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HepQuant SHUNT Detects Portal Hypertension in Early Stages of Clinically Compensated Chronic Liver Disease

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Physicians use portal pressure measurements in clinical practice and research but the methods are invasive, can cause complications, and are resource intensive.[1–3] Herein we describe preliminary findings of the minimally invasive HepQuant-SHUNT test in the diagnosis of portal hypertension in precirrhotic and compensated cirrhotic patients.

Methods

The Institutional Review Boards of the University of Colorado Denver and National Institute of Diabetes and Digestive and Kidney Diseases approved the studies. Wedged hepatic venous pressure, hepatic venous pressure gradient (HVPG), liver histology, and HepQuant SHUNT were measured in 20 adults with clinically stable chronic liver disease. Direct portal pressure (dPP) via percutaneous transhepatic cannulation of the portal vein and HepQuant SHUNT were measured in 28 adults with clinically stable chronic hepatitis C virus. Transplant recipients and patients with prior transjugular intrahepatic portosystemic shunt or surgical portal-systemic shunts were excluded.

HepQuant SHUNT quantifies hepatic acinar function and effective sinusoidal perfusion by simultaneously measuring the flow-dependent clearance of cholate from both portal and systemic circulations. Test outputs include hepatic filtration rates, portal-systemic spillover of d4-cholate (SHUNT%), d4-cholate at 60 minutes (STAT), and a Disease Severity Index (DSI).[4,5] Tolerability was determined by a 10-point Likert scale.

Wedged hepatic venous pressure and dPP were considered equivalent, portal hypertension was defined as HVPG >5 mm Hg or dPP >17 mm Hg, and clinically significant portal hypertension was an HVPG >10 mm Hg or dPP >22 mm Hg. Relationships of the HepQuant-SHUNT test to portal pressure were evaluated by linear and logistic regression and receiver-operator characteristic curves (C statistic) analyses.

Results

Subject Characteristics

The mean age was 55 years, 26 were female, 40 were White, and 9 were Hispanic. Body mass index ranged from 21.1 to 40.6 kg/m^2. Etiologies included hepatitis C virus (n = 32), nonalcoholic steatohepatitis (n = 9), autoimmune hepatitis (n = 3), Wilson disease, Budd-Chiari syndrome, primary sclerosing cholangitis, and cryptogenic liver disease. Twenty six had F0–F2 (n = 26), F3 (n = 5), and F4 (n = 17). Blood tests, Model for End-Stage Liver Disease, and Child-Turcotte-Pugh scores indicated precirrhotic or compensated liver disease. The Budd-Chiari case and patients with venovenous collaterals (n = 5) were excluded leaving 42 study subjects.

HepQuant SHUNT Results

Half the subjects (n = 21) had portal hypertension, 7 without cirrhosis, which was clinically significant in 13. The wedged hepatic venous pressure or dPP was 24.3 ± 4.4 mm Hg in those with portal hypertension compared with 12.3 ± 3.9 mm Hg in those without portal hypertension. Patients with portal hypertension had lower hepatic filtration rates and greater SHUNT%, DSI, and STAT (Supplementary Table 1). In univariate analysis, SHUNT%, portal hepatic filtration rates, DSI, and STAT correlated significantly with portal pressure. In multivariate analysis, a model including SHUNT% ($P = .0028$), liver stiffness measurements (LSM; $P = .0002$), and platelet count ($P = .0106$) (result for model, $r = .86$, $P < .0001$) correlated best with portal pressure.

Supplementary Tables 2 and 3 show the receiver operating characteristic curves and univariate analyses in the diagnosis of portal hypertension and clinically significant portal hypertension. The most informative individual test for both was SHUNT% with C = 0.922 (confidence interval, 0.796–0.982) and C = 0.859 (confidence interval, 0.717–0.947). In the 28 subjects with both dPP and LSM, diagnostic models of portal hypertension including LSM with either SHUNT%, DSI, or STAT had C statistics of 0.954, 0.959, and 0.938, respectively. A model with SHUNT%, LSM, and FIB-4 had nearly perfect diagnostic performance for portal hypertension (C = 0.979), comparing favorably with the component tests

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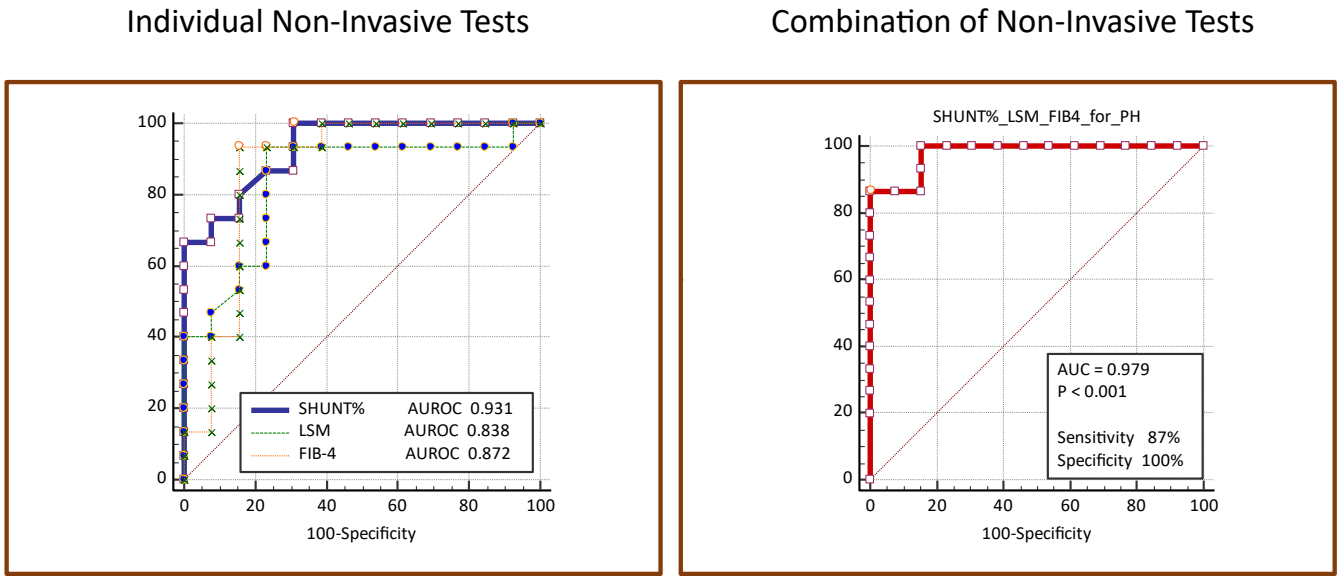

Figure 1. ROCs for diagnosis of portal hypertension are shown for the 28 patients that had dPP and LSM. (*Left*) Individual ROCs for SHUNT%, quantifying portal-systemic shunting, LSM (a surrogate for liver fibrosis), and FIB-4 (a surrogate for liver injury and fibrosis). The functional measurement, SHUNT%, had the highest C statistic (C = 0.931). The *open circles* are cutpoints based on Youden-J statistic. (*Right*) ROC for the noninvasive model with near perfect diagnostic performance based on the combination of SHUNT%, LSM, and FIB-4. AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; PH, portal hypertension; FIB-4, fibrosis-4 score; ROC, receiver operating characteristic curve; SHUNT, calculated from the ratio of clearances of 13C-cholate to d4-cholate.CJ

(SHUNT, C = 0.931; LSM, C = 0.838; FIB-4, C = 0.872) (Figure 1).

The self-reported patient survey (Supplementary Table 4) confirmed high tolerability of the SHUNT test and willingness to undergo repeat testing.

Discussion

This study demonstrates the HepQuant-SHUNT test detects portal hypertension and clinically significant portal hypertension with similar reliability to invasive pressure measurements. A key finding was the ability of the SHUNT test to detect portal hypertension early in the course of disease not only in clinically stable compensated cirrhosis but also in patients without cirrhosis. The clinical importance of this finding is reinforced by a recent report showing more than 80% of patients with precirrhotic primary biliary cholangitis had portal hypertension and of those more than 30% had clinically significant portal hypertension.[6] The improved tolerability and acceptability of the SHUNT test, compared with HVPG, strongly supports a role for the SHUNT test in the early detection of portal hypertension.

In contrast to current noninvasive tests that use surrogates for increased portal pressure,[7] the SHUNT test directly measures the liver's function, dual circulation, and portal systemic shunting.[4,5,8] In comparison with HVPG, the SHUNT test is simple, minimally invasive, highly tolerated, and patients are readily willing to undergo repeat testing.

We conclude that the noninvasive HepQuant-SHUNT test, either alone or in combination with other noninvasive tests, warrants further evaluation as an alternative to the existing invasive methods for assessing portal pressure and portal hypertension.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.04.030.

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Reprint requests
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Conflicts of interest
These authors disclose the following: Steve M. Helmke, Gregory T. Everson, and University of Colorado Denver have several issued and pending patents relevant to the analytical procedures used in this study. Ohad Etzion is a member of HepQuant LLC Scientific Advisory Board. Steve M. Helmke is an employee of HepQuant LLC. Gregory T. Everson is an equity owner/member and CEO and CMO of HepQuant LLC. The other authors disclose no conflicts.

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Supplementary Table 1. HepQuant SHUNT Test Results by Portal Hypertension and Cirrhosis

	Portal hypertension			Normal portal pressure			
	N	Mean	SD	N	Mean	SD	*P* value[a]
Systemic HFR, *mL/min/kg*	21	4.11	1.15	21	4.64	1.06	.13
Portal HFR, *mL/min/kg*	21	11.26	3.95	21	18.17	4.98	< .0001
SHUNT%	21	38.7	9.8	21	26.2	4.6	< .0001
DSI (rtuln)	21	20.38	4.64	21	15.06	3.64	.0002
STAT	21	1.04	0.51	21	0.61	0.26	.0012
	Cirrhosis			No cirrhosis			
Systemic HFR, *mL/min/kg*	14	3.86	0.90	28	4.64	1.15	.0317
Portal HFR, *mL/min/kg*	14	10.14	3.67	28	17.00	5.07	< .0001
SHUNT%	14	40.8	10.5	28	28.3	6.4	< .0001
DSI (rtuln)	14	21.67	4.62	28	15.74	3.79	.0001
STAT	14	1.15	0.52	28	0.66	0.32	.0005

DSI, disease severity index; HFR, hepatic filtration rate; rtuln; SD, standard deviation; SHUNT%, the percentage of orally administered d4-cholate escaping first-pass hepatic extraction from portal inflow; STAT, weight-adjusted (d4-cholate) at 60 minutes.
[a]*P* values were determined by 2-sided, unpaired Student *t* tests.

Supplementary Table 2. ROCs for Portal Hypertension

	AUROC	CI	*P* value	Youden J	Criterion	Se	Sp
SHUNT%	0.922	0.796–0.982	< .0001	0.6667	>0.295	85.71	80.95
Port HFR	0.862	0.720–0.949	< .0001	0.6667	≤13.41	76.19	90.48
DSI	0.819	0.669–0.920	< .0001	0.619	>19.04	66.67	95.24
STAT	0.78	0.626–0.893	.0001	0.4286	>0.8	61.9	80.95
Fibrosis stage	0.859	0.717–0.947	< .0001	0.6667	>1	90.48	76.19
LSM	0.838	0.651–0.949	< .0001	0.7026	>9.5	93.33	76.92
APRI	0.782	0.628–0.895	.0002	0.5714	>1.04	71.43	85.71
FIB4	0.84	0.694–0.935	< .0001	0.7143	>2.49	80.95	90.48
CTP	0.571	0.410–0.723	NS	0.1429	>5	14.29	100
MELD	0.759	0.602–0.877	.0004	0.4762	>7	61.9	85.71
MELD Na	0.705	0.545–0.836	.012	0.4286	>7	71.43	71.43

APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CTP, Child-Turcotte-Pugh score; DSI, disease severity index; FIB4, fibrosis-4 score; Fibrosis stage, Brunt-Kleiner or METAVIR stage of liver biopsies; LSM, liver stiffness measurement by transient elastography; MELD, Model for End-Stage Liver Disease score; Na, sodium; NS, not significant; p, level of significance versus AUROC of 0.5; Port HFR, portal hepatic filtration rate; ROC, receiver operating characteristic curve; STAT, d4-cholate concentration at 60 minutes; Se, sensitivity; SHUNT %, the percentage of orally administered d4-cholate escaping first-pass hepatic extraction from portal inflow; Sp, specificity

Supplementary Table 3. ROCs for Clinically Significant Portal Hypertension

	AUROC	CI	*P* value	Youden J	Criterion	Se	Sp
SHUNT%	0.859	0.717–0.947	< .0001	0.6658	>0.35	76.92	89.66
Port HFR	0.748	0.590–0.869	.0031	0.3846	≤7.96	38.46	100
DSI	0.698	0.537–0.830	.0339	0.3846	>22.32	38.46	100
STAT	0.668	0.506–0.806	NS	0.3581	>1.07	46.15	89.66
Fibrosis stage	0.761	0.605–0.879	.0032	0.5199	>3	69.23	82.76
LSM	0.804	0.611–0.929	.0058	0.6199	>15.3	77.78	84.21
APRI	0.666	0.504–0.804	NS	0.382	>1.040462428	69.23	68.97
FIB4	0.744	0.586–0.866	.0046	0.4589	>2.49	76.92	68.97
CTP	0.561	0.400–0.714	NS	0.1194	>5	15.38	96.55
MELD	0.714	0.553–0.842	.0181	0.3395	>7	61.54	72.41
MELD Na	0.688	0.527–0.822	.0308	0.2785	>7	69.23	58.62

APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CTP, Child-Turcotte-Pugh score; DSI, disease severity index; FIB4, fibrosis-4 score; Fibrosis stage, Brunt-Kleiner or METAVIR stage of liver biopsies; LSM, liver stiffness measurement by transient elastography; MELD, Model for End-Stage Liver Disease score; Na, sodium; NS, not significant; p, level of significance versus AUROC of 0.5; Port HFR, portal hepatic filtration rate; ROC, receiver operating characteristic curve; STAT, d4-cholate concentration at 60 minutes; Se, sensitivity; SHUNT %, the percentage of orally administered d4-cholate escaping first-pass hepatic extraction from portal inflow; Sp, specificity

Supplementary Table 4. Survey of Tolerability of the HepQuant SHUNT Test and HVPG Procedure

	HepQuant SHUNT test			HVPG procedure			
	N	Mean	SD	N	Mean	SD	*P* value[a]
Pain (0 none, 10 maximum)	20	0.35	0.59	20	3.90	3.14	< .0001
Discomfort (0 none, 10 maximum)	20	0.50	0.89	20	4.20	2.89	< .0001
Interference with daily life (0 none, 10 very)	20	1.25	1.41	20	5.90	3.14	< .0001
Overall experience (0 worst, 10 best)	20	9.60	0.68	20	6.20	2.73	< .0001
Willingness to repeat (0 never, 10 very)	20	9.85	0.37	20	5.65	3.59	< .0001
Time commitment for testing, *h*		Subjects, n			Subjects, n		
0–3		18			4		
3–6		2			5		
6–9		0			3		
>9		0			8		

HVPG, hepatic venous pressure gradient; SD, standard deviation.
[a]*P* values were determined by 2-sided paired Student *t* tests.