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Arterial compliance in patients with cirrhosis: stroke volume-pulse pressure ratio as simplified index

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Henriksen, Jens H., Stefan Fuglsang, Flemming Bendtsen, Erik Christensen, and Søren Møller. Arterial compliance in patients with cirrhosis: stroke volume-pulse pressure ratio as simplified index. *Am J Physiol Gastrointest Liver Physiol* 280: G584–G594, 2001.—Arterial function may be altered in patients with cirrhosis. We determined compliance of the arterial tree (C_1) in relation to systemic and splanchnic hemodynamic derangement and clinical variables. C_1 and the stroke volume-pulse pressure index (SV/PP) were significantly higher (+62% and +40%, respectively; $P < 0.001$) in cirrhotic patients ($n = 49$) than in control subjects ($n = 19$), and a close correlation between C_1 and SV/PP was found in both cirrhotic patients ($r = 0.86$, $P < 0.001$) and control subjects ($r = 0.96$, $P < 0.001$). Univariate analysis showed significant relations between C_1 and SV/PP on one side and age, sex, body weight, portal pressure, systemic hemodynamics, biochemical variables, and severity of disease on the other. In the multiple-regression analysis, sex, age, mean arterial blood pressure, systemic vascular resistance, and biochemical variables were significant independent predictors of SV/PP ($P < 0.005$–0.00001). In conclusion, arterial compliance is elevated in cirrhosis. A simplified SV/PP index seems to reflect abnormalities in the arterial compliance of these patients.

cardiac output; circulatory regulation; hyperdynamic circulation.

OVER THE LAST DECADE, it has become apparent that abnormal distribution of blood flow and volume in patients with cirrhosis is important for the development of cardiovascular dysfunction, renal sodium-water retention, and clinical outcome (5, 9, 11, 24, 25). In addition to the presence of portal hypertension, these patients typically present with a hyperdynamic systemic circulation with increased heart rate, cardiac output, and plasma volume and low overall vascular resistance (9, 33). The balance between vasodilating and vasoconstricting forces is abnormal, especially in decompensated patients (14, 26, 27). In addition to changes in systemic vascular resistance, which is mainly located in small arteries and arterioles, the function of larger arteries may also be modulated in cirrhosis (2, 23).

Over the last decade attention has focused on the central vasculature and, in particular, on assessing biophysical properties of the large arteries, which have emerged as predictors of circulatory events (34). Arterial compliance (i.e., change in luminal arterial volume relative to change in transmural arterial blood pressure) is largely unknown in cirrhosis, but recently in a preliminary study (18) we found indications of elevated arterial compliance in advanced disease that could indicate changes in static composition of the arterial wall or dynamic changes in the smooth muscle tone of the large arteries. Arterial compliance was recently assessed in a simple way as stroke volume relative to pulse pressure and was described in a large reference population (4).

The present study was undertaken to measure the arterial compliance from the arterial pressure curve and to evaluate the stroke volume-pulse pressure ratio (SV/PP) as an index of arterial compliance in patients with cirrhosis. In addition, we have determined its relation to systemic and splanchnic hemodynamics and clinical variables.

PATIENTS AND METHODS

Study population. The study population comprised 49 patients with cirrhosis who were referred for hemodynamic investigation to diagnose and quantify portal hypertension. Of these, 44 patients had biopsy-verified cirrhosis. The age range was 32–81 yr with an average of 50 yr. The etiology was alcoholic in 43 and chronic hepatitis in 4, and no specific etiology could be established in 2 patients. None of the patients had experienced recent gastrointestinal bleeding or had encephalopathy above grade I. All were abstaining from alcohol and had no signs of withdrawal symptoms at the time of the study. None had signs of heart failure, organic renal disease, diabetes, cancer, or any other major disease. The patients were divided into three groups with increasing severity of disease according to the modified Child-Turcotte criteria (8). Fourteen patients belonged to class A, twenty to class B, and fifteen to class C. Ultrasonography showed

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ascites in 15 patients, but none had signs of subacute spontaneous bacterial peritonitis. The patients with ascites were prescribed a diet with 40 mmol of sodium a day. Twenty-five patients received diuretics (100–400 mg spironolactone/day in 22, 2–4 mg bumetanide/day in 6, 40–160 mg furosemide/day in 14, and 5 mg bendroflumethiazide/day in 2). One patient was treated with a beta blocker, one with a calcium antagonist, and one with a nitrate. The clinical and biochemical characteristics are summarized in Table 1.

One control group comprised 19 patients without liver disease who were referred for hemodynamic investigation to exclude circulatory disorders (mainly intestinal ischemia), for which no evidence was found. All had normal arterial blood pressure (i.e., diastolic pressure <90 mmHg). Five patients received diuretics (80 mg furosemide/day), one a calcium antagonist, and one a nitrate. Clinical and biochemical data of these normotensive controls are summarized in Table 1.

A second control group consisted of 16 patients with arterial hypertension (i.e., untreated diastolic pressure >95 mmHg) referred for hemodynamic 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 hypertension in all 16 patients. Ten patients received diuretics (40–160 mg furosemide/day in 3 and 5 mg bendroflumethiazide/day in 7), four patients were treated with calcium antagonists, and one was treated with a beta blocker. Clinical and biochemical data are summarized in Table 1.

All the patients consented to participate in the study, which was approved by the Ethics Committee for Medical Research in Copenhagen and performed in accordance with the guidelines established in the Helsinki Declaration II. No complications or side effects were encountered during the study.

Catheterization. Catheterization was performed to quantify arterial and portal hypertension, to determine the response of food-induced splanchnic flow, and to collect elective renin samples. All the subjects were studied in the morning after an overnight fast and at least 1 h in the supine position, as described elsewhere (13, 25, 27). In brief, a Cournand catheter (7 F) or a Swan-Ganz catheter (7 F) was guided to the hepatic/renal veins through the femoral route under fluoroscopic control with the patient under local analgesia. A small indwelling polyethylene catheter (5 F) was introduced into the femoral artery by the Seldinger technique with the tip of the catheter located at the aortic bifurcation.

Pressures were measured with a capacitance transducer (Simonsen and Weel, Copenhagen, Denmark), as previously described (27). Frequency characteristics and reliability of dynamic intravascular pressure measurement, including determination of systolic and diastolic pressures, had been assessed earlier with this equipment (27). Systolic arterial blood pressure (SAP) was determined as the average of the maximum blood pressure over 20–30 s [$SAP = (\Sigma P_s)/n$; where P_s is systolic pressure of a single cycle and n is number of cycles], and diastolic arterial blood pressure [$DAP = (\Sigma P_d)/n$; where P_d is diastolic pressure] was determined as the average of the minimum blood pressure in the same period. The start of the diastolic pressure was determined at the dicrotic notch [$DAP_o = (\Sigma P_o)/n$]. Pulse pressure (PP, i.e., SAP − DAP) was determined as the average amplitude of the arterial pressure over 20–30 s. The mean arterial pressure (MAP) was determined independently by electronic integration of the pressure signal. Right atrial pressure (RAP) was determined as the mean pressure over 15 s. The hepatic venous pressure gradient (HVPG) was determined as wedged minus free hepatic venous pressure. Zero reference was the midaxillary level, and all pressures were measured in millimeters of mercury. The time (Δt) from the start of the electrical systole [start of the R wave in the electrocardiogram (ECG)] to the start of the aortoiliac mechanical systole was determined from simultaneous registration of the ECG and pressure curve (see Fig. 1). QT interval (in s) was determined

Table 1. *Clinical and biochemical data for patients with cirrhosis and control groups*

	Cirrhosis (Child-Turcotte Class)			Controls		
	A (n = 14)	B (n = 20)	C (n = 15)	Normotensive (n = 19)	Hypertensive (n = 16)	ANOVA P
Age, yr	49 ± 2.2	49 ± 2.3	52 ± 4.0	50 ± 3.4	50 ± 2.8	ns
Sex, M/F	10/4	16/4	8/7	9/10	8/8	ns
Body height, cm	170 ± 1.7	173 ± 2.2	171 ± 2.4	167 ± 2.4	170 ± 2.4	ns
Body weight, kg	67 ± 4.5	78 ± 3.4[a]	69 ± 3.8	60 ± 3.9	81 ± 5.0[b]	<0.01
Ideal body weight, kg	65 ± 1.3	67 ± 1.7	66 ± 1.8	62 ± 1.8	65 ± 1.8	ns
Ascites	0	3	12	0	0	
Diuretics, no/yes	10/4	10/10	4/11	14/5	6/10	
Hemoglobin, mmol/l (7.0–10.9)	8.1 ± 0.4	7.5 ± 0.3[f]	6.7 ± 0.2[cf]	7.9 ± 0.3[f]	9.1 ± 0.2	<0.02
S-albumin, μmol/l (540–800)	563 ± 19	501 ± 14[dg]	394 ± 21[dg]	541 ± 17	591 ± 15	<0.001
S-alanine aminotransferase, U/l (10–40)	57 ± 13[g]	49 ± 7[g]	141 ± 95[g]	31 ± 10		<0.005
S-bilirubin, μmol/l (2–17)	12 ± 2	26 ± 3	65 ± 12[e]	10 ± 3	12 ± 1	<0.001
S-alkaline phosphatase, U/l (50–275)	540 ± 198[g]	300 ± 29	535 ± 79[g]	194 ± 24	145 ± 11	<0.001
Coagulation factors 2, 7, 10, index (0.70–1.30)	0.93 ± 0.06	0.57 ± 0.03[e]	0.42 ± 0.04[e]	0.98 ± 0.05	1.15 ± 0.05	<0.001
S-Na, mmol/l (136–146)	139 ± 0.7	138 ± 0.8	132 ± 1.5[e]	139 ± 0.6	139 ± 1.3	<0.001
S-K, mmol/l (3.5–5.0)	4.0 ± 0.07	3.9 ± 0.1	3.7 ± 0.1	4.2 ± 0.1	3.9 ± 0.1	ns
S-creatinine, μmol/l (49–121)	69 ± 5	78 ± 3	77 ± 11	82 ± 4	113 ± 12[e]	<0.001
pH (7.35–7.46)	7.41 ± 0.01	7.42 ± 0.01	7.44 ± 0.01	7.40 ± 0.01	7.43 ± 0.01	ns

Values are means ± SE. ns, Not significant. Units and reference intervals are given for biochemical data. Ideal body weight was calculated as [body height (cm) − 100] − ¼ [body height (cm) − 150]. Nonsignificance of sex determined by χ^2 test. Significant difference ($P < 0.05$): [a]Child-Turcotte B vs. normotensive controls; [b]hypertensive vs. normotensive controls; [c]Child-Turcotte C vs. Child-Turcotte A; [d]vs. Child-Turcotte A; [e]vs. all other groups; [f]vs. hypertensive controls; [g]vs. controls.

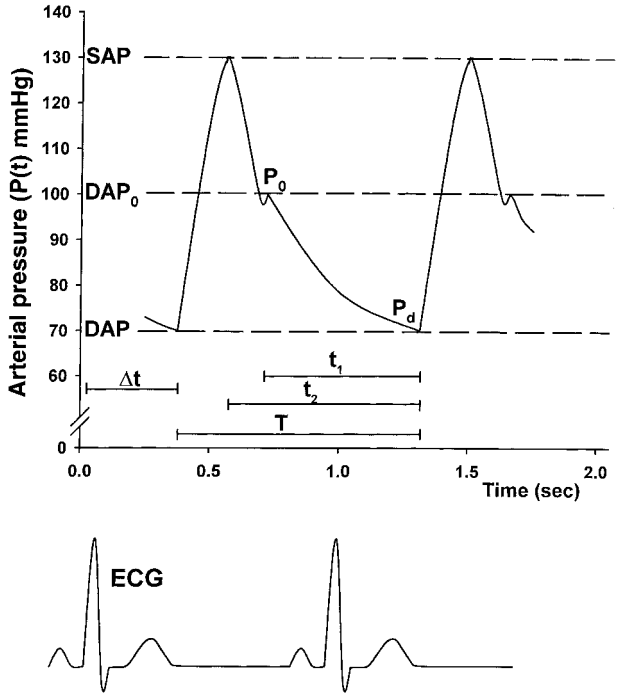

Fig. 1. Illustration of pressures and time relations. P(t), arterial blood pressure as a function of time; SAP, average systolic arterial pressure; DAP, average diastolic arterial pressure; DAP_o, average start of diastolic pressure; P_o, start of diastolic blood pressure; P_d, end of diastolic blood pressure; MAP, mean arterial blood pressure; t_1, time from start to end of diastole; t_2, time from peak systole to end of diastole; T, time of 1 cardiac cycle; Δt, time from start of electrical systole to aortoiliac mechanical systole; ECG, electrocardiogram.

from the ECG, and the frequency was adjusted by standard equation: $QT_c = QT/\sqrt{T}$, where T (in s) is the time of the RR interval.

Cardiac output (CO_I, in l/min) for the determination of arterial compliance was measured by the indicator-dilution technique after a bolus injection of 150 KBq of ^{125}I-labeled human serum albumin (IFE IT.20S, Institute of Energy Technique, Kjeller, Norway) into the right atrium, followed by arterial sampling as previously described (13, 25).

Plasma volume (PV_{Tc}), blood volume (BV_{Tc}), central circulation time, and additional measurement of cardiac output (CO_{Tc}) were determined by another indicator, independent of the ^{125}I indicator determination, as described elsewhere (13). A quantitative injection of 0.5 MBq of ^{99m}Tc-labeled human serum albumin (Vasculocis, CIS bio international, Grif-sur-Yvette, France) was given into the right atrium, followed by automatic arterial sampling for 60 s and at 10 min as previously described (13, 25). Systemic vascular resistance (SVR, dyn·s·cm^{-5}) was determined as $SVR_{Tc} = 80\ (MAP - RAP)/CO_{Tc}$.

Arterial compliance was estimated in different ways as outlined in the APPENDIX. The compliance of the central arterial tree was determined according to a two-element windkessel model (3, 20, 37) that assumes that compliance (C) and hemodynamic resistance (R) are constant during the measurement. An acceleration component was ignored because it contributed <10% (see APPENDIX).

Figure 1 illustrates arterial pressure over time [P(t)]. As shown in the APPENDIX, P(t) can be expressed during diastole as

$$P(t) = P_o \cdot e^{-t/RC} \quad (1)$$

where P_o is the start of diastolic pressure. The end of the diastolic pressure (P_d) is then

$$P_d = P_o \cdot e^{-t_1/RC} \quad (2)$$

Isolation of C in *Eq. 2* gives C_1 with the corresponding time t_1

$$C_1 = \frac{t_1}{R \cdot \ln (P_o/P_d)} \quad (3)$$

where t_1 is the time from the start to the end of diastole (in s).

Substitution of R, P_o, and P_d in *Eq. 3* with the directly measured values gives

$$C_1 = \frac{CO_1 \cdot t_1 \cdot 1{,}000/60}{(MAP - RAP) \cdot \ln (DAP_o/DAP)} \quad (4)$$

In the entire interval of declining pressure, another estimate of arterial compliance, C_2, can be obtained

$$C_2 = \frac{CO_1 \cdot t_2 \cdot 1{,}000/60}{(MAP - RAP) \cdot \ln (SAP/DAP)} \quad (5)$$

(see APPENDIX), where t_2 = time (in s) from the systolic maximum to the diastolic minimum pressure.

As described in the APPENDIX, arterial compliance can be estimated in a more simple way (decay time principle) as

$$C_1' = [SV_I/(DAP_o - DAP)] \cdot (t_1/T) \quad (6)$$

where SV_I is stroke volume (in ml) determined by the ^{125}I indicator as CO_I divided by heart rate (HR) and T is the time (in s) of one heartbeat [i.e., 1/HR (in s)].

Similarly, another simplified estimate is C_2'

$$C_2' = [SV_I/(SAP - DAP)] \cdot (t_2/T) = (SV_I/PP) \cdot (t_2/T) \quad (7)$$

In the case in which t_2/T is relatively constant, a simplified index *of* arterial compliance can be determined as SV_I/PP (= SV/PP).

Statistical evaluation. Data are presented as means ± SE. Statistical analysis was performed by one-way ANOVA with Tukey's correction or by the Kruskal-Wallis ANOVA on ranks with Dunn's correction or, in the case of bivariate data, by unpaired/paired Student's t-test or the Mann-Whitney and/or Wilcoxon rank tests. Correlations between variables were performed with the Pearson regression test (method of least squares) or by Spearman's rank correlation test. Multiple-regression analysis was performed to evaluate the relation between estimates of arterial compliance on the one hand and pertinent clinical, biochemical, and hemodynamic variables on the other. All variables were initially examined and included stepwise with the forward selection method. $P < 0.05$ was considered to be significant.

RESULTS

Hemodynamics, time intervals, and arterial compliance. Table 2 summarizes the hemodynamics. As expected, the cirrhotic patients were hyperdynamic with elevated CO (+31%, $P < 0.001$), HR (+8%, $P < 0.05$) and SV (+22%, $P < 0.001$). The mean central circulation time shortened with the progression of the liver disease (−24%, $P < 0.05$). The arterial blood pressure was slightly (−7%, $P < 0.01$) reduced or frankly (−16%, $P < 0.001$) reduced in the patients with severe disease. In the control subjects, MAP was close to DAP_o but significantly lower (104 ± 2.9 vs. 108 ± 3.2 mmHg, difference 3.7 ± 1.1 mmHg, $P < 0.001$; $r = 0.94$, $P <$

Table 2. *Hemodynamics in patients with cirrhosis and control groups*

	Cirrhosis (Child-Turcotte Class)			Normotensive Controls (n = 19)	Hypertensive Controls (n = 16)	ANOVA P Value
	A (n = 14)	B (n = 20)	C (n = 15)			
Arterial blood pressure						
Systolic, mmHg	140 ± 6.0	138 ± 4.1	118 ± 3.7[ad]	146 ± 7.2	179 ± 7.4[e]	<0.005[f]
Diastolic, mmHg	69 ± 4.1	67 ± 2.4	58 ± 2.3	67 ± 2.4	81 ± 3.0[e]	<0.05[f]
Pulse pressure, mmHg	72 ± 3.2	69 ± 3.1	60 ± 2.4[bd]	79 ± 5.6	98 ± 6.9[e]	<0.05[f]
Mean, mmHg	95 ± 5.0	91 ± 2.7	81 ± 3.4[bd]	96 ± 3.3	114 ± 3.7[e]	<0.05[f]
Start diastolic, mmHg	95 ± 3.8	92 ± 2.9	80 ± 2.9[ad]	99 ± 3.7	118 ± 4.3[e]	<0.005[f]
Cardiac output, l/min	6.30 ± 0.46	7.31 ± 0.34[d]	6.95 ± 0.43[d]	5.26 ± 0.26	5.27 ± 0.45	<0.001[g]
Cardiac index, l/min·m^2	3.60 ± 0.23	3.89 ± 0.19[d]	3.84 ± 0.21[d]	3.19 ± 0.14	2.71 ± 0.18	<0.001[g]
Heart rate, beats/min	77 ± 3.9	76 ± 3.0	78 ± 3.7	72 ± 2.4	71 ± 3.1	ns
Stroke volume, ml	82 ± 4.7	100 ± 6.7[d]	94 ± 8.7	75 ± 4.6	77 ± 7.8	<0.05[g]
Mean circulation time, s	15.7 ± 1.5	12.7 ± 0.9[d]	11.9 ± 0.7[bd]	16.5 ± 1.4	16.3 ± 0.8	<0.001[f]
Plasma volume						
in liters	3.21 ± 0.18	4.29 ± 0.18[cd]	3.87 ± 0.24[d]	2.84 ± 0.14	2.87 ± 0.19	<0.002[f]
in ml/kg	50.7 ± 3.4	56.0 ± 2.5[d]	58.6 ± 0.35[d]	49.4 ± 2.6	35.1 ± 1.5[e]	<0.01[g]
Blood volume, liters	4.92 ± 0.25	6.31 ± 0.27[cd]	5.51 ± 0.35[d]	4.37 ± 0.23	4.72 ± 0.32	<0.01[f]
Wedged hepatic vein pressure, mmHg	16.5 ± 1.6[d]	23.1 ± 1.1[cd]	26.2 ± 1.8[bd]	7.6 ± 0.6	<11	<0.001[f]
Free hepatic vein pressure, mmHg	7.0 ± 0.8	8.0 ± 0.6	8.5 ± 1.1	4.5 ± 0.5	<6	ns
Hepatic venous pressure gradient, mmHg	9.4 ± 1.1[d]	15.1 ± 1.0[cd]	17.5 ± 1.6[bd]	3.1 ± 0.2	<5	<0.001[f]
Right atrial pressure, mmHg	2.7 ± 0.2	3.8 ± 0.3	3.4 ± 0.3	2.8 ± 0.2	3.0 ± 0.2	ns
Systemic vascular resistance, dyn·s/cm^{-5}	1,206 ± 95	1,019 ± 85	998 ± 105	1,479 ± 111	1,639 ± 182	<0.05[f]

Values are means ± SE. Significant difference: [a]Child-Turcotte C vs. A and B ($P < 0.05$); [b]Child-Turcotte C vs. A ($P < 0.05$); [c]Child-Turcotte B vs. A ($P < 0.05$); [d]vs. normotensive and hypertensive controls ($P < 0.05$); [e]hypertensive controls vs. others ($P < 0.05$); [f]ANOVA of cirrhosis, cirrhosis + normotensive controls, cirrhosis + normotensive controls + hypertensive controls [g]ANOVA of cirrhosis + normotensive controls + hypertensive controls.

0.001). In the patients with cirrhosis, MAP and DAP_o were almost identical: 89.4 ± 2.2 vs. 89.6 ± 2.0 mmHg (difference 0.2 ± 1.4 mmHg, not significant; $r = 0.92$, $P < 0.001$). PV_{Tc} and BV_{Tc} were elevated [+35% ($P < 0.001$) and +30% ($P < 0.001$)], and SVR_{Tc} was reduced (−28%, $P < 0.001$), especially in the patients with severe disease (−34%, $P < 0.01$). RAP was normal, and the splanchnic pressures, especially HVPG, were substantially increased (+358%, $P < 0.001$). The differences between the normotensive and hypertensive control subjects were solely related to the higher arterial blood pressure in the latter group (MAP: 114 vs. 96 mmHg, $P < 0.001$).

Time intervals t_1, t_2, T, t_1/T, and t_2/T were remarkably similar in the patients with cirrhosis and the control subjects, except for a slightly higher t_2/T in the patients with severe cirrhosis (+3%, $P < 0.05$; see Table 3). The small differences could be ascribed solely to the slight differences in HR of the cirrhotic patients and controls.

C_1 was directly related to the time from the start of the electrical systole to the start of the aortoiliac mechanical systole (Δt) (Fig. 2), which indicates a direct relation between pulse propagation time and arterial compliance. The different estimates of arterial compliance showed the same trend in the different groups

Table 3. *Times and time relations of arterial pulse curve from patients with cirrhosis and control groups*

	Cirrhosis (Child-Turcotte Class)			Normotensive Controls (n = 19)	Hypertensive Controls (n = 16)
	A (n = 14)	B (n = 20)	C (n = 15)		
t_1, s	0.46 ± 0.04	0.48 ± 0.03	0.44 ± 0.03	0.51 ± 0.03	0.50 ± 0.02
t_2, s	0.65 ± 0.04	0.65 ± 0.03	0.64 ± 0.04	0.67 ± 0.03	0.67 ± 0.02
T, s	0.81 ± 0.04	0.79 ± 0.03	0.79 ± 0.04	0.85 ± 0.03	0.84 ± 0.03
$T - t_1$, s	0.35 ± 0.02	0.31 ± 0.02	0.34 ± 0.02	0.33 ± 0.01	0.34 ± 0.01
t_1/T	0.56 ± 0.02	0.60 ± 0.02	0.56 ± 0.02	0.60 ± 0.01	0.59 ± 0.01
$1 - t_1/T$	0.44 ± 0.02	0.40 ± 0.02	0.44 ± 0.02	0.40 ± 0.01	0.41 ± 0.01
t_2/T	0.79 ± 0.01	0.81 ± 0.01	0.81 ± 0.01	0.79 ± 0.01	0.79 ± 0.01
t_1/ln (DAP_o/DAP), s	0.92 ± 0.07	0.93 ± 0.05	0.92 ± 0.06	0.91 ± 0.06	0.88 ± 0.06
t_2/ln (SAP/DAP), s	1.45 ± 0.17	1.59 ± 0.12	1.38 ± 0.08	1.31 ± 0.07	1.48 ± 0.16
QT, s	0.38 ± 0.01	0.39 ± 0.01	0.39 ± 0.01	0.40 ± 0.01	0.44 ± 0.02
QT_c, s$^{1/2}$	0.42 ± 0.01	0.44 ± 0.01	0.44 ± 0.01	0.42 ± 0.01	0.46 ± 0.02

Values are means ± SE. t_1, time from start to end of diastole; t_2, time from systolic maximum to diastolic minimum pressure; T, time of 1 heart beat (1/heart rate); DAP_o, start diastolic pressure; DAP, diastolic pressure; SAP, systolic pressure; QT, QT interval; QT_c, frequency-adjusted QT interval. All differences ns by ANOVA.

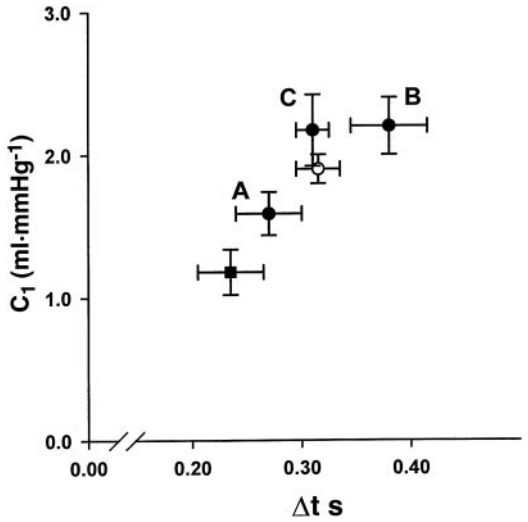

Fig. 2. Relation between arterial compliance (C_1) and Δt. ■, Control subjects; ●, cirrhosis patients (Child-Turcotte classes A, B, and C); ○, all patients with cirrhosis.

(Table 4). The lowest values of compliance were found in the hypertensive control subjects. The cirrhotic patients had substantially higher values than both control groups either taken separately or together (40–79%, $P < 0.001$). In the cirrhotic group, the compliance estimates in Child-Turcotte class A patients were higher, although not significantly (14–26%, $P = 0.07$–0.2), compared with the normotensive control subjects. A significant increase was observed through Child-Turcotte classes A to C, with the values in the class B and C patients significantly above the control values (+74–76%, $P < 0.01$). The C_1 and C_1' values were significantly higher than all other compliance estimates ($P < 0.0001$). C_1 and C_1' were not significantly different in the control groups, but C_1' was somewhat higher than C_1 in the patients with cirrhosis (+13.8%, $P < 0.001$). In contrast, C_2 and C_2' were not significantly different, either in the cirrhotic patients or in the control subjects. The SV/PP values were significantly higher than the C_2 and C_2' values ($P < 0.0001$). A close correlation was found between C_1 on the one hand and C_1', C_2, C_2', and SV/PP on the other, with the highest relation found among the controls (Fig. 3). A somewhat smaller, but still close and highly significant, relation was present in the cirrhotic patients (Table 5 and Fig. 3). The relationship between C_1 and SV/PP revealed a somewhat lower slope in the patients with cirrhosis than in the control subjects (0.54 vs. 0.82, $P < 0.001$), which means that the high values of SV/PP in patients with cirrhosis may underestimate the even higher values of C_1. This was also found with respect to the relation of C_1 to C_2 and C_2' (see Table 5). C_1 is in the main a diastolic compliance, whereas C_2 and SV/PP are both mixed diastolic and systolic compliance estimates.

Relation of arterial compliance to clinical, biochemical, and hemodynamic variables. The univariate correlations are summarized in Table 6. SV/PP showed a significant correlation to age, sex, body weight, Child-Turcotte score, coagulation factors 2, 7, and 10, MAP, SVR_{Tc}, PV_{Tc}, BV_{Tc}, and HVPG. SV/PP was determined independently of MAP, PV_{Tc}, and SVR_{Tc} and can therefore be stochastically analyzed with these and other variables. SV/PP was inversely related to MAP in both the cirrhotic patients and the control subjects (Fig. 4; cirrhotic patients: $r = -0.44$, $P < 0.002$ and control subjects: $r = -0.45$, $P < 0.01$). A direct relation was found between SV/PP and PV_{Tc} (Fig. 5; cirrhotic patients: $r = 0.52$, $P < 0.005$ and control subjects: $r = 0.39$, $P = 0.05$), and SV/PP was inversely related to SVR_{Tc} (Fig. 6; cirrhotic patients: $r = -0.73$, $P < 0.0001$ and control subjects: $r = -0.69$, $P < 0.001$). SV/PP was directly related to HVPG (Fig. 7; cirrhotic patients: $r = 0.31$, $P < 0.02$). Higher SV/PP values were recorded in men than in women (+46% in cirrhotic patients, $P < 0.01$; +31% in control subjects, $P < 0.01$), but this difference was not marked after adjustment for body size ($P = 0.05$).

In addition to the above-mentioned correlations, multiple-regression analysis demonstrated that age, sex, coagulation factors 2, 7, and 10, MAP, and SVR_{Tc} were independent predictors of SV/PP. Body weight, PV_{Tc}, and BV_{Tc} were borderline significant ($P = 0.1$). The analysis identified the same variables in separate analyses of patients with cirrhosis with and without the inclusion of controls (see Table 6).

Table 4. *Different determinations of arterial compliance in patients with cirrhosis and control groups*

	Cirrhosis (Child-Turcotte Class)			Normotensive Controls ($n = 19$)	Hypertensive Controls ($n = 16$)	ANOVA P Value
	A ($n = 14$)	B ($n = 20$)	C ($n = 15$)			
C_1, ml/mmHg	1.59 ± 0.15‡	2.2 ± 0.20*†‡	2.17 ± 0.25*‡	1.26 ± 0.10	1.12 ± 0.22	<0.001
C_1', ml/mmHg	1.79 ± 0.17	2.5 ± 0.25*†	2.47 ± 0.29*	1.43 ± 0.11	1.2 ± 0.13	<0.001
C_2, ml/mmHg	1.03 ± 0.10	1.30 ± 0.10*	1.43 ± 0.16*	0.88 ± 0.08	0.70 ± 0.07	<0.001
C_2', ml/mmHg	0.96 ± 0.10	1.24 ± 0.11*	1.40 ± 0.16*	0.82 ± 0.08	0.65 ± 0.07	<0.001
SV/PP, ml/mmHg	1.19 ± 0.12	1.52 ± 0.13*	1.61 ± 0.17*	1.04 ± 0.10	0.81 ± 0.08	<0.001

Values are means ± SE. C, arterial compliance; CO, cardiac output; MAP, mean arterial blood pressure; RAP, right atrial pressure; SV, stroke volume; PP, pulse pressure; $C_1 = 16.7 \cdot CO_I \cdot t_1/[(MAP - RAP) \cdot \ln (DAP_o/DAP)]$; $C_1' = [SV_I/(DAP_o - DAP)] \cdot (t_1/T)$; $C_2 = 16.7 \cdot CO_I \cdot t_2/[(MAP - RAP) \cdot \ln (SAP/DAP)]$; $C_2' = [SV_I/PP] \cdot (t_2/T)$; $SV/PP = SV_I/PP$. For descriptions of estimates of arterial compliance, see text. *Significantly different from normotensive controls and hypertensive controls ($P < 0.05$); †significantly different from Child-Turcotte A ($P < 0.05$); ‡significant difference between C_1 and C_1' ($P < 0.001$).

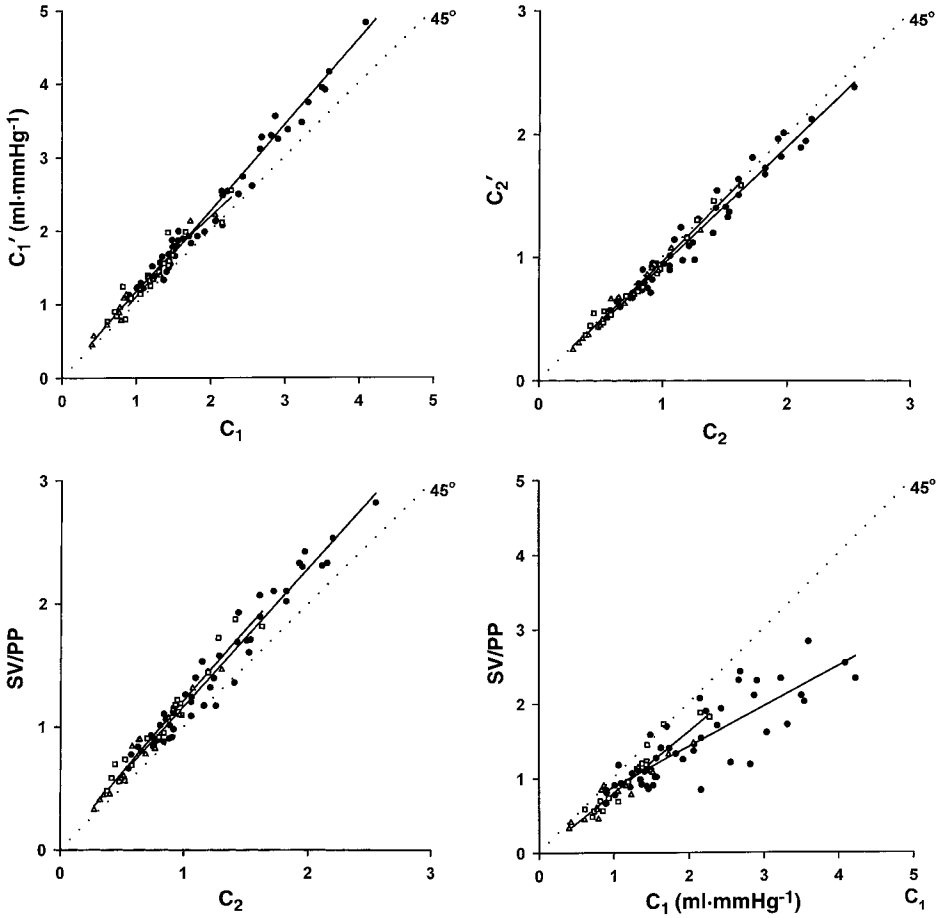

Fig. 3. Different estimates of arterial compliance in patients with cirrhosis and control subjects (C_1, C_1', C_2, C_2') and stroke volume-pulse pressure ratio (SV/PP) (see text and Table 4). ●, Patients with cirrhosis; □, normotensive control subjects; △, hypertensive control subjects. Correlations are summarized in Table 5.

DISCUSSION

This study is the first to analyze in depth arterial compliance in cirrhosis. We found that *1*) arterial compliance is increased in patients with cirrhosis; *2*) a simplified SV/PP index can be applied as an estimate of arterial compliance in cirrhosis; and *3*) in addition to a relation to demographic variables, the increased arterial compliance in patients with cirrhosis is related to hemodynamic derangement and indicators of severity of disease.

Determination of arterial compliance is complex (3, 20, 32, 37). The static and dynamic characteristics of the walls of large and small arteries may be different, and a detailed investigation involves analysis of the relation between volume changes over time and the arterial pressure curve. Accurate determination of arterial compliance requires a definite stroke output-time relation and a blood pressure-time relation at the aortic arch (41). Although these complex registrations can be obtained with a combination of several techniques in a highly experimental setup, in humans they are made seldom or only during very invasive investigations of coronary arteries (34, 37). An accurate blood pressure-time relation is most often combined with a more lumped registration of output from the left ventricle (3, 18, 20, 37). Other clinical methods are measurements of pulse wave velocity, echo tracking, and volume oscillometry (20, 29, 30, 42). Compliance may also be determined in a specific segment of the arterial tree (20, 34, 35, 37).

Table 5. *Slopes and correlations between different estimates of arterial compliance in controls and patients with cirrhosis*

	Controls		Cirrhosis	
	Slope	*r* Value	Slope	*r* Value
C_1 vs. C_1'	1.06 ± 0.047	0.970	1.17 ± 0.029†	0.986
C_1 vs. C_2	0.71 ± 0.031†	0.971	0.50 ± 0.037*†	0.893
C_1 vs. C_2'	0.69 ± 0.035†	0.960	0.47 ± 0.041*†	0.857
C_1 vs. SV/PP	0.82 ± 0.049†	0.960	0.54 ± 0.05*†	0.847
C_2 vs. C_2'	1.00 ± 0.025	0.990	1.01 ± 0.028	0.983
C_2 vs. SV/PP	0.81 ± 0.030†	0.979	0.85 ± 0.026†	0.978

Values are means ± SE. *Significantly lower than controls ($P < 0.001$); †significantly different from 1.00 ($P < 0.0001$).

SV/PP as an index of arterial compliance. C_1 is the average arterial compliance in diastole, as determined by a catheterization technique with registration of the pressure-time relationship in the aorta and mass-energy balance equations (2-element windkessel model). It should be kept in mind that the differential compliance (dV/dP) is dependent on the level of the arterial pressure in a nonlinear, inverse relation. Thus systolic compliance is smaller simply because of the higher pressure in this part of the cardiac cycle. C_1 and C_1'

Table 6. *Relation between estimates of arterial compliance and clinical and hemodynamic variables*

Univariate Analysis of SV/PP vs. Variables				
	Cirrhosis (n = 49)		Cirrhosis + normotensive controls (n = 68)	
Variables	r value	P value	r value	P value
Age	−0.20	<0.05	−0.28	<0.05
Sex	0.43	<0.01	0.44	<0.001
Body weight	0.50	<0.01	0.49	<0.0001
CF 2, 7, 10	−0.50	<0.01	−0.49	<0.0001
Child-Turcotte score	0.31	<0.02		
MAP	−0.44	<0.01	−0.51	<0.0001
PV_{Tc}	0.50	<0.01	0.50	<0.0001
BV_{Tc}	0.30	<0.05	0.38	<0.001
SVR_{Tc}	−0.59	<0.0001	−0.62	<0.0001
HVPG	0.31	<0.02	0.41	<0.001

Multiple-Regression Analysis			
Variables	Regression coefficient	SE	P value
SV/PP vs. variables (cirrhosis, n = 49)			
Sex	0.451	0.107	<0.0001
Age	−0.0166	0.0042	=0.0003
SVR_{Tc}	−0.00059	0.00018	=0.003
CF 2, 7, 10	−0.631	0.203	=0.003
MAP	−0.0110	0.003	=0.004
Adjusted R^2 for model = 0.672, ($P < 10^{-6}$)			
SV/PP vs. variables (cirrhosis + normotensive controls, n = 68)			
Sex	0.400	0.082	<0.0001
Age	−0.0133	0.0031	<0.0001
MAP	−0.0121	0.003	<0.0001
SVR_{Tc}	−0.00050	0.00012	<0.0001
CF 2, 7, 10	−0.621	0.160	=0.0003
Adjusted R^2 for model = 0.700, ($P < 10^{-6}$)			

Tc, technetium indicator; PV, plasma volume; BV, blood volume; SVR, systemic vascular resistance; HVPG, hepatic venous pressure gradient; CF 2, 7, 10, coagulation factors 2, 7, and 10.

were close in the control group, thus indicating that the assumption of an exponential decline in diastolic pressure is correct (Refs. 3, 20, and 41; see below). In the patients with cirrhosis, C_1 and C_1' were closely related but slightly higher values of C_1' were registered. The reason is most likely a slight but systematic deviation from the exponential fall in pressure in these patients, especially in those with advanced disease (Child-Turcotte class C: r^2 = 0.978, compared with r^2 = 0.984, 0.986, 0.984, and 0.981 in class A, class B, normotensive control subjects, and hypertensive control subjects, respectively). Propagation velocities of the pressure pulse and its reflected wave in a compliant aorta are reduced, thus moving the reflected wave from early diastole to late diastole.

C_2 includes compliance in the systole and is, as expected, below the C_1 estimate in both patients and control subjects but closely related to C_1. The very close

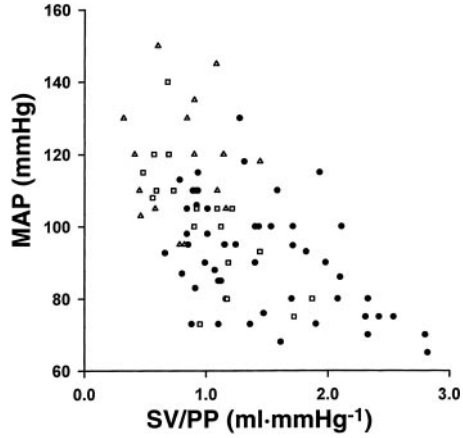

Fig. 4. Relations between SV/PP estimate of arterial compliance and MAP. Symbols are as in Fig. 3 (cirrhosis patients: r = −0.443, P < 0.002; control subjects: r = −0.453, P < 0.01).

relation between C_2 and C_2' illustrates that the assumptions of constant time ratios (see Table 3) and an exponential decline in pressure even when parts of systole are included are reasonably correct. C_2' and SV/PP only differ in the factor t_2/T. Thus SV/PP contains components of both systolic and diastolic arterial compliance, and it had a rather close relation to C_1, but the numerical value of SV/PP was somewhat lower than that of C_1 (−15% in the normotensive control group). However, in patients with cirrhosis this discrepancy became somewhat larger, especially with very high values of arterial compliance (−24%). Thus the true value of arterial compliance in a patient with a high SV/PP index may be even higher than the value estimated from this index. The reason may be that, although arterial blood pressure and pulse pressure are reduced in patients with cirrhosis, especially in advanced disease, the ratio of PP to the fall in pressure during diastole may be higher in patients with advanced disease than in those with early disease and in control subjects. However, the reason is not clear, and

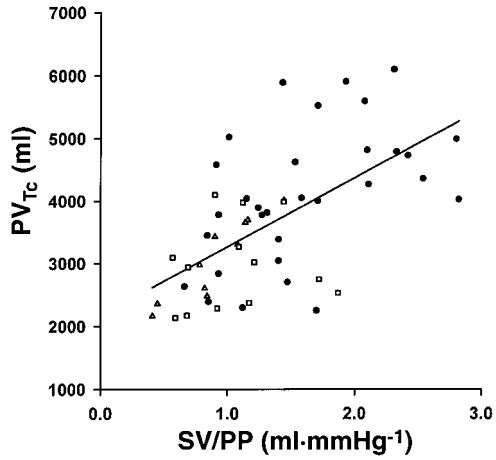

Fig. 5. Relation between SV/PP estimate of arterial compliance and independent determination of plasma volume with technetium indicator (PV_{Tc}). Symbols are as in Fig. 3 (cirrhosis patients: r = 0.516, P < 0.01; control subjects: r = 0.391, P = 0.05).

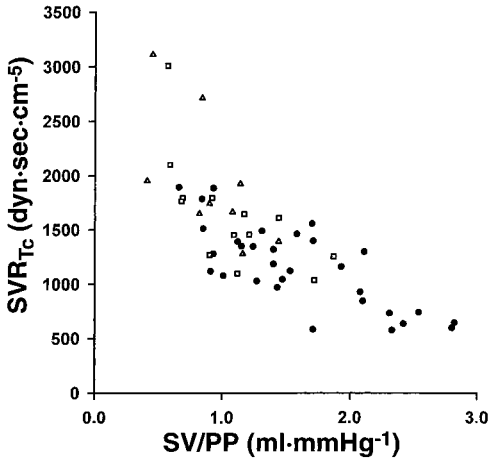

Fig. 6. Relation between SV/PP estimate of arterial compliance and independent determination of systemic vascular resistance with technetium indicator (SVR_{Tc}). Symbols are as in Fig. 3 (cirrhosis patients: $r = -0.730$, $P < 0.00001$; control subjects: $r = -0.694$, $P < 0.001$).

from a practical point of view the difference is negligible.

The simplified SV/PP index of compliance of the arterial tree was recently substantiated in a large population (4). Thus SV measurements by echocardiography and PP measurements by arm cuff proved to be adequate in large population studies (4, 32). In our study, we determined PP and MAP directly and independently at the aortic bifurcation/iliac arteries, which are taken to be representative of the large arteries (40). SV is accurately determined by HR and the indicator dilution flow over ~20 s (7), and evaluations have shown a close similarity to values obtained by echocardiography (4, 19). The reason for applying direct measurement and using the indicator-dilution technique is that these methods are highly standardized (13, 16, 17). Owing to a somewhat higher pulse amplitude found by direct measurement compared with that by the cuff method (27), SV/PP values are somewhat lower in the control subjects in the present study than those found by the indirect cuff method (4).

The time relation between maximal systolic blood pressure, the start of diastolic blood pressure, and the end-diastolic blood pressure was remarkably similar in the different groups, and when adjusted for the small differences in heart rate any difference almost disappeared. A low arterial compliance may contribute to early peripheral reflection of the arterial pulse curve (owing to the fast rate of pulse propagation) with a delayed and higher maximum of the systolic blood pressure (29, 30, 42). This was not observed, probably because our hypertensive controls had almost normal arterial compliance and the patients with cirrhosis had elevated values (with a slow rate of pulse propagation). The importance of the constancy of time ratios and time-pressure relations is considered in the APPENDIX. An increase in error has been reported when the duration of the diastolic phase is reduced. This was the case with high heart rate and mild exercise, in which the duration of the diastole was shortened from 0.63 s to 0.27 s. (37). In the present study this figure was not problematic (0.44 s). A long QT_c (frequency-adjusted electric systole) has been reported in cirrhotic patients with advanced disease (1). We did not find significantly prolonged QT_c or frequency-adjusted mechanic systole $(1 - t_1/T)$ in patients with advanced disease, and $T - t_1$ and QT were closely related and similar in the different groups (Table 3). In addition to the isovolumetric time interval, the registration of the arterial blood pressure curve at the aortic bifurcation instead of the aortic arch may contribute to the difference between $T - t_1$ and QT.

Relation to gender, body size, and severity of disease. As expected, estimates of arterial compliance increased with increasing body size. Moreover, the difference in gender (higher values in males) was less pronounced when values were adjusted for difference in body size. SV/PP increased with increasing severity of the disease, and it was shown earlier that patients with advanced cirrhosis, although hyperkinetic, are hyporeactive at the arteriolar level (2, 22, 23, 28). In addition, a number of in vitro studies showed decreased reactivity of medium-sized and large arteries to several vasoconstrictors in experimental cirrhosis (2, 21, 23, 43). Changed dynamic and static functions of the arterial tree may contribute to abnormal reactions of volume and baroreceptors (30, 34). Elevated compliance may not only be confined to the large and medium-sized arteries. All compliance estimation methods are sensitive to compliance contributions from small peripheral vessels (>1 mm in diameter) (37). It was shown earlier that peripheral compliance represents only a small fraction (~20% of the total compliance), and the bulk of the compliance in normal subjects (~65%) is contained in the aortic trunk (ascending, descending, thoracic, and abdominal aorta). Therefore, the compliance estimation methods are sensitive not only to what happens in the aorta and large proximal arteries but also to a lesser extent to the smaller arteries. Thus, if present in the smaller arteries in the mesenteric tree, increased

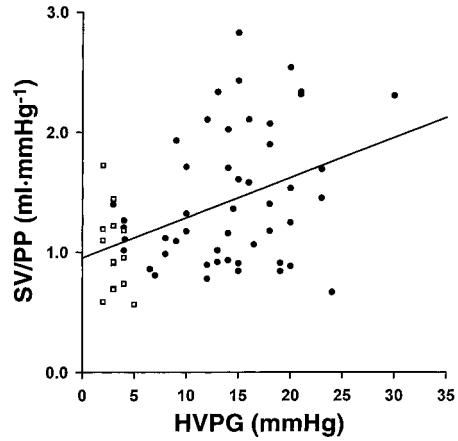

Fig. 7. Relation between SV/PP estimate of arterial compliance and portal pressure (hepatic venous pressure gradient: HVPG). Symbols are as in Fig. 3 (cirrhosis patients: $r = 0.31$, $P < 0.02$; cirrhosis patients + normotensive control subjects: $r = 0.41$, $P < 0.01$).

compliance may contribute to splanchnic blood flow abnormalities in cirrhosis (12). Increased vascular distensibility may, especially in areas with increased shear stress, contribute to local dilatations and potentially to the development of arteriovenous communications (40).

The level of coagulation factors 2, 7, and 10 contains major prognostic information (the lower the level, the higher the mortality). Because arterial compliance was inversely related to coagulation factors 2, 7, and 10, in both the univariate and multiple-regression models, arterial compliance may contain prognostic information. However, this aspect needs further clarification.

Relation to arterial pressure and hemodynamic derangement. One of the most important determinants of arterial compliance is the level of the arterial pressure (3, 20, 32, 37). This holds true both for the control groups and the patients with cirrhosis. However, the regression analyses identified relations other than that with the arterial pressure. A larger volume of blood and plasma was related to increased arterial compliance. This is somewhat surprising because most of the surplus blood and plasma in cirrhosis are contained within the venous system (13). Another important relation was to SVR. The latter reflects tonus in the arterioles. However, the arteriolar tonus adjusts the level of arterial blood pressure and may thereby also influence large artery compliance. In fact, arterial compliance should depend on the properties of arterial intrinsic elastic and smooth muscle, whereas arteriolar tone should result more from the balance between vasoconstrictors and vasodilators. Recent data suggest that the hyperdynamic circulation is mainly caused by circulatory alterations in the splanchnic area (6, 10, 39). Thus arteriolar vasodilatation would be a more localized event, whereas elevation in arterial compliance may be more "systemic." Arterial compliance may be influenced by vasoactive drugs, which potentially may be used for correction of the circulatory derangement in cirrhosis (15). However, in the present study only a few patients in the cirrhotic and control groups received drugs with potential vasoactive effects. The discrimination of static (relating to collagen, elastin, deposit) versus dynamic (relating to smooth muscle cell tonus) compliance requires manipulation, for instance, with vasoactive drugs, without changing the mean arterial blood pressure (isobaric conditions). Thus a simplified index of arterial compliance may be an integral variable for vascular responsiveness, together with the systemic vascular resistance. However, these aspects are for future studies.

In conclusion, arterial compliance is elevated in cirrhosis. Besides a relation to age, body size, sex, and the level of the arterial blood pressure, arterial compliance is directly related to the severity of cirrhosis and the hyperdynamic circulatory derangement. A simplified stroke volume/pulse pressure index reflects the arterial compliance and thereby the cardiac load.

APPENDIX

Derivation of a simplified expression of arterial compliance. All compliance estimation methods are based on either a two-element windkessel model or a three-element windkessel model of the systemic arterial tree. The fundamental relation between blood pressure (P), volume flow ($\dot{V}$), and hemodynamic resistance (R) can be simplified as

$$P = R \cdot \dot{V} \qquad (A1)$$

or

$$\dot{V} = P/R \qquad (A1a)$$

Power delivery (E) from the heart to the aorta is

$$E = P \cdot \dot{V} + \tfrac{1}{2}\dot{V} \cdot \vartheta^2 \qquad (A2)$$

simplified as

$$E = P \cdot \dot{V} \qquad (A2a)$$

because the contribution of acceleration ($\frac{1}{2}\cdot\dot{V}\cdot\vartheta^2$) is small (<10%; if P = 120 mmHg and $\dot{V}$ = 10 l/min (~10 kg/min), then the product $E = P\cdot\dot{V}$ = 160 J/min = 2.7 W, and if it is assumed that the linear velocity in the aorta is up to ϑ = 1.5 m/s, then $2\,\dot{V}\cdot\vartheta^2$ = 11.3 J/min = 0.2 W).

Arterial compliance (C) is defined as a change in volume (dV) relative to a change in transmural pressure (dP)

$$C = dV/dP \qquad (A3)$$

In the following, it is assumed that R and C are constant in time, whereas E and P are functions of time [E(t) and P(t), respectively], and that $\dot{V} = dV/dt$.

From *Eq. A2a* follows

$$E(t) = P(t) \cdot dV/dt \qquad (A4)$$

The volume displacement (dV) from the heart in systole can be divided into a fraction retained in the arterial tree (dV_a) and a fraction passing through arterioles (dV_b)

$$dV = dV_a + dV_b \qquad (A5)$$

With this notation, *Eqs. A3* and *A1a* can be rearranged.

$$dV_a = C \cdot dP(t) \qquad (A6)$$

$$dV_b = (P(t)/R) \cdot dt \qquad (A7)$$

By multiplication with $P(t)/dt$ on both sides in *Eq. A5* and substitution with *Eqs. A6*, *A7*, and *A2a*, the following equations can be derived

$$E(t) = C \cdot P(t) \cdot dP(t)/dt + P(t)^2/R \qquad (A8)$$

and dividing by $C\cdot P(t)$

$$\dot{V}/C = dP(t)/dt + P(t)/(R \cdot C) \qquad (A9)$$

During diastole, power and volume flow are zero [E(t) = 0 and $\dot{V}$ = 0]; consequently, *Eqs. A8* and *A9* can be reduced to

$$dP(t)/P(t) = -(1/RC)dt \qquad (A10)$$

and integrated from 0 to t

$$P(t) = P_o \cdot e^{-t/RC} \qquad (A11)$$

where P_o is pressure at the start of diastole (2-element windkessel model; Ref. 37).

By substitution in *Eq. A11* of diastolic pressure [P_d = P(t)], t becomes the time (t_1) from P_o to P_d

$$P_d = P_o \cdot e^{-t_1/RC} \qquad (A12)$$

and isolation of C, which in this time interval is termed C_1, gives

$$C_1 = \frac{t_1}{R \cdot \ln (P_o/P_d)} \quad (A13)$$

The hemodynamic resistance can be expressed as

$$R = p/\dot{V} \quad (A14)$$

where p is the difference in mean pressure from the arterial system to the right atrium. Substitution of *Eq. A14* in *Eq. A13* gives

$$C_1 = \frac{t_1 \cdot \dot{V}}{p \cdot \ln (P_o/P_d)} \quad (A13a)$$

or by applying the variables measured in the present study

$$C_1 = \frac{t_1 \cdot CO}{(MAP - RAP) \cdot \ln (DAP_o/DAP)} \quad (A13b)$$

where CO is cardiac output, MAP is mean arterial pressure, RAP is right atrial pressure, DAP_o is the start of diastolic pressure, DAP is end-diastolic pressure, and t_1 is the time from DAP_o to DAP.

In a strict mathematical sense, the method is valid only when the local flow is zero (i.e., ascending aorta during diastole). However, the central arterial tree may be lumped and input may be considered close to zero at peak systolic pressure. If t_2 is the time from SAP to DAP, another expression of C in the time interval t_2 (C_2) can be derived from *Eq. A13a*

$$C_2 = \frac{t_2 \cdot CO}{(MAP - RAP) \cdot \ln (SAP/DAP)} \quad (A13c)$$

Several studies have substantiated that the pressure decay from P_o to P_d can be approximated to a monoexponential function in the resting condition (20, 37). In this case, $p = (P_o - P_d)/\ln(P_o/P_d)$, where p is assumed to be equal to the temporal average between P_o and P_d and almost equal to the mean pressure gradient from the arterial system to the right atrium. From *Eq. A14* follows

$$R = (P_o - P_d)/\ln (P_o/P_d) \cdot \dot{V} \quad (A14a)$$

From Eqs. *A13a* and *A14a* an approximate compliance (C_1') can be determined

$$C_1' = \dot{V} \cdot t_1/(P_o - P_d) \quad (A14b)$$

and by directly measured values

$$C_1' = CO \cdot t_1/(DAP_o - DAP) \quad (A15)$$

or dividing by heart rate (HR)

$$C_1' = [SV/(DAP_o - DAP)] \cdot (t_1/T) \quad (A16)$$

where SV is stroke volume and T is the time of one heartbeat (= 1/HR).

Similarly, from *Eqs. A13a*, *A13c*, and *A14a*

$$C_2' = CO \cdot t_2/(SAP - DAP) \quad (A15a)$$

and

$$C_2' = (SV/PP) \cdot (t_2/T) \quad (A15b)$$

where PP is pulse pressure (i.e., SAP − DAP).

If t_2/T is constant (Table 3), the simplified expression

$$SV/PP \quad (A17)$$

may be taken as an index of arterial compliance.

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