Virtual Hepatic Venous Pressure Gradient with CT Angiography (CHESS 1601): A Prospective Multicenter Study for the Noninvasive Diagnosis of Portal Hypertension

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Conflicts of interest are listed at the end of this article.

See also the editorial by Malayeri in this issue.

Purpose: To develop and validate a computational model for estimating hepatic venous pressure gradient (HVPG) based on CT angiographic images, termed virtual HVPG, to enable the noninvasive diagnosis of portal hypertension in patients with cirrhosis.

Materials and Methods: In this prospective multicenter diagnostic trial (ClinicalTrials.gov identifier: NCT02842697), 102 consecutive eligible participants (mean age, 47 years [range, 21–75 years]; 68 men with a mean age of 44 years [range, 21–73 years] and 34 women with a mean age of 52 years [range, 24–75 years]) were recruited from three high-volume liver centers between August 2016 and April 2017. All participants with cirrhosis of various causes underwent transjugular HVPG measurement, Doppler US, and CT angiography. Virtual HVPG was developed with a three-dimensional reconstructed model and computational fluid dynamics.

Results: In the training cohort (n = 29), the area under the receiver operating characteristic curve (AUC) of virtual HVPG in the prediction of clinically significant portal hypertension (CSPH) was 0.83 (95% confidence interval [CI]: 0.58, 1.00). The diagnostic performance was prospectively confirmed in the validation cohort (n = 73), with an AUC of 0.89 (95% CI: 0.81, 0.96). Inter- and intraobserver agreement was 0.88 and 0.96, respectively, suggesting the good reproducibility of virtual HVPG measurements. There was good correlation between virtual HVPG and invasive HVPG (R = 0.61, P < .001), with a satisfactory performance to rule out (7.5 mm Hg) and rule in (13.0 mm Hg) CSPH.

Conclusion: The accuracy of a computational model of virtual hepatic venous pressure gradient (HVPG) shows significant correlation with invasive HVPG. The virtual HVPG also showed a good performance in the noninvasive diagnosis of clinically significant portal hypertension in cirrhosis.

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Portal hypertension is a common complication of chronic liver disease and is associated with most clinical consequences of cirrhosis, such as variceal hemorrhage, ascites, and hepatic encephalopathy (1–3). The most reliable method for assessing portal hypertension is the measurement of the hepatic venous pressure gradient (HVPG), by which clinically significant portal hypertension (CSPH) is defined as an HVPG of at least 10 mm Hg. Variceal hemorrhage may occur when the HVPG is at least 12 mm Hg (4,5). CSPH can become symptomatic, and the development of varices and hypodynamic circulation puts patients at high risk of decompensation (6,7). Thus, there is an increasing need to predict and select patients with CSPH who are at risk...
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Abbreviations
AST = aspartate aminotransferase, AUC = area under the receiver operating characteristic curve, CI = confidence interval, CSPH = clinically significant portal hypertension, HVPG = hepatic venous pressure gradient

Summary
Calculated from CT angiographic images, the noninvasive virtual hepatic venous pressure gradient correlates well with an invasive hepatic venous pressure gradient and shows good performance in diagnosing clinically significant portal hypertension in patients with cirrhosis.

Implications for Patient Care
- The virtual hepatic venous pressure gradient is promising to serve as a noninvasive surrogate measurement of hepatic venous pressure gradient.
- The virtual hepatic venous pressure gradient may facilitate decision making for individualized diagnosis and monitoring in patients with cirrhosis.

for variceal hemorrhage. However, the reference standard for the measurement of HVPG for diagnosing CSPH (transjugular HVPG) is invasive and impractical for routine clinical practice (4,8). Therefore, noninvasive tests that correlate well with invasive HVPG are urgently needed.

Liver stiffness measurement by means of transient elastography (FibroScan; Echosens, Paris, France) is considered a promising noninvasive tool for predicting portal hypertension and esophageal varices; however, concerns exist regarding the unreliable measurement in patients with obesity, intrahepatic inflammatory activity, or severe ascites (2,4). Recent advances in imaging-based three-dimensional modeling combined with computational fluid dynamics analysis have permitted noninvasive calculation of blood flow pressure (9,10). Relevant techniques have been successfully applied in the coronary artery for the diagnosis of ischemia (9). In this study, we aimed to develop a computational model based on CT angiographic images, which we termed virtual HVPG, and validated that virtual HVPG could allow the accurate estimation of HVPG in patients with cirrhosis. Herein, we evaluated the correlation between virtual HVPG and transjugular HVPG and the accuracy of virtual HVPG in the diagnosis of CSPH.

Materials and Methods
The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board at each site. All participants provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Study Design and Participants
The study (CHESS-1601 trial) is a prospective multicenter diagnostic trial in three high-volume liver centers in China (ClinicalTrials.gov identifier: NCT02842697). The training cohort enrolled consecutive participants at Beijing Shijitan Hospital (Beijing, China) between August 2016 and November 2016, and the developed virtual HVPG method was further validated in a cohort recruited from two other centers (The 302 Hospital of PLA, Beijing, China; Nanfang Hospital, Guangzhou, China) between December 2016 and April 2017. Inclusion criteria were as follows: (a) participants in whom cirrhosis was diagnosed by means of liver biopsy; (b) participants who underwent transjugular HVPG measurement, abdominal CT angiography, and Doppler US; (c) adult participants; and (d) participants who provided written informed consent. Exclusion criteria were as follows: (a) participants who had previously undergone creation of a transjugular intrahepatic portosystemic shunt, splenectomy, partial splenic embolization, balloon-occluded retrograde transvenous obliteration, endoscopic therapies, and liver transplantation; (b) participants with hepatocellular carcinoma; and (c) pregnant participants. Laboratory assessments were conducted the day before HVPG measurement, whereas CT angiography and Doppler US were performed within 14 days before catheterization.

Transjugular HVPG Measurement
Transjugular HVPG measurement (reference standard) was performed by F.L., L.W., and R.Q., with 20, 10, and 8 years of experience in interventional radiology, respectively, according to the standard protocol (11). The recording and interpretation of the pressure was supervised by X.Q., Z. Li, and J. Hou (hepatologists with 10, 25, and 30 years of experience, respectively). Pressure measurements were conducted by using a balloon catheter (Edwards Lifesciences, Irvine, Calif) with a pressure transducer at the tip. A zero measurement with transducer open to air was needed before the transjugular catheterization. The free hepatic venous pressure was measured in the right hepatic vein (approximately 1–3 cm from the inferior vena cava). Then, as the balloon was inflated for total occlusion of the right hepatic vein, the wedged hepatic venous pressure was measured. Continuous recording was necessary until the pressure reached a plateau. HVPG is calculated by subtracting the free venous hepatic pressure from the wedged hepatic pressure. All measurements were performed in triplicate and then averaged.

Doppler US
Doppler US was performed by two technicians (including W.A.) with more than 10 years of experience in US. Participants fasted for 8 hours before undergoing US, and all measurements were conducted with the participants lying supine and breathing normally by using a 3.5-MHz transducer (iU22 Ultrasound System; Philips Healthcare, Reedsdale, Pa). The diameters of the portal vein were measured by using B-mode US. Doppler examination was used to measure portal vein velocities. All measurements were performed in triplicate and then averaged.

CT Image Acquisition
CT angiography was performed in all participants by Changchun Liu (with 12 years of experience in abdominal imaging) and a radiologist with 10 years of experience in abdominal
imaging with use of one of the following systems: Discovery CT750 HD (GE Healthcare, Milwaukee, Wis) or Brilliance iCT (Philips Healthcare, Best, the Netherlands). The following parameters were used for contrast material–enhanced abdominal CT: tube voltage, 120 kVp or 100 kVp; tube current, 150–600 mA; section thickness, 1.25 mm; and pitch, 1.375. All participants received intravenous administration of a nonionic contrast agent (iodine concentration, 370 mg/mL; volume, 1.5–2.0 mL per kilogram body weight; contrast agent type, iopromide injection [Bayer Pharma, Berlin, Germany]) at a rate of 3–5 mL/sec. The arterial and portal venous phases were scanned at 21 and 41 seconds, respectively. The following interval between hepatic venous and portal venous phases was 10–30 seconds, depending on the image quality of the arterial and portal venous phases. For participants with poor liver enhancement in arterial or portal venous phases, the hepatic venous phase scan was started at 71 seconds after the start of the contrast agent injection. A volume of 20 mL saline was injected after the injection of the contrast agent.

CT Image Analysis and Virtual HVPG Estimation

For CT image analysis and virtual HVPG estimation, original images from CT angiography (Digital Imaging and Communications in Medicine format) were split into thin layers (1.25 mm) and imported into MIMICS 10.0 and 17.0 (Materialise, Leuven, Belgium). Then, a three-dimensional model of the hepatic-portal venous system could be reconstructed from two-dimensional composite images and surrounding tissue on the basis of CT angiographic images, which were then meshed into internal tetrahedra in the computational fluid dynamics solver ANSYS13.0 (Ansys, Canonsburg, Pa). Portal vein velocity was measured with Doppler US and set as a boundary condition. Afterward, finite element analysis and computational fluid dynamics analysis were applied to compute the pressure distribution in a three-dimensional model. The right hepatic vein was virtually blocked to simulate wedged hepatic venous pressure measurement with balloon occlusion (see Appendix E1 [online] for details). The average time for a virtual HVPG calculation was about 2.5 hours, with 1.5 hours for the human processing and 1.0 hour for machine computation. The virtual HVPG estimation was performed by Y.X., J. Hui, Chuan Liu, and Z. Liu, all with 3 years of experience in hemodynamic analysis. All technicians were blinded to the participants’ baseline characteristics, laboratory examination results, and transjugular HVPG values.

Noninvasive Parameters

Three imaging-based indexes—liver stiffness measured with transient elastography (FibroScan) (12), CT-based portal pressure score (13), and portal diameter measured with US—were assessed. Liver stiffness and portal diameter measurements were conducted within 14 days before HVPG measurement. CT-based portal pressure score was calculated as follows: 17.37 – 4.91 · In (liver-to-spleen volume ratio) + 3.8 (if perihepatic ascites is present) (13). In addition, serum biomedical indexes, including aspartate aminotransferase (AST), alanine aminotransferase, and platelet count, were measured with a conventional automated analyzer at the day of HVPG measurement. The AST-to–ala-
nine aminotransferase ratio was calculated as follows: AST/alanine aminotransferase. The AST-to–platelet count ratio index was calculated as follows: AST (upper limit of normal)/platelet count \((\times 10^9/L) \times 100\). The fibrosis index based on four factors was calculated as follows: \([\text{age} \times \text{AST (U/L)}]/[\text{platelet count} (\times 10^9/L) \times \text{alanine aminotransferase (U/L)})^{0.23}]\) (14,15).

### Assessment of Inter- and Intraobserver Agreement

The interobserver agreement was analyzed in 16 of 29 (55%) randomly chosen participants by using a computer in a blinded fashion. Then, four technicians (Y.X., J. Hui, Chuan Liu, Z. Liu) conducted the virtual HVPG estimation. To study intraobserver agreement, one of the technicians (J. Hui) repeated the interpretation process twice in the same participants included in the intraobserver agreement analysis with a 1-month interval between the two readings to reduce the recall bias.

### Statistical Analysis

Categorical data are expressed as numbers and percentages, and continuous variables are expressed as means ± standard deviations. The diagnostic performance of virtual HVPG was assessed by using receiver operating characteristic curves and the areas under the receiver operating characteristic curves (AUCs). The cutoff values were defined as the maximal sum of sensitivity and specificity, the maximal sum of sensitivity and specificity when specificity is greater than 90%, and the maximal sum of sensitivity and specificity when sensitivity is greater than 90% regarding different aims of the test, that is, to diagnose, rule in, and rule out CSPH. The Jackknife cross-validation test was used to assess the accuracy of virtual HVPG. During the process of the test, each case was singled out in turn as a test sample and the remaining cases were used as training samples. The intraclass correlation coefficient was used to analyze the inter- and intraobserver agreement. Spearman correlation coefficient analysis (\(R\) value) and the Bland-Altman plot were used to assess the correlation and the agreement, respectively, between virtual and transjugular HVPG. Two-sided \(P<.05\) was considered indicative of a statistically significant difference. The analyses were performed by using R language 3.0.2 (R Core Team, 2013) and SPSS 20.0 (IBM, Armonk, NY).

### Results

**Participant Characteristics**

In the training cohort, a total of 36 consecutive participants were screened and 34 eligible patients recruited at Beijing Shijitan Hospital (Beijing, China). One patient was excluded because of nonevaluable CT images, and four patients were excluded during three-dimensional remodeling. Of the 34 eligible patients, 29 (85%; 18 men, 11 women; mean age, 51 years; age range, 21–75 years) were included in the final analysis (Fig 1). In addition, 92 consecutive participants...
were screened and 89 eligible participants were enrolled from two additional centers (The 302 Hospital of PLA, Beijing, China; Nanfang Hospital, Guangzhou, China) with use of the same inclusion and exclusion criteria. Six participants were excluded because of nonevaluable CT images and 10 were excluded during three-dimensional remodeling. Of the 89 eligible participants, 73 (82%) were included in the validation cohort (Fig 1). There were 50 men and 23 women with a mean age of 45 years (range, 22–73 years). The median duration between HVPG measurement and CT angiography plus Doppler US was 8 days (range, 3–14 days). No adverse events were identified during these procedures. Baseline demographic characteristics of the study population are summarized in Table 1. The most common cause of cirrhosis was hepatitis B virus infection, which was found in 15 of the 29 participants (52%) in the training cohort and in 51 of the 73 participants (70%) in the validation cohort.

**Virtual HVPG Interpretation and Diagnostic Performance**

Virtual HVPG was successfully calculated on the basis of the three-dimensional reconstructed model and computational fluid dynamics analysis. A representative example of virtual HVPG interpretation is shown in Figure 2. In the training cohort, the AUC of virtual HVPG for the noninvasive prediction of CSPH (HVPG ≥10 mm Hg) was 0.83 (95% confidence interval [CI]: 0.58, 1.00). The performance of virtual HVPG was prospectively confirmed in the validation cohort, with an AUC of 0.89 (95% CI: 0.81, 0.96). In the diagnosis of CSPH, a virtual HVPG of more than 11.03 mm Hg resulted in a sensitivity of 74% (95% CI: 62%, 89%) and specificity of 93% (95% CI: 80%, 100%) (Fig 3, A).

**Correlation between Virtual and Transjugular HVPG**

We found a statistically significant correlation between virtual and transjugular HVPG in the overall participants (n = 102, R = 0.605, P < .001) (Fig 4, A). A similar result was achieved with the Bland-Altman plot (Fig 4, B). The accuracy of virtual HVPG with the Jackknife cross-validation test was 75.5%. By using two cutoff values, one with a sensitivity of

![Figure 2](image_url)

*Figure 2:* Interpretation of virtual hepatic venous pressure gradient (HVPG). Arrows show measurement location of free hepatic venous pressure (FHVP) or wedged hepatic venous pressure (WHVP). (a) Examples of virtual and invasive HVPG interpretation in study participant with clinically significant portal hypertension (CSPH). Virtual HVPG was 22.7 mm Hg, and invasive HVPG was 23.2 mm Hg. (b) Examples of virtual and invasive HVPG interpretation in study participant without CSPH. Virtual HVPG was 7.4 mm Hg and invasive HVPG was 6.2 mm Hg.
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more than 90% (sensitivity: 90%, specificity: 58%) to rule out CSPH (virtual HVPG = 7.3 mm Hg) and one with a specificity of more than 90% (sensitivity: 64%, specificity: 95%) to rule in CSPH (virtual HVPG = 13.0 mm Hg), 75 of 102 participants (74%) showed definite results categories, with 56 of the 102 participants (55%) classified as having CSPH and 19 as having no CSPH (19%). Among the 75 participants with definite results, results for 65 of the 102 participants (64%) were well classified and those for 10 (10%) were misclassified. Conversely, 27 of the 102 participants (26%) had an indeterminate result that necessitated further evaluation (Fig 4, C).
Table 2: Performance of Virtual HVPG and Other Noninvasive Models in the Diagnosis of Clinically Significant Portal Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Virtual HVPG (mm Hg)</th>
<th>Transient Elastography (kPa)</th>
<th>CT-based Portal Pressure Score*</th>
<th>AAR</th>
<th>Portal Diameter (mm)</th>
<th>FIB-4</th>
<th>APRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>88 (80, 95)</td>
<td>71 (48, 95)</td>
<td>60 (46, 74)</td>
<td>58</td>
<td>(43, 72)</td>
<td>58</td>
<td>(45, 70)</td>
</tr>
<tr>
<td>Cutoff</td>
<td>11.03</td>
<td>13.45</td>
<td>19.11</td>
<td>11.3</td>
<td>14.05</td>
<td>4.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76 (64, 93)</td>
<td>62 (45, 79)</td>
<td>43 (31, 54)</td>
<td>29</td>
<td>(21, 40)</td>
<td>63</td>
<td>(52, 73)</td>
</tr>
<tr>
<td>Specificity</td>
<td>90 (74, 100)</td>
<td>80 (65, 100)</td>
<td>94 (83, 100)</td>
<td>56</td>
<td>(31, 81)</td>
<td>83</td>
<td>(67, 100)</td>
</tr>
<tr>
<td>PPV</td>
<td>97 (93, 100)</td>
<td>95 (85, 100)</td>
<td>91 (82, 100)</td>
<td>96</td>
<td>(87, 100)</td>
<td>88</td>
<td>(83, 95)</td>
</tr>
<tr>
<td>NPV</td>
<td>46 (37, 58)</td>
<td>27 (14, 42)</td>
<td>26 (21, 33)</td>
<td>23</td>
<td>(20, 26)</td>
<td>23</td>
<td>(14, 32)</td>
</tr>
</tbody>
</table>

Note.—Except for cutoff, data are given as percentages. Numbers in parentheses are 95% confidence intervals. Clinically significant portal hypertension is defined as hepatic venous pressure gradient (HVPG) of at least 10 mm Hg. AAR = aspartate aminotransferase–to–alanine aminotransferase ratio, APRI = aspartate aminotransferase–to–platelet count ratio index, AUC = area under the receiver operating characteristic curve, FIB-4 = fibrosis index based on four factors, NPV = negative predictive value, PPV = positive predictive value.

* CT-based portal pressure was calculated as follows: 17.37 – 4.91 · ln (liver-to-spleen volume ratio) + 3.8 (if perihepatic ascites is present).

Comparison between Virtual HVPG and Other Reported Noninvasive Parameters

We further compared the diagnostic performance of virtual HVPG with that of other noninvasive parameters in all cohorts (n = 102). Virtual HVPG exhibited the highest diagnostic performance for predicting CSPH, with an AUC of 0.88 (95% CI: 0.80, 0.95). In addition, the AUCs for other noninvasive tests, including transient elastography (n = 30), CT-based portal pressure score (n = 85), AST-to–alanine aminotransferase ratio (n = 100), portal diameter (n = 100), fibrosis index based on four factors (n = 99), and AST-to–platelet count index (n = 100) were 0.71 (95% CI: 0.48, 0.95), 0.60 (95% CI: 0.46, 0.74), 0.58 (95% CI: 0.43, 0.72), 0.58 (95% CI: 0.45, 0.70), 0.57 (95% CI: 0.43, 0.72), and 0.51 (95% CI: 0.36, 0.66), respectively (Fig 3, B). The performance of all noninvasive tests in the diagnosis of CSPH is summarized in Table 2.

Reproducibility of Virtual HPVG

Intraclass correlation coefficients for inter- and intraobserver agreement assessment were 0.877 and 0.959, respectively, suggesting the robust reproducibility of virtual HVPG.

Discussion

In this prospective multicenter study, we developed a CT angiography–based virtual HVPG from a three-dimensional hepatic portal vein model and computational fluid dynamics analysis and further validated its performance in the noninvasive diagnosis of portal hypertension in patients with cirrhosis. As expected, virtual HVPG showed good performance for CSPH detection in both training and validation cohorts, with AUCs of 0.83 and 0.89, respectively, and had significant agreement with invasive HVPG.

Because transient elastography (FibroScan) was recommended by the Baveno VI Consensus Workshop to identify CSPH (4,16), we further evaluated the performance of transient elastography in this study. According to our results, the performance of liver stiffness measured with transient elastography was just fair in our study (AUC for CSPH, 0.71 [95% CI: 0.48, 0.95]), likely because of the limited sample size and wider-ranging causes of cirrhosis compared with previous studies (16). Due to the increasing relevance of extrahepatic factors in portal hypertension progression, HVPG cannot be reliably estimated by means of liver stiffness in severe portal hypertension (6,7,17). Therefore, we suggest that virtual HVPG could serve as an auxiliary parameter for liver stiffness, especially in patients with obesity, liver necrotic inflammation, or severe ascites.

Another CT-based model, namely the CT-based portal pressure score, was proposed by Iranmanesh and colleagues (13,18) and showed promising results for diagnosing CSPH in patients with hepatocellular carcinoma, with an AUC of 0.911 (95% CI: 0.847, 0.975). However, this model showed insufficient performance in hepatitis B virus–related cirrhosis, with an AUC of 0.57 (95% CI: 0.42%, 79%) (17). Thus, we must be aware that the cause of cirrhosis may have an influence on the performance of a diagnosis method.

Virtual HVPG is a noninvasive approach that combines individual anatomic characteristics and hemodynamic changes of hepatic-portal veins, which allows direct simulation of invasive HVPG that imaging-based models and serum markers fail to do (12–15). In addition, virtual HVPG shows a robust reproducibility and is available for repeated applications in routine clinical practice. The reported rule-in and rule-out cutoff values for identifying CSPH could help make decisions on whether to pursue further treatment easier and quicker. More important, it could help identify patients who could safely avoid invasive HVPG procedures. Virtual HVPG may also be helpful in evaluating drug therapeutic efficacy and intervention outcome, which requires the repeated monitoring of HVPG changes.

Our study had some limitations. First, virtual HVPG interpretation is relatively time consuming (about 2.5 hours per case). Second, the CT angiography procedure for virtual HVPG should be further personalized. Finally, the number of participants without CSPH was low in our study, and virtual HVPG should be further validated in rigorously designed studies with more patients with mild portal hypertension and well-defined causes.
In conclusion, we developed and prospectively validated the accuracy of a computational model of virtual HVPG that showed significant correlation with invasive HVPG. Virtual HVPG also showed good performance in the noninvasive diagnosis of CSPH in cirrhosis. It has the potential of dramatically increasing the availability of this important information if routinely calculated in patients with compensated chronic liver disease.

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