RAPID COMMUNICATION

Ultrasonography in differentiation between chronic viral hepatitis and compensated early stage cirrhosis

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minate CVH from CIR. The alternative Doppler indexes can accurately differentiate chronic virus hepatitis from cirrhosis. These indexes can be used in monitoring chronic virus hepatitis and avoiding unnecessary biopsies.

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Key words: Liver cirrhosis; Virus hepatitis; Portal hypertension; Doppler ultrasonography

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Abstract

AIM: To assess the value of gray scale (GS) and colour Doppler ultrasonography (CDU) in differentiating the progression of chronic viral hepatitis (CVH) and compensated liver cirrhosis (CIR).

METHODS: Seventy-two patients and 32 normal individuals who were used as controls were studied. Forty-four patients suffered from CVH and 28 from CIR. All patients were underwent to liver biopsy. Multiple qualitative and quantitative variables were studied in liver, portal vein (PV), hepatic artery (HA) and spleen with GS and CDU. On the basis of the obtained CDU data, several known indexes were calculated. In addition, alternative indices [PV diameter (D)/time average mean velocity (V_{TAM}), HA/PV V_{TAM} ratio] were calculated and studied.

RESULTS: ROC analysis showed that PV congestion index, PV D/ V_{TAM} and HA/PV V_{TAM} indices had the best sensitivity and specificity in discriminating CVH from CIR. Stepwise discriminant analysis showed that 88.9% of the originally grouped cases could be correctly classified by the three qualitative and four quantitative variables selected as statistically significant predictors. Among the CVH patients who underwent to biopsy, statistically significant changes were found in those at fibrosis stage 5 compared to fibrosis stages 1-4.

CONCLUSION: Simple GS and CDU parameters discri-

INTRODUCTION

Chronic viral hepatitis, mainly caused by hepatitis virus B or C, results in liver parenchyma damage and inflammation and may lead to fibrosis, cirrhosis and/or hepatocellular carcinoma^[1-3]. Cirrhosis often occurs as an indolent disease and a lot of patients remain asymptomatic^[4,5] until the occurrence of decompensation, and are characterised by portal hypertension, variceal bleeding, ascites and hepatic encephalopathy.

Liver biopsy is the gold standard for diagnosis and determination of the fibrosis and necroinflammatory changes in chronic viral hepatitis and cirrhosis. However, the use of biopsy in clinical practice has some limitations related to sample errors with an estimated false negative percentage of 24% morbidity and mortality in series of blind biopsies^[6] and complications^[7].

The non-invasive assessment of chronic liver disease has been attempted by various research groups using either clinical signs^[8,9], gray scale^[10-15] and colour Doppler ultrasound (CDU) signs and indexes^[16-32], or biochemical parameters in the blood^[9]. The use of CDU in diagnosis and staging of chronic viral liver disease has been based on the hypothesis that alteration in liver haemodynamics due to chronic inflammatory changes may indirectly reflect histological alterations. Therefore, positive correlation studies have usually referred to the velocity ratio of hepatic

artery to portal vein or the resistive index in hepatic artery. However, the role of CDU remains controversial regarding the reproducibility^[33-36] and the statistical significance^[37,38] of the measurements in hepatic fibrosis and cirrhosis.

The aim of the present study was to determine the alterations in liver haemodynamics by using the Doppler indexes and measurements of spleen size that may lead to differentiation between chronic viral liver disease and compensated cirrhosis in a group of patients with a well-delineated histological profile. Furthermore, an effort was made to isolate predictive factors for discrimination between patients with chronic viral hepatitis and cirrhosis.

MATERIALS AND METHODS

Patient population

Seventy-two patients were enrolled in this controlled prospective study and divided into chronic viral hepatitis (CVH) group and cirrhotic (CIR) group. The CVH group included 44 patients (mean age 53 ± 12 years, 29 males and 18 females) with chronic viral hepatitis. Of them, 20 were positive for hepatitis B surface antigen and 24 were positive for hepatitis C serum markers. All patients underwent needle biopsy at the time of study.

The CIR group consisted of 28 patients suffering from compensated early stage cirrhosis (Child-Pugh A score, mean age 63 ± 9 years, 16 males and 13 females) due to viral hepatitis B or C. All cirrhotic patients had previous needle biopsy that confirmed their disease and endoscopic investigation of the upper GI tract.

All patients included in the study gave their written informed consent and had no known liver tumour or decompensated liver disease. The study was approved by the ethics committee of our institution.

Thirty-two healthy individuals (mean age 50 ± 15 years, 18 males and 14 females) served as controls. They were chosen from healthy volunteers with normal blood profile without evidence of liver disease. Volunteers with complex anatomy related to the hepatic artery were excluded from the study. The alcohol consumption was no more than 28 units a week (one unit = 8 g) for each individual in the control group. None of them had a history of cardiac or liver disease and risk factors for viral hepatitis, or was receiving therapy known to alter liver haemodynamics.

CDU technique and indexes

All sonographic scans were performed by a single experienced radiologist (first author), who was unaware of the clinical and laboratory data. All asymptomatic patients and healthy adults were fasted overnight before the examination. Patients did not take drugs that could affect their portal or systemic haemodynamics twenty-four hours prior to examination.

All scans were performed with the individuals lying supine using the same sonography system (ATL, HDI 3500) with a curvilinear 2.5-5 MHz transducer. The machine was supported with the proper software for direct and automatic calculation of the haemodynamic parameters based on the spectral Doppler waveform. The examination was started with the observation in gray-

scale scanning of the liver size (normal or enlarged if the midclavicular longitudinal diameter of the organ was greater than 12.6 cm ^[39], taking the value 1 for enlarged and 0 for normal), contour (nodular yes/no, taking the value 1 for yes and 0 for no) and parenchyma (homogeneity diffuse yes/no, and echogenic yes/no, taking the value 1 for yes and 0 for no). Subsequently, the examination proceeded to study CDU and a transverse section was obtained at the epigastrium to locate the proper hepatic artery in its longitudinal axis. The same method was used at the midlevel of the portal vein trunk to calculate venous indices, since no aberrant anatomy was present in the subjects participating in this study. To decrease the effect of respiration on the portal blood flow, all measurements were obtained during a short time breath-holding to avoid deep respiration. An occasional problem of overlying bowel gas was handled either by extending the scanning time or by setting a new appointment on the following day. For quantitative flow measurements, the position of the scanner was optimised until a Doppler angle of less than 60° was achieved. Haemodynamic parameters were calculated over four cardiac cycles. The sample volume size was always equal to the lumen diameter of blood vessels.

The following portal vein (PV) variables were measured: diameter (D) in cm, cross-sectional area (AR) in cm^2 , time-averaged maximum velocity (V_{MAX}) in cm/s , time-averaged mean velocity (V_{TAM}) in cm/s , blood flow volume (BF) in mL/min and the congestion index which was calculated as the ratio between cross-sectional area and time-averaged mean velocity ($\text{CI} = \text{AR}/V_{\text{TAM}}$) in cm^2/s ^[11]. The time-averaged mean portal venous velocity was determined electronically using the software package provided with the ultrasound machine.

Hepatic artery (HA) measurements included: diameter (D) in cm, cross-sectional area (AR) in cm^2 , time-averaged mean velocity (V_{TAM}) in cm/s and blood flow volume (BF) in mL/min . Resistance index (RI) of HA (percentage) was the ratio of $100 \times$ the difference of peak systolic velocity minus end diastolic velocity to peak systolic velocity, automatically given by machine's software. In addition, Doppler perfusion index (DPI)^[22] was calculated according to the formula: $\text{DPI} = \text{BF}_{\text{HA}}/(\text{BF}_{\text{HA}} + \text{BF}_{\text{PV}})$.

We also evaluated two alternative indexes for liver haemodynamics: the ratio of portal vein diameter to V_{TAM} ($\text{PV r}_1 = \text{D}/V_{\text{TAM}}$) in cm and the artery to portal vein ratio (A/P), which was calculated by the following formula: $\text{Time-averaged HA mean velocity } (V_{\text{TAM}})/\text{time-averaged PV mean velocity } (V_{\text{TAM}})$.

Two consecutive measurements of the anatomic and Doppler parameters were made in each blood vessel and the average value was taken for statistical analysis.

The spleen size was estimated by measuring the maximum craniocaudal and transverse diameters^[40,41].

Liver biopsies

Liver biopsies were fixed in formalin and embedded in paraffin. Individual histological sections were prepared and stained using standard procedures. All patients were classified on the basis of the histologic activity index according to Ishak *et al*^[42] in six fibrosis stages (F1-F6) with

the sixth (F6) to be cirrhosis stage and necroinflammatory score varying from 0 to 18 in each stage.

Statistical analysis

The quantitative variables (predictors) were compared by *t*-test and ANOVA between CVH and CIR patients and between controls. Quantitative variables between CVH patients at fibrosis stages lower than 5 and between patients with CVH at the fifth fibrosis stage were compared using Wilcoxon rank sum test since few observations were carried out in the second group and therefore parametric assumption of the *t*-test was violated. $P < 0.05$ was considered statistically significant.

Analysis of variance between the two consecutive Doppler measurements showed a very high reproducibility.

The predictive value for each of the predictors was evaluated by the area under the receiver operating characteristic (ROC) curves. Accuracy was calculated for the best cut-off value (BCV) of the current data set, defined as the highest sum of sensitivity and specificity. Stepwise discriminant analysis was performed to predict group membership from the set of predictors by the classification functions. All statistical analyses were performed using the SPSS program (version 13).

RESULTS

According to the histological findings (Table 1), 9 CVH patients were at F1 stage with necroinflammatory score (NI) ranging from 2 to 4, 9 patients at F2 stage with NI ranging from 3 to 6, 9 patients at F3 stage with NI ranging from 3 to 8, 7 patients at F4 stage with NI ranging 5 to 8 and 10 patients at F5 stage with NI ranging 3 to 9. All the 28 cirrhotic patients were at F6 fibrosis stage. No change was observed endoscopically in 8 cirrhotic patients, while first degree varices were found in 16 patients, portal gastropathy in 3 patients, first degree varices and portal gastropathy in 1 patient, respectively.

Ultrasonography

CVH group vs control group: There was a significant decrease in the portal vein mean value related to time average maximum velocity (V_{TAM}) and diameter (D) to V_{TAM} ratio between CVH and control groups ($P = 0.03$ and 0.037 , respectively). In addition, there was a significant increase in the spleen volume between the two groups ($P = 0.011$). The other haemodynamic parameters and indexes did not show any statistical significance (Table 2).

CIR group vs CVH group: There was a significant decrease related to the mean value of portal vein blood flow velocities (V_{MAX} and V_{TAM}) and blood flow (BF) between the CIR and CVH groups ($P < 0.00007$, $P < 0.00002$, $P < 0.005$ respectively, Table 1). In addition, there was a significant increase in BF of the hepatic artery and the spleen volume ($P < 0.013$, $P > 0.002$, Table 2). According to the qualitative data, liver in early stage cirrhotic patients had nodular surface, diffuse parenchymal echogenicity and was larger than that in CVH patients (Table 1).

Descriptive statistics and comparative data on qualitative,

Table 1 Liver qualitative parameters in controls, CVH and CIR groups

Variables		Chronic viral hepatitis group (CVH)	Cirrhosis group (CIR)
		<i>n</i>	<i>n</i>
Size	Enlarged	10	12
Contour	Nodular	6	13
Echogenic	Raised	11	1
Homogeneity	Diffuse	11	18

quantitative anatomic and haemodynamic variables as well as the calculated indexes in portal vein, hepatic artery and spleen are presented in Table 2. The *P* values for the quantitative variables between the two groups are listed in Table 2.

In comparison with the CVH patients, the mean values of portal vein congestion index, diameter to time average mean velocity ratio, Doppler perfusion index (DPI) as well as hepatic artery RI and HA/PV time average mean velocity ratio were all significantly increased in the early-stage cirrhotic patients ($P < 0.01$, Table 2).

CVH patients at F5 stage vs other fibrosis stages (F1-F4): Wilcoxon's test between CVH patients at F5 stage to F1-F4 showed a significant increase in portal vein congestion index (CI) ($P = 0.041$). In addition, there was a marginally significant increase in diameter, cross sectional area ($P = 0.051$) and D/V_{TAM} ratio ($P = 0.055$) in CVH patients (Table 3). Portal Vein V_{MAX} and V_{TAM} values were marginally decreased ($P = 0.056$ and 0.08 respectively) while all other variables were not significantly different (Table 3).

CIR group and F5 CVH group vs other CVH groups (F1-F4): A significant increase in portal vein's diameter ($P < 0.05$) and cross section area ($P < 0.05$) was observed, while PV V_{MAX} and PV V_{TAM} were significantly decreased ($P < 0.001$) in cirrhotic patients and CVH patients (incomplete cirrhosis) at F1-F4. In addition, a significant increase was observed in PV CI and PV D/V_{TAM} ratio ($P < 0.01$) as well as in DPI ($P < 0.05$) and HA/PV V_{TAM} ratio between the two groups of patients ($P < 0.001$) (Table 2). Spleen volume was also increased ($P < 0.05$, Table 3).

ROC and stepwise discriminant analysis of CIR group vs CVH group: Portal vein D/V_{TAM} ratio, CI and HA/PV V_{TAM} ratio had the same sensitivity of 85.71% and specificities of 59.09%-68.18% respectively, between CIR and CVH patients. Doppler perfusion index (best cut-off value of 0.29) had a very good specificity (90.91%) but a low sensitivity (42.86%) between the two groups. The area under the curve (AUC), comparing CVH group with CIR group, for each variable as measured by receiver operating characteristic curve (ROC) analysis is presented in Table 4. PV CI, D/V_{TAM} ratio and HA/PV V_{TAM} ratio under AUC curves are shown in Figure 1 A-C. The best cut-off value (BCV) for each statistically significant quantitative variable defined as the highest sum of sensitivity and specificity is summarized in Table 5.

Table 2 Quantitative and haemodynamic parameters in controls, CVH and CIR groups

Quantitative variables	Controls (a)	CVH (b)	CIR (c)	t-test		ANOVA a/b/c
				a vs b	b vs c	
Portal vein	mean ± SD	mean ± SD	mean ± SD		P value	
D (cm)	1.14 ± 0.12	1.14 ± 0.17	1.17 ± 0.19	0.88	0.481	0.739
AR (cm ²)	1.02 ± 0.20	1.03 ± 0.32	1.11 ± 0.37	0.81	0.37	0.509
V _{MAX} (cm/s)	41.56 ± 9.30	36.27 ± 9.40	27.60 ± 6.75	0.03	7.00E-05	4.00E-07
V _{TAM} (cm/s)	22.88 ± 5.69	20.64 ± 5.92	14.80 ± 3.82	0.14	2.00E-05	6.00E-07
BF	1369.76 ± 349.41	1238.06 ± 392.03	980.06 ± 319.58	0.17	0.005	6.00E-04
Hepatic artery						
AR (cm ²)	0.16 ± 0.05	0.16 ± 0.05	0.17 ± 0.06	0.75	0.772	0.867
V _{TAM} (cm/s)	29.62 ± 10.55	29.39 ± 12.70	34.06 ± 12.34	0.92	0.128	0.244
BF (mL/min)	281.07 ± 125.79	288.79 ± 163.30	341.27 ± 144.16	0.84	0.013	0.067
Indexes						
PV D/V _{TAM} [cm/(cm*s)]	0.05 ± 0.02	0.06 ± 0.02	0.09 ± 0.05	0.166	0.002	2.00E-04
PV CI (cm*s)	0.05 ± 0.02	0.06 ± 0.03	0.09 ± 0.07	0.251	0.01	0.003
HA RI	0.73 ± 0.08	0.70 ± 0.07	0.74 ± 0.04	0.252	0.169	0.257
Total BF (mL/min)	1657.21 ± 379.72	1526.85 ± 477.80	1321.33 ± 345.78	0.254	0.053	0.016
DPI	0.17 ± 0.07	0.19 ± 0.07	0.26 ± 0.11	0.41	0.001	3.00E-04
HA/PV V _{TAM}	1.34 ± 0.50	1.49 ± 0.66	2.50 ± 1.25	0.34	3.00E-05	1.00E-06
Spleen volume (cm ³)	364.63 ± 114.01	587.09 ± 408.30	937.13 ± 525.98	0.011	0.002	6.00E-06

PV: Portal vein; HA: Hepatic artery; n: Number of patients; D: Diameter; AR: Area; V_{MAX}: Time averaged maximum velocity; V_{TAM}: Time averaged mean velocity; RI: Resistance index; CI: Congestion index; BF: Blood flow volume; DPI: Doppler perfusion index; CVH: Chronic virus hepatitis; CIR: Cirrhosis.

Table 3 Quantitative variables in CVH patients at other fibrosis stages and those at fibrosis stage 5

Variables	1th-4th fibrotic stages (a)	5th fibrotic stage (b)	5th stage and cirrhotics (c)	Wilcoxon's test		t-test a vs c
				a vs b	P	
Portal vein	mean ± SD	mean ± SD	mean ± SD			P <
D (cm)	1.1 ± 0.16	1.25 ± 0.19	1.19 ± 0.19	0.051		0.05
AR (cm ²)	0.97 ± 0.28	1.25 ± 0.37	1.14 ± 0.37	0.051		0.05
V _{MAX} (cm/s)	37.5 ± 9.86	32.15 ± 6.44	28.8 ± 6.9	0.056		0.001
V _{TAM} (cm/s)	21.4 ± 6.06	18.02 ± 4.79	15.65 ± 4.27	0.08		0.001
FV (mL/min)	1227.3 ± 423.02	1274.55 ± 276.1	1057.55 ± 332.2	0.68		0.06
Hepatic Artery						
AR (cm ²)	0.16 ± 0.057	0.17 ± 0.04	0.17 ± 0.06	0.85		0.75
V _{TAM} (cm/s)	29.9 ± 13.1	27.61 ± 11.69	32.37 ± 12.35	0.60		0.41
FV (mL/min)	291.7 ± 171.32	278.79 ± 140.17	324.83 ± 143.9	0.81		0.37
Indexes						
PV CI (cm*s)	0.05 ± 0.023	0.077 ± 0.035	0.045 ± 0.02	0.04		0.01
PV D/V _{TAM} [cm/(cm*s)]	0.056 ± 0.02	0.075 ± 0.026	0.085 ± 0.046	0.055		0.01
HA RI	0.7 ± 0.07	0.697 ± 0.034	0.73 ± 0.045	0.63		0.2
TOTAL BF (mL/min)	1519.05 ± 517.6	1553.33 ± 327.8	1382.38 ± 352.3	0.8		0.2
DPI	0.19 ± 0.075	0.177 ± 0.074	0.24 ± 0.11	0.6		0.05
HA/PV V _{TAM}	1.46 ± 0.66	1.6 ± 0.67	2.26 ± 1.19	0.56		0.001
Spleen volume (cm ³)	574.06 ± 402.11	631.4 ± 448.12	856.7 ± 519	0.72		0.05

PV: Portal vein; HA: Hartery; n: Number of patients; D: Diameter; AR: Area; V_{MAX}: Time averaged maximum velocity; V_{TAM}: Time averaged mean velocity; RI: resistance index; CI: Congestion index; BF: Blood flow volume; DPI: Doppler perfusion index.

The statistically significant variables selected by the stepwise discriminant analysis are ENLARGED, ECHOGENIC, DIFFUSE, PV AR, HA RI, HA/PV V_{TAM}, and SPLEEN. The classification scores for the CVH and CIR groups are * = multiply

W₁ = -89.090 - 1.657*ENLARGED + 12.769*ECHOGENIC + 4.202*DIFFUSE - 0.764*PV AR + 235.564*HA RI + 2.961*HA/PV V_{TAM} + 0.007*SPLEEN, and W₂ = -105.029 + 0.755*ENLARGED + 10.406*ECHOGENIC + 7.683*DIFFUSE - 5.849*PV AR + 251.99*HA RI + 5.473*HA/PV V_{TAM} + 0.010*SPLEEN.

Based on these scores, we classified any new patient in the CVH group if w₁ > w₂ and in the CIR group if

w₂ > w₁. According to the classification formula, 41 CVH patients (93.18%) were correctly classified in CVH group while 23 cirrhotic patients (82.14%) were correctly classified in CIR group.

DISCUSSION

In our study, two major findings are of interest to note regarding haemodynamic parameters and indexes. The first finding is related to a statistically significant increase in PVCI between CVH patients at fibrosis stage 5 and those at fibrosis stages 1-4. At the same time, a marginally significant increase was recorded in PV diameter, cross

Table 4 Area under the curve (AUC) for each variable measured by receiver operating characteristic curve (ROC) analysis

Variables	ROC Area	Std. Err.	95% CI	P value
Liver				
Enlarged	0.60	0.06	0.49 0.71	
Echogenic ¹	0.61	0.04	0.53 0.68	
Diffuse	0.70	0.06	0.59 0.81	
Nodular	0.66	0.05	0.56 0.77	
Portal vein				
D	0.54	0.07	0.40 0.68	0.56
AR (cm ²)	0.56	0.07	0.42 0.70	0.38
V _{MAX} ¹ (cm/s)	0.77	0.06	0.66 0.88	< 0.0002
V _{TAM} ¹ (cm/s)	0.79	0.05	0.68 0.89	< 0.0001
FV ¹ (mL/min)	0.68	0.06	0.56 0.81	< 0.01
Hepatic artery				
AR (cm ²)	0.51	0.07	0.37 0.65	0.86
V _{TAM} (cm/s)	0.64	0.07	0.51 0.77	0.053
FV (mL/min)	0.63	0.07	0.49 0.76	0.07
Indexes				
PV CI (cm*s)	0.74	0.06	0.62 0.86	< 0.001
PV D/V _{TAM} [cm/(cm/s)]	0.74	0.06	0.63 0.86	< 0.001
HA RI	0.66	0.06	0.53 0.78	< 0.05
Total BF (mL/min)	0.37	0.07	0.24 0.50	0.058
DPI	0.70	0.06	0.58 0.83	< 0.005
HA/PV V _{TAM}	0.80	0.05	0.70 0.90	< 0.0001
Spleen volume (cm ³)	0.71	0.07	0.58 0.84	< 0.005

PV: Portal vein; HA: Hepatic artery; D: Diameter; AR: Area; V_{MAX}: Time averaged maximum velocity; V_{TAM}: Time averaged mean velocity; RI: Resistance index; CI: Congestion index; BF: Blood flow volume; DPI: Doppler perfusion index; CIR: Compensated liver cirrhosis; CVH: Chronic viral hepatitis. ¹Denotes CIR vs CVH.

Table 5 The best cut-of value (BCV) defined as the highest sum of sensitivity and specificity as statistically significant predictors

Variable	BCV	Sensitivity (%)	Specificity (%)
PV V _{MAX} ¹ (cm/s)	30.10	77.27	71.43
PV V _{TAM} ¹ (cm/s)	16.00	75.00	71.43
PV BF ¹ (mL/min)	1106.64	59.09	75.00
PV CI (cm*s)	0.06	85.71	65.91
PV D/V _{TAM} [cm/(cm*s)]	0.07	85.71	68.18
HA RI	0.72	71.43	54.55
DPI	0.29	42.86	90.91
HA/PV V _{TAM}	1.45	85.71	61.36
Spleen volume (cm ³)	553.00	75.00	70.45

PV: Portal vein; HA: Hepatic artery; D: Diameter; AR: Area; V_{MAX}: Time averaged maximum velocity; V_{TAM}: Time averaged mean velocity; RI: Resistance index; CI: Congestion index; BF: Blood flow volume; DPI: Doppler perfusion index. ¹Denotes CIR vs CVH.

section area and D/V_{TAM} ratio, while V_{MAX} and V_{TAM} velocities were marginally reduced. Blood flow volume in the hepatic artery and the portal vein as well as DPI index remained unchanged at all CVH fibrosis stages. Decrease in portal vein blood flow velocities related to fibrotic stage in CVH patients was firstly described by Koda *et al*^[23], who also found that portal vein blood flow volume is not significantly affected in the same patients. Tziafalia *et al*^[32] reported that portal vein blood velocities are decreased in CVH patients. In our study, PV V_{MAX} velocity was also decreased in CVH patients.

Gaiani *et al*^[25] also found that portal vein V_{TAM} velocity

Figure 1 Portal vein congestion index (A), portal vein diameter/time averaged mean velocity (V_{TAM}) ratio (B), and hepatic arterial/portal vein time averaged mean velocity (V_{TAM}) ratio (C).

is the only haemodynamic variable that is independently associated with the histopathological diagnosis in CVH patients. Bernatik *et al*^[37] reported that V_{MAX} and V_{TAM} velocities are reduced at end-stage fibrosis, while DPI does not change significantly and progression of liver fibrosis is associated with a continuous increase in HA resistive index (RI), suggesting that Doppler parameters are not useful in assessing the stage of liver fibrosis. In our study, although the mean HA RI value was significantly increased ($P = 0.013$) in CIR group compared to CVH group, it was not affected in CVH patients at different fibrosis stages.

In our study, the portal vein diameter (D) was significantly enlarged at end-stage fibrosis patients, which is consistent with the reported data^[31]. Walsh *et al*^[29] found that hepatic artery blood flow (BF) and DPI are increased in CVH C patients at different fibrosis stages, while portal vein CI values remain unchanged. Our data do not support these findings regarding HA BF volume and DPI. However, we observed a significant change in PV CI.

The second major finding is that there were differences in anatomic, haemodynamic parameters and indexes

between CVH and CIR groups, suggesting that when early cirrhosis and portal hypertension are settled, portal vein blood flow velocity is reduced. This phenomenon is accompanied with enlargement of portal vein D and AR at end-stage fibrosis. On the other hand, hepatic artery blood flow volume increases in an effort to maintain liver blood flow volume. Portosystemic shunts and varices that may subsequently occur decrease portal hypertension. Portal vein D and AR remain for some time unchanged while blood flow velocities are further reduced. These phenomena dramatically increase most haemodynamic indexes such as portal vein CI and DPI as well as the calculated alternative ratios of $PV D/V_{TAM}$, $HA/PV V_{TAM}$.

The same observations regarding portal vein CI and DPI have been reported by other investigators^[17,20-26], which are consistent with our findings. In the present study, ROC analysis showed that portal vein CI and PVD/ V_{TAM} for the best cut-off values of 0.06 and 0.07 also had a very good sensitivity of 85.71% and a sensitivity of 65.91%-68.18% (Figures 1A and B, AUC = 0.74).

In our study, spleen volume was increased in CVH and cirrhotic patients compared with the controls, which is consistent with the findings in other studies^[19,20,22,24-26,28-31,38].

It is well known that a relative interobserver variability may limit the value for gray scale and Doppler ultrasonography^[33-36]. In this study, we tried to simplify Doppler indexes and haemodynamic parameters such as congestion index^[17] which is the ratio of area to time average mean blood velocity in portal vein. In the most recent studies, portal vein's area was assumed to be circular and is automatically calculated by the machine's software from the equation $area = \pi \cdot r^2$, because $r^2 = (diameter/2)^2$. Therefore, we replaced the area with diameter of the vessel. The $HA/PV V_{TAM}$ ratio at proper hepatic artery has never been described.

Stepwise discriminant analysis showed that the main predictors for discriminating CVH from CIR patients included three liver qualitative variables: ENLARGED, ECHOGENIC, DIFFUSE and four quantitative variables: PV AR, HA RI, $HA/PV V_{TAM}$ ratio and SPLEEN volume. By calculating the formula, 88.9% of the patients were correctly classified either in CVH group or in CIR group. The interesting finding is that the $HA/PV V_{TAM}$ alternative ratio was included in the classification function, while other indexes such as PVI and DPI were not included. ROC analysis confirmed the high predictive value of $HA/PV V_{TAM}$ index for discriminating CVH from CIR patients (best-cut-off value = 1.45, sensitivity = 85.71% and specificity = 61.36%, = 0.80, Figure 1C).

In the past, the "arteriportal index"^[43] was described as the ratio between V_{MAX} velocities in HA and PV right and left branches. We consider that the calculation of $HA/PV V_{TAM}$ ratio would be easier to perform. We also suggest that it can be used in routine practice since these velocities are automatically measured in most studies evaluating liver haemodynamics.

The accuracy of US in assessing diffuse liver disease has been evaluated in previous studies^[25,26]. The reported sensitivity of gray scale and US is 57%-95% in distinguishing normal from abnormal livers^[44-47]. However, attempts to identify specific pathological processes, such as fatty

infiltration and fibrosis, have produced conflicting results^[31,45], probably related to the different US criteria employed in the studies, such as distribution of the parenchymal echoes and attenuation of the ultrasonic beam. In our study, liver parenchymal changes were simply described and classified by yes or no (1 or 0). For routine practice and simplicity reasons, no further analysis was attempted in echo structure of the liver.

Percutaneous needle biopsy and histological examination of the samples are considered the gold standard for the severity of fibrosis and cirrhosis. However, several studies^[25,28] have questioned this because liver biopsies lead to false negative diagnoses of cirrhosis due to sampling errors in an estimated average of 24% pooled blind liver biopsy series^[6]. Schalm^[28] has reviewed the diagnostic methodology of liver cirrhosis and found that percutaneous liver biopsy has a sensitivity of below 85% in detection of liver cirrhosis.

It was reported that percutaneous liver biopsy sampling errors are significantly decreased when automated spring loaded true-cut needles are used^[47]. The standard of practice we used in liver biopsies is in agreement with the recently published data^[47] and unsuccessful biopsies and complications were kept at their minimum. We routinely performed a thorough sonographic investigation of the liver to assess the liver parenchyma and exclude the presence of lesions, such as a cyst. Subsequently, we performed the biopsy after marking the skin with automated cutting needles that according to our experience provide superior liver biopsy specimens in subjects with advanced fibrosis and cirrhosis; more than one samples were always taken.

On the other hand, cirrhosis is a common disease, which is frequently undiagnosed^[4,5]. The risk of biopsy (morbidity 3%, mortality 0.03%)^[7] may limit its use in screening for this disease. Finally, cirrhosis is reversible^[48], making the use of alternative non-invasive diagnostic tools essential.

Gaiani *et al*^[25] suggested that ultrasonography may be used to identify cirrhosis with a diagnostic accuracy of 80% for cirrhosis even in the absence of a typical histopathological pattern. In our study, stepwise discriminant analysis showed that its diagnostic accuracy in discriminating cirrhosis from chronic viral hepatitis patients was 82.14%.

In conclusion, gray scale and Doppler ultrasonography can accurately and non-invasively assess liver haemodynamics and discriminate CVH patients at end fibrosis stage from those at other CVH stages as well as CVH patients from early stage cirrhotic patients with compensated function. The method can easily be performed with routine upper abdominal ultrasonography, and is inexpensive and safe.

COMMENTS

Background

In recent years, many papers have been published regarding the efforts to correctly classify chronic virus hepatitis (CVH) and distinguish this entity from liver cirrhosis by bloodless means. Blood tests and ultrasonography, or other imaging modalities (CT, MRI) are used to achieve this goal. Doppler ultrasonography of portal vein and hepatic artery has gained its ground in the estimation of portal haemodynamics. Simple recording of portal vein's blood flow velocities is common in daily practice in many institutions. Haemodynamic indexes, although old as a

conception, have not been thoroughly investigated, probably due to the difficulty of producing them from the Doppler measurements in day practice.

Research frontiers

Our study investigated the value of the most popular liver haemodynamic indexes (congestion index, Doppler perfusion index, arteriportal index). We also simplified these indexes by introducing new alternative to them. Finally our data were compared to those published in literature.

Innovations and breakthroughs

The major finding of our study is that end CVH at the 5th fibrotic stage can be distinguished from those at other stages. In daily practice, incomplete and complete early stage cirrhosis may be predicted by simple haemodynamic indexes. Stepwise discriminant analysis produced a formula (including qualitative and quantitative variables) that differentiates liver cirrhosis from CVH in 80% of the originally classified cases. ROC analysis could find the best cut off values for discriminating CVH from cirrhosis. The new alternative indexes, particularly "arteriportal index" have been proved to be of great value in discriminating CVH from cirrhotic patients. The "arteriportal index" is first used in porta hepatis (portal vein's trunk and proper hepatic artery). Another major point is that the best cut-off values are similar to those from other investigators contributing to the establishment of internationally accepted values for Doppler haemodynamic indexes.

Applications

Our data suggest that the "congestion index" and alternative indexes are of value and can be added in daily practice for monitoring CVH and cirrhotic patients. Because the arteriportal index of porta hepatis is first used, more studies are needed to establish more precise best cut off values.

Terminology

"Arteriportal index": The ratio of time average mean blood velocity in proper hepatic artery to time average blood velocity in portal vein's trunk.

Peer review

In this study, the authors assessed the value of gray scale (GS) and colour Doppler ultrasonography (CDU) in differentiating the progression of CVH and compensated liver cirrhosis (CIR). Significant differences in haemodynamic parameters and indexes were found between CVH patients at fibrosis stage 5 and those at other fibrosis stages, suggesting that simple GS and CDU parameters can discriminate CVH from CIR.

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