LIVER DISEASE

Arterial hypertension in cirrhosis: arterial compliance, volume distribution, and central haemodynamics

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Background and aim: Arterial hypertension is a common disorder. Hyperkinetic circulation and reduced effective volume are central elements in the haemodynamic dysfunction in cirrhosis. The aim of the present study was to investigate whether cirrhotic patients with arterial hypertension are normokinetic and normovolaemic or whether they reveal the same circulatory dysfunction as their normotensive counterparts.

Material and methods: Thirty three patients with arterial hypertension were identified among 648 patients with cirrhosis: 14 in Child class A, 12 in class B, and seven in class C. Controls were 130 normotensive cirrhotic patients, 19 controls with normal arterial blood pressure and without liver disease, and 16 patients with essential arterial hypertension. All groups underwent haemodynamic investigation with determination of cardiac output (CO), plasma volume (PV), central blood volume (CBV), hepatic venous pressure gradient (HVPG), hepatic blood flow (HBF), arterial compliance (AC), and systemic vascular resistance (SVR) in the supine position.

Results: Liver function, as evaluated by galactose elimination capacity, indocyanine green clearance, HBF, and Child score, was significantly better in hypertensive cirrhotics than in their normotensive counterparts ($p < 0.05$ – 0.01) but portal pressure was similar (HVPG 13 ± 15 mm Hg; NS). AC was significantly lower and normal in the arterial hypertensive cirrhotic group (1.07 ± 1.39 mm Hg/ml; $p < 0.02$) and SVR was significantly higher and normal (1475 ± 1020 dyn $\times$ s/cm 5 ; $p < 0.01$). Arterial hypertensive cirrhotic patients were hyperdynamic (CO 6.80 ± 7.14 l/min; NS) and central hypovolaemic (CBV 19.8 ± 20.6 ml/kg; NS), as were normotensive patients, but differences were found in relation to arterial blood pressure. Whereas arterial pressure was inversely correlated with CO, PV, and Child score in the normotensive group ($p < 0.01$), the same correlations were either direct or insignificant in arterial hypertensive cirrhotics.

Conclusion: Arterial hypertensive cirrhotic patients are hyperkinetic and central hypovolaemic, in common with their normotensive counterparts, but vasodilatation is reduced and regulation of arterial blood pressure may be less deranged.

Patients with cirrhosis are generally hyperdynamic with increased cardiac output (CO), low systemic vascular resistance (SVR), and low normal or low arterial blood pressure.^{1,2} Abnormal distribution of an increased blood volume with decreased effective blood volume, neuro-humoral activation, and abnormal sodium water handling are major features in advanced cirrhosis.^{3,4} Moreover, static and dynamic properties of the large arteries are changed.^{5,6}

Essential arterial hypertension is a common disorder with a prevalence of 10–15% in subjects in their forties to sixties, the characteristic age of patients with cirrhosis. However, it has been known for a long time that patients with chronic liver disease seldom exhibit arterial hypertension.^{7–10} In line with these observations, arterial hypertension of renal vascular origin seldom becomes manifest in cirrhotic patients with organic renal disease.¹¹ Gentilini *et al* found, based on non-invasive methods, that cirrhotic patients with arterial hypertension were normokinetic and showed fewer signs of renal impairment,¹² and Veglio *et al* found signs of enlarged effective plasma volume (PV) in hypertensive cirrhotic patients.¹³

The present study was undertaken to investigate the central haemodynamics of patients with cirrhosis and arterial hypertension, using direct methods, to determine the degree of central filling and normo- or hyperkinetics. We determined CO, central blood volume (CBV), and indicators of vasodilatation (SVR and arterial compliance (AC)) and compared these values with normotensive cirrhotic patients, essential hypertensive patients without liver disease, and controls with neither hypertension nor liver disease.

MATERIAL AND METHODS

Study population

Arterial hypertensive cirrhotic patients

The study comprised 33 patients (six women, 27 men) with cirrhosis and arterial hypertension. Cirrhosis was verified by biopsy in 27 patients and diagnosed on established clinical, biochemical, and ultrasonographic criteria in the remaining six. Mean age was 51 years (range 31–70). Thirty one patients had a history of alcohol abuse (that is, consumption exceeding 50 g/day for more than five years). In two patients cirrhosis was cryptogenic. All patients had abstained from alcohol for at least two weeks before the study. No withdrawal symptoms were present at the time of study. According to the modified Child-Turcotte classification,¹⁴ 14 patients were in class A, 12 in class B, and seven in class C. Ten patients had ascites. Ten patients were receiving diuretics because of fluid retention (spironolactone 50–200 mg/day, furosemide 40–80 mg/day, bendroflumethiazide 2.5 mg/day) and had been put on a sodium restricted diet of 40 mmol sodium per day. None of the patients had experienced recent gastrointestinal bleeding or had encephalopathy above grade I. Clinical and biochemical data are summarised in table 1.

Abbreviations: AC, arterial compliance; CBV, central and arterial blood volume; CO, cardiac output; HBF, hepatic blood flow; HVPG, hepatic venous pressure gradient; PV, plasma volume; SVR, systemic vascular resistance; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; MAP, mean arterial pressure

Table 1 Clinical and biochemical data of patients with cirrhosis

	Controls (n = 19)	Cirrhosis with normotension (n = 130)	Cirrhosis with arterial hypertension (n = 33)	Essential hypertension (n = 16)
Age (y)	56 (4.8)	52 (0.9)	51 (1.8)	50 (2.8)
Sex (M/F)	(9/10)	(92/38)	(27/6)	(8/8)
Body height (cm)	168 (3.3)	171 (0.8)	172 (1.4)	170 (2.4)
Body weight (kg)	64 (4.9)	73 (1.4)	76 (3.1)	81 (5.0)
Body mass index (kg/m ²)	23.1 (1.5)	24.8 (0.4)	25.6 (1.0)	28.0 (1.4)*†
Ascites (+/-)		(41/89)	(10/23)	(0/16)
Child (A/B/C)		(34/53/43)	(14/12/7)	
Diuretics (no/yes)		(83/47)	(23/10)	(8/8)
Serum albumin (μmol/l; 540–800)‡	541 (17)	456 (16)*	500 (17)	591 (15)
Serum alanine aminotransferase (U/l; 10–40)	31 (10)	77 (9)*	53 (9)	
Serum bilirubin (μmol/l; 2–17)	10 (3)	43 (8)*	23 (3)*	12 (1)
Serum alkaline phosphatase (U/l; 50–275)	194 (24)	447 (66)*	300 (31)*	145 (11)
Coagulation factors 2, 7, 10 (index; 0.70–1.30)	0.98 (0.05)	0.64 (0.03)*	0.72 (0.06)*	1.15 (0.05)
Galactose elimination capacity (mmol/min; M > 1.70, F > 1.40)		1.62 (0.05)	2.00 (0.16)†	
Indocyanine green clearance (ml/min; 300–700)	503 (41)	216 (11)*	288 (27)*†	
Serum Na (mmol/l; 136–146)	139 (0.6)	134 (1.0)	137 (1.1)	139 (1.3)
Serum K (mmol/l; 3.5–5.0)	4.2 (0.1)	4.0 (0.1)	4.1 (0.1)	3.9 (0.1)
Serum creatinine (μmol/l; 40–110)	82 (4)	85 (7)	91 (8)	113 (12)
Haemoglobin (mmol/l; 7.5–10.9)	8.0 (0.3)	7.3 (0.2)	7.7 (0.3)	9.1 (0.2)

Value are mean (SEM).

‡Unit, reference interval in parentheses.

Significant differences: *p < 0.05 compared with controls; †p < 0.02 compared with cirrhosis with normotension.

Patients were recruited from among 648 cirrhotic patients referred for liver vein catheterisation. All patients had arterial hypertension according to the JNC VI classification of blood pressure (that is, diastolic blood pressure ≥ 90 mm Hg and systolic blood pressure ≥ 140 mm Hg). Twelve patients were in JNC IV stage 1, 13 in stage 2, and eight in stage 3. None of the patients had received treatment for their arterial hypertension. QTc was above 440 ms in 36% of patients, which is average for patients with cirrhosis.^{2, 12} None had signs of heart failure, diabetes, or cancer. Three patients had serum creatinine above the upper normal reference limit (152–232 μmol/l) but signs of organic renal disease were absent.

Three reference populations served as controls: normotensive cirrhotic patients, patients with arterial hypertension but without cirrhosis, and subjects with neither hypertension nor liver disease.

Normotensive cirrhotic patients

A total of 130 patients (38 women, 92 men) had cirrhosis. Mean age was 52 years (range 25–74). One hundred and twenty one patients had a history of alcohol abuse. Thirty four patients were in Child class A, 53 in class B, and 43 in class C. Forty seven patients had received diuretics (spironolactone 50–200 mg/day, furosemide 40–160 mg/day). Data are summarised in table 1. In addition, a 2:1 matching (according to age, sex, body size, and Child class) to hypertensive cirrhotic patients was performed in order to eliminate any effect of different liver function.

Essential arterial hypertension

A second reference group consisted of 16 patients with arterial hypertension referred for haemodynamic investigation to exclude renovascular hypertension with unilateral renal generation of renin. None had signs of heart failure, diabetes, cancer, or any other major disease. The final diagnosis was essential arterial hypertension in all 16 patients. Ten patients received diuretics (furosemide 40–160 mg/day, bendroflumethiazide 5 mg/day). Four patients were treated with calcium antagonists and one with a beta-blocker. Treatment was withdrawn two days before the haemodynamic investigation. Data are summarised in table 1.

Controls (with normal arterial blood pressure and without liver disease)

A third reference group comprised 19 patients with neither liver disease nor arterial hypertension who had been referred for haemodynamic investigation to exclude circulatory disorders (mainly intestinal ischaemia) for which no evidence was found. Data are summarised in table 1.

Patients and controls participated after giving their informed consent according to the Helsinki II Declaration. No complications or side effects were encountered during the study.

Catheterisation

Catheterisation was performed to quantify arterial and portal hypertension. All patients were studied in the morning after an overnight fast and at least one hour of resting supine. Catheterisation of the hepatic veins was done as described previously.¹⁵ A small indwelling polyethylene catheter (5F) was introduced into the femoral artery and advanced to the aortic bifurcation by the Seldinger technique. Pressures were measured with a capacitance transducer (Simonsen and Weel, Copenhagen, Denmark) as previously described.^{15, 16} Frequency characteristics and reliability of dynamic intravascular pressure measurements, including determination of systolic and diastolic pressures, have been assessed previously with this equipment.¹⁵ Systolic arterial blood pressure (SAP) was determined as the average of maximum blood pressure over 20–30 seconds. Diastolic arterial blood pressure (DAP) was determined as the average of minimum blood pressure over 20–30 seconds. Mean arterial pressure (MAP) was determined independently by electronic integration of the pressure signal. The hepatic venous pressure gradient (HVPG) was determined as wedged minus free hepatic venous pressure. Zero reference was the mid-axillary level.

CO was determined by the indicator dilution technique (150 kBq ¹²⁵I albumin), as described previously.¹⁷ Stroke volume was measured as CO divided by heart rate. AC was determined as pulse pressure (SAP–DAP) divided by stroke volume.¹⁸

SVR was assessed as $80 \times (\text{MAP} - \text{right atrial pressure}) / \text{CO}$.^{15, 18} Central circulation time was determined as the time weighted area under the indicator concentration time curve, as described elsewhere.^{15, 19} Central and arterial blood volume

Figure 1 Controls, normotensive, and hypertensive patients with cirrhosis stratified according to Child class A, B, or C. (A) Hepatic venous pressure gradient (HVPG); (B) indocyanine green (ICG) clearance; and (C) galactose elimination capacity (GEC). Controls from Tygstrup.²¹ Significance within the boxes = analysis of variance; p values denote significant differences between groups.

Figure 2 Central blood volume as a per cent of blood volume (CBV/BV) in controls, normotensive, and hypertensive patients with cirrhosis, and patients with essential hypertension. Symbols and signs as in fig 1.

(CBV) was measured as CO times central circulation time.^{15 19} PV and blood volume were determined by the indicator dilution technique, as described previously.¹⁵

Hepatic blood flow (HBF) was determined by the indocyanine green constant infusion technique.²⁰ Only extractions above 0.10 (average 0.39) were accepted. Coefficient of variation of HBF was 4.4% (~54 ml/min). HBF was determined in 87% of cirrhotic patients. Indocyanine green clearance was measured as the infusion rate divided by arterial plasma concentration. Galactose elimination capacity was determined as described by Tygstrup.²¹

Statistics

Data are expressed as mean (SEM). One way analysis of variance (ANOVA) with Tukey's post hoc pairwise multiple comparison procedure was used to analyse group data. In the case of non-normality, the Kruskal-Wallis test (with Dunn's pairwise comparison) was applied. Bivariate data were compared using the Student's unpaired *t* test. In the case of non-normality, the Mann-Whitney test was applied. Correlations were performed by Pearson regression analysis or in the case of non-linearity by the Spearman rank test. Multiple regression analysis was performed to evaluate the

Table 2 Circulating volumes in normotensive and hypertensive patients with cirrhosis, normotensive controls, and patients with essential hypertension

	Cirrhosis							
	Controls	Normotension			Hypertension			Essential hypertension
		Child A	Child B	Child C	Child A	Child B	Child C	
CBV (ml/kg)	24.9 (2.5)	21.7 (1.1)	20.8 (0.6)*	20.9 (1.3)* NS	20.2 (1.1)*	18.7 (2.1)*	20.9 (1.3)*	21.5 (1.3)
BV (ml/kg)	71.8 (3.8)	77.5 (2.2)*	81.3 (1.6)*	78.0 (1.9)* NS	71.3 (2.3)	83.0 (7.5)*	84.7 (8.2)*	57.3 (21)*
BV (l)	4.74 (0.26)	5.66 (0.28)*	5.75 (0.22)*	5.76 (0.18)* NS	5.55 (0.24)*	6.07 (0.51)*	5.97 (1.28)*	4.72 (0.32)
PV (ml/kg)	50.7 (3.0)	50.0 (1.7)	55.3 (1.2)*	54.9 (1.4) NS	44.6 (1.8)	54.5 (4.1)*	59.9 (4.4)*	43.7 (1.9)*

CBV, central blood volume; BV, blood volume; PV, plasma volume.

Values are mean (SEM).

Significant difference: compared to controls: * $p < 0.05$; non-significant (NS) difference between normotensive and hypertensive patients with cirrhosis.

Figure 3 Systolic and diastolic blood pressure in the study groups. There was a significant difference between controls and normotensive patients with cirrhosis on the one hand and hypertensive patients with cirrhosis and patients with essential hypertension (▲) on the other. * $p < 0.001$ compared with controls.

relation between SVR and AC on the one hand and pertinent haemodynamic and liver function variables (galactose elimination capacity, indocyanine green clearance, Child score) on the other. A p value of <0.05 was considered significant.

RESULTS

Liver function and portal pressure

The percentage of patients in the different Child classes in the hypertensive (A/B/C = 42/36/21) and normotensive cirrhotic (26/41/33) groups were similar ($p = 0.15$) but the average Child score was lower in the former group (6.3 ± 7.5 ; $p < 0.02$). Similarly, indocyanine green clearance (288 ± 216 ml/min; $p < 0.01$) and galactose elimination capacity (2.00 ± 1.62 mmol/min; $p < 0.02$) were significantly higher, which indicated better liver function in the hypertensive cirrhotic patients than in their normotensive counterparts (fig 1). Substantial portal hypertension was present in both groups (13.0 ± 15.0 mm Hg; $p = 0.08$) but the significant increase from Child class A to Child class C in normotensive patients was absent in hypertensive patients with cirrhosis (fig 1). HBF was somewhat higher in hypertensive than in normotensive cirrhotic patients ($1.38 (0.13)$ ($n = 29$) ν $1.18 (0.05)$ l/min; $p < 0.05$).

Plasma and blood volumes

Plasma and blood volumes in patients with cirrhosis were significantly higher than in controls and in the patients with essential hypertension ($+2$ to $+23\%$; $p < 0.01$) (table 2). No significant differences were recorded among normotensive and hypertensive cirrhotic patients as a whole or when compared with matched Child classes. The size of the blood volume in patients with essential hypertension was normal in litres, but low when related to body weight, owing to their high body mass index (table 1).

As illustrated in fig 2, CBV was significantly reduced in patients with cirrhosis compared with controls ($p < 0.01$) and patients with essential hypertension ($p < 0.05$) but there was no significant difference between normotensive and hypertensive cirrhotic patients.

Haemodynamics

Arterial blood pressure is illustrated in fig 3. Whereas SAP, DAP, and MAP fell significantly from Child class A to Child class C ($p < 0.001$) in normotensive cirrhotic patients, a similar pattern was not seen in their hypertensive counterparts. MAP was 33 mm Hg higher in the latter group (82 ± 115 mm Hg; $p < 0.001$) and no significant difference was seen compared with patients with essential hypertension (115 ± 114 mm Hg; NS) (fig 4A).

CO was significantly increased in cirrhotic patients (normotensive $7.14 \pm$ hypertensive 6.80 l/min; NS) compared with controls (5.66 l/min; $p < 0.02$) and patients with essential hypertension (5.27 l/min; $p < 0.01$) but no significant difference was present between the two cirrhotic groups (fig 4B).

Normotensive cirrhotic patients had a significantly reduced SVR ($p < 0.001$) and the value decreased from Child class A to Child class C (fig 4C). However, their hypertensive counterparts had significantly higher ($p < 0.001$) and normal SVR ($1474 \pm$ controls 1323 dyn $\times$ s/cm 5 ; NS).

AC was significantly higher in normotensive cirrhotic patients than in controls ($1.39 \pm$ 1.04 ml/mm Hg; $p < 0.01$). In contrast, hypertensive cirrhotic patients had normal AC ($1.07 \pm$ control 1.04 ; NS), a value significantly lower than that of their normotensive counterparts ($p < 0.002$). The lowest value of AC was found in patients with arterial hypertension (fig 4D).

Heart rate, stroke volume, and central circulation time are shown in table 3. Heart rate was significantly ($p < 0.001$) and similarly increased in both groups of cirrhotic patients. Stroke volume was somewhat, but significantly, smaller in cirrhotics with hypertension than in their normotensive counterparts (85 ± 92 ml; $p < 0.002$). Cirrhotic patients had a shorter central circulation time than controls and patients with essential hypertension (both -19% ; $p < 0.05$) and no significant difference was seen between hypertensive and normotensive patients with cirrhosis. In hypertensive patients with cirrhosis, no significant effects of diuretics were detected on arterial blood pressure, CO, CBV, SVR, or AC.

When normotensive cirrhotics were matched to their hypertensive counterparts according to anthropometry and liver function, hypertensive patients with cirrhosis were hyperdynamic and centrally contracted to the same degree as their normotensive matched controls, and SVR and AC were significantly different (table 4).

Correlations with arterial pressure

Arterial blood pressure was inversely correlated with CO in normotensive cirrhotic patients ($r = -0.26$, $p < 0.01$) whereas this relation was direct in their hypertensive counterparts ($r = 0.34$, $p < 0.05$). Arterial blood pressure was inversely correlated with PV in normotensive patients ($r = -0.24$, $p < 0.01$) whereas no relation was found in hypertensive cirrhotic patients ($r = +0.04$, NS). Arterial blood pressure was directly correlated with central circulation time in normotensive patients ($r = +0.37$, $p < 0.005$) but no relation was found in hypertensive patients with cirrhosis ($r = -0.04$, NS). Arterial blood pressure was inversely correlated with the Child score in normotensive patients ($r = -0.25$, $p < 0.01$) but no relation was found in hypertensive patients with cirrhosis ($r = +0.1$, NS).

Figure 4 (A) Mean arterial blood pressure, (B) cardiac output, (C) systemic vascular resistance, and (D) arterial compliance in controls, normotensive and hypertensive patients with cirrhosis, and in patients with essential hypertension. Symbols and signs as in fig 1.

Multiple regression analysis

Multiple regression analysis showed that SVR in cirrhosis was independently related to systolic blood pressure, PV, CBV, and central circulation time (table 5). AC was independently related to mean arterial blood pressure, blood volume, CBV, central circulation time, HVP, and HBF. Child score, galactose elimination capacity, and indocyanine green

clearance were significant in the univariate analysis but did not achieve statistical significance in the multiple analysis.

DISCUSSION

The present study shows that patients with cirrhosis and arterial hypertension have: (1) a hyperkinetic systemic circulation with central hypovolaemia; (2) absence of overt

Table 3 Heart rate, stroke volume, and central circulation time in normotensive and hypertensive patients with cirrhosis, normotensive controls, and patients with essential hypertension

	Controls	Cirrhosis			Essential Hypertension		
		Normotension	Hypertension		Normotension	Hypertension	
		Child A	Child B	Child C	Child A	Child B	Child C
Heart rate (/min)	68 (3)	73 (2)	78 (2)*	85 (2)* NS	83 (4)*	77 (4)	93 (5)*
Stroke volume (ml)	84 (5)	91 (1)*	91 (0.4)*	94 (0.4)*†††	83 (1)	93 (1)*	79 (1)
Central circulation time (s)	16.4 (1.5)	15.3 (0.7)	13.2 (0.5)*	11.2 (0.4)* NS	14.6 (1.1)	13.2 (1.5)*	11.1 (0.7)*

Values are mean (SEM).

Significant difference: *p<0.05 compared with controls; †††p<0.001 between normotensive and hypertensive patients with cirrhosis; NS, not significant.

Table 4 Normotensive cirrhotic patients matched (2:1) to hypertensive cirrhotic patients according to age, sex, body size, and Child class

	Cirrhosis with normotension matched (n=66)	Cirrhosis with arterial hypertension (n=33)	p Value
Age (y)	51 (1.2)	51 (1.8)	†
Sex (M/F)	54/12	(27/6)	†
Body height (cm)	173 (1.0)	172 (1.4)	†
Child score	6.7 (0.3)	6.4 (0.4)	†
Body weight (kg)	75 (1.9)	76 (3.1)	NS
Ideal body weight (kg)	66.9 (0.8)	66.7 (1.0)	NS
Galactose elimination capacity (mmol/min)	1.70 (0.07)	2.00 (0.16)	NS
Indocyanine green clearance (ml/min)	288 (27)	246 (19)	NS
Hepatic venous pressure gradient (mm Hg)	13.6 (0.7)	13.0 (1.1)	NS
Mean arterial blood pressure (mm Hg)	82 (1)	115 (1)	<0.0001*
Heart rate (/min)	77 (2)	82 (3)	NS
Cardiac output (l/min)	7.10 (0.24)	6.80 (0.37)	NS
Central circulation time (s)	13.4 (0.5)	13.3 (0.8)	NS
Central blood volume %	26.6 (0.8)	26.0 (1.4)	NS
(ml/kg)	20.7 (0.7)	19.8 (1.0)	NS
Plasma volume (ml/kg)	53.3 (1.2)	51.2 (2.2)	NS
Arterial compliance (ml/mm Hg)	1.40 (0.07)	1.07 (0.07)	<0.005
Systemic vascular resistance (dyn×s/cm ²)	1011 (45)	1474 (78)	<0.001

Values are mean (SEM).

†Matching criteria, *diagnostic criteria.

vasodilatation with normal SVR and AC; and (3) signs of better liver function than their normotensive counterparts. Moreover, the study confirms that the combination of arterial hypertension and cirrhosis is relatively rare.

Liver function and prevalence of hypertension

It is well known that alcoholic patients with fatty liver may have raised arterial blood pressure.²² Liver disease per se is not otherwise associated with increased arterial blood pressure; on the contrary, in patients with liver disease it is most often low normal or decreased.¹⁻³ Studies on arterial hypertension in patients with cirrhosis show that the frequency is reduced, with a prevalence of raised arterial blood pressure of 3–7%.^{7–11} This is in keeping with the present value of 5%. In advanced cirrhosis, increased arterial pressure is uncommon.¹⁰⁻¹¹ This agrees with the present findings of better liver function and a lower Child score in hypertensive than in normotensive patients with cirrhosis. When hypertensive patients with cirrhosis were compared with their

normotensive counterparts matched according to anthropometry and liver function (table 4), the characteristic haemodynamic findings ((1) and (2) above) were still present. This rules out a simple effect of better liver function or earlier stage of disease.

Diagnostic criteria of hypertension and clinical differences

The standard criteria for hypertension were applied in our study.²³ Mean blood pressures in the two hypertensive and two normotensive groups were similar (fig 4). However, hypertensive cirrhotic patients differed in several aspects from patients with essential hypertension. Thus the former were hyperkinetic and central hypovolaemic with a short central circulation time and normal SVR and AC. Moreover, hypertensive cirrhotic patients had an almost normal body mass index, in contrast with the high value in essential hypertensive patients (table 1). SVR and AC are important determinants of blood pressure. Obviously, selecting a group

Table 5 Multiple regression analysis of systemic vascular resistance (SVR), arterial compliance (AC), and haemodynamic and liver function variables in 163 patients with cirrhosis

	Regression coefficient	SE	p Value
SVR v variable			
Systolic blood pressure	2.246	1.111	<0.05
Plasma volume	-0.253	0.0243	<0.001
Central blood volume	11.294	3.275	<0.001
Central circulation time	61.377	6.835	<0.001
Constant	1461.208		
r ² for model = 0.806, p<10 ⁻⁶			
AC v variable			
Mean arterial blood pressure	-0.00919	0.00247	<0.001
Blood volume	0.000105	0.0000167	<0.001
Central blood volume	0.0343	0.00468	<0.001
Central circulation time	-0.0290	0.00606	<0.001
Hepatic venous pressure gradient	-0.0153	0.00409	<0.001
Hepatic blood flow	-0.0816	0.0400	<0.05
Constant	1.563		
r ² for model = 0.700, p<10 ⁻⁶			

of patients who have high blood pressure is likely to give rise to significant differences. However, it should be emphasised that only statistically independent variables were correlated.

Vasodilatation and vasoconstriction

The main finding of the present study was that hypertensive cirrhotic patients had normal SVR and AC and hence no signs of substantial vasodilatation (table 4). This is in marked contrast with normotensive cirrhotic patients who had the well known signs of progressive vasodilatation with increasing severity of cirrhosis (fig 4). Fifteen years ago, Schrier *et al* proposed the peripheral arterial vasodilatation theory.³ According to this theory, peripheral and splanchnic vasodilatation leads to a reduction in SVR, effective blood volume, and arterial pressure, which are primary events in the retention of sodium and water. Experimental and clinical observations favour the presence of a surplus of circulating vasodilators in cirrhosis. Combined with resistance to pressor substances, this leads to vasodilatation with reduced vascular resistance.^{1 24 25} The present study suggests that these changes are less pronounced in hypertensive cirrhotic patients. Coexistence of increased peripheral resistance (as in essential arterial hypertension) and decreased splanchnic resistance (as in cirrhosis) may depend on tonus of the autonomic system, vasoactive substances, reactivity of vasomotor systems, etc.^{12 26} The result may be a combination of increased and decreased vascular resistance in parallel. Normal overall SVR, as found in the present study, may thus cover splanchnic vasodilatation and peripheral vasoconstriction, a balance which may change with progression of liver disease. This needs further investigation.

The present study shows that AC is raised in normotensive, but normal in hypertensive patients with cirrhosis. Recent investigations have shown that the altered static and dynamic characteristics of the wall of large arteries in patients with cirrhosis are closely associated with circulatory and homeostatic derangement.^{12 18 27 28} These investigations have also revealed that changes in arterial mechanics are, at least in part, reversible.¹⁴ AC is an important determinant of coupling between the heart and arterial system, and of the dynamics of intravascular volume relocation.²⁹ This was confirmed by the present multiple regression analysis (table 5). Normal AC is in keeping with a normal or near normal vascular tone, and it could therefore be expected that hypertensive cirrhotic patients had a less abnormal volume distribution.

Blood volume distribution and flow

Patients with cirrhosis have increased blood and PVs,^{1 16} and the distribution of blood to the different vascular beds is abnormal in relation to the severity of disease,^{16 19 30–32} as found in our normotensive patients with cirrhosis. The effective blood volume (as evidenced by CBV³³) was decreased, and central circulation time was substantially reduced. These typical alterations were found in both normotensive and hypertensive patients with cirrhosis (fig 2, tables 2 and 3). Thus the present study presents no evidence of a less contracted or even expanded CBV in hypertensive cirrhotic patients. Whether raised arterial blood pressure is indicative of normal arterial filling or the result of arterioconstrictive adaptation to a low arterial blood volume must await future studies.

CO was significantly increased in hypertensive cirrhotic patients compared with controls and patients with essential hypertension (fig 4B) but no significant difference was found compared with their normotensive counterparts. However, arterial blood pressure was directly related to CO in hypertensive cirrhotic patients whereas the relation was inverse in the normotensive cirrhotic group. Similarly,

different relations were found for PV and central circulation time. This suggests that there are major differences in the regulation of blood pressure in the two cirrhotic groups (see below). Moreover, cardiac dysfunction may be present^{3 4 16 19} but we did not detect an especially high prevalence of QT prolongation.

As to the pathophysiological mechanisms behind the reduced coexistence of arterial hypertension and cirrhosis, Gentilini *et al* investigated patients with non-alcoholic cirrhosis and arterial hypertension.¹² Their main finding was that arterial hypertensive cirrhotic patients were normodynamic with a normal heart rate and CO. Moreover, these authors found no difference in the plasma renin activity of normotensive and hypertensive cirrhotics.¹² This conflicts with the results of Veglio *et al*, who found that hypertensive cirrhotic patients had a lower plasma renin activity.¹³ Veglio concluded that arterial hypertensive cirrhotic patients had an increased peripheral pressor effect of vasoactive hormones and an enhanced effective blood volume.¹³ The present study does not confirm Gentilini's result of a normodynamic circulation in hypertensive cirrhotic patients, or Veglio's hypothesis of an enhanced effective blood volume in these patients.

Blood pressure regulation

Most likely hypertensive cirrhotics are patients with essential hypertension which developed either before or during the chronic liver disease. In some ways they are haemodynamically between essential hypertension and cirrhosis (fig 4, tables 2 and 3). Arterial hypertensive cirrhotic patients may have less impaired cardiovascular reflexes^{12 24 34} but this topic needs further investigation. The fact that a hyperkinetic systemic circulation may exist simultaneously with arterial hypertension points to mechanisms other than peripheral vasodilatation in a subset of patients with cirrhosis. Splanchnic vasodilatation, as evidenced by substantial portal hypertension and high liver blood flow (fig 1), probably plays a major role, and the subsequent central volume contraction may be the afferent limb of the cardioaccelerative mechanisms.

Whether these patients are less susceptible to fluid retention is open to question as about a third of patients with essential hypertension are salt sensitive.³⁵ The various relations between arterial blood pressure on the one hand and CO, central circulation time, and PV on the other suggest that haemodynamic regulation is different in these patients with both cirrhosis and arterial hypertension.

CONCLUSION

Patients with cirrhosis and arterial hypertension are hyperdynamic and central hypovolaemic, like their normotensive counterparts, but have no signs of overall peripheral vasodilatation, and regulation of arterial blood pressure may be less deranged. Whether these patients are "protected" from vasodilatory complications, such as the hepatopulmonary syndrome, or they are more or less prone to develop hepatorenal syndrome, are topics for future research.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 373

The abdominal x ray showed a distended stomach, aerobilia, and gall stones, with no evidence of small bowel dilatation. Computed tomography confirmed gall stone impaction in the duodenum which resulted in gastric outlet obstruction. The clinical picture was compatible with a diagnosis of Bourevet's syndrome, which is a special form of gall stone ileus.

Extracorporeal shockwave lithotripsy has been reported for the initial relief of obstruction. Conventional open surgical treatment remains the treatment of choice. However, this is associated with a high morbidity and even mortality. This is particularly true for elderly patients with a one stage radical procedure.

For this patient we performed laparoscopic assisted enterolithotomy. The impacted gall stones at the distal duodenum were first milked into the jejunum by a laparoscopic instrument. The small bowel loop was then exteriorised through a 4 cm wound in the right upper abdomen and enterolithotomy performed (fig 3). The patient made an uneventful recovery and was discharged from hospital three days after the operation.

Figure 3 The small bowel loop was exteriorised through a 4 cm wound in the right upper abdomen and enterolithotomy performed.

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