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Prostaglandin E_1 Infusion and Functional Hepatic Flow in Control Subjects and in Patients with Cirrhosis

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Metabolic effects of prostaglandin E_1 have been previously demonstrated in cirrhosis, apparently independent of changes in large splanchnic vessel hemodynamics. The effects of prostaglandin E_1 on functional liver blood flow were tested by measuring the extrarenal clearance of D-sorbitol in six controls and eight patients with cirrhosis during systemic superinfusion of saline or prostaglandin E_1 (30 μg/hr), in random order. Doppler ultrasonography of systemic and splanchnic circulation was also performed before the test and at the end of the two study periods. Prostaglandin E_1 infusion increased femoral blood flow by nearly 60% in controls and over 30% in cirrhosis, without any effect on mean arterial pressure and heart rate. Mesenteric artery and portal blood flow were unchanged, as were Doppler-measured resistance indices in the liver, spleen and kidney. Sorbitol-assessed functional hepatic flow was 30% lower in cirrhosis, and did not change systematically during prostaglandin E_1 infusion. We conclude that prostaglandin E_1, at doses able to elicit metabolic effects and changes in systemic hemodynamics, does not affect splanchnic blood flow and/or hepatic microcirculation in normal subjects and in portal–hypertensive patients with cirrhosis.

KEY WORDS: cirrhosis; liver blood flow; prostaglandin E_1; sorbitol hepatic clearance; splanchnic hemodynamics.

Experimental and clinical investigations indicate a potential benefit of prostaglandins of the E series in a variety of patients with acute liver diseases (1–3). It has been suggested that some of these effects may be mediated by the vasodilator activity of prostaglandins on smooth muscle, counteracting the vasoconstrictive stimuli leading to ischemia. The mechanism might be amplified by antiplatelet and fibrinolitic activity, leading to a general cytoprotective effect of prostaglandins in the prevention of microvascular hepatic injury (1, 4, 5). More recently, favorable metabolic effects have also been demonstrated in cirrhosis (6), where the infusion of a prostaglandin E_1 (PGE_1) analog has a nitrogen-sparing activity, improving nitrogen economy possibly by decreased amino acid efflux at peripheral level.

Only a few studies are available in humans on the hemodynamic effects of prostaglandin infusion on splanchnic circulation. In patients with liver disease, prostaglandin infusion into the superior mesenteric artery increased portal and hepatic vein flow (7), and, conversely, oral administration of indomethacin, an inhibitor of PGs synthesis, was shown to decrease hepatic blood flow (8). In cirrhosis, the metabolic

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TABLE 1. CLINICAL AND LABORATORY DATA OF PATIENTS WITH CIRRHOSIS

Case	Age (yr)	Cirrhosis etiology	Albumin (g/liter)	Prothrombin activity (%)	Bilirubin (mg/dl)	Galactose elimination (mg/kg/min)	Child-Pugh score	Varices grade*
1	51	Alcohol	35.6	62	1.6	4.0	6	0
2	50	Alcohol	38.0	75	1.2	3.9	6	I
3	46	Alcohol	35.9	60	1.1	3.9	6	III
4	59	Alcohol	32.6	44	11.5	4.2	10	III
5	69	Alcohol	34.7	54	2.0	3.4	8	0
6	74	Alcohol	31.0	60	1.9	3.4	7	I
7	49	HCV	42.5	63	0.9	4.1	6	II
8	59	Alcohol	32.6	44	11.4	4.2	10	I
Mean ± SD	57 ± 10		35.4 ± 3.7	58 ± 10	3.9 ± 4.6	3.9 ± 0.3	7 ± 2	
Controls ($N = 6$)	53 ± 8		39.4 ± 0.5	92 ± 4	0.7 ± 0.3	nt†		
Normal values			>35.0	>80	<1.0	>6.0		

* 0, absent; I, small; II, medium sized; III, large.
† nt = not tested.

activity of peripheral PG infusion was reported to be independent of any effect on large-vessel splanchnic hemodynamics, but the potential contribution of changes in hepatic microcirculation has not been ruled out.

The amount of blood perfusing the liver, making close contact with functioning hepatocytes and responsible for their metabolic activity, ie, the functional hepatic flow, may be measured by the hepatic clearance of continuously-infused D-sorbitol. This noninvasive procedure has been validated by comparison with more invasive techniques in several studies, where liver blood flow was also measured by means of the hepatic extraction of sorbitol and indocyanine green, according to the Fick principle and hepatic vein catheterization (9, 10).

We measured the functional hepatic flow and peripheral and splanchnic hemodynamics by echo Doppler in control subjects and in patients with cirrhosis during systemic PGE_1 infusion. The results confirm previous data suggesting that the beneficial metabolic effects of PGE_1 in cirrhosis are not mediated by their vasoregulatory activity.

MATERIALS AND METHODS

Subjects. Eight patients with cirrhosis (five men, three women; median age 57.1 ± 10.1, range 46–74 years), with optimal echo Doppler visualization of the splanchnic vessels were selected. Their cirrhosis was related to alcohol abuse (seven cases) or hepatitis C virus (one case). Patients with alcoholic cirrhosis had been abstaining from alcohol for at least one year prior to the study. Their clinical and laboratory data were reported in Table 1. According to the Child-Pugh classification (11), four patients were in class A, two were in class B, and two were in class C. Esophageal varices were present in six patients (small in three, medium-sized in one, and large in two). Only one patient had suffered from episodes of variceal bleeding one year before the study; the patient had been repeatedly treated with endoscopic sclerosis, and the varices were completely eradicated.

No patients had clinically evident ascites, but in three cases it was detected at ultrasonography and was treated with diuretics before the study [spironolactone (100–200 mg/day) and/or furosemide (25 mg/day)]. Clinical evidence of hepatic encephalopathy was not present, but all patients were actively treated with lactulose (15–30 g/day).

Renal function was normal (plasma creatinine <1.3 mg/dl) without evidence of previous or actual endocrinopathies or complicating disorders.

Six healthy subjects, without any clinical and laboratory evidence of liver disease were selected as controls. In our department, the echo Doppler assessment of splanchnic hemodynamics is feasible in approximately 70% of healthy subjects, and this was the selection criterion. They were matched with patients with cirrhosis for sex and age as summarized in Table 1.

All subjects gave informed consent to take part in the study, and the protocol was approved by the senior staff committee of the department.

Sorbitol Study. The study was carried out on fasting subjects, starting at 8:30 in the morning. Two catheters were inserted into both antecubital veins for blood sampling and infusion of D-sorbitol, saline, and PGE_1. The functional hepatic plasma flow was determined by the hepatic clearance of D-sorbitol, calculated as suggested by Molino et al. (9), using a 2-g intravenous bolus of 10% w/v sorbitol solution followed by an infusion at a constant rate of 54 mg/min. The protocol for the measurement of sorbitol clearance was modified, to allow comparison of functional hepatic flow in response to saline and to PGE_1 infusion (Figure 1).

To do this, the studies were carried out under superinfusion of saline or a PGE_1 analog solution (alprostadil-α-cyclodextrin, Schwarz Pharma AG), at a constant rate of 25 ml/hr. They were rotated at the end of the first steady state. In random sequence, half the subjects in both groups received PGE_1 during the first 2 hours, half received PGE_1 in the last 100 min. PGE_1 solution was adjusted to a final

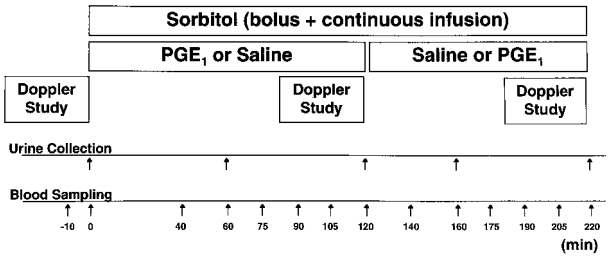

Fig 1. Experimental protocol for the measurement of functional hepatic flow with or without PGE$_1$ superinfusion and echo Doppler-assessed splanchnic and systemic hemodynamics.

infusion rate of 30 μg/hr, calculated to yield plasma concentrations of 5–6 pg/ml, ie, approximately three times normal values (normal plasma levels of 1.3–1.8 pg/ml) (12).

The continuous infusion of sorbitol was continued for 220 min, and the clearance was calculated twice, in the periods between 75 and 120 min and between 175 and 220 min from the bolus load. Based on previous experience, it was expected that sorbitol steady-state levels might be reached between 75 and 120 min. The period from 120 to 175 min was allowed for reequilibration after crossover (saline–PGE$_1$), and it was assumed that a second steady state could be reached between 175 and 220 min. Blood samples were drawn at time −10 and 0 min before the infusion; at 40, 60, and 140 min during non-steady states; and at 15-min intervals during steady state. Urine was collected overnight before the test for basal sorbitol excretion, and during steady-state for the calculation of the renal clearance of sorbitol. During the steady-state periods, the plasma levels of D-sorbitol in four consecutive samples varied nonsystematically within ±0.5 mg/dl from the mean, with intraassay variation <5%. Total, renal, and hepatic clearance of sorbitol were calculated according to standard equations, as (10):

$$\text{Total clearance} = \text{IR}/\text{Conc}_{s\text{-}s}$$

$$\text{Renal clearance} = U_s * U_{vol}/\text{Conc}_{s\text{-}s}$$

$$\text{Hepatic clearance} = \text{Total clearance} - \text{renal clearance}$$

where IR is the infusion rate, $\text{Conc}_{s\text{-}s}$ is the steady-state concentration of sorbitol, corrected for basal values, U_s is the urinary concentration of sorbitol, and U_{vol} is urinary volume per minute during the last 60 min of each experimental period. Hepatic sorbitol clearance is a measure of functional liver plasma flow. The functional hepatic blood flow was then calculated by correcting hepatic sorbitol clearance by the hematocrit value.

The total amount of saline given in the whole study was approximately the same, ie, 1000 ml without remarkable fluid retention in any experiment.

There were no side effects or complications in relation to sorbitol infusion. During PGE$_1$ infusion, one patient with cirrhosis and two control subjects showed erythema over the infused vein, and two control subjects experienced progressive flushing, but the effects were tolerated and the study protocol was completed in all cases.

Echo Doppler Study. The echo Doppler measurement of splanchnic and peripheral hemodynamics was performed at 8:00 AM, before beginning the metabolic study, and in the last 30 min of both sorbitol steady states. Echo Doppler was performed using equipment that combines a real-time electronic convex scanner and an echo Doppler unit (AU4-Idea, Esaote Ansaldo, Genoa, Italy). We measured blood velocity and flow in the superior mesenteric artery (13) and in the portal vein (14), as previously described. The θ angle (the angle between ultrasonic beam and blood flow direction) was maintained below 55° in each measurement. Hepatic artery flow was not measured, since it may only be assessed in selected patients with cirrhosis, due to technical difficulties and because of frequent anatomic variants (15).

From the wave-form record of blood flow velocity and the measurement of peak systolic, end diastolic, and temporal mean flow velocity, we also calculated intraparenchymal arterial resistive index (RI) and pulsatility index (PI) in the liver, spleen and kidney, according to the following formulas (16):

$$RI = (\text{peak systolic} - \text{end diastolic velocity})/(\text{peak systolic velocity})$$

$$PI = (\text{peak systolic} - \text{end diastolic velocity})/(\text{mean velocity})$$

RI and PI of the intrahepatic artery were obtained as the mean of left and right branches.

Heart rate, mean arterial pressure, and femoral artery velocity and flow were also recorded at baseline and during the two steady-state periods. Blood flow in superficial femoral artery was measured as previously described by Katz et al (17), with the transducer positioned on the medial portion of the thigh at the inferior border of the femoral triangle. Great care was taken to visualize the vessel at its largest diameter.

The echo Doppler examination was always performed by the same investigator, who had more than five years experience in Doppler examination of deep abdominal vessels, and who was unaware of the clinical diagnosis and experimental treatment of subjects.

Patients were examined in the supine position and in the course of Doppler recording were asked to hold their breath during normal respiration. According to previous experiences, the measurements were then repeated until three consistent values of blood velocity and flow were consecutively obtained (maximum variability: portal velocity, 1 cm/sec; hepatic artery velocity, 5 cm/sec), and the mean values were considered for statistical purposes (13–15). The final intraobserver coefficient of variability of blood flow was ±8%.

Statistical Analysis. All data were analyzed by means of a personal computer and StatView II program (Abacus Concepts, Inc., Berkeley, California). Differences between control subjects and patients with cirrhosis were analyzed for differences by Student's *t* test. Data between values measured in the course of the same experiment were analyzed by paired *t* test. $P < 0.05$ (two-tailed analysis) was considered statistically significant. Data in the text and in tables are given as mean ± SD, whereas in the figures they are given as means ± 2 SE.

TABLE 2. STEADY-STATE SORBITOL LEVEL; TOTAL, RENAL, AND HEPATIC CLEARANCE OF D-SORBITOL; AND FUNCTIONAL HEPATIC BLOOD FLOW IN CIRRHOTICS AND CONTROLS IN PAIRED EXPERIMENTS WITH OR WITHOUT PGE_1 SUPERINFUSION (MEAN ± SD)

	Controls		*Cirrhosis*	
	Saline	*PGE_1*	*Saline*	*PGE_1*
Steady-state sorbitol levels (mg/dl)	8.0 ± 1.3	8.3 ± 1.0	12.3 ± 4.2*	12.5 ± 4.0*
Total clearance (ml/min)	724 ± 112	688 ± 78	517 ± 188*	501 ± 177*
Renal clearance (ml/min)	15 ± 5	15 ± 6	20 ± 18	13 ± 9
Hepatic clearance (ml/min)	709 ± 109	673 ± 76	496 ± 188*	488 ± 177*
Functional hepatic flow (ml/min)	1190 ± 165	1130 ± 144	806 ± 336*	777 ± 284*

* Significantly different from the corresponding value in the control group.

RESULTS

Functional Hepatic Flow. Sorbitol plasma concentrations were nearly undetectable in the fasting state, and increased several times during the test, being close to steady-state 40 min after bolus injection. In the period between 75 and 120 min, sorbitol concentration fitted the criteria for being in steady state in all experiments. On average, sorbitol concentrations were 50% higher in cirrhosis and largely variable in relation to the different degree of hepatocellular dysfunction (Table 2). They were considerably higher in patients who were infused according to the sequence PGE_1/saline, in comparison to patients infused with saline first, whereas in control subjects no differences were observed between the two series. After crossover to the alternative infusion, sorbitol levels changed a little in all cases, but the resulting steady-state concentrations in the period between 175 and 220 min were not systematically different from those calculated in the first part of the experiment (Figure 2).

Total sorbitol clearance calculated during saline infusion was 30% lower in cirrhosis in comparison to controls, without differences in the renal clearance of sorbitol, which accounted for only 2–4% of the total. Consequently, the hepatic clearance and the resulting functional hepatic flow were also reduced on average by 30% in cirrhosis in comparison to control subjects (Table 2). In both control and cirrhotic subjects, the total, renal, and hepatic clearance of D-sorbitol and the resulting functional hepatic flow were not systematically different during PGE_1 infusion (Table 2; Figure 3), and the 95% confidence interval in the variability of repeated measurements of functional hepatic flow was −14% to +5% in controls and −10% to +8% in cirrhosis.

Doppler-Assessed Hemodynamics. At baseline, peripheral and splanchnic hemodynamics in cirrhosis were characterized by a moderate, nonsignificant reduction in mean arterial pressure and by increased

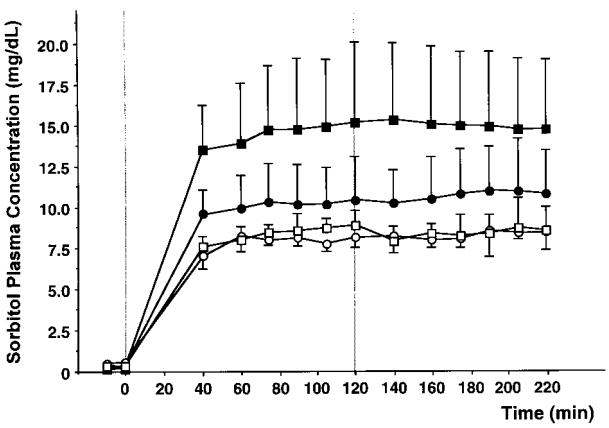

Fig 2. Plasma concentration of sorbitol during continuous sorbitol infusion with or without PGE_1 superinfusion. Open symbols are controls; closed symbols are patients with cirrhosis. The circles identify subjects infused first with saline and then PGE_1; the squares identify subjects infused with PGE_1 first. Data are presented as means ± 2 SE.

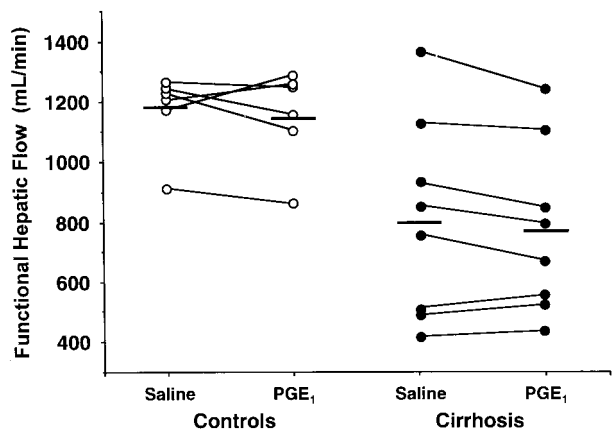

Fig 3. Functional hepatic blood flow in control subjects (open circles) and in patients with cirrhosis (closed circles) measured during the infusion of sorbitol plus saline or PGE_1. Data obtained in the same subject are connected by lines. Mean values are indicated by horizontal bars.

TABLE 3. EFFECTS OF SYSTEMICALLY INFUSED PGE_1 ON SYSTEMIC AND SPLANCHNIC HEMODYNAMICS IN CONTROLS AND CIRRHOTICS (MEAN ± SD)

	Baseline	*Saline*	*Prostaglandin*
Controls ($N = 6$)			
Femoral blood flow (ml/min)	430 ± 45	456 ± 25	675 ± 144*
Heart rate (beats/min)	68 ± 14	68 ± 12	71 ± 13
Mean arterial pressure (mm Hg)	97 ± 5	96 ± 6	92 ± 7
Portal flow (ml/min)	766 ± 93	800 ± 131	782 ± 211
Mesenteric artery flow (ml/min)	608 ± 122	583 ± 119	574 ± 141
Cirrhosis ($N = 8$)			
Femoral blood flow (ml/min)	701 ± 204†	742 ± 182†	920 ± 172*
Heart rate (beats/min)	72 ± 14	72 ± 13	74 ± 13
Mean arterial pressure (mm Hg)	90 ± 6	89 ± 7	86 ± 6
Portal flow (ml/min)	1056 ± 436	1037 ± 444	1028 ± 444
Mesenteric artery flow (ml/min)	580 ± 148	578 ± 136	595 ± 190

* Significantly different from baseline values.
† Significantly different from the corresponding value in the control group; $P < 0.01$.

femoral artery flow (+63%), due to increased blood velocity (31.3 ± 5.3 cm/sec vs 22.8 ± 4.9 in controls; $P < 0.05$). In addition, portal venous flow was larger on average by 27%, due to enlarged portal vein diameter (range, 12–15 mm vs 10–11 in controls; $P < 0.05$), with large interindividual variability. Mesenteric artery flow was not different between groups, whereas resistive indexes in the various splanchnic organs and pulsatility indexes were increased in cirrhosis (Tables 3 and 4).

During PGE_1 infusion, femoral artery flow increased significantly by 38% in cirrhosis (range: 14–116%) and by 57% in controls (range: 20–114%), due to increased blood velocity (42.1 ± 7.2 cm/sec in cirrhosis and 35.4 ± 7.8 in controls) and a modest increase in heart rate. Mean arterial pressure decreased slightly, and no differences at all were observed in splanchnic hemodynamics (Table 3). Saline infusion only slightly increased femoral artery velocity (to 33.5 ± 4.5 in cirrhosis and 24.9 ± 6.8 in controls; P vs baseline <0.1) and femoral artery flow (by 4–6%), without any change in splanchnic hemodynamics.

TABLE 4. EFFECTS OF SYSTEMICALLY INFUSED PGE_1 ON INTRAPARENCHYMAL SPLANCHNIC RESISTANCE INDICES IN CONTROLS AND CIRRHOTICS (MEAN ± SD)

	Baseline	*Saline*	*Prostaglandin*
Controls ($N = 6$)			
Resistive index			
Liver	0.56 ± 0.03	0.57 ± 0.03	0.58 ± 0.02
Spleen	0.50 ± 0.05	0.52 ± 0.03	0.53 ± 0.06
Kidney	0.54 ± 0.06	0.55 ± 0.05	0.59 ± 0.03
Pulsatility index			
Liver	0.86 ± 0.10	0.89 ± 0.12	0.85 ± 0.07
Spleen	0.71 ± 0.12	0.73 ± 0.08	0.71 ± 0.12
Kidney	0.83 ± 0.14	0.81 ± 0.16	0.91 ± 0.09
Cirrhosis ($N = 8$)			
Resistive index			
Liver	0.65 ± 0.09	0.61 ± 0.07	0.67 ± 0.07*
Spleen	0.62 ± 0.05*	0.68 ± 0.13*	0.66 ± 0.06*
Kidney	0.65 ± 0.07	0.65 ± 0.06	0.68 ± 0.10
Pulsatility index			
Liver	1.14 ± 0.22*	1.20 ± 0.20*	1.23 ± 0.21*
Spleen	0.96 ± 0.12*	1.09 ± 0.19*	1.08 ± 0.17*
Kidney	1.13 ± 0.24	1.11 ± 0.27	1.14 ± 0.22

* Significantly different from the corresponding value in the control group; $P < 0.01$.

DISCUSSION

The results of our study show that intravenous PGE_1 infusion, at doses able to elicit an effect on the systemic circulation, does not produce significant effects on functional hepatic blood flow, measured by the hepatic clearance of D-sorbitol, or on splanchnic hemodynamics, measured by echo Doppler technique, in either control subjects or patients with liver cirrhosis. Our data do not support the hypothesis that the beneficial effects of PGE_1 in cirrhosis are mediated by a vasoregulatory activity.

We tested the effects of PGE_1 analogs using two different techniques, ie, sorbitol clearance and Doppler sonography. The first has been proposed as a quantitative measure of functional hepatic flow, that is, the amount of blood flowing through sinusoids, making close contact with hepatocytes, and responsible for metabolic activity. The second is merely a measure of the amount of blood flowing towards the liver in large splanchnic vessels, irrespective of any contact with hepatocytes and metabolic function. In cirrhosis, due to the capillarization of the space of

Disse and intra- or extrahepatic shunting, the two values are not closely related (15).

Sorbitol, a naturally occurring polyol with prevailing hepatic metabolism, is almost completely extracted by the liver during the first passage, and extrahepatic elimination is negligible. Its hepatic clearance proved to be a reliable, noninvasive technique to measure the functional hepatic blood flow. The method was validated by comparison to invasive procedures based on hepatic extraction of D-sorbitol and indocyanine green according to the Fick principle (9, 10).

The method has also been applied to the study of functional hepatic blood flow in cirrhosis and is probably helpful to determine the relative importance of intrahepatic shunting (18, 19), possibly contributing to decreased metabolic cell activity (20). D-Sorbitol clearance was reported to be reduced in cirrhosis, in relation to the Child-Pugh score (17) and impaired hepatocellular function (10). Interestingly, we have previously shown that functional hepatic flow is reduced in cirrhosis in the presence of normal, or even increased, Doppler-assessed total hepatic flow, suggesting that a considerable amount of blood flowing through the liver is diverted by intrahepatic shunts (15).

Any PGE_1-mediated increase in hepatic blood flow, due to vasodilation of splanchnic arterial vessels, would be expected to decrease plasma steady-state sorbitol concentration, whereas arterial vasoconstriction and/or increase in intrahepatic shunting would be accompanied by increased sorbitol levels. Neither event occurred in the present study, and the resulting functional hepatic flow was unchanged.

There is a special problem regarding the potential effects of PGE_1 infusion on renal blood flow, responsible for the renal clearance of sorbitol. Prostaglandins were reported to increase renal flow in experimental animals (21), and in a recent study in liver transplanted patients the beneficial effects of PGE_1 were related to improved renal function (22). Any renal effect was ruled out in the present experiments; diuresis was not different, and renal sorbitol clearance was a negligible fraction of total sorbitol clearance (on average 2–4%). This value is lower than previously reported (9, 10), possibly in relation to a shorter period of urine collection. However, it did not change in relation to treatment in both groups.

The data are largely confirmed by the echo Doppler evaluation, which was carried out with care to minimize the errors intrinsic to the technique (13, 14). In contrast to previous reports in patients with cirrhosis (7, 8), we failed to demonstrate any increase in splanchnic vessel flow in response to PGE_1 infusion. Mesenteric artery flow was normal and did not change; portal blood flow was increased by nearly 50%, as reported in a few patients with cirrhosis (23, 24), and also did not change. In this series, due to difficulties in the measurement of hepatic artery flow, this value was not recorded and total hepatic flow was not calculated. However, there is nothing to suggest a potential selective effect of systemic PGE_1 infusion on hepatic artery flow.

The lack of effect of a large splanchnic vessel does not exclude *a priori* any potential influence on microvascular circulation. The echo Doppler study may also give clues to this problem. Blood velocity in arterial vessels may be used to calculate the intraparenchymal resistance indices (25), representing the downstream arterial resistance. These indices have the advantage of being independent of the angle between the vessel and the ultrasound beam axis, which is a major bias in the calculation of blood flow. In addition, the resistive index is also independent of mean velocity and is therefore much easier to compute, more reliable, and more reproducible. In several renal diseases characterized by increased vascular resistance (26–28), these indices were increased in relation to renal vasoconstriction. In the splanchnic bed, a significant reduction of resistance indices was observed following meals, in relation to meal-induced splanchnic vasodilation (24), whereas portal vein thrombosis, which reduces liver perfusion, was reported to be associated with increased hepatic arterial resistance indexes (16).

Both indices were in the range of the literature in our control population and increased in cirrhosis, as previously reported in relation to portal hypertension (16). Any PGE_1-related benefit on hepatic microcirculation would be expected to be associated with a reduction in resistance indices, but this did not happen either in cirrhotics or controls, and renal indices were also unchanged. We conclude that the echo Doppler data support the results of the functional evaluation of both hepatic and renal sorbitol clearance.

The negative results of PGE_1 infusion on splanchnic hemodynamics were accompanied by significant effects on systemic circulation, which are in keeping with previous studies (29). At baseline, patients with cirrhosis were characterized by a hyperdynamic state. PGE_1 infusion further increased femoral artery velocity and flow in both groups, the percent increase being larger in normal subjects. Such effects are probably

dose-related, and previous studies have shown that infusion rates in the range of 58–100 ng/kg/min (8–15 times the dose we used) produce a hyperkinetic circulation, characterized by increased heart rate and cardiac output and decreased peripheral vascular resistances (30). The dose we used (30 μg/hr, equal to approximately 7 ng/kg/min) is definitely a dose able to affect systemic hemodynamics, while minimizing side effects. Such a dose was previously shown to have significant metabolic effects in cirrhosis (6) and to be useful in liver transplant recipients (31).

In recent years several studies have been performed on the potential benefits of PGE synthetic analogs in clinical hepatology. Their use in liver transplantation is no longer recommended and remains an unfulfilled promise (32). Only recently an analysis based on the cost of PGE therapy and saving on hospital charges ws favourable to treatment (33). The recent demonstration of the metabolic effects of PGE$_1$ on urea synthesis in cirrhosis widened the potential indications for PGE$_1$ (6). However, according to the present data, careful reconsideration of the mechanism responsible for PGE$_1$ activity is needed. PGE$_1$ might act primarily by a direct cytoprotective, non-circulatory-mediated effect, potentially involved in clinical results, and not merely by counteracting the vasoconstrictive mechanism of ischemia-induced toxic effect on intrahepatic sinusoids (1). Along this line are also studies showing that PGE$_1$ infusion blocks hepatic glycogenolysis and glucose production induced by stress hormones (34). This metabolic area of research is worth more extensive studies.

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