

Gray and Color Doppler Ultrasonography in Differentiation between Chronic Viral Hepatitis and Compensated Early Stage Cirrhosis

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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). **Patients and methods.** Seventy-two patients and 32 normal individuals used as controls were studied. Forty-four patients suffered from CVH and 28 from CIR. All patients underwent liver biopsy. Multiple qualitative and quantitative variables were studied with GS and CDU in the Liver, Portal Vein (PV), Hepatic Artery (HA) and spleen. On the basis of the obtained Doppler data several known indexes were calculated. Alternative indexes [PV diameter (D)/time average maximum velocity (V_{MAX}), PV diameter/time average mean velocity (V_{TAM}), HA/PV V_{TAM} ratio] derived from them were calculated. **Results.** ROC analysis showed that PV Congestion Index, PVD/V_{TAM} and $HA/PV V_{TAM}$ indexes had the best sensitivity and specificity in discriminating CVH from CIR. Stepwise discriminant analysis selected as significant predictors 3 qualitative and 4 quantitative variables that correctly classify 88.9% of the original grouped cases. In CVH patients that underwent biopsy we found statistically significant changes in those at fibrotic stage 5 compared to fibrotic stages 1-4. **Conclusion.** We found significant differences in haemodynamic parameters and indexes for CVH patients at fibrosis stage 5 compared to all other stages. Simple GS and CDU parameters may discriminate CVH from CIR. The alternative Doppler indexes suggested that accurate differentiation between CVH and CIR is possible. These indexes could be useful for monitoring CVH and avoiding unnecessary biopsies.

Key words

Color Doppler ultrasonography - haemodynamic indexes - chronic viral hepatitis - cirrhosis

Introduction

Chronic viral hepatitis (CVH) mainly caused by the 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 (CIR) often occurs as an indolent disease; many patients remain asymptomatic (4,5) until the occurrence of decompensation.

Liver biopsy is the gold standard for diagnosis and assessment of the fibrosis and necroinflammatory changes in CVH and CIR. However, the use of biopsy in clinical practice has some limitations related to sample errors with estimated false negatives percentage of 24% in series of blind biopsies (6) and to complications such as morbidity and mortality (7).

The non-invasive assessment of chronic liver disease has been attempted by various research groups comprising either clinical signs (8,9), gray scale (10-15) and colour Doppler ultrasound signs and indexes (16-34), or biochemical parameters in the blood (9). The use of Colour Doppler Ultrasonography (CDU) in diagnosis and staging of chronic viral liver disease has been based on the hypothesis that alteration of liver haemodynamics due to chronic inflammatory changes may indirectly reflect histological alterations. Therefore, positive correlation studies have usually referred to velocity ratios of the hepatic artery (HA) to the portal vein (PV) or the resistivity index in the HA. However, the role of CDU remains controversial regarding the reproducibility (35-38) and the statistical significance (39, 40) of the measurements in hepatic fibrosis and cirrhosis.

The aim of the present study was to find alterations in liver haemodynamics by means of Doppler indexes and measurements of spleen size that may lead to differentiation between chronic viral liver disease and compensated CIR in a group of patients with a well-established histological profile. Furthermore, there was an effort to isolate predictive factors in order to discriminate between patients with CVH and CIR.

Patients and methods

Patient population

Seventy-two patients were enrolled in this controlled prospective study, divided into two groups. Forty-four (44) patients suffered from CVH (mean age 53 ± 12 years, 29 males, 18 females) and formed the CVH group. Twenty patients had positive tests for hepatitis B surface antigen and 24 were positive for hepatitis C serum markers. All patients had recent needle biopsy at the time of study.

Twenty-eight patients suffered from compensated early stage CIR and formed the CIR group (Child-Pugh A score, mean age 63 ± 9 years, 16 males, 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 gastrointestinal tract.

The patients included in the study had no known liver tumour or decompensated liver disease. All gave written informed consent in order to participate. The ethics committee of our institution approved the above study.

Finally, 32 healthy individuals (mean age 50 ± 15 years, 18 males, 14 females) were examined as controls. They were chosen from healthy volunteers with normal blood profile without evidence of liver disease. Volunteers with complex anatomy related to the HA were excluded from the study in order to technically facilitate the measurements required. The alcohol consumption was no more than 28 units a week (one unit = 8g) for each individual of the control group. None of them had a history of cardiac or liver disease, risk factors for viral hepatitis, or were receiving therapy with medication 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 subjects were fasted overnight before the examination. They were not taking drugs that could possibly affect their portal or systemic haemodynamics for 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 2.5-5MHz 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 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 12.6cm (41)] and parenchyma. Subsequently, the examination proceeded with CDU study obtaining a transverse section at the epigastrium to locate the proper HA in its longitudinal axis. The same method was used at the mid-level of the PV 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 short time breath-holding, avoiding deep respiration. The occasional problem of overlying bowel gas was handled with either extension of the

scanning time or by setting a new appointment the following day. For quantitative flow measurements, the position of the scanner was optimised until a Doppler angle of less than 60° was achieved. The haemodynamic parameters were calculated over four cardiac cycles. Sample volume size was always equal to vessels' lumen diameter.

The following PV variables were measured: diameter (D) in cm, cross-sectional area (AR) in cm^2 , time-averaged maximum velocity (V_{MAX}) in cm/sec, time-averaged mean velocity (V_{TAM}) in cm/sec, 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/sec (Moriyasou et al (11)). The time-averaged mean portal venous velocity was determined electronically with the software package of the ultrasound machine.

Hepatic artery measurements included: diameter (D) in cm, cross-sectional area (AR) in cm^2 , time-averaged mean velocity (V_{TAM}) in cm/sec 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 minus end diastolic velocity to peak systolic velocity and it was automatically given by machine's software. In addition to the above indexes, Doppler Perfusion Index (DPI) (22) was calculated according to the following formula:

$$\text{DPI} = \text{BF}_{\text{HA}} / (\text{BF}_{\text{HA}} + \text{BF}_{\text{PV}})$$

We also evaluated three alternative indexes for liver haemodynamics: the ratio of PV diameter to V_{TAM} ($\text{PV } r_1 = \text{D} / V_{\text{TAM}}$) in cm, the ratio of PV diameter to (V_{MAX}) ($\text{PV } r_2 = \text{D} / V_{\text{MAX}}$) in cm, and the artery to PV 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 every vessel and the average values were taken for statistical analysis.

The spleen size was estimated by measuring the maximum craniocaudal and transverse diameters (45, 46).

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 (47) in six fibrosis stages (F1 – F6) with F6 to be cirrhosis stage, and necroinflammatory (NI) score varied from 0 to 18 in each stage.

Statistical analysis

T-test and ANOVA were used for comparing quantitative variables (predictors) between CVH and CIR patients as well as versus controls. Quantitative variables between CVH patients at lower than F5 stage and CVH patients at F5 stage were compared using the Wilcoxon rank sum test since the second group had few observations and therefore parametric assumptions of the t-test were violated. The p value was considered statistically significant when < 0.05 .

Regarding the intraobserver variability, there was a satisfactory degree of agreement related to anatomic and Doppler measurements; kappa (K) value ranged between 0.87 and 0.93.

The predictive value for each of the predictors was evaluated by the area under the curve (AUC) of 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 performed to predict group membership from the set of predictors by the classification functions. The above statistical analysis was obtained using the SPSS program (version 13).

Results

CVH vs control group

There was a statistically significant decrease in PV mean values related to time average maximum velocity (V_{TAM}) and diameter (D) to V_{TAM} ratio between CVH and control group ($p=0.03$ and 0.037 , respectively). In addition to that, there was a statistically significant increase of the spleen volume

between the above groups ($p=0.011$). The other haemodynamic parameters and indexes did not show significant alterations (Table I).

CIR vs CVH group

According to histological findings, 9 CVH patients were at F1 stage with NI score range 2 to 4, 9 patients at F2 with NI 3 to 6, 9 patients at F3 with NI 3 to 8, 7 patients at F4 with NI 5 to 8 and 10 patients at F5 with NI 3 to 9. All cirrhotics (28) were at F6 stage. Endoscopically nothing was observed in 8 cirrhotics, while from the remaining 20 patients in 16 first degree varices had occurred, 3 had portal gastropathy and 1 patient first degree varices and portal gastropathy.

There was a significant decrease related to the mean values of PV blood flow velocities (V_{MAX} and V_{TAM}) and blood flow (BF) between CIR and CVH groups ($p<0.00007$, $p<0.00002$, $p<0.005$ respectively, Table I). In addition to that, there was a significant increase observed in the BF of the HA and the spleen volume ($p<0.013$, $p>0.002$). According to the qualitative data, liver in cirrhotics had nodular surface, diffuse parenchymal echogenicity and was probably larger as compared to CVH patients (Table I).

Table I Qualitative data, descriptive statistics and comparative data of anatomic and haemodynamic parameters as of indexes between controls, CVH and CIR groups. In bold, statistically significant p values. $\uparrow\downarrow$ denotes increase or decrease of these values

Variables	Controls	Chronic viral hepatitis group (CVH)	Cirrhosis group (CIR)	t-test		ANOVA
	n	n	n	a vs b	b vs c	a/b/c
<i>Liver</i>						
Normal	32	34	16			
Enlarged		10	12			
Echogenic		11	1			
Diffuse		11	18			
Nodular		6	13			
<i>Portal vein</i>						
	Controls	CVH	CIR	t-test		ANOVA
	a	b	c	a vs b	b vs c	a/b/c
	Mean \pm SD	Mean \pm SD	Mean \pm SD	p value		
D (cm)	1.14 \pm 0.12	1.14 \pm 0.17	1.17 \pm 0.19	0.88	0.481	0.739
AR (cm ²)	1.02 \pm 0.20	1.03 \pm 0.32	1.11 \pm 0.37	0.81	0.37	0.509
V_{MAX} (cm/sec)	41.56 \pm 9.30	36.27 \pm 9.40	27.60 \pm 6.75	0.03 \downarrow	7E-05 \downarrow	4E-07 \downarrow
V_{TAM} (cm/sec)	22.88 \pm 5.69	20.64 \pm 5.92	14.80 \pm 3.82	0.14	2E-05 \downarrow	6E-07 \downarrow
BF	1369.76 \pm 349.41	1238.06 \pm 392.03	980.06 \pm 319.58	0.17	0.005 \downarrow	6E-04 \downarrow
<i>Hepatic artery</i>						
AR (cm ²)	0.16 \pm 0.05	0.16 \pm 0.05	0.17 \pm 0.06	0.75	0.772	0.867
V_{TAM} (cm/sec)	29.62 \pm 10.55	29.39 \pm 12.70	34.06 \pm 12.34	0.92	0.128	0.244
BF (ml/min)	281.07 \pm 125.79	288.79 \pm 163.30	341.27 \pm 144.16	0.84	0.013 \uparrow	0.067
<i>Indexes</i>						
PV D/ V_{MAX} (cm/cm*sec ⁻¹)	0.028 \pm 0.008	0.034 \pm 0.01	0.05 \pm 0.02	0.037-	0.002 \uparrow	8E-05 \uparrow
PV D/ V_{TAM} (cm/cm*sec ⁻¹)	0.05 \pm 0.02	0.06 \pm 0.02	0.09 \pm 0.05	0.166	0.002 \uparrow	2E-04 \uparrow
PV CI (cm*sec)	0.05 \pm 0.02	0.06 \pm 0.03	0.09 \pm 0.07	0.251	0.01 \uparrow	0.003 \uparrow
HA RI	0.73 \pm 0.08	0.70 \pm 0.07	0.74 \pm 0.04	0.252	0.169	0.257
TOTAL BF (ml/min)	1657.21 \pm 379.72	1526.85 \pm 477.80	1321.33 \pm 345.78	0.254	0.053	0.016 \downarrow
DPI	0.17 \pm 0.07	0.19 \pm 0.07	0.26 \pm 0.11	0.41	0.001 \uparrow	3E-04 \uparrow
HA/PV V_{TAM}	1.34 \pm 0.50	1.49 \pm 0.66	2.50 \pm 1.25	0.34	3E-05 \uparrow	1E-06 \uparrow
<i>Spleen volume</i> (cm ³)	364.63 \pm 114.01	587.09 \pm 408.30	937.13 \pm 525.98	0.011 \uparrow	0.002 \uparrow	6E-06 \uparrow

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

Table II Wilcoxon's and t- tests for comparing median differences of quantitative variables between CVH patients at fibrosis stage lower than 5 vs CVH patients at stage 5 and the group of unified cirrhotics and F5 stage CVH patients. $\uparrow\downarrow$ denote increase or decrease of these values

Variables	1 – 4 th fibrotic stages a	5 th fibrotic stages b	5 th stage and cirrhotics c	a vs b wilcoxon's test	a vs c t-test
<i>Portal vein</i>	Mean \pm SD	Mean \pm SD	Mean \pm SD	<i>p</i> =	<i>p</i> <
D (cm)	1.1 \pm 0.16	1.25 \pm 0.19	1.19 \pm 0.19	0.051 \uparrow	0.05 \uparrow
AR (cm ²)	0.97 \pm 0.28	1.25 \pm 0.37	1.14 \pm 0.37	0.051 \uparrow	0.05 \uparrow
V _{MAX} (cm/sec)	37.5 \pm 9.86	32.15 \pm 6.44	28.8 \pm 6.9	0.056 \downarrow	0.001 \downarrow
V _{TAM} (cm/sec)	21.4 \pm 6.06	18.02 \pm 4.79	15.65 \pm 4.27	0.08 \downarrow	0.001 \downarrow
FV (ml/min)	1227.3 \pm 423.02	1274.55 \pm 276.1	1057.55 \pm 332.2	0.68	0.06
<i>Hepatic artery</i>					
AR (cm ²)	0.16 \pm 0.057	0.17 \pm 0.04	0.17 \pm 0.06	0.85	0.75
V _{TAM} (cm/sec)	29.9 \pm 13.1	27.61 \pm 11.69	32.37 \pm 12.35	0.60	0.41
FV (ml/min)	291.7 \pm 171.32	278.79 \pm 140.17	324.83 \pm 143.9	0.81	0.37
<i>Indexes</i>	856.7 \pm 519				
PV CI	0.05 \pm 0.023	0.077 \pm 0.035		0.04 \uparrow	0.01 \uparrow
PV D/V _{MAX} (cm/cm*sec ⁻¹)	0.032 \pm 0.01	0.0402 \pm 0.01	0.085 \pm 0.046	0.03 \uparrow	0.01 \uparrow
PV D/V _{TAM} (cm/cm*sec ⁻¹)	0.056 \pm 0.02	0.075 \pm 0.026	0.045 \pm 0.02	0.055 \uparrow	0.01 \uparrow
HA RI	0.7 \pm 0.07	0.697 \pm 0.034	0.085 \pm 0.046	0.63	0.2
TOTAL BF (ml/min)	1519.05 \pm 517.59	1553.33 \pm 327.8	0.73 \pm 0.045	0.8	0.2
DPI	0.19 \pm 0.075	0.177 \pm 0.074	1382.38 \pm 352.3	0.6	0.05 \uparrow
HA/PV V _{TAM}	1.46 \pm 0.66	1.6 \pm 0.67	0.24 \pm 0.11	0.56	0.001 \uparrow
<i>Spleen volume (cm³)</i>	574.06 \pm 402.11	631.4 \pm 448.12	2.26 \pm 1.19	0.72	0.05 \uparrow

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

Descriptive statistics and comparative data of qualitative, quantitative anatomic and haemodynamic variables as well as the calculated indexes in PV, HA and spleen are presented in Table I, among the patient groups and the control group. *T*-test and ANOVA resulted *p*-values between study's groups are listed for each of the quantitative variables.

In comparison with CVH patients, mean values of PV CI, diameter to time average maximum or mean velocity ratios Doppler perfusion index (DPI) as well as HA RI and HA/PV time average mean velocity ratio were all statistically significantly increased in the early-stage cirrhotic group (Table I).

CVH group: patients at F5 stage vs all other fibrotic stages (F1 – F4)

Wilcoxon's test between CVH patients at F5 to all other stages (F1 - F4) showed a significant increase of portal vein congestion index (CI) and D/V_{MAX} ratio (*p*=0.041 and 0.031 respectively). There was a marginally significant increase in diameter, cross sectional area (*p*=0.051) and D/V_{TAM} ratio (*p*=0.055) in the former group (Table II). 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 II).

CIR and F5 CVH group vs all other CVH groups (F1-F4)

When we unify for simplicity and day practice reasons cirrhotics with F5 CVH patients (incomplete cirrhosis) and compare them to all other CVH stages (F1-F4) patients, a statistically significant increase in PV 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). Additionally statistically significant increase was observed in PV CI and PV D/V_{TAM}, D/V_{MAX} ratios (*p*<0.01) as well as in DPI (*p*<0.05) and HA/PV V_{TAM} ratio (*p*<0.001) (Table II). Spleen volume was also increased (*p*<0.05) (Table II)

ROC and Stepwise discriminant analysis CIR vs CVH group

Ratios of portal vein D/V_{MAX}, D/V_{TAM}, CI and HA/PV V_{TAM} have the same sensitivity 85.71% and varying specificities 59.09, to 68.18% respectively, between CIR and CVH patients. Doppler perfusion index for (best cut-off value 0.29) has very good specificity (90.91%) but low sensitivity (42.86%) between the two groups. The resulted area under the curve (AUC), comparing CVH with CIR group, for each variable as measured by receiver operating characteristic curve (ROC) analysis is presented in Table III. Table IV presents a summary of the best cut-off value (BCV) for each statistical significant quantitative variable defined as the highest sum of sensitivity and specificity.

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 the CIR group are:

$$W_1 = -89.090 - 1.657*\text{enlarged} + 12.769*\text{echogenic} + 4.202*\text{diffuse} - 0.764*\text{PV AR} + 235.564*\text{HA RI} + 2.961*\text{HA/PV V}_{\text{TAM}} + 0.007*\text{spleen}, \text{ and } W_2 = -105.029 + 0.755*\text{enlarged} + 10.406*\text{echogenic} + 7.683*\text{diffuse} - 5.849*\text{PV AR} + 251.99*\text{HA RI} + 5.473*\text{HA/PV V}_{\text{TAM}} + 0.010*\text{spleen}, \text{ respectively.}$$

Table III The resulted area under the curve (AUC), comparing CVH with CIR group, for each variable, as measured by receiver operating characteristic curve (ROC) analysis (*denotes that the comparison is CIR vs CVH)

Variables	ROC area	Std. err.	95% CI	p	
<i>Liver</i>					
Enlarged	0.60	0.06	0.49	0.71	
Echogenic*	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	
<i>Portal vein</i>					
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} * (cm/sec)	0.77	0.06	0.66	0.88	<0.0002
V _{TAM} * (cm/sec)	0.79	0.05	0.68	0.89	<0.0001
FV* (ml/min)	0.68	0.06	0.56	0.81	<0.01
<i>Hepatic artery</i>					
AR (cm ²)	0.51	0.07	0.37	0.65	0.86
V _{TAM} (cm/sec)	0.64	0.07	0.51	0.77	0.053
FV (ml/min)	0.63	0.07	0.49	0.76	0.07
<i>Indexes</i>					
PV CI (cm*sec)	0.74	0.06	0.62	0.86	<0.001
PV D/V _{MAX} (cm/cm*sec ⁻¹)	0.74	0.06	0.62	0.85	<0.001
PV D/V _{TAM} (cm/cm*sec ⁻¹)	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, n= number of patients, D= diameter, AR= area, V_{MAX} = time averaged maximum velocity, V_{TAM} = time averaged mean velocity

Table IV The best cut-of value (BCV), defined as the highest sum of sensitivity and specificity, is indicated for the statistical significant predictors (* denotes that the comparison is CIR vs CVH)

Variable	BCV	Sensitivity(%)	Specificity(%)
PV V _{MAX} * (cm/sec)	30.10	77.27	71.43
PV V _{TAM} * (cm/sec)	16.00	75.00	71.43
PV BF* (ml/min)	1106.64	59.09	75
PV CI (cm*sec)	0.06	85.71	65.91
PV D/V _{MAX} (cm/cm*sec ⁻¹)	0.03	85.71	59.09
PV D/V _{TAM} (cm/cm*sec ⁻¹)	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, n= number of patients, D= diameter, V_{MAX} = time averaged maximum velocity, V_{TAM} = time averaged mean velocity

For these scores we classified any new patient in the CVH group if $w_1 > w_2$ and in the CIR group if $w_2 > w_1$. According to the classification formula, 41CVH patients (93.18%) were correctly classified in CVH group while 23 cirrhotics (82.14%) were correctly classified in the CIR group.

Discussion

Two major findings are of interest in our study regarding haemodynamic parameters and indexes. The first finding was related to the statistically significant increase in PV CI and D/V_{MAX} ratio between CVH patients at F5 stage compared to F1-F4 stages. At the same time, marginal significant increase was recorded in the PV diameter, cross section area and D/V_{TAM} ratio, while V_{MAX} and V_{TAM} velocities were marginally reduced. Blood flow volume of the HA and the PV as well as DPI index remained unchanged throughout CVH fibrosis stages. Decrease of PV blood flow velocities related to fibrosis stage in CVH patients was firstly described by Koda M et al. (23) who also found that PV blood flow volume was not significantly affected in the same patients. In the same study, as well as in a recent study by Tziafalia C et al (34) the authors observed a decrease of PV blood velocities in CVH patients compared to controls. These findings were confirmed by our results as we also found reduction of PV V_{MAX} velocity and elevation of PVD/V_{MAX} ratio in CVH group compared to controls.

Gaiani S et al (25) also found that PV V_{TAM} velocity was the only haemodynamic variable that was independently associated with the histopathological aspect in CVH patients. Bernatik T et al (39) reported that V_{MAX} and V_{TAM} velocities were reduced in end-stage fibrosis, while DPI was not correlated or changed significantly. In the same study, progression of liver fibrosis was associated with a continuous increase of HA RI but finally the authors concluded that Doppler parameters are not clinically useful in assessing the stage of liver fibrosis. In our study, although the mean HA RI values were significantly increased ($p=0.013$) in the CIR group as compared with the CVH group, they were not influenced by the fibrotic stages in CVH.

We observed a significant enlargement of the PV diameter (D) in end-stage fibrosis patients, as was reported recently by Lei Shen et al (33). Walsh et al (29) found an increase of HA blood flow (BF) and DPI among fibrosis stages in CVH C patients, while portal vein CI values remained unchanged. Our data on the contrary do not support these findings regarding HA BF volume and DPI, but a statistically significant change in PV CI was observed.

The second major finding was focused on the differences that were recorded in anatomic, haemodynamic parameters and indexes between CVH and CIR groups and the unified group of cirrhotics and CVH at F5 stage patients. Our data could suggest that when early cirrhosis and portal hypertension is settled, PV blood flow velocity is reduced. This phenomenon is accompanied with enlargement of the PV diameter and AR at end-stage fibrosis. On the other hand, HA BF volume increases in an effort to maintain liver BF volume. Portosystemic shunts and varices that may subsequently occur decrease portal hypertension. Portal vein diameter and AR remain for some time unchanged while BF velocities are further reduced. These phenomena produce the dramatic increase in most haemodynamic indexes such

as PV CI and DPI as well as the calculated alternative ratios PVD/V_{MAX} , PVD/V_{TAM} , $HA/PV V_{TAM}$.

The same observations regarding PV CI and DPI have already been reported by other investigators and are confirmed in our study (17, 20–26). ROC analysis showed that PV CI, PVD/V_{MAX} and PVD/V_{TAM} for best cut-off values 0.06, 0.03, 0.07 respectively had the same very good sensitivity 85.71% and varying sensitivity 65.91%, 59.09% and 68.18% respectively (Figs.1-3) AUC 0.74 respectively).

Our study also confirmed the increase of spleen volume during chronic liver disease. This was obvious comparing either controls with CVH patients or CVH patients with cirrhotics. Changes in spleen size are perhaps the only finding that is described as significant by the majority of studies regarding liver haemodynamics (19, 20, 22, 24-26, 28–32, 40).

It is well known that a relative interobserver variability limits the value of GS and CDU. Our aim was not to investigate interobserver variability as already done by others (35-38), but only the significance of the most popular and commonly measured Doppler indexes in the differentiation of chronic viral liver disease stages. For this reason all examinations were performed by the same experienced radiologist. But as other investigators have already described, the variability problem can be eliminated through co-training programs and repeated measurements of the Doppler parameters (35-38). We accepted the criteria of previous investigators and adopted them. Indexes although difficult to calculate in daily practice, better reflect the liver haemodynamics at a certain time, and they also decrease the variability of haemodynamic parameters themselves. We tried to simplify these indexes. For example, CI (17) is the ratio of area to time average mean blood velocity in PV. In the most recent studies PV area has been assumed to be circular and is automatically calculated by the machine's software from the equation $area = d * (diameter/2)^2$ so we replaced area with the diameter of the vessel. $HA/PV V_{TAM}$ ratio at proper HA had never been granted previously.

Stepwise discriminant analysis showed that the main predictors for discriminating CVH from CIR patients are three liver qualitative variables enlarged, echogenic, diffuse and four quantitative variables PVAR, HARI, $HA/PV V_{TAM}$ ratio and spleen volume. By calculating the resulted formula, 88.9% of the patients were correctly classified either in CVH or CIR group. The interesting finding is that the alternative ratio introduced by us $HA/PV V_{TAM}$ is included in the classification function, while other well-known indexes such as PV CI and DPI are not. 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%, AUC 0.80) (Fig.4).

The previous finding could have significant clinical relevance and was for the first time observed and described. In the past the "arterioportal index" (48) was given 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 its use in

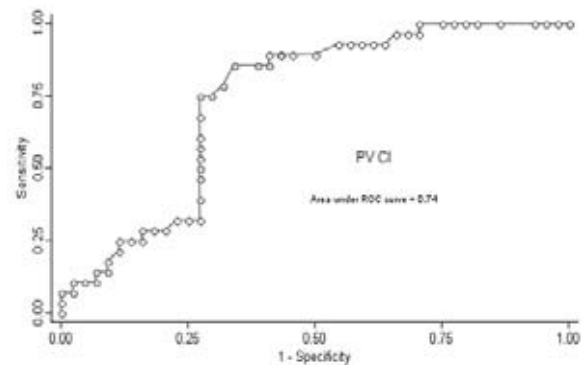


Fig.1 Portal vein congestion index AUC.

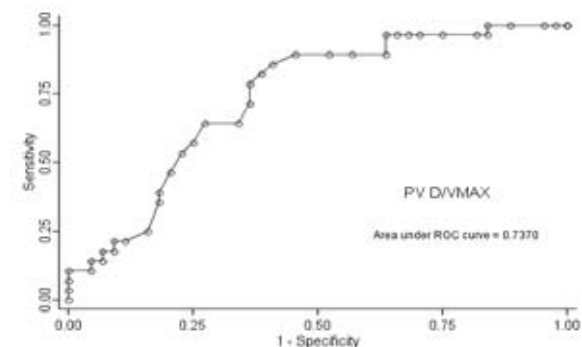


Fig.2 Portal vein diameter/ V_{MAX} ratio AUC.

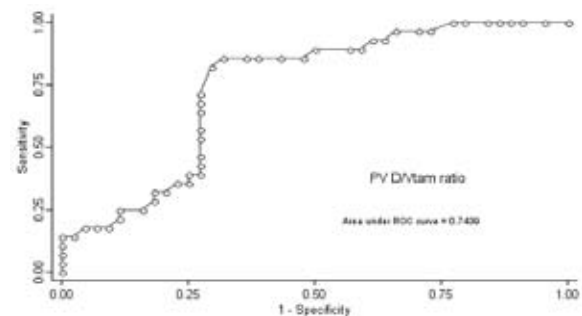


Fig.3 Portal vein diameter/ V_{TAM} ratio AUC.

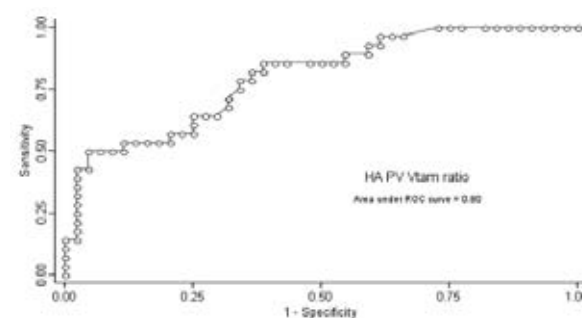


Fig.4 Hepatic arterial/portal vein V_{TAM} ratio AUC.

routine practice since in most studies which evaluate liver haemodynamics these velocities are automatically measured.

The reported sensitivity of gray scale US in assessing diffuse liver disease varies between 57 to 95% in distinguishing normal from abnormal livers (49-53). However, attempts to identify specific pathological processes, such as fatty infiltration and fibrosis, have produced conflicting

results (33, 50, 51), probably related to the different US criteria employed, such as the distribution of parenchymal echoes and the attenuation of the US beam. In our study, liver parenchymal changes were simply described and classified by yes or no (1 or 0 value). For routine practice and simplicity reasons no further analysis was attempted for the liver echo structure.

Percutaneous needle biopsy and histological examination of the samples is considered as the gold standard for the severity of fibrosis and cirrhosis. However, Schalm reviewed the diagnostic methodology of liver cirrhosis and found that percutaneous liver biopsy has a sensitivity of below 85% in detection liver CIR (28).

Recently published data (54) showed that percutaneous liver biopsy sampling errors are significantly decreased when we use automated spring loaded true-cut needles. The standard practice we use for liver biopsies is in agreement with the recently published data and keeps unsuccessful biopsies and complications to a minimum.

On the other hand, CIR is a common disease, which is frequently undiagnosed (4,5) and the risks and limits of biopsy (morbidity 3%, mortality 0.03%) (7) prevent its use for screening of this condition. Finally, the recent confirmation that CIR is reversible (55) makes the use of alternative non-invasive diagnostic tools essential.

Gaiani et al (25) have suggested that US may be used to identify CIR with a diagnostic accuracy for CIR of 80% by discriminant analysis even in the absence of a typical histopathological pattern. In our study, stepwise discriminant analysis showed a diagnostic accuracy of 82.14%, using GS and CDU parameters together with spleen volume for discriminating CIR from CVH patients.

According to our findings, we suggest that gray scale and Doppler Ultrasonography can accurately and non-invasively assess liver haemodynamics and at least discriminate CVH end fibrosis stage patients from all other CVH stages. It is also of great value in differentiating CVH patients from early stage cirrhotics with compensated disease. The method can easily be performed simultaneously with routine upper abdominal ultrasonography. It is inexpensive and can be safely repeated in order to reach a definitive conclusion.

Conflicts of interests

None to declare.

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