 ± 2.3), and postoperative pain (1.5 ± 1.8) scores differed significantly from each other.

TABLE 4 Acceptance of HVPG measurement by patients with cirrhosis (n = 271).

Parameter	Value
Understand the value of HVPG measurement	
Very clear	14 (5.2)
Generally	123 (45.4)
A little	107 (39.5)
Not at all	27 (10.0)
Helpfulness of HVPG measurement	
A lot	165 (60.8)
A little	95 (35.1)
Not at all	11 (4.1)
Would choose to measure HVPG again	
Will choose	42 (15.5)
High probability	127 (46.9)
Maybe	81 (29.9)
Unlikely	12 (4.4)
Certainly not	9 (3.3)
Acceptability of the cost of HVPG measurement	
Acceptable	170 (62.7)
Relatively high	89 (32.8)
Unbearable	12 (4.4)

Note: Data are presented as n (%).
Abbreviation: HVPG, hepatic venous pressure gradient.

3.4 | Acceptance of HVPG measurement

Although some patients reported that they fully (5.2%) or generally (45.4%) understood the value of HVPG measurement, 39.5% reported little and 10.0% stated that they had no understanding of the value of this procedure (Table 4). Most patients (60.8%) reported that HVPG measurement was quite helpful, whereas 35.1% and 4.1% regarded HVPG measurement as being of little or no help, respectively. Although small numbers of patients reported being unlikely (4.4%) and definitely unwilling (3.3%) to measure HVPG again, larger numbers of patients would definitely (15.5%), probably (46.9%), and possibly (29.9%) choose to undergo additional HVPG measurements. In addition, 62.7% of patients regarded the cost of the procedure as acceptable.

4 | DISCUSSION

Tolerance and acceptance are crucial factors for patients choosing to use a medical technique.[14] This prospective multicenter study showed that HVPG measurement was well-tolerated in patients with cirrhosis, although the acceptance of HVPG measurement was not as high as expected.

The patient complication rate in the present study was 0.4%, which is lower than those in most previous studies of HVPG measurement (1.1%–7.5%).[13,17,22] Except for one patient with fever after the procedure, no other complications (e.g., local injury at the puncture site, allergic reaction to the contrast medium, or thrombosis) were experienced by any other patients during or after the procedure. In addition, pain scores during (2.2 ± 2.3) and after (1.5 ± 1.8) the procedure were significantly lower than expected pain scores (2.7 ± 2.1) before the procedure, suggesting that the level of pain experienced by patients was not as high as they expected and that these patients tolerated pain arising from the procedure. In addition, only three patients (1.1%) reported an intolerable level of discomfort. Taken together, these findings show that tolerance of HVPG measurement was high in the current study, consistent with previous results.[13] In Casu et al.,[13] tolerance of hepatic hemodynamic procedures was calculated by combining the average duration of pain and pain scores, both determined on visual analog scales. These scales and methods of calculation were not used in the current study because these self-determined scales were regarded as too inaccurate for determining tolerance to HVPG measurements. Rather, tolerance in this study was measured using questionnaires addressing preoperative, intraoperative, and postoperative evaluations of pain and discomfort associated with HVPG measurements.

A high level of acceptance is crucial for adopting a medical technique. One example is the acceptance of COVID-19 vaccination, as the number of persons vaccinated correlated with the risk of infection in the general population.[14] To date, however, factors affecting the acceptance of HVPG measurement had not been

investigated. The current study found that about half the patients surveyed understood little or nothing about HVPG measurement, almost 40% regarded HVPG measurement as being of little or no value, and 37% regarded the cost of HVPG measurement as relatively high or unaffordable. These findings could explain why only 62% of patients would choose to undergo repeat HVPG measurement. Thus, the acceptance of HVPG measurement was not as high as expected.

One reason for the low acceptance of HVPG measurement may be the unsuitable physician–patient relationship in this clinical scenario. In the parental model (or relationship), characterized by insufficient interactions and communications between physicians and patients, patients are usually provided the "best" diagnostic or treatment option based on the physician's knowledge and experience.[23–25] Although all the patients with cirrhosis in the current study underwent HVPG measurement, half of these patients did not fully understand the value of this procedure, suggesting that communications between physicians and patients were insufficient and that the autonomy of patients was not fully respected. This lack of communication may have impaired the acceptance of medical interventions provided by physicians. Therefore, the performance of HVPG measurements in patients with cirrhosis requires physicians and interventional radiologists to pay more attention to their patient education and communication skills, listen to these patients, and help them understand the value of HVPG measurements. Patients should then be allowed to choose the best option for themselves.

This study had several limitations. First, the questionnaires used in this study have not been externally validated. The questionnaires were designed based on the clinical experience of physicians and interventional radiologists. To our knowledge, no widely used questionnaire has been proposed to quantitatively or directly assess the tolerance and acceptance of HVPG measurement. Second, 48% of patients underwent other interventional radiological procedures after HVPG measurement, including TLB, TIPS, and/or PSE, which may have affected the evaluation of some parameters.

In conclusion, HVPG measurement was safe and well-tolerated in patients with cirrhosis. However, more in-depth patient education and physician–patient communications are warranted to improve the acceptance of this procedure.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

Xiaolong Qi is the Editor-in-Chief of *Portal Hypertension & Cirrhosis*. Necati Örmeci is the Editorial Board Member of Portal Hypertension & Cirrhosis. They are therefore excluded from the peer-review process and all editorial decisions related to the publication of this manuscript. The remaining authors declared that they have no other conflicts of interest with reference to this manuscript.

DATA AVAILABILITY STATEMENT

The datasets used in the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was performed in compliance with the Declaration of Helsinki, and was approved by the involved centers. All patients participated this study provided the written informed consent.

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