Virtual Hepatic Venous Pressure Gradient with CT:
Ready for Prime Time?

Ashkan A. Malayeri, MD

From the Department of Radiology, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115. Received October 10, 2018; accepted October 11. Address correspondence to the author (e-mail: amalayeri@bwh.harvard.edu).

Conflicts of interest are listed at the end of this article.
See also the article by Qi et al in this issue.

Portal hypertension is the main culprit for severe complications of cirrhosis, including hepatic encephalopathy, ascites, and gastroesophageal variceal bleeding (1). The pathophysiology is increased resistance at the level of hepatic sinusoids secondary to fibrosis and architectural distortion. Hepatic venous pressure gradient (HVPG) measurement by means of catheterization of the right hepatic vein, a well-established method of estimating portal venous pressure, is calculated by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure (1). An HVPG of 10 mm Hg or greater is considered “clinically significant portal hypertension” (CSPH) (2) and is a criterion used to predict clinical outcomes in patients with portal hypertension. For example, in a large prospective study with a median follow-up of 51 months, HVPG was a better predictor of clinical outcomes in patients with portal hypertension than were other clinical variables, including the model for end-stage liver disease, or MELD, score and serum albumin concentration (3). HVPG also plays an important role in the evaluation of response to treatment. In a recent meta-analysis, the risk of variceal bleeding was significantly reduced when HVPG decreased at least 20% from that at baseline or was less than 12 mm Hg (4). Findings from these and other studies have led multiple professional societies to endorse HVPG as the reference standard for diagnosing and monitoring treatment response in patients with portal hypertension (1,2). However, HVPG measurement has not become routine practice in the treatment of patients with portal hypertension due to the cost, perceived risks, and limited availability. Therefore, the need for an alternative noninvasive method to measure HVPG has been a research focus for the past 2 decades.

In this issue of Radiology, Qi and colleagues (5) report on the development and validation of a novel noninvasive method of HVPG measurement based on multiphase contrast agent–enhanced CT. Building on prior experience (6), they designed a prospective, multicenter clinical study, using Doppler US and contrast-enhanced CT of the liver in the arterial, portal, and hepatic venous phases for virtual measurement of HVPG (virtual HVPG). All patients in the training and validation sets underwent conventional HVPG measurement, Doppler US, and liver biopsy. The training set consisted of 29 participants who were recruited from a single center. Two computational methods were applied to the manually reconstructed three-dimensional model of the portal-hepatic venous system. The first method, finite element analysis, measures the distribution of the field variables such as pressure or displacement in small elements of a three-dimensional model. The second method, computational fluid dynamics, uses mathematical models to define the interactions of fluid with adjacent structures. In this study, these two methods were combined in a simulation system that also included the main portal vein velocity obtained from venous Doppler US to estimate the pressure across the reconstructed three-dimensional model of the portal-hepatic venous system.

To determine the robustness of their model, Qi and colleagues (5) set out to validate the performance of virtual HVPG in a separate group of 79 participants from two other centers. The performance of virtual HVPG in the training set for the prediction of CSPH was impressive, with an area under the receiver operating characteristic curve of 0.83, compared with 0.89 in the validation cohort. When considering all the participants in the cohort, virtual HVPG outperformed all other six noninvasive methods for the diagnosis of CSPH: transient elastography (FibroScan; Echosens, Paris, France), CT-based portal pressure score (calculated as follows: 17.37 + 4.91 · In [liver/spleen volume ratio] + 3.8 [if perihepatic ascites is present]), aspartate aminotransferase-to–alanine aminotransferase ratio, portal vein diameter, fibrosis index based on four factors (age, aspartate aminotransferase level, alanine aminotransferase level, and platelet count), and aspartate aminotransferase-to–platelet count ratio index. Importantly, there was a statistically significant, albeit moderate, correlation between virtual HVPG and invasive HVPG ($R = 0.61, P < .001$).

The findings of Qi et al may have a considerable effect on the noninvasive diagnosis of patients with portal hypertension. As of now, the most widely accepted noninvasive imaging method for the detection of CSPH is transient elastography—FibroScan (2)—with a reported pooled sensitivity of 87.5% and specificity of 85.3% for the diagnosis of CSPH in at least one meta-analysis (7). In the current study, virtual HVPG outperformed transient elastography in the diagnosis of CSPH in a small subset of 30 patients. This may have been related to the makeup of the cohort and the fact that transient elastography has a worse correlation between US-derived stiffness indexes and HVPG in patients at more advanced stages of cirrhosis, as shown by Reiberger et al (8). Virtual HVPG may prove to have higher diagnostic efficacy than transient elastography in patients with more advanced cirrhosis.
Can virtual HVPG be used to screen for CSPH in patients with cirrhosis? The answer is not easy; the correlation between virtual HVPG and invasive HVPG was only moderate in strength (R = 0.61). When Qi et al used cutoff values to rule in and rule out participants with CSPH with 90% sensitivity and specificity, only 64% of participants were correctly classified; 26% were deemed to have indeterminate results and required further testing. Can virtual HVPG be used in the follow-up of patients with portal hypertension? The short answer is that we do not know. Qi et al reported excellent inter- and intraobserver reproducibility of the image analysis; however, the reproducibility of the results for patients who undergo different CT examinations at two separate time points and the correlation with the repeated HVPG is not known.

A limitation of the study is that the cohorts were skewed toward participants with higher HVPG (mean ± standard deviation: 17.1 mm Hg ± 8.8). This may explain some of the unexpected results, such as lower performance of transient elastography in the diagnosis of CSPH, because transient elastography may not perform as robustly in patients with advanced liver fibrosis (8,9). In addition, a relatively small number of patients without CSPH can potentially lead to a lower power of the test to detect patients without CSPH. Another limitation of the study was the different baseline characteristics between the training and validation sets. Although the virtual HVPG model was developed in a group of participants with a more advanced stage of the disease, with only 3.4% of participants in the training cohort having Child-Pugh class A disease, the validation was performed in a group of participants who were less affected by the disease, with 82.2% having class A disease. One may assume that the resistance at the level of the sinusoids, based on which the model was developed, was significantly higher within the training group compared with the validation group. Finally, there are technical limitations with the test that can potentially affect the clinical implementation. At present, it takes approximately 2.5 hours to perform the analysis, 1.5 hours of which is the manual processing time.

There are compelling data that support the use of contrast-enhanced CT as a screening method for esophageal varices, with a pooled sensitivity and specificity for identifying esophageal varices of 0.89 and 0.72, suggesting that CT could potentially replace endoscopy (10). There may be even more value in virtual HVPG when combined with morphologic data from three-phase CT, for example in the detection of clinically relevant gastroesophageal varices, because variceal bleeding is the most common cause of death in patients with CSPH.

In conclusion, the development of noninvasive methods of measuring HVPG is an exciting field of research. This study is a promising step forward in the validation of intravenous contrast-enhanced CT–based virtual HVPG as a surrogate for diagnosing and monitoring portal hypertension. Virtual HVPG could improve clinical outcomes for patients through earlier detection of CSPH and more accurate response evaluations. I encourage Dr Qi and colleagues to evaluate their methods in a larger and more diverse cohort of patients so that virtual HVPG may one day become a reality in the clinic.

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References