Non-Invasive Assessment of Fibrosis Using Color Doppler Ultrasound in Patients with Hepatitis C Virus in the Amazon Rainforest, Brazil

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Abstract. The purpose of this study was to correlate morphologic and hemodynamic Doppler ultrasound findings as indicators of the degree of inflammation and fibrosis and to diagnose chronic vital hepatitis complications and progression. A prospective, descriptive study of a case series was conducted that analyzed Doppler ultrasound images of the liver and portal system and used the portal vein congestion index, hepatic and splenic artery impedance indices, and the liver vascular index. Of 50 patients positive for antibodies against hepatitis C virus, morphologic changes highlighted increased hepatic parenchyma echogenicity in 24%, and increased gall bladder echogenicity and wall thickness in 4%. The most common hemodynamic changes observed were reduced flow velocity in the portal vein trunk in 26%, congestion index changes in 12%, liver vascular index changes in 16%, and splenic and hepatic artery impedance index changes in 14%. These indices were shown to be associated with alanine aminotransferase levels, which suggested that they are important liver damage indicators in the early phase of infection with hepatitis C virus.

INTRODUCTION

Hepatitis C is a disease caused by hepatitis C virus (HCV) and has a high potential for chronicity. Approximately 130–170 million persons worldwide are infected with the virus. Of these persons, approximately 350,000 have chronic liver disease.¹ The Brazilian Ministry of Health² estimates that approximately three 3 million inhabitants have chronic hepatitis.^{3,4} The prevalence of HCV infection in northern Brazil differs among the states: 3.7% in Acre, 0.32% in Amazonas, and 0.13% in Pará.^{5–7} Symptoms of chronic hepatitis C are mild, and in most cases, are non-existent or non-specific.^{3,4} Cirrhosis develops in approximately 20–30% of patients with chronic disease and liver cancer develops in 1–4%.^{4,8,9}

Ultrasonography is the method of choice for initial assessment of the liver.⁹ It shows high specificity and sensitivity for studying chronic liver diseases compared with anatomic and clinical changes,¹⁰ and shows 74–88% concordance for detecting hepatic cirrhosis.¹⁰ The advent of Doppler ultrasonography brought a non-invasive means of assessing hemodynamic changes secondary to chronic liver disease.¹¹ This kind of assessment makes it possible to detect whether the portal vein has reduced flow velocity and increased caliber, both of which are features of portal hypertension.^{11–14}

When pulsed Doppler ultrasound is used to examine the portal vein, a monophasic wave pattern is shown, with variations in velocity caused by respiration.^{9,15,16} The normal direction of flow in the portal vein is hepatopetal, with slight undulation and laminar, and variations that depend on respiratory dynamics.¹⁷ A value of 15 cm/sec is considered to be the best cut-off point in tests to detect portal hypertension, with high sensitivity and specificity of 88% and 96%, respectively.^{9,17,18}

The congestion index described by Moriyasu and others¹² has been used to diagnose cirrhosis and portal hypertension. It looks at the increase in the cross-sectional area of the portal vein and the reduction in velocity. The index is calcu-

lated from the ratio of the cross-sectional area of the portal vein (cm²) and the average flow velocity (cm/sec), with values ≤ 0.07 cm/sec considered normal.¹² The normal wave pattern of hepatic veins is triphasic.^{13,19} Pattern changes in Doppler ultrasound of the right hepatic vein in patients with non-alcoholic fatty liver disease may suggest reduced vascular compliance because of fat infiltration.²⁰

The hepatic artery shows increased resistance in chronic liver disease and cirrhosis.^{9,11} Normal values are ≤ 0.66 on the hepatic artery resistance index and ≤ 1.1 on the pulsatility index (PI).¹¹ This index (PI = peak systolic velocity – mean velocity/peak systolic velocity) and resistance index are increased in patients with cirrhosis.^{21,22} New indices have been introduced in an attempt to improve the diagnostic accuracy of the method. The liver vascular index is calculated from the ratio between the maximum portal vein velocity and the hepatic artery PI. A normal value on the liver vascular index for diagnosing cirrhosis and/or portal hypertension is ≥ 12 cm/sec, with 97% sensitivity and 93% specificity.¹⁸

Splenic hemodynamics plays an important role in patients with cirrhosis and portal hypertension. Splenic impedance is increased in hepatic cirrhosis and reflects portal resistance.¹¹ Doppler velocimetry indices are calculated within the parenchyma of the spleen, and values ≥ 0.63 for the resistance index and > 1.0 for the PI are considered indicative of disease.¹¹

The objective of this study was to correlate morphologic and hemodynamic findings of color Doppler ultrasound as indicators of the degree of inflammatory activity and fibrosis, establish early diagnoses in complications of hepatitis C, and monitor progression of cases already diagnosed.

MATERIALS AND METHODS

A consecutive sample of 50 patients with chronic hepatitis C was studied prospectively, during March–November 2007, from among spontaneous visitors to the Virology Outpatient Department of the Fundação de Medicina Tropical do Amazonas (Amazon Foundation of Tropical Medicine). The inclusion criteria were a diagnosis of chronic hepatitis C confirmed by the presence of antibodies against HVC and persistently increased aminotransferase levels for a minimum of six months. Patients with co-infections, those who were pregnant,

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TABLE 1

Risk factors of 50 patients assessed and their risk factors for infection with hepatitis C virus, Amazon rainforest, Brazil*

Risk factor	No. (n = 50)	%
Alcohol	31	62.0
Surgical or other risk process	29	58.0
Multiple sexual partners	29	58.0
Previous personal history of hepatitis	13	26.0
Previous personal history of STD	12	24.0
Personal history of blood transfusion	11	22.0
Use of injectable drugs	6	12.0
Family history of HCV	4	8.2
Tattoos and piercings	4	8.0
Familial liver cancer	4	8.0

* STD = sexually transmitted disease; HCV = hepatitis C virus.

those given a diagnosis of an autoimmune disease, or those using immunosuppressant drugs were excluded.

A color Doppler ultrasound assessment was carried out by a single observer. Assessments of the liver, gall bladder, and spleen were conducted and considered the size, surface, internal echogenicity of the parenchyma, borders, presence of focal and/or diffuse changes, diameter of the portal veins, gall bladder wall thickness, and internal composition of the veins. Blood flow in the hepatic and splenic vessels was measured in fasting patients with normal respiration. The volume of the sample was regulated for a narrower diameter than that of the vessels, a corrected angle of 60 degrees, and spectral Doppler traces lasting 4–6 cycles. The shape of the Doppler wave and direction of blood flow in the trunk of the portal vein, hepatic veins, hepatic arteries and splenic arteries were analyzed. The liver congestion index, splenic and hepatic artery impedance indices, and liver vascular index were used.

A computerized system of recording ultrasound and Doppler was developed for inputting information. Statistical analysis was conducted by using the Statistical Package for the Social Sciences, SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL). Continuous variables were represented as mean values,

standard deviations, and median values. Analysis of variance was used to compare mean values. Categorical variables were assessed by relative frequency (%) using Fisher's test and Mann-Whitney's test. The significance tests were two-tailed, and a significance level of 0.05 ($\alpha = 5\%$) was adopted.

This study was approved by the Research Ethics Committee of the Fundação de Medicina Tropical do Amazonas (no. 665–2005–FMTAM).

RESULTS

The mean $\pm$ SD age of the patients studied was 47.9 ± 11.68 years; 74% (37 of 50) were male. The predominant risk factors for HCV infection in the population studied are shown in Table 1. Biochemical profiles of patients showed high levels of alanine aminotransferase (ALT), but mean albumin levels, prothrombin times, and platelet counts were within normal ranges, which suggested a condition of compensated chronic viral hepatic disease.

Results of the morphologic evaluation were that 24% (12 of 50) showed increased echogenicity of the liver compatible with steatosis. Of these patients, 58.3% (7 of 12) had grade I steatosis, 16.7% (7 of 12) had grade II steatosis, and 25% (3 of 12) had grade III steatosis (Figure 1). Spleen volume and index were increased in 14% (7 of 50) of the patients (Figure 2). Increased echogenicity and thickness of the gall bladder walls were seen in 4% (2 of 50) of the patients (Figure 3). The only gall bladder complication seen was gallstones in 8% (4 of 50) of the patients (Figure 4). A patent paraumbilical vein was seen in 2% (1 of 50) of the patients (Figure 5). In 2% (1 of 50) of the patients, hepatofugal flow in the trunk of the portal vein was seen. The mean maximum velocity in the trunk of the portal vein was 16.18 cm/sec and the mean flow volume was 55.78 L/min (Figure 6).

Among the morphologic changes, we found a statistically significant positive association between disease time (length

FIGURE 1. Ultrasound scan of a patient with hepatitis C, showing raised echogenicity of the hepatic parenchyma.

FIGURE 2. Ultrasound scan of a patient with hepatitis C, showing increased spleen volume.

of time the patient has had the disease), splenomegaly, and diameter of the trunk of the portal vein and mean serum levels of ALT (Table 2). Echogenicity of the hepatic parenchyma showed a statistically significant association with high ALT levels ($P < 0.01$, by analysis of variance) (Table 3). We also found a significant association between hemodynamic changes and increased serum levels of ALT (mean velocity in the trunk of the portal vein, $P < 0.008$; congestion index, $P < 0.001$; liver vascular index, $P < 0.008$; hepatic artery impedance index, $P < 0.002$; and splenic artery impedance index, $P < 0.002$) (Table 2).

DISCUSSION

This study assessed the main morphologic and hemodynamic parameters of the liver in patients with a diagnosis of HCV infection and clinical signs and laboratory results indicative of compensated chronic viral hepatic disease that were investigated by color Doppler ultrasound examination of the

liver and portal system. The profile of the patients assessed can be characterized as men approximately 47 years of age who were alcohol dependant and had a clinical diagnosis, supported by laboratory test results, of chronic parenchymal liver disease of viral origin.

Araújo²³ investigated the clinical-epidemiologic profile and geographic distribution of known cases of hepatitis B and C in Manaus, Brazil, reported similar results with a predominance of male patients approximately 40 years of age. The strongly associated risk factors were a previous history of surgery and blood transfusion. Regarding sexual transmission, the study showed that heterosexual relationships were as much of a risk factor as homosexual relationships.²³ Infection by the use of injectable drugs did not appear to be among the main means of transmission in the population studied, in contrast to studies conducted on populations in the urban centers of southern and southeastern Brazil, in which use of illegal drugs appeared to be the main source of infection.²³ These differences might be explained by cultural factors. Regarding a history of previous surgery, this factor raises an important question about the quality of hospital services.

Paraná and others studied the prevalence of HCV infection among health care workers in the western Amazon region of Brazil in Rio Branco, and identified a high prevalence (3.7%) most commonly in persons more than 40 years of age; genotypes 1 and 3 were most common.⁵ Torres and others showed an association between HCV RNA and age of blood donors in the Amazon. This finding suggested that in northern Brazil, older persons with longer exposure were more likely to be infected with HCV genotypes 1 and 3.⁶ De Oliveira-Filho and others reported that the prevalence of HCV among blood donors in the Pará State was low (0.13%), but more positive cases detected with a higher frequency of genotype 1.⁷ Our study showed a similar epidemiologic profile in northern Brazil, which indicated the need for public health programs for prevention and control of HCV infection.

Changes were seen in the echogenicity of the surface of the hepatic parenchyma in 12% of cases, and hepatic steatosis was predominantly classified as grade I (58.3%), which indicated a significant association between hepatic steatosis and infection by HCV. The increased echogenicity of the hepatic

FIGURE 3. Ultrasound scan of a patient with hepatitis C, showing increased echogenicity and wall thickness in the gall bladder.

FIGURE 4. Ultrasound scan of a patient with hepatitis C, showing increased echogenicity and wall thickness in the gall bladder containing stones.

parenchyma showed a statistically significant association with increased serum levels of ALT ($P < 0.01$).

Mathiensen and others in their study on increased liver echogenicity through ultrasound examination in asymptomatic patients with slightly or moderately increased levels of aminotransferases observed that assessing liver echogenicity is more valuable in detecting or ruling out moderate or high fat infiltration in these patients.²⁴ D'Onofrio and others investigated the accuracy of ultrasonography in detecting liver fibrosis in patients with chronic viral hepatitis, assessed liver borders, parenchymal echogenicity, caliber of the portal vein, and diameter of the spleen, and compared them with histopathologic results.²⁵ They reported a good correlation, which confirmed that ultrasonography is a reliable method in establishing a diagnosis of hepatic steatosis.^{13,14,25,26}

In our study, the thickness and echogenicity of the gall bladder walls increased in 4% of cases. Zhong and others observed that this increased thickness and echogenicity of the gall bladder walls is related to the progression of fibrosis in patients with chronic viral hepatitis.²⁷

In the population studied, a patent paraumbilical vein was seen in 2% of cases, which can be explained by a recent diagnosis. Most patients were asymptomatic. De Oliveira and others in a study on permeable paraumbilical veins also observed patent, permeable paraumbilical veins, and concluded that this finding is an indicator of disease severity, corresponding to portosystemic collateral circulation, and that its presence, together with hepatofugal flow, is associated with portal hypertension.²⁸

In our study, increased caliber of the trunk of the portal vein showed a statistically significant association with a disease time of more than six months ($P < 0.02$) and increased serum levels of ALT ($P < 0.03$), which suggested that these findings are indicators of inflammatory activity and fibrosis. Two other studies on use of ultrasonography in the diagnosis portal hypertension reported a statistically significant association between portal vein caliber and the onset of portal hypertension.^{29,30}

The hemodynamic changes assessed did not show any association with sex, age, or disease time. This finding confirms that

FIGURE 5. Ultrasound scan of a patient with hepatitis C, showing collateral circulation in a paraumbilical vein. **A**, Mapping with color Doppler highlights the presence of a flow and its direction in a patent paraumbilical vein. **B**, Two-dimensional image of a patent paraumbilical vein.

FIGURE 6. Ultrasound scan of a patient with hepatitis C, showing the diameter of the portal vein and spectral Doppler of the trunk of portal vein. **A**, Diameter of the trunk of the portal vein with an increased caliber of 17 mm. **B**, Spectral Doppler of the trunk of the portal vein highlighting reduced flow velocity (9.7 cm/sec). **C**, Volume of flow in the trunk of the portal vein maintained (90.95 L/min).

the population studied was homogenous in terms of demography and clinical progression of HCV infection. However, we found a statistically significant association between high serum ALT levels and the mean velocity of the trunk of the portal vein ($P < 0.008$), congestion index ($P < 0.001$), liver vascular index ($P < 0.008$), and hepatic and splenic artery PIs (both $P < 0.002$), which suggested that these findings are important indicators of liver damage in the early phase of the disease.

A reduced mean flow velocity in the trunk of the portal vein suggests increased parenchymal resistance that might be caused by fibrosis.^{18,31,32} It was also shown that flow velocity in the trunk of the portal vein returns to normal after interferon therapy.³³ In our study, the mean flow velocity in the trunk of the portal vein decreased in 12% of the cases. The portal vein congestion index showed changes in 12% of cases, and a congestion index of over 0.07 cm/sec is associated with chronic liver disease, as shown by Moriyasu and others¹² in their study on the portal vein congestion index.¹⁵

The liver vascular index decreased to < 12 cm/sec in 16% of cases, and is related to the increased flow resistance. Iawo and others in a study on the value of Doppler ultrasonography of the portal vein and hepatic artery in diagnosing cirrhosis and

portal hypertension reported a sensitivity of 97% and a specificity of 93% as diagnostic indicators of liver cirrhosis and portal hypertension.¹⁸ The hepatic artery impedance indices were increased in 14% of cases, which showed that these factors were indicators of chronic viral liver disease, as confirmed by Haktanir and others.³⁴

Piscaglia and others investigated the influence of hepatic fibrosis on the hepatic artery resistance index in patients with chronic viral hepatitis.¹¹ They observed that an increase in this index is affected by the degree of fibrosis, and reported a significant difference between patients with chronic liver pathologies and cirrhosis, and healthy persons.¹¹

In our study, we observed changes in waveform pattern in the hepatic veins in 4% of cases and the presence of splenomegaly in 14%. O'Donohue and others³⁵ studied the diagnostic value of Doppler ultrasonography of the portal and hepatic vessels and spleen in chronic viral liver disease. They observed that increased spleen size and changes in hepatic vein waveforms are predictors of chronic viral liver disease and cirrhosis.³⁵⁻³⁷

The advent of color Doppler ultrasonography used in investigating chronic viral liver pathologic changes was a

TABLE 2
Analysis of patients infected with hepatitis C virus who underwent color Doppler ultrasound scan, outpatient clinic at Fundação de Medicina Tropical Heitor Vieira Dourado, Manaus, Brazil*

Characteristic	TPV-Tamax				CI			LVI			II-HA			II-SA			DPV			SI		
	No.	Mean	SD	P	Mean	SD	P	Mean	SD	P	Mean	SD	P	Mean	SD	P	No.	Mean	SD	Mean	SD	P
Sex	36	16.2	2.4	0.584	0.042	0.018	0.226	17.27	3.62	0.589	0.95	0.108	0.287	0.9	0.88	0.039	36	8.9	1.21	41.39	12.1	0.042
M	14	15.7	3.1		0.051	0.035		16.58	5.08		1	0.218		0.97	0.14		14	9.3	1.86	55.93	37.5	
F				0.382			0.057			0.233			0.708			0.832						0.194
Time (months)	32	16.3	2.4		0.039	0.025		17.59	4.1		0.93	0.173		0.91	0.113		32	8.5	1.35	48.62	26	
≤ 6	18	15.6	3		0.053	0.02		16.16	3.88		0.98	0.088		0.92	0.104		18	9.8	1.16	39.83	14.6	
> 6							0.001			0.008			0.002			0.002						0.009
ALT	17	15.62	3	0.008	15.62	3		16.36	4.53		0.98	0.144		0.94	0.86		17	9.1	1.31	45.59	20.9	
Changed	29	16.8	1.8		16.8	1.8		18.2	2.62		0.93	0.037		0.88	0.08		29	8.7	1.19	41	11.3	
Normal																						

* TPV-Tamax = mean velocity of the trunk of the portal vein; CI = congestion index; LVI = liver vascular index; II-HA = impedance index of the hepatic artery; II-SA = impedance index of the splenic artery; DPV = diameter of the trunk of the portal vein; SI = spleen index; Time = time with disease; ALT = alanine aminotransferase.

TABLE 3

Characteristics of patients with infected with hepatitis C virus who underwent color Doppler ultrasound scan that showed echogenicity of hepatic parenchyma, outpatient clinic at Fundação de Medicina Tropical Heitor Vieira Dourado, Manaus, Brazil*

Characteristic	Liver echogenicity, changed (increased)			P
	No.	%	PR	
Sex				0.63
M	36	22.2	1.03	
F	14	21.4		
Total	50	9		
Time (months)				0.621
≤ 6	32	21.9	0.98	
> 6	18	22.2		
Total	50	9		
ALT				0.01
Changed	17	17.6	1.28	
Normal	29	13.8		
Total	46	0.59		

* PR = prevalence ratio; Time = time with the disease; ALT = alanine aminotransferase.

major advance, not only because it enabled morphologic analysis of patients with this disease, but also because it provided a non-invasive method of plotting hemodynamic changes contributing to the early detection of signs indicating severe disease, staging, and prognosis. Thus, our finding that 26% (13 of 50) of patients had blood flow changes in the trunk of the portal vein, which seemed to be the most relevant parameter, could potentially be used in large-scale public health screening programs for prevention of chronic viral hepatitis. Determination of the presence and degree of hepatic fibrosis is essential for the prognosis and treatment planning of patients with HCV infection, and methods of non-invasive diagnosis that provide fast and efficient evaluation of fibrosis are critically needed.

The morphologic and hemodynamic parameters assessed in this study could potentially be used as indicators to assess the degree of inflammatory activity and fibrosis in patients with compensated chronic viral liver disease because they are important tools for non-invasive investigation of the liver in the early stages of illness. From this study, we can conclude that steatosis may be associated with HCV infection; increased caliber of the trunk of the portal vein may indicate a more advanced stage of fibrosis; increased gall bladder wall thickness is suggestive of chronic liver disease; and the mean flow velocity of the trunk of the portal vein, the congestion index, the liver vascular index, and the splenic and hepatic artery PIs are important indicators of liver damage in the early stage of HCV infection. The morphologic and hemodynamic changes showed a significant association with serum ALT levels, which suggests that the color Doppler ultrasound scan has an important place in the clinical assessment of patients with chronic hepatitis.

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