CHAPTER

68

Liver Disease and the Kidney

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The presence of abnormalities of kidney function in patients with liver diseases has been recognized for several decades.[1] More than a century ago, Frerichs in Europe and Flint in the United States reported the association between liver diseases and kidney dysfunction.[2,3] These reports described the development of oliguria in patients with chronic liver disease in the setting of normal kidney histology and proposed the first pathophysiologic interpretation of kidney dysfunction in liver disease by linking the abnormalities in kidney function to disturbances in the systemic circulation. Since then, the relationship between the liver and kidney function has been the object of a considerable amount of research and substantial progress has been made in the last two decades with regard to the pathophysiology and management of renal dysfunction in liver diseases. Several books have been published specifically devoted to this topic.[4–13]

Most derangements of renal function in liver diseases occur in patients with cirrhosis and are pathophysiologically related to the presence of an expanded extracellular fluid volume which leads to the development of ascites and/or edema. This chapter deals with the pathophysiology, clinical features, and treatment of ascites and renal functional abnormalities in cirrhosis. The abnormalities in kidney function due to other liver diseases are not discussed.

RENAL ABNORMALITIES IN CIRRHOSIS

Most abnormalities of kidney function in cirrhosis are of functional origin (i.e., they occur in the absence of significant alterations in kidney histology).[14–18] These abnormalities are usually referred to as functional renal abnormalities, as opposed to nonfunctional renal abnormalities, which may also develop in patients with cirrhosis (i.e., glomerulonephritis).

The most common functional renal abnormalities in cirrhotic patients are an impaired ability to excrete sodium, an impaired ability to excrete solute-free water, and a reduction of the glomerular filtration rate (GFR) secondary to vasoconstriction of the renal circulation. Sodium retention is a key factor in the expansion of the extracellular fluid volume and development of ascites and edema, whereas solute-free water retention is responsible for dilutional hyponatremia. Renal vasoconstriction, when severe, leads to hepatorenal syndrome (HRS). Chronologically, sodium retention is the earliest alteration of kidney function observed in patients with cirrhosis, whereas dilutional hyponatremia and HRS are late findings. In most patients, abnormalities of kidney function usually worsen with time as the liver disease progresses. However, in some patients, a spontaneous improvement or even normalization of sodium and solute-free water excretion may occur during the course of their disease.[19–21] This improvement in renal function occurs particularly in patients with alcoholic cirrhosis after abstinence from alcohol. Spontaneous improvement of renal function after the development of type-1 HRS (see later) is extremely unusual.[22,23]

Sodium Retention and Ascites

Sodium retention is the most frequent abnormality of kidney function in patients with cirrhosis and ascites. The existence of sodium retention in cirrhosis was first documented more than 60 years ago when methods to measure electrolyte concentration in organic fluids became available.[24–26] Since then, it has been well established that sodium retention plays a key role in the pathophysiology of ascites and edema formation in cirrhosis. The amount of sodium retained within the body is dependent on the balance between the sodium ingested in the diet and the sodium excreted in the urine. As long as the amount of sodium excreted is lower than that ingested, patients accumulate ascites and/or edema. The important role of sodium retention in the pathogenesis of ascites formation is supported by the fact that ascites can disappear just by reducing the dietary sodium content in some patients or by increasing the urinary sodium excretion with the administration of diuretics in others.[26,27] Conversely, a high-sodium diet or diuretic withdrawal leads to the reaccumulation of ascites.[25,26] The achievement of a negative sodium balance (i.e., excretion higher than intake) is the essence of pharmacologic therapy of ascites. Although no studies assessing the chronologic relationship between sodium retention and the formation of ascites have been performed in patients with

cirrhosis, studies in experimental animals have provided conclusive evidence indicating that sodium retention precedes ascites formation, further emphasizing the important role of this abnormality of renal function in the pathogenesis of ascites in cirrhosis.[28–32] This observation suggests that sodium retention is the cause and not the consequence of ascites formation in cirrhosis.

The severity of sodium retention in cirrhosis with ascites varies considerably from patient to patient. Some patients have relatively high urinary sodium excretion, whereas urine sodium concentrations are very low or even undetectable in others (Fig. 68.1). The proportion of patients with marked sodium retention depends on the population of cirrhotic patients considered. Most patients who require hospitalization because of severe ascites have marked sodium retention (less than 10 mEq per day). Sodium retention is particularly intense in patients with ascites refractory to diuretic treatment.[33,34] By contrast, in a population of cirrhotic patients with mild or moderate ascites, the proportion of patients with marked sodium retention is low and most patients excrete more than 10 mEq per day spontaneously (without diuretic therapy). The response to diuretic treatment is usually better in patients with moderate sodium retention than in those with marked sodium retention.[27,35,36]

Nephron Sites of Sodium Retention

In healthy subjects approximately 95% of filtered sodium is reabsorbed in the renal tubules. Approximately 60% to 70% is absorbed in the proximal tubules, another 30% to 40% gets absorbed in the thick ascending limb, and 5% to 10% of sodium is reabsorbed in the collecting ducts.[37]

In many instances, sodium retention in cirrhosis is due to increased tubular reabsorption of sodium because it occurs in the presence of normal or only moderately reduced GFR.[27,38] The exact contribution of the different segments of the nephron to this increased sodium reabsorption is not completely known. Micropuncture studies in rats with cirrhosis and ascites have demonstrated an enhanced reabsorption of sodium in the proximal tubule.[28,39] On the other hand, it has been shown that the development of a positive sodium balance and the formation of ascites in cirrhotic rats can be prevented by aldosterone antagonists, which suggests that the collecting ducts are important sites of the increased sodium reabsorption in experimental cirrhosis.[31,40,41] Studies assessing the protein abundance of renal tubular sodium transporters in rats with CCL_4– induced cirrhosis showed an increased expression of the sodium chloride cotransporters of the distal tubule (NCC/TSC) and the epithelial sodium channel of the collecting duct (ENaC), both of which are regulated by aldosterone, consistent with a major role of hyperaldosteronism in sodium retention in this animal model.[41] An increased abundance of the Na^+-K^+-$2Cl^-$ cotransporter of the thick ascending limb (NKCC/BSC1) and a decreased abundance of the proximal sodium transporters (sodium hydrogen exchanger type 3–NH-3, and sodium phosphate cotransporter isoform 2–NaPi-2) was also found, consistent with increased sodium reabsorption in the ascending limb of the loop of Henle and reduced reabsorption in the proximal tubule.[41] Other factors such as the influence of calcium on the bumetanide-sensitive $Na^+K^+2Cl^-$ cotransporter (BSC-1) located in the luminal membrane of epithelial cells lining the thick ascending limb of the loop of Henle may play a role in sodium retention.[41]

Investigations in patients with cirrhosis have also provided discrepant findings as to the most important nephron site of sodium retention. Results from earlier studies using sodium, water, or phosphate clearances to estimate the tubular handling of sodium suggest that the distal nephron is the main site of sodium retention.[42–45] Results of studies using lithium clearance, which estimates sodium reabsorption

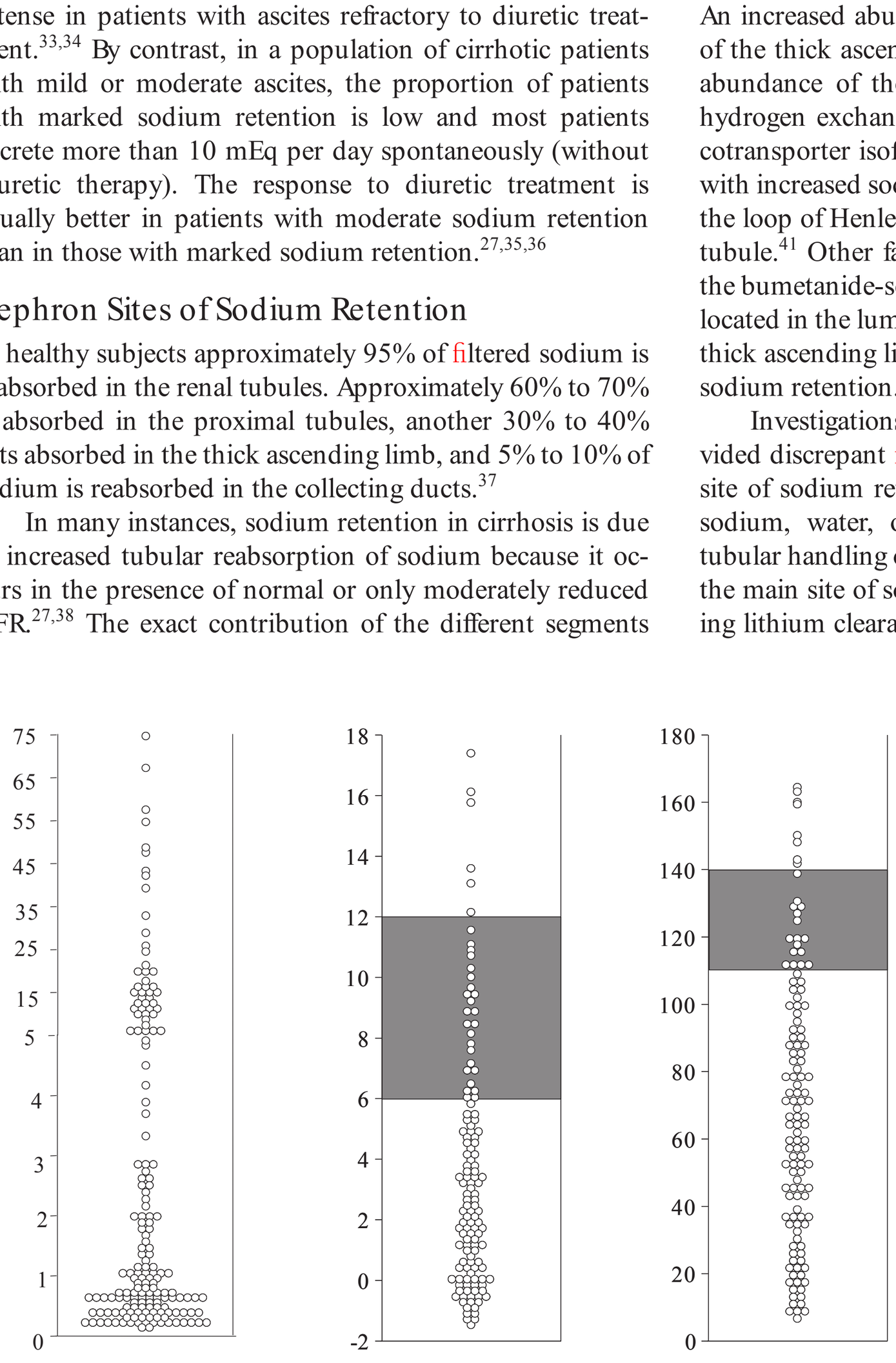

FIGURE 68.1 Individual values of sodium excretion, solute-free water clearance, and glomerular filtration rate in a large series of patients with cirrhosis and ascites without diuretic therapy and under a low-sodium diet. Lines indicate normal ranges. For urine sodium normal range is 80 to 100 mEq per day.

in the proximal tubule, suggest that cirrhotic patients with ascites show a marked increase in proximal sodium reabsorption.[46,47] Nevertheless, distal sodium reabsorption is also increased, especially in patients with more avid sodium retention.[47] Clinical studies using spironolactone to antagonize the mineralocorticoid receptor indicate that this agent induces natriuresis in a large proportion of cirrhotic patients with ascites without renal failure, which supports a major role for increased sodium reabsorption in distal sites of the nephron in these patients.[36,48–51] Taken together, these results suggest that in patients with cirrhosis without renal failure, an enhanced reabsorption of sodium in both proximal and distal tubules contributes to sodium retention. Potential mediators of this increased sodium reabsorption include changes in the hydrostatic and colloidosmotic pressures in the peritubular capillaries and increased activity of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). Sodium retention is usually more marked in patients with renal failure than in those without renal failure due to both a reduction in filtered sodium load and a more marked activation of sodium-retaining mechanisms.

Clinical Consequences

Because sodium is retained together with water isoosmotically in the kidneys, sodium retention is associated with fluid retention, leading to expansion of extracellular fluid volume and increased amount of fluid in the interstitial tissue. In some patients with advanced cirrhosis, the total extracellular fluid volume may increase up to 40 L or even more (compared to the average 14 L in a 70–kg healthy adult), which represents an approximate cumulative gain of 3,400 mEq of sodium (26 L of excess extracellular fluid volume times 130 mEq per L). In most patients with advanced cirrhosis, sodium retention is manifested by the development of ascites. The most common clinical symptom of ascites is discomfort due to abdominal swelling. In cases with marked accumulation of fluid, physical activity and respiratory function may be impaired. Other clinical consequences related to the presence of ascites are the appearance of abdominal wall hernias and hydrocele and spontaneous infection of ascitic fluid (also known as spontaneous bacterial peritonitis).[52] These complications, especially infection, contribute markedly to the increased morbidity and mortality associated with the presence of ascites.

Accumulation of fluid in the subcutaneous tissue, as edema, is also common in patients with cirrhosis and sodium retention and in most cases occurs concomitantly with the existence of ascites. Edema is most commonly observed in the lower extremities, but generalized edema may occur as well. Mild or moderate pedal edema may decrease or even disappear during bed rest and reappear during the daytime, reflecting an increased natriuresis in the supine position as compared with the upright position.[53,54] Both hypoalbuminemia and increased venous pressure in the inferior vena cava due either to constriction of the vena cava within the liver or increased intra-abdominal pressure caused by ascites may contribute to the high incidence of edema in cirrhotic patients with ascites. Leg edema may occur in patients with cirrhosis treated with either surgical portacaval shunts or transjugular intrahepatic portosystemic shunts (TIPS), presumably because of the increased pressure in the inferior vena cava secondary to these procedures.

Other clinical manifestations of sodium retention in cirrhosis include pleural and/or pericardial effusions. Hepatic hydrothorax is defined as a pleural effusion in patients with cirrhosis without associated cardiac and/or pulmonary disease. This complication occurs in approximately 10% of patients with cirrhosis.[55,56] In most cases the effusion is mild or moderate, more frequent on the right side, and associated with the presence of ascites. Left-sided effusions are uncommon. Occasionally, large right pleural effusions may exist in the absence of clinically evident ascites and constitute the main manifestation of the disease.[56,57] These pleural effusions are very difficult to manage, usually recur after therapy, and are due to the existence of anatomic defects in the diaphragm which cause a communication between the peritoneal and pleural cavities. The gradient between the positive intra-abdominal pressure and the negative intrathoracic pressure explains the passage of the fluid formed in the peritoneal cavity to the pleural cavity. Although less commonly than ascitic fluid, pleural fluid may also become infected spontaneously, a condition known as spontaneous bacterial empyema.[58] Finally, between one and two thirds of cirrhotic patients with ascites also have mild or moderate pericardial effusions as demonstrated by echocardiography.[59] These disappear after the elimination of ascites and are not associated with clinical symptoms.

Assessment of Sodium Excretion in Clinical Practice

The assessment of the urinary excretion of sodium is very useful in the clinical management of patients with cirrhosis and ascites because it allows the precise quantification of sodium retention. Urine must be collected under conditions of fixed and controlled sodium intake (usually a low-sodium diet of approximately 90 mEq per day during the previous 5 to 7 days), as sodium intake may influence sodium excretion. Although the measurement of sodium concentration in a spot of urine may provide a rough estimate of sodium excretion, the assessment of sodium excretion in a 24–hour period is preferable because it is more representative of sodium excretion throughout the day and takes into account the urine output.

In clinical practice, sodium excretion should be measured without diuretic therapy when patients with ascites are first seen or when there are signs suggestive of disease progression (e.g., marked increase in ascites or edema despite compliance with the sodium-restricted diet and diuretic therapy). Baseline sodium excretion is one of the best predictors of the response to diuretic treatment and is very helpful to establish the therapeutic schedule in cirrhotic patients with ascites. Patients with marked sodium retention

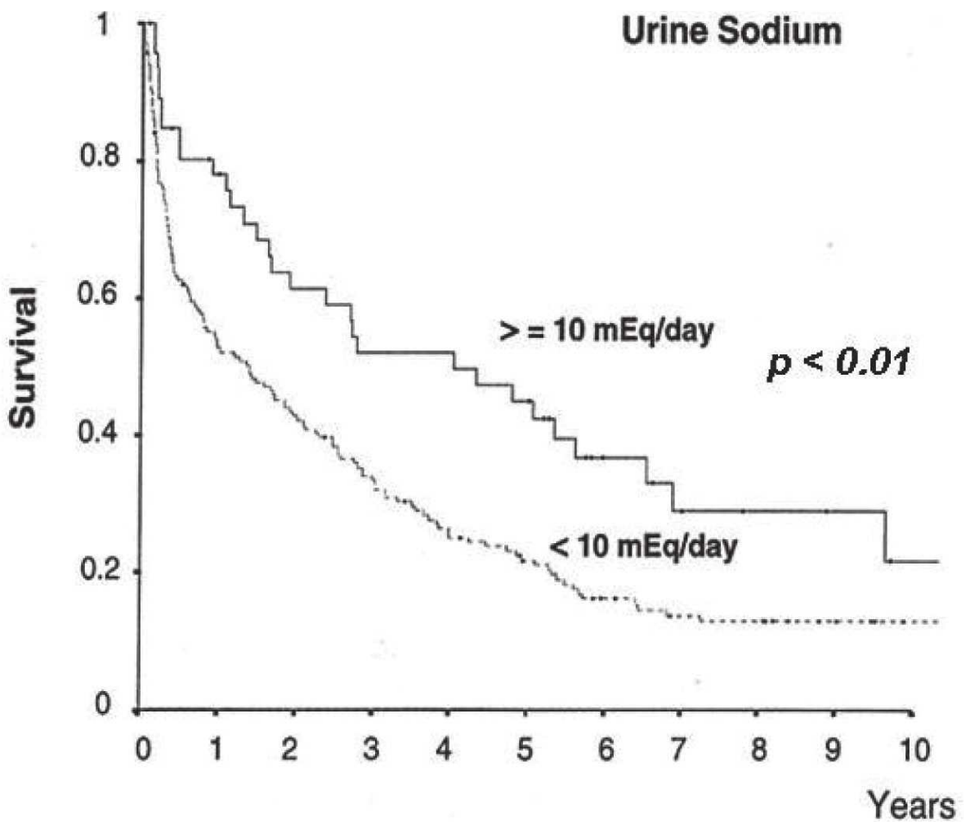

FIGURE 68.2 Long-term survival according to sodium excretion in a series of 204 patients with cirrhosis admitted to the hospital for the treatment of ascites.

(i.e., urine sodium <10 mEq per day) in whom a positive sodium balance is anticipated despite a restriction in sodium intake should be started on moderately high doses of aldosterone antagonists (e.g., spironolactone 100 to 200 mg per day) alone or in association with loop diuretics (e.g., furosemide 40 mg per day). Conversely, patients with moderate sodium retention (i.e., urine sodium >10 mEq per day) would likely respond to low doses of aldosterone antagonists (i.e., spironolactone 25 to 100 mg per day). The use of higher doses of spironolactone in these latter patients may induce overdiuresis and cause dehydration, hypovolemic hyponatremia, and prerenal renal failure. Besides its importance in helping establish the dose of diuretics, the intensity of sodium retention also provides prognostic information in patients with ascites. Patients with baseline urine sodium lower than 10 mEq per day have a median survival time of only 1.5 years compared with 4.5 years in patients with urine sodium higher than 10 mEq per day (Fig. 68.2).[60–62] Finally, the measurement of sodium excretion in patients under diuretic therapy is very useful to monitor the response to treatment.

Water Retention and Dilutional Hyponatremia

Since the pioneer studies by Papper and Saxon and Shear and colleagues,[63,64] it is well known that a derangement in the renal capacity to regulate water balance occurs in advanced cirrhosis. Cirrhotic patients without ascites usually have normal or only slightly impaired renal water handling as compared with healthy subjects. Therefore, in these patients total body water, plasma osmolality, and serum sodium concentration are normal and hyponatremia does not develop, even in conditions of excessive water intake. By contrast, an impairment in the renal capacity to excrete solute-free water is common in patients with ascites and usually it occurs late after the development of sodium retention.[63–67] In patients with ascites there is a direct correlation between urinary sodium excretion and water excretion as estimated by urine flow after a water load.[64,67] However, no correlation exists between these two parameters when only patients with marked sodium retention are considered. Therefore, sodium retention is necessary but not sufficient for the development of solute-free water retention in cirrhotic patients.

As with sodium retention, the impairment of solute-free water excretion is not uniform in all patients with ascites; rather, it varies markedly from patient to patient (Fig. 68.1). In some patients, water retention is moderate and can only be detected by measuring solute-free water excretion after a water load. These patients are able to eliminate water normally and maintain a normal serum sodium concentration as long as their fluid intake is kept within normal limits, but they may develop hyponatremia when fluid intake is increased. In other patients, the severity of the disorder is such that they retain most of their regular water intake causing hyponatremia and hypoosmolality. Therefore, hyponatremia in cirrhosis with ascites is almost always dilutional in origin since it occurs in the setting of an increased total body water. Hyponatremia is paradoxical in that it is associated with sodium retention and a marked increase in total body exchangeable sodium. The occurrence of spontaneous dilutional hyponatremia requires a profound impairment in solute-free water excretion, since it usually develops with a solute-free water clearance after a water load below 1 mL per minute.[65]

Hyponatremia in cirrhosis is currently defined as a reduction in serum sodium below 130 mEq per L.[68] The prevalence of hyponatremia using this cutoff is 22%. If the cutoff level of 135 mEq per L is used, the prevalence increases up to 49%.[69] The presence of dilutional hyponatremia in a cirrhotic patient is associated with a poor survival (Fig. 68.3).[62,65,70–79] The development of dilutional hyponatremia after a precipitating event such as hemorrhage or infection is associated with a better prognosis when compared to the spontaneous appearance of this complication.[80] This is possibly related to a higher incidence of renal dysfunction and a more advanced stage of decompensated cirrhosis associated with spontaneous dilutional hyponatremia.

Several factors may aggravate the impairment of solute-free water excretion in cirrhotic patients and precipitate the appearance of hyponatremia. These include treatment with diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs), large-volume paracentesis without plasma volume expansion,[67,81–83] bacterial infections, and treatment with terlipressin for variceal bleeding.[84] Hyponatremia may also develop after the administration of hypotonic fluids in patients with ascites.

Mechanisms of Impaired Renal Water Handling

The pathogenesis of water retention in cirrhosis and dilutional hyponatremia is complex and probably involves several factors, including a reduced delivery of filtrate to the

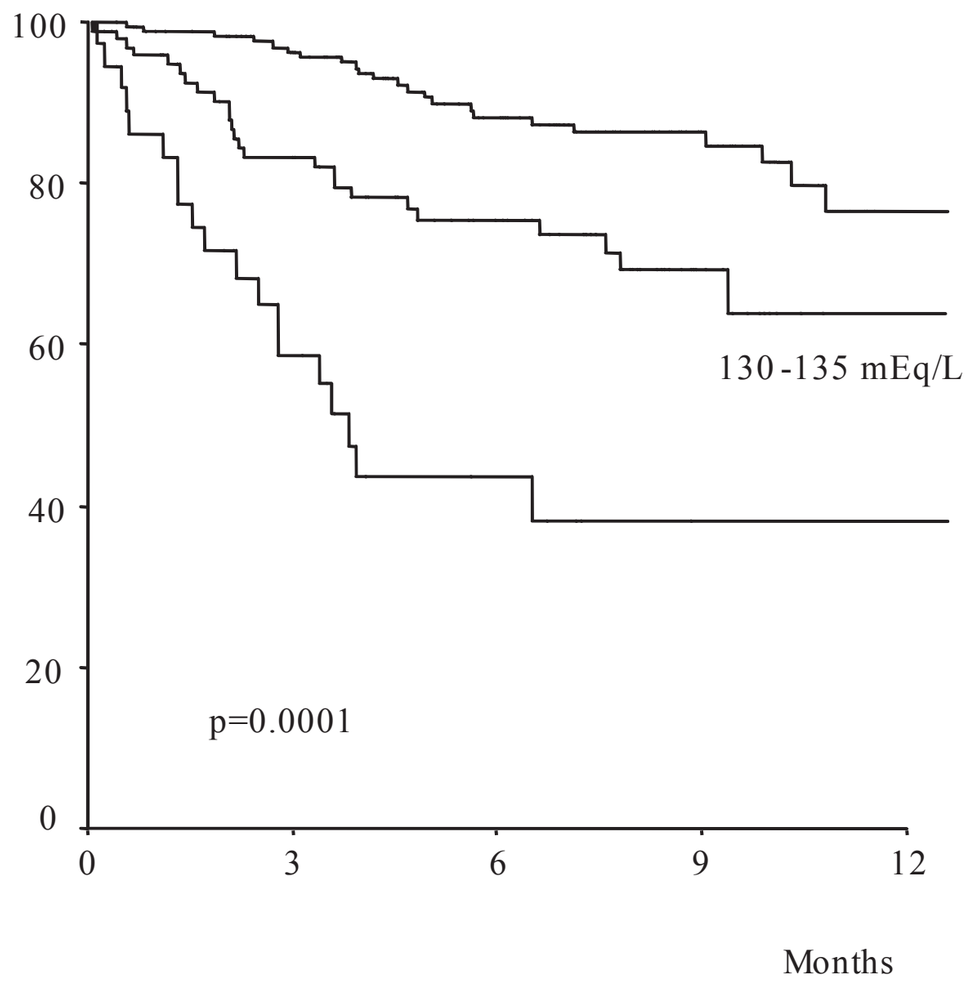

FIGURE 68.3 One-year survival before transplantation in a series of 308 patients with cirrhosis according to different values of serum sodium. (Reproduced with permission from Londoño MC, Cárdenas A, Guevara M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. *Gut*. 2007;56:1283–1290.)

ascending limb of the loop of Henle, reduced renal synthesis of prostaglandins, and nonosmotic hypersecretion of arginine vasopressin (AVP).[68,85–87] Although definitive data about the relative importance of these factors in the pathogenesis of hyponatremia in patients with cirrhosis is lacking, it is likely that AVP hypersecretion plays a major role. This contention is supported by studies in animals and patients with cirrhosis showing that the administration of vaptans, drugs that antagonize the tubular effects of AVP (V2 receptor antagonists), improve solute-free water excretion and increase serum sodium concentration.[88–95] However, it is important to note there is a significant number of patients in whom hyponatremia does not improve despite the administration of vaptans, thus suggesting that factors other than AVP play also a role in the pathogenesis of solute-free water retention in cirrhosis. In patients with renal failure it is likely that besides AVP, a reduced distal delivery of filtrate due to decreased filtered load and increased proximal sodium and water reabsorption plays a role in solute-free water retention.

Clinical Consequences

The consequence of an impairment in solute-free water excretion is the development of dilutional hyponatremia. As indicated previously, dilutional hyponatremia in cirrhotic patients is defined as serum sodium $<$130 mEq per L in the presence of an expanded extracellular fluid volume, with ascites and/or edema.[68] It is associated with sodium retention and increased total body sodium and should be distinguished from hypovolemic hyponatremia that, although less common, may develop in cirrhotic patients with ascites and edema who are maintained on high doses of diuretics and sodium restriction after resolution of ascites and edema. There is limited information on the clinical consequences specifically caused by hyponatremia in cirrhosis because hyponatremia almost always occurs in the setting of advanced liver failure, which causes a wide array of clinical manifestations. Therefore, the precise identification of the clinical consequences of hyponatremia versus those of other causes has so far not been possible. This has been further hindered by the lack of an effective treatment of hyponatremia.

Hyponatremia and neurologic function. In patients without liver disease, hyponatremia is primarily associated with a broad variety of neurologic manifestations related to the existence of brain edema, such as headache, disorientation, confusion, focal neurologic deficits, seizures, and, in some cases, death due to cerebral herniation.[96] Severity of neurologic symptoms in patients with hyponatremia without liver disease correlates roughly with the levels of osmolality and sodium in the extracellular fluid. However, rather than the absolute reduction in serum sodium levels, the most important factor in determining the severity of neurologic symptoms is the rate of fall in serum sodium levels, patients with acute hyponatremia having a much higher incidence of neurologic symptoms than those with chronic hyponatremia.

Studies specifically assessing neurologic symptoms in cirrhosis with hyponatremia are lacking. However, the clinical experience indicates that significant neurologic manifestations such as headache, focal motor deficits, seizures, and cerebral herniation are very uncommon. It is likely that the relatively low incidence of neurologic manifestations in patients with cirrhosis and dilutional hyponatremia is related to the fact that in most of these patients hyponatremia is chronic rather than acute, and this gives sufficient time for the brain to adjust to hypo-osmolality of the extracellular fluid. The effects of hyponatremia on brain function have to be discussed in light of the recent hypothesis that proposes a role for a low-grade cerebral edema in the pathogenesis of hepatic encephalopathy.[97] According to this hypothesis, ammonia and other neurotoxins act synergistically to induce a low-grade cerebral edema as a result of swelling of astrocytes, which is mainly due to increased intracellular content of glutamine, secondary to ammonia metabolism. The cerebral edema would not be sufficient to cause an increase in intracranial pressure, but astrocyte swelling would result in a number of alterations of neurologic function, which would facilitate the development of hepatic encephalopathy. Evidence for such a low-grade cerebral edema derives from experimental and human studies using magnetic resonance.[98–100] In this context of low-grade cerebral edema, hyponatremia may represent a second osmotic hit to astrocytes, causing further depletion of osmotic counteractive systems (i.e., organic osmolytes). In this situation, cells

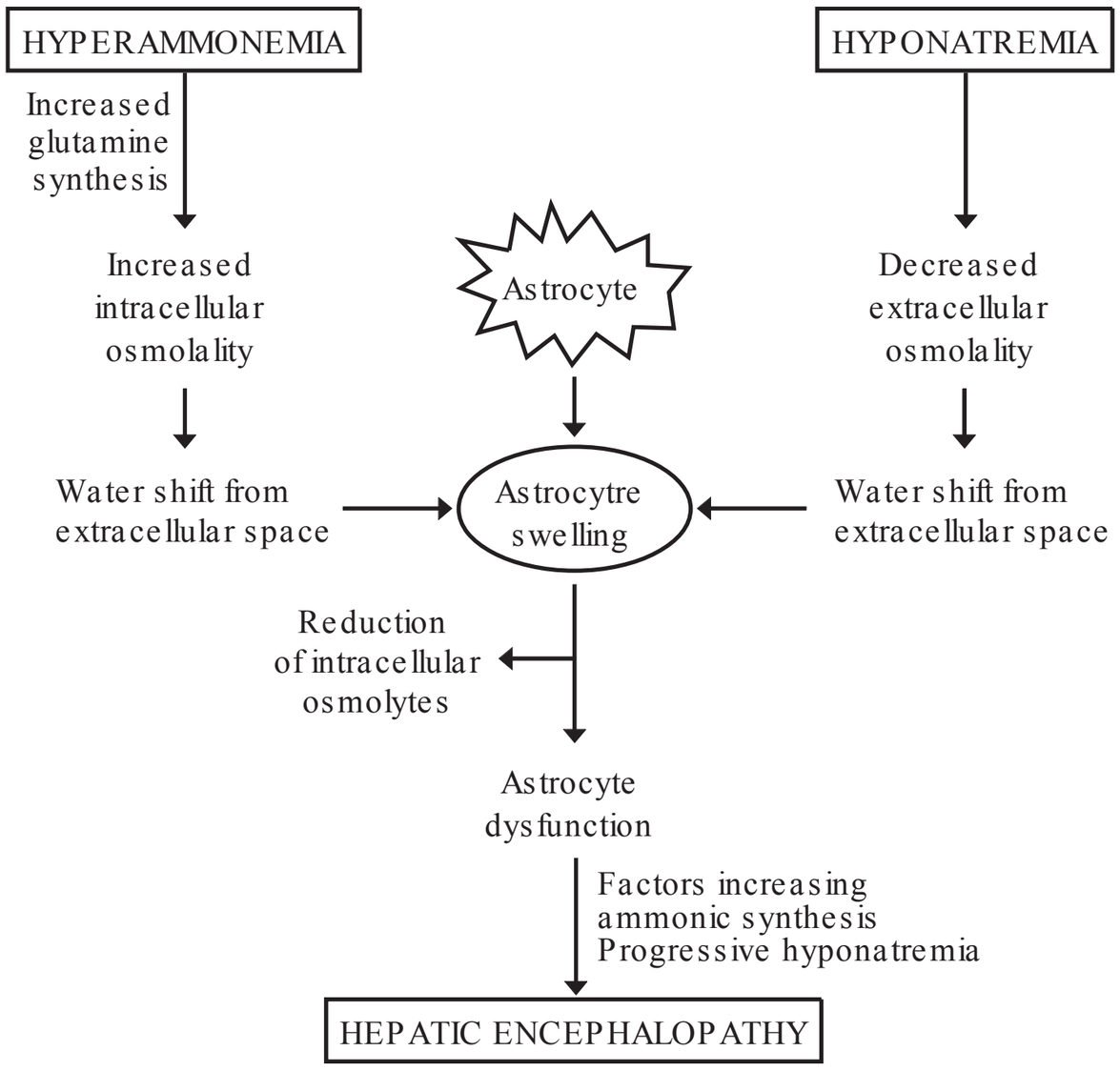

FIGURE 68.4 Proposed interaction between hyperammonemia and hyponatremia on brain astrocytes and possible pathogenic relationship with hepatic encephalopathy. (Reproduced with permission from Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. *Hepatology*. 2008;48:1002–1010.)

would probably not tolerate a further challenge to cell volume, and encephalopathy would develop due to any other osmotic stimulus, including situations associated with an increased ammonia load to the brain (gastrointestinal hemorrhage, infection) or further impairment in serum sodium concentration (Fig. 68.4). Several lines of evidence support the existence of a relationship between hepatic encephalopathy and low serum sodium concentration. First, serum sodium levels and serum ammonia levels are major factors determining electroencephalographic abnormalities in cirrhosis.[101] Second, in patients treated with transjugular intrahepatic portosystemic shunts, hyponatremia is a major risk factor for hepatic encephalopathy.[102] Third, in patients treated with diuretics (a clinical situation associated with a high incidence of hepatic encephalopathy), hyponatremia is a risk factor for hepatic encephalopathy (P. Ginès, unpublished data). Finally, serum sodium has been shown to be an independent predictive factor of hepatic encephalopathy in several series of patients with advanced cirrhosis.[103–105]

Hyponatremia and Complications of Cirrhosis. Besides hepatic encephalopathy, hyponatremia has also been reported to be associated with other complications of cirrhosis, yet information is limited. Specifically, hyponatremia is a frequent finding in patients with cirrhosis and bacterial infections.[106] In the majority of patients, hyponatremia occurs in close association with renal failure and correlates with a poor prognosis. Patients with ascites and hyponatremia constitute a unique population with a very high risk of developing HRS.[23] On the other hand, low serum sodium levels are a very common finding in patients with HRS. Information on the impact of hyponatremia on health-related quality of life in patients both with and without liver disease is very limited. In patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid intake to prevent further reductions in serum sodium concentration, and this is usually poorly tolerated. Moreover, in a recent study in a large population of patients with cirrhosis, hyponatremia was an independent predictive factor of the impaired health-related quality of life.[107]

Hyponatremia and Liver Transplantation. Patients with cirrhosis and hyponatremia are at increased risk of neurologic complications after transplantation, central pontine myelinolysis being the most severe, related to a rapid change in serum sodium in the early postoperative period.[108,109] The existence of hyponatremia before transplantation is associated not only with an increased risk of neurologic complications after transplantation, but also with an increased risk of renal failure and infectious complications, greater use of blood products, longer duration of hospital stay, and, more importantly, increased short-term mortality after transplantation.[110,111]

Renal Vasoconstriction and Hepatorenal Syndrome

Investigations performed by Sherlock, Schroeder, and Epstein during the late 1960s and early 1970s provided conclusive evidence indicating that the renal failure of functional origin—the so-called hepatorenal syndrome (HRS)—was due to a marked vasoconstriction of the renal circulation.[112–114] Further studies showed that, besides the striking renal vasoconstriction present in patients with HRS, mild to moderate degrees of vasoconstriction in the renal circulation are very common in patients with cirrhosis and ascites.[115–118] It has also been recognized that this vasoconstriction leading to HRS may

be triggered by some precipitating factors, particularly bacterial infections.[119–121] When renal perfusion is estimated by sensitive clearance techniques, such as para-aminohippurate or inulin clearances, in a population of hospitalized patients with ascites, normal values are found in only one fifth of cases. In another 15% to 20%, renal hypoperfusion is very intense and meets the criteria of HRS. In the remaining patients, mild or moderate reductions in renal perfusion exist (Fig. 68.1). These latter patients show slightly increased serum creatinine and/or blood urea nitrogen (BUN) levels in baseline conditions (in the absence of diuretic therapy). This moderate renal vasoconstriction is clinically relevant for several reasons: first, it is often associated with marked sodium and water retention and the presence of refractory ascites[122]; second, it predisposes to the development of HRS[23,120,123]; and third, it is associated with an impaired survival.[62,73]

Definition of Hepatorenal Syndrome

The most recent definition of HRS proposed by the International Ascites Club, which is the most widely accepted, is as follows: "Hepatorenal syndrome is a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure, as well as in patients with acute liver failure or alcoholic hepatitis. It is characterized by impaired renal function, marked alterations in cardiovascular function and over-activity of the sympathetic nervous system and renin-angiotensin systems. Severe renal vasoconstriction leads to a decrease of glomerular filtration rate. It appears spontaneously, but can also follow a precipitating event." This description was first proposed in 1999 and was adapted in 2007.[122,124] Although in the former definition, the existence of an ongoing bacterial infection precluded the diagnosis of HRS, with the current definition HRS can be diagnosed in the presence of an infection except in cases with septic shock.[124]

Pathogenic Mechanisms

The pathophysiologic hallmark of HRS is a vasoconstriction of the renal circulation.[114,122,125,126] Studies of renal perfusion with renal arteriography, $_{133}$Xe washout technique, para-aminohippuric acid excretion, and duplex Doppler ultrasonography have demonstrated the existence of marked vasoconstriction in the kidneys of patients with HRS, with a characteristic reduction in renal cortical perfusion.[113,126–132] The functional nature of HRS has been conclusively demonstrated by the lack of significant morphologic abnormalities in the kidney histology,[15–18,133] the normalization or improvement of renal function after liver transplantation,[134–138] and the reversibility of the syndrome by pharmacologic treatment with vasoconstrictors and albumin.[139]

The mechanism of this vasoconstriction is likely multifactorial involving changes in systemic hemodynamics, increased pressure in the portal venous system, activation of vasoconstrictor factors, and suppression of vasodilator factors acting on the renal circulation (discussed later). Contrary to the previous belief of marked vasodilation in extrarenal beds, other vascular beds besides the renal circulation are also vasoconstricted in patients with HRS, including the extremities and the cerebral circulation.[140–143] This indicates the existence of a generalized arterial vasoconstriction in nonsplanchnic vascular beds of patients with HRS and confirms that the only vascular bed responsible for arterial vasodilation and reduced total peripheral vascular resistance in cirrhosis with HRS is the splanchnic circulation.

Clinical and Laboratory Findings

HRS is a common complication of patients with cirrhosis. In patients with ascites, the probability of developing HRS during the course of the disease was reported as 18% at 1 year and 40% after 5 years of follow-up (Fig. 68.5).[23] The occurrence of HRS has been investigated in two recent studies. In one study of 129 patients, 22% of patients developed HRS during a follow-up period of 3.5 years.[144] In another study including 562 consecutive patients admitted to the hospital with renal failure, the frequency of HRS was 49% (associated with infection in 38% of cases and non-associated in 11%).[145] The clinical manifestations of patients with HRS include a combination of signs and symptoms related to renal, circulatory, and liver failure. Nonetheless, there are no specific clinical findings in HRS.

Renal failure in HRS may have a rapid or insidious onset and is associated almost constantly with intense urinary sodium retention (urine sodium $<$10 mEq per L), and spontaneous dilutional hyponatremia (serum sodium $<$130 mEq per L).[122,125,145] HRS may occur in two different clinical patterns, according to the intensity and form of onset of renal failure (Table 68.1).[122,124,146] Type 1 HRS is the classic type of HRS and represents the end of the spectrum of changes in renal perfusion in cirrhosis. The dominant clinical features of type 1 HRS are those of acutely severe renal failure

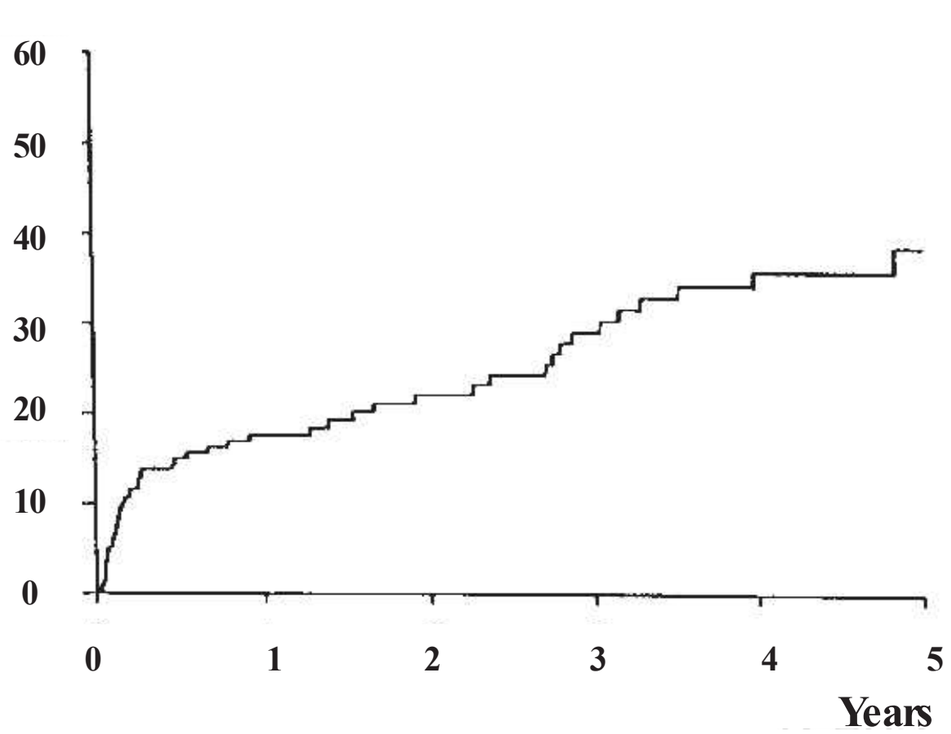

FIGURE 68.5 Probability of developing hepatorenal syndrome in a series of 234 nonazotemic cirrhotic patients with ascites. (Reproduced with permission from Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology.* 1993;105:229.)

68.1 Clinical Types of Hepatorenal Syndrome

Type 1	Rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 mL/min in less than 2 weeks.
Type 2	Impairment in renal function (serum creatinine >1.5 mg/dL) that does not meet the criteria of type 1.

with rapid increase in serum levels of urea and creatinine and low urine volume in some cases, but not all of them. Type 1 HRS is characterized by a rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg per dL in less than 2 weeks. Despite an important reduction of GFR in these patients, serum creatinine levels are commonly lower than values observed in patients with acute renal failure of similar intensity with respect to the reduction in GFR, but without liver disease.[125,132,147,148] This is probably due to the lower endogenous production of creatinine secondary to reduced muscle mass in patients with cirrhosis compared with patients without liver disease. Type 1 HRS is associated with a very low survival expectancy, the median survival time being only 2 weeks (Fig. 68.6).[146] Type 2 HRS is characterized by a more subtle course with serum creatinine levels around 1.5 to 2.0 mg per dL. Patients are usually in a better clinical condition than those with type 1 HRS and their survival expectancy is longer, approximately 6 months (Fig. 68.6).[146] The dominant clinical feature of these patients is diuretic-resistant ascites due to the combination of intense sodium retention, reduced GFR, and marked activation of antinatriuretic systems.[122,124,146] Severe spontaneous hyperkalemia is an uncommon feature of HRS. However, marked hyperkalemia may occur if patients are treated with aldosterone antagonists, especially patients with type 1 HRS. Severe metabolic acidosis and pulmonary edema, which are frequent complications of acute renal failure of patients without liver disease, are uncommon findings in patients with HRS. Because HRS is a form of functional renal failure, the characteristics of urine are those of prerenal azotemia, with low urine sodium concentration, and increased urine osmolality and urine-to-plasma osmolality ratio.[122,149] Urine volume is not extremely reduced—in a recent series the average urine volume in 60 patients with HRS was 733 mL per day[145] and in some cases urine sodium concentration is not extremely reduced.[149,150] Table 68.2 shows the current diagnostic criteria of HRS.[124]

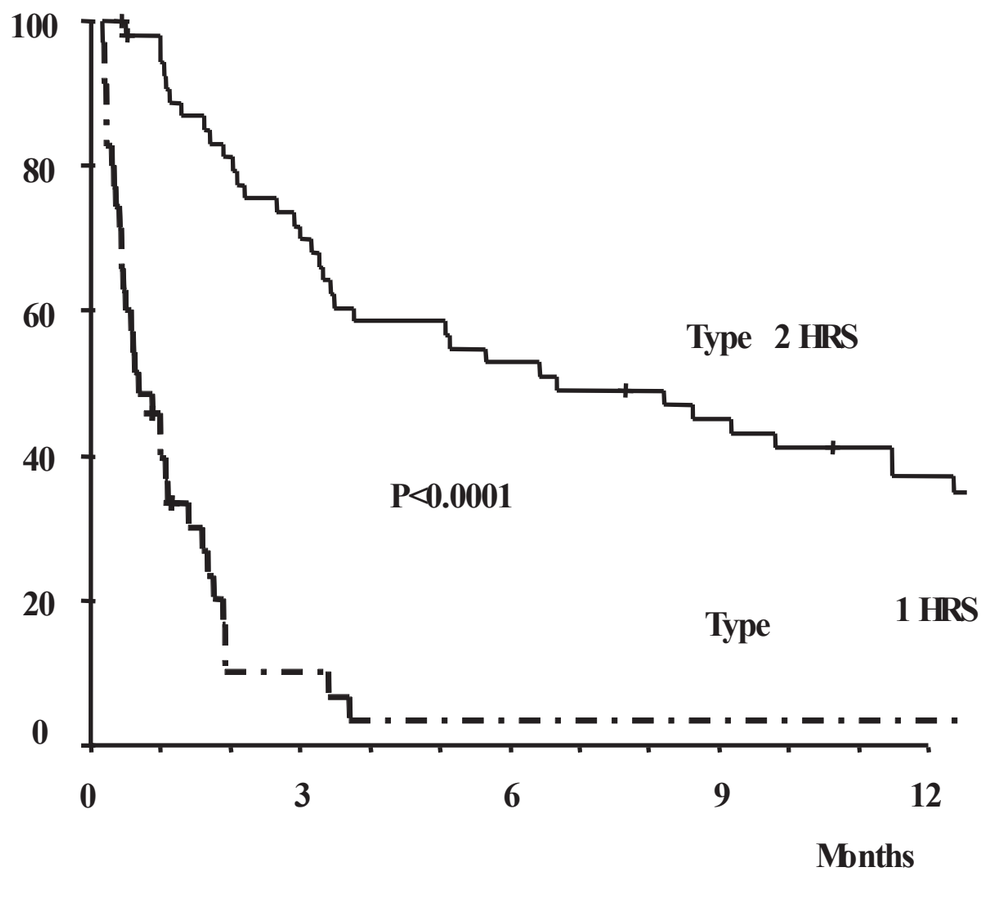

FIGURE 68.6 Survival of patients with cirrhosis according to the type of hepatorenal syndrome. (Reproduced with permission from Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: Relevance to liver transplantation. *Hepatology*. 2005;41:1282–1289.)

Circulatory failure in patients with HRS is characterized by arterial hypotension (most patients have a mean arterial pressure in the range of 70 mm Hg), and low total systemic vascular resistance, despite marked activation of the vasoconstrictor systems and the existence of severe vasoconstriction in several vascular beds, as already discussed.[122,142,143]

68.2 Diagnostic Criteria of Hepatorenal Syndrome

1. Cirrhosis with ascites.
2. Serum creatinine >133 mmol/L (1.5 mg/dL).
3. No improvement of serum creatinine (decrease to a level of ≤133 mmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
4. Absence of shock.
5. No current or recent treatment with nephrotoxic drugs.
6. Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

Adapted from Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310–1318.

In addition, several studies have shown that cardiac output is low in patients with HRS, either in absolute values or relative to the reduction in total systemic vascular resistence.[151–153] This reduction in cardiac output may contribute to the reduction in the effective arterial blood volume and subsequent renal vasoconstriction.[152–154] In a longitudinal study in patients with cirrhosis it was shown that a reduction in cardiac output was associated with the occurrence of HRS.[155] Similarly, in a small series of patients with cirrhosis, those with a low cardiac output had a greater risk of HRS development.[156]

Finally, the third type of clinical manifestations of HRS is related to the existence of liver failure. The majority of patients have features of advanced liver disease with hyperbilirubinemia, elevated prothrombin time, thrombocytopenia, hepatic encephalopathy, hypoalbuminemia, poor nutritional status, and a large amount of ascites. In general, patients with type 1 HRS have more severe liver failure compared with patients with type 2 HRS.[146]

Precipitating Factors

In some patients, HRS develops without any identifiable precipitating factor, whereas in others it occurs in close chronologic relationship with bacterial infections, particularly spontaneous bacterial peritonitis.[119,122,124,157] Approximately one third of patients with spontaneous bacterial peritonitis develop renal failure during or immediately after infection, and in the absence of shock, which is currently defined as HRS[119,124] and occurs in the setting of a further decrease in effective arterial blood volume of patients with ascites, as indicated by a marked activation of vasoconstrictor systems, and increased serum and ascitic fluid levels of cytokines.[120,157] In approximately one third of patients with spontaneous bacterial peritonitis, HRS is reversible after resolution of infection. However, in the remaining patients HRS is not reversible after the resolution of the infection. Patients who develop type 1 HRS after spontaneous bacterial peritonitis have a dismal outcome, with an almost 100% hospital mortality if not treated appropriately (see below).[119,120] Similarly, large-volume paracentesis (> 5 L) without albumin expansion may precipitate type 1 HRS in up to 15% of cases.[83] This is one of the main reasons that supports the administration of intravenous albumin when large-volume paracenteses are performed.[158,159] Gastrointestinal bleeding has been classically considered as a precipitating factor of HRS.[149] However, the development of renal failure after this complication is not very common in patients with cirrhosis (approximately 10%) and occurs mainly in patients with hypovolemic shock, in most cases associated with ischemic hepatitis, which suggests that renal failure in this setting is probably related to the development of acute tubular necrosis (ATN) and not to HRS.[160] Diuretic treatment has also been classically described as a precipitating factor of HRS, but there is no clear evidence to support such a relationship.

There are several predictive factors in patients with cirrhosis and ascites associated with a greater risk of developing HRS.[23] For the most part these are related to circulatory and renal function and include severe urinary sodium retention, spontaneous dilutional hyponatremia, and low mean arterial blood pressure (<80 mm Hg). Interestingly, neither the degree of liver failure, as assessed by classic parameters of liver function (serum bilirubin, albumin, and prothrombin time) or the Child-Pugh classification, correlate with the risk of developing HRS.[23]

Diagnosis

The diagnosis of HRS is currently based on several diagnostic criteria (Table 68.2).[124] The minimum level of serum creatinine required for the diagnosis of HRS is 1.5 mg per dL (133 μmol per L). Patients with cirrhosis with a serum creatinine above 1.5 mg per dL usually have a GFR below 30 mL per minute.[125] In patients receiving diuretics, serum creatinine measurement should be repeated after diuretic withdrawal because, in some patients, serum creatinine may decrease after diuretic withdrawal.

Because no specific laboratory tests are available for the diagnosis of HRS and patients with advanced cirrhosis may develop renal failure of other etiologies (prerenal failure due to volume depletion, ATN, drug-induced nephrotoxicity, and glomerulonephritis in patients with hepatitis B or C), the most important step in the diagnosis of HRS is to rule out renal failure secondary to volume depletion or parenchymal diseases.[122,124,161] Gastrointestinal fluid losses, due to vomiting or diarrhea, or renal fluid losses, due to excessive diuresis, should be sought in all patients with cirrhosis presenting with renal failure. If renal failure is secondary to volume depletion, renal function improves rapidly after volume repletion (i.e., with intravenous saline or albumin) and treatment of the precipitating factor. Shock is another common condition in patients with cirrhosis that may lead to renal failure due to ATN. Although hypovolemic shock related with gastrointestinal bleeding is easily recognized, the presence of septic shock may be more difficult to diagnose because of the paucity of symptoms of bacterial infections in some patients with cirrhosis. Moreover, arterial hypotension due to the infection may be erroneously attributed to the underlying liver disease. In some patients with septic shock oliguria is the first sign of infection. These patients may be misdiagnosed as having HRS if signs of infection (cell blood count, examination of ascitic fluid) are not intentionally examined. On the other hand, as discussed before, patients with cirrhosis and spontaneous bacterial peritonitis may develop HRS during the course of the infection.[119,120] Renal failure in these patients may either improve with the antibiotic therapy or persist or progress, even after the resolution of the infection has been achieved. The administration of NSAIDs is another common cause of acute renal failure in patients with cirrhosis and ascites, which is clinically indistinguishable from HRS.[81,162,163] In hospitalized patients with renal failure, the administration of NSAIDs accounts for approximately 7% of all cases with renal failure.[145] Therefore, treatment with these drugs should always be ruled out

before the diagnosis of HRS is made. Studies in patients with cirrhosis and ascites indicate that drugs that inhibit selectively the cyclooxygenase 2 enzyme (COX-2) do not cause renal failure, at least when administered for a short period of time.[164,165] However, studies with longer treatment duration should be performed before these drugs can be confirmed as safe for patients with cirrhosis and ascites. Patients with cirrhosis are also at high risk of developing renal failure due to ATN when treated with aminoglycosides.[162,166,167] Because of this high risk of nephrotoxicity and the existence of other effective antibiotics (e.g., third-generation cephalosporins) treatment with aminoglycosides should be avoided in patients with chronic liver disease. Finally, patients with cirrhosis due to hepatitis B and C may also develop renal failure due to glomerulonephritis.[168–170] In these cases, proteinuria and/or hematuria are almost constant and provide a clue for the diagnosis, which may be confirmed by renal biopsy in selected cases.[171]

FACTORS INVOLVED IN FUNCTIONAL RENAL ABNORMALITIES IN CIRRHOSIS

Circulatory Abnormalities

Hepatic and Splanchnic Circulation

The existence of cirrhosis causes marked structural abnormalities in the liver that result in severe disturbance of intrahepatic circulation causing increased resistance to portal flow and subsequent hypertension in the portal venous system.[172] Progressive collagen deposition and formation of nodules alter the normal vascular architecture of the liver. Moreover, selective deposition of collagen in the space of Disse, the space between sinusoidal cells and hepatocytes, may constrict the sinusoids, resulting in further mechanical obstruction to flow.[173,174] In addition to this passive resistance to portal flow there is an active component of intrahepatic resistance, which is due to the contraction of hepatic stellate cells (myofibroblastlike cells) present in sinusoids and terminal hepatic venules[175–177] and low levels of intrahepatic vasodilators. The contraction of these cells is affected by endogenous vasoconstrictors and can be modulated by vasodilators and drugs that antagonize the vasoconstrictor factors.[178–180] Moreover, there is a strong body of evidence indicating that despite the overproduction of the vasodilator nitric oxide (NO) in the splanchnic and systemic circulation in cirrhosis, there is a reduced production of NO in the intrahepatic circulation of cirrhotic livers that contributes to the increased intrahepatic resistance characteristic of portal hypertension.[181–183] There is also evidence that besides the role of fibrosis and vasoactive factors, increased hepatic neoangiogenesis and inflammation can play a role in the pathogenesis of increased intrahepatic resistance in experimental cirrhosis.[184]

Portal hypertension induces profound changes in the splanchnic circulation.[185–188] Classically, portal hypertension was considered to cause only changes in the venous side of the splanchnic circulation. However, studies in experimental animals indicate that portal hypertension also causes marked changes in the arterial side of the splanchnic vascular bed. In the venous side, the main changes consist of increased pressure and formation of portocollateral circulation, which causes the shunting of blood from the portal venous system to the systemic circulation. In the arterial side, there is marked arterial vasodilation which increases portal venous inflow.[185–189] This high portal venous inflow plays an important role in the increased pressure in the portal circulation and may explain, at least in part, why portal pressure remains increased despite the development of collateral circulation. This arteriolar vasodilation is also responsible for marked changes in splanchnic microcirculation that may predispose to increased filtration of fluid. It has been shown that chronic portal hypertension causes a much greater increase in intestinal capillary pressure and lymph flow than does an acute increase in portal pressure of the same magnitude.[190,191] This is probably due to a loss of the normal autoregulatory mechanism of the splanchnic microcirculation. The acute elevation of venous pressure in the intestine elicits a strong myogenic response, which leads to a reduction in blood flow. This phenomenon is thought to be a homeostatic response to protect the intestine against edema formation. This protective mechanism is not operative in chronic portal hypertension and arteriolar resistance is reduced and not increased.[191,192] The resultant increases in capillary pressure and filtration may be important factors in the formation of ascites in cirrhosis. The mechanism(s) by which portal hypertension induces splanchnic arteriolar vasodilation is not completely understood although a number of vasoactive mediators have been proposed (and will be discussed subsequently).[185]

Several lines of evidence indicate that portal hypertension is a major factor in the pathogenesis of ascites. First, patients with early cirrhosis without portal hypertension do not develop ascites or edema. Moreover, a certain level of portal hypertension is required for ascites formation. Ascites rarely develops in patients with portal pressure below 10 mm Hg, as assessed by the difference between wedged and free hepatic venous pressure (normal portal pressure: 5 mm Hg).[193–196] Second, cirrhotic patients treated with surgical portosystemic shunts for the management of bleeding gastroesophageal varices have lower risk of developing ascites than do patients treated with procedures that obliterate gastroesophageal varices but do not affect portal pressure (i.e., sclerotherapy, esophageal band ligation).[197] Finally, reduction of portal pressure with side-to-side or end-to-side portacaval anastomosis or TIPS (placement of a stent between a hepatic vein and the intrahepatic portion of the portal vein using a transjugular approach) is associated with an improvement of ascites, renal function, and suppression of antinatriuretic systems[198,199] in cirrhotic patients with fluid retention. The mechanism(s) by which portal hypertension contributes to renal functional abnormalities and ascites and edema formation is not completely understood, yet three pathogenic mechanisms have been

proposed: (1) alterations in the splanchnic and systemic circulation which result in activation of vasoconstrictor and antinatriuretic systems and subsequent renal sodium and water retention; (2) hepatorenal reflex due to increased hepatic pressure which would cause sodium and water retention; and (3) putative antinatriuretic substances escaping from the splanchnic area through portosystemic collaterals that would have a sodium-retaining effect in the kidney. There is a large body of evidence supporting the first of these three pathogenic mechanisms.

Systemic Circulation

The development of portal hypertension is associated with marked hemodynamic changes not only in the hepatic and splanchnic circulation but also in the systemic circulation. These changes, which have been well characterized in human and experimental cirrhosis, consist of reduced systemic vascular resistance and arterial pressure, increased cardiac index, increased plasma volume, and activation of systemic vasoconstrictor and antinatriuretic factors. These changes in systemic hemodynamics appear before the formation of ascites and are more marked as the disease progresses.[40,188,200–205] The hemodynamic profile of patients with cirrhosis in different stages of the disease is summarized in Table 68.3. The factor that appears to trigger all these hemodynamic changes of cirrhosis is an arterial vasodilation located mainly in the splanchnic circulation.[185–189,205–207] The existence of a splanchnic arterial vasodilation causes an abnormal distribution of blood volume, which results in a reduction of central blood volume (heart, lungs, and aorta) that is sensed by arterial and cardiopulmonary receptors. This central underfilling triggers a neurohormonal response by activating the SNS, RAAS, and arginine vasopressin (AVP). This explains why systemic vasoconstrictor factors are activated despite an increased plasma volume that in normal conditions would suppress the activation of these systems. Investigations in patients with cirrhosis have assessed central blood volume by measuring the mean circulation time of an indicator or by magnetic resonance imaging.[205,208–211] These studies have confirmed that central blood volume is reduced in patients with cirrhosis, particularly in those with ascites and correlates directly with systemic vascular resistance and inversely with portal pressure, indicating that the greater the vasodilation and the pressure in the portal system, the lower the central blood volume. The crucial role played by the reduced central blood volume in the activation of vasoconstrictor systems has been further corroborated by studies showing that improvement of central blood volume by the combination of expansion of plasma volume or head-out water immersion and administration of pressor agents, suppresses the activation of vasoconstrictor systems.[212–215] Whether or not arterial vasodilation occurs also in nonsplanchnic territories is still controversial but most data indicate that the splanchnic circulation accounts for most, if not all, of the reduced arterial resistance in patients with cirrhosis.[185,205,216]

Despite extensive investigation, the mechanism(s) responsible for arterial vasodilation in cirrhosis is not completely understood. Several explanations have been proposed, including opening of arteriovenous fistulas, reduced sensitivity to vasoconstrictors, and increased circulating levels of vasodilator substances.[185,187,207,216–220] This latter mechanism has

68.3 Hemodynamic Profile of Patients with Cirrhosis in Different Stages of Disease

	Preascitic Cirrhosis	Cirrhosis with Ascites	Hepatorenal Syndrome
Cardiac output	Normal or increased	Increased	Normal or reduced
Arterial pressure	Normal	Normal or reduced	Reduced
Systemic vascular resistance	Normal or reduced	Reduced	Markedly reduced
Plasma volume	Normal or increased	Increased	Increased
Portal pressure	Normal or increased	Increased	Increased
Vasoconstrictor systems activity	Normal	Increased[a]	Markedly increased
Renal vascular resistance	Normal	Normal or increased	Markedly increased
Brachial or femoral vascular resistance	Normal or reduced	Normal or increased	Increased
Cerebral vascular resistance	Normal	Increased	Increased

[a]May be normal in 20%–30% of patients.

been the most extensively studied. Increased production of NO, carbon monoxide, glucagon, endocannabinoids, prostaglandins, vasoactive intestinal peptide, adenosine, bile salts, platelet activating factor, substance P, calcitonin gene-related peptide, natriuretic peptides, and adrenomedullin have been proposed as possible factors of the development of splanchnic arterial vasodilation.[185,191,205,216,221–231] At present, most available data, obtained mainly from experimental cirrhosis, indicate that NO is the main mediator of arterial vasodilation in cirrhosis (Table 68.4).[232] NO synthesis from cirrhotic arterial vessels is markedly increased compared to that of normal vascular tissue. This increased NO synthesis appears to be generalized, except for the intrahepatic circulation, but predominates in the splanchnic territory. Among the different isoforms of NO synthase, the constitutive form appears to be the one responsible for the increased NO synthesis. The normalization of NO synthesis in experimental cirrhosis by the administration of inhibitors of NO synthesis is associated with a marked improvement of splanchnic and systemic hemodynamics, suppression of the increased activity of the RAAS and AVP concentration, increased sodium and water excretion, and reduction or disappearance of ascites.[233] So far, only few studies have investigated the effect of acute NO synthesis inhibition in patients with cirrhosis on systemic hemodynamia and/or renal function, with discrepant findings.[234–236] Unfortunately, no study has been reported investigating the effects of a prolonged inhibition of NO synthesis in human cirrhosis.

Neurohumoral Systems

The functional renal abnormalities that occur in cirrhosis are the result of a complex interrelationship between different systems and factors with effects on renal function. The relative contribution of a particular system in the pathogenesis of these abnormalities in cirrhosis has, therefore, been difficult to assess. This section reviews the different systems that may participate in renal dysfunction in cirrhosis. The evidence indicating their role in the pathogenesis of these abnormalities is discussed.

Renin–Angiotensin–Aldosterone System

Of all potential factors involved in pathogenesis of sodium retention in cirrhosis, aldosterone has been the most extensively studied. Plasma aldosterone levels are increased in most cirrhotic patients with ascites and marked sodium retention.[45,117,202,237–243] In ascitic patients with moderate sodium retention plasma aldosterone is either only slightly elevated or normal. It should be pointed out, however, that these "normal" concentrations occur in the presence of an increase in total body sodium of a degree that would suppress aldosterone concentration in normal subjects. Three lines of evidence indicate that aldosterone plays an important role in the pathogenesis of sodium retention in cirrhosis: (1) there is an inverse correlation between urinary sodium excretion and plasma aldosterone levels[45,117,202,237,243,244]; (2) studies in animals with experimental cirrhosis have

68.4 Evidences for a Role of an Increased Vascular Production of Nitric Oxide (NO) in the Pathogenesis of Arterial Vasodilation and Subsequent Sodium and Water Retention in Cirrhosis

Experimental Cirrhosis

1. Reversal of the impaired pressor response to vasoconstrictors of isolated aortic rings or splanchnic vascular preparations by NO synthase inhibition.
2. Enhanced vasodilator response to NO-dependent vasodilators.
3. Increased pressor effect of systemic NO synthase inhibition.
4. Increased NO synthesis in vascular tissue.
5. Normalization of the hyperdynamic circulation, activity of antinatriuretic systems, and sodium and water retention by chronic NO synthase inhibition.
6. Increased expression of NO synthase isoenzymes in vascular tissue.

Human Cirrhosis

1. Correction of the arterial hyporesponsiveness to vasoconstrictors by NO synthase inhibition.
2. Enhanced vasodilatory response to NO-dependent vasodilators.
3. Increased plasma levels of NO and NO metabolites.
4. Increased NO in the exhaled air.
5. Increased NO synthase activity in polymorphonuclear cells and monocytes.

shown the existence of a chronologic relationship between hyperaldosteronism and sodium retention[31]; and (3) the administration of spironolactone, a specific aldosterone antagonist, is able to reverse sodium retention in the great majority of patients with ascites without renal failure.[48,49,245–248] The observation that sodium retention occurs in some cirrhotic patients in the absence of increased plasma aldosterone levels has raised the suggestion that other factors in addition to aldosterone may also contribute.[249] Nevertheless, it has also been suggested that cirrhotic patients may have an increased tubular sensitivity to aldosterone.[45,237] This may explain the natriuretic response to spironolactone in patients with normal aldosterone levels.[49,247] Thus, the possibility exists that aldosterone may participate in renal sodium retention in cirrhosis even in the presence of normal plasma concentrations of the hormone. In addition to aldosterone, increased intrarenal levels of angiotensin II may also contribute to sodium retention in patients with cirrhosis by a direct effect on tubular sodium reabsorption.[250]

The increased plasma aldosterone levels in cirrhotic patients with ascites are due to a stimulation of aldosterone secretion and not to impaired degradation, as the hepatic clearance of aldosterone is normal or only slightly reduced in these patients.[238,249,251] Among the different mechanisms that regulate aldosterone secretion an increased activity of RAAS is the most likely to be responsible for hyperaldosteronism in cirrhosis (Fig. 68.7). In fact, plasma renin activity (PRA), which estimates the activity of the RAAS, is increased in most patients with ascites and correlates closely with plasma aldosterone concentration.[117,202,239,240,252–254] Investigations using pharmacologic agents which interrupt RAAS have provided evidence suggesting that this system is activated as a result of a profound disturbance in systemic hemodynamics. The administration of angiotensin II receptor antagonists or converting-enzyme inhibitors to cirrhotic patients with ascites and increased PRA induces a marked reduction in arterial pressure and systemic vascular resistance, which suggests that the activation of RAAS is a homeostatic response to maintain arterial pressure in these patients.[255–258]

The activation of RAAS is particularly intense in patients with HRS, suggesting a role for angiotensin II in the pathogenesis of renal vasoconstriction in HRS.[259–264] This role is further supported by studies showing that the improvement of renal function in patients with HRS achieved by the administration of the vasopressin analogs ornipressin or terlipressin associated with albumin or the insertion of a TIPS is associated with a marked suppression of the activity of the RAAS.[214,215,265,266] However, because the interruption of RAAS is associated with arterial hypotension in patients with high PRA, the effects of RAAS on renal function independent of those on systemic hemodynamics have not been possible to assess. Although administration of angiotensin II blockers like losartan may induce natriuresis when given at low doses to patients with preascitic cirrhosis,[250] the use of these drugs should be avoided in patients with ascites because of a high risk of hypotension and renal failure.

Sympathetic Nervous System

Numerous studies have presented evidence indicating an increased activity of the SNS in cirrhosis. The plasma concentration of norepinephrine (NE) in the systemic circulation, an index of the activation of the SNS, is increased in most patients with ascites and normal or only slightly elevated in patients without ascites.[260,267–273] This "normal" plasma NE concentration, however, is relatively increased in the presence of plasma volume expansion, which occurs in early cirrhosis. Investigations using titrated NE, to provide a more

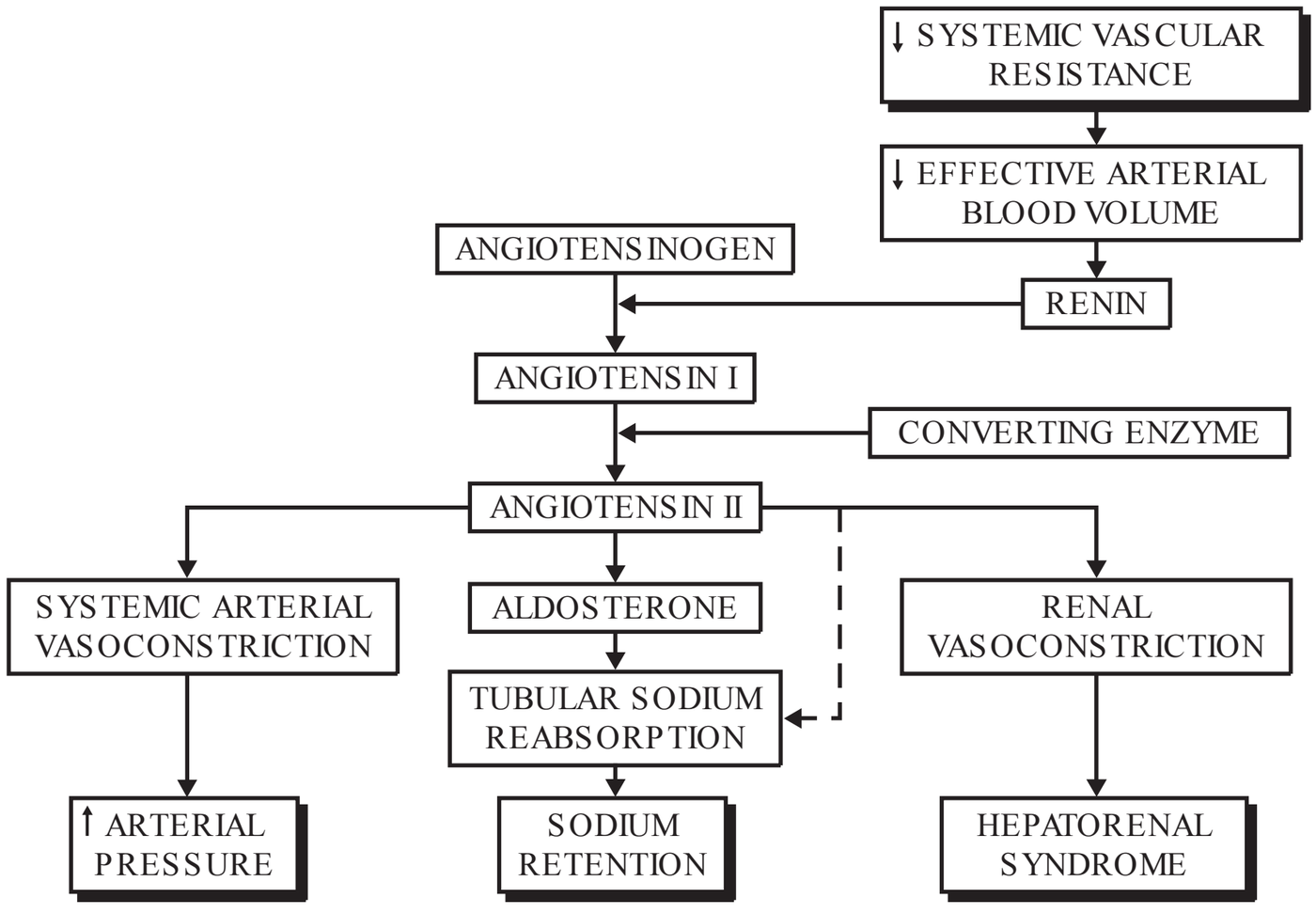

FIGURE 68.7 Proposed mechanism of activation and renal and systemic effects of renin–angiotensin–aldosterone system in cirrhosis with ascites.

accurate assessment of the SNS activity, have confirmed that the high plasma NE levels are due to an increased activity of the SNS and not to an impaired elimination of NE, as the total spillover of NE to plasma is markedly increased in cirrhotic patients with ascites whereas the plasma clearance of NE is normal.[273–278] Measurements of NE release and spillover in specific vascular beds have shown that the activity of the SNS is increased in many vascular territories, including kidneys, splanchnic organs, heart, and muscle and skin, supporting the concept of a generalized activation of the SNS.[275–279] Direct evidence of the overactivity of the SNS in cirrhosis has been provided by measuring the sympathetic nerve discharge rates from a peripheral muscular nerve. Muscular sympathetic nerve activity is markedly increased in patients with ascites and normal in patients without ascites and correlates directly with plasma NE concentration.[280]

Because the SNS has profound effects on renal function,[281] it is reasonable to presume that the increased renal sympathetic nervous activity in cirrhosis may play a role in the pathogenesis of functional renal abnormalities (Fig. 68.8). In fact, evidence suggests that the SNS is involved in sodium and water retention in cirrhosis. The activity of the SNS, either estimated by plasma NE or total NE spillover to plasma or measured from intraneural recordings, correlates inversely with sodium and water retention.[268,275,280] In addition, bilateral renal denervation increases urine volume and sodium excretion in animals with experimental cirrhosis and ascites and restores the renal capacity to eliminate a water load.[282–284] Similarly, anesthetic blockade of the lumbar SNS, a maneuver that reduces the activity of the kidney SNS, improves sodium excretion in patients with cirrhosis and ascites.[285] A study in a limited number of patients with ascites showed that administratation of diuretics together with clonidine to inhibit the sympathetic nervous activity is more effective than diuretics alone.[286] Moreover, the acute inhibition of the renal sympathetic outflow with clonidine in patients with cirrhosis is associated with a reduction in renal vascular resistance and an increase in GFR and filtration fraction, suggesting that the activation of the SNS causes renal vasoconstriction by increasing arterial tone in the afferent arteriole.[278] It has also been shown that the increased sympathetic nervous activity impairs renal blood flow autoregulation in cirrhosis.[287] On the other hand, patients with HRS have significantly higher plasma levels of NE than do patients without renal failure, and arterial and renal venous NE correlate inversely with renal blood flow (RBF), suggesting that the SNS may participate in the renal vasoconstriction observed in patients with HRS.[242,260,287,288] Moreover, the circulating levels of neuropeptide Y, a neurotransmitter with a very potent vasoconstrictor action in the renal circulation released in the setting of a marked activation of the SNS, are increased in patients with HRS but not in those with ascites without renal failure.[289] Finally, it is worth mentioning that a recent study in experimental cirrhosis suggests that the increased activity of the SNS in the splachnic circulation may contribute to bacterial infection in cirrhosis by causing increased bacterial translocation and spreading of gram negative bacteria.[290] Therefore, the SNS has important effects on the circulatory and renal function in cirrhosis.

The cause of the increased activity of the SNS in cirrhosis with ascites is not completely understood. Two major explanations have been proposed: either a baroreceptor-mediated response to a decrease in effective arterial blood volume due to arterial vasodilation[205,273,291] or a hepatorenal reflex resulting from activation of hepatic baroreceptors due to sinusoidal hypertension.[292–294] The first explanation seems more likely since the estimated central blood volume (i.e., the blood volume in the heart cavities, lungs, and central arterial tree) is reduced in cirrhotic patients and correlates inversely with SNS activity.[208,209] Furthermore, the activity of the SNS can be suppressed by maneuvers that increase effective arterial blood volume, such as the administration of vasopressin analogs and albumin, and the insertion of a peritoneovenous shunt or transjugular intrahepatic portosystemic shunt (TIPS).[214,215,265,274,295]

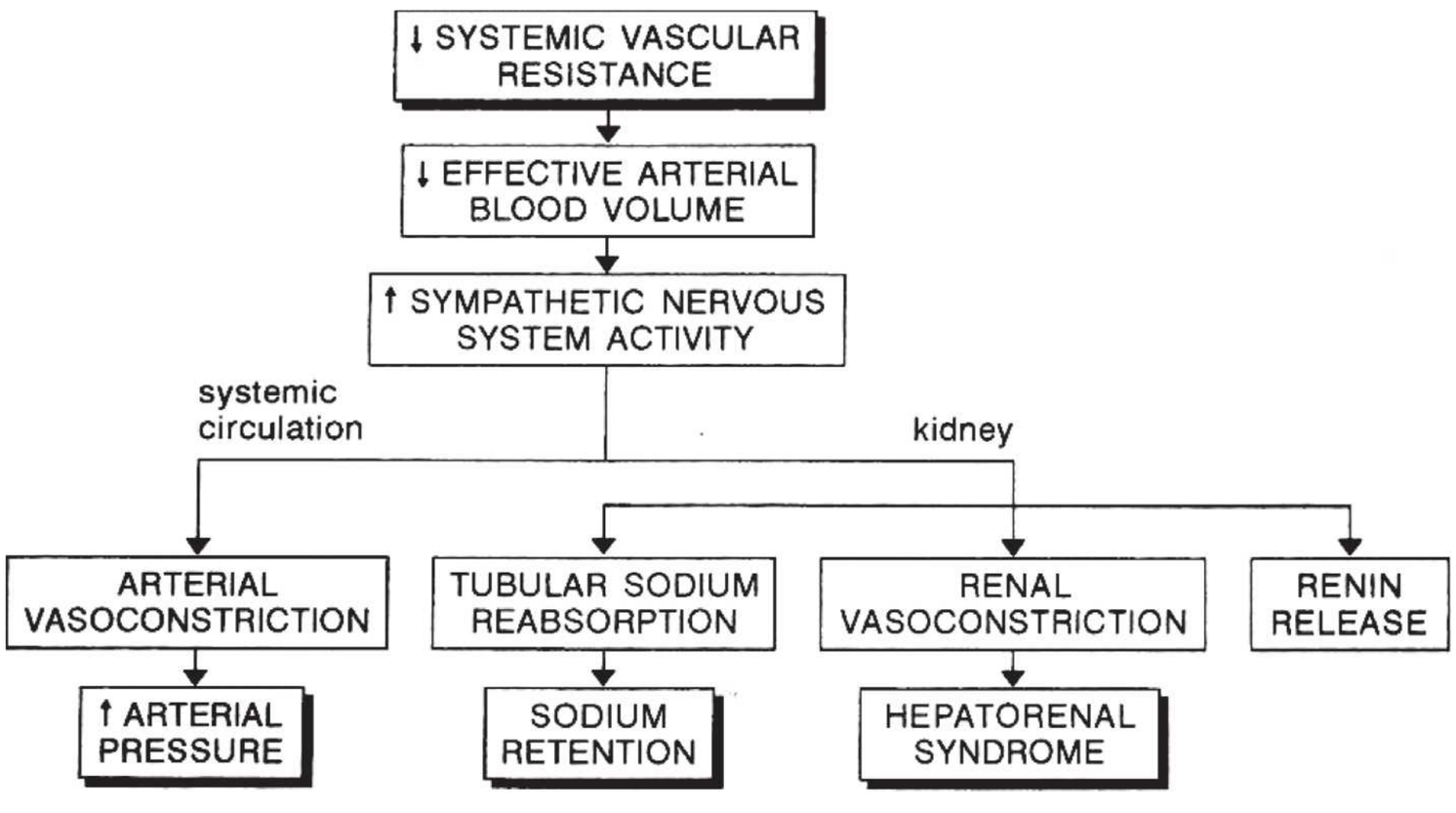

FIGURE 68.8 Proposed mechanism of activation and renal and systemic effects of sympathetic nervous system in cirrhosis with ascites.

Prostaglandins and Other Eicosanoids

Prostaglandins are known to have a protective effect on renal circulation in pathophysiologic situations associated with increased activity of renal vasoconstrictor systems.[296] According to this formulation, prostaglandins appear to play a key role in the homeostasis of renal circulation and water excretion in cirrhotic patients with ascites. The urinary excretion of prostaglandin E2 (PGE2) and 6-keto-prostaglandin F1α, which estimate the renal synthesis of PGE2 and PGI2, respectively, are increased in patients with cirrhosis and ascites without renal failure as compared to healthy subjects and patients without ascites.[118,259,260,297,298] Further evidence supporting a role for renal prostaglandins in the maintenance of RBF and GFR in cirrhosis with ascites derive from studies using NSAIDs to inhibit prostaglandin synthesis. The administration of NSAIDs, even in single doses, to cirrhotic patients with ascites causes a profound decrease in RBF and GFR in patients who have a marked activation of vasoconstrictor systems but has little or no effect in patients without activation of these systems.[81,163,260,298,299] An increased renal production of PGE2 also contributes to the maintenance of solute-free water excretion in nonazotemic cirrhotic patients with ascites as the inhibition of prostaglandin synthesis by NSAIDs in these patients impairs solute-free water excretion independently of changes in renal hemodynamics.[82]

The relationship between the renal prostaglandin system and HRS is controversial. Several studies have reported that patients with HRS have lower urinary excretion of PGE2 and 6-keto-PGF1α than do patients with ascites without renal failure, which suggests that a reduced renal synthesis of vasodilator prostaglandins may play a role in the pathogenesis of HRS.[118,259,300–302] The finding of low renal content of PGH2 synthase (medullary cyclooxygenase) in patients with HRS is also consistent with this hypothesis.[303] Other studies, however, did not find reduced urinary excretion of vasodilator prostaglandins in patients with HRS.[304,305] Nevertheless, "normal" synthesis of prostaglandins may be low relative to the increased activity of vasoconstrictor systems in cirrhosis. Because patients with HRS have the greatest activation of renal vasoconstrictor systems, an imbalance between vasoconstrictor systems and the renal production of vasodilator prostaglandins has been proposed to explain the marked reduction of RBF and GFR that occurs in this condition.[259] It has also been suggested that HRS could be the consequence of an imbalance between the renal synthesis of vasodilator and vasoconstrictor prostaglandins based on the observation of reduced urinary excretion of PGE2 and 6-keto-PGF1α and increased urinary excretion of TXB2 in patients with HRS.[302–305] These findings, however, were not confirmed by subsequent investigations.[118,301,306] Moreover, the administration of inhibitors of TXA2 synthesis does not improve renal function in these patients.[307]

Prostaglandin synthesis in cirrhosis is also increased in extrarenal organs. Patients with cirrhosis have high urinary excretion of 2-3–dinor-6-keto-PGF1α, a metabolite of PGI2 considered to be an index of systemic PGI2 production.[221,304] As prostaglandins are potent vasodilators in the systemic circulation these observations raise the possibility that an increased prostaglandin synthesis may contribute to arterial vasodilation in cirrhosis. This suggestion is consistent with the observation that the NSAID indomethacin increases systemic vascular resistance and ameliorates the hyperdynamic circulation in cirrhotic patients.[308]

Studies in rats with experimental cirrhosis and ascites have investigated the metabolic pathways leading to the increased synthesis of prostaglandins. Increased activity and expression of cytosolic phospholipase A2 (cPLA2) (the first enzyme of the metabolic cascade of eicosanoid synthesis) and cyclooxygenase-1 have been found in arterial and renal tissue of rats with cirrhosis and ascites compared with normal rats.[309–311]

The possible role of eicosanoids other than prostaglandins in the pathogenesis of functional renal abnormalities in cirrhosis is not completely understood. The urinary excretion of leukotriene E4 and N-acetyl-leukotriene E4, compounds with a vasoconstrictor effect in the renal circulation, is increased in cirrhotic patients with HRS as compared to healthy subjects and patients without ascites, suggesting that leukotrienes may participate in the pathogenesis of this syndrome.[312,313] Likewise, the urinary excretion of the vasoconstrictor compound 20-hydroxyeicosatetraenoic acid (20-HETE) is also increased in patients with cirrhosis as compared to healthy subjects.[314]

Arginine Vasopressin

Studies in humans and experimental animals have provided several pieces of evidence indicating that AVP plays a key role in the pathogenesis of water retention in cirrhosis with ascites. These include: (1) plasma AVP levels are often increased in cirrhotic patients and correlate closely with the reduction in solute-free water excretion, patients with higher plasma AVP levels being those with the more severe impairment in water metabolism[82,85–87,315–318]; (2) a chronologic relationship between AVP hypersecretion and impairment in water excretion can be found in rats with cirrhosis and ascites[319,320]; (3) Brattleboro rats (rats with a congenital deficiency of AVP) with cirrhosis do not develop an impairment in water excretion[321]; (4) kidneys from cirrhotic rats with ascites show increased gene expression or redistribution to plasma membrane of aquaporin-2, the AVP-regulated water channel[322,323]; (5) the administration of specific antagonists of the tubular effect of AVP (V2 antagonists) improve the renal ability to excrete solute-free water in animal as well as in human cirrhosis[88–95,324]. Nevertheless, factors other than AVP play a role in the pathogenesis of solute-free water retention because in a significant proportion of patients solute-free water excretion and serum sodium concentration do not improve despite the administration of vaptans.[93–95]

The increased plasma AVP concentrations in cirrhosis are due to an increased hypothalamic synthesis and not to a reduced systemic clearance of the peptide.[86,325–327] The hemodynamic changes occuring in cirrhosis (low arterial

blood pressure, high cardiac output, and low total systemic vascular resistance) cause arterial hypotension which unloads the high pressure baroreceptors and stimulates a nonosmotic release of AVP with the subsequent increase in water reabsorption.[82,315] The mechanism of this nonosmotic hypersecretion is hemodynamic, as plasma AVP levels correlate with PRA and plasma NE concentration[82,268] and are suppressed by maneuvers that increase effective arterial blood volume, such as head-out water immersion or peritoneovenous shunting in human cirrhosis[316,328] or inhibition of NO synthesis in experimental animal cirrhosis.[233] This hemodynamic mechanism of AVP release in cirrhosis is also supported by the observation that the administration of a specific antagonist of the vascular effect of AVP (V1 antagonist) induces arterial hypotension in rats with experimental cirrhosis and ascites and water retention but not in control rats.[329] This finding suggests that AVP hypersecretion in cirrhosis contributes not only to water retention but also to the maintenance of arterial pressure (Fig. 68.9).

Natriuretic Peptides

The natriuretic hormones, represented by the atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are increased in patients with cirrhosis and ascites.[330–339] In patients without ascites, plasma ANP levels may be either normal or increased. In patients with ascites, the high plasma levels of ANP are due to increased cardiac secretion of the peptide and not reduced hepatic or systemic catabolism, as cardiac production of ANP is increased in cirrhotic patients with ascites but splanchnic and peripheral extraction are normal.[330,340] Consistent with these observations is the finding of increased messenger RNA expression for ANP in ventricles from cirrhotic rats with ascites.[341] In contrast to other diseases showing increased cardiac ANP secretion, in cirrhosis with ascites this increased secretion occurs in the presence of normal atrial pressure and reduced estimated central blood volume.[208,330] The mechanism(s) responsible for this increased cardiac secretion of ANP is not known. The existence of increased plasma levels of ANP in cirrhosis with ascites sufficient to have a natriuretic effect in healthy subjects, together with the presence of renal sodium retention, indicates a renal resistance to the effects of ANP. This renal resistance has been confirmed in studies in human and experimental cirrhosis in which pharmacologic doses of natriuretic peptides (ANP or BNP) were administered.[342–347] In these investigations patients with activation of antinatriuretic systems (RAAS and SNS) had a blunted or no natriuretic response after ANP infusion. This blunted response can be reversed by maneuvers that increase distal sodium delivery in human cirrhosis or by bilateral renal denervation in experimental cirrhosis, suggesting that the renal resistance to ANP in cirrhosis is related to the increased activity of antinatriuretic systems.[283,348] Limited information exists on other peptides of the natriuretic peptide family. As with ANP, the plasma concentration of BNP is increased in cirrhotic patients with ascites as compared to healthy subjects.[349] In contrast to ANP and BNP levels, the plasma levels of C-natriuretic peptide are decreased in cirrhosis, whereas the urinary excretion is increased. The plasma levels correlate inversely with arterial compliance and decreased vascular resistance, which suggests a compensatory downregulation of this peptide.[350,351] Finally, the urinary excretion of urodilatin, a member of the natriuretic peptide family exclusively synthesized in the kidney, which probably reflects the renal production of the peptide, is normal in patients with cirrhosis and ascites.[352]

The role of natriuretic peptides in cirrhosis is not entirely clear. Because most of ANP and BNP have vasodilator properties, a role in the pathogenesis of arterial vasodilation in cirrhosis has been proposed but not proved. By contrast, data from experimental studies suggest that they play an important role in the maintenance of renal perfusion and modulation of RAAS activity, as the selective blockade of the natriuretic peptide A and B receptors causes renal vasoconstriction and increased PRA and aldosterone levels in experimental cirrhosis.[353] It could be speculated, therefore, that the cardiac synthesis of ANP and BNP is increased in an attempt to maintain renal perfusion within normal levels and limit the activation of the RAAS. Although the mechanism(s) leading to this increased synthesis of natriuretic peptides remains unknown, the hypothesis has been raised that BNP in cirrhosis may reflect the existence of a cirrhotic myocardiopathy,[339,354,355] a condition characterized by impaired myocardial function in the context of cirrhosis.[356]

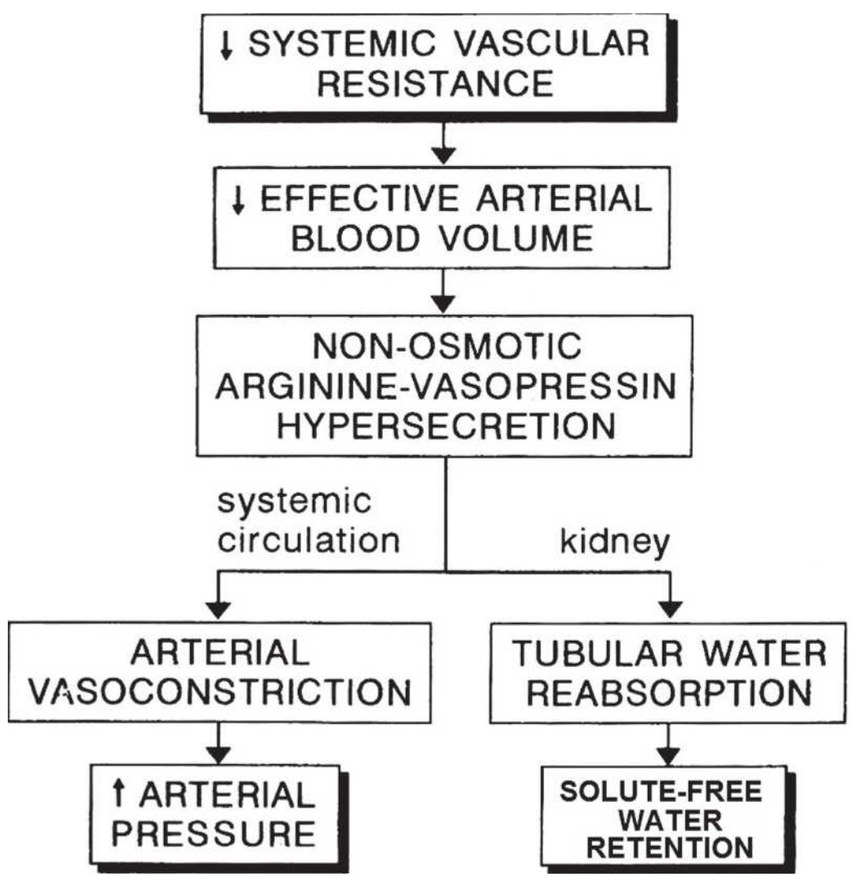

FIGURE 68.9 Proposed mechanism of hypersecretion and renal and systemic effects of arginine vasopressin in cirrhosis with ascites.

Endothelins

Endothelins comprise three homologous peptides (ET-1, ET-2, and ET-3) with a very potent vasoconstrictor action.[357]

Increased plasma levels of ET-1 and ET-3 have been found in patients with cirrhosis and ascites and in patients without ascites, albeit to a lesser extent.[358–365] The increased plasma levels of ET-1 found in cirrhosis derive either from an increased production in the splanchnic circulation and/or an increased intrahepatic production. Increased levels of ET-1 and its precursor Big-ET-1 have been found in plasma samples obtained from the portal and hepatic veins of patients with cirrhosis.[366] Moreover, increased levels of ET-1 have been demonstrated in hepatic tissue in human and experimental cirrhosis.[367–370] In human cirrhosis, the increased hepatic ET-1 levels correlate with portal hypertension and the severity of ascites and liver failure.[369,370] As opposed to other vasoconstrictor factors (e.g., angiotensin II or norepinephrine), the activity of which is increased in cirrhosis, it is unlikely that hyperendothelinemia in cirrhosis is a compensatory mechanism triggered by effective arterial hypovolemia. Endothelin levels are not suppressed by maneuvers that improve circulatory function, such as plasma volume expansion with or without concomitant administration of splanchnic vasoconstrictors.[214,361,363] A role for endotoxemia in the increased endothelin levels in cirrhosis has also been proposed[358] but plasma endothelin concentration does not parallel endotoxin levels in cirrhotic patients.[363]

The role that these increased circulating ET-1 levels play in the pathogenesis of abnormalities in renal, systemic, and hepatic circulation in cirrhosis is not known. A role for ET-1 in the pathogenesis of renal vasoconstriction in HRS has been proposed on the basis of markedly increased plasma endothelin levels in patients with HRS as compared with patients with ascites without HRS[146,360] and improvement of renal function after the administration of a selective antagonist of ET_A receptors in a small group of patients.[371] Paradoxically, the administration of tezosentan, a nonselective endothelin receptor antagonist to patients with cirrhosis and type 2 HRS, was associated with a deterioration in renal function, which suggests that at least in advanced cirrhosis endothelin contributes to maintenance of renal function and not to the pathogenesis of HRS.[372] A contribution of the increased endothelin levels to the maintenance of arterial pressure in cirrhosis is unlikely because most studies in experimental models of cirrhosis and portal hypertension have found no changes in arterial pressure after chronic endothelin receptor blockade.[369,373–375] Because of the well-known vasoconstrictor effect of ET-1 in the intrahepatic circulation when infused through the portal vein, ET-1 has been postulated as a mediator of the increased intrahepatic resistance characteristic of diseases associated with portal hypertension. The results of these studies are conflicting and the role of endothelin in these abnormalities is unclear.[376] Finally, recent studies suggest an important role for ET-1 in hepatic fibrogenesis by increasing collagen synthesis from hepatic stellate cells.[368] In support of this hypothesis, a marked reduction in liver fibrosis has been demonstrated in bile duct-ligated rats chronically treated with an oral ET_A receptor antagonist.[374] Despite the great efforts aimed at elucidating the role of ET in cirrhosis its relevance in circulatory homeostasis in cirrhosis is still unclear. Further studies are needed to understand and characterize the role of ET in advanced cirrhosis.

Nitric Oxide

In addition to its effects in the regulation of systemic hemodynamics and arterial pressure, as described before NO also participates in the regulation of renal function.[377] Constitutive NO synthase has been found in several cell types in the kidney, including endothelial cells, mesangial cells, and some tubular epithelial cells. Inducible NO synthase has also been demonstrated in mesangial cells and epithelial cells. Under normal circumstances, NO participates in the regulation of glomerular microcirculation by modulating arteriolar tone and mesangial cell contractility. Moreover, NO facilitates natriuresis in response to changes in renal perfusion pressure, and regulates renin release.[377]

Three lines of evidence indicate that the renal production of NO is increased in experimental cirrhosis. First, kidneys from cirrhotic rats show enhanced endothelium-dependent vasodilator response as compared to control animals.[378] Second, infusion of L-arginine, the precursor of NO, causes a greater increase in renal perfusion in cirrhotic rats as compared to control rats.[379] Finally, increased expression of NO synthase in kidney tissue from cirrhotic rats has been found in two studies.[379,380] However, both studies showed discrepant findings with respect to the NO synthase isoform responsible for the increased NO synthesis.

The inhibition of NO synthesis in rats with cirrhosis and ascites does not result in renal hypoperfusion because of a marked rise in prostaglandin synthesis.[381] However, the simultaneous inhibition of NO and prostaglandin synthesis in experimental cirrhosis results in a marked renal vasoconstriction suggesting that NO probably interacts with prostaglandins to maintain renal hemodynamics.[382]

Endocannabinoid System

The endocannabinoid system appears to play a role in the pathogenesis of hemodynamic abnormalities (cardiovascular dysfunction and portal hypertension) in cirrhosis.[383–387] The endocannabinoid system consists of CB receptors and circulating endocannabinoids. Two G protein–coupled types of receptors (CB1 and CB2) have been identified in several tissues including the cardiovascular system and the liver.[383,384] In patients with cirrhosis, CB1 receptors in the vascular and cardiac tissue are activated by two circulating endogenous endocannabinoids; arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG).[383,384] The source of the anandamide and 2-AG are lipopolysaccharide activated macrophages.[385,386] Levels of anandamide are elevated in circulating macrophages of cirrhotic rats; in fact, injection of these macrophages into normal rats causes hypotension.[387] The role of the cannabinoid system in the hemodynamic alterations of cirrhosis is also supported by the fact that hypotension in cirrhotic rats is reversible by CB1

blockade, an effect that also reduces increased portal pressure and mesenteric blood flow.[387,388] In cirrhosis, underlying endotoxemia which activates macrophages is thought to be the principal source of endocannabinoid production by means of a lipopolysaccharide that leads to the increased levels of anandamide.[383,384] In addition, in cirrhosis there is increased expression of CB1 in vascular endothelial cells[387] and mesenteric arteries[389,390] which in turn augment the vasodilatory effects of anandamide.[388–391] In patients with cirrhosis peripheral anandamide (but not 2-AG) is increased in advanced stages; however, hepatic vein and liver tissue levels of anandamide are not increased suggesting that the liver is not the source of endogenous cannabinoids.[392,393] Experiments on isolated mesenteric resistance arteries of rats with cirrhosis and ascites demonstrate that anandamide exerts a greater vasodilatory effect when compared to control rats.[389] Interestingly, this response is not altered by L-NAME (an inhibitor of nitric oxide synthase), indicating that the effect of anadamide in resistance arteries of cirrhotic rats is perhaps independent of the functional integrity of endothelium.[389] Moreover, the effect of anandamide is selective in the mesenteric vessels because there are no changes in vascular reactivity of distal femoral arteries of cirrhotic and control rats.[389] In cirrhotic rats, rimonabant (an anandamide antagonist) caused a significant reduction in the volume and formation of ascites.[394] The antagonist also significantly improved sodium balance after 2 weeks in cirrhotic animals.[394] The role of endocannabinoids in the pathogenesis of cardiac dysfunction in cirrhosis which is mainly due to a decrease in contractility and β-adrenergic hyposensitivity is thought to be due to activation of cardiac CB1 receptors.[356,395] Studies in animals with cirrhosis have demonstrated that a decrease in baseline cardiac contractility normalizes with the administration of an endocannabinoid antagonist.[396] Although these findings suggest a potential role of endocannabinoid blockade in the treatment of complications related to portal hypertension, there are no studies evaluating the effects of rimonabant in human cirrhosis because the drug was withdrawn from the market due to significant side effects in relation to depression and anxiety.

Heme-oxygenase System

Another potential mediator in the pathogenesis of hemodynamic abnormalities in cirrhosis is the heme-oxygenase (HO) system.[397] The main byproducts of HO are carbon monoxide (CO) and biliverdin which is converted to bilirubin. There are three isoforms of HO: inducible (HO-1), constitutive (HO-2), and a secondary constitutive form with minimal activity (HO-3).[397] Several experimental and human studies indicate that CO contributes to the splanchnic vasodilation that occurs in cirrhosis and also plays a role in the regulation of hepatic vascular tone.[398–401] The mechanism by which CO causes relaxation of smooth muscle cells is by activation of soluble guanylyl cyclase which leads to an increased production of cGMP thereby opening large-conductance calcium activated channels.[397] Levels of carboxy-hemoglobin and CO in the exhaled air in patients with compensated and decompensated cirrhosis are increased and both parameters are higher in those with ascites and correlate with the Child–Pugh score but not with arterial pressure or plasma renin activity.[229] In addition, both parameters increase even more in patients with spontaneous bacterial peritonitis compared to those without infection.[229] Similar data indicate plasma-free CO is elevated in patients with cirrhosis compared with healthy controls.[229] In addition increased plasma free CO in cirrhosis without ascites correlates with plasma cGMP and is associated with impaired hemodynamics (high cardiac index and lower arterial pressure) more so than in those with ascites. Finally HO-1 activity is increased in polymorphonuclear cells of patients with cirrhosis indicating that high levels likely correlate with systemic endotoxemia. These data provide evidence that the HO pathway is activated in cirrhosis, and suggest that it may play a role in the pathogenesis of the hyperdynamic circulation of cirrhosis.[229,400] The effect of the HO system in the kidney is less studied; however, it is known that there is reduced renal expression of HO-1 in experimental cirrhosis.[402,403] One study that evaluated the renal effects of CO in cirrhotic rats indicates that impaired HO-1 expression promotes renal vasoconstriction and that chronic HO induction normalizes the sensitivity to vasoconstrictors (phenylephrine) and promotes sodium excretion.[404] Taken together, all these findings suggest that the HO system plays a role in the development of splanchnic arterial vasodilation and renal abnormalities in cirrhosis.

THE THEORIES OF ASCITES FORMATION IN CIRRHOSIS

Ascites as Primary Edema: The Overflow Theory

The existence of a primary renal sodium retention in cirrhosis with ascites was proposed in an attempt to explain the paradox of coexistence of sodium retention and increased plasma volume in patients with ascites.[405,406] According to this theory, the expansion of plasma volume would result in increased cardiac index and reduced systemic vascular resistance as adaptive circulatory mechanisms to the excess of intravascular volume. The existence of portal hypertension and circulating hypervolemia would lead to "overflow" of fluid within the peritoneal cavity. It has been proposed that the primary signal for sodium retention would arise from the liver, either as a consequence of intrahepatic portal hypertension, by means of hepatic low pressure baroreceptors, or liver failure, by means of decreased hepatic clearance of a sodium-retaining factor or reduced hepatic synthesis of a natriuretic factor.[292–294,407–411] However, the hemodynamic pattern of cirrhotic patients with ascites does not correspond with that predicted by the overflow theory because the arterial vascular compartment is not overfilled, as arterial pressure is low in most patients despite the increased plasma volume and cardiac index (Table 68.3). Moreover, there is

marked overactivity of vasoconstrictor mechanisms, which would be suppressed if there were overfilling in the systemic circulation.[205,216]

Because of the increasing evidence against the existence of vascular overfilling in cirrhosis with ascites, the overflow theory has been redefined to exclusively explain changes that occur in the preascitic stage of cirrhosis. Proponents of this theory suggest that in the preascitic stage of cirrhosis subtle sodium retention leading to plasma volume expansion would have two components: one related to the circulatory changes occurring in the splanchnic circulation aimed at maintaining the effective arterial blood volume (EABV) and one related to the existence of intrahepatic portal hypertension.[412,413] Recent studies in patients with cirrhosis without ascites indicate that the existence of arterial vasodilation is of crucial importance in the development of sodium retention and ascites formation. In fact, preascitic cirrhotic patients with sinusoidal portal hypertension treated with mineralocorticoids do not show mineralocorticoid escape and develop ascites only when marked arterial vasodilation is present.[414] Moreover, pharmacologically induced vasodilation in preascitic cirrhotic patients by means of the administration of prazosin, an α-adrenergic blocker, is associated with the development of ascites and/or edema in a significant proportion of patients.[415] It is important to note that the development of sodium retention in these two studies was neither related to the degree of portal hypertension nor to the intensity of liver failure. In fact, in patients receiving prazosin, sodium retention occurred despite a reduction of portal pressure and improvement of liver perfusion.

Ascites as Secondary Edema: From the Traditional Theory to the Arterial Vasodilation Theory

The traditional concept of ascites formation in cirrhosis[416,417] considers that the key event in ascites formation is a "backward" increase in hydrostatic pressure in the hepatic and splanchnic circulation due to the increased resistance to portal flow. This would cause a disruption of the Starling equilibrium and an increased filtration of fluid into the interstitial space. Initially, this capillary hyperfiltration is compensated by an increased lymphatic flow which returns the fluid to the systemic circulation via the thoracic duct. However, as portal hypertension increases, the lymphatic system is not able to drain the excess of interstitial fluid which then accumulates in the peritoneal cavity as ascites. Loss of fluid from the intravascular compartment results in true hypovolemia which is then sensed by cardiopulmonary and arterial receptors resulting in a compensatory renal sodium retention. The retained fluid cannot adequately fill the intravascular compartment and suppress the sodium-retaining signals to the kidney because fluid is continuously leaking in the peritoneal cavity, thus creating a vicious cycle. In cases with extreme hypovolemia, renal vasoconstriction develops, leading to HRS. This hypothesis is similar to the "backward" theory of edema formation in heart failure, which suggests that sodium retention and formation of edema is secondary to the disruption of the Starling equilibrium in the microcirculation due to the backward increase in capillary hydrostatic pressure.[418] The "classic underfilling" theory of ascites formation, however, does not correspond with the systemic hemodynamic abnormalities associated with cirrhosis (Table 68.3). If this theory were correct, changes in systemic circulation would consist of reduced plasma volume and cardiac index and increased systemic vascular resistance. However, findings in patients with cirrhosis and ascites are exactly the opposite, with increased plasma volume and cardiac index and reduced systemic vascular resistance.[204,205,216]

These traditional backward theories of edema formation in cirrhosis and heart failure have been substituted by new theories that fit more precisely with the modern concepts of regulation of extracellular fluid volume, which consider that a reduction in effective arterial blood volume (EABV) is the main determinant of sodium retention in major edematous states.[419–421] Arterial vasodilation would be the triggering factor for sodium retention in cirrhosis, whereas a reduction in cardiac output would be the triggering factor in heart failure. The "arterial vasodilation" theory considers that the reduction in EABV in cirrhosis with ascites is not due to true hypovolemia, as proposed by the "traditional" theory, but rather to a disproportionate enlargement of the arterial tree secondary to arterial vasodilation (Fig. 68.10).[216,422,423] According to this theory, portal hypertension is the initial event with resultant splanchnic arteriolar vasodilation causing underfilling of the arterial circulation. The arterial receptors then sense the arterial underfilling and stimulate the SNS and the RAAS and cause nonosmotic hypersecretion of AVP. Renal sodium and water retention are the final consequence of this compensatory response to a reduction in EABV. In early stages of cirrhosis, when splanchnic arteriolar vasodilation is moderate and the lymphatic system is able to return the increased lymph production to the systemic circulation, the EABV is preserved by transient periods of sodium retention. The fluid retained by the kidneys increases plasma volume and suppresses the signals stimulating the antinatriuretic systems and sodium retention terminates. Therefore, no ascites or edema is formed at this stage and the relationship between EABV and extracellular fluid volume is maintained. As liver disease progresses, splanchnic arterial vasodilation increases, thus resulting in a more intense arterial underfilling and more marked sodium and water retention. At this time, the EABV can no longer be maintained by the increased plasma volume, probably because the retained fluid leaks from the splanchnic circulation into the peritoneal cavity as ascites and/or from the systemic circulation to the interstitial tissue as edema. A persistent stimulation of vasoconstrictor systems occurs in an attempt to maintain EABV. The activation of these systems perpetuates renal sodium and water retention, which accumulates as ascites. The correlation between EABV and extracellular fluid volume is no longer maintained as EABV remains contracted despite

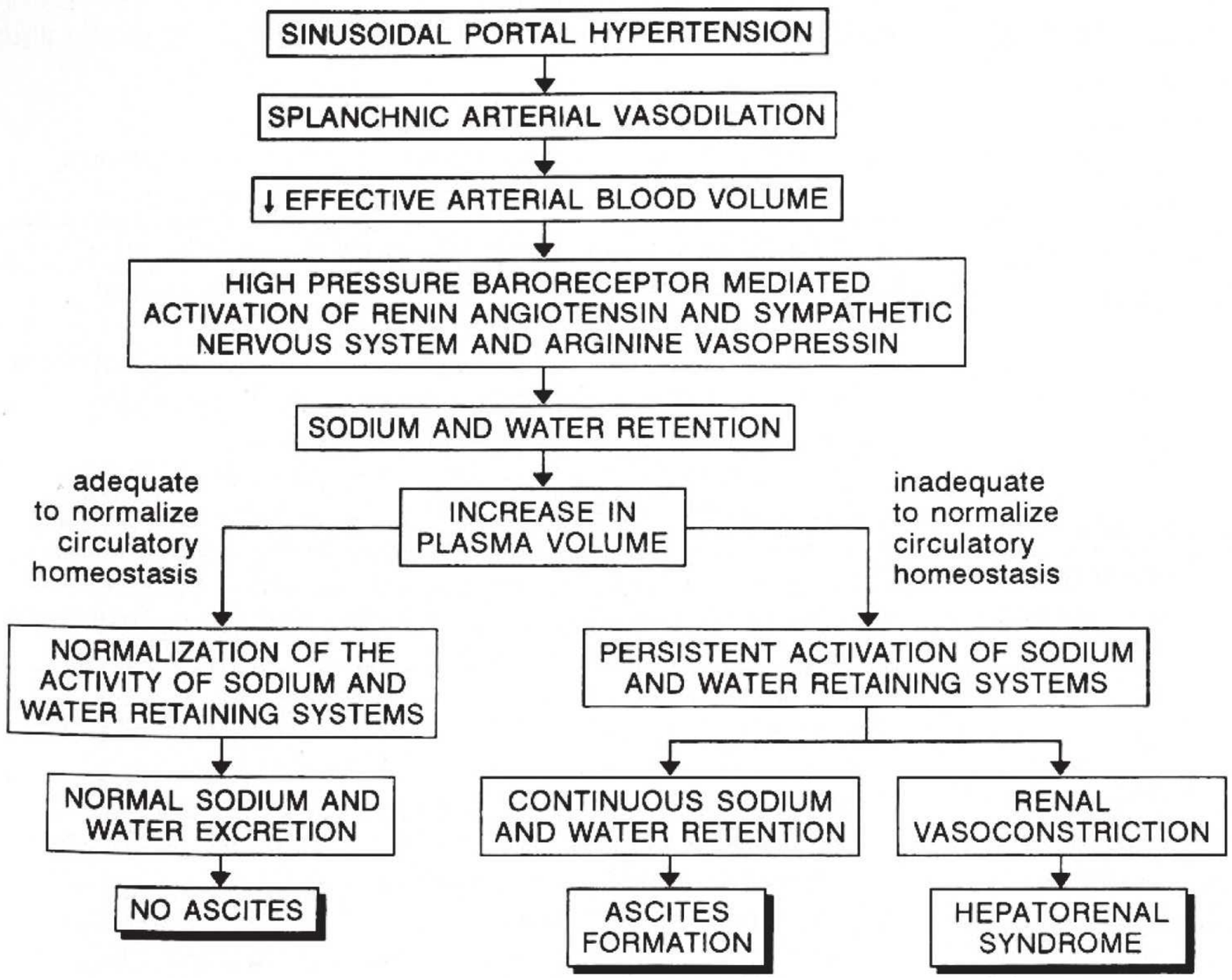

FIGURE 68.10 Pathogenesis of functional renal abnormalities and ascites formation in cirrhosis according to the arterial vasodilation hypothesis.

progressive expansion of extracellular fluid volume. HRS probably represents the most extreme manifestation of the reduction in EABV. Studies in experimental models of portal hypertension aimed at carefully investigating the chronologic relationship between abnormalities in the systemic circulation and sodium retention indicate that arterial vasodilation with reduced systemic vascular resistance precedes sodium retention and subsequent plasma volume expansion.[424]

The arterial vasodilation theory not only provides a reasonable explanation for the circulatory changes and activation of antinatriuretic systems observed in cirrhosis with ascites, but also for the preferential location of retained fluid in the peritoneal cavity. The existence of splanchnic arterial vasodilation causes a "forward" increase in splanchnic capillary pressure that enhances the effects of portal hypertension on the filtration coefficient in splanchnic capillaries, which facilitates the formation of ascites.[188,190,191]

MANAGEMENT OF COMPLICATIONS DUE TO RENAL FUNCTION ABNORMALITIES

Management of Ascites

An important step in the management of ascites is education of patients regarding a sodium-restricted diet of approximately 90 mmol per day[425,426] which may help cause a negative sodium balance and loss of ascites. A more stringent restriction is generally not well tolerated and patients become noncompliant. Additionally, fluid restriction is not necessary unless patients have associated hyponatremia. The current classification of ascites defined by the International Ascites Club divides patients in three groups.[426] Patients with grade 1 ascites are those in whom ascites is detected only by ultrasonography; these patients do not require any specific treatment, but they should be warned about avoiding foods with large amounts of salt. Patients with grade 2 ascites are those in which ascites causes moderate distension of the abdomen associated with mild/moderate discomfort. Patients with grade 3 ascites have large amounts of ascitic fluid causing marked abdominal distension and associated with significant discomfort. Patients with refractory ascites are those that do not respond to high doses of diuretics or develop side effects that preclude their use.[122]

Nonrefractory Ascites

Grade 2 ascites. These patients typically can be managed as outpatients unless other complications of cirrhosis are present. A negative sodium balance with loss of ascites is quickly and easily obtained in most cases with combination of sodium-restricted diet and diuretics.[49,159,248,427] Patients with new onset ascites respond to spironolactone 50 to 100 mg per day and the dose may be increased progressive-

ly if needed. Patients with prior episodes of ascites should receive the combination of spironolactone 100 mg per day with furosemide (20 to 40 mg per day).[49,159,248,427] If there is no response, compliance with diet and medications should be confirmed and diuretics may then be increased until there is response in a stepwise fashion every 7 days by doubling doses to a maximal dose of spironolactone of 400 mg per day and a maximal dose of furosemide of 160 mg per day. Diuretic therapy is effective in the elimination of ascites in nearly 85% to 90% of all patients.[425] Spironolactone-induced gynecomastia may cause patients to stop the drug; in these cases amiloride (5–10 mg per day) may be useful, although its potency is lower than that of spironolactone. Eplerenone, another aldosterone antagonist, has fewer endocrine adverse effects compared with spironolactone and could be a good alternative to spironolactone in patients with spironolactone-induced gynecomastia but there is limited data.[428] The goal of diuretic therapy is to achieve a maximum weight loss of 500 g per day in patients without edema and 1,000 g per day in those with peripheral edema. A greater degree of weight loss may induce volume depletion and renal failure. After minimizing ascites, the dose of diuretics should be reduced to maintain a neutral sodium balance with no more weight loss. The management of patients with grade 2 ascites is summarized in Table 68.5.

Grade 3 ascites. Patients with grade 3 ascites (large ascites) are best managed by large-volume paracentesis. Complete removal of ascites in one tap (as many liters as possible) with intravenous albumin (8 g per liter tapped) has been shown to be quick, effective, and associated with a lower number of complications than conventional diuretic therapy.[429] After a large-volume tap, postparacentesis circulatory dysfunction may develop if albumin is not given; this is a circulatory derangement with marked activation of the renin-angiotensin system that occurs 24 to 48 hours after the procedure.[430] This disorder is clinically silent, not spontaneously reversible, and associated with hyponatremia and renal impairment in up to 20% of patients.[83,429,430] In addition, it is associated with decreased survival. Postparacentesis circulatory dysfunction is prevented with the administration of albumin (8 g per L tapped).[83,431,432] Although the use of albumin after paracentesis is controversial due to the lack of data proving a survival benefit and high cost in some countries, the protective effect of albumin on the circulatory system favors its use. Thus, current guidelines recommend the use of albumin after large-volume paracentesis.[159,426,433,434] Patients with grade 3 ascites and a known history of cirrhosis and without any complications can be managed as outpatients. However, patients in whom tense ascites is the first manifestation of cirrhosis or those with associated hepatic encephalopathy, gastrointestinal bleeding, or bacterial infections require hospitalization. Most of these patients have marked sodium retention and need to be started or continued on relatively high doses of diuretics after large-volume paracentesis together with a low sodium diet (Table 68.6).

68.5 Therapeutic Approach to Management of Patients with Cirrhosis and Grade 2 or Moderate Ascites

Initial Therapy

1. Start with low-sodium diet (80–120 mEq/day) and spironolactone starting at 50–100 mg/day as a single dose in patients with new onset ascites. The dose may be increased stepwise every 7 days (in 100-mg steps) to a maximum of 400 mg/day if there is no response. In patients with no response to aldosterone antagonists, low doses of loop diuretics (furosemide, 20–40 mg/day) may be used in combination with spironolactone to increase the natriuretic effect. Monitor body weight daily and urine sodium weekly. Ideal weight loss should be 300–500 g/day in patients without peripheral edema and 800–1000 g/day in patients with peripheral edema. Outpatients should be instructed to reduce the diuretic dosage in case of greater weight loss.
2. Patients with prior episodes of ascites should receive the combination of spironolactone 100 mg/day with furosemide (20–40 mg/day). If no response is seen, check compliance with treatment and low-sodium diet. Increase the dose of diuretics stepwise every 7–10 days up to 400 mg/day of spironolactone and 160 mg/day of furosemide.

Maintenance Therapy

1. Maintain sodium restriction and reduce diuretic treatment to the minimum dose necessary to prevent reaccumulation of ascites.
2. If ascites or edema does not recur, increase sodium intake progressively and maintain a low dose of diuretics.

Refractory Ascites

Nearly 10% of patients with ascites are refractory to treatment with diuretics.[122,159] In refractory ascites, a significant increase in sodium excretion cannot be achieved either because patients do not respond to high doses of diuretics (spironolactone 400 mg per day and furosemide 160 mg per day) or because they develop side effects that preclude their use.[122,435] These patients in general have features of advanced liver disease, a high recurrence rate of ascites after large-volume paracentesis, an increased risk of HRS, and a poor prognosis. Current treatment strategies include repeated large-volume paracentesis plus intravenous albumin as needed, and transjugular intrahepatic portosystemic shunts (TIPS). Large-volume paracentesis is the accepted initial therapy for refractory ascites.[159] Patients, on average, require a tap every

68.6 Therapeutic Approach to Management of Patients with Cirrhosis and Grade 3 or Large-volume Ascites

Initial Therapy

1. Large-volume paracentesis plus intravenous albumin (8 g/L of ascites removed). Patients can be treated as outpatients.

Maintenance Therapy

1. Low-sodium diet (80–120 mEq/day) associated with diuretic therapy.
2. If the patient was not taking diuretics before the development of severe ascites, start with spironolactone (50–100 mg/day as a single dose) and then adjust the dose to maintain the patient with mild or no ascites or edema. Check body weight daily and urine sodium weekly. Closely monitor the patient during the first weeks of therapy. Add loop diuretics (furosemide 40 mg/day), if necessary.
3. If the patient was taking diuretics before the development of severe ascites, start with a dose slightly higher than the dose taken before paracentesis.
4. If ascites or edema increases, check compliance with treatment and the low-sodium diet. Increase the dose of diuretics stepwise every 7–10 days up to 400 mg/day of spironolactone and 160 mg/day of furosemide.
5. If ascites or edema does not recur, a balance should be maintained between sodium intake and diuretic therapy.

2 to 4 weeks and the majority may be treated as outpatients, making this option easy to perform and cost effective. TIPS, a nonsurgical method of portal decompression, reduces portal pressure and decreases ascites and diuretic requirements in these patients.[436,437] A disadvantage with TIPS is the development of side effects that include hepatic encephalopathy and impairment in liver function.[436–442] Additionally, uncovered TIPS may be complicated by stenosis of the prosthesis (18%–78%).[437] Meta-analyses of randomized controlled studies comparing TIPS versus large-volume paracentesis conclude that TIPS is better at controlling ascites but does not improve survival compared to paracentesis and increases the risk of hepatic encephalopathy.[443,444] In view of these findings, the preferred initial treatment for refractory ascites is large-volume paracentesis with albumin replacement.[159] In patients not suitable for repeated large-volume paracentesis plus albumin, TIPS placement should be evaluated on a case-by-case basis and probably reserved for patients aged <70, with preserved liver function, without hepatic encephalopathy or severe cardiopulmonary disease. The management of refractory ascites is summarized in Table 68.7.

Management of Hyponatremia

Management of dilutional hyponatremia includes water restriction of approximately 1 to 1.5 liters per day; however, this measure rarely works and although it may halt the progressive decrease in serum sodium concentration it does not correct hyponatremia. The administration of hypertonic saline solutions is not recommended because it invariably leads to further expansion of extracellular fluid volume and accumulation of ascites and edema. Several nonpeptide V2 receptor AVP antagonists including mozavaptan, lixivaptan, satavaptan, tolvaptan, and conivaptan have been evaluated in patients with cirrhosis and ascites with hyponatremia. These studies show that these drugs are effective at increasing solute-free water excretion and improve serum sodium concentration in hyponatremic patients with cirrhosis and ascites.[93–95,324,445,446] The short-term administration of vaptans is associated with an increase in serum sodium concentration that occurs within the 4 to 5 days of treatment with normalization of serum sodium concentration occurring in 30% to 55% of patients. Conivaptan is approved in the United States for short term (4 to 5 days) intravenous use (dose 20 mg per day), whereas tolvaptan is approved as an oral compound (dose starting at 15 mg per day with sequential 15 mg increments up to 60 mg per day).[324,446] The most frequent side effect of vaptans in patients with cirrhosis is thirst which can occur in up to 30% of patients. Other side effects are uncommon; however, these drugs need to be used with caution and the patient must be carefully monitored as very rapid correction of hyponatremia

68.7 Therapeutic Approach to Management of Patients with Cirrhosis and Refractory Ascites

Initial Therapy

1. Repeated large-volume paracentesis plus intravenous albumin (8 g/L of ascites removed)

Maintenance Therapy

1. Maintain a low-sodium diet (80–120 mEq/day) constantly.
2. In patients taking the highest doses of diuretics, check urinary sodium. If less than 30 mEq/day, stop diuretic therapy.
3. Large-volume paracentesis plus intravenous albumin when necessary (approximately every 2–3 weeks).
4. Consider use of TIPS in patients with preserved hepatic function, no hepatic encephalopathy, either with loculated fluid, or unwilling to have repeated paracentesis.

TIPS, transjugular intrahepatic portosystemic shunt.

(e.g., >12 mEq/L/24 hours) can theoretically cause osmotic demyelination. No case of this syndrome, however, has been reported in studies so far published. The use of these agents in cirrhosis has been assessed in short-term studies; notwithstanding long-term controlled studies are needed to evaluate the safety, efficacy, and applicability of these agents in the long-term management of hyponatremia in patients with cirrhosis.

Management of Hepatorenal Syndrome

The main objective of patients with HRS, particularly those awaiting liver transplantation, is reversing renal failure in order to provide a successful bridge to transplantation. The best available therapy for HRS, other than liver transplantation, is the use of splanchnic vasoconstrictors plus albumin. Other modalities such as TIPS, renal replacement therapy, and albumin dialysis may be useful in some patients, but data on these approaches is very limited.

Vasoconstrictors

The administration of vasoconstrictors is the best medical therapy currently available for the management of HRS.[159] The rationale of this therapy is to improve circulatory function by causing vasoconstriction of the extremely dilated splanchnic arterial bed, which subsequently improves arterial underfilling, reduces the activity of the endogenous vasoconstrictor systems, and increases renal perfusion. The available vasoconstrictors used in HRS are vasopressin analogues (terlipressin) and alpha-adrenergic agonists (noradrenaline or midodrine), which act on V1 vasopressin receptors and α-1 adrenergic receptors, respectively, present in vascular smooth muscle cells (Table 68.8). In most studies, vasoconstrictors have been given in combination with intravenous albumin to further improve the arterial underfilling. Most of the published data comes from the use of intravenous terlipressin for type 1 HRS.[215,447–458] Results from randomized controlled studies and systematic reviews indicate that treatment with terlipressin together with albumin is associated with marked improvement of renal function in approximately 40% to 50% of patients.[454–458] Terlipressin is started at 1 mg per 4 to 6 hours intravenously, and the dose is increased up to a maximum of 2 mg per 4 to 6 hours after 3 days if there is no response to therapy as defined by a reduction of serum creatinine >25% of pretreatment values. Response to therapy is considered when there is marked reduction of the high serum creatinine levels, at least below 1.5 mg per dL, which is usually associated with increased urine output and improvement of hyponatremia.[454–458] The incidence of side effects (usually ischemic) requiring the discontinuation of treatment is of approximately 10%. Two randomized studies described previously[454,455] have shown that the overall population of patients treated with terlipressin and albumin do not have an improved survival compared to that of patients treated with albumin alone. However, both studies showed that responders in terms of improvement of renal function after therapy had a significant (but moderate), increase in survival compared to nonresponders. Recurrence of HRS after withdrawal of therapy occurs in less than 15% of patients and retreatment with terlipressin is generally effective. Factors associated with poor response include a bilirubin level ≥10 mg per dL, no increase in mean arterial pressure >5 mm Hg or lack of a drop in serum creatinine >0.5 mg per dL at day 3 of therapy.[459] Alpha-adrenergic agonists (noradrenaline, midodrine) represent an attractive alternative to terlipressin because of low cost, wide availability, and apparently similar efficacy compared with that of terlipressin.[266,453,460,461] However, the information on the efficacy and side effects of alpha-adrenergic agonists in patients with type 1 HRS is still very limited. Table 68.8 summarizes the treatment of HRS in patients with cirrhosis.

There are limited data on use of vasoconstrictors plus albumin for patients with type 2 HRS. However data from uncontrolled studies suggest that they are effective in decreasing serum creatinine levels in these patients. In two controlled studies, patients with type 2 HRS that received terlipressin plus albumin had a response between 67% and 88%; however, few were treated with this strategy in both studies and therefore more studies are needed in order to better define the role of vasoconstrictors plus albumin in the management of type 2 HRS.[453,455]

68.8 Pharmacologic Therapies for Hepatorenal Syndrome

Vasoconstrictors

Terlipressin: 1 mg/4–6 hours intravenously; the dose is increased up to a maximum of 2 mg/4–6 hours after 3 days if there is no response to therapy as defined by a reduction of serum creatinine >25% of pretreatment values. Response to therapy is considered when there is marked reduction of the high serum creatinine levels, at least below 1.5 mg/dL (133 μmol/L). Treatment is usually given from 5–15 days.

Midodrine: 7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed.

Octreotide: 100 μg subcutaneously three times daily, increased to 200 μg three times daily if needed.

Norepinephrine: 0.5–3 mg/h as continuous intravenous infusion aimed at increasing mean arterial pressure by 10 mm Hg. Treatment is maintained until serum creatinine decreases below 1.5 mg/dL.

Albumin Administration

Concomitant administration of albumin together with vasoconstrictor drugs (1g/kg body weight at day 1 followed by 20–40 g/day).

Transjugular intrahepatic portosystemic shunts. The use of TIPS for therapy of HRS has been suggested for years, but the applicability in patients with such advanced liver disease is very limited. Two small studies indicate that TIPS may improve GFR as well as reduce the activity of the RAAS and the SNS in approximately 60% of patients with type 1 HRS.[265,462] However, these studies only included patients with moderately severe liver failure and excluded those with a history of hepatic encephalopathy, Child-Pugh score ≥12 or serum bilirubin >5 mg per dL. The applicability of TIPS in patients with type 1 HRS is low because TIPS is considered contraindicated in patients with features of severe liver failure, which are common findings in the setting of type 1 HRS. The use of TIPS in type 2 HRS may improve renal function and reduce the risk of progression to type 1 HRS, but these data require confirmation in specifically designed studies.

Renal replacement therapy and other dialysis methods. Renal replacement therapy (RRT), mainly hemodialysis, has been used in the management of patients with type 1 HRS, especially in candidates for liver transplantation, in an attempt to maintain patients alive until liver transplantation is performed.[463] Unfortunately, the potential beneficial effect of this approach has not been evaluated in randomized studies comparing RRT to other forms of therapy such as vasoconstrictors. Most patients develop side effects during RRT which include severe arterial hypotension, bleeding, and infections that may contribute to death during treatment. Additionally, indications for RRT (severe fluid overload, acidosis, or hyperkalemia) are uncommon in type 1 HRS, at least in the early stages. Other methods such as the use of the molecular readsorbent recirculating system (MARS), an alternative of dialysis that clears albumin-bound substances, including vasodilators, is promising but more data are needed in order to consider it as a therapeutic device for HRS.[464–466]

Liver transplantation. Liver transplantation is the treatment of choice for candidate patients with cirrhosis and HRS. However, a major problem in liver transplantation for type 1 HRS is the high mortality rate in the waiting list due to the combination of short survival expectancy and prolonged waiting times in many transplant centers. This limitation is usually overcome by assigning these patients a high priority for transplantation. Because pretransplant renal failure is an independent risk factor of both short-term and long-term posttransplantation patient and graft survival all efforts should be made to improve renal function in order to obtain a better outcome after transplantation. The reversal of both type 1 and 2 HRS using vasoconstrictors before transplantation may help patients not only reach transplantation, but also reduce the relatively high morbidity and mortality after liver transplantation characteristic of HRS.

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