Hepatorenal syndrome

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Hepatorenal syndrome (HRS) is defined as a functional renal failure in patients with liver disease with portal hypertension and it constitutes the climax of systemic circulatory changes associated with portal hypertension. This term refers to a precisely specified syndrome featuring in particular morphologically intact kidneys, where regulatory mechanisms have minimised glomerular filtration and maximised tubular resorption and urine concentration, which ultimately results in ureaemia. The syndrome occurs almost exclusively in patients with ascites. Type 1 HRS develops as a consequence of a severe reduction of effective circulating volume due to both an extreme splanchnic arterial vasodilatation and a reduction of cardiac output. Type 2 HRS is characterised by a stable or slowly progressive renal failure so that its main clinical consequence is not acute renal failure, but refractory ascites, and its impact on prognosis is less negative. Liver transplantation is the most appropriate therapeutic method, nevertheless, only a few patients can receive it. The most suitable “bridge treatments” or treatment for patients ineligible for a liver transplant include terlipressin plus albumin. Terlipressin is at an initial dose of 0.5-1 mg every 4 h by intravenous bolus to 3 mg every 4 h in cases when there is no response. Renal function recovery can be achieved in less than 50% of patients and a considerable decrease in renal function may reoccur even in patients who have been responding to therapy over the short term. Transjugular intrahepatic porto-systemic shunt plays only a marginal role in the treatment of HRS.

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Key words: Liver cirrhosis; Hepatorenal syndrome; Ascites; Vasoconstrictors; Terlipressin

PATHOPHYSIOLOGY

The organic intactness of kidneys, a condition for the diagnosis of this syndrome, has been demonstrated repeatedly in terms of morphology as well as by normal function of kidneys from an individual with hepatorenal syndrome (HRS) transplanted to a person without any liver disease. The main pathophysiological mechanisms include increased renal arterial resistance, especially affecting the cortex of kidneys, which results in renal hypoperfusion, and arterial hypotension. The small volume of the ultrafiltrate is reabsorbed almost completely in the proximal tubule whereas almost a zero quantity of sodium flows to the Henle’s loop. As a result, enhanced aldosterone activity is of little application in this phase and standard diuretics have no effect either. Due to the diuretin-vasopressin activity, final urine is produced through an essentially zero hyperosmolar natriuresis, and its quantity ranges between oliguric and anuric values. Under such conditions, the local prostaglandin regulation system, which is of little clinical significance other-
wise, comes to play a crucial role in the maintenance of residual renal perfusion, and its elimination (e.g., by nonsteroidal antiinflammatories) can have distinct consequences.

The principal mechanisms leading to renal vasoconstriction consist of alterations in systemic circulation, accompanying portal hypertension\textsuperscript{[8]}, which are represented by decreased peripheral vascular resistance with subsequent vasodilatation (a consequence of the hyperactivity of vasodilating agents), central hypervolemia, hyperkinetic circulation, and the activation of compensatory mechanisms, i.e., the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and adrenergic-vasopressin. What is more, adenosine, for example, which has a vasodilating effect in most tissues, produces vasoconstriction in kidneys\textsuperscript{[9]}. The direct impact of the SNS and RAAS also stimulates the reabsorption of sodium in the proximal tubule\textsuperscript{[10]}

It is important to point out that renal vasoconstriction itself is not sufficient for the development of hepatorenal syndrome. Arterial hypotension is the key factor which, even if it does not reach shock values, causes simultaneous renal vasoconstriction and renal hypoperfusion with decreased glomerular filtration\textsuperscript{[11]}. Thus, cardiac output is the relevant factor. Cardiac output may be low, normal or high, but is relatively insufficient\textsuperscript{[12]} to prevent a severe reduction of effective circulating volume due to the splanchnic arterial vasodilatation in patients with HRS. The reasons why cardiac output is relatively insufficient in end-stage liver disease is still unknown, but in recent years several specific cardiac abnormalities, such as reduced systolic and diastolic responses to stress stimuli, electrophysiological repolarisation changes or enlargement of cardiac ventricles, have been recognised as so-called “cirrhotic cardiomyopathy”\textsuperscript{[13,14]}

In addition to this, other factors such as the release of endotoxins and a further release of biologically active substances such as inflammatory cytokines, nitric oxide, carbon monoxide and others as a result of a bacterial infection may further impair cardiac function in patients with end-stage liver disease.

The once considered theory of a direct reflex link between the liver (or the portal system) and renal circulation has been abandoned lately, although several experiments in the past managed to prove renal vasoconstriction (accompanied by renal function alterations in terms of sodium and water retention) as a result of portal (or intrasinusoidal) pressure elevation\textsuperscript{[15,16]}

Because the above-mentioned circulatory alterations can virtually be observed from very early stages in diseases with portal hypertension, HRS has to be viewed as their climax, and the refractory ascites stage constitutes a significant turning point in such development. Nevertheless, there is surprisingly little connection to the progression of hepatic lesions; in other words, it cannot be assumed automatically that a patient with HRS has reached their terminal liver failure stage. In fact, a patient with a Child-Pugh Score of 8 or less has the same risk of HRS development as a patient in C class. In this respect, determination of sympathetic activity (plasma noradrenaline) or RAAS\textsuperscript{[17]}, or renal arterial resistance (“resistive index” in ultrasonography) has a considerably better prognostic value\textsuperscript{[18]}. In principle, a high risk of hepatorenal failure must be expected in patients with liver disease and ascites, with an indication of dilution hyponatremia, with tachycardia and mean arterial pressure below 80 torr.

Consistent with the adopted diagnostic criteria, it would be suitable to differentiate between diagnoses of “hepatorenal syndrome” and “hepatorenal failure”. In both cases, the clinical parameters of renal function are identical; however, the fundamental difference lies in the circumstances of their occurrence and prognosis. Hepatorenal syndrome means a precisely specified state of kidney function failure where all of its eliminable causes and precipitant factors have been excluded. “Hepatorenal failure” is a more general term which can be applied to any kidney function failure in liver disease with portal hypertension which adds a significant disposition to it. This implies that the presence of liver disease with liver function alterations and with portal hypertension is of crucial importance as well as the absence of an organic renal defect (proteinuria < 0.5 g/d, erythrocyturia < 50/field of view in high-resolution, normal ultrasound findings in kidneys and the excurrent duct system).

### CLINICAL PRESENTATION

HRS occurs almost exclusively in patients with ascites. The occurrence probability in patients having an ascites for more than 5 years reaches 40%. Besides the above-mentioned laboratory prognostic factors, ascitic patients with a small liver, oesophageal varicose veins and an unbalanced diet have a higher risk of HRS incidence. Dilution hyponatremia, tachycardia and arterial hypotension with a mean arterial pressure of approximately 80 torr or less must be perceived as warning signs.

The prevalence of HRS in patients affected by liver cirrhosis with ascites is in effect equal to 18% after 1 year, rising to 39% at 5 years. In almost half of the cases of HRS, one or more precipitating factors can be identified, among which we can include bacterial infections (57%), gastrointestinal haemorrhage (36%) and therapeutic paracentesis (7%)\textsuperscript{[19]}

According to the progression, or more precisely according to clinical seriousness, HRS can be classified in 2 types\textsuperscript{[15]}: Type 1 - rapidly progressive, where the serum creatinine doubles in 2 wk and values of approximately 350 μmol/L (2.5 mg/dL) are usually achieved. This type accompanies clinically more serious conditions and it is typically unstable. Its main clinical feature is acute renal failure. Type 2 - slowly progressive, this state was described later and, despite the otherwise typical signs of hepatorenal failure, it is quite stable. Serum creatinine rises slowly or not at all and it usually does not exceed 180 μmol/L (1.3 mg/dL). The clinical record is dominated by refractory ascites and relatively stable liver function\textsuperscript{[20]}

The difference in prognosis between the two types
Hepatorenal syndrome

of HRS is essential as the median survival of type 1 is about 2 wk while that of type 2 is generally around 4-6 mo\(^{[7]}\). Type 1 HRS is often induced by the occurrence of a precipitating stimulus. The important factor seems to be infections (e.g., urinary tract infections and infections of the biliary or intestinal tract)\(^{[8]}\) but the most important thing is the development of a spontaneous bacterial peritonitis\(^{[9]}\). Almost one third of patients with spontaneous bacterial peritonitis develop a non-transient form of renal failure which in most cases fits the diagnostic criteria of type 1 HRS. The independent predictive factors for the development of renal failure as a consequence of bacterial infections are the severity of infection, the model for end-stage liver disease score at the diagnosis of infection and the lack of resolution of infection by means of antibiotics\(^{[10,11]}\).

Up to the end of the last century, the prognosis for cirrhotic patients developing HRS was very poor. Thereafter, some new effective treatments of HRS which improve survival have been introduced with encouraging results.

**DIAGNOSIS**

There is no specific test to determine an unequivocal diagnosis of HRS. The prime finding consists of reduced glomerular filtration (creatinine clearance) < 40 mL/min or serum creatinine increase > 135 μmol/L under the exclusion of other causes of renal failure. The most relevant indications of the functional character of such failure include: natriuresis < 10 mmol/L, urine osmolality higher than plasma osmolality, natremia < 130 mmol/L and diuresis < 500 ml/d.

The criteria for diagnosing HRS have recently been re-examined by the International Ascites Club\(^{[20]}\) (Table 1).

The main changes in the new diagnostic criteria of HRS as compared to those previously used\(^{[21]}\) are the removal of minor diagnostic criteria and the removal of ongoing bacterial infection as an exclusion criterion for the diagnosis of HRS. Other important changes are that plasma volume expansion should no longer be performed with saline but with albumin, and creatinine clearance is no longer considered as a tool for diagnosis. The presence of shock, even of septic shock, as well as previous treatment with nonsteroidal anti-inflammatory drugs, other nephrotoxic drugs (i.e., aminoglycosides) and vasodilators (i.e., nitrates, prazosin and renin-angiotensin system inhibitors) are still considered exclusion criteria for the diagnosis of HRS, along with the presence of proteinuria, hematuria or ultrasound alterations of the kidneys.

In clinical practice, it is absolutely essential to examine urinalysis and sodium concentration in urine in order to differentiate organic renal insufficiency.

Certain diagnostic difficulties regarding differentiation may be the result of acute tubular necrosis which has been observed by approximately 5% of patients dying of renal failure. It is potentially reversible and is characterised by higher Na concentration in urine, iso-osmolar urine, and the ratio of urine and plasma creatinine below 20:1. This disease often develops after the administration of a contrast medium to cirrhotic patients in computed tomography examination. Therefore, a very precise indication for use of computed tomography is required by such patients, or a substitution by magnetic resonance.

Even the presence of hepatitis B and C virus can damage kidneys as it leads to membranous glomerulonephritis or vasculitis as well as chronic autoimmune liver disease. In such patients, renal failure may also be induced by cyclosporine treatment.

Finally, it is again worth pointing out that the risk of an organic renal defect tends to be higher in patients with advanced liver disease due to the impact of reduced blood perfusion of kidneys as well as alterations of immune and metabolic functions, and this needs to be taken into account.

**TREATMENT**

Although HRS is a terminal manifestation of portal hypertension in parenchymatous liver disease, it no longer ranks among the fundamentally insolvable issues. In specific cases, however, availability matters and the rational and ethical grounds for this rather costly treatment have to be considered.

**Influence on causative factors**

If there are indications of renal failure, first of all, the causative factors have to be eliminated and treated, such as: elimination of nephrotoxic medications; elimination or treatment of a suspect bacterial infection including spontaneous bacterial peritonitis with focus on gram-negative flora; elimination of bleeding in gastrointestinal tract and, if need be, adequate compensation for losses; elimination of nonsteroidal antiinflammatories; elimination of diuretics (they enhance central hypervolemia and the sympathetic and RAAS activity); supplementation of intravascular volume, preferably through hypoalbuminemia correction (albumin is the most reliable volume expander with the longest lasting impact). Another effect, even if just transitory, may be brought about by the

| Table 1 New diagnostic criteria of hepatorenal syndrome |
|-----------------------------------------------|
| **New diagnostic criteria of hepatorenal syndrome** |
| Cirrhosis with ascites |
| Serum creatinine > 133 μmol/L (1.5 mg/dL) |
| No sustained improvement of serum creatinine (decrease to a level of 133 μmol/L or less) after at least 2 d of 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/d |
| Absence of shock |
| No current or recent treatment with nephrotoxic drugs |
| Absence of parenchymal disease as indicated by proteinuria > 500 mg/d microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography |

WJG | www.wjgnet.com 4980 September 28, 2012 | Volume 18 | Issue 36 |
partial evacuation of tension ascites accompanied by a consistent compensation for albumin. Efforts concerning hyponatremia substitution must be avoided (risk of cerebral oedema) - fluid restriction is more suitable.

Liver transplantation
Naturally, liver transplantation is the only rational solution in cases of advanced liver disease. However, the presence of a kidney function failure considerably aggravates the prognosis of such patients\[34,35\].

During the last century, only a few patients with HRS underwent liver transplantation, because most patients died before surgery as a consequence of the rapid evolution of type 1 HRS.

Novel treatment approaches, especially terlipressin plus albumin therapy, provide a “treatment bridge” towards liver transplantation. Treatment with terlipressin 4-6 mg/d for up to eight mo has been described, completed by successful liver transplantation\[26,27\]. The number of transplanted patients is still very low, however. In a prospective study, none of 15 type 1 HRS patients referred to a tertiary care transplant centre was transplanted: 12 patients had contraindications against transplantation and the remaining three patients died while awaiting transplantation\[28\].

Hypovolemia correction
With regards to the fact that the HRS laboratory finding is similar to prerenal uraemia, attempts have been made since the very beginning to influence this syndrome by means of hypovolemia correction. A physiological solution or Dextran has been administered, which is unfortunately inappropriate in this case. Nevertheless, human albumin has proven the most suitable. Nowadays, it is used for expansion of circulatory blood volume and has been shown to successfully reduce the incidence of HRS type 1. When used for treatment of HRS, it has shown better results when used in combination therapy as it amplifies the effect of other pharmacologic therapies in the treatment of HRS. Often, the quantity to be administered is high - up to 50 g/d. Anyway, hypovolemia correction is required before, as well as during, the subsequent treatment with medicaments\[29\] and albumin is now the basis of the therapy in combination with vasoconstrictors.

Vasoconstrictors
The first group of medicaments used for this indication in an effort to reduce intrarenal vascular resistance were prostaglandins. In spite of the fact they used to be recommended, they have not shown any provable improvement in renal function\[30\].

On the other hand, the application of systemic vasoconstrictors has been justified with respect to known pathogenetic factors. In HRS, marked reduction of effective circulating volume was found, which is related to a splanchnic arterial vasodilation and inadequate cardiac output, which implies an extreme overactivation of the endogenous systemic vasoconstrictor systems, i.e., the RAAS, SNS and nonosmotic release of vasopressin. This means that the final aim of the therapeutic approach is to reduce severe renal arterial vasoconstriction\[31\]. In the early years of treatment, dopamine was tested in a small to medium dose. Dopamine has been shown to reduce renal vascular resistance and increase renal blood flow. It was therefore thought to be potentially useful in the treatment of HRS and was tested in a small to medium dose. But its clinical effect has not been confirmed unequivocally\[32\], alone or even in combination with ornipressin\[33\].

Nonetheless, the application of synthetic analogues of vasopressin-terlipressin (N-triglycyl-8-lysine-vasopressin synthesised in the laboratories of the Czechoslovak Academy of Sciences in Prague, Czech Republic in 1964), or ornipressin represented a considerable step forward. Analogues act on the abundant V1 receptors in the splanchnic vasculature, causing greater vasoconstrictive effects in the mesenteric circulation than in renal or other vascular systems.

In retrospective studies, as well as in small prospective pilot studies, it has been demonstrated that prolonged use of an ornipressin\[33,34\], terlipressin\[35-48\] or α-agonist vasoconstrictor (midodrine plus octreotide, noradrenaline alone)\[49-56\] in association with human albumin is capable of recovering renal function in 40%-60% of patients with type 1 HRS. The use of ornipressin was, however, abandoned because of its high rate of ischemic side effects.

Currently, terlipressin is the preferred product. Treatment with terlipressin and albumin has become a major breakthrough in the field of cirrhosis\[37\]. It has been used in a broad range of HRS treatment applications and there are many studies demonstrating its efficiency. In 2006, The Cochrane Library published a review with the conclusion that terlipressin treatment was promising but its results had to be confirmed\[38\].

Nowadays, however, it has become the clearly preferred treatment in general recommendations and is the most widely used agent in the treatment of type 1 HRS. The terlipressin treatment protocol comprises an initial dose of 0.5-1 mg terlipressin applied by intravenous injection every 4-6 h or continuous intravenous infusion starting at an initial dose of 2 mg/d. Unless the creatinine level has dropped by 25% on the third day, the dose is raised to 2 mg every 4 h or 12 mg/d by continuous intravenous infusion, respectively. Intravenous albumin is administered in case of failure to maintain the central venous pressure at 10-15 cm H\(\text{O}\) (initially 1 g of albumin/kg for two days up to a maximum of 100 g/d followed by 20-40 g/d)\[59\].

The treatment continues until laboratory values have improved, otherwise no longer than 2 wk. Complete reversal (i.e., decrease of serum creatinine with a final value < 133 μmol/L) or partial reversal (defined with a decrease of serum creatinine > 50% with a final value ≥ 133 μmol/L) of type 1 HRS has been observed in almost 59% of patients\[60\].

Usually, diuretics are not administered during therapy...
with terlipressin and albumin; however, some surveys have used furosemide and albumin. Type 2 HRS is more frequent in clinical practice than type 1 and liver transplantation can cure this syndrome as well as other complications relating to hepatic insufficiency. Treatment efficiency has reached 80% in this indication. Nevertheless, recurrence is very common after discontinuation of treatment.[61]

Recurrence of HRS after treatment withdrawal (i.e., a sharp increase in serum creatinine within a few days) occurs in approximately 20% of patients. Treatment with terlipressin should be repeated in these patients and this measure is frequently effective. This can result in long-term treatment (up to 8 mo) in some cases. The dose of terlipressin can be up to 4-6 mg/d and albumin up to 100 g/d.[20,27,59]

An important question is prediction of response to this treatment. The most consistent predictor of response to terlipressin and of survival is the baseline serum creatinine, bilirubin and an increase in mean arterial pressure of ≥ 5 mm Hg at day 3 of treatment. Patients most likely to benefit from terlipressin have earlier onset renal failure [i.e., serum creatinine < 445 μmol/L (5.0 mg/dL)]. The cutoff level of serum bilirubin that best predicted response to treatment was 170 μmol/L (10 mg/dL). Improvement in the hyperdynamic circulation (measured by sustained rise in mean arterial pressure) is also important for reversal of HRS.[62,63]

Other treatment alternatives, with a similar effect on circulatory parameters, may include alpha-adrenergic agonists. Their advantage compared to terlipressin is their lower price, but they seem to be less effective than terlipressin now. Several small studies have shown promise for norepinephrine in the treatment of HRS, however just one study showed a better (but not statistically significant) response to terlipressin.

Miodrline is an alpha-agonist and appears more convenient than norepinephrine. It offers the advantage of oral administration; however it was used in combination with octreotide (and albumin). It has been shown to moderately improve the systemic and renal hemodynamics.

**Transjugular intrahepatic portosystemic shunt**
Transjugular intrahepatic portosystemic shunt (TIPS) interferes with the hepatorenal reflex and brings about reduced sympathetic and RAAS activity through intensified hyperdynamic circulation. TIPS results in a positive effect on renal function, including HRS, demonstrated by a rapid increase in urinary sodium excretion, urinary volume, and improvement in plasma creatinine concentration. Its positive impact on renal function in liver cirrhosis with ascites has already been proven in several studies.[64-67] The first prospective survey with a well-documented type 1 HRS was published as early as 1999[88] and the effectiveness of TIPS has been confirmed since. TIPS can be applied to patients with a certain liver function reserve, either as a bridge treatment extending the waiting period for a liver transplant, or as a long-term, definitive therapy in case of satisfactory and stabilised liver function. As a rule however, the curative effect only comes after several days or weeks following intervention.[89]

According to surveys published to date, it has been effective in ascites treatment in principle, and moreover, it can contribute to improvement of renal function.[70,71]

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