Hepatorenal Syndrome

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Abstract

Hepatorenal syndrome is a form of acute kidney injury that occurs in chronic liver disease and acute fulminant liver failure. This syndrome features a rapid progressive decline in renal function in the absence of other obvious causes of renal dysfunction. The pathophysiology of this syndrome is still not completely understood, and several mechanisms have been proposed to explain its pathogenesis. The characteristic feature of hepatorenal syndrome is intense renal vasoconstriction. The local production of vasodilator substances as a result of portal hypertension have a central role in the pathogenesis of the hepatorenal syndrome as they lead to splanchnic pooling and decreased effective systemic arterial plasma volume and renal vasoconstriction. Hepatorenal syndrome is a diagnosis of exclusion and is considered a challenging medical condition in both diagnosis and treatment as it is associated with a poor prognosis. This article will review the two main hypotheses about the pathogenesis, diagnostic criteria, and treatment approaches to the hepatorenal syndrome.

Keywords: hepatorenal syndrome, liver cirrhosis, portal hypertension, splanchnic vasodilatation, nitric oxide, hepatorenal reflex

Introduction

The hepatorenal syndrome (HRS) is a form of acute kidney injury that occurs in chronic liver disease and in acute fulminant liver failure[1] which is characterized by a rapidly progressive decline in renal function in the absence of any obvious causes of renal dysfunction. The concept of liver related kidney injury dates back to the 19th century when Frerichs, a German pathologist (1861), and Austin Flint, an American physician (1863), noted an association between advanced liver disease and oliguric renal failure in the absence of histological changes in the kidneys. In 1932, Helvig and Schutz introduced the term "a liver and kidney syndrome" to describe a type of acute renal impairment that occurred following biliary surgery, and since then the term has evolved to hepatorenal syndrome. Hepatorenal syndrome is defined as the development of renal failure in patients with chronic liver cirrhosis or in patients with fulminant hepatic failure characterized by a marked reduction in glomerular filtration rate and renal plasma flow in the absence of underlying renal pathology.[1] The renal failure is functional and reversible, since the kidneys from patients with HRS can be successfully transplanted into other patients with chronic renal failure, and the renal failure is reversible after liver transplantation.[2-4]

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DOI: 10.12746/swrccc.v6i22.439

Renal biopsies in HRS reveal thinning of proximal tubular epithelial cells with widening of tubular lumens but no glomerular abnormalities.[5] Tubular function is usually maintained with the absence of obvious proteinuria or histologic changes in the kidney.[5] Gines et al reported that the incidence of HRS is 18% at one year and 39% at five years in patients with cirrhosis and ascites.[6] A prospective study reported of 562 consecutive patients with cirrhosis and renal impairment admitted to a single institution found an HRS prevalence of 13%.[7] The

distinctive feature of HRS is severe renal vasoconstriction with splanchnic arterial vasodilation. Using Doppler-duplex ultrasonography, the estimated interlobar arterial resistance index ([peak systolic velocity-end diastolic velocity]/peak systolic velocity) was >0.70 in patients with hepatorenal syndrome compared to <0.7 in patients with liver cirrhosis without HRS.[8]

There are two subtypes of HRS. Type 1 HRS is defined as a rapidly progressive decline in renal function characterized by a doubling of serum creatinine to >2.5 mg/dl in less than two weeks.[9] It is characterized by high mortality with a median survival of 1 to 2 weeks. Type 2 HRS is not as severe as type1 HRS; it involves a slower decline in renal function with a serum creatinine of >1.5 mg/dl usually associated with diuretic refractory ascites. Rarely, type 2 HRS may progress into type 1 HRS as a result of a triggering event. The prognosis is poor and ranges from months in type 2 HRS to weeks in type 1 HRS.[9]

Pathophysiology

The hepatorenal syndrome is considered the end stage of pathophysiological changes associated with liver cirrhosis and is characterized by markedly reduced renal blood flow.[9,10] There are several theories describing the pathophysiology; peripheral arterial vasodilation is the most widely accepted explanation for the changes in renal blood flow. Hemodynamic changes, especially splanchnic vasodilatation, have a central role in the development of HRS.[10] The increased intrahepatic vascular pressure in a cirrhotic liver leads to portal hypertension, which is defined as a hepatic-portal vein pressure gradient ≥ 6 mmHg.[12] Portal hypertension subsequently leads to the release of vasodilators, such as nitric oxide and to a lesser extent carbon monoxide and endocannabinoids. The latter cause splanchnic vasodilatation with pooling of blood in the abdomen and decrease the effective blood volume.[11,12] Splanchnic pooling and plasma transudation into the abdominal cavity leads to the development of ascites.[13] The decreased effective blood volume stimulates the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) promoting renal vascular constriction and water and sodium retention, thereby aggravating the formation of ascites (Figure 1).[14]

In 1956, Hecker and Sherlock studied nine patients with advanced liver disease and renal impairment characterized by oliguria, hyponatremia, low urinary sodium

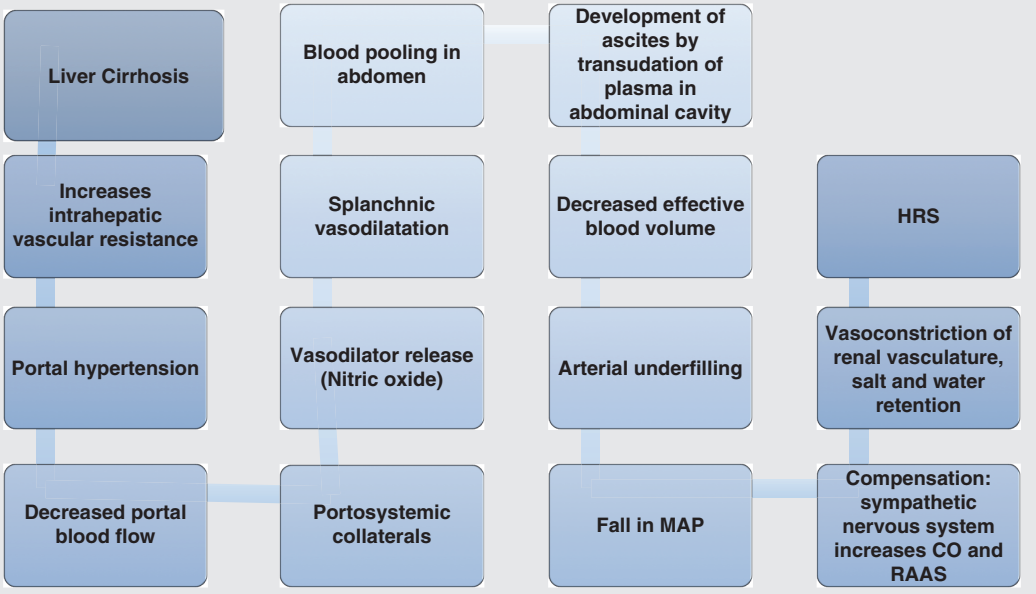

Figure 1. Flow diagram of HRS pathogenesis (vasodilatation theory).

excretion, and the absence of proteinuria. Postmortem findings showed normal renal histology in all patients. The authors correlated patients' clinical observations, such as low blood pressure, high cardiac output, and highly oxygenized peripheral venous blood, with the renal pathology and postulated that peripheral arterial vasodilation was the key underlying mechanism for the development of HRS.[15] This eventually formed the basis for the use of vasoconstrictors, such as terlipressin in the treatment for type 1 HRS. These drugs induce splanchnic vasoconstriction resulting in increased systemic vascular return and increased mean arterial pressure, which in turn suppress the RAAS and SNS and improve renal perfusion.[16]

Another hypothesis for the development of HRS involves hepatorenal reflex. It has been shown that acute reductions in blood flow or increased hepatic resistance cause rapid stimulation of the SNS resulting in renal vasoconstriction and reduced kidney function with stimulation of the RAAS (Figure 2).[16,17]

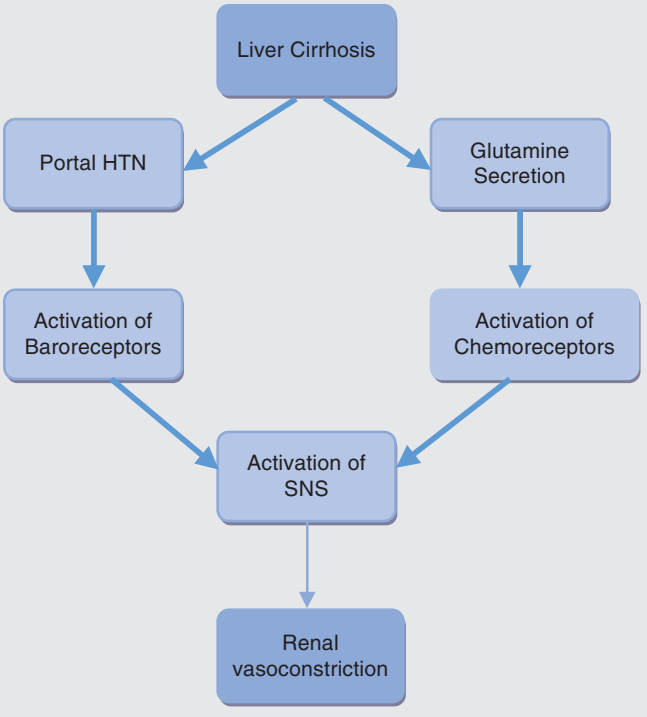

Figure 2. Flow diagram of HRS pathogenesis (hepatorenal reflex theory).

Liver cirrhosis is associated with a substantial release of glutamine into the portal vein, and that causes hepatocyte swelling and activates chemoreceptors that lead to more activation of the SNS.[17] The reflex nature of the response to low hepatic blood flow is supported by studies which show that denervation of the liver and/or kidney decreases SNS and improves renal blood flow and Na^+ excretion.[18]

Diagnosis

Hepatorenal syndrome has no specific diagnostic markers but is a diagnosis of exclusion. This diagnosis is made in patients with renal failure in association with liver cirrhosis and ascites after excluding other causes of acute renal failure.[16] A meticulous search for other causes of renal failure is essential before this diagnosis is made since the management and the prognosis may differ significantly.[19] There are several diagnostic criteria used to diagnose HRS. One of the more widely used diagnostic criteria are the International Club of Ascites criteria. These include:

1. The presence of cirrhosis and ascites
2. Serum creatinine >1.5 mg/dL or 24h creatinine clearance <40 mL/min
3. No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin.
4. The absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. The absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 RBCs/high power field, and/or abnormal renal ultrasound scanning.[20]

There are also additional criteria which include: 1) Urine volume <500 mL/day, 2) Urine sodium <10 mEq/L, 3) Urine osmolality higher than plasma osmolality, 4) Urine red blood cells <50 per high power field, and 5) Serum sodium <130 mEq/L.

However, these criteria have some limitations, especially the serum creatinine. Serum creatinine should be interpreted with caution in patients with cirrhosis, since these patients often have lower baseline serum creatinine due to reduced endogenous creatinine production related to decreased muscle mass from malnutrition, medication related increased tubular secretion of creatinine, and laboratory based underestimation of serum creatinine due to interactions with bilirubin.[21]

Prevention

At present, there are no effective methods to prevent the development of HRS. Spontaneous bacterial peritonitis (SBP) is a risk factor for HRS, and type 1 HRS occurs in 25% of patients with SBP. A prospective study demonstrated that antibiotic administration with albumin infusion in cirrhotic patients with SBP was associated with improved renal function and hemodynamics.[22] This intervention suppressed plasma renin activity and increased cardiac output and systemic vascular resistance.[22,23] Another randomized controlled trial in patients with cirrhosis and SBP showed that patients treated with antibiotics (cefotaxime) alone had a higher in-hospital (29% vs.10%) and 3 month mortality (41% vs. 22%) than patients treated with antibiotics and albumin infusions.[23] The albumin infusion group had a 66% reduction in the incidence of HRS (10% vs. 33%). In this study, albumin was given at 1.5 g/kg at the time of SBP diagnosis, followed by 1 g/kg on day 3. Renal impairment developed in 33% of cefotaxime only group and 10% in cefotaxime with albumin group. Salerno et al suggested that cirrhotic patients with a serum bilirubin > 4 mg/dl and serum creatinine >1 mg/dl are prone to develop type 1 HRS and recommended prophylactic albumin infusion in these patients.[24]

Outcome and prognosis

Prerenal failure occurs in 70% of patients with cirrhosis. Hepatorenal syndrome is the underlying etiology in 30% of these patients; the remaining patients have gastrointestinal bleeding, hypovolemia, and/or infection.[25] Hepatorenal syndrome occurs in about 20% of patients hospitalized with decompensated cirrhosis.[26] The prognosis of HRS remains very poor, with a median survival time of 2-10 weeks for type 1 and 3-6 months for type 2.[27] A nationwide retrospective study identified patients with chronic liver disease by using ICD-9-CM codes who were hospitalized between 2002 and 2012. This study showed that patients with HRS had an overall higher incidence of complications, including hepatic coma, SBP, and variceal bleeding, than patients without HRS. Furthermore, patients with HRS underwent more procedures, including renal dialysis, transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation. Overall, the outcome was worse in patients with HRS; the adjusted mortality rate was 32% with HRS vs. 10.3 % without HRS, the median hospital length of stay was 7 vs. 5 days, and hospital costs were $5,000 higher.[28]

Alessandria et al reported a retrospective study in 2005 which identified variables associated with a poor prognosis and reduced survival at 3 months; these included serum bilirubin ≥3 mg/dL, prothrombin time ≥60% of normal level, model of end-stage liver disease (MELD) score ≥20, Child-Turcotte-Pugh score >10, serum creatinine >2 mg/dL, blood urea nitrogen ≥60 mg/dL, serum sodium ≤130 mEq/L, and type 1 HRS. However, in multivariate analysis, only the MELD score and type 1HRS had independent prognostic value. Patients with type 1HRS had shorter median survival than patients with type 2 HRS (1 month vs. 6.7 months). The worse prognosis in type 1 HRS may be related to the greater impairment of renal function and severity of circulatory failure. Patients with MELD score ≥20 had a median survival of 1 month, compared to 8 months in those with a MELD <20. An increasing MELD score was associated with a progressive decline in survival of type 2 HRS patients; type 1 HRS patients had only a small reduction in survival. Both type 1 and type 2 HRS patients had a markedly lower 3 month probability of survival when compared with patients awaiting for liver transplantation.[29]

Treatment

Identifying the precipitating insult to the kidney is a critical step, especially in type 1 HRS in which kidney impairment is unlikely to be spontaneous. This

includes early identification and treatment of SBP,[30] early liver transplantation referral, and use of transplant bridging therapy, such as TIPS and vasoconstrictors, in patients with severe disease who have short survival times. In 2016, the American Association for the Study of Liver Diseases, British Society of Gastroenterology, and the European Association for the Study of the Liver recommended cefotaxime as the antibiotic of choice for SBP in addition to large-volume paracentesis for ascites greater than 5 L. Liver transplantation is the preferred treatment, but the long waiting lists make it practically difficult, and death often occurs before transplantation occurs.

Vasoconstrictor therapy

Since the speculated pathogenesis of HRS involves splanchnic vasodilation resulting in reduction of total vascular resistance, the first-line therapy for HRS is vasoconstrictors, such as vasopressin analogues (terlipressin and ornipressin) and norepinephrine. Oral midodrine is also used in patients who are hemodynamically stable. Vasoconstrictors are administered along with albumin to help expand the intravascular volume which is reduced in cirrhosis.

Terlipressin activates V1 receptors resulting in vasoconstriction which increases splanchnic vascular resistance and raises the arterial blood pressure. Several clinical studies have shown improvement in kidney function and blood pressure with terlipressin treatment.[31-33] A randomized controlled trial with 46 patients with cirrhosis and HRS compared the outcomes with terlipressin administration with albumin against albumin alone in patients with cirrhosis and either type 1 or 2 HRS.[34] A significant improvement in renal function in terlipressin with albumin group was noted as indicated by the decrease in serum creatinine (43.5% vs. 8.7%) and improvement in arterial blood pressure. Although the survival at 3 months was not significantly different between the groups, the survival rate across their study was higher than the actual rate of patients who received no treatment.

Terlipressin is an expensive drug and not widely available. Hence, noradrenaline is often used as an alternative. Noradrenaline is a strong alpha receptor agonist which increases vascular resistance. It also acts as a mild beta-agonist and improves cardiac output.[35] A head-to-head randomized controlled trial of 46 patients with type 2 HRS compared terlipressin therapy to noradrenaline with albumin infusion and demonstrated a significant reduction in serum creatinine, with increased mean arterial pressures, urine output, and urine sodium excretion in both groups.[36] There was no difference between the two groups in the 90 day survival rate, and no major adverse effects occurred in either group. However, noradrenaline was less expensive. A similar study reported an improvement in renal failure in patients with type 1 HRS but no difference in hemodynamic parameters or 30 day survival rates.[37] The study concluded that noradrenaline is as effective as and less expensive than terlipressin ($p < 0.05$).

Oral midodrine with subcutaneous octreotide is also used in HRS treatment. Midodrine is an alpha-receptor agonist that increases systemic blood pressure. Octreotide is an antagonist of endogenous vasodilators which cause splanchnic vasodilation and increases vascular resistance. The combination of midodrine and octreotide theoretically improves hemodynamics and consequently improves renal function. Cavallin and colleagues[38] conducted a randomized controlled trial on patients with HRS to compare terlipressin plus albumin (27 patients) therapy to midodrine and octreotide plus albumin (22 patients). This study revealed a better recovery rate from HRS and lower MELD scores in the terlipressin plus albumin group. However, the 30 day and 90 day survival rates remained similar between the groups. A meta-analysis by Gluud et al[39] investigated 10 randomized trials (367 patients) to evaluate the outcome of vasoconstrictor drugs in reducing the mortality in patients with type 1 or type 2 HRS. The study interventions included: (1) terlipressin alone or with albumin, (2) octreotide plus albumin, or (3) noradrenalin plus albumin. Treatment with terlipressin plus albumin was associated with a short-term mortality reduction in patients with type 1 HRS but not in patients with type 2 HRS. Trials using octreotide and noradrenaline therapies were smaller and found neither harmful nor beneficial effects from these treatments. A recent meta-analysis included studies using terlipressin, midodrine, octreotide, noradrenaline, and dopamine

alone or in combination with placebo or each other along with albumin. This study included 13 randomized controlled trials.[36] Terlipressin was shown to reduce the short-term mortality compared to placebo, which was supported by moderate-quality evidence. However, only low-quality evidence supported the use of noradrenaline or midodrine plus octreotide over placebo to reduce the short term mortality. Overall, both terlipressin with albumin and noradrenaline with albumin were superior to midodrine plus octreotide with albumin for reversal of HRS (OR 26.25, 95% CI 3.07-224.21 and OR 4.17, 95% CI 1.37-12.5, respectively).

Albumin dialysis

Albumin dialysis is an option as a rescue therapy before liver transplantation is available. The Molecular Adsorbent Recirculating system (MARS) is a modified dialysis using albumin-enriched dialysate to remove albumin-bound and hydrophobic toxins in the blood that are not removed by conventional dialysates. An observational study by Wong et al assessed the outcome of MARS in six HRS patients who did not respond to vasoconstrictor treatment.[37] There were no significant changes in systemic hemodynamics and glomerular filtration rate post-treatment, despite a significant reduction of nitric oxide which is believed to have an important role in splanchnic vasodilation. An earlier randomized controlled trial demonstrated a significant survival benefit in MARS group compared to the conventional-hemodialysis group (25.2 $\pm$ 34.6 days vs. 4.6 $\pm$ 1.8). A larger retrospective study by Lavassiere et al[40] in 32 type 1 HRS patients who underwent MARS therapy reported a survival rate of 47% at day 28. Forty percent of the patients had improved renal function with lower serum creatinine and higher glomerular infiltration rates.

Transjugular intrahepatic portosystemic shunt

A transjugular intrahepatic portosystemic shunt (TIPS) is a low-resistance shunt connecting the intrahepatic portal vein and the hepatic vein to reduce portal pressure by shunting blood from portal to systemic circulation bypassing a diseased liver. This helps return blood volume from splanchnic into the systemic circulation. Consequently, it improves venous return and cardiac output leading to a reduction of the renin-angiotensin-aldosterone response and increased blood flow to kidneys. The efficacy of TIPS was evaluated in 14 cirrhotic patients with HRS who failed prior medical therapy with albumin, midodrine, and octreotide. The TIPS procedure improved renal function with increasing GFR and renal blood flow and reduced renal vascular resistance.[41] In another study of patients with HRS, TIPS significantly improved the survival rates at one year post-procedure when compared to non-shunted patients.[42] New onset or worsening encephalopathy after TIPS was reported in 20-31%.[43] Fewer studies have evaluated the role of TIPS in the treatment of HRS compared to its role in refractory ascites. These shunts prevent and treat ascitic fluid re-accumulation and consequently should reduce the incidence of SBP, a known risk factor for the development of HRS; consequently, outcome studies in patients with TIPS seem relevant. Transjugular intrahepatic portosystemic shunts might be an effective therapy for patients with type 2 HRS, who commonly develop refractory ascites, do not tolerate frequent large volume paracentesis, and are not candidates for liver transplantation.

Liver transplantation

The preferred treatment for hepatorenal syndrome is liver transplantation. However, the majority of patients die before an organ is available. A retrospective review of the outcome of 62 liver transplanted patients for advanced cirrhosis and type 1 HRS showed HRS reversal in 76% at a mean interval of 2 weeks following transplantation. Patients who had a reversal of HRS lived significantly longer compared than patients with no reversal of HRS (median of 77 vs. 50 months).[44] Predictive indicators for non-reversal of HRS included pre-transplant dialysis duration with a 6% increase in risk for every day of dialysis. A cut off point of 14 days showed a significant risk increment that was 9 times more unlikely to have an HRS reversal. The incidence of chronic kidney disease post-transplant was similar in a recent study comparing the outcomes of living versus deceased donor liver transplantation in patients with HRS.[45] Overall,

the survival rate at 3 years was approximately 60%, which was only slightly less than transplant recipients without HRS (70-80%), and was much better than the survival rate of patients without transplantation (0%).

Conclusion

Patients with chronic liver disease and ascites admitted to the hospital have an increased risk for the development of HRS. In particular, patients with spontaneous bacterial peritonitis are at risk for this syndrome. The renal dysfunction develops as a consequence of blood pooling in the splanchnic circulation resulting in vasoconstriction and reduced renal plasma flow. Patients with a type 1 HRS develop acute changes over 2 weeks or less. Patients with type 2 HRS develop changes in renal function over longer periods of time. The diagnosis depends on exclusion of other causes of renal dysfunction and the measurement of serial changes in creatinine with the creatinine >1.5 mg/dl. The prognosis in patients with type 1 HRS is quite poor. Initial management usually requires the administration of terlipressin or norepinephrine with albumin. Some patients have improved with modified dialysis using albumin enriched dialysate or with the placement of a transjugular intrahepatic portosystemic shunt. When possible, patients should be referred for liver transplantation.

Article citation: Shredi A, Suchartlikitwong S, Edriss H. Hepatorenal Syndrome. Southwest Respiratory and Critical Care Chronicles 2018;6(22):21–28.
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX
Submitted: 7/23/2017
Accepted: 1/6/2018
Reviewers: Sreeram Parupudi MD
Conflicts of interest: none

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