

Hepatorenal Syndrome in Cirrhosis: Pathogenesis and Treatment

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Hepatorenal syndrome (HRS) is a major complication in cirrhosis, with an annual incidence in patients with ascites of approximately 8%.¹ It develops at the latest phase of the disease and, although initially considered without impact in prognosis (patients would die with and not by the renal failure), there is now evidence that it is an important determinant in survival. There are more reviews than original articles on HRS, reflecting the difficulty in investigating this syndrome. On the other hand, there is no experimental model of HRS. Many aspects of HRS are therefore still poorly understood. The current article does not attempt a deep review of HRS. The reader is referred to other reviews for this purpose.²⁻¹⁰ Diagnosis of HRS, which has been discussed in detail elsewhere,² is superficially considered. The treatment of refractory ascites, a common event in patients with HRS, is not reviewed. The aim of this work is to highlight those aspects of HRS that are important to understand the pathogenesis and the rational basis of the modern therapy of the syndrome.

Evolution of Our Knowledge on HRS

The Early Period

The term HRS was created by surgeons to define the occurrence of renal failure after biliary surgery or hepatic trauma.¹¹⁻¹³ Subsequently, it was extended to other types of acute renal failure in liver diseases. During the 1960s and the 1970s, American nephrologists popularized the term to define the renal failure of cirrhosis. In Europe, however, names such as functional renal failure or simply renal failure of cirrhosis were preferred by most hepatologists. It was after the consensus conference of the International Ascites Club in Chicago, IL, almost 10 years ago, in which investigators from the 5 continents proposed new definition and diagnostic criteria of HRS,² when this term was generally accepted for the functional renal failure that develops in patients with advanced cirrhosis.

HRS in cirrhosis was first recognized by Hecker and Sherlock¹⁴ in 1956 in an article describing 9 patients with cirrhosis or acute hepatitis who developed azotemia,

progressive oliguria, and hyponatremia in the setting of a severe hepatic insufficiency. All patients died during hospitalization, and postmortem examination of the kidneys showed normal histology. This study is remarkable because it proposed almost 50 years ago current concepts on the pathogenesis and treatment of HRS. Because patients had arterial hypotension and highly oxygenated peripheral venous blood, and cardiac output was very high in the only patient in whom this parameter was measured, they proposed that HRS is caused by a reduction in renal perfusion secondary to arterial vasodilation. They treated 3 patients with volume expansion and noradrenaline. In the only patient in which this treatment was applied during several days, there was a decrease in blood urea and an increase in urine volume and serum sodium concentration. Finally, they suggested that not only renal function but also hepatic function could be affected by the circulatory dysfunction.

Studies during the 1960s showed that glomerular filtration rate (GFR) in decompensated cirrhosis decreases with the progression of the disease in parallel with a fall in renal perfusion, with HRS being the extreme expression of this process.¹⁵⁻²⁰ Because the plasma volume is increased in cirrhosis,^{21,22} the concept of effective hypovolemia was proposed for the pathogenesis of the syndrome.²³ Although plasma volume is increased, a substantial part of this volume is used to refill the dilated splanchnic venous bed (splanchnic pooling), and the effective circulating blood volume is actually decreased. Despite the fact that this hypothesis was not in agreement with previous studies showing high cardiac output and low peripheral vascular resistance in cirrhosis with ascites,²⁴ thus suggesting an arterial vasodilation, it was the generally accepted mechanism of renal dysfunction in cirrhosis during many years. In view of this

Abbreviations used in this paper: GFR, glomerular filtration rate; HRS, hepatorenal syndrome; TIPS, transjugular intrahepatic portacaval shunt.

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concept, treatment of HRS during the 1960s and 1970s was mainly directed to expand the circulating blood volume. The Rhodioascit apparatus and the LeVein shunt were the main exponents of this approach.^{25,26} The first consisted of a machine with specific filters and pumps that extracted and concentrated the ascitic fluid. The ultrafiltration was discarded and the concentrated ascitic fluid reinfused into the systemic circulation. The objective of the LeVein shunt was to produce a continuous expansion of the circulation.

The Intermediate Period

It started with the 1970s and finished at the beginning of the 1990s. During this period, the pathogenesis of HRS was delineated. It was shown that the kidneys from patients with HRS regained a normal renal function when transplanted to patients with chronic renal failure²⁷ and that HRS disappeared after liver transplantation.²⁸ HRS was, therefore, a reversible functional renal impairment. The endogenous vasoactive systems were studied in patients with cirrhosis and ascites,^{29–38} and the concept that HRS was caused by renal hypoperfusion secondary to an imbalance between an increased activity of the renin-angiotensin and sympathetic nervous systems and antidiuretic hormone, which are renal vasoconstrictors, and a reduced renal synthesis of vasodilators, such as prostaglandins or bradikinin, was first suggested.³⁹

Great advances were also made in circulatory function in cirrhosis. Investigations using specific antagonists of the vascular effect of angiotensin II and antidiuretic hormone and inhibitors of the sympathetic nervous activity showed that arterial pressure in cirrhosis with ascites is critically dependent on the stimulation of the sympathetic nervous system, renin-angiotensin system, and antidiuretic hormone.^{40–43} The activation of these systems represents a concerted response to counteract the arterial vasodilation present in these patients and therefore to maintain arterial pressure. The arterial resistance to the effect of vasoconstrictors^{44–46} and the potential role of several vasodilator substances such as glucagon and prostaglandins were also explored.^{47,48} Finally, the first investigations on experimental animals with cirrhosis and ascites were performed and their results, as well as those from human studies, showed that circulatory dysfunction was the consequence of an arterial vasodilation and not of a reduced circulating blood volume.^{42,45,49–51} Based on these studies, a new hypothesis (the peripheral arterial vasodilation theory) of renal dysfunction in cirrhosis was proposed during a consensus meeting in Barcelona, Spain, at the end of the 1980s.⁵²

No major changes in the treatment of HRS occurred within this period. Only some attempts to reverse HRS

pharmacologically by short-term administration of dopamine, prostaglandins, α -adrenergic antagonists, angiotensin-II antagonists, metaraminol, and octapressin were performed without success.^{20,53–62} However, therapeutic paracentesis was reintroduced in the 1980s, and this represented a major advance for the management of patients with type 2 HRS and refractory ascites.^{63,64}

The Current Period

It started at the beginning of the 1990s and can be defined as the nitric oxide period because there were many studies showing that this substance is of major importance in the pathogenesis of circulatory dysfunction in cirrhosis.^{65,66} It was also shown that the site of arterial vasodilation in cirrhosis is the splanchnic circulation, there being vasoconstriction in other organs such as the muscle, skin, kidneys, and brain.^{67–72} Because splanchnic arterial vasodilation is caused by portal hypertension and nitric oxide synthesis is increased in this vascular compartment⁶⁶ in cirrhosis, a relationship between the diseased liver, circulatory dysfunction, and HRS was clearly established.

The delineation of the mechanism of circulatory dysfunction and HRS in cirrhosis was essential for the design of new treatments. If the initial event of HRS is a splanchnic arterial vasodilation secondary to portal hypertension, the administration of vasoconstrictors with preferential effect on the splanchnic circulation should be an effective treatment.^{73–75} Fortunately, this contention has been proved to be true. At present, there are several studies indicating that HRS can be reversed by the simultaneous administration of volume expanders and vasoconstrictors, such as ornipressin or terlipressin. The same effect has been obtained after relieving portal hypertension by the percutaneous insertion of a portocaval shunt.⁷⁶

Renal Dysfunction in Cirrhosis

Sodium retention, impaired free-water excretion, and decreased renal perfusion and GFR are the main renal function abnormalities in cirrhosis. The onset of each of these abnormalities differs in time and, consequently, the course of cirrhosis can be divided in phases according to renal function. Renal dysfunction in cirrhosis usually follows a progressive course. Therefore, at the latest phase of the disease, when HRS develops, the 3 abnormalities are invariably present.

Impairment in Renal Sodium Metabolism in the Absence of Activation of the Renin-Angiotensin-Aldosterone and Sympathetic Nervous Systems

Chronologically, the first renal function abnormality in cirrhosis is a reduced ability to excrete sodium.

When cirrhosis is still compensated (no ascites), subtle abnormalities in renal sodium metabolism can be detected. Patients may not be capable of escaping from the effect of mineralcorticoids and develop continuous sodium retention and ascites.⁷⁷ Arterial vasodilation is already present in compensated cirrhosis with portal hypertension,⁷⁸ and it is interesting to note that patients who are not able to escape from mineralcorticoids are those with lower peripheral vascular resistance.

As the disease progresses, the impairment in sodium metabolism increases, and a critical point is achieved at which patients are unable to excrete the sodium intake. Sodium is then retained and accumulates as ascites. Renal perfusion, GFR, the renal ability to excrete free water, plasma renin activity, and the plasma concentrations of aldosterone and norepinephrine are normal.⁷⁹ Sodium retention is therefore unrelated with the renin-aldosterone system and sympathetic nervous system, the 2 most important sodium-retaining systems so far identified. The plasma levels of natriuretic peptides are markedly increased,⁸⁰ indicating that sodium retention is not caused by a reduced production of endogenous natriuretic substances. Renal function is not dependent on renal prostaglandins, and nonsteroidal anti-inflammatory drugs do not reduce renal perfusion and GFR.³⁹ It has been proposed that circulatory dysfunction at this phase of the disease, although greater than in compensated cirrhosis, is not intense enough to stimulate the sympathetic nervous activity and the renin-angiotensin-aldosterone system. However, it would activate a still-unknown, extremely sensitive, sodium-retaining mechanism (renal or extrarenal).⁸¹ An alternative proposal is that sodium retention is unrelated with circulatory function. An increased renal sensitivity to aldosterone, a decreased hepatic synthesis of a natriuretic factor, and a hepatorenal reflex promoting sodium retention have been suggested.⁸²⁻⁸⁴ However, this is unlikely. Sodium retention in the absence of a circulatory dysfunction would increase arterial pressure, a feature not observed at this stage of the disease.

The Stimulation of the Renin-Angiotensin and Sympathetic Nervous Systems and Antidiuretic Hormone With Preserved Renal Perfusion and GFR

With the exception of alcoholic cirrhosis in which hepatic, circulatory, and renal function may improve after alcohol withdrawal, the degree of sodium retention increases with the progression of disease. When it is intense, the plasma renin activity and the plasma concentrations of aldosterone and norepinephrine are elevated.^{30,78,82,85} The plasma volume, cardiac output, and

peripheral vascular resistance do not differ from the previous phase.⁷⁸ Circulatory dysfunction, however, is greater at this stage of the disease because an increased activity of the sympathetic nervous and renin-angiotensin systems is needed to maintain the arterial pressure.

Renal perfusion and GFR are normal or moderately decreased, and there is evidence that at this phase they are critically dependent of an increased renal production of prostaglandins.³⁹ These are vasodilators that antagonize the vasoconstrictor effect of angiotensin-II and noradrenaline. A syndrome indistinguishable from HRS can be produced in patients with cirrhosis, ascites, and increased plasma renin activity after prostaglandin inhibition with nonsteroidal anti-inflammatory drugs (Figure 1).^{30,86} The renal kallikrein-kinin system is also stimulated in decompensated cirrhosis³⁸ and could participate in the maintenance of renal hemodynamics.

Experimental studies suggest that other factors are important in the regulation of renal perfusion in cirrhosis.^{87,88} Prostaglandin inhibition with nonsteroidal anti-inflammatory drugs in rats with ascites induces a moderate decrease in renal perfusion. Nitric oxide inhibition does not affect renal hemodynamics but increases the renal production of prostacyclin. In contrast, the simultaneous inhibition of both substances produces a profound fall in renal blood flow (Figure 2). Therefore, both prostacyclin and nitric oxide cooperate in the maintenance of renal perfusion in cirrhosis. The inhibition of 1 substance is partially or totally compensated by the other, and renal blood flow is maintained. Inhibition of the vascular effect of natriuretic peptides reduces renal perfusion in normal rats and in rats with cirrhosis and ascites, but the impairment in renal hemodynamics is far

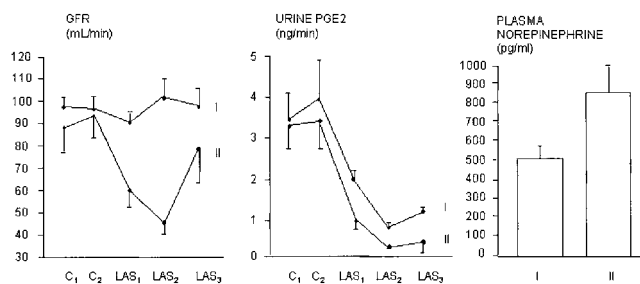


Figure 1. Glomerular filtration rate and urinary excretion of prostaglandin E2 (mean \pm standard error of the mean) before and after the IV injection of 450 mg of lysine acetylsalicylate in 19 patients with cirrhosis and ascites. Patients are divided in 2 groups according to whether they developed renal insufficiency (II, 11 patients) or not (I, 8 patients) after the administration of the drug. C1 and C2 represent 2 30-minute periods before the administration of lysine acetylsalicylate. LAS1, LAS2, and LAS3 represent 3 30-minute periods after the administration of lysine acetylsalicylate. Values of plasma noradrenaline correspond to those of samples obtained before lysine acetylsalicylate injection. Reprinted with permission.³⁰

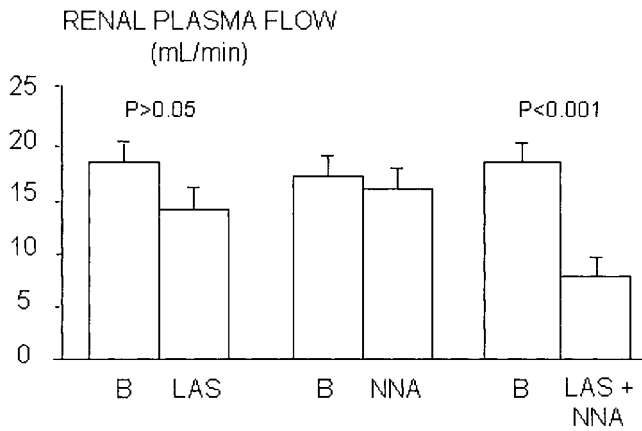


Figure 2. Renal plasma flow in baseline conditions (B) after prostaglandin inhibition with lysine acetylsalicylate (LAS), after nitric oxide inhibition with L-nitro-arginine (NNA), and after the administration of both inhibitors in rats with cirrhosis and ascites. Reprinted with permission.⁸⁷

more intense in the later group (Figure 3). Therefore, renal perfusion in advanced cirrhosis with ascites is maintained within normal or near normal levels because an increased renal production of vasodilator substances antagonizes the vasoconstrictor effect of the renin-angiotensin and sympathetic nervous systems.

The renal ability to excrete free water is reduced at this stage of the disease.³⁶ However, only few patients show significant hyponatremia (serum sodium concentration <130 mEq/min). Water retention and dilutional hyponatremia develops when renal water metabolism is severely impaired (free-water clearance after water load <1

mL/min; normal, 6–12 mL/min), and this rarely occurs in cirrhosis in the absence of renal failure.⁸⁹ Impairment in free-water clearance in cirrhosis is related to a hypersecretion of antidiuretic hormone.³⁷ An increased synthesis of prostaglandin E2 by the collecting tubules, which antagonizes the tubular effect of antidiuretic hormone, explains why the renal ability to excrete free water is relatively preserved at this phase of the disease despite high plasma levels of this hormone.³⁶

The Development of HRS

This occurs at the latest phase of the disease. HRS is characterized by low arterial pressure; marked increase in the plasma levels of renin, norepinephrine, and antidiuretic hormone; and very low GFR (<40 mL/min).^{14–20} Impairment in GFR in HRS occurs because of a fall in renal perfusion secondary to renal vasoconstriction.²⁰ Renal histology shows no lesions or lesions that do not justify the decrease in renal function. Because renal vascular resistance correlates closely with the activity of the renin-angiotensin and sympathetic nervous system in cirrhosis,^{29,69,70,90–92} HRS is thought to be related to an extreme stimulation of these systems.

The plasma concentration of endothelin, a vasoconstrictor peptide of endothelial origin, is increased in cirrhosis with ascites, and it has been proposed as an additional factor in the homeostasis of arterial pressure and therefore in the pathogenesis of HRS.⁹³ The following features do not support this contention: (1) arterial pressure in cirrhosis with ascites does not decrease after

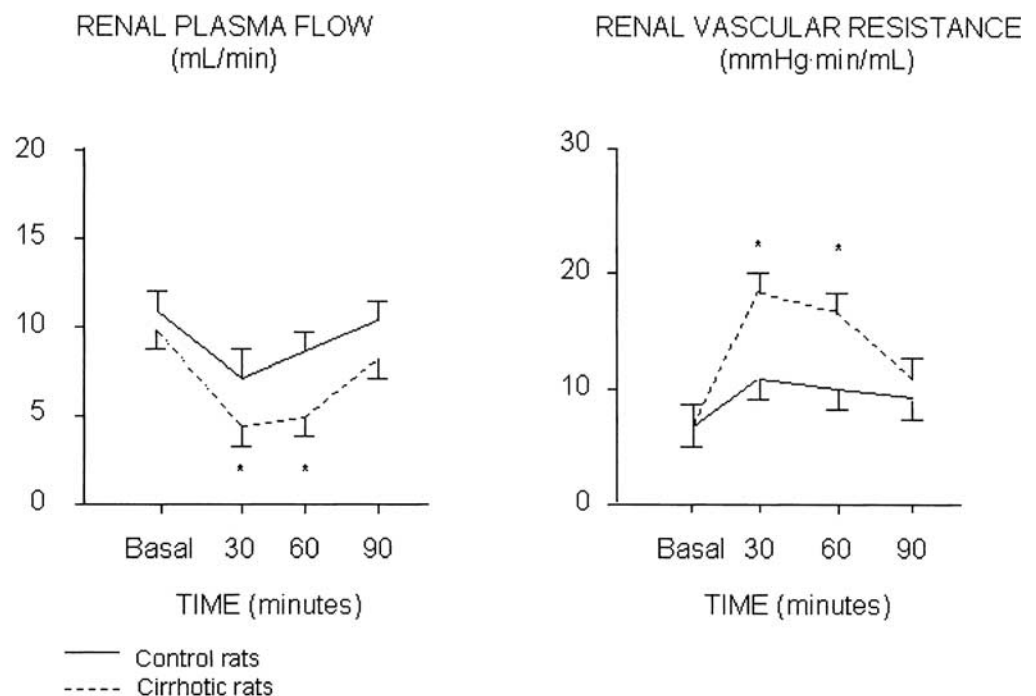


Figure 3. Renal plasma flow and renal vascular resistance in control (solid line) and cirrhotic rats with ascites (dotted line) under baseline conditions and at 30, 60, and 90 minutes after administration of a specific antagonist of endogenous natriuretic peptide receptors. Significance denoted in the figure is versus baseline values. *P < 0.05. Reprinted with permission.⁸⁸

the administration of endothelin antagonists,⁹⁴ (2) plasma endothelin concentration is similar in patients with and without HRS,⁹⁵ and (3) plasma endothelin does not change after volume expansion or after HRS resolution.^{11,96} There is evidence that the high-plasma endothelin levels in cirrhosis derive from the liver and may be related with the activation of stellate cells.⁹⁷

The urinary excretion of prostaglandin E₂, 6-keto prostaglandin F₁α (a prostacyclin metabolite), and kallikrein is decreased in patients with HRS, which is compatible with a reduced renal production of these substances.^{30,33} Renal failure in HRS could therefore be the consequence of an imbalance between the activity of the systemic vasoconstrictor systems and the renal production of vasodilators. The observation that HRS may be reproduced in nonazotemic, hyperreninemic cirrhotic patients with ascites with nonsteroidal anti-inflammatory drugs is compatible with this hypothesis.³⁹ Another possibility, however, is that the renal vasoconstriction caused by the renin-angiotensin and sympathetic nervous systems is the primary cause of HRS, with the reduced synthesis of prostaglandins and kallikrein being a secondary event that accentuates the renal insufficiency.

Renal hypoperfusion in HRS could also be amplified by the stimulation of intrarenal vasoconstrictors. For example, renal ischemia increases the generation of angiotensin II by the juxtaglomerular apparatus, the production of adenosine, which, in addition to being a renal vasoconstrictor, potentiates the vascular effect of angiotensin II, and the synthesis of endothelin. The observation that dipyridamol, an inhibitor of adenosine metabolism, impairs renal perfusion in patients with cirrhosis and ascites but not in normal subjects, indicates an increased sensitivity to intrarenal vasoconstrictors in decompensated cirrhosis.⁹⁸ Other intrarenal substances with vasoconstrictor effect that have been implicated in HRS are leukotrienes and F₂-isoprostanes.⁹⁹

Because the pathogenesis of renal vasoconstriction in HRS is multifactorial, it is unlikely to be improved by acting in only one of the renal mechanisms, as previously attempted with inhibitors of the renin-angiotensin system, α-adrenergic, endothelin and adenosine antagonists, and prostaglandins.¹⁰⁰ A more rational approach is to treat the initial events of the syndrome such as the circulatory dysfunction or portal hypertension.

HRS is usually associated with an extremely low urinary sodium excretion. The renal ability to excrete free water is also markedly reduced, and most patients present with significant hyponatremia. Sodium retention in patients with HRS is caused by decreased filtered sodium and an increased sodium reabsorption in the

proximal tubule. The amount of sodium reaching the loop of Henle and distal nephron, the site of action of furosemide, and spironolactone, respectively, is very low. The delivery of furosemide and spironolactone to the renal tubules is also reduced because of renal hypoperfusion. Therefore, it is not surprising that patients with HRS respond poorly to diuretics.¹⁰¹ The mechanism of the impaired renal water metabolism is multifactorial.¹⁰² The generation of free water, which is the result of the reabsorption of sodium chloride without a concomitant reabsorption of water in the loop of Henle, is reduced in HRS because of the low distal delivery of filtrate. On the other hand, the plasma levels of antidiuretic hormone are markedly elevated, and the renal synthesis of prostaglandin E₂, the physiologic antagonist of this hormone, may be reduced.³⁶

Clinical Aspects of HRS

Diagnosis

The first step in the diagnosis of HRS is the demonstration of a reduced GFR, and this is not easy in advanced cirrhosis.^{13,14} The muscle mass and, therefore, the release of creatinine is considerably reduced in these patients, and they may present normal serum creatinine concentration in the setting of a very low GFR. Similarly, urea is synthesized by the liver and may be reduced as a consequence of hepatic insufficiency. Therefore, the false-negative diagnosis of HRS is relatively common.^{103,104}

The second step is the differentiation of HRS from other types of renal failure. For many years, this was based on the traditional parameters used by the nephrologists to differentiate functional renal failure from acute tubular necrosis or rapidly progressive glomerulonephritis (oliguria, low urine sodium concentration, urine-to-plasma osmolality ratio greater than unity, normal fresh urine sediment, and no proteinuria). However, subsequently, this was found to be clearly unsatisfactory. Acute tubular necrosis in patients with cirrhosis and ascites usually presents with oliguria, low urine sodium concentration, and urine osmolality greater than plasma osmolality.¹⁰⁵ On the contrary, relatively high urinary sodium concentrations have been reported in patients with HRS.¹⁰⁶ For this reason, the International Ascites Club proposed different diagnostic criteria of HRS.² Serum creatinine concentration should be greater than 1.5 mg/dL or creatinine clearance lower than 40 mL/min in the absence of other potential causes of renal failure (Table 1).

Table 1. Major Diagnostic Criteria of HRS (International Ascites Club)

Hepatic failure and portal hypertension
Creatinine >1.5 mg/dL or GFR <40 mL/min
No shock, no ongoing bacteria infection, nephrotoxic agents, or fluid losses
No improvement after diuretic withdrawal and IV saline infusion (1.500)
Preteinuria <500 mg/d, normal renal ecography

Clinical Types of HRS

HRS is classified into 2 types according to the intensity and form of presentation of renal failure (Figure 4).² Type 1 HRS is characterized by a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks. Although type 1 HRS may arise spontaneously, it frequently occurs in close relationship with a precipitating factor such as severe bacterial infection, gastrointestinal hemorrhage, major surgical procedure, or acute hepatitis superimposed to cirrhosis. The association of HRS and spontaneous bacterial peritonitis has been carefully investigated.¹⁰⁷⁻¹⁰⁹ Type 1 HRS develops in approximately 30% of patients with spontaneous bacterial peritonitis despite a rapid resolution of the infection with nonnephrotoxic antibiotics. Patients with intense inflammatory response and high cytokine levels in plasma and ascitic fluid are especially prone to develop type 1 HRS after the infection. Besides renal failure, patients with type 1 HRS after spontaneous bacterial peritonitis show signs and symp-

toms of severe liver insufficiency (jaundice, coagulopathy, and hepatic encephalopathy) and circulatory dysfunction (arterial hypotension, very high plasma levels of renin, and norepinephrine) that worsen with the impairment in renal function. Type 1 HRS is the complication of cirrhosis with the poorest prognosis with a median survival time after the onset of HRS of only 2 weeks (Figure 5).¹

Type 2 HRS is characterized by a moderate and steady decrease in renal function (serum creatinine <2.5 mg/dL). Patients with type 2 HRS show signs of liver failure and arterial hypotension but to a lesser degree than patients with type 1 HRS. The dominant clinical feature is severe ascites with poor or no response to diuretics (a condition known as refractory ascites). Patients with type 2 HRS are especially predisposed to develop type 1 HRS after infections or other precipitating events.¹⁰⁷⁻¹⁰⁹ Median survival of patients with type 2 HRS (6 months) is worse than that of patients with nonazotemic cirrhosis with ascites.¹¹⁰

Although type 1 and type 2 HRS are included under the same pathogenesis, this is unlikely because they show many differences (Figure 6). As expected, circulatory dysfunction is stable in type 2 HRS and progressive in type 1 HRS (Ruiz de Arbol, unpublished data). Both types of HRS may also differ in the degree of impairment of intrarenal mechanisms regulating renal perfusion. Renal failure is moderate and steady in type 2 HRS probably because the intrarenal synthesis of vasodilators are capable to diminish the effects of systemic and intrarenal vasoconstrictors. In contrast, the rapid deterioration of renal function in type 1 HRS suggests a progressive reduction in the intrarenal synthesis of vasodilators, an increase in the intrarenal production of vasoconstrictors, or both features. An aggravation of the circulatory and renal dysfunction promoted by the precipitating factor could be the trigger of these intrarenal mechanisms.

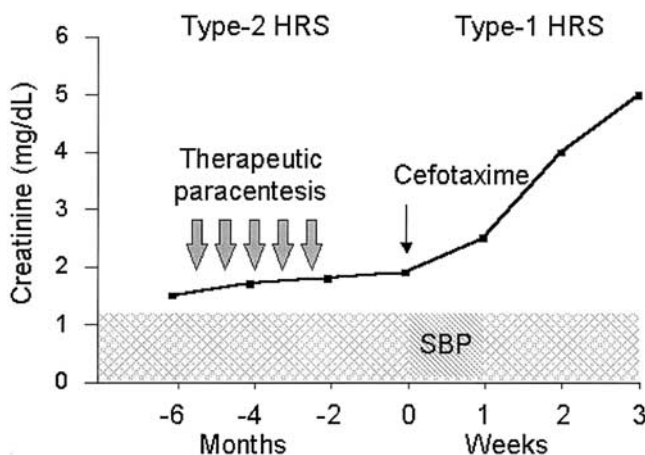


Figure 4. Course of renal function in a cirrhotic patient admitted to hospital for the treatment of an episode of tense ascites. The patient had type 2 HRS and refractory ascites. He was treated with repeated therapeutic paracentesis. In the follow-up, the patient developed signs of spontaneous bacterial peritonitis (SBP) and was treated with cefotaxime. Despite resolution of spontaneous bacterial peritonitis, a rapid deterioration of renal function (Type-1 HRS) developed. The patient died 3 weeks after infection diagnosis.

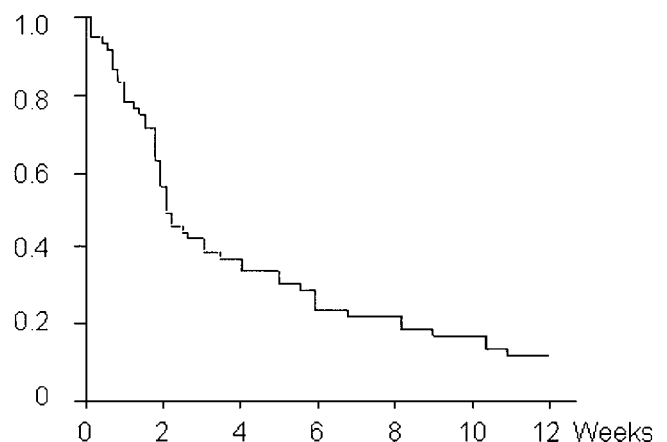


Figure 5. Probability of survival of patients with severe HRS. Reprinted with permission.¹¹³

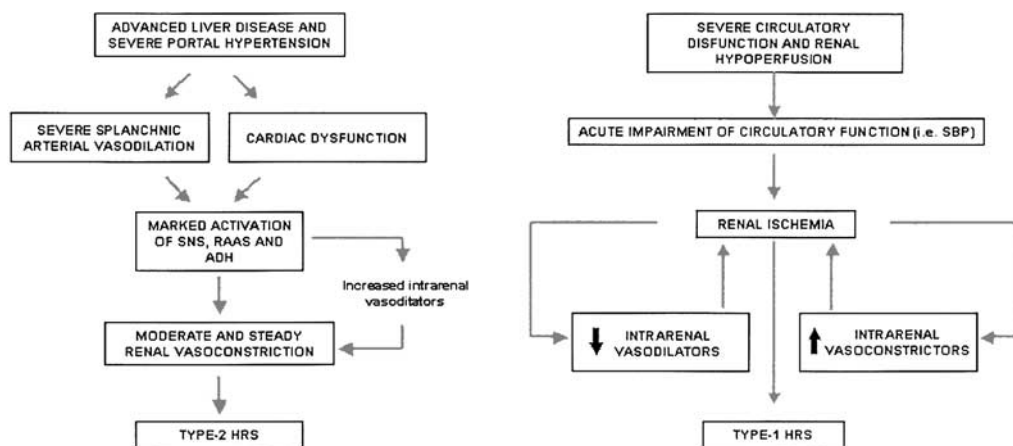


Figure 6. Possible mechanisms of type 1 (right) and type 2 (left) HRS. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ADH, antidiuretic hormone.

Therefore, type 1 HRS could be related with the development of intrarenal vicious circles by which hypoperfusion leads to an imbalance in intrarenal vasoactive systems, which in turn causes more vasoconstriction.¹¹¹ The demonstration of a clear temporal disassociation between the improvement in circulatory function and the increase in renal perfusion and GFR in patients with type 1 HRS treated with albumin infusion and vasoconstrictors is in keeping with this concept.⁷² This treatment normalizes plasma renin activity and norepinephrine concentration within 3 days. In contrast, a significant increase in renal perfusion and GFR do not occur until 1 week later. A delay in the deactivation of intrarenal mechanisms may account for this finding.

The Cardiocirculatory Dysfunction in Cirrhosis

In addition to being the cause of renal failure in HRS, circulatory dysfunction also affects other organs such as the brain, the lungs, the gastrointestinal tract, and the liver. Not surprisingly, the degree of impairment of circulatory function is the most sensitive prognostic marker in decompensated cirrhosis.^{112,113} Our concepts on circulatory dysfunction of cirrhosis have considerably changed during the last decade. Initially, it was thought to be caused by a generalized arterial vasodilation related

with increased levels of circulating vasodilators. At present, however, there is evidence that it occurs in the splanchnic circulation as a consequence of a local release of vasodilator substances. At the latest stage of cirrhosis, when HRS develops, the mechanism of circulatory dysfunction is even more complex because it also involves a decrease in cardiac function.

The Hyperdynamic Circulation

Patients with cirrhosis and ascites without HRS show increased plasma volume, cardiac index, and heart rate and reduced arterial pressure and peripheral vascular resistance.^{70,78} The incidence of arterial hypertension is extremely low. The central blood volume, that is the volume of blood contained in the heart, pulmonary circulation, and aorta before the renal arteries is reduced (Figure 7).¹¹⁴ The right atrial pressure and pulmonary pressures are normal or reduced.⁷⁸ Finally, the circulatory transit time from the right atria to the aorta is shortened (Figure 7).¹¹⁴ These features define what is called a hyperdynamic circulation, which is an increased blood volume circulating very rapidly within the central vascular compartment as a consequence of a high cardiac output. This high cardiac output is because of low cardiac preload and increased heart rate. Although the flow of blood throughout the central vascular compartment is

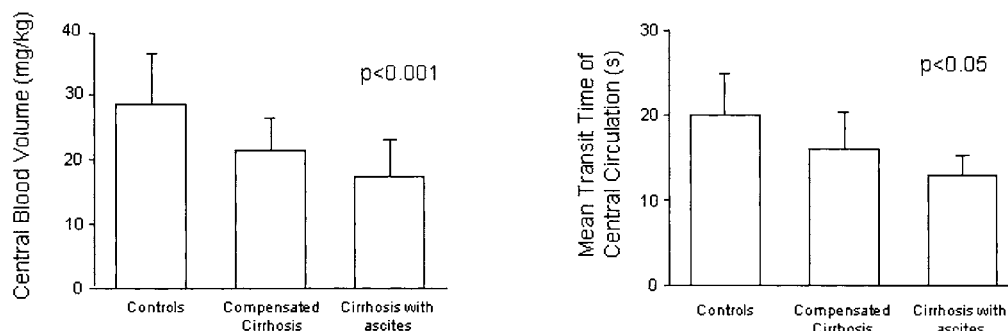


Figure 7. Central blood volume and mean transit time of central circulation in healthy subjects and patients with compensated cirrhotic patients and patients with ascites. Reprinted with permission.¹¹⁴

increased, the central blood volume is decreased, and when the reduction in central blood volume is sufficient to stimulate the volume receptors (low-pressure receptors) in the right atria and pulmonary circulation and the pressure receptors (high-pressure receptors) in the aorta and carotid sinus, there is a reflex stimulation of the sympathetic nervous system and the renin-angiotensin system and vasopressin release.⁵² The hyperdynamic circulation is a compensatory mechanism to the splanchnic arterial vasodilation. Not surprisingly, it correlates directly with the severity of cirrhosis.^{114–117} HRS has been traditionally considered as the extreme expression of the hyperdynamic circulatory state.⁵² However, there are data suggesting that HRS develops when the hyperdynamic circulation cannot be maintained because of a decrease in cardiac output.^{118–121}

Homeostasis of Arterial Pressure

The homeostasis of arterial pressure in cirrhosis was first explored by using saralasin, a specific antagonist of angiotensin II.^{40,41} The administration of this substance to patients with cirrhosis, ascites, and normal plasma renin activity did not produce changes in arterial pressure. In contrast, in patients with high renin, it induced arterial hypotension because of a decrease in peripheral vascular resistance. The hypotensive response correlated directly with the plasma renin activity (Figure 8). These observations were confirmed with other inhibitors of the system.^{122–124} The role of vasopressin in the homeostasis of arterial pressure in cirrhosis has been explored in experimental animals.⁴² The administration of a specific antagonist of the vascular receptors of vasopressin (V1 receptors) to control rats did not produce changes in arterial pressure. In contrast in cirrhotic rats with ascites, it reduced arterial pressure. The hypotensive response was extreme when V1 antagonist and saralasin were simultaneously given to these animals. Finally, studies with clonidine, a central inhibitor of the sympathetic nervous system, have shown that cirrhotic patients with ascites are very sensitive to the hypotensive effect of this drug.¹²⁵ These data indicate that the low arterial pressure and peripheral vascular resistance of patients with cirrhosis and ascites would be much lower if the endogenous vasoconstrictor systems were not activated and that the stimulation of these systems represents a concerted response to maintain arterial pressure. Systemic hemodynamics in cirrhosis with ascites must always be considered together with activity of these neurohormonal systems. For example, the small differences in peripheral vascular resistance between patients with compensated cirrhosis and patients with cirrhosis and ascites does not mean small differences in the degree of

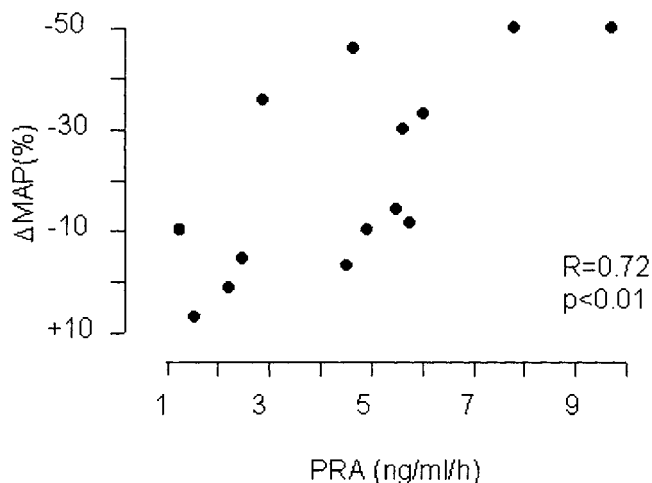


Figure 8. Relationship between the decrease in mean arterial pressure (MAP) after angiotensin II blockade with saralasin and the base-line plasma renin activity (PRA). Reprinted with permission.⁴¹

arterial vasodilation because the latter is obscured in the patients with ascites by the effect of the sympathetic nervous activity, the renin-angiotensin system, and vasopressin.

Site and Mechanism of Arterial Vasodilation

Splanchnic arterial vasodilation is a constant feature when there is chronic increase in portal pressure and plays a major role in the syndrome associated with portal hypertension.^{126–131} It increases the inflow of blood into the portal venous system, and by this mechanism, portal pressure remains elevated despite the development of collateral circulation.¹³² It is also an important factor in the increased hydrostatic pressure and permeability in the splanchnic capillaries and in the formation of ascites.^{133,134} Finally, it reduces the transit time of blood through the splanchnic circulation, which behaves as an arteriovenous fistula.^{127–129} There is a splanchnic resistance to the vasoconstrictor agents in cirrhosis.^{135–136} This explains why the hyperdynamic circulation increases with the progression of the disease despite the stimulation of the renin angiotensin and sympathetic nervous systems and antidiuretic hormone. In contrast, in patients with ascites, these systems induce vasoconstriction in other organs, such as the kidneys, brain, muscle, and skin (Figure 9).^{69–71,137}

Nitric oxide is an important effector of the splanchnic vasodilation in cirrhosis. First, it is a local vasodilator and may be activated only in regional circulation.¹³⁸ Second, nitric oxide production is increased in the splanchnic circulation in cirrhosis.^{139,140} Finally, nitric oxide inhibition normalizes the hyperdynamic circulation and the

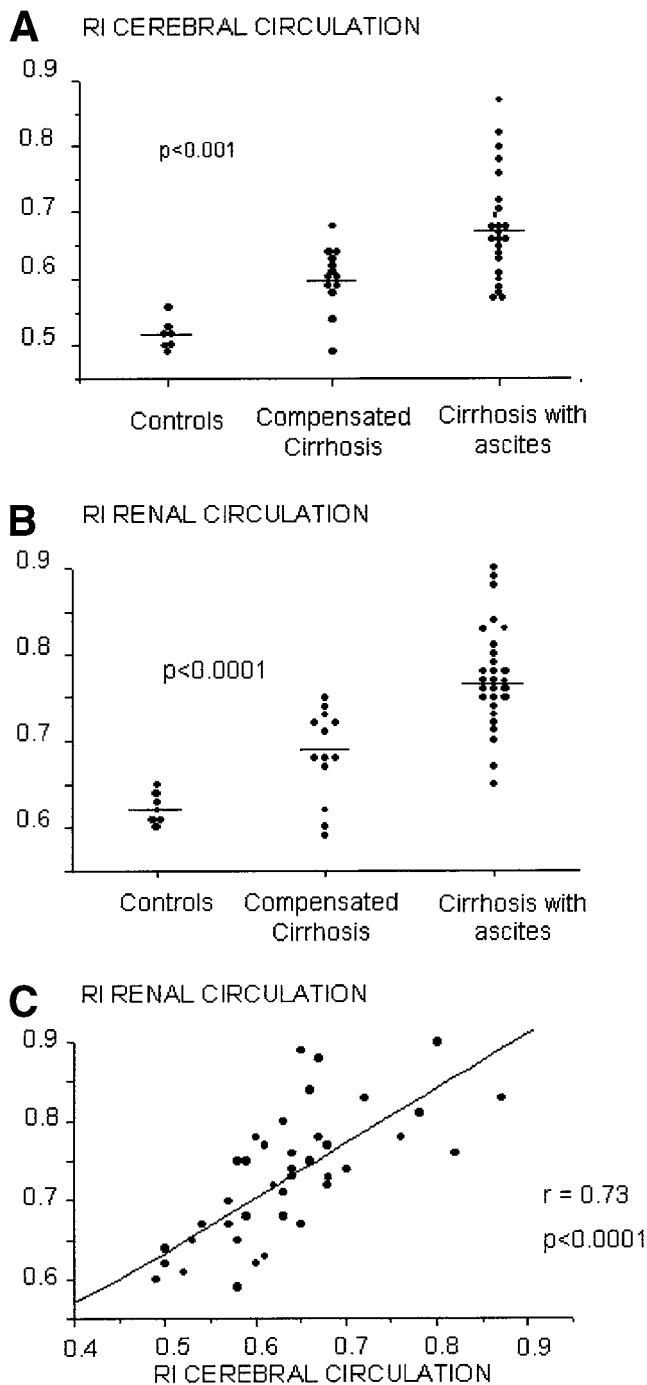


Figure 9. Resistive index (RI) in the mean cerebral artery (A) and in the arcuate or interlobar intrarenal artery (B) in healthy subjects, patients with compensated cirrhosis and patients with ascites. C illustrates the relationship between both measurements in the patients with cirrhosis. Reprinted with permission.¹³⁷

response to vasoconstrictors in cirrhosis.^{135,136,141-147} It has been proposed that vascular endothelial and smooth muscle cells are the sites of nitric oxide hyperproduction in cirrhosis and that this is related with cytokines released locally as a consequence of bacterial translocation from the intestinal lumen.^{148,149} Nitric oxide and other

vasodilators such as substance P, vasointestinal peptide, and calcitonin gene-related peptide are neurotransmitters of the splanchnic nonadrenergic, noncholinergic nervous system.¹⁵⁰ Therefore, it may also be possible that changes in the splanchnic organs secondary to portal hypertension stimulate the nonadrenergic, noncholinergic nervous system and the release of vasodilator neurotransmitters by the nervous terminals. In fact, the circulating plasma levels of vasointestinal peptide, substance P, and calcitonin gene-related peptide are increased in decompensated cirrhosis.¹⁵¹⁻¹⁵⁵

Cardiovascular Function in HRS

There are few investigations on circulatory function in HRS. Tristani and Cohn in 1967¹¹⁸ showed that arterial hypotension was associated with normal or reduced cardiac output and low right atrial pressure in a significant number of patients with HRS. The peripheral vascular resistance was higher than that reported by other authors in patients without HRS. In 1979, the same group of investigators assessed cardiovascular function in patients with refractory and diuretic responsive ascites.¹¹⁹ The cardiac output was lower and the peripheral vascular resistance higher in the former group of patients. Finally, González-García et al.¹²⁰ and Fernández et al.¹²¹ have recently studied patients with spontaneous bacterial peritonitis at infection diagnosis and after infection resolution. At infection diagnosis, blood urea nitrogen, plasma levels of renin and norepinephrine, and peripheral vascular resistance were higher and cardiac output lower in patients who subsequently developed HRS. During treatment, a further increase in renin and norepinephrine and a reduction in arterial pressure and cardiac output were observed in these patients. At the end of treatment, mean arterial pressure and cardiac output were 10% and 30% lower, peripheral vascular resistance 32% higher, and the plasma levels of renin and norepinephrine between 5 and 10 times higher in patients developing HRS compared with those without HRS. The reduction in cardiac output in patients with HRS occurred in the absence of changes in right atrial and wedged pulmonary pressures, which were reduced in most cases.

These studies confirm that arterial vasodilation is a major factor in HRS. Although peripheral vascular resistance is higher in patients with HRS than in those without HRS, it is inappropriately low in relation to the extremely high levels of renin, norepinephrine, and antidiuretic hormone present in these patients. However, HRS clearly develops in the absence of an aggravation of the arterial vasodilation already present before the syndrome; it appears to be related to cardiac dysfunction.

The combination of arterial vasodilation and decreased cardiac output is the most likely mechanism of the severe impairment in the effective arterial blood volume in HRS.

A specific cardiomyopathy characterized by impaired ventricular contractibility has been described in cirrhosis.¹⁵⁶ Down-regulation of α -receptors, impaired α -adrenergic receptor signal transduction, alterations in myocardial plasma membrane, increased levels of cardiodepressant substances, and ventricular overload because of hyperdynamic circulation has been proposed as pathogenetic mechanisms.¹⁵⁶ Cirrhotic cardiomyopathy is asymptomatic because arterial vasodilation significantly reduces the afterload to the ventricle. However, because of the hyperdynamic circulation, cardiac reserve function may be borderline in advanced cirrhosis. The chronotropic function of the heart is also impaired because of autonomic dysfunction.¹⁵⁶ Therefore, circumstances requiring further increase in cardiac work such as bacterial infections or other precipitating factors of HRS may unmask cirrhotic cardiomyopathy.

Another possible mechanism for the reduced cardiac output in HRS is a decreased venous return secondary to an increased venous compliance. The cardiopulmonary pressures are normal or reduced in HRS.¹¹⁸ The expansion of the plasma volume in patients with HRS is associated with a marked increase in the cardiac output, indicating a preserved cardiac reserve.¹¹⁸ Finally, circulatory function can be normalized and HRS reversed by the administration of albumin infusion plus vasoconstrictors⁷² but not by the isolated use of one of these measures.¹⁵⁷

Interactions Between Hepatic and Systemic Hemodynamics

The mechanisms by which portal hypertension induces splanchnic arterial vasodilation and hyperdynamic circulation has been deeply investigated. However, the reverse (i.e., that systemic circulatory dysfunction may impair the intrahepatic hemodynamics in cirrhosis) has received little attention.

A significant part of the increased intrahepatic vascular resistance in cirrhosis is unrelated with architectural changes,^{97,158} and there are data that in decompensated cirrhosis the renin-angiotensin and sympathetic nervous systems may be involved in this functional component of portal hypertension. Angiotensin II and catecholamines reduce hepatic blood flow and increase intrahepatic vascular resistance and portal pressure.¹⁵⁹ The hepatic arterioles and venules and the sinusoidal pericytes (stellate cells) are the sites of action of these substances.^{97,158} The degree of portal hypertension in cirrhosis correlates di-

rectly with the plasma levels of renin and norepinephrine.^{78,160} The blockade of angiotensin II with saralasin or the inhibition of the sympathetic nervous activity with clonidine in cirrhotic patients with ascites decreases the wedged hepatic venous pressure in the absence of changes in the hepatic blood flow, indicating a reduction in the intrahepatic vascular resistance.^{41,160,161} Finally, during paracentesis, the stimulation of the renin-angiotensin and sympathetic nervous systems is associated with an increase in the hepatic venous pressure gradient.¹⁶²

Impairment in circulatory function in HRS during spontaneous bacterial peritonitis also has been shown to be associated with an increase in intrahepatic vascular resistance.¹²¹ Infected patients who subsequently developed HRS showed higher wedged hepatic venous pressure gradient than those not developing HRS. During treatment, hepatic venous pressure gradient further increased with the deterioration in circulatory function in the first group but not in the second. The increase in hepatic venous pressure gradient correlated closely with the increase in plasma renin activity and noradrenaline concentration. At infection resolution, the hepatic venous pressure gradient was 43% higher in patients developing HRS.

Therefore, circulatory dysfunction in HRS affects not only the renal circulation and the circulation in other organs such as the brain, muscle, and skin but also the intrahepatic circulation. This may explain some clinical features associated with HRS such as the rapid deterioration of hepatic function and the frequent development of hepatic encephalopathy.

Treatment of HRS

During the last decades, many vasoactive drugs (dopamine, fenoldopam, prostaglandins, misoprostol, saralasin, phentolamine, dazoxiben, norepinephrine, metaraminol, octopressin) have been assessed in HRS.¹⁰⁰ In no case did renal function improve. Therefore, HRS was considered as an intractable terminal event of cirrhosis, and this reduced the interest in the management of the syndrome. However, in these studies, drugs were given during hours or a few days, and we now know that this is insufficient to reverse HRS. Improvement of HRS after portacaval shunt or liver transplantation does not occur until 1 week to 1 month after treatment. The same has been observed after the administration of volume expanders and vasoconstrictors.

The introduction of the LeVein shunt in 1974²⁶ was a second reason for decreasing interest in the pharmacologic treatment of HRS. For many years, this was con-

sidered an effective therapy for this complication. In fact, it was not until 15 years later that the LeVeen shunt was proved to be ineffective in type 1 HRS.¹⁶³ In type 2 HRS with refractory ascites, it did not improve the results obtained with therapeutic paracentesis.^{164,165} The LeVeen shunt is associated with severe complications such as superior vena cava thrombosis or intestinal obstruction and a high rate of obstruction requiring reoperation. These features have led to the abandonment of this treatment.

Finally, the poor prognosis of patients with HRS has been traditionally considered to be caused by hepatic failure. Consequently, any improvement in renal function would have little impact in survival. Treatment of renal failure in HRS, therefore, has not been taken as a real challenge to improve the natural history of the disease. The generalization of liver transplantation and, particularly, the introduction of living donor liver transplantation for adults have changed the scenario. A small increase in survival may allow patients to reach a transplant and to increase the 10-year probability of survival to 50%. This, together with a better understanding of the pathogenesis of the syndrome, has stimulated clinical investigators to assess new treatment in HRS.

Liver Transplantation

Liver transplantation is the treatment of choice for HRS.^{166–170} Immediately after transplantation, a further impairment in GFR may be observed, and many patients require hemodialysis (35% of patients with HRS compared with 5% of patients without HRS). Because cyclosporine or tacrolimus may contribute to this impairment in renal function, it has been suggested to delay the administration of these drugs until a recovery of renal function is noted, usually 48–72 hours after transplantation. After this initial impairment in renal function, GFR starts to improve and reaches an average of 30–40 mL/min by 1–2 months postoperatively. This moderate renal failure persists during follow-up, is more marked than that observed in transplantation patients without HRS, and is probably because of a greater nephrotoxicity of cyclosporine or tacrolimus in patients with renal impairment before transplantation. The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after the operation, and the patients regain a normal ability to excrete sodium and free water.¹⁷¹

Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS.^{166–170} The long-term survival of patients with HRS who undergo

liver transplantation, however, is good, with a 3-year probability of survival of 60%.^{166–170} This survival rate is only slightly reduced compared with that of transplantation in patients without HRS (which ranges between 70% and 80%).

Cirrhotic patients with type 2 HRS have a sufficiently prolonged survival to enable them to receive a liver graft. However, this is not the case in patients with type 1 HRS, in whom the expected survival is less than 2 weeks. This poor prognosis makes the applicability of liver transplantation very unlikely in this subset of patients unless survival could be increased by other measures.

Volume Expansion and Vasoconstrictors

The first study showing that HRS can be reversed pharmacologically was performed by Guevara et al.⁷² They assessed the hemodynamic, neurohormonal, and renal effects of intravenous albumin and a continuous infusion of ornipressin in 16 patients with HRS. Eight patients were treated for 3 days; albumin was given at a dose of 1 g/kg on the first day and 20–60 g/d for the next 2 days, and ornipressin was given as an intravenous stepped dose infusion of 2–6 IU/h. A normalization of the plasma levels of renin and norepinephrine was obtained, indicating a marked improvement in circulatory function. However, only a slight increase in GFR (from 15 ± 4 mL/min to 24 ± 4 mL/min, normal values over 100 mL/min) was observed (Figure 10). The remaining 8 patients were treated for 15 days. Ornipressin was given at a dose of 2 IU/h. Albumin was given at a dose of 1 g/kg during the first day. The amount of albumin during the following days was adjusted according to plasma renin activity. In 4 patients, treatment was stopped after 4 and 9 days because of ischemic complications in 3 cases and a bacteremia in 1 case. In these 4 patients, a marked decrease in serum creatinine during therapy and a progressive impairment of renal function after treatment withdrawal was observed. In the remaining 4 patients who completed treatment, there was a significant elevation in mean arterial pressure, a normalization of plasma renin activity, a marked decrease in plasma norepinephrine concentration, an increase in GFR, and normalization in serum creatinine concentration. These 4 patients died 12, 60, 62, and 133 days after treatment; HRS did not recur in any of them during follow-up.

In a subsequent study, the same group treated 9 patients with HRS (6 with type 1 and 3 with type 2 HRS) with terlipressin (0.5–2 mg/4 hours intravenously [IV]) and IV albumin during 5–15 days.¹⁷² Reversal of HRS (normalization of serum creatinine) was observed in 7 patients (Figure 11). No case developed ischemic complications. HRS did not recur in any patient. Five cases

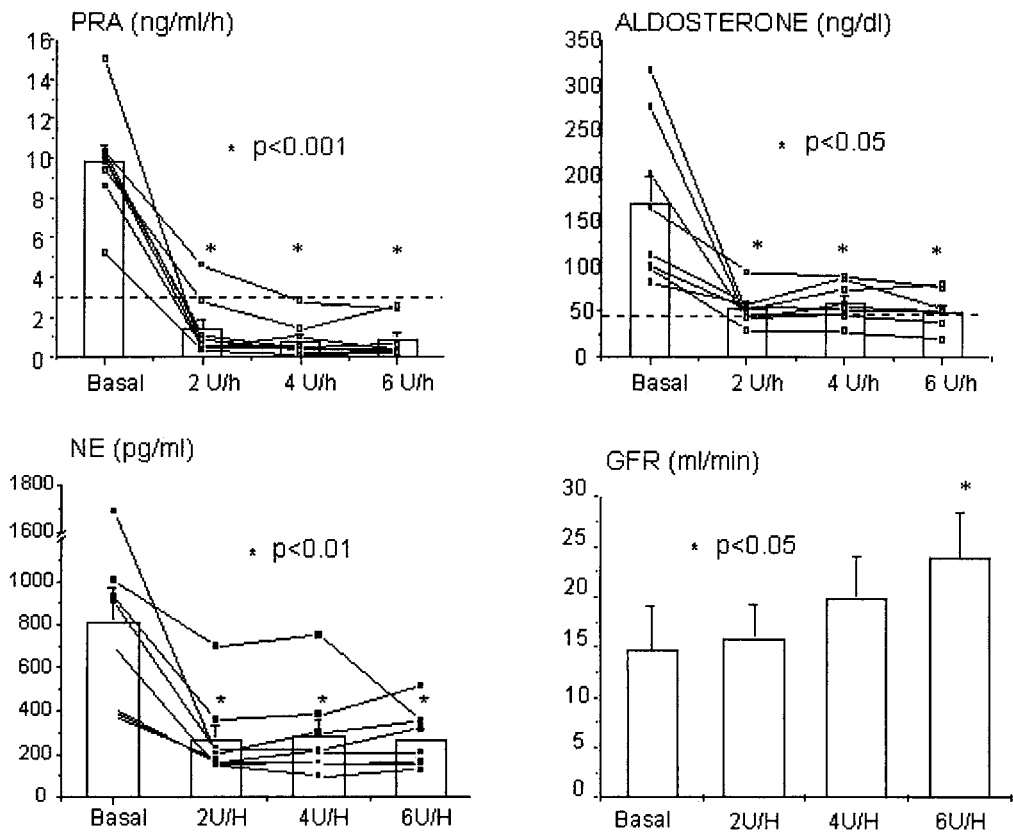


Figure 10. Changes in plasma renin activity (PRA), plasma aldosterone, and norepinephrine (NE) concentration, and GFR (inulin clearance) in patients with HRS treated with ornipressin (2 U/h the first day, 4 U/h the second day, and 6 U/h the third day) plus IV albumin infusion. There was a marked suppression of the neurohormonal systems without clinically significant increase in GFR. Reprinted with permission.⁷²

were transplant candidates, and 3 were transplanted 5, 12, and 99 days after treatment. The 2 other patients died 30 and 121 days after the inclusion. The remaining 4 patients died 13–102 days after treatment. In both studies, dilutional hyponatremia was corrected with the normalization of serum creatinine. The results obtained in this group of investigation in the 17 patients treated

with ornipressin and terlipressin and IV albumin for more than 3 days are summarized in Table 2.

These observations have been confirmed by other groups. Gülberg et al.¹⁷³ treated 7 patients with type 1 HRS with ornipressin (6 IU/h), dopamine (2–3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and IV albumin.¹⁷³ HRS was reverted in 4 patients after 5–27 days of treatment. In 1 patient, treatment had to be stopped because of intestinal ischemia. The remaining 2 patients did not respond. In 2 of the 4 patients responding to treatment, HRS recurred 2 and 8 months later, and they were retreated. HRS was

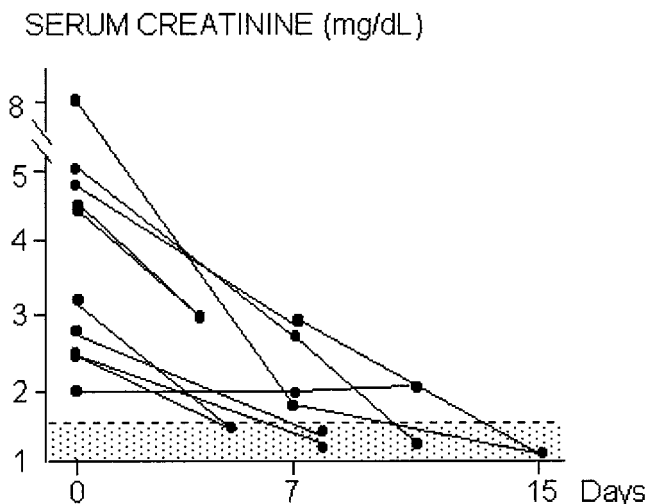


Figure 11. Evolution of serum creatinine in patients with HRS treated by terlipressin (0.5–2 mg/4 h) and IV albumin infusion. Reprinted with permission.¹⁷²

Table 2. Effect of Vasoconstrictors (Ornipressin and Terlipressin) and Volume Expansion in HRS

	Baseline (n = 15)	Day 3 (n = 12)	Day 7 (n = 9)	Day 14 (n = 7)
MAP (mm Hg)	70 ± 8	70 ± 8	77 ± 9	79 ± 12
PRA (ng/mL/h)	15 ± 15	4 ± 2	2 ± 3	1 ± 1
NE (pg/mL)	1257 ± 938	550 ± 382	550 ± 410	316 ± 161
Creatinine (mg/dL)	3 ± 1	3 ± 1	2 ± 1	1 ± 1

NOTE. Normal values: PRA < 1.4 ng/mL/h, NE < 260 pg/mL; P < 0.001 for all values (analysis of variance).

MAP, mean arterial pressure; NE, norepinephrine; PRA, plasma renin activity.

Data from references 92 and 172.

reverted in 1 patient. In the other patient, treatment had to be stopped because of ventricular tachyarrhythmia. In total, 2 patients reached liver transplantation, and 1 patient was alive 1 year after inclusion after 2 successful treatments. Mulkay et al.¹⁷⁴ treated 12 patients with type 1 HRS with terlipressin (2 mg every 8–12 hours) and albumin infusion (0.5–1 g/kg day during 5 days) for 1–9 weeks.¹⁷⁴ HRS was reverted in 7 patients. In the remaining 5 cases, serum creatinine also decreased but not to a normal level. Withdrawal of terlipressin without recurrence of HRS was obtained in 6 patients. No patient developed complications related with the treatment. Three patients were transplanted 34, 36, and 111 days after inclusion. The remaining patients died with a median survival time of 42 days.

Catecholamines are also effective for the treatment of HRS. Angeli et al.¹⁷⁵ used oral midodrine, an α -adrenergic agonist, IV albumin, and subcutaneous octreotide (to suppress glucagon) in 5 patients with type 1 HRS. Midodrine dosage was adjusted to increase in mean arterial pressure 15 mm Hg or more. Patients received treatment for at least 20 days in hospital and subsequently continued treatment at home. In all cases, there was a dramatic improvement in renal perfusion, GFR, blood urea nitrogen, serum creatinine, and serum sodium concentration and a suppression of plasma renin, aldosterone, and antidiuretic hormone to normal or near normal levels. Two patients were transplanted 20 and 64 days after inclusion while on therapy. One patient who was not a candidate for liver transplantation was alive without treatment 472 days after discharged from hospital. The remaining 2 patients died 29 and 75 days after the inclusion. These results were compared with those obtained in 8 patients with type 1 HRS treated with IV albumin plus dopamine ($2\text{--}4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). In these 8 patients, a progressive worsening in renal function was observed. One patient was transplanted but died 15 days after transplantation from a fungal infection. The remaining 7 patients died within 2 weeks after the initiation of treatment. Duvoux et al.¹⁷⁶ treated 12 patients with type 1 HRS with IV albumin (to maintain central venous pressure over 7 mm Hg) and noradrenalin (0.5–3 mg/h) for a minimum of 5 days. A significant improvement in serum creatinine in association with a marked suppression of plasma renin activity was observed in 10 patients. Transient myocardial ischemia was observed in 1 patient. Three patients were transplanted, and 3 were still alive after 8 months of follow-up.

Finally, Ginès et al.¹⁵⁷ have recently assessed whether albumin is necessary in the treatment of HRS with vasoconstrictors. Twenty-one patients with HRS were

studied. The first 13 were treated with terlipressin (0.5–2 g/4 h) and albumin (1 g/kg the first day; 20–40 g/day thereafter). The last 8 patients received terlipressin alone. Treatment was given until normalization of serum creatinine or for a maximum of 15 days. In patients treated with terlipressin plus albumin, there was a significant increase in mean arterial pressure, a marked suppression of plasma renin activity, and a decrease in serum creatinine. In contrast, no significant changes in these parameters were observed in patients treated with terlipressin alone. A complete response (normalization of serum creatinine) was achieved in 10 patients treated with terlipressin plus albumin and in only 2 treated without albumin. Recurrence of HRS only occurred in 2 patients. One-month survival without transplantation was 87% in patients receiving terlipressin plus albumin and 13% in patients receiving terlipressin alone.

These studies show that (1) type 1 HRS is reversible after treatment with IV albumin and vasoconstrictors, (2) the 2 components of the treatment are important because HRS does not reverse when vasoconstrictors or plasma volume expansion are given alone, (3) the constant infusion of vasoconstrictors (ornipressin or noradrenalin) is associated with ischemic complications (a feature not observed when they are given intermittently), (4) there is a delay of several days between the improvement in circulatory function and the increase in GFR, and (5) reversal of HRS improves survival and a significant number of patients may reach liver transplantation.

Transjugular Intrahepatic Portacaval Shunt

Because portal hypertension is the initial event of circulatory dysfunction in cirrhosis, the decrease of portal pressure by portacaval anastomosis is a rational approach for the treatment of HRS. There are several case reports showing reversal of HRS after surgical portacaval shunt.^{177,178} However, the applicability of major surgical procedures in patients with HRS is small. The development of transjugular intrahepatic portacaval shunt (TIPS) has reintroduced the idea of treating HRS by reducing portal pressure.

Four studies assessing TIPS in the management of type 1 HRS have been reported^{179–182} and recently reviewed by Brensing et al.⁷⁶ In total, 30 patients were treated. In 2 series, no liver transplantation was performed, whereas in the other 2 series, 3 out of 9 patients were transplanted 7, 13, and 35 days after TIPS. TIPS insertion was technically successful in all patients. One patient died as a consequence of the procedure. GFR improved markedly within 1–4 weeks after TIPS and stabilized thereafter. In 1 study specifically investigating the neurohormonal systems, improvement in GFR and

serum creatinine was related to a marked suppression of the plasma levels of renin and antidiuretic hormone.¹⁸⁰ The suppression of plasma norepinephrine is lower than that of renin, a feature also observed in refractory ascites treated by TIPS. Follow-up data concerning hepatic function were obtained from 21 patients. De novo hepatic encephalopathy or deterioration of preexisting hepatic encephalopathy occurred in 9 patients, but in 5, it could be controlled with lactulose. Survival rates based on the 27 patients without early liver transplantation at 1 month, 3 months, and 6 months were 81%, 59%, and 44%, respectively. These studies strongly suggest that TIPS is useful in the management of type 1 HRS. Studies comparing TIPS with pharmacologic treatment in type 1 HRS are needed.

Other Therapeutic Methods

Hemodialysis and arteriovenous or venovenous hemofiltration are frequently used in patients with HRS, but their efficacy has not been adequately assessed.¹⁸³ Recently, extracorporeal albumin dialysis, a system that uses an albumin-containing dialysate that is recirculated and perfused through charcoal and anion-exchanger columns, has been shown to improve systemic hemodynamics and reduce the plasma levels of renin in patients with type 1 HRS.^{184,185} In a small series of patients, an improved survival has been reported. Further studies are needed to confirm these findings.

Prevention of HRS

Two randomized controlled studies in a large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,¹⁸⁶ the administration of albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg IV 48 hours later) together with cefotaxime in patients with cirrhosis and spontaneous bacterial peritonitis markedly reduced the incidence of impairment in circulatory function and the occurrence of type 1 HRS compared with a control group of patients receiving cefotaxime alone (10% incidence of HRS in patients receiving albumin vs. 33% in the control group). Moreover, the hospital mortality rate (10% vs. 29%) and the 3-month mortality rate (22% vs. 41%) were lower in patients receiving albumin. In a second study,¹⁸⁷ the administration of the tumor necrosis factor inhibitor pentoxifylline (400 mg 3 times a day) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% in the pentoxifylline group vs. 35% in the placebo group) and hospital mortality (24% vs. 46%, respectively). Because bacterial infections and acute alcoholic hepatitis are 2 important precipitating

factors of type 1 HRS, these prophylactic measures may decrease the incidence of this complication.

Summary

HRS is a major clinical event during the course of decompensated cirrhosis. Although the most characteristic feature of the syndrome is a functional renal failure caused by an intense renal vasoconstriction, it is a more generalized process affecting the heart, brain, and the splanchnic organs. There are 2 types of HRS. Type 1 HRS is characterized by a rapidly progressive impairment in circulatory and renal function. It usually develops in a closed chronological relationship with a precipitating event, particularly severe bacterial infections, superimposed acute alcoholic, toxic, or viral hepatitis, or major surgical procedures and is associated with a very poor prognosis (median survival rate, <2 weeks). Type 2 HRS is characterized by a steady impairment in circulatory and renal function. Patients with type 2 HRS have a median survival of 6 months, and their main clinical problem is refractory ascites. The pathogenesis of HRS is a deterioration in effective arterial blood volume because of a splanchnic arterial vasodilation and a reduction in venous return and cardiac output. It is therefore not surprising that the syndrome can be reversed by the simultaneous administration of IV albumin and arterial vasoconstrictors. Intrarenal mechanisms are also important and require a prolonged improvement in circulatory function to be deactivated. Vasoconstriction in the brain, muscles, and skin; increased intrahepatic vascular resistance and portal pressure; and impairment in hepatic function are other components of the syndrome. Long-term administration of IV albumin and vasoconstrictors or the correction of portal hypertension with a TIPS are effective treatments of HRS, improve the survival rate, and may serve as a bridge to liver transplantation, which is the treatment of choice in these patients.

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