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Abstract #375

Non-invasive Measurement of the Portal Circulation Using Cholates Quantifies Disease Severity in Primary Sclerosing Cholangitis

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Introduction Primary Sclerosing Cholangitis (PSC) preferentially causes portal fibrosis, altering the portal circulation, and ultimately leading to portal hypertension (PHTN). Liver biopsy is risky and characterized by significant sampling variability, laboratory measurements only detect late stages of disease, and Hepatic Venous Pressure Gradient is invasive and expensive. Accurate assessment of disease severity in PSC represents an unmet medical need. In this study we defined the reproducibility of three tests, Hepatic Filtration Rate (HFR), portal-systemic shunt fraction (SHUNT), and a single point cholate concentration (STAT), and their relationship to clinical features.

Methods PSC patients (n=38) were recruited from our Hepatology Clinic and underwent history, physical exam, and standard lab assessment. PSC severity ranged from CTP 4-10, MELD 6-20, and Mayo PSC model scores of -0.67 to 2.37. PHTN features were defined as presence of splenomegaly or varices. Decompensation was defined by history of variceal bleed, hepatic encephalopathy, or ascites. HFR (mL/min/kg) was defined as the clearance of 40 mg orally administered cholate-2,2,4,4-d4. SHUNT (%) was calculated from the ratio of HFR to the clearance of 20 mg intravenously administered cholate-24-^{13}C. STAT (μM) was the serum level of oral cholate after 60 min. Prior studies established test values in healthy controls. Reproducibility was assessed by duplicate testing (n=37) within 1 month and defined by the intra-class correlation (ICC). The relationships of HFR, SHUNT, and STAT to clinical features were analyzed by t-tests and ROC curves.

Results The ICC in PSC patients was 0.90 for HFR, 0.92 for SHUNT, and 0.94 for STAT indicating excellent reproducibility. PSC patients had significantly lower HFR, increased SHUNT, and higher STAT relative to controls (table). Patients with PHTN, especially those with varices, were significantly more functionally impaired than those without PHTN. Within the PHTN group, those with varices had significantly worse function than those without varices. ROC analysis demonstrated the potential of HFR, SHUNT, and STAT to identify PSC patients with PHTN or varices. The small number of decompensated patients with either ascites or variceal bleed (n=4) had extremely poor function (HFR 3.1±0.4, SHUNT 71±5, STAT 3.7±0.5).

Conclusions HFR, SHUNT, and STAT reproducibly quantify hepatic function in PSC. These tests differentiate PSC patients from healthy controls, and distinguish those with advanced disease from well compensated patients. HFR, SHUNT, and STAT may be useful in measuring and tracking disease severity in PSC.

	N	HFR (mL/min/kg)			P-value	c-stat	SHUNT (%)			P-value	c-stat	STAT(uM)			P-value	c-stat
Healthy Controls	32	30.1	±	1.7			19	±	1			0.4	±	0.02		
PSC Patients	38	14.2	±	1.1	<0.001		44	±	3	<0.001		1.1	±	0.2	<0.001	
PSC w/o PHTN	22	16.9	±	1.1			36	±	3			0.7	±	0.1		
PSC w PHTN	16	10.5	±	1.7	0.003	0.76	55	±	5	<0.001	0.83	1.6	±	0.4	0.006	0.71
PHTN w/o Varices	5	18.5	±	2.2			38	±	5			0.4	±	0.1		
PHTN w Varices	11	6.9	±	1.1	<0.001	0.94	63	±	5	0.005	0.93	2.2	±	0.4	0.015	0.94

HFR, SHUNT, and STAT test values are the mean+/-SEM. P-values from t-tests are PSC vs Controls, PSC w PHTN vs PSC w/o PHTN, and PHTN w Varices vs PHTN w/o Varices. C-statistics from ROC curves were calculated for PHTN vs all PSC or for Varices vs all PSC.