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RESEARCH ARTICLE

NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS BY SIMPLE DOPPLER ULTRASOUND PARAMETERS

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ABSTRACT

Background and Aim: Doppler ultrasonography of hepatic vasculature might indirectly reflect histological alteration, namely liver fibrosis. This study aimed to assess different Doppler parameters which might non-invasively predict the stage of liver fibrosis.
Methods: 55 patients with HCV related chronic liver disease were included. They were divided into: **Group I:** 32 patients with chronic hepatitis C without cirrhosis and **Group II:** 23 patients with cirrhosis (Child A). All were subjected to clinical evaluation, laboratory investigations, abdominal ultrasonography, Doppler for evaluation of hepatic artery resistance index (HARI), splenic artery resistance index (SARI) and hepatic vein (HV) waveform and percutaneous liver biopsy (for **Group I** only) with fibrosis staging according to METAVIR score.
Results: HV waveform was an accurate parameter for predicting significant fibrosis and cirrhosis as it showed the highest degree of agreement with METAVIR score. The best cutoff value of HARI was (> 0.74) for predicting cirrhosis (F4) and significant fibrosis (F ≥ 2). HARI was proved to be more sensitive and specific than SARI to predict cirrhosis (F4).
Conclusion: Doppler ultrasonography, especially HV waveform analysis, may non-invasively predict liver fibrosis stage.

INTRODUCTION

Accurate assessment of liver fibrosis is essential for therapeutic decisions and surveillance of chronic liver diseases of various etiologies (Germani *et al*., 2011). To date, liver biopsy is still the gold standard for staging of liver fibrosis, however, it has several well-documented drawbacks including sampling error and inaccuracy due to inter- and intraobserver variability of histopathologic interpretation. Also, it is associated with significant risks for the patient and cannot be used as a standard follow-up procedure for disease monitoring (Kleiner *et al*., 2005 and Sebastiani and Alberti, 2012). It has been previously reported that the combination of different non-invasive markers might be able to replace liver biopsies in a significant number of cases (Boursier *et al*., 2012 and Lutz *et al*., 2012). A number of studies demonstrated that the assessment of some haemodynamic parameters by Doppler ultrasonography of hepatic vessels might indirectly reflect histological alteration, namely liver fibrosis with variable results (Nguyen and Sterling, 2012). This study was performed to assess different Doppler ultrasound parameters which might non-invasively predict the stage of liver fibrosis.

PATIENTS AND METHODS

This prospective randomized study was conducted on 55 patients with HCV related chronic liver disease, who were presented to Internal Medicine and Tropical Medicine Departments, and outpatient clinics at Ain Shams University Hospital. They were divided into 2 groups:

- ***Group I:*** 32 patients with chronic hepatitis C without cirrhosis and in need for histopathologic staging for decision-making in therapeutic pathways.
- ***Group II:*** 23 patients with established cirrhosis (Child-Pugh class A).

Diagnosis of chronic hepatitis C was based on virological studies. Diagnosis of liver cirrhosis was based on clinical, laboratory and radiological data. Patients with other etiologies for chronic liver disease (other than HCV), those with

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decompensated liver disease, hepatocellular carcinoma, portal vein thrombosis, patients treated with portal pressure-reducing agents, such as beta-blockers as well as those with any other co-morbidities were excluded.

All included patients were subjected to the following

1. ***Complete clinical evaluation***
2. ***Laboratory investigations:*** CBC, ESR, liver profile (alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, serum total bilirubin, prothrombin time, INR and renal function tests.
3. ***Abdominal ultrasonography:*** for liver size, echogenicity, spleen size, echogenicity and confirming absence of ascites, liver or spleen focal lesions or portal vein thrombosis.
4. ***Ultrasound guided percutaneous liver biopsy for Group I patients:*** was assessed according to METAVIR scoring system (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 =portal fibrosis and few septa, F3 = numerous septa without cirrhosis and F4 = cirrhosis) **(The French METAVIR Cooperative Study Group, 1994).**
5. ***Doppler ultrasonography of the hepatic vessels:*** was performed by one experienced consultant radiologist using real time scanning device Sonoscape SSI 8000 with convex probe 3.5 MHz. Each patient was fasting for at least 6 hours and placed in the supine position to avoid influence of ingested food and posture on splanchnic hemodynamics. Three parameters were evaluated; hepatic artery resistance index (HARI), splenic artery resistance index (SARI) and hepatic vein (HV) waveform. The HARI and SARI were measured automatically by the machine, after obtaining the waveform trace for 3 cardiac cycles, by placing the Doppler gate in the branches of hepatic artery in porta hepatis and in the branches of intrasplenic artery near the splenic hilum. HV waveforms were recorded for at least 4-6 seconds. They were mainly performed in the right hepatic vein, sometimes in the middle but never in the left to avoid artefacts due to transmitted cardiac pulsations. The Doppler gate was placed in the vein 2-3 cm away from IVC. Respiratory manoeuvres can alter HV flow pattern, so measurements of parameters were carried on during end-expiration breath holding. The HV waveforms were classified into:

   A. Triphasic waveform: two hepatofugal or antegrade phases related to atrial and ventricular diastole and a short phase of hepatopetal or retrograde flow caused by the pressure increase in the right atrium at atrial systole;
   B. Biphasic waveform: decreased amplitude of the phasic oscillation without the short phase of reversed blood flow (lack negative waves and show oscillation of positive waves); and
   C. Monophasic waveform: completely flat waveform without any phasic oscillation (Altinkaya *et al*., 2011).

Informed consent was obtained from all of the included patients, and the study protocol was approved by the ethical guidelines committee.

Statistical analysis was conducted using SPSS version 17. Data were expressed as mean ± standard deviation (SD), number and percentages. The following tests were used: Student t test (t), Chi-square test (X^2), analysis of variance test (ANOVA) and Receiver Operator Characteristic Curve (ROC) to determine the cutoff value of measured parameter for the best sensitivity, specificity, positive and negative predictive values.

P value < 0.05 was considered statistically significant & P< 0.01 as highly significant.

RESULTS

This study included 55 patients with chronic liver disease who were divided into two groups:

Group I: included 32 chronic hepatitis patients without cirrhosis. They were 16 males (50%) and 16 females (50%) with a mean age of 35.4 ± 9.9 years. All patients had percutaneous liver biopsy and staging of liver fibrosis according to METAVIR scoring system which revealed F0 in one patient (3.13%), F1 in 19 patients (59.38%), F2 in 8 patients (25%), F3 in 4 patients (12.5%) and none of them was F4 (0%).

Group II: included 23 patients with established cirrhosis (Child-Pugh class A). They were 18 males (78.3%) and 5 females (21.7%) with a mean age of 56.6 ± 4.4 years. All were F4 according to METAVIR scoring system.

Comparison between **Group I** and **Group II** regarding laboratory data (Mean±SD) showed highly significant difference between both groups (P <0.001) (serum albumin = 4.3±0.3 *versus* 3.3±0.2 gm/dl, ALT = 62.4±30.9 *versus* 37.8±12.7 IU/ml, AST = 58.5±26.6 *versus* 39.9±13.1 IU/ml, bilirubin= 0.7±0.1 *versus* 1.2±0.3 mg/dl, platelet count = 210468±51665 *versus* 124043±34632, INR= 1.08±0.09 *versus* 1.31±0.05 respectively). Regarding Doppler parameters, there was highly significant statistical difference between the two studied groups regarding hepatic vein (HV) waveform (P <0.001). **Group I** showed Triphasic flow in 62.5% and Biphasic flow in 37.5% of patients. None of patients in **Group I** had Monophasic flow (0%). While in **Group II**, Monophasic flow was detected in 56.52%, Biphasic flow in 39.13% and Triphasic flow in 4.35% of patients.

Table (1) shows highly significant relation between HV waveform and METAVIR score (P < 0.001). In subsequent analysis for detecting significance of HV waveform in differentiation between non-significant fibrosis (F0,1) from significant fibrosis (F2,3,4), there was a highly significant relation between HV waveform and METAVIR score (F0,1) *versus* (F2,3,4) (P < 0.001). Thus, HV waveform was an accurate parameter for predicting significant fibrosis and cirrhosis as it showed the highest degree of agreement with METAVIR score.

Table 1 Relation between HV waveform and METAVIR score.

METAVIR score	HV waveform						Chi-Square	
	Biphasic		Triphasic		Monophasic			
	N	%	N	%	N	%	X^2	P-value
F0	0	0.00	1	4.76	0	0.00	80.384	<0.001*
F1	0	0.00	19	90.48	0	0.00		
F2	8	38.10	0	0.00	0	0.00		
F3	4	19.05	0	0.00	0	0.00		
F4	9	42.86	1	4.76	13	100.00		
Total	21	100.00	21	100.00	13	100.00		

Table (2) shows a significant increase in hepatic artery resistance index (HARI) parallel to the increase in METAVIR

score (P = 0.036). The mean level of HARI in F0 patients was 0.56±0.0, in F1 was 0.718±0.089, in F2 was 0.724±0.028, in F3 was 0.690 ±0.084 and in F4 was 0.760±0.066.

The best cutoff value of HARI was (> 0.74) for predicting cirrhosis (F4) with sensitivity (65.2%), specificity (75%), positive predictive value (PPV) (65.2%), negative predictive value (NPV) (75%) and accuracy (0.712). At the best cutoff value (> 0.74), HARI could predict significant fibrosis (F ≥ 2) with sensitivity (51.4%), specificity (75%), PPV (78.3%), NPV (46.9%) and accuracy (0.633).

Table 2 Relation between hepatic artery resistance index (HARI) and METAVIR score.

METAVIR score	HARI Range			Mean	±	SD	ANOVA F	P-value
F0	0.560	-	0.560	0.560	±	.		
F1	0.560	-	0.910	0.718	±	0.089		
F2	0.680	-	0.760	0.724	±	0.028	2.792	0.036*
F3	0.600	-	0.800	0.690	±	0.084		
F4	0.610	-	0.860	0.760	±	0.066		

Table (3) shows a non-significant increase in splenic artery resistance index (SARI) parallel to the increase in METAVIR score (P =0.338). The mean level of SARI in F0 patients was 0.45±0.0, in F1 was 0.616±0.084, in F2 was 0.588±0.077, in F3 was 0.608 ±0.059 and in F4 was 0.61±0.079. The best cutoff value of SARI was (> 0.56) for predicting cirrhosis (F4) with sensitivity (69.6%), specificity (40.6%), PPV (45.7%), NPV (65%) and accuracy (0.53)

Table 3 Relation between splenic artery resistance index (SARI) and METAVIR score.

METAVIR score	SARI Range			Mean	±	SD	ANOVA F	P-value
F0	0.450	-	0.450	0.450	±	.		
F1	0.420	-	0.750	0.616	±	0.084		
F2	0.510	-	0.750	0.588	±	0.077	1.163	0.338
F3	0.560	-	0.680	0.608	±	0.059		
F4	0.450	-	0.760	0.610	±	0.079		

Figure (1) shows comparison between area under ROC curve (AUC) for HARI and SARI. HARI was proved to be more sensitive and specific than SARI to predict cirrhosis (F4) (P = 0.03, Difference between Areas = 0.182, Standard Error = 0.084, 95% Confidence Interval = 0.017 - 0.347).

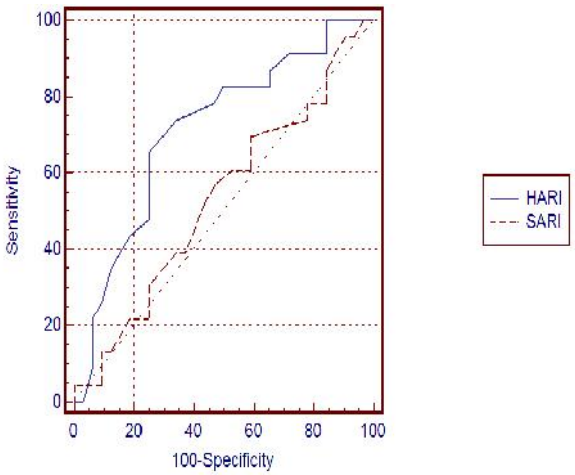

Figure 1 Comparison between area under ROC curve (AUC) for HARI and SARI to predict cirrhosis (F4).

Figure (2) shows Monophasic hepatic vein waveform and hepatic artery RI = 0.8 in patient with METAVIR score F4.

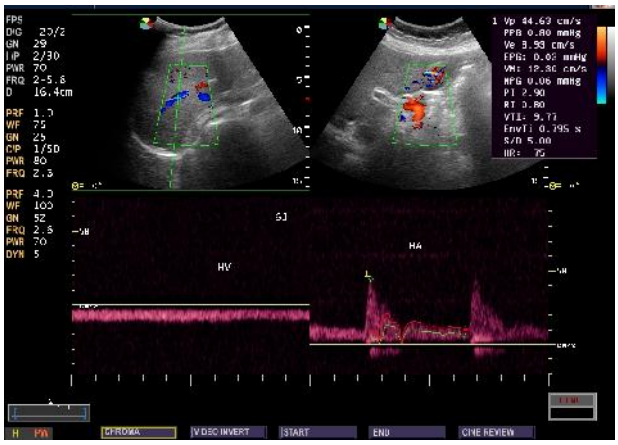

Figure 2 Monophasic hepatic vein waveform and Hepatic artery RI = 0.8 in a patient with METAVIR score F4.

DISCUSSION

This study was performed to assess different Doppler parameters which might non-invasively predict the stage of liver fibrosis. We found that HV waveform was the most accurate measured parameter for predicting significant fibrosis and cirrhosis. It showed the highest degree of agreement with METAVIR score (P <0.001)

In the present study, 23 cases were F4: from them, one case (4.35%) had triphasic, 9 cases (39.13%) had biphasic, and 13 cases (56.52%) had monophasic HV waveform. Previous studies found variable results. Joseph *et al.* (2011) who examined 51 cirrhotic patients found triphasic waves in 7.8%, biphasic in 51% and monophasic in 41.2%. Kawanaka *et al.* (2008) examined 103 cirrhotic patients and observed triphasic waveform in 33%, biphasic in 61% and monophasic in 6%.

The exact causes of changes in Doppler HV waveforms remain unclear. Some investigators have suggested that parenchymal fibrosis and fat infiltration surrounding the wall of the HV compress the wall and reduce its compliance leading to the disappearance of a reversed phase of HV waveform (Ohta *et al.*, 1995). Other authors thought that the pathogenic mechanism causing intrahepatic shunts is responsible for the abnormal waveform (Kim; *et al.*, 2007 and Sudhamshu *et al.*, 2011).

Regarding hepatic artery and splenic artery resistance indices, we found a significant increase in hepatic artery resistance index (HARI) parallel to the increase in METAVIR score (P-value = 0.036). The best cutoff value of HARI to predict cirrhosis (F4) was > 0.74 by sensitivity 65% and specificity 75%. The best cutoff value to predict significant fibrosis (F ≥2) was > 0.74 by sensitivity 51% and specificity 75%. However, splenic artery resistance index (SARI) did not significantly increase with the advance in liver fibrosis METAVIR score. The best cutoff value of SARI to predict cirrhosis (F4) was > 0.56 by sensitivity 69% and specificity 40%.

Hepatic artery normally has a resistive index ranging from 0.55 to 0.7. Splenic artery normally has a resistive index ranging from 0.46 to 0.56 (Bolognesi *et al.*, 1996). Previous studies

have shown that hepatic impedance indices (hepatic artery resistance index and hepatic artery pulsatility index) were correlated with the severity of hepatic fibrosis, based on the assumption of distortion of hepatic architecture (Bolognesi *et al*., 2007). With the advance of hepatic fibrosis, the portal resistance increases causing the increased outflow resistance of the splenic artery resulting in increased splenic impedance indices (splenic artery resistance index and splenic artery pulsatility index) (Bolognesi *et al*., 1996 and Piscaglia *et al*., 2001).

In conclusion, Doppler ultrasound of hepatic blood flow, especially hepatic vein waveform analysis, may non-invasively predict the stage of liver fibrosis.

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