New Challenge of Hepatorenal Syndrome: Prevention and Treatment

FLORENCE WONG1 AND LAURENCE BLENDIS1,2

Hepatorenal syndrome (HRS) remains one of the major therapeutic challenges in hepatology today. The pathogenesis is complex, but the final common pathway seems to be that sinusoidal portal hypertension, in the presence of severe hepatic decompensation, leads to splanchnic and systemic vasodilatation and decreased effective arterial blood volume. Renal vasoconstriction increases concomitantly, renal hemodynamics worsens, and renal failure occurs. Renal failure was shown 15 years ago to be potentially reversible after liver transplantation. This potential reversibility together with increased understanding of the pathogenesis has led to successful preliminary attempts to reverse HRS nonsurgically with combinations of splanchnic vasoostrictors and colloid volume expansion, insertion of transjugular intrahepatic portovenous shunt radiologically, and improved forms of dialysis. Recent classification of HRS into the acute onset or severe type I with virtually 100% mortality and the more insidious less severe type II promises to shed more light on the pathogenesis of HRS, especially on the currently unrecognized precipitating factors. It is hoped that this classification will be included in the necessary and carefully performed clinical trials, which should lead to clearer indications for the available therapies. The challenge now is to use all this information to improve our management of cirrhotic patients to prevent occurrence of HRS in the future. (HEPATOLOGY 2001;34:1242-1251.)

Progressive oliguric renal failure is a common and severe complication in patients with advanced liver disease. In a large prospective follow-up study of cirrhotic patients with ascites, development of renal failure occurred in 18% and 39% of the patients at 1 year and at 5 years, respectively, with a median survival of 1.7 weeks or a 90% mortality at 10 weeks.1 Hepatorenal syndrome (HRS) originally referred to occurrence of renal failure following biliary surgery.2 The definitions of HRS gradually evolved to describe the renal failure observed in patients with liver failure associated with low urinary sodium levels and absence of renal pathology.3 A recent consensus conference further defined HRS as types I and II with the following diagnostic criteria: type I HRS is characterized by rapidly progressive renal failure with a doubling of serum creatinine to a level greater than 2.5 mg/dL or a halving of the creatinine clearance to less than 20 mL/min in less than 2 weeks; type II HRS is a more chronic form with a slowly progressive increase in serum creatinine level to greater than 1.5 mg/dL or a creatinine clearance of less than 40 mL/min and has a corresponding better prognosis. Until recently, liver transplantation was the only definitive treatment for HRS.3,6 However, even then, the reported survival rates of these HRS patients posttransplantation have been less than in transplanted patients with normal renal function, and the return of renal function to normal may be delayed for months or years.7,8 Furthermore, liver transplantation is not readily available to every patient, nor is every patient with HRS a suitable candidate for this surgery. We review herein possible ways of preventing HRS and how the new therapies for HRS9-12 have shed light on the pathophysiology resulting in improvement in the prognosis of patients with HRS.

THE PATHOPHYSIOLOGY OF HRS AND ITS ROLE IN PREVENTION

The hallmark of HRS is hypoperfusion of the kidney resulting from combined renal vasoconstriction and decreased total renal blood flow13 in response to generalized systemic arterial vasodilatation.14 Patients with advanced cirrhosis and liver failure have a hyperdynamic circulation with lowered systemic vascular resistance and increased cardiac output.15,16 As a result of splanchnic and systemic arterial vasodilatation, there is relative underfilling of the systemic circulation and a fall in mean arterial pressure.17,18 Consequently, renal perfusion pressure is reduced, leading to decreased renal blood flow.19 Compensatory activation of various vasoconstrictor systems maintains hemodynamic stability, whereas vasoconstriction occurs in some nonsplanchnic vascular beds including the kidneys,20 thereby further reducing renal perfusion with consequent reduction in glomerular filtration rate.21 However, two patients with similarly reduced renal blood flow may or may not have HRS.22 Dagher et al.23 suggested that mesangial contraction due to increased circulating levels of renal vasoconstrictors (Fig. 1) lowers the glomerular capillary ultrafiltration coefficient (Kf) causing further reduction of glomerular filtration. Such vasoconstrictors include endothelin-1,24,25 leukotrienes,26,27 and products of lipid peroxidation.28 However, the role of these vasoconstrictors in causing mesangial contraction is unclear because levels of immunoreactive endothelins do not correlate with the extent of renal dysfunction in these patients29 or with the improvement of renal function following insertion of a transjugular intrahepatic portosystemic shunt (TIPS).30

The suggestion that sinusoidal or postsinusoidal portal hypertension is an important factor in the development of renal

Abbreviations: HRS, hepatorenal syndrome; TIPS, transjugular intrahepatic portosystemic shunt; NOS, nitric oxide synthase; PRA, plasma renin activity; SBP, spontaneous bacterial peritonitis; MARS, molecular adsorbent recirculating system.

From the 1Division of Gastroenterology, Department of Medicine, The Toronto General Hospital, University of Toronto, Ontario, Canada, and 2Institute of Gastroenterology, Sourasky Tel Aviv Medical Centre, Tel Aviv, Israel.

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Address reprint requests to: Laurence Blendis, M.D., Institute of Gastroenterology, Sourasky Tel Aviv Medical Centre, Tel Aviv, Israel. E-mail: maxin@netvision.net.il, fax: 416-340-5019.

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dysfunction\textsuperscript{31} is supported by recent reports of patients in whom HRS was successfully treated by reduction of portal pressure by a TIPS.\textsuperscript{12} Furthermore, occlusion of a TIPS by an angioplasty balloon was associated with acute reduction of renal blood flow.\textsuperscript{32} Upon release of the balloon, with elimination of portal hypertension, renal blood flow returned to baseline levels. Portal hypertension with portosystemic shunts and splanchic dilatation leads to development of hyperdynamic circulation with attendant systemic arterial vasodilatation and effective arterial underfilling and hence renal hypoperfusion. However, this is unlikely to be the whole explanation. Presinusoidal portal hypertension due to portal vein thrombosis, nodular regenerative hyperplasia, or schistosomiasis is associated with hemodynamic changes similar to those of compensated cirrhosis\textsuperscript{17,33} but not associated renal sodium retention\textsuperscript{34} or HRS. Animal studies suggest the important afferent factor for the development of HRS is sinusoidal portal hypertension. For example, infusion of glutamine into the portal vein, which induces hepatocyte swelling and hence increases sinusoidal portal pressure, was associated with a significant decrease of both renal plasma flow and glomerular filtration rate. These effects were abolished by sectioning the renal sympathetic nervous supply.\textsuperscript{35} Furthermore, increased intrahepatic pressure resulted in greater efferent renal sympathetic nervous activity,\textsuperscript{36} and renal sympathectomy improved glomerular filtration rate in cirrhotic rats.\textsuperscript{37,38} Finally, renal sympathetic block resulted in transient improvement in renal blood flow and function in patients with HRS.\textsuperscript{39}

Bataller et al.\textsuperscript{14} proposed that renal hypoperfusion in cirrhosis could also be related to liver dysfunction, which influences the synthesis or release of renal vasodilators such as the renal prostaglandins\textsuperscript{\textsuperscript{40,41}} from the kidney. In decompensated cirrhosis but without renal failure, increased renal production of prostaglandins has been reported.\textsuperscript{42} In HRS, urinary excretion of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and prostacyclin metabolite 6-oxo-PGF\textsubscript{1α} are decreased compared with patients with ascites alone.\textsuperscript{43} This may partly result from a fall in glomerular filtration rate\textsuperscript{44} and decreased renal production of PGE\textsubscript{2} and 6-oxo-PGF\textsubscript{1α}.\textsuperscript{45} In addition, the use of nonsteroidal anti-inflammatory drugs, which are cyclo-oxygenase inhibitors, in patients with cirrhosis and ascites can precipitate HRS.\textsuperscript{46}

Another renal vasodilator that could be involved in the pathogenesis of HRS is nitric oxide.\textsuperscript{47} In portal hypertension endothelial nitric oxide synthase (NOS) activity is significantly increased, leading to increased circulating levels of nitric oxide.\textsuperscript{48} In normal animals and humans, short-term inhibition of NOS results in renal vasoconstriction and reduced renal plasma flow.\textsuperscript{49,50} In contrast, NOS inhibition in cirrhotic rats with ascites does not affect renal blood flow or function\textsuperscript{51,52} despite an increased systemic pressor effect.\textsuperscript{53} Furthermore, renal vasoconstriction may occur in the presence of increased glomerular nitrite production\textsuperscript{51,52} and increased urinary nitrate excretion\textsuperscript{55} in ascitic patients compared with compensated nonascitic cirrhotics. This suggests that renal microcirculation in ascites is less sensitive to nitric oxide.\textsuperscript{56} However, infusion of nitric oxide substrate L-arginine in cirrhotic patients with ascites, in contrast to controls, causes increased nitriuresis with increased urinary nitrate/nitrite excretion.\textsuperscript{57}

Finally, there is a possible role of natriuretic peptides.\textsuperscript{58} In experimental cirrhosis with ascites in rats, blockade of natriuretic peptide receptors was followed by a significant reduction of both renal blood flow and glomerular filtration rate.\textsuperscript{59} Renal vasodilatation with acetylcysteine improved renal function in patients with HRS without affecting liver function or systemic hemodynamics.\textsuperscript{59} Furthermore, not all patients with seemingly equally severe hepatic dysfunction develop HRS. Therefore, the role of liver dysfunction in the pathogenesis of

Fig. 1. The pathophysiology of hepatorenal syndrome.
HRS appears to be an important background factor, or “first hit,” that requires an additional factor, or “second hit,” to initiate HRS (Fig. 2). In the same way splanchnic and systemic vasodilation and sinusoidal portal hypertension appear to be primary factors in the pathogenesis, but all require additional factors to initiate HRS.

**DEFINITION OF HRS—ITS ROLE IN CLARIFYING THE PATHOGENESIS AND PREVENTION**

The recent consensus conference of the International Ascites Club clearly posed the diagnostic criteria of HRS (Table 1) and defined types I and II. Although the definition describes renal failure complicating liver failure, and helps in the clinical management of these patients, it is not clear whether types I and II HRS are two different stages on the same continuum of the end-stage cirrhotic process or two distinct entities. The definition does not explain what determines whether a patient with normal serum creatinine will gradually evolve into type II HRS with progressively worsening glomerular filtration rate or acutely develop renal failure with its grave prognosis. Finally, the definition does not explain why most but not all patients with HRS have ascites. We will attempt to answer some of these questions while focusing on the two types of HRS from a pathogenetic point of view. We also are taking the opportunity to suggest certain recommendations in the literature for prevention of HRS.

**TABLE 1. Definition of Hepatorenal Syndrome**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Chronic or acute liver disease with liver failure and portal hypertension</td>
<td>Urine volume &lt; 500 mL/d</td>
</tr>
<tr>
<td>Low glomerular filtration rate as indicated by a serum creatinine &gt; 1.5 mg/dL or a creatinine clearance of &lt;40 mL/min</td>
<td>Urine sodium &lt; 10 mmol/L</td>
</tr>
<tr>
<td>Absence of shock, ongoing bacterial infection, and recent treatment with nephrotoxic drugs. Absence of excessive fluid loss including gastrointestinal loss</td>
<td>Urine osmolality &lt; plasma osmolality</td>
</tr>
<tr>
<td>No sustained improvement in renal function following expansion with 1.5 L of isotonic saline</td>
<td>Urine red cell count &lt; 50 per high power field</td>
</tr>
<tr>
<td>Proteinuria of &lt;0.5 g/d and no ultrasonographic evidence of renal tract disease</td>
<td>Serum sodium &lt; 130 mmol/L</td>
</tr>
</tbody>
</table>

**Fig. 2.** The first hit and the second hit hypothesis of hepatorenal syndrome.

**TYPE I**

Gines et al. reported that hyponatremia and high plasma renin activity (PRA) are independent predictors for development of type 1 HRS in cirrhotic patients with ascites. They suggested that it is the extent of the systemic arterial vasodilation with consequent effective arterial underfilling (the first hit), causing a rise in the PRA that is important in the pathogenesis of type 1 HRS. Indeed, HRS frequently develops as a consequence of precipitating events (the second hit), which exaggerate the effective arterial underfilling. Such events may include the overzealous use of diuretics, large volume paracentesis, or development of spontaneous bacterial peritonitis (SBP) in ascitic patients as well as in patients with gastrointestinal bleeding. However, at least 24% of patients with type 1 HRS develop renal failure without any obvious precipitating factor. This suggests that other as yet unrecognized factors may also be involved in the pathogenesis of HRS, which we shall address later.

**Diuretics**

Patients with refractory ascites have significantly higher PRA compared with patients with responsive ascites, sug-
gesting reduction in effective arterial blood volume. Furthermore, these patients have a poor natriuretic response to furosemide.63 Gines et al. reported a significantly higher incidence of reversible renal impairment in hospitalized patients with tense ascites treated with diuretics compared with those treated with large-volume paracentesis,64 which is associated with further increases in PRA. These findings support the contention that diuretics cause a further contraction of intravascular volume with compensatory increases in the vasoconstrictor activities predisposing patients to development of renal failure. However, the same investigators also reported that diuretics do not increase the incidence of postparacentesis circulatory dysfunction (defined as an increase in renin of greater than 50% over baseline levels up to a value higher than 4 ng/mL/h on the third day after paracentesis).65 The possibility remains that diuretic therapy in nonhospitalized, severely decompensated patients might induce the onset of HRS. In hospitalized patients, addition of a colloid solution such as albumin to diuretic therapy prevented a diuretic-induced rise in serum creatinine and blood urea nitrogen despite an unchanged hematocrit and lack of protection from a fall in systemic blood pressure,66 indicating an unchanged intravascular volume. Thus albumin may have a local effect on the physical factors of the tubule.67 This suggests that diuretics may also induce renal impairment via mechanisms other than reduction in intravascular volume.67 This may occur via some local effects of diuretics on the nephron, as structural changes have been observed following prolonged diuretic therapy.68 Although overzealous use of loop diuretics in particular can cause a rise in serum urea and creatinine, it is nearly always reversible with cessation of diuretics.69 Furthermore, patients with peripheral edema appear to be protected by more rapid mobilization of edema fluid.70 Therefore, the indication for the protective and synergistic use of albumin with diuretics remains controversial.71

**Recommendation.** In patients with ascites, spironolactone should not be increased above 400 mg daily. The pharmacodynamics of loop diuretics in cirrhotic ascitic patients are altered, and the diminished response to furosemide is not enhanced by large doses.72 These patients should be treated with divided doses of furosemide of up to 160 mg daily and be followed closely with monitoring of electrolytes and serum creatinine, especially in the absence of peripheral edema. Patients who do not respond to these generally accepted maximal doses of diuretic therapy should not have their diuretic doses increased further, but other treatment options for ascites should be considered. In the future, simple tests such as the natriuretic response to an acute intravenous infusion of furosemide63 may help to predict diuretic nonresponsiveness and possibly avoid unrecognized precipitation of HRS, especially in outpatients.

**Large-Volume Paracentesis**

Ruiz-del-Arbol et al.73 described development of circulatory dysfunction after large-volume paracentesis that led to deterioration in renal function. They interpreted this as an exaggeration of the arterial vasodilatation already present in cirrhotic patients with ascites, with further activation of the already stimulated vasoconstrictor systems74 leading to further renal vasoconstriction. The intriguing observation is that only 32% of patients had activation of the vasoconstrictor systems after large-volume paracentesis.74 The answer may lie in the extent of the hemodynamic instability before paracentesis. Because PRA is one of the independent predictors for development of HRS,7 those patients with higher baseline PRA (first hit) are more likely to develop HRS after large-volume paracentesis (second hit). However, use of albumin as a volume expander after large-volume paracentesis does not always prevent postparacentesis renal failure.

**Recommendation.** Before starting a course of repeated paracenteses, it is important to measure serum creatinine levels and, if possible, perform PRA determinations to identify patients at greatest risk of developing postparacentesis circulatory dysfunction. Such patients should be maximally protected with 6 to 8 grams of intravenous albumin per liter of ascites.

**Gastrointestinal Bleeding**

Acute blood loss leads to acute blood volume contraction with decreased renal perfusion and acute tubular necrosis. However, the pathogenesis of acute renal failure secondary to variceal bleeding has been poorly documented, and some patients are diagnosed as having (type 1) HRS. For example, in a recent study 40% of 85 patients with decompensated cirrhosis (first hit) and variceal bleeding developed a systemic inflammatory response syndrome, manifesting with increased temperature, tachycardia, tachypnea, and leukocytosis, with or without an infection,75 associated with exacerbation of the hyperdynamic circulation (second hit). The inflammatory response is associated with activation of many cytokines,76 some of which stimulate production of nitric oxide and other vasodilators.76 Thus, the patient with gastrointestinal bleeding is also predisposed to further exaggeration of systemic arterial vasodilation because the accompanying inflammatory response will yield more vasodilators and aggravate the effective arterial underfilling. Superimposition of this systemic inflammatory response (second hit) on decompensated liver disease can lead to organ failure. In one report, 3 patients died of documented HRS after acute gastrointestinal bleeding.75 However, in such cases, the classic differentiation of acute tubular necrosis from HRS by an active urinary sediment with casts and urinary sodium concentration greater than 20 mmol/L may be blurred. Development of renal failure after gastrointestinal bleeding is related to an advanced stage of cirrhosis77 and renal impairment before the bleeding is a predictor of mortality.77 Cirrhotic patients with marked systemic arterial vasodilatation and effective underfilling are less able to tolerate intravascular volume depletion, predisposing them to development of renal failure and a poor outcome.

**Recommendation.** Cirrhotic patients with acute gastrointestinal bleeding and poor liver function and/or decreased renal function should be managed in an intensive care unit where optimal monitoring can provide maximum protection of their effective circulating blood volume and renal perfusion. In addition, cirrhotic patients, particularly those with ascites, with acute variceal bleeding, should be given a prophylactic course of antibiotics.78 Recommended antibiotic regimens include norfloxacin, 400 mg 12 hourly for a minimum of 7 days, or a combination of ciprofloxacin, 400 mg daily, and amoxicillin-clavulanic acid, 3 g daily, intravenously and then orally and continued for 3 days after the bleeding stops. In a meta-analysis of randomized controlled trials,79 prophylactic antibiotics significantly reduced the incidence of SBP and consequently mortality from septic shock and renal failure.80
Spontaneous Bacterial Peritonitis

SBP is another common precipitant of HRS. At least 30% of patients with SBP develop HRS despite adequate treatment of infection. Previous renal impairment and a marked inflammatory response, indicated by the polymorphonuclear cell count and cytokine concentrations in ascitic fluid, result in further arterial vasodilatation and are important predictors for development of type 1 HRS. Sepsis decreases both spontaneous and agonist-induced vascular contractile activity in the cirrhotic rat. Sort et al. postulated that sepsis in cirrhosis induces an increased production of various cytokines and endotoxins, which in turn stimulate the production of nitric oxide and other vasodilators causing further arterial vasodilatation. Indeed, intestinal decontamination with oral antibiotics in cirrhotic patients was associated with improvement in systemic hemodynamics and reduction in systemic arterial vasodilatation, probably as a result of a reduction of nitric oxide–induced systemic arterial vasodilatation. Thus, circulatory dysfunction in patients with SBP is in many ways similar to that observed in patients with gastrointestinal bleeding: the inflammatory response leads to further reduction of effective arterial blood volume resulting in incremental activation of the already elevated neurohumoral vasoconstrictor systems with development of renal vasoconstriction and dysfunction. Therefore, it is not surprising that the same investigators reported significant reduction in the incidence of renal impairment when patients with SBP were given volume expansion in the form of intravenous albumin in a randomized controlled study. However, circulatory dysfunction worsened, indicated by rising PRA, despite adequate treatment of the infection. It appears that a precipitant will only induce type I HRS in a susceptible patient. For example, renal impairment in patients with SBP only occurred in those with a direct bilirubin level greater than 4 mg/dL.

**Recommendation.** Patients who develop SBP with evidence of renal impairment or with serum bilirubin levels greater than 4 mg/dL should be managed in a setting that allows optimal monitoring to protect volume status and renal function and should be treated initially with intravenous albumin 1.5 g/kg per day.

Cholestasis

The presence of cholestatic jaundice may be an unrecognized factor in the development of type 1 HRS. This is not surprising because historically obstructive jaundice can be an important factor (first hit) in patients subjected to circulatory changes, such as surgery (second hit), and can lead to renal failure. It is now well accepted that cholestasis per se, in the absence of portal hypertension, causes vasodilatation and a hyperdynamic circulation associated with impaired vascular responsiveness to circulating vasoconstrictors. Therefore, cholestasis superimposed on cirrhosis and portal hypertension is likely to compound the circulatory changes, thus predisposing the patient to HRS. It is not surprising to find both elevated bilirubin levels as a major component of prognostic indexes, such as the Child-Pugh score, and creatinine clearance frequently decreased to 60% of normal with biliary obstruction. The mechanism is still unknown, but could include endotoxemia, nephrotoxic effects of elevated levels of bile acids, and/or disturbances of renal prostaglandin/thromboxane synthesis. Holt et al. observed that acute biliary obstruction was associated with the development of renal impairment. They postulated that the increased production of F2-isoprostanes in cholestasis was responsible for the development of renal failure because F2-isoprostanes are potent renal vasoconstrictors, and administration of antioxidants that reduced F2-isoprostanes levels was associated with improvement of renal function. HRS is also a common cause of death in patients with severe acute alcohol-induced hepatitis in whom sinusoidal portal hypertension is exacerbated and liver function deteriorates further. Severity in this context can be defined using the Maddrey discriminant function: 1 of the 2 components is serum bilirubin level and the other is prothrombin time, i.e., $4.6 \times (\text{prothrombin time} - \text{control time in seconds}) + \text{serum bilirubin in mg/dL}$. Therefore, the onset of cholestatic jaundice in advanced cirrhosis may be a less well recognized second hit, contributing to the development of type 1 HRS in patients.

**Recommendation.** Cirrhotic patients who as a consequence of decompensation have developed significant cholestasis, e.g., serum bilirubin greater than 4 mg/dL, should be considered at increased risk for developing HRS in the presence of a second hit, SBP, or variceal bleeding and treated accordingly. In patients with severe acute alcohol-induced hepatitis and jaundice, further control trials are needed to confirm the use of pentoxifylline to prevent onset of HRS and to reduce mortality in these patients.

**TYPE II**

Type II HRS has been regarded as an extension of the stage of refractory ascites in cirrhosis and shares the same pathophysiology, namely, splanchnic and systemic vasodilatation with renal vasoconstriction, leading to progressive deterioration in renal function. However, Papper et al. reported on a series of 200 patients with HRS, in which only 75% of the patients had massive ascites. Furthermore, in the only long-term follow-up study of Gines et al. assessing the natural history of a cohort of ascitic cirrhotic patients, the presence of ascites was not an independent predictor for development of HRS. Newer predictive factors such as renal-resistive index, measured by doppler ultrasound, or the Mayo End-Stage Liver Disease Index (MELD), based on the initial elevation of serum creatinine together with total bilirubin and a reduction in prothrombin time, may increase our ability to predict the onset of HRS in these patients. Despite this, patients with refractory ascites are poised to develop renal failure. Subtle factors such as a further deterioration in liver function with increasing cholestatic jaundice, which in itself causes systemic vasodilatation, further compromises the pathophysiology of refractory ascites and triggers development of renal failure.

It is clear that while the definition separates HRS into two clinically distinct entities, for some patients both types of HRS are a continuum of the same condition: type II HRS can evolve into type I HRS, especially in the presence of precipitating factors.

**NEW THERAPIES FOR HRS**

Although liver transplantation remains the only effective permanent treatment for HRS, preoperative renal dysfunction frequently reduces patient and graft survival after liver transplantation. Therefore, medical treatments have attempted to reverse HRS, either definitively or to improve renal function sufficiently to allow liver transplantation to proceed. All manipulate some aspects of the pathophysiology of HRS,
with varying degrees of success. We therefore will examine various nonsurgical treatments for HRS from a pathophysiologic standpoint with the aim of improving prevention and overall management of HRS.

Vasopressin Analogues

The rationale for using vasopressin analogues as a treatment for HRS is based on the observation that the vasopressin-1 receptor agonist, 8-ornithin vasopressin or ornipressin, a vasoconstrictor, increased splanchnic and systemic vascular resistance in cirrhotic patients with impaired renal function, resulting in redistribution of circulating blood volume. This improved systemic blood pressure and therefore renal perfusion pressure, thereby increasing renal plasma flow and glomerular filtration rate after only 4 hours of intravenous infusion.103,104 Infusion longer than 48 hours further improved renal function, resulting in a suppression of the renin-angiotensin and sympathetic activities with consequent further improvement in renal plasma flow and glomerular filtration rate. When ornipressin was infused for up to 15 days, together with plasma volume expansion with intravenous albumin, the improvement in renal function was even more impressive, but serious life-threatening ischemic complications limited the use of this therapy.11 In contrast, infusion of another vasopressin analogue, terlipressin, over 48 hours improved renal function, suppressed PRA and aldosterone levels, and increased the atrial natriuretic factor levels without increasing sodium excretion, all without serious side effects.105 Lack of a natriuretic response after improvement of renal function may be related to severe liver dysfunction in these patients, as onset of natriuresis has been shown to be related to a threshold of liver function.106-109 When terlipressin was combined with either intravenous albumin110 or a renal vasodilator such as low-dose dopamine,10 the result was even more encouraging, with suppression of the renin-angiotensin activity and normalization of serum creatinine in a number of patients without serious ischemic side effects. These observations further support the concept that both splanchnic and systemic arterial vasodilatation with effective arterial underfilling, resulting in increased circulating levels of vasoconstrictors, play pathogenetic roles in the development of HRS. However, in some patients improvement in renal function persisted despite discontinuation of the vasopressin analogue, yet vasoconstrictor levels returned to their previously elevated levels.11

α-Adrenergic Agonists

In HRS, systemic vasoconstrictors such as metaraminol improved urinary sodium excretion but not renal function,111 whereas norepinephrine112 or dopamine10 were ineffective. Oral administration of an α-adrenergic agonist, midodrine, improved systemic and renal hemodynamics in nonazotemic cirrhotic patients but had no effect in patients with HRS.113 However, when midodrine was combined with plasma volume expansion and octreotide, a nonspecific inhibitor of the release of endogenous vasodilators, there was significant improvement in both the systemic and renal hemodynamics and urinary sodium excretion9 although renal function did not return to normal despite suppression of all measured neurohormonal systems to within the normal range. This may be because of continued renal hyperperfusion, maintained as a result of persistent intrarenal activation of vasoconstrictors.114

Endothelin Antagonists

Endothelin has been postulated as one such mediator of intrarenal vasoconstriction in HRS. Therefore, an endothelin antagonist was assessed in a preliminary study to determine its efficacy in reversing HRS. Consecutive and increasing doses of an endothelin antagonist, BQ123, were infused for 60 minutes in 3 patients with HRS.115 All patients showed a dose-related increase in both glomerular filtration rate and renal plasma flow that approached 100% with the highest dose. However, these results have only appeared in the form of a Letter to the Editor and therefore cannot be recommended outside a clinical trial setting.

Antioxidants

Another group of intrarenal vasoconstrictors, the products of lipid peroxidation such as F2-isoprostanes, have been implicated in the pathogenesis of HRS.116 The synthesis of F2-isoprostanes is regulated through processes of lipid peroxidation. In a recent study, 12 patients received continuous infusion of N-acetylcysteine, an antioxidant, for 5 days. Creatinine clearance improved from 24 ± 3 mL/min to 43 ± 4 mL/min without any change in liver function or systemic hemodynamics,40 suggesting that it was the reduction in oxidant stress per se that caused the improvement in renal function. Again, these are preliminary data and they need to be confirmed by clinical controlled trials. We cannot recommend this therapy outside the setting of a clinical trial.

Molecular Adsorbent Recirculating System

Molecular adsorbent recirculating system (MARS) is a modified dialysis method that uses an albumin-containing dialysate that selectively removes albumin-bound substances. The device consists of a dialysis module with an asymmetric permeable polysulfone-saturated membrane with human albumin on both the patient and dialysate sides of the membrane. During dialysis, a closed loop dialysate circuit allows the transfer of albumin-bound toxins from plasma onto the membrane. The membrane-bound albumin plus toxin is recycled by continuous deligandization. Water-soluble toxins can also be removed by using charcoal columns and ion-exchange resins as the adsorbents. The system is connected to a continuous venovenous hemofiltration system to remove most molecules except those with a molecular weight greater than 50 kd. Although conventional dialysis has not been shown to be effective in the treatment of HRS,117,118 the use of albumin-enriched dialysate fluid seems to help in the management of HRS. In a randomized controlled trial of MARS-assisted dialysis versus conventional hemodialysis and standard medical therapy,119 the patients who received MARS-assisted dialysis had a significant reduction in serum bilirubin and creatinine (from 3.8 ± 1.6 mg/dL to 2.3 ± 1.5 mg/dL) that was associated with a prolongation of survival; however, survival was still low (40%) at 2 weeks. Although hemodynamic measurements were not performed, mean arterial pressure did not change in the MARS patients. MARS dialysate removes cytokines, such as tumor necrosis factors and interleukin 6,120,121 among other substances, that have been implicated in the production of various vasodilators.70 Therefore, excessive toxins such as cytokines appear to be important in the pathogenesis of HRS but only via the intermediary of arterial vasodilation. At the very least, MARS appears to have potential as bridging therapy for HRS patients awaiting definitive treat-
ment. In addition, it may open up new avenues of research into the pathogenesis of HRS. We must await further confirmatory trials of this exciting approach. Therefore, MARS should not be used in the treatment of patients with HRS except in the context of a clinical trial.

**TIPS**

Successful insertion of a TIPS, which lowers portal pressure, was associated with improved renal function in patients with HRS, thereby supporting a central role of splanchnic portal hypertension in the pathogenesis of renal dysfunction in these patients. From a pathophysiologic point of view, TIPS returns a significant portion of the splanchnic volume into the systemic circulation, suppressing various vasoactive neurohormones, and thus improves renal hemodynamics. However, TIPS does not reverse every case of HRS, and even in those patients who do respond, it does not completely normalize renal function. This may be related to the fact that TIPS acutely exacerbates the hyperdynamic circulation. Many of the systemic vasoconstrictors such as ET1 also remained elevated post-TIPS despite refilling of the systemic circulation; this can also explain the slow recovery of renal function. In the first small controlled trial of TIPS for 25 patients with refractory ascites, a forerunner of HRS, that included 8 jaundiced Child class C patients, the mortality rate after 2 years in patients treated with TIPS was 56%, which was significantly greater than in patients treated with repeat large-volume paracentesis (29%). This finding was recently reversed, with TIPS significantly improving the chances of survival in patients with refractory ascites compared with paracentesis. However, the second study excluded cholestatic patients with serum bilirubin greater than 5 mg/dl and serum creatinine greater than 3 mg/dl. In the largest study of TIPS for HRS to date, the survival rate at 2 years was 35%. Of further interest, the patients were separated into types I and II HRS. Survival was 70% at 1 year for type II HRS patients and significantly greater than the 20% for type I HRS patients. Thus, Cox regression analysis found both HRS type (P < .05) and serum bilirubin (P < .001) to be independent survival predictors post-TIPS. It still remains to be seen whether further correction of the pathophysiology, such as reduction of portal pressure into the normal range or infusion of volume expanders, such as albumin, in the post-TIPS period, may help to return renal function to normal.

We obviously still do not understand every pathophysiologic change that occurs after TIPS nor do we know what determines which patients will or will not respond to TIPS placement. Perhaps there are critical levels of renal dysfunction and cholestatic jaundice that determine no response no matter what medical treatment is provided. The answers to these questions will have to await the results of randomized controlled trials. After that, we may be able to select the ideal candidates for TIPS insertion.

**Recommendation.** TIPS therapy for HRS should only be performed in the setting of a clinical trial, optimally with types I and II patients being studied separately.

**SUMMARY**

Recent advances made in the understanding of the pathophysiology of HRS have improved the prognosis of many patients. However, there is still a great deal to be learned about HRS. Treatments now available prolong the survival of many of these patients and allow liver transplantation to proceed more electively. Furthermore, by improving renal function before liver transplantation, we may improve patient and graft survival after transplantation and avoid the necessity of liver-kidney transplants. Alternatively, by identifying patients at risk earlier in the natural history of HRS, by using predictive indices such as the renal arteriolar-resistive index or MELD, we may be able to develop management strategies to further prevent development of HRS and thereby reduce the morbidity and mortality of these severely ill patients. Finally, future clinical trials in HRS should separate types I and II patients to clarify the therapeutic responses for both groups. These considerations are important because clinical investigators will find randomized placebo-controlled trials difficult to conduct ethically in this group of patients because of the virtual 100% mortality of HRS type I.

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