

Circulatory Function and Hepatorenal Syndrome in Cirrhosis

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The pathogenic mechanism of hepatorenal syndrome is not well established. We investigated the circulatory function in cirrhosis before and after the development of hepatorenal syndrome. Systemic and hepatic hemodynamics and the activity of endogenous vasoactive systems were measured in 66 patients who had cirrhosis with tense ascites and normal serum creatinine levels; measurements were repeated at follow-up in 27 cases in whom hepatorenal syndrome had developed. At baseline, mean arterial pressure and cardiac output were significantly higher, and hepatic venous pressure gradient, plasma renin activity, and norepinephrine concentration were significantly lower in patients who did not develop hepatorenal syndrome compared with those presenting with this complication. Peripheral vascular resistance was decreased to the same extent in the two groups. Plasma renin activity and cardiac output were the only independent predictors of hepatorenal syndrome. Hepatorenal syndrome occurred in the setting of a significant reduction in mean arterial pressure (83 ± 9 to 75 ± 7 mmHg; $P < .001$), cardiac output (6.0 ± 1.2 to 5.4 ± 1.5 L/min; $P < .01$), and wedged pulmonary pressure (9.2 ± 2.6 to 7.5 ± 2.6 mmHg; $P < .001$) and an increase in plasma renin activity (9.9 ± 5.2 to 17.5 ± 11.4 ng/mL · hr; $P < .001$), norepinephrine concentration (571 ± 241 to 965 ± 502 pg/mL; $P < .001$), and hepatic venous pressure gradient. No changes were observed in peripheral vascular resistance. **In conclusion**, these data indicate that hepatorenal syndrome is the result of a decrease in cardiac output in the setting of a severe arterial vasodilation. (HEPATOLOGY 2005;42:439-447.)

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Hepatorenal syndrome is a functional renal failure due to intense renal vasoconstriction that frequently develops in patients with cirrhosis and ascites.¹ Two types of hepatorenal syndrome have been identified.² Type 1 is characterized by rapidly progressive renal failure. It frequently follows a precipitating event—usually an infection—and is associated with extremely short survival. Type 2 is characterized by moderate and

steady renal failure that develops insidiously. It is usually detected in patients who respond poorly to diuretics and is associated with longer survival.

Hepatorenal syndrome occurs in the setting of a circulatory dysfunction characterized by arterial hypotension and marked activation of the renin-angiotensin and sympathetic nervous systems.² Because there is vasoconstriction in the kidneys³ and in other extrasplanchnic territories,^{4,5} the suggestion has been raised that hepatorenal syndrome is caused by an accentuation of the splanchnic arterial vasodilation present in nonazotemic patients with cirrhosis and ascites.⁶ However, there is no study proving this contention. The potential differences in systemic hemodynamics between type 1 and type 2 hepatorenal syndrome have never been explored.

This article reports a study assessing systemic and hepatic hemodynamics and the activity of the endogenous vasoactive systems in a large series of patients who had cirrhosis with ascites before and after the development of hepatorenal syndrome.

Patients and Methods

Study Design. Patients under 75 years of age without insulin-dependent diabetes mellitus, arterial hyperten-

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sion, or any significant disease other than cirrhosis who were admitted to the hospital with tense ascites and normal serum creatinine concentration (<1.2 mg/dL) were considered for the study. Patients with tense ascites and infection or gastrointestinal hemorrhage were considered after 5 days of recovery from these complications; patients with encephalopathy were considered after 2 days of recovery provided they showed normal serum creatinine concentration at the time of resolution of these complications. Diagnosis of cirrhosis was based on histology or on clinical, laboratory, and ultrasonography findings. Complete history and physical examination, chest and abdominal X-rays, electrocardiography, abdominal ultrasonography, laboratory tests, and blood and ascitic fluid cultures were performed. Patients were excluded if they had proteinuria above 500 mg/dL, abnormal renal ultrasonography, or hepatocellular carcinoma. Patients gave written informed consent to participate in the study, which was approved by the Ethics Committee of the Hospital Ramón y Cajal and conducted according to the guidelines of Good Clinical Practice.

A baseline study was performed after at least 4 days on a 50-70 mmol/d sodium diet and without diuretics or beta-blockers. At 8 A.M. of the fifth day, after overnight fasting and following 1 hour of bed rest, samples were obtained to measure liver and renal function tests, plasma renin activity, and plasma concentrations of aldosterone and norepinephrine. Urine was subsequently collected for 24 hours. Hemodynamic measurements were performed on the sixth day. Patients were then treated by total paracentesis plus intravenous albumin (8 g/L of ascitic fluid removed; Grifols International S.A., Barcelona, Spain), discharged from the hospital with diuretics, and followed up until the end of the study (1 year after the inclusion of the last patient), liver transplantation, or death. Diuretic dosage was adjusted to prevent ascites recurrence. Patients were advised to avoid nonsteroidal anti-inflammatory drugs.

Patients who developed hepatorenal syndrome during follow-up were studied again using an identical protocol. Because of the high prevalence of prerenal azotemia in decompensated patients with cirrhosis who were treated with diuretics, and because of the complexity of the differential diagnosis of hepatorenal syndrome, which requires an acute expansion of the plasma volume, renal failure detected in otherwise uncomplicated patients during their regular follow-up visits to the outpatient clinic were considered to be diuretic-induced. Hepatorenal syndrome was therefore diagnosed in all patients during a hospital admission for the treatment of a complication: tense ascites refractory to diuretics in most patients with type 2 hepato-

renal syndrome and in some with type 1 hepatorenal syndrome; encephalopathy; infection; or gastrointestinal hemorrhage. In 1 patient, hepatorenal syndrome was detected in the postoperative period of a partial hepatectomy to remove a hepatocellular carcinoma. The diagnostic criteria for hepatorenal syndrome were those proposed by the International Ascites Club.² In patients with bacterial infections or gastrointestinal hemorrhage and in patients with hepatic encephalopathy, the protocol was repeated after 5 and 2 days, respectively, of recovery from these complications. Ascites was treated after completion of the protocol. No patient had more than one follow-up investigation.

Hemodynamic and Neurohormonal Measurements.

Under local anesthesia, a catheter introducer (USCI International, Galway, Ireland) was placed in the right jugular vein using the Seldinger technique. Under fluoroscopic guidance, a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was advanced into the pulmonary artery for measurement of cardiopulmonary pressures and cardiac output via thermodilution. A 7 French balloon-tipped catheter (MediTech Cooper Scientific Corp., Watertown, MA) was advanced into the main right hepatic vein to measure wedged and free hepatic venous pressures and the hepatic venous pressure gradient. Measurements were performed in triplicate, and the average was taken.⁷ The external zero-pressure point was at the level of the right atrium (midaxillary line). The hepatic blood flow was measured during a continuous intravenous infusion of an indocyanine green solution (Serb; Laboratoires Pharmaceutiques, Paris, France) at a constant rate of 0.1 or 0.2 mg/min⁻¹ (Child-Turcotte-Pugh class C and B patients, respectively) as previously described.⁸ A hepatic extraction of more than 10% and steady venous indocyanine green solution levels were required for the calculation of hepatic blood flow. Heart rate and arterial pressure were measured with an automatic sphyngomanometer (Dinamap-Critikion, Tampa, FL). Systemic vascular resistance was calculated as mean arterial pressure (mm Hg) - right atrial pressure (mm Hg)/cardiac output (L/min⁻¹) \times 80. Stroke work was calculated as (MAP-PWCP) \times (stroke volume) \times 0.0136 (gm-m). Left ventricular stroke work was calculated as systolic arterial pressure \times systolic volume \times 0.0136 (gm-m).

Plasma renin activity and plasma concentration of aldosterone and norepinephrine were determined via radioimmunoassay (Clinical Assays, Cambridge, MA; Diagnostic and Products Corp., Los Angeles, CA; and CAIBL Laboratories, Hamburg, Germany, respectively).^{9,10} Values in healthy subjects on a low sodium diet

were: 1.35 ± 0.94 ng/mL · hr, 24.2 ± 11.3 ng/dL, and 253 ± 114 pg/mL, respectively.

Statistical Analysis. Calculations were performed with SPSS version 10.0 software (SPSS, Chicago, IL). Comparisons between groups were performed with the chi-square test or Fisher exact test for categorical data and the Student *t* test and Mann-Whitney test for continuous data. Stepwise logistic regression was used to identify independent predictors for development of hepatorenal syndrome. Probability of survival curves was constructed using the Kaplan-Meier method and was compared with the log-rank test. Patients submitted to liver transplantation or who were lost from follow-up were considered censored. Results are expressed as the mean \pm SD. All reported *P* values are two-tailed, with values less than .05 considered significant.

Results

Clinical Data. Eighty-two patients admitted between February 1995 and November 1999 who agreed to participate in the study were considered. Nine patients were excluded before baseline investigations because of hepatocellular carcinoma (*n* = 5) or renal, cardiac, or respiratory disease (*n* = 4). Seven additional patients were excluded after baseline investigations because they were lost from follow-up (*n* = 6) or refused to continue in the study (*n* = 1). The investigation thus included 66 patients. Forty-seven of the patients were male, and the mean age was 60 ± 9 years. The cause of cirrhosis was alcoholic in 35 patients, hepatitis C virus infection in 25, and alcohol plus hepatitis C in 6. Fifteen of the 41 patients with alcoholism were active drinkers at inclusion. Four of them stopped drinking during follow-up. On the other hand, 5 out of the 26 abstainers at inclusion reassumed alcohol intake during the study period. Most of the patients were admitted to the hospital for the treatment of an episode of tense ascites alone (*n* = 54) or associated to hepatic encephalopathy (*n* = 6). The remaining 6 patients were admitted with ascites and severe infections (*n* = 4) or gastrointestinal hemorrhage (*n* = 2). In these 6 patients, arterial pressure, pulse rate, and renal function remained stable during the 5-day washout period between recovery from these complications and the initiation of the protocol. At inclusion, 34 patients were Child-Turcotte-Pugh grade C, and 32 were grade B. Five patients (2 with hepatorenal syndrome) underwent transplantation.

The 7 patients excluded after baseline measurements did not differ from the 65 included into the study regarding the cause of cirrhosis (4 had alcoholic cirrhosis and 3 had cirrhosis associated with hepatitis C) and Child-Turcotte-Pugh grade (3 were grade B and 4 were grade C).

There were also no differences between patients excluded after baseline measurements and those included into the study in age, sex, renal and hepatic function, systemic and hepatic hemodynamics, and degree of activity of the renin-angiotensin and sympathetic nervous systems (data not shown).

Thirty-nine patients did not develop hepatorenal syndrome during the study period (group A). The remaining 27 patients developed hepatorenal syndrome (group B). The prevalence of hepatorenal syndrome was unrelated to the cause of cirrhosis. On the other hand, in patients with alcohol-associated cirrhosis, the prevalence of hepatorenal syndrome was similar in active drinkers (8 cases with hepatorenal syndrome from the 20 active drinkers at inclusion or during follow-up) and abstainers (7 cases with hepatorenal syndrome from the 21 patients who abstained throughout the study period). Hepatorenal syndrome was type 1 in 12 cases and type 2 in 15. Type 1 hepatorenal syndrome was chronologically related to severe bacterial infection in 6 cases and to surgical operation and variceal hemorrhage in 1 case. Type 1 hepatorenal syndrome was detected during a hospitalization for refractory ascites (*n* = 2) and hepatic encephalopathy (*n* = 3) in the 5 patients without a precipitating event. The time between baseline and follow-up studies in patients developing hepatorenal syndrome was 359 ± 212 days (275 ± 153 and 425 ± 233 in patients with type 1 and type 2 hepatorenal syndrome, respectively). The mean follow-up period in the group A patients was 639 ± 329 days.

Differences Between Patients From Groups A and B at Baseline and Changes Associated With the Development of Hepatorenal Syndrome in Patients From Group B. At baseline, patients from group A showed significantly higher mean arterial pressure, cardiac output, stroke volume, stroke work, and urinary sodium excretion and significantly lower plasma renin activity, plasma concentrations of aldosterone and norepinephrine, wedged hepatic venous pressure, and hepatic venous pressure gradient compared with patients from group B (Table 1). Although baseline serum creatinine was within the normal limits in all cases, the mean value was significantly lower in group A. There were no differences in peripheral vascular resistance and heart rate. Of the 10 variables showing significant difference between groups, only plasma renin activity (RR: 31.3; 95% CI: 6.5-150.3; *P* < .0001) and cardiac output (RR: 5.8; 95% CI: 1.3-25.2; *P* < .05) were independently associated with the development of hepatorenal syndrome according to a multivariate analysis (Fig. 1).

Development of hepatorenal syndrome in group B was associated with a significant decrease in prothrombin in-

Table 1. Baseline Measurements in Patients Who Did Not Develop Hepatorenal Syndrome (Group A) and Baseline and Follow-up Measurements in Patients Who Presented With Hepatorenal Syndrome (Group B)

	Group A (n = 39)		Group B (n = 27)	
	Baseline Measurements		Baseline Measurements	Follow-up Measurements
Serum bilirubin (mg/dL)	2.7 ± 1.9		3.8 ± 3.9	4.3 ± 3.9
Serum albumin (g/L)	24 ± 4		24 ± 5	24 ± 4
Prothrombin index (%)	64 ± 14		59 ± 14	51 ± 13††††
Child-Turcotte-Pugh score (points)	9.7 ± 1.3		9.9 ± 1.3	10.8 ± 2.1†
MELD score (points)	13.7 ± 4.0		15.8 ± 4.6	25.7 ± 6.8††††
Serum creatinine (mg/dL)	0.85 ± 0.18		1.05 ± 0.26***	3.03 ± 1.49††††
Serum sodium (mmol/L)	134.5 ± 4.8		132.6 ± 4.6	127.0 ± 5.1††††
Urinary sodium (mmol/L)	17.4 ± 18.9		7.0 ± 6.1***	4.0 ± 4.5†
MAP (mmHg)	88 ± 9		83 ± 9*	75 ± 7††††
HR (bpm)	87 ± 15		85 ± 13	82 ± 14
RAP (mmHg)	6.7 ± 2.5		6.9 ± 2.6	5.7 ± 2.2†
PAP (mmHg)	15.2 ± 3.8		14.3 ± 4.3	12.8 ± 2.8††
PCWP (mmHg)	9.2 ± 3.2		9.2 ± 2.6	7.5 ± 2.6††††
CO (L/min)	7.2 ± 1.8		6.0 ± 1.2**	5.4 ± 1.5†††
SVR (dyne · s/cm ⁻⁵)	962.0 ± 256.4		1,058.6 ± 265.6	1,096.1 ± 327.6
Stroke volume (mL/beat)	85.2 ± 17.0		73.2 ± 18.9*	65.3 ± 18.8†
Stroke work (gm-m)	91.3 ± 17.9		75.3 ± 22.9**	62.7 ± 21.3††††
Left ventricular stroke work (gm-m)	140.0 ± 32.6		114.2 ± 43.5*	88.5 ± 32.3††††
Plasma renin activity (ng/mL · hr)	3.1 ± 2.3		9.9 ± 5.2****	17.5 ± 11.4††††
Plasma aldosterone (ng/dL)	32.0 ± 30.7		130.5 ± 69.4***	202.5 ± 130.0††††
Plasma norepinephrine (pg/mL)	221.6 ± 68.2		571.1 ± 241.1****	965.0 ± 502.5††††
WHVP (mmHg)	28.0 ± 4.0		30.5 ± 4.0*	29.5 ± 5.0
FHVP (mmHg)	11.5 ± 3.0		11.0 ± 4.0	8.5 ± 3.5††
HVPG (mmHg)	16.5 ± 3.0		19.5 ± 3.0***	21.0 ± 4.0††
HBF (mL/min)‡	1,123 ± 328.0		948 ± 221.1	713 ± 188.4††††

NOTE. Data are presented as mean ± SD.

Abbreviations: MELD, Model for End-Stage Liver Disease; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow.

* $P < .05$; ** $P < .01$; *** $P < .005$; **** $P < .001$ with respect to baseline values of group A.

† $P < .05$; †† $P < .01$; ††† $P < .005$; †††† $P < .001$ with respect to baseline values of group B.

‡A hepatic extraction greater than 10% was required for the calculation of hepatic blood flow in 15 patients of group A and 19 patients of group B.

dex; an increase in Child-Turcotte-Pugh score, Model for End-Stage Liver Disease score, and hepatic venous pressure gradient; a reduction in hepatic blood flow; dilutional hyponatremia; a significant decrease in mean

arterial pressure, cardiac output, stroke volume, stroke work, and cardiopulmonary pressures (pulmonary capillary wedged pressure, pulmonary artery pressure, and right atrial pressure); and marked stimulation of the renin-angiotensin-aldosterone system and sympathetic nervous system (Table 1; Figs. 2, 3). No significant changes were observed in heart rate and peripheral vascular resistance (Table 1; Fig. 3).

Differences Between Patients With Type 1 and Type 2 Hepatorenal Syndrome. The only significant difference between patients who developed type 1 and type 2 hepatorenal syndrome at baseline was a higher plasma renin activity and higher aldosterone and norepinephrine concentration ($P < .001$) in the former group of patients (Tables 2, 3).

Renal failure in type 2 hepatorenal syndrome was moderate in most patients (Table 2), and associated with discrete hyponatremia, a significant decrease in mean arterial pressure, and a significant increase in the degree of activity of the renin-aldosterone and sympathetic nervous systems. Cardiac output, stroke volume, stroke work, and

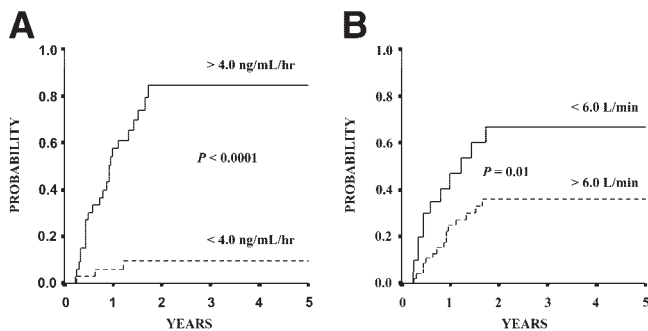


Fig. 1. (A) Probability of developing hepatorenal syndrome during follow-up in patients with baseline plasma renin activity equal or lower and higher than 4 ng/mL · hr (upper value in healthy subjects on a 50-mEq sodium diet during 5 days). (B) Probability of developing hepatorenal syndrome during follow-up in patients with baseline cardiac output higher and lower than 6 L/min (median value in the entire series of patients).

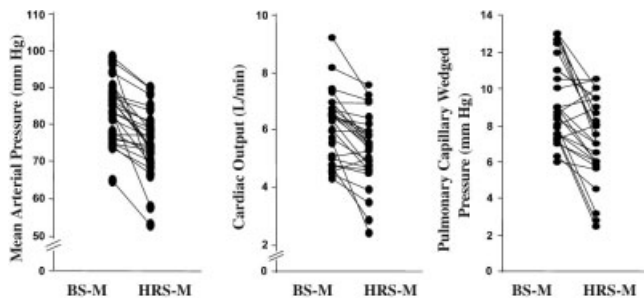


Fig. 2. Individual changes of mean arterial pressure, cardiac output, and pulmonary capillary wedged pressure associated with hepatorenal syndrome in patients from group B. BS-M, baseline measurements; HRS-M, measurements after development of hepatorenal syndrome.

cardiopulmonary pressures decreased, although differences were not significant. No significant changes were observed in liver function and hepatic hemodynamics, with the exception of a significant decrease in hepatic blood flow. In contrast, renal failure in patients with type 1 hepatorenal failure was severe and was associated with profound hyponatremia; a marked decrease in mean arterial pressure, cardiac output, stroke volume, and stroke work; a significant reduction in cardiopulmonary pressures; intense stimulation of the renin-aldosterone and sympathetic nervous systems; impairment in hepatic function; a decrease in free hepatic venous pressure and hepatic blood flow; and an increase in wedged hepatic venous pressure gradient (Table 3). Changes associated with type 1 hepatorenal syndrome were similar in patients with and without precipitating events or in patients with and without severe bacterial infections (data not shown).

At follow-up, patients with type 1 hepatorenal syndrome showed significantly higher serum creatinine levels, Child-Turcotte-Pugh score, and Model for End-Stage Liver Disease score; lower serum sodium concentration, mean arterial pressure, cardiac output, stroke volume, and stroke work; greater stimulation of the renin-aldosterone and sympathetic nervous systems; higher wedged hepatic venous pressure and hepatic venous pressure gradient; and lower hepatic blood flow compared with patients with type 2 hepatorenal syndrome (Tables 2, 3). Significant differences were not found in peripheral vascular resistance, heart rate, and cardiopulmonary pressures. The probability of survival after diagnosis of hepatorenal syndrome was lower in patients with type 1 hepatorenal syndrome (Fig. 4).

Discussion

The current concept of the pathogenesis of circulatory and renal dysfunction in cirrhosis is based on the peripheral arterial vasodilation hypothesis. It proposes that the initial mechanism is the splanchnic arterial vasodilation

that develops in these patients as a consequence of portal hypertension.¹¹ At the early stages of disease, there is a homeostatic increase in the cardiac output as a result of the decrease in cardiac afterload and the stimulation of the sympathetic nervous activity, leading to the characteristic hyperdynamic circulation of cirrhosis. However, as the disease progresses and splanchnic arterial vasodilation becomes more intense, this increase in cardiac output is not sufficient to maintain circulatory homeostasis. Patients then develop arterial hypotension; baroreceptor-mediated stimulation of the sympathetic nervous system, renin-angiotensin system, and antidiuretic hormone; renal sodium and water retention; and ascites. Hepatorenal syndrome is the extreme expression of this circulatory dysfunction and occurs in the setting of an intense stimulation of these endogenous vasoconstrictor systems that overcomes the compensatory effect of renal vasodilatory substances (*e.g.*, prostaglandins, nitric oxide).⁶

Type 1 and type 2 hepatorenal syndrome are clinically different. Type 2 develops insidiously in patients with advanced cirrhosis and ascites. Circulatory function and hepatic and renal function in these patients remain steady for months. Their main clinical problem is refractory ascites.¹² In contrast, the onset of type 1 hepatorenal syndrome is acute and, in most cases, associated with a precipitating event, usually an infection. In type 1 hepatorenal syndrome there is rapid deterioration of circulatory, renal, and hepatic function. The patient dies within days or weeks after the onset of the syndrome with arterial hypotension, severe renal failure, jaundice, coagulopathy, and hepatic encephalopathy. Despite these differences, both types of hepatorenal syndrome are currently consid-

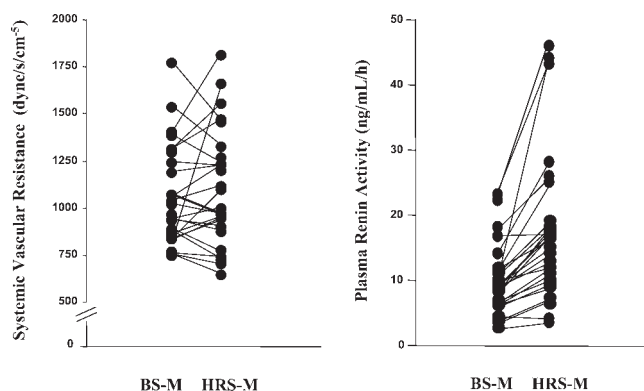


Fig. 3. Individual changes in systemic vascular resistance and plasma renin activity associated with hepatorenal syndrome in patients from group B. Systemic vascular resistance remained unchanged despite a marked increase in plasma renin activity, suggesting an accentuation of the arterial vasodilatation already present in nonazotemic cirrhosis with ascites compensated by a stimulation of the renin-angiotensin system and other endogenous vasoconstrictors. BS-M, baseline measurements; HRS-M, measurements after development of hepatorenal syndrome.

Table 2. Baseline and Follow-up Measurements in Patients Who Developed Type 2 Hepatorenal Syndrome

	Baseline Measurements (n = 15)	Follow-up Measurements (n = 15)	P Value
Serum bilirubin (mg/dL)	3.7 ± 4.6	3.2 ± 3.0	NS
Serum albumin (g/L)	26 ± 5	26 ± 4	NS
Prothrombin index (%)	59 ± 13	55 ± 14	NS
Child-Turcotte-Pugh score (points)	9.8 ± 1.6	9.8 ± 1.9	NS
MELD score (points)	15.6 ± 4.9	21.9 ± 5.7	<.001
Serum creatinine (mg/dL)	1.05 ± 0.2	2.11 ± 0.4	<.001
Serum sodium (mmol/L)	133.2 ± 4.7	129.6 ± 4.0	.01
Urinary sodium (mmol/L)	7.2 ± 6.2	5.6 ± 5.1	NS
MAP (mmHg)	86 ± 10	79 ± 7	.005
HR (bpm)	84 ± 12	80 ± 14	NS
RAP (mmHg)	6.8 ± 2.1	6.1 ± 1.8	NS
PAP (mmHg)	14.0 ± 3.0	12.9 ± 2.1	NS
PCWP (mmHg)	8.9 ± 1.6	8.3 ± 2.0	NS
CO (L/min)	6.2 ± 1.4	5.8 ± 1.2	NS
SVR (dyne · s/cm ⁻⁵)	1,032.0 ± 251.3	1,014.3 ± 276.4	NS
Stroke volume (mL/beat)	75.6 ± 19.8	71.7 ± 18.2	NS
Stroke work (gm-m)	79.5 ± 28.1	73.9 ± 20.3	NS
Left ventricular stroke work (gm-m)	120.8 ± 53.5	106.5 ± 29.9	NS
Plasma renin activity (ng/mL · hr)	7.5 ± 3.7	11.9 ± 4.8	<.001
Plasma aldosterone (ng/dL)	86.8 ± 61.3	118.4 ± 80.1	.01
Plasma norepinephrine (pg/mL)	411.8 ± 155.4	628.8 ± 320.3	<.01
WHVP (mmHg)	29.5 ± 5.5	27.5 ± 5.5	<.005
FHVP (mmHg)	10.5 ± 4.0	8.0 ± 3.0	<.005
HVPG (mmHg)	19.0 ± 3.2	19.5 ± 2.0	NS
HBF (mL/min)*	1,064 ± 223	824 ± 180	<.005

NOTE. Data are presented as mean ± SD.

Abbreviations: NS, not significant; MELD, Model for End-Stage Liver Disease; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow.

*A hepatic extraction greater than 10% was required for the calculation of hepatic blood flow in 10 patients.

ered distinct expressions of a common underlying disorder. Type 2 hepatorenal syndrome is a consequence of the natural course of the disease with a slow progression of hepatic failure, portal hypertension, and circulatory dysfunction. In type 1 hepatorenal syndrome, however, the acute effect of the precipitating event leads to rapid deterioration of circulatory function, renal and hepatic failure, encephalopathy, and death.

Many of these proposals are supported by this study. First, in baseline conditions, patients from group B were clearly at a more advanced stage of disease than patients from group A, as indicated by higher portal pressure and lower arterial pressure and urinary sodium excretion. Total peripheral vascular resistance was decreased to the same extent in the two groups, despite the existence of marked differences in the degree of stimulation of the renin-angiotensin and sympathetic nervous systems, which was higher in group B than in group A. This suggests a more intense arterial vasodilation in group B obscured by a homeostatic activation of the endogenous vasoconstrictor systems. Renal, muscular, cutaneous, and cerebral vascular resistance are increased in decompensated cirrhosis and correlate directly with the plasma levels of renin and norepinephrine.³⁻⁵ The most likely explana-

tion of our findings, therefore, is a progression of splanchnic arterial vasodilation before the development of hepatorenal syndrome, which does not translate into the total systemic vascular resistance because of vasoconstriction in extrasplanchnic vascular territories. Second, the development of hepatorenal syndrome in group B was associated with a decrease in mean arterial pressure and stimulation of the renin-angiotensin and sympathetic nervous systems in the absence of changes in total peripheral vascular resistance supporting a further progression of splanchnic arterial vasodilation. Finally, baseline portal pressure was higher in group B than in group A, and the development of hepatorenal syndrome in the former group of patients was associated with a further increase in portal pressure, supporting the proposal that impairment in circulatory function in cirrhosis parallels the progression of portal hypertension.

Two unexpected findings were observed in our patients, however. The first is that baseline cardiac output was significantly lower in group B than in group A. The second is that development of hepatorenal syndrome in the former group of patients occurred in the setting of a further reduction in cardiac output. These observations indicate that the progression of circulatory dysfunction in

Table 3. Baseline and Follow-up Measurements in Patients Who Developed Type 1 Hepatorenal Syndrome

	Baseline Measurements (n = 12)	Follow-up Measurements (n = 12)	P Value
Serum bilirubin (mg/dL)	3.8 ± 2.8	5.6 ± 4.5	<.05
Serum albumin (g/L)	23 ± 4	22 ± 4	NS
Prothrombin index (%)	59 ± 15	46 ± 10	<.05
Child-Turcotte-Pugh score (points)	10.1 ± 0.9	12.0 ± 1.7**	<.005
MELD score (points)	16.0 ± 4.5	30.4 ± 5.1****	<.001
Serum creatinine (mg/dL)	1.04 ± 0.3	4.26 ± 1.4****	<.001
Serum sodium (mmol/L)	132.0 ± 4.6	124.0 ± 4.6***	<.005
Urinary sodium (mmol/L)	6.9 ± 6.3	1.8 ± 2.7*	.01
MAP (mmHg)	84 ± 9	70 ± 8**	<.001
HR (bpm)	86 ± 16	84 ± 14	NS
RAP (mmHg)	7.0 ± 3.0	5.0 ± 2.0	.01
PAP (mmHg)	15.5 ± 5.5	11.5 ± 2.5	<.05
PCWP (mmHg)	9.0 ± 2.5	6.0 ± 2.5	<.001
CO (L/min)	5.8 ± 0.9	4.6 ± 1.3*	<.01
SVR (dyne · s/cm ⁻⁵)	1099.3 ± 279.5	1211.7 ± 346.7	NS
Stroke volume (mL/beat)	70.1 ± 18.0	55.5 ± 12.1***	<.01
Stroke work (gm-m)	70.0 ± 13.5	48.8 ± 13.1***	<.005
Left ventricular stroke work (gm-m)	105.7 ± 26.2	66.0 ± 18.1****	<.005
Plasma renin activity (ng/mL-hr)	12.9 ± 5.3****	25.8 ± 12.0***	<.005
Plasma aldosterone (ng/dL)	181.4 ± 43.3****	304.5 ± 107.1	<.005
Plasma norepinephrine (pg/mL)	735.7 ± 242.0****	1,384.9 ± 346.2****	<.001
WHVP (mmHg)	32.5 ± 4.5	31.5 ± 4.5*	NS
FHVP (mmHg)	12.5 ± 4.0	9.0 ± 4.5	<.05
HVPG (mmHg)	20.0 ± 0.5	22.5 ± 0.2*	<.01
HBV (mL/min)†	818 ± 135	589 ± 103***	<.05

NOTE. Data are presented as mean ± SD.

Abbreviations: NS, not significant; MELD, Model for End-Stage Liver Disease; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow.

* $P < .05$; ** $P < .01$; *** $P < .005$; **** $P < .001$ with respect to values (baseline and follow-up) of patients who developed type 2 hepatorenal syndrome shown in Table 2.

†A hepatic extraction greater than 10% was required for the calculation of hepatic blood flow in 9 patients.

cirrhosis is not only due to an accentuation of the splanchnic arterial vasodilation, which is the proposal of the peripheral arterial vasodilation hypothesis, but also to a reduction in cardiac output. The decrease in cardiopulmonary pressures observed in group B patients suggests a reduction in cardiac preload as an important mechanism

of the fall in cardiac output. An impaired chronotropic function is also a contributory mechanism. In fact, heart rate in baseline conditions was similar in patients in both groups, despite important differences in the degree of stimulation of the sympathetic nervous system. Moreover, in patients developing hepatorenal syndrome, no change in heart rate was observed, despite a marked deterioration in circulatory function and an increase in sympathetic nervous activity. There are studies supporting the existence of a cirrhosis-related cardiomyopathy associated with an impairment in left ventricular function,¹³⁻¹⁶ which may also play a role in the reduction in cardiac output.

Our data suggest that this decrease in cardiac output is a very relevant event in the clinical course of cirrhosis, because it is an independent predictor of hepatorenal syndrome, the most important prognostic factor in patients with decompensated cirrhosis. This feature is not surprising. Following impairment in cardiac output, arterial pressure homeostasis is solely dependent on the activity of the renin-angiotensin system, sympathetic nervous sys-

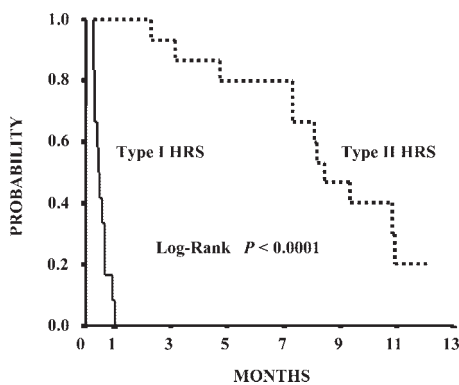


Fig. 4. Probability of survival after the diagnosis of hepatorenal syndrome (HRS). Patients are grouped according to the type of hepatorenal syndrome.

tem, and antidiuretic hormone, which have detrimental effects on the renal circulation and probably also in the circulation of other organs. Previous studies have shown that cutaneous and muscular blood flow are markedly decreased and cerebral vascular resistance is increased in patients with hepatorenal syndrome.³⁻⁵ In the current study, we have observed that hepatorenal syndrome is also associated with an intense reduction in hepatic blood flow. Vasoconstriction and reduction of blood flow to essential organs such as the kidneys, brain, and liver may offer a rational explanation of many features observed in patients with hepatorenal syndrome, including the deterioration in renal and hepatic function and the development of encephalopathy.

Changes in mean arterial pressure and peripheral vascular resistance and in the activity of the renin-angiotensin system and sympathetic nervous system were qualitatively similar in patients developing type 1 and type 2 hepatorenal syndrome, although the intensity of the changes was higher in the former group of patients. This is consistent with the concept that the two types of hepatorenal syndrome develop as a consequence of an accentuation of the arterial vasodilation already present in nonazotemic cirrhosis with ascites. In patients with type 1 hepatorenal syndrome, arterial hypotension and the stimulation of the endogenous vasoconstrictor systems occurred in the setting of a significant decrease in cardiac output and cardiopulmonary pressures. In contrast, no significant changes in these parameters were observed in patients with type 2 hepatorenal syndrome. These data indicate that circulatory dysfunction in patients with type 1 hepatorenal syndrome is related to the simultaneous occurrence of an increase in the degree of arterial vasodilation and a reduction in cardiac output, whereas it would be related only to an accentuation of arterial vasodilation in type 2 hepatorenal syndrome. This could account for the greater severity of circulatory dysfunction in type 1 hepatorenal syndrome. Nevertheless, our data also indicate that cardiac function in patients with type 2 hepatorenal syndrome is normal. Although not significantly, cardiac output decreased in these patients, whereas it would be expected to increase owing to the reduction in arterial pressure. Moreover, the impairment in chronotropic function was comparable in patients with type 1 and type 2 hepatorenal syndrome. The mechanism of the reduction in cardiopulmonary pressures in type 1 hepatorenal syndrome can not be ascertained from our data. It could be related to a decrease in plasma volume, an increase in venous compliance, or both. Further studies assessing cardiovascular

hemodynamics in hepatorenal syndrome are needed to clarify these features.

The combined administration of intravenous albumin and vasoconstrictors (*e.g.*, terlipressin^{17,18} and alfa-1 agonists¹⁹⁻²¹) normalizes circulatory function and serum creatinine in most patients with type-1 hepatorenal syndrome. These effects, however, are rarely obtained when vasoconstrictors or intravenous albumin are given alone.²² In contrast, the intravenous administration of albumin alone is highly effective in the prevention of circulatory dysfunction and type 1 hepatorenal syndrome in patients with spontaneous bacterial peritonitis.²³ Our study offers a rational explanation for these features. The increase in cardiac preload that follows intravenous albumin administration increases cardiac output and eliminates one of the pathogenic factors of the circulatory dysfunction in decompensated cirrhosis. This would be sufficient to prevent hepatorenal syndrome. However, when renal failure is already established, correction of the two pathogenic factors—the splanchnic arterial vasodilation and the impaired cardiac output—is required to reverse the intense circulatory dysfunction and renal vasoconstriction associated with type 1 hepatorenal syndrome.

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