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Renal and circulatory dysfunction in liver cirrhosis. Pathogenesis and treatment

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SUMMARY

The clinical course of patients with cirrhosis is complicated by several disorders independent of the cause of the underlying liver disease. These include portal hypertension with development of esophageal varices, ascites and spontaneous bacterial peritonitis, hepatorenal syndrome (HRS) and hepatocellular carcinoma. Among these complications the development of renal dysfunction and hepatorenal syndrome are associated with a very poor prognosis. During the course of cirrhosis a derangement in renal function leads to an inability to maintain the extracellular fluid volume of the body within normal limits. This abnormal extracellular fluid volume regulation is associated with alterations in the splanchnic and systemic circulation as well as functional renal abnormalities that favor sodium and water retention. For the most part, the predominant renal function abnormality is sodium retention and its main clinical consequence is the recurrent accumulation of extracellular fluid as ascites and edema. In late stage cirrhosis, as renal function becomes more impaired, the kidney is unable to handle water properly and in addition the renal vasculature becomes severely vasoconstricted. The main clinical consequences of these two latter abnormalities are dilutional hyponatremia and hepatorenal syndrome (HRS), respectively. HRS is therefore a functional renal failure. In fact, renal function returns to normal after patients with HRS receive a liver transplantation. However, it should noted that some patients with cirrhosis due to hepatitis B or C are at risk of developing organic renal failure secondary to cryoglobulinemia or glomerulonephritis and these conditions should be excluded prior to making the diagnosis of HRS.

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FUNCTIONAL RENAL ABNORMALITIES

Sodium Retention

Sodium retention is probably the most common renal function abnormality in patients with cirrhosis and ascites and plays a key role in the pathophysiology of ascites and edema formation. It is the first manifestation of renal impairment cirrhotics develop. It appears before ascites formation, impaired free water excretion and functional renal failure[1,2] (Figure 1). This observation suggests that sodium retention is a cause and not a consequence of ascites formation in cirrhosis.

The amount of sodium retained by cirrhotic patients depends on the amount they ingest in their diet. There is finite balance: if they excrete less than what they take in, they accumulate fluid as ascites or edema. Patients with compensated cirrhosis regularly do not retain sodium but some, when exposed to a high sodium intake by means of diet, intravenous saline solutions, mineralocorticoids or non-steroidal anti-inflammatory drugs (these increase sodium reabsorption), can develop ascites.[1,3] However, the degree and intensity of this abnormality varies among patients, some having a relatively high sodium excretion, whereas others avidly retain sodium. As expected, the response to diuretics is usually better in those with normal sodium excretion. Although sodium retention in cirrhosis is not a fixed disorder, there seems to be a correlation with the degree of underlying portal hypertension and peripheral vasodilation. It is our experience that in most cases the intensity of retention increases over time. However, in some patients with marked sodium reten-

tion, sodium excretion may improve spontaneously and they may remain without ascites for prolonged periods of time.

Sodium retention is due to an increased renal tubular reabsorption of sodium in the proximal and distal tubules because it may occur in the presence of an almost normal glomerular filtration rate (GFR).[4,5] Although numerous mechanisms have been proposed to explain sodium retention in cirrhosis, the two main sodium-retaining systems responsible are the renin-angiotensin-aldosterone-system (RAAS) and the sympathetic nervous system (SNS). These are activated as a homeostatic response (see later). The two final products of the RAAS system, angiotensin II and aldosterone, induce sodium retention by acting in the proximal tubule and the collecting duct, respectively.[6] The SNS stimulates sodium reabsorption in the proximal tubule, loop of Henle and distal and collecting tubules.[7-9] Even though both systems have an important role in the pathogenesis of sodium retention, in 30-40% of these patients the serum levels of renin, aldosterone and norepinephrine are normal. This is an unanswered question. It has been suggested that small changes in effective arterial blood volume, insufficient to stimulate RAAS and SNS, could induce sodium retention at the early stages of decompensated cirrhosis, by a more sensitive mechanism than traditional sodium-retaining.[10,11] This may be related to changes in intrarenal hemodynamics or to unknown circulatory antinatriuretic hormones.

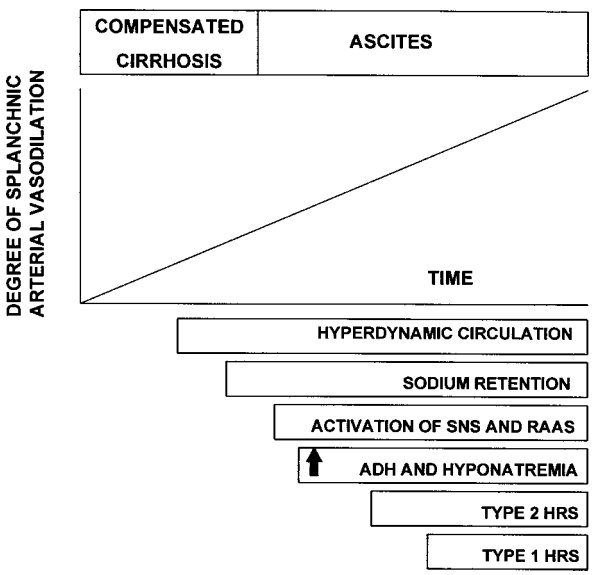

Figure 1. The time course of the circulatory, neurohormonal and renal function abnormalities in cirrhosis. Sympathetic nervous sytem (SNS), renin-angiotensin-aldosterone sytem (RAAS), antidiuretic hormone (ADH) and hepatorenal syndrome (HRS).

Water retention

The normal kidney generates free water in the ascending loop of Henle by separating solutes from water. From there on, the final volume of free water depends on the action of the antidiuretic hormone or arginine vasopressin (AVP) on the distal collecting duct, which controls water excretion and reabsorption. It is well known that patients with advanced cirrhosis have trouble regulating water in the kidney.[12,13] The clinical consequence is the development of dilutional hyponatremia, which occurs despite avid sodium retention because water is retained in excess of sodium. It has been estimated that the prevalence of spontaneous dilutional hyponatremia in hospitalized patients with cirrhosis and ascites can be as high as 35%.[14] Although the severity of this disorder is not the same in all patients, it is usually more intense in advanced stages of cirrhosis. In some patients, the impairment of free water excretion is mild or moderate and can only be detected after the administration of a water load of 20 mg/kg of body weight. These patients have no problem with the amount of water they regularly take in their diet, but if they exceed this, they will develop hyponatremia. So, the fact that some patients have a normal serum sodium concentration does not mean that they can handle water properly. Since this derangement worsens with progression of the disease, patients with marked impairment in water excretion (free water clearance less than 3 ml/min) have a high risk of developing hyponatremia during follow-up.[15]

The pathogenesis of water retention in cirrhosis is related to three events: 1) a reduced delivery of filtrate to the ascending limb of the loop of Henle (the diluting segment of the nephron), 2) a reduced renal synthesis of prostaglandins and 3) an increased secretion of arginine vasopressin (AVP)[16] (Figure 2). Among these, AVP has been widely implicated as the major factor in the pathogenesis of water retention in cirrhosis with ascites. The levels of AVP are high in cirrhosis because there is a non-osmotic activation in response to a reduced effective intravascular volume (see later).[17] The renal synthesis of prostaglandin E-2 is increased in patients with cirrhosis in order to antagonize the effects of AVP which is why NSAIDS may impair the renal ability to excrete free water.

The impairment in water excretion in cirrhosis usually occurs weeks to months after the onset of sodium retention. Dilutional hyponatremia is a late complica-

tion in the clinical course of cirrhosis and indicates a poor prognosis in these patients.

Renal vasoconstriction

Renal vasoconstriction is the renal functional abnormality that develops latest in patients with cirrhosis and ascites (Figure 1). An increased activity of vasoconstrictor factors and a reduced activity of renal vasodilator factors acting on the renal circulation play a crucial role in the pathogenesis of renal vasoconstriction.[18] This vasoconstriction is more intense in the renal cortex and may result in a reduction of renal blood flow and glomerular filtration rate (GFR). The degree of renal vasoconstriction varies; it can be mild and impairment can only be detected only by measuring GFR and renal plasma flow by clearance techniques, or severe renal failure with elevation of blood urea nitrogen and serum creatinine concentration and oliguria. The pathogenesis of renal vasoconstriction in cirrhosis is related to changes in systemic hemodynamics. The most accepted theory considers that renal vasoconstriction is the consequence of the extreme arterial underfilling secondary to splanchnic arteriolar vasoconstriction, which activates systemic vasoconstrictors, whose effect on the kidney vasculature cannot be counterbalanced by either systemic or renal vasodilators.[19] As a consequence, severe vasoconstriction of renal vessels occurs and HRS ensues.

SYSTEMIC CIRCULATORY CHANGES IN CIRRHOSIS

In human cirrhosis there is a characteristic disturbance in the systemic circulation manifested by arterial hypotension, a reduced systemic vascular resistance and an increased cardiac output. These changes are very prominent in patients with advanced cirrhosis and HRS.[19,20]

The initial event of systemic circulatory dysfunction in cirrhotic patients is the development of splanchnic vasodilation. The increased resistance to portal flow and the augmented vascular tone caused by portal hypertension induce a severe disturbance in the hepatic and splanchnic circulation. The main consequence is the development of a porto-collateral circulation (esophageal and gastric varices) and splanchnic arterial vasodilation. Arterial vasodilation in the splanchnic circulation causes a drop in systemic blood pressure. This event causes activation of vasoconstrictor and antinatriuretic systems (RAAS, SNS and AVP) as a compensatory response to maintain the blood pressure within normal limits. In contrast to the splanchnic vasodilation, other highly vascularized areas of the body like the kidneys, brain, and muscles and skin display intense vasoconstriction. This hyperdynamic circulation is also observed in experimental models of cirrhosis and occurs chronologically before the formation of ascites and is more marked as the disease progresses .

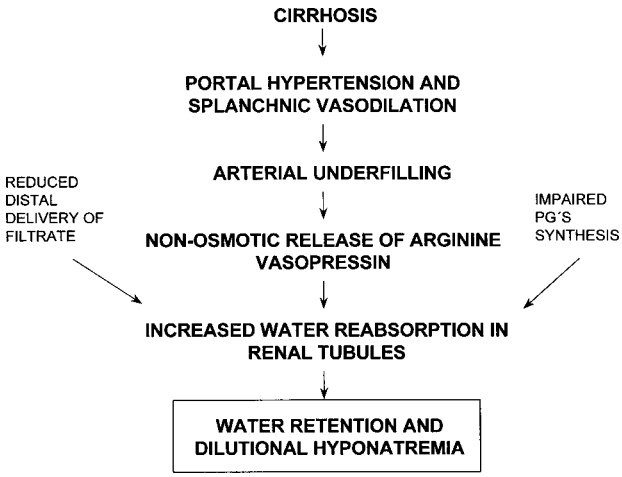

Figure 2. Pathogenesis of water retention and dilutional hyponatremia in cirrhosis as proposed by the peripheral arterial vasodilation theory.

The reason why cirrhosis and portal hypertension induce splanchnic arterial vasodilation has not been completely elucidated. Early studies indicated that high levels of circulating vasodilators, such as glucagon could be involved.[21] However recent investigations indicate that local vasodilators (nitric oxide (NO), carbon monoxide, glucagon, eicosanoids, adenosine, bile salts, platelet activating factor, substance P and calcitonin gene-related peptide) synthesized in the splanchnic circulation are responsible for the development of splanchnic arterial vasodilation. In the last decade, NO has been implicated as the most important factor responsible for the hyperdynamic circulation in cirrhosis.[22,23] There are three possible mechanisms by which NO is increased in patients with cirrhosis and ascites. The first is increased production by the vascular endothelium, however it is unclear what triggers NO release in this case.[24] The second is related to bacterial translocation into the interstitial space, this could be mediated by circulating endotoxin or cytokines (i.e. tumor necrosis factor) that may be increased in cirrhosis and could stimulate the inducible NO synthase.[25] The increase in portal venous inflow and the consequent increase in "shear stress" would then activate the constitutive endothelial NO synthase, which would amplify the vasodilatory response. The third is related to the non-adrenergic non-cholinergic nervous

system.[26] This is a sensitive system widely distributed in the splanchnic area, which participates in gastrointestinal and biliary motility. Upon stimulation, it releases numerous neurotransmitters including the vasodilators NO, substance P, calcitonin gene related peptide and vasoactive intestinal peptide.

Evidence supporting the role of NO also comes from both animal and human studies. In cirrhotic rats with ascites the inhibition of NO synthase normalizes the vascular NO production and corrects the hyperdynamic circulation, arterial vasodilation and improves sodium and water excretion.[27] In patients with ascites and cirrhosis, NO levels are found to be elevated in the portal system when compared to levels in a peripheral vein.[28] In addition, the serum metabolites of NO (nitrite and nitrate) and the concentration of NO in exhaled air is abnormally elevated in cirrhosis and ascites.[29] In summary, these findings indicate that NO levels are increased in cirrhosis and play an important role in the pathogenesis of arterial vasodilation.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a clinical condition that develops in patients with chronic liver disease and advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR). There is vasoconstriction in other vascular territories such as the muscle, spleen and brain. In the splanchnic circulation, there is an intense arteriolar vasodilation that results in reduction of total systemic vascular resistance and arterial hypotension. A similar syndrome can also develop in the setting of acute liver failure.[30]

PATHOGENESIS

The regulation of renal circulation in cirrhosis is believed to depend on the interaction between vasoconstrictor and vasodilator factors acting on the renal vasculature (Table 1). In the early stages of decompensated cirrhosis, for example, renal blood flow can be kept within normal limits due to the effect of local vasodilators which antagonize the renal vascular effect of the systemic vasoconstrictor systems. Whenever there is stimulation of the endogenous vasoconstrictors, there is also an activation of the renal vasodilators (prostaglandins, nitric oxide and natriuretic peptides) in order to maintain renal perfusion and GFR. The renal production of prostaglandins and the circulating levels of natriuretic peptides are increased in patients with cirrhosis and ascites without HRS. However HRS will ensue when circulating vasoconstrictors overcome the effect of renal vasodilators, leading to renal vasoconstriction and reduction in GFR. Once renal vasoconstriction develops, intrarenal mechanisms seem to contribute to the perpetuation of HRS because established renal hypoperfusion activates intrarenal vasoconstrictor factors and/or decreases the synthesis of renal vasodilators.[31]

Table 1. Vasoactive substances and systems thatmay be influenced in the regulation of renal perfusion in patients with cirrhosis and ascites.

Renal Vasodilators
Nitric oxide
Prostaglandin E2
Kallikrein-kinin system
Prostacyclin
Renal Vasoconstrictors
Leukotrienes
Endothelin-1
Adenosine
Thromboxane A2
Angiotensin II
Neuropeptide Y
Systemic Vasodilators
Nitric oxide
Atrial natriuretic peptide
Systemic Vasoconstrictors
Angiotensin II
Norepinephrine
Antidiuretic hormone
Neuropeptide Y

The peripheral arterial vasodilation theory proposed to explain sodium and water retention in cirrhosis is also the most rational hypothesis for the development of HRS[19] (Figure 3). The proposed theory states that renal vasoconstriction is the final effect of an extreme underfilling of arterial circulation due to vasodilation in the splanchnic bed and blood pooling in this area. Since this leads to arterial hypotension, a progressive homeostatic response takes place and endogenous vasoconstrictors are released into circulation. The splanchnic area is not affected by the effect of these vasoconstrictors (higher concentration of local vasodilators) and "escapes" their effect. The RAAS and the SNS are very sensitive to these

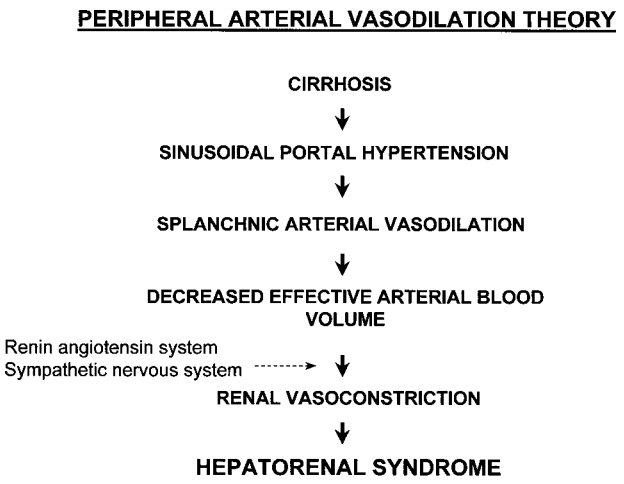

Figure 3. The peripheral vasodilation theory and its role in the development of hepatorenal syndrome.

changes in effective intravascular volume and from a chronological view, they are the first to be stimulated causing sodium retention and ascites (Figure 1). The hypersecretion of antidiuretic hormone a later event and occurs when there is a severe impairment in circulatory function. Finally, HRS then develops as a result of the extreme progression of the decreased effective arterial blood volume. At this point a critical level of vascular underfilling is achieved and renal vasodilator systems are unable to counteract the maximal activation of the endogenous vasoconstrictor systems, leading to uncontrolled renal vasoconstriction and HRS.

CLINICAL FEATURES AND DIAGNOSIS

The incidence of HRS in patients with cirrhosis hospitalized for ascites is of approximately 10%.[32] Two types of HRS have been described.[30] Type I HRS is characterized by rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction of the initial 24-hr creatinine clearance to a level lower than 20 mL/min in less than 2 weeks. In some cases type I HRS occurs spontaneously without any inciting event. However, in most patients it occurs in close association with alcoholic hepatitis, systemic infections and gastrointestinal bleeding. In addition, large volume paracentesis without plasma volume expansion, and major surgical procedures can also precipitate type 1 HRS. In recent years, spontaneous bacterial peritonitis (SBP) has been recognized as the most common precipitating cause of type I HRS. Type I HRS occurs in approximately 25% of cases with SBP despite a rapid resolution of the infection with intravenous antibiotics.[32,34] Without treatment, the median survival time of patients with type I HRS is less than 2 weeks and practically all patients die within 8-10 weeks after the onset of renal failure (Figure 4).

Type II HRS is characterized by a moderate and stable reduction of GFR (serum creatinine levels are usually less than 2.0 mg/dl). The main clinical consequence of type II HRS is diuretic-resistant ascites due to the combination of intense sodium retention and reduced GFR. As expected, survival is much longer in patients with type II HRS than in those with type I HRS, but is shorter than that of cirrhotic patients with ascites without renal failure.[34]

The predictive factors associated with a greater risk of developing HRS have been reported in a large series of cirrhotic patients with ascites (Table 2).[32] Patients with intense sodium retention (<10 mEq/L day), dilutional hyponatremia (serum sodium < 130 mEq/L), low mean arterial blood pressure (< 80mmHg) and a marked activation of the RAAS and SNS have a higher probability of developing HRS. Interestingly the degree of liver failure, as assessed by classic parameters of liver function (bilirubin, albumin, and prothrombin time) or the Child-Pugh classification, however, do not correlate with the development of HRS.

There is no specific test or marker for the diagnosis of HRS, which diagnosis is based on the demonstration of a reduced GRF in the absence of data suggesting other causes of renal failure. Recently, the International Ascites Club has proposed the new and revised criteria for the diagnosis of HRS (Table 3). Low GFR is defined as serum creatinine greater than 1.5 mg/dL or 24-h- creatinine clearance lower than 40 mL/min. Other criteria include the absence of clinical conditions that predispose

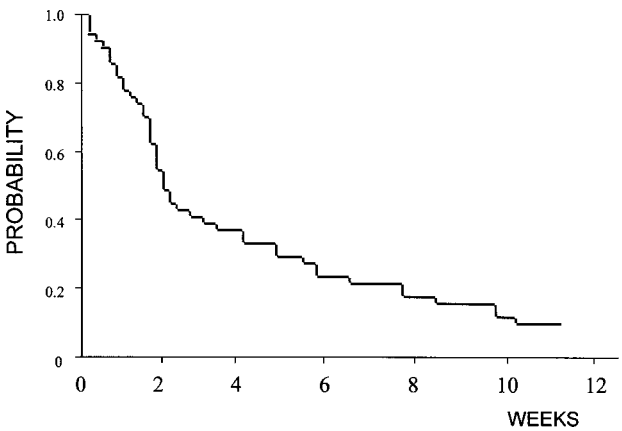

Figure 4. Probability of survival in cirrhotic patients after the development of type I hepatorenal syndrome.

Table 2. Parameters associated with a higher risk of hepatorenal syndrome development in nonazotemic cirrhotic patients with ascites(*)

Previous episodes of ascites
Absence of hepatomegaly
Poor nutritional status
Moderately-reduced glomerular filtration rate (**)
Moderately-increased BUN (**)
Moderately-increased serum creatinine (**)
Low serum sodium
High serum potassium
Low urinary sodium excretion
Low baseline plasma osmolality
High baseline urine osmolality
High plasma renin activity
Low arterial pressure
Reduced free water excretion after water load
Increased plasma norepinephrine
Presence of esophageal varices

(*) All measurements were obtained after a minimum of 5 days on a low-sodium diet and without diuretics.

(**) All patients had a glomerular filtration rate higher than 50 mL/min and BUN and serum creatinine lower than 30 mg/dL and 1.5 mg/dL, respectively.

Table 3. Diagnostic Criteria of Hepatorenal Syndrome according to the International Ascites Club (*).

Major criteria

1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-h creatinine clearance lower than 40 ml/min.
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs.
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander.
4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Additional criteria

1. Urine volume lower than 500 ml/day.
2. Urine sodium lower than 10 mEq/L.
3. Urine osmolality greater than plasma osmolality.
4. Urine red blood cells less than 50 per high power field.
5. Serum sodium concentration lower than 130 mEq/L.

(*) Only major criteria are necessary for the diagnosis of Hepatorenal Syndrome.

to the development of prerenal failure or acute tubular necrosis, no improvement of renal function following to diuretic withdrawal or plasma expansion, no proteinuria and a normal renal ultrasound. Most cases of HRS have urine sodium below 10 mEq/L and urine osmolality above plasma osmolality because of a normal tubular function. Nevertheless, some patients may have higher urine sodium and low urine osmolality, similar to values found in acute tubular necrosis. Conversely, some cirrhotic patients with acute tubular necrosis may have low urine sodium and high osmolality. For these reasons, urinary indices are not considered major criteria for diagnosis of HRS.

MANAGEMENT

Prevention

There are three ways of preventing HRS. The first is to perform liver transplantation in those patients that have a high risk of developing HRS based on the parameters listed on table 2. The second approach is based on recent data showing that renal impairment can be prevented in two groups of patients. In patients with spontaneous bacterial peritonitis the administration of albumin (1.5 g/kg iv at the diagnosis of the infection and 1 g/kg iv 48h later) prevents the circulatory dysfunction and subsequent activation of vasoconstrictor systems that occur during the infection.[35] The incidence of HRS in patients receiving albumin is 30% of that in patients not receiving albumin. Most importantly, the administration of albumin improves survival in these patients. Finally, in patients with acute alcoholic hepatitis the administration of pentoxifylline (an inhibitor of tumor necrosis factor) also prevents the development of HRS and improves mortality.[36]

Pharmacological Treatment

Numerous vasodilators have been used in order to reverse the intense renal vasoconstriction present in HRS.[37] Dopamine was one of the first medications used given its vasodilatory effects on the kidney when given at low doses.[38] However several studies have shown no effect of this drug on GFR in patients with HRS. The administration of prostaglandins based on the fact that there is a reduced synthesis in the kidney in patients with HRS, was also unsuccessful.[39] Other drugs such as angiotensin II antagonists and receptor antagonists, phentolamine and inhibitors of thromboxane synthesis have been used without any significant effect.[40-43]

In recent years the administration of vasoconstrictors seems to be the most promising approach in treating HRS. The rationale is based on the fact that the initial event in the pathogenesis of HRS is an arterial vasodilation causing activation of endogenous vasoconstrictors. In recent years, promising results have been achieved using the agonists of the vasopressin V1 receptors. These drugs have a predominant action in the splanchnic vessels, with little effect on the renal circulation. Lenz et al., demonstrated that short term IV infusion of ornipressin in patients with HRS led to a rise in total peripheral vascular resistance, a fall in cardiac output, marked suppression of the RAAS and SNS and a modest but significant increase in creatinine clearance.[44] Based on this study and prior data suggesting that albumin infusion and vasoconstrictors were effective in normalizing renal sodium and water metabolism in cirrhotic patients with ascites, Guevara et al, studied the hemodynamic, neurohormonal, and renal effects of the combination of ornipressin with albumin in a series of 16 patients with HRS.[45] In 8 patients a short course of ornipressin and albumin was able to normalize an overactivity of the RAAS and SNS. However, only a slight improvement in renal function was observed. The prolonged treatment in the other 8 patients resulted in a remarkable improvement in renal function, with normalization of serum creatinine, a marked increase in renal plasma flow and GFR and suppression in the activity of vasoconstrictor systems. Interestingly, in those patients in which creatinine normalized, HRS did not recur after discontinuation of therapy. Unfortunately, some of the patients had serious ischemic complications.

In view of the high incidence of severe adverse effects with ornipressin, the same authors investigated the effects of terlipressin, another vasopressin analogue with fewer side effects. In this study, 9 patients with HRS were treated with terlipressin and IV albumin.[46] Treatment (5-15 days) was associated with an important reduction of serum creatinine, a successful improvement in circulatory function as assessed by plasma renin activity, a marked decrease in norepinephrine levels and a significant rise in mean arterial pressure. Reversal of HRS was observed in 7 of the 9 patients without side-effects. Three out of the 5 patients who were candidates for liver transplantation were transplanted at 5, 12 and 99 days after the initiation of therapy and were still alive at the end of the study. The other 2 patients died while waiting for liver transplantation 30 and 121 days after starting therapy. No patient developed signs of intestinal, myocardial or distal ischemia. HRS did not recur after stopping the infusion in the patients that responded. According to this study the use of terlipressin associated with IV albumin infusion seems to be a safe and effective treatment of HRS. Another recent investigation from a group in France also tested the use of terlipressin in patients with HRS without IV albumin and reported improvement in renal function, unfortunately pre and post values of vasoactive hormones, GFR and water clearance were not measured.

Another study from Angeli et al. showed that the long-term administration of midodrine (an alpha-adrenergic agonist) plus octreotide (an inhibitor of the release of glucagon) and IV albumin was effective in improving renal failure in 8 patients with type I HRS.[47] This therapeutic approach was compared with the traditional administration of dopamine at low doses. None of the patients treated with dopamine showed any improvement in renal function and all but one died within two weeks. On the contrary, 8 patients treated with midodrine and octreotide plus albumin showed a significant reduction in the activity of endogenous vasoactive systems followed by a significant improvement in renal function. Most importantly, in 4 patients survival after treatment was long enough to reach liver transplantation. No remarkable side effects were noted with this treatment.

In a study by Gulberg et al. the response to the continuous infusion of IV ornipressin and dopamine was assessed in 7 cirrhotic patients with type I HRS.[48] The patients who responded had significant increase in creatinine clearance, urinary sodium excretion, mean arterial blood pressure and serum sodium. HRS was reverted in 4 out of the 7 patients. One patient had an ischemic complication. In 2 of the 4 responders recurrent HRS was observed 2 and 8 months after initial therapy, respectively. One of these patients was retreated and HRS reverted, the other patient had to be withdrawn due to a ventricular tachyarrythmia. Taken together, 3 of the 7 patients survived type I HRS, two with liver transplantation and one with treatment and retreatment. These authors concluded that this therapeutic option might be useful as a treatment option in patients with HRS type I, especially as a bridge to liver transplantation.

Several conclusions can be reached from these studies that could be important for future research. The first is that giving of vasoconstrictors with albumin is a good and effective treatment for HRS. However, more studies are needed to determine which is the best vasoconstrictor, which is the optimal dose and whether the association of albumin infusion with vasoconstrictor agents is necessary or not. Also it would be important to compare pharmacological therapy with other effective treat-

ments of HRS such as the transjugular intrahepatic portocaval shunt (TIPS). The second conclusion is that renal function remains stable after treatment in those who respond. This is important because it means that renal failure in some of the patients with type 1 HRS could be triggered by a transitory precipitating factor (spontaneous bacterial peritonitis or alcoholic hepatitis) that can be treated. Finally, the third conclusion is that there is a lag between the improvement in blood pressure, cardiac output and systemic vascular resistance and the suppression of the systemic vasoconstrictor systems (RAAS and SNS) after the reversal of HRS, suggesting that other factors, such as intrarenal vasoactive mechanisms, which can be activated (vasodilators) or deactivated (vasoconstrictors) more slowly, are very important in the maintenance of renal hypoperfusion in HRS.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

This non-surgical method of portal decompression has evolved as an alternative therapy for cirrhotic patients bleeding from esophageal or gastric varices that are refractory to endoscopic and medical treatment.[49] Although the use of TIPS has been evaluated for the treatment of refractory ascites, not a lot of information exists regarding its use in the management of HRS.[50] The rationale for using TIPS is based on the fact that reducing portal pressure may ameliorate RAAS and SNS activity. Uncontrolled studies indicate that TIPS may improve renal function and GFR as well as reduce the activity of RAAS and SNS in cirrhotics with type I HRS.[51-53] The effects and the course after TIPS insertion varies among patients, in the majority an improvement in renal function is observed after several weeks, in others no effect is observed even after 1 month, and finally in others renal impairment may worsen transiently right after TIPS placement.

Recently the outcome after TIPS insertion in 41 non-transplant cirrhotics with HRS was evaluated in a phase II study by Brensing et al.[54] In this prospective study 31 patients with HRS (14 type I, 17 type II) received TIPS and were followed for 2 years. Renal function and sodium excretion improved and remained stable in the shunted group. One-year survival rates were higher in the shunted group (48%) when compared to the non-shunted group (39%). The authors concluded that TIPS provided long-term renal function and survival benefit in non-transplant cirrhotics. Nevertheless the results of this study need to be confirmed in a controlled trail comparing TIPS with other therapies for HRS.

Dialysis

Hemodialysis as a therapeutic maneuver has been ineffective in the management of HRS. In a recent study by Mitzer et al, the use of an extracorporeal albumin dialysis molecular absorbent re-circulating system (MARS) was assessed in 13 patients with Child C cirrhosis and type I HRS.[55] This system is a modified dialysis method that enables the selective removal of albumin bound substances that accumulate in liver failure by the use an albumin containing dialysate. This system has been used successfully in the treatment of fulminant hepatic failure. In this study 5 patients treated with hemodialysis and standard medical therapy (low-dose dopamine and albumin) and 8 patients were treated with the same plus MARS. The authors reported a significant decrease in bilirubin and creatinine, an improvement in serum sodium, urine volume, mean arterial blood pressure and decreased mortality in the MARS group. The procedure was well tolerated in all patients. Unfortunately, no parameters evaluating other systemic hemodynamics and renal function such as cardiac output, peripheral vascular resistance, renal blood flow, GFR and hormonal measurements were determined. The improvement in serum values of bilirubin, creatinine and sodium could represent only the effect of the dialysis process and not a significant change in hepatic and renal function. These findings are encouraging, however, as with TIPS, larger studies are needed in order to consider MARS as a therapeutic tool for HRS.

Liver transplantation

Liver transplantation is the best treatment for patients with HRS, as it offers a cure to both the diseased liver and the circulatory and renal dysfunction. The long-term outcome of cirrhotic patients with HRS treated by liver transplantation is usually good, although the presence of HRS is associated with increased morbidity and early mortality.[56] Immediately after transplantation, a further impairment in renal function may be observed, and more than one third of patients require hemodialysis. Nonetheless, a small proportion (5%) of patients may progress to end stage renal disease and require long-term hemodialysis. Because cyclosporine treatment may contribute to this degree of renal impairment postoperatively, it has been suggested that this drug should not be administered until recovery of renal function is observed, which usually occurs within 48 to 72 hours after transplantation. After this initial impairment, GFR starts to improve and reaches an average of 40 to 50ml/min by the sixth week after the surgery. This moderate renal failure persists during follow up and is more marked than that observed

in patients transplanted without HRS. Besides the impairment in renal function, transplanted patients develop more complications, spend more days in the intensive care unit and in the hospital, and have a higher in-hospital mortality rate than patients without HRS. Despite this increased morbidity, long-term survival of transplanted patients with HRS is excellent; the probability of survival after 3 years of surgery is approximately 60%.[56]

The main problem with regard to liver transplantation and the management of patients with HRS is the poor prognosis that patients with HRS type I have. Most of these patients die before transplantation is reached because of the long waiting lists in most transplant centers. Therefore, there is a need for more effective treatments that increase survival in these patients until transplantation is reached. Unfortunately, these new types of treatment are for the most part used in large university centers as part of clinical trails and are not approved therapies for HRS. For this reason, an alternative to this problem has been proposed by identifying the need for transplantation in patients with cirrhosis and ascites before the development of HRS.[32] As discussed above some patients with cirrhosis and ascites are at high risk of developing HRS, and patients who have some or all of these predictive factors should be considered for liver transplantation before the development of HRS (Table 2).

REFERENCES

1. Ginès P, Rodés J: Clinical disorders of renal function in cirrhosis with ascites. In: Arroyo V, Ginès P, Rodés J, Schrier RW, (eds). Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell Science, 1999; p 36-62.
2. Jiménez W, Martínez-Pardo A, Arroyo V, et al: Temporal relationship between hyperaldosteronism, sodium retention and ascites formation in rats with experimental cirrhosis. Hepatology 1985; 5:245-250.
3. Caregaro L, Lauro S, Angeli P, et al: Renal water and sodium handling in compensated liver cirrhosis: mechanism of the impaired natriuresis after saline loading. Eur J Clin Invest 1985; 15:360-365.
4. Chaimovitz C, Szylman P, Alroy G, Better OS: Mechanism of increased renal tubular sodium reabsorption in cirrhosis. Am J Med 1972; 52:198-202.
5. Angeli P, Gatta A, Caregaro L, et al: Tubular site of renal sodium retention in ascitic liver cirrhosis evaluated by lithium clearance. Eur J Clin Invest 1990; 20:111-117.
6. Bernardi M, Trevisani F, Caraceni P: The renin-angiotensin-aldosterone system in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, (eds). Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell Science, 1999; p 175-197.
7. Dudley FJ, Esler MD: The sympathetic nervous system in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, (eds). Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell Science, 1999; p 198-219.
8. Henriksen JH, Ring-Larsen H, Christensen NJ: Sympathetic nervous activity in cirrhosis: a survey of plasma catecholamine studies. J Hepatol 1984; 1:55-56.
9. DiBona GF. Neural control of the kidney: functionally specific renal sympathetic nerve fibers. Am Physiol Regul Integr Comp Physiol 2000; 279:R1517-R1524.
10. Bernardi M, Trevisani F, Santini C, et al: Aldosterone related blood volume expansion in cirrhosis before and after the early phase of ascites formation. Gut 1983; 24:761-766.
11. Kostreva DR, Castaner A, Kampine JP: Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nervous activity. Am J Physiol 1980; 238:R390-R394.
12. Arroyo V, Clària J, Saló J, et al: Antidiuretic hormone and the pathogenesis of water retention in cirrhosis with ascites. Semin Liv Dis 1994; 14:44-58.
13. Papper S, Rosenbaum JD: Abnormalities in the excretion of water and sodium in «compensated» cirrhosis of the liver. J Lab Clin Med 1952; 40:523-539.
14. Arroyo V, Rodés J, Gutiérrez-Lizarraga MA, Revert L: Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976; 21:249-256.
15. Fernandez-Esparrach G, Sanchez A, Ginés P, et al. A prognostic model for predicting survival in cirrhosis. J Hepatol 2001, 34:46-52
16. Cárdenas A, Ginès P: Treatment of water retention and dilutional hyponatremia in cirrhosis. In: Arroyo V, Bosch J, Brugera M, Rodıs J, Sαnchez-Tapias JM, (eds). Treatment of Liver Diseases. Barcelona: Masson 1999; p 61-71.
17. Ishikawa S, Schrier RW: Arginine vasopressin in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, (eds). Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell Science, 1999; p 220-230.
18. Gines P. Hepatorenal syndrome. Baillieres Best Pract Res Clin Gastroenterol 2000; 14:945-957.
19. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988; 8:1151-1157.
20. Gines P, Schrier RW: The arterial vasodilation hypothesis of ascites formation in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, (eds). Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell Science, 1999; p 411-430.
21. Benoit JM, Zimmerman B, Premen AJ, et al: Role of glucagon in splanchnic hyperemia of chronic portal hypertension. Am J Physiol 1986; 251:G674-G677.
22. Vallance P, Moncada S: Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991; 337:776-777.
23. Martin PY, Gines P, Schrier RW: Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. N Engl J Med 1998; 339:533-541.
24. Arnal JF, Dinh-Xuan AT, Pueyo M, Darblade B, Rami J: Endothelium-derived nitric oxide and vascular physiology and pathology. Cell Mol Life Sci 1999; 55:1078-1083.

25. Garcia-Tsao G. Bacterial translocation: cause or consequence of decompensation in cirrhosis? J Hepatol 2001; 34:150-155.
26. Chowdhary S, Townshend N: Role of nitric oxide in the regulation of cardiovascular autonomic control. Clin Scin 1999; 97:5-11.
27. Martin PY, Ohara M, Gines P, et al: Nitric oxide synthase (NOS) inhibition for one week improves renal sodium and water excretion in cirrhotic rats with ascites J Clin Invest 1998; 101:235-242.
28. Guarner C, Soriano G, Tomas A, et al: Increased serum nitrite and nitrate levels in patients with cirrhosis: relationship with endotoxemia. Hepatology 1993; 18:1139-1145.
29. Forrest EH, Jones AL, Dillon JF, et al: The effect of nitric oxide synthase inhibition on portal pressure and azygos blood flow in patients with cirrhosis. J Hepatol 1995; 23: 254-260,
30. Arroyo V, Ginès P, Gerbes A, et al: Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996; 23:164-176.
31. Cárdenas A, Uriz J, Arroyo V. Hepatorenal syndrome. Liver Transplantation 2000, 4 suppl 1 S63-71.
32. Ginès A, Escorsell A, Ginès P, et al: Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. Gastroenterology 1993; 105:229-236.
33. Follo A, Llovet JM, Navasa M, et al: Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994; 20:1495-1501.
34. Ginès P, Arroyo V. Hepatorenal syndrome. J Am Soc Nephrol 1999; 10:1833-1839.
35. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 5:403-409.
36. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119:1637-1648.
37. Arroyo V, Bataller R, Guevara M: Treatment of hepatorenal syndrome in cirrhosis. In Arroyo V, Ginès P, Rodés J, Schrier RW (eds). Ascites and renal dysfunction in liver disease. Pathogenesis, diagnosis, and treatment. Malden, Blackwell Science, 1999; 492-510.
38. Bennet WM, Keefe E, Melnyk C, et al. Response to dopamine hydrochloride in the hepatorenal syndrome. Arch Intern Med 1975; 135:964-969.
39. Zussman RM, Axelrod L, Tolkoff-Rubin N. The treatment of the hepatorenal syndrome with intrarenal administration of prostaglandin E1. Prostaglandins 1977; 13:819-824.
40. Arroyo V, Bosch J, Mauri M, et al. Effect of angiotensin-II blockade on systemic and hepatic haemodynamics and on the renin-angiotensin-aldosterone system in cirrhosis with ascites. Eur J Clin Invest 198; 111:221-229.
41. Schroeder ET, Anderson GH, Goldman SH, et al. Effect of blockade of angiotensin II on blood pressure, renin and aldosterone in cirrhosis. Kidney Int 1976; 9:511-519.
42. Henriksen JH, Ring-Larsen H. Hepatorenal disorders: role of the sympathetic nervous system. Sem Liver Dis 1994; 14:35-43.
43. Ariyan S, Sweeney T, Kerstein MD. The hepatorenal syndrome: recovery after portacaval shunt. Ann Surg 1975; 181:847-849.
44. Lenz K, Hörnatgl H, Druml W, et al. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. Gastroenterology 1991; 101:1060-1067.
45. Guevara M, Ginès P, Fernández-Esparrach G, et al: Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. Hepatology 1998; 27:35-41.
46. Uriz J, Ginés P, Cárdenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000; 33:43-48.
47. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999; 29:1690-1697.
48. Gólberg V, Bilzer M, Gerbes AL. Ornipressin for treatment of hepatorenal syndrome (HRS) type I: Results of long-term therapy or retreatment. Hepatology 1999; 30:870-875.
49. Shiffman ML, Jeffers L, Hoofnagle JH, et al. The role of transjugular intrahepatic portosystemic shunt for the treatment of portal hypertension and its complications: a conference sponsored by the National Digestive Disease advisory board. Hepatology 1995; 25:1591-1597.
50. Arroyo V, Cárdenas A: TIPS in the treatment of refractory ascites. In: Rodes J, Arroyo V, Bosch J, Brugera M, eds. Therapy in Liver Disease. Barcelona: Masson 1999; p 43-51.
51. Somberg KA: Transjugular intrahepatic portosystemic shunt in the treatment of refractory ascites and hepatorenal syndrome. In Epstein M (ed): The Kidney in Liver Disease, 4th ed. Hanley & Belfus Inc., Philadelphia, 1996, p 507-516.
52. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome. Effects on renal function and vasoactive systems. Hepatology 1998; 27:416-422.
53. Sturgis TM: Hepatorenal syndrome: resolution after transjugular intrahepatic portosystemic shunt. J Clin Gastroenterol 1995; 20:241-243.
54. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000; 47:288-295.
55. Mitzer SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 2000; 6:277-286.
56. Rimola A, Navasa M, Grande L: Liver transplantation in cirrhotic patients with ascites. In Arroyo V, Ginès P, Rodés J, Schrier RW: Ascites and renal dysfunction in liver disease. Pathogenesis, diagnosis, and treatment. Malden, Blackwell Science, 1999; p 522-537.