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Quantitative Tests of Liver Function Measure Hepatic Improvement after Sustained Virologic Response: Results from the HALT-C Trial

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Abstract

Aim—We determined the relationships of quantitative tests of liver function (QLFTs) to virologic responses to peginterferon (PEG) ± ribavirin (RBV) in patients with chronic hepatitis C and used serial QLFTs to define the spectrum of hepatic improvement after sustained virologic response (SVR).

Methods—Participants (N=232) were enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, had failed prior therapy, had bridging fibrosis or cirrhosis, and were retreated with PEG/RBV. All 232 patients had baseline QLFTs; 24 patients with SVR and 68 nonresponders had serial QLFTs. Lidocaine, [24-^{13}C]cholate, galactose, and ^{99m}Tc-sulfur colloid were administered intravenously; [2,2,4,2-^{2}H]cholate, [1-^{13}C]methionine, caffeine, and antipyrine were administered orally. Clearances (Cl), breath $^{13}CO_2$, monoethylglycylxylidide (MEGX), perfused hepatic mass (PHM), and liver volume were measured.

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Results—Rates of SVR were 18 to 26% in patients with good function by QLFTs but <6% in patients with poor function. Hepatic metabolism, measured by caffeine k_{elim} (P=0.02), antipyrine k_{elim} (P=0.05), and antipyrine Cl (P=0.02), and the portal circulation, measured by cholate Cl_{oral} (P=0.0002) and cholate shunt (P=0.0003), and PHM (P=0.03), improved after SVR.

Conclusions—Hepatic dysfunction impairs the virologic response to PEG/RBV. SVR improves hepatic metabolism, the portal circulation, and perfused hepatic mass.

Keywords

Cholate clearance; Cholate Shunt; SPECT liver-spleen scan; Methionine breath test; Caffeine elimination; Antipyrine clearance; Galactose elimination capacity; MEGX; Hepatitis C; Fibrosis; Cirrhosis; Sustained virologic response; Peginterferon; Ribavirin

Introduction

More than 2.7 million Americans are infected with the hepatitis C virus, 8,000 to 10,000 die annually due to complications of chronic hepatitis C, and the number of Americans infected for 20 or more years will not peak until 2015 (1-4). As a consequence, the number of patients who will decompensate, advance to hepatocellular carcinoma, and need liver transplantation will increase (5-10).

Rates of sustained virologic response (SVR) with peginterferon/ribavirin treatment of chronic hepatitis C (11-14) are lower in patients with advanced hepatic fibrosis or cirrhosis (15-17). In the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, patients with chronic hepatitis C with bridging fibrosis or compensated cirrhosis (Child-Turcotte-Pugh ≤6) and prior nonresponse were retreated with peginterferon/ribavirin (18). In this cohort, SVR after retreatment declined stepwise, from 23% to 9%, with increasing severity of disease, as defined by liver histology and platelet count (15). Because quantitative tests of liver function (QLFTs) measure the continuum of liver impairment, we reasoned that the relationship between SVR and disease severity might be better defined by QLFTs.

SVR reduces hepatic inflammation, fibrosis (19,20), and rates of clinical outcomes (21-25). The principal clinical manifestations of advanced chronic hepatitis C, such as varices, ascites, and encephalopathy, are linked to portal hypertension and impaired hepatic function. Beneficial effects of SVR on hepatic fibrosis and clinical outcomes are likely mediated through improvements in the portal circulation and hepatic function – improvements which could be detected by QLFTs but not by standard laboratory tests.

In this study of retreatment of patients with chronic hepatitis C with peginterferon/ribavirin, we utilized a battery of QLFTs to measure hepatic metabolism, hepatic and portal blood flow, portal-systemic shunting, and hepatic parenchymal mass. One goal was to define the relationships between severity of hepatic impairment, as measured by QLFTs, and virologic responses. In addition, we used serial QLFTs to define hepatic improvement after achievement of sustained virologic response.

Patients and Methods

This study was approved by the Data Safety and Monitoring Board, appointed for this purpose by the National Institute of Diabetes and Digestive and Kidney Disease; the US Food and Drug Administration, and the Institutional Review Boards and General Clinical Research Centers of the participating centers. The study was conducted according to the principals of the Declaration of Helsinki regarding the proper procedures for human

research. Patients participating in this study had Child-Turcotte-Pugh scores ≤6 and lacked history of variceal hemorrhage, ascites, encephalopathy, spontaneous bacterial peritonitis, hepatocellular carcinoma, or biochemical deterioration. Participants signed individual informed consents for both the main HALT-C trial and the QLFT ancillary study.

The design of the main HALT-C Trial and procedures used in this QLFT study have been previously described (18,26,27). Hepatic microsomal function was measured from the elimination or metabolism of caffeine, antipyrine, and lidocaine-MEGX. Hepatic mitochondrial function was assessed using the methionine breath test. Hepatic blood flow was measured from the elimination of intravenously administered galactose and cholate. Portal inflow and portal-systemic shunt were measured from the clearance of orally administered cholate and cholate shunt. Perfused hepatic mass and liver volume were measured from SPECT liver-spleen scans. Baseline histology was staged according to Ishak – fibrosis scores from 2 to 4, and cirrhosis scores 5 or 6 (28). VR20 was defined as a negative HCV RNA at week 20 of peginterferon/ribavirin therapy, and SVR by negative HCV RNA six months or more after the end of treatment. Nonresponders had a positive HCV RNA at week 20 of treatment. Patients achieving SVR had 48 weeks of treatment and nonresponders were treated for only 24 weeks. Dose reduction or discontinuation was defined as <80 percent of target doses for both peginterferon and ribavirin in the first 20 weeks.

Study Groups

A total of 1145 patients were enrolled and retreated with peginterferon/ribavirin during the Lead-In Phase of the main HALT-C Trial (18). Two hundred thirty two of these 1145 underwent QLFTs prior to retreatment. The outcome of these 232 patients is shown in Figure 1. Relationships between hepatic function measured at baseline by QLFTs and subsequent achievement of VR20 or SVR were evaluated in these 232 patients.

The change in hepatic function was assessed by serial studies and the impact of SVR on hepatic function was evaluated by comparison of two subgroups – patients who achieved SVR, and nonresponders undergoing long-term observation without treatment during the randomized phase of the HALT-C Trial (18). Seventy three of the 232 patients experienced VR20 (31 percent) and 32 achieved SVR (14 percent). Followup QLFT studies were performed in 24 of the 32 patients who achieved SVR. One hundred forty nine patients remained HCV RNA positive at week 20 of treatment. One hundred forty two were randomized, 65 to continued treatment and 77 to long term observation. Sixty-eight of the 77 had followup QLFT studies (Figure 1).

Forty one patients relapsed, 32 were randomized - 18 to continued treatment and 14 to long term observation (Figure 1). Twelve of the 14 patients in long-term observation underwent followup QLFT studies. The low sample size of relapsers undergoing serial QLFTs (N=12) precluded statistical comparison with the other groups.

For patients achieving SVR, the median time between baseline and followup studies was 28.8 months and the median time between end of treatment and followup studies was 19.7 months. For nonresponders, the median time between baseline and followup studies was 24.8 months and the median time between end of treatment and followup studies was 18.8 months.

Statistical Considerations

All analyses were performed with Statistical Analysis System version 9.1.3 (29,30). Patient characteristics were defined by mean, standard deviation and frequency. Differences between groups were assessed with Fisher's Exact and t-tests. Distributions of QLFT test

results for the 232 Lead-In patients were defined by quartiles of results. Associations of QLFTs with VR20 and SVR, cirrhosis, and dose reduction were evaluated by Fisher's Exact and Mantel-Haenszel Chi Square tests. Univariate associations between VR20 and SVR and QLFTs were assessed using logistic regression. The independent associations of QLFTs with VR20 were evaluated in models including QLFTs, cirrhosis, and other baseline characteristics (African American race, HCV genotype, and HCV RNA level). The small number of patients achieving SVR precluded meaningful multivariate analyses of models of SVR. For the paired studies, the changes between baseline and followup test results and differences between study groups (patients achieving SVR versus nonresponders) were analyzed by paired t-tests and two-sample t-tests.

Results

Characteristics of the Study Populations

We compared selected characteristics of the 232 study patients to the remaining 913 HALT-C patients (Table 1). Study patients had lower albumin (Mean±SD: 3.76±0.4 vs 3.92±0.4, p<0.0001) and prothrombin time (INR) (1.02±0.10 vs 1.04±0.11, p=0.01), fewer were African American (10 vs. 17 percent, p=0.01), and they had higher prevalences of esophageal varices (35 vs. 22 percent, p<0.0001) and splenomegaly (37 vs. 29 percent, p=0.04). Key characteristics of the study patients were mean age 49.8 years, 75 percent male, mean body mass index (BMI) 29.5, 40 percent cirrhosis, 92% HCV genotype 1, and mean HCV RNA 6.41 ± 0.50 $\log_{10}$ IU/ml. Mean (± SD) laboratory values were within the normal range: bilirubin 0.7 ± 0.4 mg/dl, INR 1.02 ± 0.10, albumin 3.76 ± 0.40 g/dl, and platelet count 169,000 ± 66,000 platelets/μl.

We also compared the baseline characteristics of the 24 patients achieving SVR to those of the 68 nonresponders (Table 2). Patients achieving SVR were non-African American (P=0.03), had lower prevalence of cirrhosis (P=0.03), were less often infected with HCV genotype 1 (P=0.004), and were more likely to have received >80% of doses of PEG/RBV (P=0.01). Nonresponders had lower albumin (P=0.01) and hemoglobin (P=0.01). Patients with relapse had a prevalence of cirrhosis (58%) similar to nonresponders.

Spectrum of Hepatic Impairment at Baseline

The spectrum of baseline hepatic functional impairment was categorized by quartiles ranging from best to worst function for each QLFT. Boundaries for the quartiles are given in Table 3. We have previously reported that the prevalences of both cirrhosis and varices increase significantly from best to worst quartiles of QLFTs (26).

QLFT Quartiles and Rates of VR20 and SVR

One hundred ten patients (47.4%) had greater than two $\log_{10}$ drop in HCV RNA by week 12 and 73 patients (32%) achieved VR20. Rates of VR20 declined as function worsened (Figure 2, Panel A). VR20 ranged from 37 to 51 percent in the quartiles of patients with the best function but was only 10 to 20 percent in the quartiles with the worst function. Rates of SVR also declined as function worsened (Figure 2, Panel B). SVR rates ranged from 18 to 26 percent in quartiles of patients with the best function, but were ≤6 percent in quartiles with worst function.

Multivariate analyses of Relationships of QLFTs to VR20

Because cirrhosis (P=0.02) and platelet count (P=0.009) correlated with VR20, we examined models including QLFTs with cirrhosis or platelet count to predict VR20. After adjustment for cirrhosis, QLFTs with an independent relationship to VR20 were caffeine k_{elim} (P=0.03), antipyrine k_{elim} (P=0.004), antipyrine Cl (P=0.005), cholate Cl_{oral} (P=0.04), cholate shunt

(P=0.02), and perfused hepatic mass (P=0.007). Similar results were obtained after adjustment for platelet count.

QLFTs with an independent relationship to VR20 after adjustment for cirrhosis, HCV genotype, HCV RNA level, and African American race, were caffeine k_{elim} (P=0.09), antipyrine k_{elim} (P=0.03), antipyrine Cl (P=0.03), $MEGX_{15min}$ (P=0.01), $MEGX_{30min}$ (P=0.003), cholate Cl_{oral} (P=0.09), cholate shunt (P=0.03), and perfused hepatic mass (P=0.002).

Impact of Virologic Response on Hepatic Function

Hepatic Metabolic Function—In patients achieving SVR, caffeine k_{elim} increased by 38 percent (P=0.02), antipyrine k_{elim} increased by 25 percent (P=0.05), and antipyrine Cl increased by 31 percent (P=0.02). $MEGX_{15min}$ increased by 30 percent and $MEGX_{30min}$ increased by 9 percent but these changes were not statistically significant (Table 4). Nonresponders had lower baseline values and did not demonstrate any significant changes for these tests between baseline and followup studies. The improvements in caffeine k_{elim}, antipyrine k_{elim}, and antipyrine clearance in patients achieving SVR were significant when compared to the changes in these tests in nonresponders (P=0.01, 0.05, and 0.02, respectively).

Hepatic Blood Flow—Cholate k_{elim}, cholate Cl_{iv}, and galactose elimination capacity, did not change with SVR (Table 4). In nonresponders there was significant decline in cholate k_{elim} (P=0.03) and cholate Cl_{iv} (P=0.0001). In comparison to patients achieving SVR, only the decline in cholate k_{elim} in nonresponders remained significant (P=0.04).

Portal blood flow and shunt—Cholate Cl_{oral} and cholate shunt improved after SVR (Figure 3) (Table 4). Cholate Cl_{oral} increased from 1371±329 ml/min to 1808±497 ml/min, an increase of 32% (P<0.0002). Cholate shunt decreased from 32±8 to 24±8 percent, a reduction in shunt of 25 percent (P<0.0003). Nonresponders had lower cholate Cl_{oral} and higher cholate shunt at baseline compared to patients who achieved SVR. In nonresponders, mean cholate Cl_{oral} decreased (P=0.03) but cholate shunt did not change. The improvements in patients achieving SVR were highly significant when compared to the changes in these tests in nonresponders (SVR vs NR: cholate Cl_{oral} P<0.0001 and cholate shunt P=0.003).

Relapsers had lower cholate Cl_{oral} (1086±605 ml/min) and higher cholate shunt (44±20%) at baseline compared to patients who achieved SVR. In followup studies mean cholate Cl_{oral} increased (1280±689 ml/min, P=0.10) and cholate shunt decreased (32±11%, P=0.03).

Perfused Hepatic Mass and Liver Volume—Perfused hepatic mass increased and liver volume did not change after SVR (Table 4). Perfused hepatic mass was 102±4 at baseline and 104±3 after SVR (P=0.03) and liver volume was 1635±358 mL at baseline and 1592±320 mL after SVR (P=NS). Nonresponders had lower perfused hepatic mass but similar liver volumes at baseline compared to patients who achieved SVR. There was no significant change in either perfused hepatic mass or liver volume in nonresponders. The increase in perfused hepatic mass in patients achieving SVR was significant when compared to the lack of change in perfused hepatic mass of nonresponders (P=0.04).

Overall, SVR was associated with increased hepatic metabolic activity, enhanced clearance from the portal circulation, reduced portal-systemic shunt, and increased perfused hepatic mass without change in liver volume (Figure 4).

Standard Laboratory Tests—At baseline means (±SD) of standard laboratory tests were in the normal range in all groups. Platelet count was the only standard laboratory test that improved (increased by 12%) with SVR (P=0.01). Although means of platelet counts remained within the normal range, the increase in the platelet counts of patients who achieved SVR was highly significant when compared to the decrease in the platelet counts of nonresponders (P=0.0001).

Discussion

Our study is unique in that it represents the most comprehensive assessment of the relationships of hepatic function to virologic clearance in response to peginterferon/ribavirin therapy in a large, extensively characterized cohort of patients with chronic hepatitis C. We quantified hepatic metabolism, the portal circulation, perfused hepatic mass, and liver volume using a battery of QLFTs. We found that QLFTs performed at baseline prior to treatment were independent predictors of virologic response to peginterferon/ribavirin. In addition, using serial QLFTs we demonstrated that patients who achieved SVR experienced significant improvement in hepatic metabolism, portal blood flow, and portal-systemic shunt – improvements that were not detected by standard clinical or laboratory assessment.

QLFTs and Virologic Responses

Patients with chronic hepatitis C and cirrhosis respond poorly to antiviral therapy (11-17). In a previous analysis of the HALT-C cohort we categorized the severity of liver disease based upon a combination of liver histology and platelet count (15). We reported that SVR declined from 23% in patients with noncirrhotic fibrosis and >125,000 platelets/μL to a low of 9% in patients with cirrhosis and <125,000 platelets/μL. Multivariate analyses indicated that cirrhosis was a key independent pre-treatment variable predicting virologic response (15).

QLFTs assess the spectrum of liver impairment (27,31-35). QLFTs are performed by administering various test compounds and measuring their clearance from the circulation or metabolism using samples of blood, saliva, or breath, or radiologic imaging. The rate of decline in concentration of the originally administered compound or the appearance of its metabolite is proportional to hepatic metabolic function, blood flow, or shunting. We have reported that our battery of QLFTs, used in this subgroup of HALT-C patients, correlates with cirrhosis, stage of fibrosis, varices, and size of varices (26,27).

As noted above, virologic response to antiviral therapy worsens with clinical disease severity (15). In the current study, we found that virologic response declined as QLFTs assessing hepatic metabolism, portal blood flow, portal-systemic shunt, and perfused hepatic mass worsened. In the case of SVR, patients with the worst hepatic impairment on baseline QLFTs had rates of SVR of only 0 to 6 percent. In multivariate analysis QLFTs remained significant predictors of virologic response after controlling for other known predictors, including histologically-defined cirrhosis and platelet count. Additional studies would be needed to determine whether QLFTs could be used, a priori, to identify nonresponders and potentially exclude them from treatment.

Improvement in Hepatic Metabolism, Portal Blood Flow, and Portal-Systemic Shunt after SVR

The goal of therapy for chronic hepatitis C is to halt disease progression. Chronic hepatitis C progresses slowly, typically over decades of a person's life, and many years of followup are required to demonstrate a benefit of SVR on clinical complications or patient survival. Because long-term followup is often impractical, standard laboratory tests, clinical scores

(MELD, CTP), and liver histology are typically used as surrogates for measuring benefits of treatment. Although SVR reduces both hepatic inflammation and hepatic fibrosis (19,20), serial assessment using liver biopsies is invasive, associated with significant risk, and prone to sampling error.

In our patients, bilirubin, INR, and albumin were essentially normal at baseline and did not improve with SVR – emphasizing the lack of sensitivity of these tests. Platelet count increased with SVR, but mean platelet count was in the normal range both at baseline and in followup after SVR – emphasizing the limited utility of platelet count as a marker for hepatic dysfunction or portal hypertension.

Impaired hepatic function and portal hypertension account for the major manifestations and clinical complications of liver disease. Because our battery of QLFTs measured both hepatic metabolism and the portal circulation we reasoned that these QLFTs could be useful surrogates to identify clinically relevant, beneficial effects of SVR. Indeed, we found that SVR was associated with improvements in hepatic metabolism, portal blood flow, and portal-systemic shunt. These physiologic improvements after SVR would, at least theoretically, reduce risk for clinical decompensation or complications. Absence of clinical complications in the long-term follow-up of patients with advanced fibrosis or cirrhosis after SVR supports this interpretation (23).

SVR improved the clearance or metabolism of caffeine, antipyrine, and lidocaine-MEGX by 9 to 38% without affecting liver volume. Caffeine is metabolized by an array of hepatic microsomal cytochrome P450 (CYP) enzymes (1A1, 1A2, 2A6, 2E1, 3A) (32), antipyrine by CYP 1A2, 2B6, 2C8, 3C9, and 2C18 (33), and lidocaine-MEGX primarily by CYP 3A4 (33,34). Ocker and colleagues used a different battery of QLFTs (aminopyrine breath test, galactose elimination capacity, sorbitol clearance, and indocyanine green clearance) to study 50 patients with chronic hepatitis C at baseline and 3 months after initiation of interferon-based therapy (35). They observed improvement in hepatic metabolism in the patients who were HCV RNA negative. We interpret these results to indicate that HCV, or inflammation and fibrosis related to HCV, interferes with the hepatic metabolism of a wide range of drugs, medications, and xenobiotics – and that these effects are reversible with effective therapy.

SVR improves portal blood flow and perfused hepatic mass, as measured by cholate Cl_{oral} and SPECT liver-spleen scan, and reduces portal-systemic shunting, as measured by cholate shunt. Reduction of hepatic inflammation and fibrosis after SVR may lower hepatic resistance to portal inflow, reduce portal pressure, and diminish portal-systemic shunt. This interpretation is further supported by our observation of a 12% increase in platelet count, and the study by Rincon and colleagues - which demonstrated a 26 percent reduction in hepatic venous pressure gradient in a subset of patients who achieved SVR (36). We observed 32 percent increase in cholate Cl_{oral} and 25 percent decrease in cholate shunt. Globally, these results suggest that SVR reverses portal hypertension, improves portal inflow, and diminishes portal-systemic shunting.

Which QLFTs carry the most promise and could potentially be applied in clinical practice? The analyses in this paper and our prior publication (26) suggest that oral cholate clearance, cholate shunt, and perfused hepatic mass by SPECT liver-spleen scan may be superior to tests of metabolism. Clearly breath tests are simplest to administer, but in our studies the methionine breath test was inferior to cholate tests or SPECT analysis. Performance of the cholate test is complex – but, we have now defined the minimal model for cholate clearance and shunt (27), reducing patient discomfort and time commitment, and limiting laboratory analytical time. SPECT requires use of radioactivity and time commitment of patient and

personnel in the nuclear medicine department – but SPECT is readily available in most hospitals.

In conclusion, QLFTs, especially those that assess the portal circulation and perfused hepatic mass, are helpful in predicting likelihood of response to retreatment with peginterferon/ribavirin in patients with chronic hepatitis C. In addition, these same QLFTs detect improvements related to virologic response that are not shown by standard laboratory tests or clinical evaluation. Although our study was limited to previous nonresponders to interferon-based therapy who also had advanced fibrosis, broader application of QLFTs in the selection of patients for treatment and assessment of the impact of therapy may be warranted.

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List of Abbreviations

SVR	sustained virologic response 6 months after the end of treatment
PEG	peginterferon
RBV	ribavirin
QLFTs	quantitative liver function tests
HALT-C	Hepatitis C Antiviral Long-term Treatment against Cirrhosis
Cl	clearance
PHM	perfused hepatic mass
VR20	viral clearance at week 20 of treatment
HCV	hepatitis C virus
GCRC	General Clinical Research Center
SD	standard deviation
INR	prothrombin time international normalized ratio

BMI	body mass index
IND	Investigational New Drug
MEGX	monoethylglycine xylidide
MBT	methionine breath test
SPECT-LSS	single photon emission computed tomographic liver spleen scan
$\mathbf{k_{elim}}$	elimination rate constant
GEC	galactose elimination capacity
CTP	Child-Turcotte-Pugh
AST	aspartate aminotransferase
ALT	alanine aminotransferase

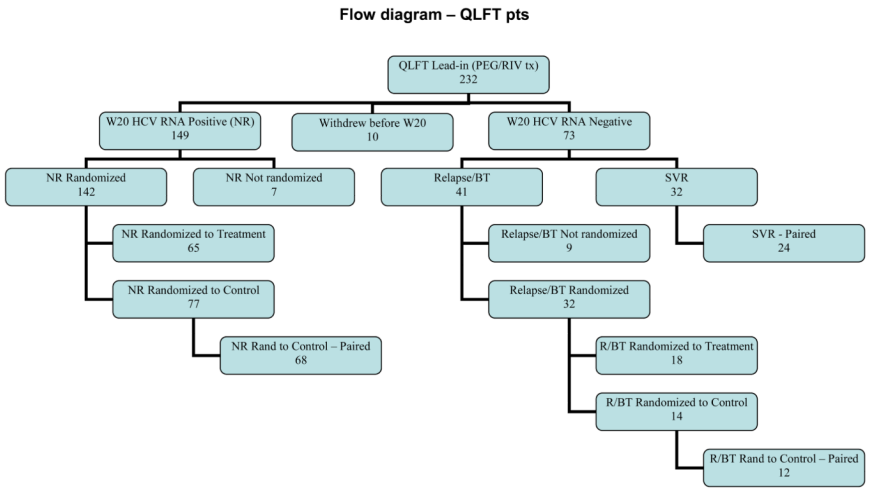

Figure 1.

Flow diagram of final outcome of the 232 patients enrolled in the Lead-In Phase of HALT-C and who participated in the QLFT study. The baseline QLFT studies of all 232 patients were used to define the associations of QLFTs with virologic responses. To examine the effect of SVR on hepatic function, we compared serial studies of QLFTs in 24 patients achieving SVR to 68 nonresponders and 12 relapsers randomized to long-term followup without additional treatment.

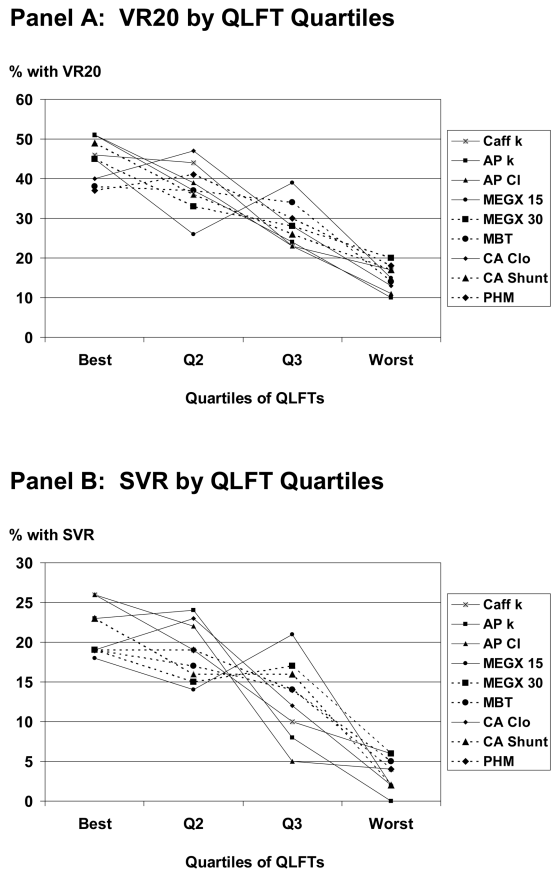

Figure 2.

Panel A: Rates of VR20 declined as caffeine k_{elim} (P=0.0001), antipyrine k_{elim} (P=0.0002), antipyrine Cl (P=0.0002), cholate Cl_{oral} (P=0.0003), cholate shunt (P=0.0001), $MEGX_{15min}$ (P=0.01), $MEGX_{30min}$ (P=0.005), methionine breath test (P=0.02), and perfused hepatic mass (P=0.01) worsened. Panel B: Rates of SVR declined as caffeine k_{elim} (P=0.002), antipyrine k_{elim} (P=0.002), antipyrine Cl (P=0.002), cholate Cl_{oral} (P=0.003), cholate shunt (P=0.002), methionine breath test (P=0.04), and perfused hepatic mass (P=0.01), $MEGX_{15min}$ (P=0.09), and $MEGX_{30min}$ (P=0.07) worsened. Cholate k_{elim}, cholate Cl_{iv}, and galactose elimination capacity, which primarily assess total hepatic blood flow, failed to correlate with either VR20 or SVR (not shown). Abbreviations: Q, quartile; QLFT, quantitative test of liver function; Caff k, rate constant of elimination of caffeine; AP k, rate constant of elimination of antipyrine; AP Cl, clearance of antipyrine; MEGX 15, concentration of monoethylglycylxylidide 15 minutes after administration of lidocaine; MEGX 30, concentration of monoethylglycylxylidide 30 minutes after administration of lidocaine; CA Clo, clearance of orally administered [2,2,4,4-^{2}H] cholate; CA Shunt, cholate shunt; GEC, galactose elimination capacity; MBT, methionine breath test; PHM, perfused hepatic mass

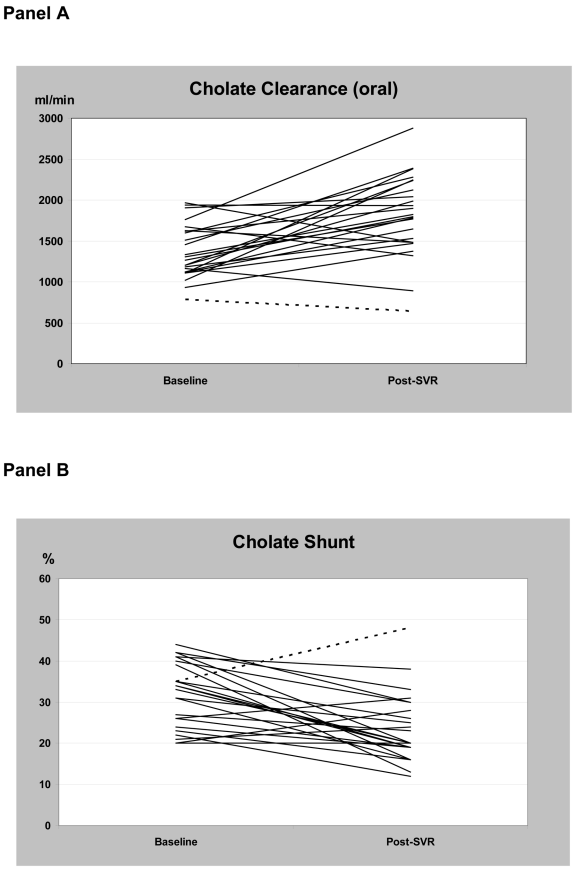

Figure 3.

SVR was associated with a 32% increase in cholate Cl_{oral} (Panel A), a measure of portal blood flow, and a 26% decrease in cholate shunt (Panel B), a measure of portal-systemic shunting. The dotted line represents one patient with increase in cholate shunt despite SVR – this patient also had the lowest cholate Cl_{oral} both at baseline and in followup.

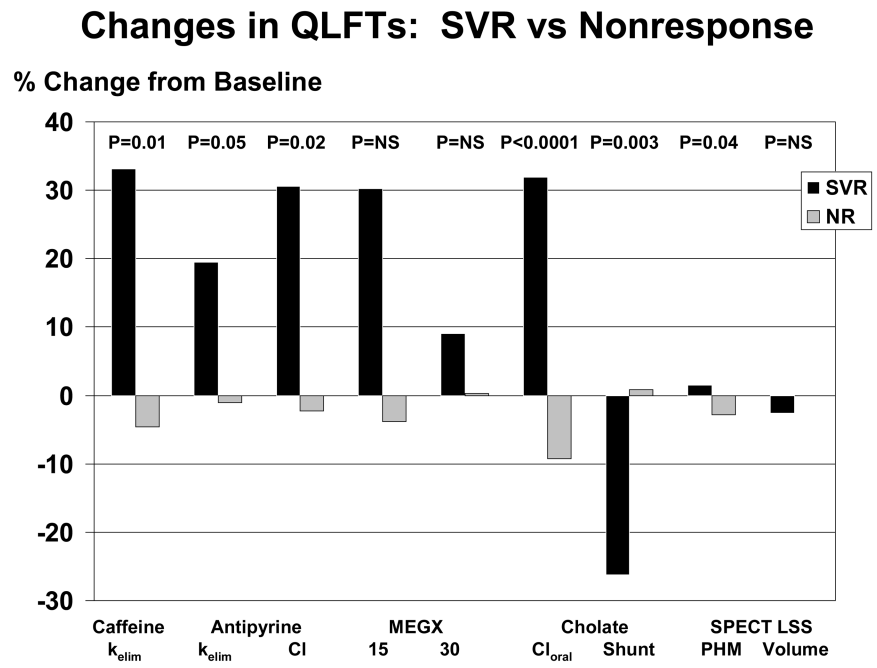

Figure 4.

The percentage change between baseline and the followup studies for QLFTs are shown. The black bars depict the changes after sustained virologic response (SVR) and grey bars show the changes in patients with nonresponse (NR). Compared to patients with nonresponse, patients experiencing SVR had significant improvements in caffeine and antipyrine elimination rates (k_{elim}), antipyrine clearance (Cl), clearance of orally administered cholate (Cl_{oral}), cholate shunt, and perfused hepatic mass (PHM).

Table 1

Characteristics of the 232 QLFT Study Subjects Compared to the Remaining 913 HALT-C Patients Treated with PEG/RBV

	QLFT N = 232		HALT-C N = 913		Fisher Exact or T-test p-value
	Mean or %	±SD	Mean or %	±SD	
Demographics					
Age	49.8	7.2	49.9	7.3	.78
BMI (kg/m^2)	29.5	4.9	29.8	5.6	.40
Male (%)	75%		71%		.25
African American (%)	10%		17%		**.01**
Disease Severity					
Cirrhosis (%)	40%		37%		.50
Esophageal varices (%)	35%		22%		**<0.0001**
Splenomegaly (%)	37%		29%		**.04**
HCV Characteristics					
Genotype 1 (%)	92%		88%		.16
HCV RNA ($\log_{10}$ IU/ml)	6.41	0.50	6.42	0.54	.78
Standard Laboratory Tests					
Bilirubin (mg/dl)	0.7	0.4	0.8	0.4	.07
Albumin (g/dl)	3.76	0.40	3.92	0.38	**<0.0001**
Prothrombin time (INR)	1.02	0.10	1.04	0.11	**.01**
Platelet Count (10^{-3}/μL)	169	66	169	64	.99
Treatment Outcomes					
SVR (%)	14%		16%		.42
> 80% PEG and RBV during the first 20 Weeks (%)	58%		51%		.09

Abbreviations: QLFT, quantitative liver function test; HALT-C, Hepatitis C Antiviral Long-Term Treatment to Prevent Cirrhosis Trial; SD, standard deviation; PEG/RBV, peginterferon/ribavirin; BMI, body mass index; SVR, sustained virologic response.

Table 2

Baseline Characteristics of Sustained Responders and Nonresponders who underwent Serial QLFT Studies

	SVR N = 24		NR N = 68		Fisher Exact or T-test p-value
	Mean or %	±SD	Mean or %	±SD	
Demographics					
Age	49.4	6.0	50.1	7.0	0.65
BMI (kg/m^2)	28.4	4.7	30.7	5.3	0.07
Male (%)	83%		68%		0.19
African American (%)	0%		17.7%		**0.03**
Disease Severity					
Cirrhotic (%)	20.8%		48.5%		**0.03**
Esophageal varices (%)	N/A		35%		N/A
Splenomegaly (%)	29%		50%		0.15
HCV Characteristics					
Genotype 1 (%)	75%		97%		**0.004**
HCV RNA ($\log_{10}$ IU/ml)	6.47	0.50	6.31	0.51	0.19
Standard Laboratory Tests					
Hemoglobin (g/dL)	15.9	1.2	15.0	1.6	**0.01**
WBC ($10^{-3}/\mu L$)	5.9	1.9	5.4	1.9	0.27
Platelet Count($10^{-3}/\mu L$)	177	59	160	71	0.31
Bilirubin (mg/dl)	0.74	0.37	0.73	0.32	0.92
Albumin (g/dl)	3.90	0.35	3.67	0.36	**0.01**
Prothrombin time (INR)	1.01	0.09	1.04	0.12	0.21
Creatinine (mg/dL)	0.81	0.17	0.78	0.15	0.35
Treatment Course					
> 80% PEG and RBV during the first 20 Weeks (%)	83%		54%		**0.01**

Abbreviations: QLFT, quantitative liver function test; PEG/RBV, peginterferon/ribavirin; SVR, sustained virologic responder; NR, nonresponder; SD, standard deviation; BMI, body mass index; WBC, white blood cell count.

Table 3

Boundaries for Quartiles of Quantitative Tests of Liver Function

	Best Function	25th Percentile	50th Percentile	75th Percentile	Worst Function
Tests of Metabolism					
Caffeine k_{elim} (h^{-1})	0.28	0.09	0.06	0.04	0.01
Antipyrine k_{elim} (h^{-1})	0.09	0.04	0.03	0.03	0.01
Antipyrine Cl (ml/min)	79	39	29	21	12
$MEGX_{15min}$ (ng/ml)	70	25	16	8	0
$MEGX_{30min}$ (ng/ml)	98	30	20	13	1
MBT	308	84	65	45	6
Tests of Total Hepatic Blood Flow					
Cholate k_{elim} (min^{-1})	0.27	0.11	0.09	0.08	0.02
Cholate Cl_{iv} (ml/min)	903	459	367	305	155
GEC (mg/kg·min)	10.1	5.6	4.7	4.0	2.1
Tests of Portal Circulation					
Cholate Cl_{oral} (ml/min)	3036	1463	1113	771	255
Cholate Shunt (%)	10	27	36	48	91
Tests of Hepatic Parenchyma					
Perfused Hepatic Mass	114	105	100	94	70
Liver Volume (ml)	2690	1867	1593	1343	769

Abbreviations: Cl, clearance; oral, orally administered; iv, intravenously administered; k, rate constant of elimination; MEGX, monoethylglycine xylidide; GEC, galactose elimination capacity.

Table 4

Test Results in Patients Achieving SVR versus Nonresponders

	SVR N	SVR QLFT at Baseline X±SD	Δ QLFT in SVR M24-Base	P value For Δ QLFT in SVR	NR N	NR QLFT at Baseline X±SD	Δ QLFT in NR M24-Base	P value For Δ QLFT in NR	P value ΔQLFT SVR vs NR
Standard Laboratory Tests									
Bilirubin (mg/dL)	24	0.74 ±0.37	0.07 ±0.27	0.21	68	0.73 plusmn;0.32	0.35 ±0.54	**<0.0001**	**0.002**
Albumin (g/dL)	24	3.90 ±0.35	0.03 ±0.37	0.70	68	3.67 ±0.36	−0.12± 0.40	**0.02**	0.11
INR	24	1.01 ±0.09	0.05 ±0.09	0.01[a]	68	1.04 ±0.12	0.07 ±0.09	**<0.0001**	0.43
Platelets (10^{-3}/μL)	24	177 ±59	22 ±40	**0.01**	68	160 ±71	−13 ±33	**0.003**	**0.0001**
Tests of Metabolism									
Caffeine k_{elim} (h^{-1})	22	0.08 ±0.04	0.03 ±0.05	**0.02**	59	0.05 ±0.04	0 ±0.03	0.57	**0.01**
Antipyrine k_{elim} (h^{-1})	17	0.04 ±0.02	0.01 ±0.02	**0.05**	40	0.03 ±0.01	0 ±0.01	0.87	**0.05**
Antipyrine Cl (ml/min)	17	39.6 ±13.6	12.1 ±19.6	**0.02**	39	28.9 ±13.7	−0.6 ±8.2	0.63	**0.02**
$MEGX_{15min}$ (ng/ml)	24	19.4 ±12.9	5.9 ±18.7	0.14	64	16.2 ±11.7	−0.6 plusmn;13.4	0.71	0.13
$MEGX_{30min}$ (ng/ml)	24	23.0 ±8.8	2.1 ±14.1	0.48	63	20.8 ±11.8	0.1 ±14.0	0.97	0.55
Tests of Total Hepatic Blood Flow									
Cholate k_{elim} (min^{-1})	24	0.09 ±0.02	0.01 ±0.03	0.25	67	0.09 +0.03	−0.01 ±0.03	**0.03**	**0.04**
Cholate Cl_{iv} (ml/min)	24	427 ±115	−33 ±107	0.14	67	394 +125	−60 ±121	**0.0001**	0.33
GEC (mg/kg·min)	23	4.88 ±1.10	0.05 ±0.84	0.80	66	4.75 +1.22	−0.16 ±0.88	0.15	0.34
Tests of Portal Circulation									
Cholate Cl_{oral} (ml/min)	24	1371 ±329	437 ±494	**0.0002**	67	1107 ±551	−102 ±377	**0.03**	**<0.0001**
Cholate Shunt (%)	24	32 ±8	−8 ±10	**0.0003**	67	41 ±15	0 ±16	0.85	**0.003**
Tests of Hepatic Parenchyma									
Perfused Hepatic Mass	20	102.3 ±4.1	1.6 ±3.1	0.03	65	96.3 ±9.0	−2.7 ±15.6	0.17	**0.04**
Liver Volume (ml)	20	1635 ±358	−42 ±178	0.30	65	1691 ±361	−55 ±318	0.17	0.82

[a] Although the change in INR was significant, the change was in the direction of worsening with SVR.

P values that are in bold typeface indicate significant change in the test from baseline or in the comparison of changes between patients achieving SVR and nonresponders. The gray shading identifies tests that improved significantly with SVR and were significant in the comparison of changes in the test between SVR and NR.

Abbreviations: Cl, clearance; oral, orally administered; iv, intravenously administered; k, rate constant of elimination; MEGX, monoethylglycine xylidide; GEC, galactose elimination capacity.