Update on peripheral arterial vasodilation, ascites and hepatorenal syndrome in cirrhosis

Mladen Knotek MD, Boris Rogachev MD, Robert W Schrier MD

M Knotek, B Rogachev, RW Schrier. Update on peripheral arterial vasodilation, ascites and hepatorenal syndrome in cirrhosis. Can J Gastroenterol 2000;14(Suppl D):112-121. In cirrhosis of the liver, according to the peripheral arterial vasodilation hypothesis, relative underfilling of the arterial tree triggers a neurohumoral response (activation of renin-angiotensin-aldosterone system, sympathetic nervous system, nonosmotic release of vasopressin) aimed at restoring circulatory integrity by promoting renal sodium and water retention. Evidence has accumulated for a major role of increased vascular production of nitric oxide as the primary cause of arterial vasodilation in cirrhosis. Ascites is a common complication in cirrhosis. Treatment of ascites consists of a low salt diet with diuretics, and paracentesis together with plasma volume expanders in diuretic-resistant patients. Progression of cirrhosis may result in hepatorenal syndrome, a state of functional renal failure that carries an ominous prognosis. Orthotopic liver transplantation has remained the only curative treatment for patients with advanced liver disease; other modalities such as transjugular intrahepatic portosystemic shunt or vasopressin analogues may serve as a bridge to transplantation. Another complication of decompensated cirrhosis is spontaneous bacterial peritonitis, the incidence of which can be reduced by primary or secondary antibiotic prophylaxis by using orally active antibiotics.

Key Words: *Aldosterone; Ascites; Cirrhosis; Hepatorenal syndrome; Nitric oxide; Sodium and water retention; Spontaneous bacterial peritonitis; Vasopressin*

Le point sur la cirrhose ET la vasodilatation artérielle périphérique, l'ascite et le syndrome hépato-rénal

Selon l'hypothèse de la vasodilatation artérielle périphérique, l'insuffisance relative de remplissage du réseau artériel dans la cirrhose du foie déclenche un mécanisme neurohormonal (activation du système rénine-angiotensine-aldostérone, du système nerveux sympathique et libération non osmotique de vasopressine) visant à restaurer l'intégrité du système circulatoire en favorisant la rétention rénale d'eau et de sodium. De plus en plus de données semblent indiquer que la production accrue d'oxyde nitrique dans les vaisseaux serait la principale cause de la vasodilatation artérielle dans la cirrhose. Par ailleurs, l'une des complications fréquentes de la cirrhose est l'ascite, dont le traitement consiste en une diète hyposodée, la prise de diurétiques et, dans les cas résistants aux diurétiques, en des paracentèses complétées par des solutions de remplissage vasculaire. La cirrhose peut aussi évoluer vers le syndrome hépato-rénal, état d'insuffisance rénale fonctionnelle, qui comporte un pronostic sombre. La transplantation orthotopique du foie reste le seul traitement curatif dans les cas d'hépatopathie avancée; entre-temps, on peut avoir recours à la dérivation transjugulaire-intrahépatique-porto-périphérique ou aux analogues de la vasopressine comme traitements de transition. Une autre complication de la cirrhose décompensée est la péritonite bactérienne spontanée, dont l'incidence peut être réduite par un traitement prophylactique primaire ou secondaire aux antibiotiques actifs, administrés par voie orale.

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Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado, USA
Correspondence and reprints: Dr Robert W Schrier, University of Colorado Health Sciences Center, Box B178, Denver, Colorado 80262, USA. Telephone 303-315-6677, fax 303-315-7702, e-mail robert.schrier@uchsc.edu
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In the United States, cirrhosis of the liver is the 11th most common cause of death (1). During progression of the disease, marked abnormalities in renal sodium and water handling result in the formation of ascites in 50% of patients over 10 years' duration (2). Progression of cirrhosis may eventually cause development of hepatorenal syndrome (HRS), a profound derangement of renal function consequent upon neurohumoral stimulation of the kidney. HRS is a catastrophic event with almost 100% mortality. Existence of ascites is linked to another major complication of cirrhosis – spontaneous bacterial peritonitis. Evidence has accumulated in support of peripheral arterial vasodilation as the underlying mechanism of renal sodium and water retention in cirrhosis (3). Results of several studies also point to the central role of nitric oxide as a mediator of vasodilation in cirrhosis. Peripheral arterial vasodilation, with arterial underfilling, stimulates compensatory mechanisms such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and arginine-vasopressin (AVP) release, which lead to sodium and water retention. Because orthotopic liver transplantation remains the only curative option for patients with terminal liver disease, recent therapeutic advances (vasopressin analogues, transjugular intrahepatic portosystemic shunt [TIPS]) provide the possibility for survival of more patients until transplantation can be performed.

PATHOPHYSIOLOGY OF RENAL SODIUM AND WATER RETENTION

Renal sodium and water retention in cirrhosis develop secondary to extrarenal mechanisms, because when kidneys from patients with cirrhosis are transplanted into persons with normal livers, renal sodium and water retention no longer occur (4). Thus, the crucial question is why do normal kidneys of patients with cirrhosis continue to retain sodium and water in spite of the expansion of total plasma and extracellular fluid volume and formation of ascites? The peripheral arterial vasodilation hypothesis (5) (Figure 1) proposes that primary peripheral arterial vasodilation in cirrhosis, mainly in the splanchnic circulation, leads to the relative underfilling of the arterial circulation and to a hyperdynamic circulation (3). Low arterial blood pressure, high cardiac output and low systemic vascular resistance are frequently observed in patients with cirrhosis, despite an increase in plasma volume and a stimulation of the RAAS, sympathetic nervous system and AVP. According to this hypothesis, acti-

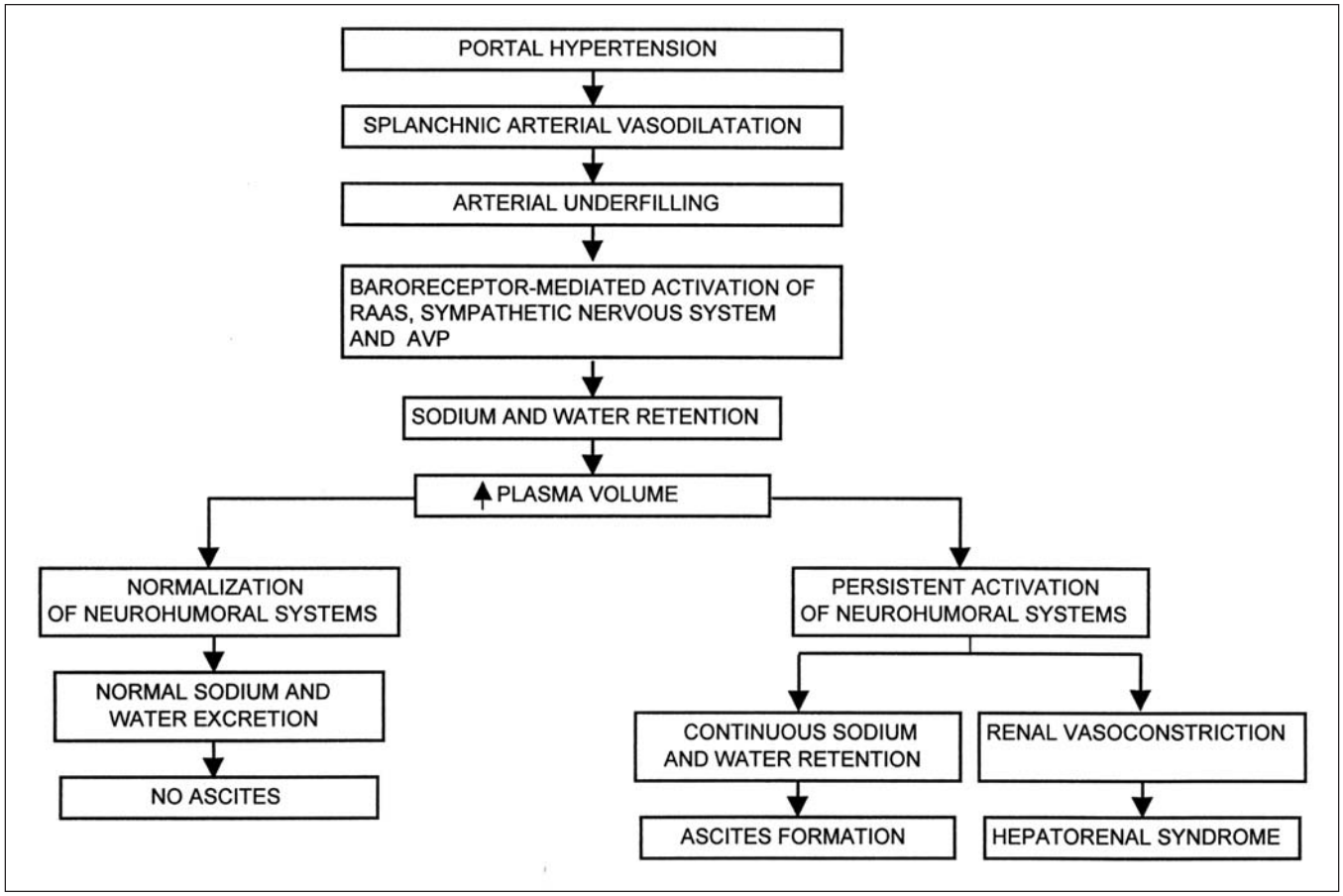

Figure 1) *Pathogenesis of functional renal abnormalities and ascites formation in cirrhosis according to the peripheral arterial vasodilation hypothesis. AVP Arginine-vasopressin; RAAS Renin-angiotensin-aldosterone system. Adapted with permission from reference 5*

vation of vasoconstrictor, and sodium- and water-retaining mechanisms in cirrhosis are secondary to arterial underfilling. The consequence is failure to escape from the sodium-retaining effect of aldosterone, an impaired capacity to excrete solute-free water, renal resistance to atrial natriuretic peptide (ANP) and ultimately ascites. Evidence has accumulated to support the major role of peripheral arterial vasodilation in the pathogenesis of ascites (5). In spite of an increase in total plasma volume, central blood volume is significantly decreased in patients with cirrhosis compared with controls (6-8). The lowest values were found in patients with gross ascites and reduced systemic vascular resistance (6). Moreover, during plasma volume expansion, central and arterial blood volumes increased significantly in patients with pre-ascitic cirrhosis and controls, while only the non-central blood volume increased in patients with advanced cirrhosis (9). Central blood volume in patients with cirrhosis inversely correlates with portal venous pressure (7), demonstrating worsening of arterial underfilling with progression of cirrhosis. In rats with partial portal vein ligation, the fall in systemic vascular resistance preceded an increase in total body sodium (10), and in spontaneously hypertensive rats with cirrhosis, a decrease in systolic blood pressure was paralleled by a decrease in urinary sodium excretion (11). Finally, centralization of blood volume by head-out water immersion together with noradrenaline administration to maintain systemic vascular resistance acutely corrects the abnormal renal sodium and water retention in cirrhotic patients with ascites (12).

MECHANISMS OF VASODILATION

During the past several years, nitric oxide has emerged as a major mediator of systemic vasodilation in cirrhosis. Nitric oxide is produced by a family of three isoenzymes: neuronal (type I), inducible (type II) and endothelial (type III) nitric oxide synthase (NOS) (13). Nitric oxide is an important regulator of basal vascular tone. There is compelling evidence that enhanced vascular synthesis of nitric oxide plays a major role in changes in the systemic hemodynamics in cirrhosis, thereby contributing to the peripheral vasodilation and hyperdynamic circulation in both laboratory animals and patients. The increase in arterial blood pressure during infusion of a nonselective NOS inhibitor was greater in cirrhotic rats with ascites than in control rats (14). In vitro responsiveness of aortic rings to endothelium-dependent vasodilators was enhanced in rats with cirrhosis compared with controls, suggesting enhanced activity of NOS in cirrhosis (15). In addition, hyporeactivity of the superior mesenteric artery isolated from rats with cirrhosis was reversed by incubation with a nonselective NOS inhibitor, *N*-omega-nitro-L-arginine (16). Endothelium denudation, or incubation with *N*-omega-nitro-L-arginine, of aortic rings from rats with cirrhosis with ascites reversed the hyporesponsiveness to angiotensin II (17). Long term treatment of cirrhotic rats with 0.5 mg/kg/day *N*-nitro-L-arginine methylester (L-NAME), another nonselective NOS inhibitor, decreased aortic cGMP concentrations to the levels measured in control rats, suggesting a normalization of nitric oxide production. This was associated with a normalization of mean arterial blood pressure (MAP), cardiac index and systemic vascular resistance (SVR), and a reduction in the elevated plasma renin activity and AVP concentration (18).

The effects of NOS inhibition extend beyond hemodynamic effects because acute administration of L-NAME to rats with cirrhosis, in a dose that did not affect blood pressure, and increased urinary flow and sodium excretion (14,17,19) with improvement (14,19) or without changes in the glomerular filtration rate (GFR) (20). Finally, in a seven-day study of rats with carbon tetrachloride-induced cirrhosis, treatment with low-dose L-NAME decreased aortic cGMP to the normal level. The expression of endothelial NOS (eNOS) in the aorta and mesenteric artery also decreased with L-NAME treatment. L-NAME increased urine volume and sodium excretion, as well as the fractional excretion of an acute water load. In addition, plasma renin activity, aldosterone and AVP significantly decreased in rats with cirrhosis treated with L-NAME. Hyponatremia was corrected and ascites was either dramatically reduced or abolished (21).

Studies of patients with cirrhosis have demonstrated elevated levels of serum nitric oxide metabolites (22,23). The forearm vasoconstriction in response to local, nonselective NOS inhibition was greater in patients with decompensated cirrhosis than in patients with compensated cirrhosis, suggesting participation of nitric oxide in the hyperdynamic state of patients with advanced cirrhosis (24). Altogether, these results suggest the role of nitric oxide in systemic hemodynamic changes and a potential beneficial effect of NOS blockade in experimental cirrhosis and humans. An important goal for future studies is to establish whether the chronic blockade of nitric oxide overproduction can alter the natural course of cirrhosis and affect survival of patients.

The issue of which isoform of NOS contributes to the hemodynamic alterations in cirrhosis has not been completely resolved. Increased eNOS expression has been demonstrated in the aorta and/or mesenteric arteries of rats with cirrhosis (21,25). Although the role of eNOS is most likely, the contribution of inducible NOS (iNOS) is also possible. In this regard, it was shown that administration of aminoguanidine, a relatively selective iNOS inhibitor, elevated MAP in rats with cirrhosis, and increased sodium and water excretion in a dose-dependent manner. The plasma concentration of nitric oxide metabolites decreased with aminoguanidine to near-control levels. However, hypotension was not completely corrected, suggesting participation of both constitutive NOS and iNOS (26). iNOS mRNA, but not protein, expression was demonstrated in arterial vessels of cirrhotic rats – being the highest in mesenteric arteries (25). However, in another study using the biliary duct ligation model of cirrhosis, increased transcription of iNOS was not demonstrated (27). It is unclear whether this discrepancy among results was due to the use of different models of cirrhosis. iNOS may play an important role in host defense against bacterial infection. Recently, the induction of iNOS in macrophages isolated

from rats with cirrhosis was demonstrated (28). Treatment of these rats with a selective iNOS inhibitor resulted in positive bacterial cultures from ascitic fluid (28). Possible involvement of iNOS in the elevated nitric oxide production in human cirrhosis was recently suggested by the results of a study in which administration of norfloxacin to patients with cirrhosis restored the forearm blood flow to normal values (22). In another study of patients with cirrhosis a correlation between serum nitrite/nitrate levels and endotoxemia was observed (29). Oral administration of colistin to these patients significantly reduced plasma endotoxin and serum nitrite/nitrate levels (29). These results incriminate endotoxemia as a possible mechanism for iNOS induction. Therefore, it is plausible that in certain situations such as spontaneous bacterial peritonitis, bacteremia or variceal bleeding, iNOS may contribute to the hemodynamics of patients with cirrhosis. However, the long term blockade of iNOS can have detrimental consequences, because of the antibacterial role of iNOS.

Besides nitric oxide, the involvement of other vasodilatory substances in hemodynamic changes in cirrhosis is possible. The plasma concentration of adrenomedullin, a recently described vasodilatory peptide, was significantly higher in the group of patients with cirrhosis and correlated directly with the Child-Pugh score of liver dysfunction, indirectly with creatinine clearance and inversely with systemic vascular resistance (30). Plasma calcitonin gene-related peptide was also increased in patients with liver cirrhosis compared with healthy controls, and levels were higher in patients with decompensated cirrhosis than in patients with compensated cirrhosis (31). An increased plasma level of substance P was also demonstrated in cirrhotic patients with ascites compared with healthy controls (32). Further experiments are necessary to evaluate the functional role of these agents in cirrhosis.

MECHANISMS OF SODIUM AND WATER RETENTION

The hallmark of advanced cirrhosis is a positive sodium balance, and there is considerable evidence implicating a major role of aldosterone. Plasma aldosterone concentration is elevated in most cirrhotic patients with ascites (33,34), and there is an inverse relationship between plasma aldosterone and urinary sodium excretion in cirrhosis. Finally, spironolactone, a mineralocorticoid receptor antagonist, has been shown to exert a natriuretic effect and reverse sodium retention in the majority of patients with cirrhosis (35). Urinary sodium retention and plasma volume expansion are present already in patients with pre-ascitic cirrhosis compared with controls (36). With the degree of sodium retention in compensated cirrhosis, plasma aldosterone is slightly elevated or normal; however, these concentrations are inappropriate for the increase in total blood volume. Moreover, in pre-ascitic cirrhosis, spironolactone combined with a low sodium diet significantly reduced the plasma volume together with a reduction in the hepatic venous pressure gradient (37). In one study, patients with compensated cirrhosis who failed to escape from exogenous mineralocorticoid hormone, and thus developed ascites, had a significantly higher cardiac index and lower peripheral vascular resistance (indicating more pronounced arterial underfilling) than compensated patients with cirrhosis who escaped from the sodium-retaining effect of mineralocorticoid and did not develop ascites (38). Failure to escape from mineralocorticoid hormone involves increased proximal reabsorption and, thus, impaired distal sodium delivery, but the exact mechanisms remain to be defined. Patients with cirrhosis have increased activity of the renin-angiotensin system, and besides stimulating aldosterone release, angiotensin II can directly stimulate proximal sodium reabsorption. The importance of this mechanism is demonstrated by the study in which a low dose of captopril promoted diuresis in diuretic-resistant patients receiving furosemide and spironolactone (39). In the majority of studies, plasma ANP levels were elevated in patients with cirrhosis (40-42), but did not correlate with plasma renin and urinary sodium excretion. Indeed, resistance to the diuretic effects of ANP may contribute to sodium and water retention in cirrhosis (43). Reversal of this resistance to ANP can be achieved by increasing distal tubule sodium delivery with mannitol in patients with cirrhosis (44) or by the renal denervation in experimental cirrhosis (45). Increased plasma levels of endothelin (ET)-1 and ET-3 in patients with pre-ascitic or ascitic cirrhosis have been demonstrated (46,47). Patients with HRS had the most elevated plasma concentrations of ET-1 and ET-3 compared with those of normal subjects (47). ET-1, the most potent renal vasoconstrictor, therefore, may contribute to the impaired renal hemodynamics in cirrhosis. ET-1 may also play a role in portal hypertension because the mixed $ET_{A,B}$ receptor antagonist, bosentan, decreased portal hypertension in rats with cirrhosis in vivo (48).

Studies in humans and experimental animals have provided strong evidence indicating that AVP plays a major role in the pathogenesis of water retention in cirrhosis with ascites. Bichet et al (49) studied patients with cirrhosis with ascites and subsequently divided them into two groups according to their response to a standard water load. Patients excreting less than 80% of the water load over 5 h were termed nonexcretors, and patients excreting 80% or more were termed excretors. The baseline plasma AVP concentration was higher in the nonexcretors, and they were unable to suppress the plasma AVP after an acute water load. A significant correlation was also found between the plasma AVP level after the water load and the percentage of the water load excreted (49). Similar findings were observed in patients with cirrhosis during head-out water immersion. Patients who excreted less than 40% of an acute water load during the water immersion had higher plasma AVP concentrations than patients who excreted more then 40% of the water load (50). In another study, plasma noradrenaline, renin activity, aldosterone and AVP were all significantly higher in nonexcretor than in excretor patients with cirrhosis. In addition, there was a positive correlation between the plasma noradrenaline and AVP concentrations after an

acute water load in patients with cirrhosis (51). An absence of circadian changes in venous plasma concentrations of AVP in patients with HRS has been found and may contribute to enhanced water retention (52). The role of AVP in water retention has also been demonstrated in experimental cirrhosis. Increased hypothalamic AVP mRNA content was demonstrated in rats with cirrhosis (53) and the expression of the AVP-regulated water channel aquaporin 2 was increased in rats with cirrhosis (54,55). Moreover, cirrhotic Bratelboro rats with congenital AVP deficiency do not develop an impairment in water excretion (56). In addition, blockade of the V2 AVP receptor results in improved water excretion in rats with cirrhosis (57,58) and humans (59).

Another mechanism by which an increase in intrahepatic sinusoidal pressure in cirrhosis may directly regulate renal function is via a hepatorenal reflex. In rats, infusion of glutamine into the superior mesenteric vein leads to marked decreases in renal GFR, renal plasma flow and urine flow. Spinal transection, renal denervation or section of the vagal hepatic nerves abolished the effect of mesenteric venous glutamine infusion (60,61). In patients with cirrhosis, renal blood flow (RBF) decreased with an increase in portal pressure following occlusion of portosystemic stent shunt, suggesting the existence of hepatorenal reflex in humans as well (62).

TREATMENT OF ASCITES ASSOCIATED WITH CIRRHOSIS

Abstinence of alcohol is mandatory because it enables repair of any reversible part of liver injury (63). For patients with mild ascites, dietary salt reduction and spironolactone are usually the first choices. In a randomized study comparing the efficacy of furosemide with that of spironolactone in cirrhotic patients with ascites, spironolactone was more efficient in evoking a diuretic response. The effect of spironolactone was correlated to the activity of the RAAS system (35). If spironolactone fails to control ascites, a loop diuretic can be added. Diuretics should be discontinued if the patient develops encephalopathy, an increase in serum creatinine of greater than 2 mg/dL or hyponatremia less than 120 mmol/L in spite of fluid restriction (64). Refractory ascites is defined as ascites that is nonresponsive to a low sodium diet and a high dose diuretic treatment (400 mg/day of spironolactone and 160 mg/day furosemide), in the absence of prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (65). In patients with refractory ascites, repeated large volume or total paracentesis followed by diuretic therapy to delay recurrence is an efficient treatment method for ascites (64,66). Paracentesis can be repeated if necessary every two weeks (64). Following large volume paracentesis, a reduction in cardiac index, and an increase in plasma renin and aldosterone, as well as a decrease in ANP, indicate effective hypovolemia (67), which can also be associated with a decrement in renal function and hyponatremia (68). In a prospective, randomized study, paracentesis without albumin was associated with a higher incidence of hyponatremia and renal failure than paracentesis with albumin infusion. Moreover, patients who developed hyponatremia and/or renal failure had decreased survival (68). Infusion of dextran 70, hemacell or hydroxyethyl starch instead of albumin was also shown to prevent hemodynamic or renal complications of total volume paracentesis efficiently (69-71), thereby reducing costs of the treatment. In cirrhotic patients with large or refractory ascites, liver transplantation should be considered.

HRS

According to the consensus conference organized by the International Ascites Club (65), HRS is a clinical condition that occurs in patients with chronic liver disease, and advanced hepatic failure and portal hypertension, as characterized by impaired renal function and marked abnormalities in the arterial circulation, and activity of the endogenous vasoactive systems. Two types of HRSs have been recognized. Type I HRS is characterized by the progressive increase in blood urea nitrogen and serum creatinine over a short period of time, days or a few weeks. Renal failure is often associated with progressive reduction in urine volume, marked sodium retention and hyponatremia. Type I HRS is common in alcoholic cirrhosis with associated alcoholic hepatitis, but it may occur in nonalcoholic cirrhosis as well. In approximately half of the cases, this type of HRS develops spontaneously without any identifiable precipitating factor, while in the remaining patients it occurs in close chronological relationship with some complications or therapeutic interventions such as bacterial infections, gastrointestinal hemorrhage, paracentesis without plasma expansion and major surgical procedures (72). The median survival time of these patients is less than two weeks. Type II HRS is characterized by a moderate and stable reduction of GFR and occurs in patients with less severe hepatic dysfunction. The main clinical consequence of this type of HRS is diuretic-resistant ascites (72). The survival of these patients is longer than that of patients with type I HRS.

In a follow-up study of 234 nonazotemic patients with cirrhosis and ascites (72), the probability of HRS occurrence was 18% at one year and 39% at five years. Three independent predictors of the development of hepatorenal syndrome were hyponatremia, high plasma renin activity and absence of hepatomegaly. Recently, the predictive role for the development of HRS by renal Doppler ultrasound was evaluated. Renal arteriolar resistive index (RI) was higher in patients with HRS than in cirrhotic patients with ascites, patients without ascites and healthy controls. An increase in RI correlated well with a decline in GFR, increased plasma renin activity and decreased solute-free water clearance (73). In a prospective study on 180 patients with cirrhosis without renal failure, subsequent kidney dysfunction developed in 55% of the patients with an elevated RI and only 6% of those with normal renal ultrasound results. HRS developed in 26% of subjects with an elevated RI and 1% of subjects with a normal RI (74). Thus, the finding of elevated RI in patients with liver cirrhosis and normal renal function identified a subgroup of patients with a higher probability of developing HRS.

PATHOGENESIS OF HRS

HRS is a terminal event during the course of liver cirrhosis. Renal failure in HRS occurs in association with impaired circulatory integrity and profound arterial underfilling as illustrated by hyperdynamic circulation, low arterial blood pressure, hyponatremia, hyper-reninemia and hyperactivity of the sympathetic nervous system (72,75). A hallmark of HRS is renal vasoconstriction. In spite of incrimination of many factors, the pathogenic mechanisms of HRS are not completely understood. Renal plasma flow in advanced cirrhosis is dependent in part on synthesis of vasodilatory prostaglandins (PGs) (19). Cirrhotic patients with or without ascites have increased renal synthesis of vasodilating PGs, while patients with HRS may have a reduced renal synthesis of vasodilating PGE_2 (76). The cysteinyl leukotrienes C4 and D4 are potent renal vasoconstrictors that can modulate glomerular function in vivo and, therefore, may be important in the pathogenesis of HRS. Urinary leukotriene E4, the major metabolite of leukotrienes C4 and D4, was found to be elevated in patients with HRS. Urinary leukotriene E4 was also elevated in subjects with decompensated (ascitic) liver disease, but normal in compensated (pre-ascitic) liver disease (77). Recently, increased urinary excretion of the arachidonic acid metabolite by the cytochrome P450 system, 20-hydroxyeicosatetraenoic acid (20-HETE), a powerful renal vasoconstrictor, was demonstrated in patients with cirrhosis. The urinary excretion of 20-HETE was highest in patients with ascites and correlated with the reduction in renal plasma flow (78). Other than the water-retaining effect mediated by V2 receptors, AVP also exerts a vasoconstrictive effect mediated by V1 receptors on the vascular smooth muscle cells. The renal vasoconstrictor effect of AVP (79,80), therefore, may also contribute to renal vasoconstriction in HRS. The increase in plasma ET-1 and ET-3 concentrations in patients with HRS (47) and the purported amelioration of HRS using an ET_A receptor antagonist in patients suggests a potential role of ET-1 in the renal vasoconstriction in HRS (81). Angiotensin II is also a potent renal vasoconstrictor that may participate in the development of HRS. However, the hypotensive effects of systemic angiotensin converting enzyme inhibitors in cirrhosis (82) and the lack of selective inhibitors of the renal action of angiotensin II prevent studies on the role of angiotensin II in HRS.

TREATMENT OPTIONS

The prognosis of HRS is poor. Care should be taken to avoid further circulatory compromise secondary to nonsteroidal anti-inflammatory drugs, paracentesis without plasma expansion, bleeding and infection. Treatment of HRS is largely ineffective except for liver transplantation (83), which unfortunately is not available to all patients because of their short survival (84) and lack of donor organs. Recent results suggest, however, the possibility of prolongation of the survival of some patients with certain forms of treatment (vide infra), which may provide more time to perform liver transplantation. Different forms of treatments are aimed at an increase in SVR (vasopressin analogues), an increase in central blood volume (head-out water immersion) or a decompression of portal circulation (TIPS). In a small, double-blind, crossover randomized study of patients with cirrhosis and HRS, patients received either terlipressin (a vasopressin analogue) or a placebo for two days. Terlipressin, but not placebo, administration significantly increased creatinine clearance without any significant change in urinary sodium excretion. In addition, terlipressin administration significantly decreased plasma concentrations of renin and aldosterone (85). In another study (86) 16 patients with cirrhosis with HRS were treated with a combination of ornipressin and plasma volume expansion with albumin for either three or 15 days (eight patients each). The three-day treatment with ornipressin and albumin was associated with a normalization of the overactivity of renin-angiotensin and sympathetic nervous systems, a marked increase in ANP levels and only a slight improvement in renal function. However, when ornipressin and albumin were administered for 15 days there was normalization of serum creatinine concentration, a marked increase in renal plasma flow and GFR, and a persistent suppression in the activity of vasoconstrictor systems. Unfortunately, there were ischemic complications of ornipressin therapy in some patients in the 15-day group such as tongue ulcers and ischemic colitis. Successful long term treatment with terlipressin for 67 days, as a bridge to liver transplantation, however, has been described in a patient with HRS (87).

TIPS is an interventional treatment resulting in the decompression of the portal system by creation of a side-to-side portosystemic anastomosis. Data suggest beneficial effects of TIPS in HRS (88,89). The role of TIPS in the management of patients with HRS was evaluated in a prospective study involving seven patients with type I HRS. Renal function improved in six of the seven patients, and three patients were alive more than three months following TIPS. These beneficial effects on renal function were associated with a significant reduction of plasma renin activity, aldosterone and noradrenaline levels. Mean survival was 4.7 months (SD ± 2 months) (89). However, randomized studies on the role of TIPS in the management of HRS are lacking.

Improvement of renal function in patients with HRS has also been reported with repeated daily courses of head-out water immersion. During this manoeuvre, there was also a concomitant decrease in the activity of the renin-angiotensin system and an increase in plasma ANP levels (90). Because ET-1 has been implicated in renal vasoconstriction in cirrhosis, antagonizing renal ET receptors in HRS is an attractive option, although there is a theoretical danger of further worsening of systemic arterial vasodilation. Amelioration of HRS (dose-dependent improvement of GFR and renal blood flow) with short infusion of a selective ET_A receptor antagonist BQ123, was described in three patients with HRS secondary to alcoholic cirrhosis, without adverse effects on systemic hemodynamics (81). Nevertheless, controlled trials are needed to draw firmer conclusions about safety and benefits from the long term use of ET antagonists in HRS. Anecdotal reports of the beneficial effect

of PG analogues in the treatment of HRS (91,92) were never evaluated in larger trials, and their routine use cannot be recommended. Dialysis is rarely used for the treatment of HRS because of potential hemodynamic instability during the procedure. However, there are reports of successful treatment with continuous arteriovenous hemofiltration in patients with HRS (93).

The only curative therapy in patients with terminal liver disease is liver transplantation. In one retrospective study with 300 patients, the actuarial two-year survival rate after orthotopic liver transplantation for patients with HRS did not statistically differ from the survival of patients without HRS (76.6% in HRS versus 82.1% in non-HRS patients). Perioperative mortality was also similar. Most patients with HRS recovered renal function substantially following transplantation. However, 10% of HRS, compared with 0.8% of non-HRS transplanted patients, eventually developed end-stage renal failure (83). Another study, however, found a decreased two-year survival probability following liver transplantation in patients with HRS compared with that of patients with normal renal function (survival of 50% in HRS versus 82% in non-HRS patients) (94). Altogether, these results suggest that liver transplantation should probably be performed before the development of HRS in high risk patients (patients with hyponatremia, absence of hepatomegaly and high plasma renin activity).

SPONTANEOUS BACTERIAL PERITONITIS

The diagnosis of spontaneous bacterial peritonitis (SBP) is based on the finding of a positive ascitic fluid bacterial culture, or an elevated ascitic fluid absolute polymorphonuclear leukocyte count (higher than 250 cells/mm^3) without an evident intra-abdominal and surgically treatable source of infection (95). A major factor in the development of SBP is bacterial overgrowth of the small intestine (96) with subsequent translocation of bacteria from intestines to mesenteric lymph nodes (97,98). In the experimental model of carbon tetrachloride-induced cirrhosis, bacterial translocation occurred in 45% of rats with ascites, compared with none in control rats (97). Defective reticuloendothelial phagocytic activity and deficient antibacterial activity of the ascitic fluid contribute to the bacterial colonization of the peritoneal cavity (99). Factors that favour the development of SBP are gastrointestinal bleeding, low protein concentration in ascitic fluid and a prior history of SBP (100,101). Selective intestinal decontamination effectively decreases the incidence of SBP. Peroral drugs, such as combination neomycin, colistin and nystatin (102); norfloxacin (103,104); ciprofloxacin (105); or sulphamethoxasole-trimethoprim (106) were demonstrated to reduce the incidence of SBP in patients with cirrhosis, low ascites protein levels or gastrointestinal bleeding. Norfloxacin decreased the incidence of further episodes of SBP in patients after the first episode of SBP (107). A recent retrospective study analyzed characteristics of SBP in patients treated and not treated with norfloxacin (108). In patients without norfloxacin, the incidence of Gram-negative peritonitis was much higher than that in patients taking norfloxacin; however, the clinical course and survival of the patients were similar in the two groups. Bacterial resistance to norfloxacin in patients after long term treatment is a controversial issue, with data demonstrating either resistance up to 90% (109) or only a rare appearance of resistance (108). Selective intestinal decontamination is a cost effective option, reducing hospitalizations for SBP of high risk patients (110,111). Primary prophylaxis is indicated in patients with a higher risk for the development of SBP, such as patients with gastrointestinal hemorrhage and low protein concentration (less than 1 g/L) in ascitic fluid. Secondary prophylaxis should be undertaken in patients after the first episode of SBP. Third generation cephalosporins are the mainstay of treatment of SBP. Cefotaxime is most commonly used. A prospective randomized trial demonstrated that low dose cefotaxime (2 g every 12 h) was equally effective as the conventional dose of 2 g every 6 h in the treatment of SBP (112). In the treatment of uncomplicated SBP, the efficacy of oral norfloxacin was comparable with that of intravenous cefotaxime (113). Recently, the administration of albumin with antibiotic therapy has been shown to improve survival in cirrhotic patients with SBP (114).

CONCLUSIONS

Primary arterial vasodilation in cirrhosis triggers a neurohumoral response, the consequence of which is a hyperdynamic circulation, and compensatory renal water and sodium retention. Elevated production of nitric oxide appears to be a major factor in the primary arterial vasodilation, while RAAS and nonosmotic AVP release play crucial roles in renal sodium and water retention, respectively. Diuretic treatment with spironolactone with or without loop diuretics is an efficient way to eliminate ascites. In unresponsive patients, large volume paracentesis, preferably combined with plasma expansion, is indicated. In refractory patients, liver transplantation should be considered. Further future progress in the treatment of ascites will no doubt include AVP V2 receptor antagonists. HRS ensues as a fatal consequence of the profound derangement of systemic hemodynamics in patients with cirrhosis. Although pathogenetic mechanisms of HRS are not completely resolved, nonosmotic AVP release, local renal action of ET-1 and angiotensin II, catecholamines and renal nerve stimulation, and increased synthesis of vasoconstrictive eicosanoids may be involved. Treatment options have recently become available for patients with HRS to provide a bridge to liver transplantation, the only curative treatment for HRS. Another complication of ascitic cirrhosis is SBP. Selective intestinal decontamination as primary or secondary prophylaxis has been demonstrated to decrease the incidence of SBP.

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