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Hepatorenal syndrome[1)]

Hepatorenales Syndrom

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Abstract

This article summarizes the literature on current definition, suggested pathogenetic mechanisms and the role of laboratory assessment in the differential diagnosis of hepatorenal syndrome (HRS) from other causes of renal disease that may arise during hepatic cirrhosis and some diseases affecting both liver and kidney. It should be remembered that the main theory suggested for the pathogenesis of HRS is the arterial vasodilation hypothesis of portal hypertension, ending in type 1 and type 2 HRS, but there is no consensus supporting either mechanism as a solid theory for initiation of HRS pathogenesis to date. No laboratory test can firmly establish a diagnosis of HRS, which is mainly based on the absence of any specific cause of renal failure. Laboratory and ultrasonographic tests based on non-invasive techniques are being investigated as possible diagnostic approaches.

Keywords: cystatin C; hepatorenal syndrome; laboratory assessment.

Zusammenfassung

Dieser Artikel fasst die Literatur über die derzeitige Definition, die angenommenen pathogenetischen Mechanismen und die Rolle labormedizinischer Tests in der Differentialdiagnose des Hepatorenalen Syndroms (HRS) zusammen. Ziel der Differentialdiagnose ist die Abgrenzung des HRS von anderen Ursachen renaler Störungen, wie sie bei Leberzirrhose und anderen Leber und Nieren betreffenden Krankheiten auftreten können. Laut der gängigen Theorie zur Pathogenese des HRS liegen seine Ursachen in arterieller Vasodilatation und portaler Hypertension, die zu Typ 1 und Typ 2 HRS führen, aber es gibt bis heute keinen Konsens, der diese Mechanismen mit Gewissheit als Auslöser der Pathogenese des HRS identifiziert. Kein Labortest kann sicher zur Diagnose des HRS führen, sie beruht daher hauptsächlich auf dem Ausschluss anderer Gründe für ein festgestelltes Nierenversagen. In der diagnostischen Vorgehensweise wird versucht, entweder labormedizinische Tests oder nichtinvasive Ultraschalluntersuchungen zur Klärung dieses Problems zu etablieren.

Schlüsselwörter: Cystatin C; Hepatorenales Syndrom; Labortests.

Introduction

Hepatorenal syndrome (HRS) is a serious complication in the patient with cirrhosis and ascites, and is characterized by worsening azotemia with avid sodium retention and oliguria in the absence of identifiable specific causes of renal dysfunction [1]. A more current definition of HRS has been established by an international consensus conference organized by the International Ascites Club [2]. According to this definition, HRS is a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure, and portal hypertension characterized by impairment of renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. There are two types of HRS, type 1 and 2.

Type 1 HRS involves an acute deterioration in renal function, as defined by doubling of the initial serum creatinine to a level greater than 225 μmol/L, or a 50% reduction in initial 24-h creatinine clearance to <20 mL/min over days or weeks, and occurs in an advanced stage of liver disease. The development of type 1 HRS has poor prognosis, with 80% mortality, and 50% of cases are precipitated by gastrointestinal bleeding, infection, dehydration from overt paracentesis or diuresis, surgery, or drug exposure, with the remaining 50% occurring

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spontaneously [1–5]. Such patients are commonly oliguric or anuric.

Type 2 HRS occurs in patients with relatively preserved liver function. These patients show a slow but progressive deterioration in glomerular filtration rate (GFR). This type of HRS usually occurs in patients with diuretic-resistant ascites. It is associated with poor prognosis, although the survival time is longer than that of patients with type 1 HRS [6]. According to a recent study, among the possible etiologies of HRS, underlying alcohol-related liver disease may be more commonly associated with HRS compared to other etiologies [7]. In vivo studies on the effects of alcohol on liver metabolism resulting in HRS are rare. Most studies are still based on experimental evaluations in the rat [3, 8].

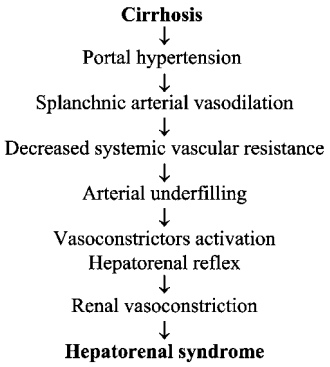

Figure 1 Pathogenesis of HRS according to arterial vasodilation theory.

Pathogenetic mechanisms and modulators

To date, several factors have been implicated in the pathogenesis of HRS [9, 10]. In recent studies, the peripheral arterial vasodilation hypothesis has become generally accepted [11, 12]. According to this hypothesis, a primary decrease in splanchnic and vascular resistance causes hyperdynamic circulation, with decreased systemic vascular resistance and increased cardiac output and arterial underfilling in the presence of portal hypertension [13, 14]. The decrease in effective arterial blood flow is possibly the first hit on renal hemodynamics. The kidney is ready to protect itself by inducing intrarenal local vasodilatory substances. However, a break point occurs in renal compensatory mechanisms by the activation of vasoconstrictors, etc., which we call the second hit. Moreover, sinusoidal portal hypertension can induce increased renal sympathetic activity; this interaction is known as the hepatorenal reflex [15]. Thus, a crucial imbalance between intra- and extra-renal vasoactive substances and complex neural interactions between the liver and kidneys lead to suitable conditions for the development of HRS (Figure 1).

The exact mechanism of the vasoconstriction is not well known. Several potential mediators play a contributory role in the pathogenesis and include the factors listed in Table 1.

Nitric oxide (NO)

Endogenous production of NO has been found to be uniformly increased in cirrhotic patients [16–19] and inhibition of NO synthesis reverses some of the systemic and splanchnic circulatory changes in animal models or patients with liver cirrhosis [20, 21]. Increased vascular production of NO has been proposed as the primary cause of arterial vasodilatation and the hyperdynamic circulation in cirrhosis. Cirrhosis-associated endothelial dysfunction seems to invalidate the capability of intrarenal vasculature to produce NO [22] and deficient NO release in these vascular tissues might contribute to the development of HRS. Furthermore, renal vasoconstriction may occur in the presence of enhanced glomerular nitrite production, and this finding suggests that renal microcirculation in cirrhosis is less sensitive to NO [23]. Splanchnic and systemic vasodilatation caused by the increased levels of NO leads to renal vasoconstriction by activation of endogenous vasoconstrictor systems. This phenomenon can be considered as the basis of the progressive renal failure that leads to HRS.

Prostaglandins

Renal prostaglandins play an important role in the preservation of renal function in all situations, such as dehydration, congestive heart failure, shock, or decompensated liver disease. In liver disease, urinary excretion of prostaglandin E2 and prostacyclin metabolites (6-oxo-PGF 1α) are usually increased. The mechanism of increased synthesis is unknown, but is likely to be secondary to increased several vasoconstrictors that induce prostaglandin formation in vitro or in vivo [24–27]. Non-selective inhibition of cyclo-oxgenase by non-steroidal anti-inflammatory drugs (NSAIDs) causes a significant decrease in renal blood flow and GFR in patients with cirrhosis and ascites, but in these patients selective cyclooxgenase-2 (COX-2) inhibition does not affect renal functions [28]. These results suggest that COX-1-derived prostaglandins are involved in the homeostasis of renal functions in patients with cirrhosis and a decrease in vasodilator prostaglandin production may participate in renal vasoconstriction in HRS.

Table 1 Mediators that contribute to the pathogenesis of HRS.

Vasodilators	Vasoconstrictors
Nitric oxide	Norepinephrine
Prostaglandin E_2	Endothelin 1
Prostacyclin	F_2-Isoprostanes
Adrenomedullin	Cytokines (TNF, IL-6)
	Angiotensin II
	Antidiuretic hormone

Adrenomedullin

Adrenomedullin is a peptide hormone that is highly expressed in cardiovascular tissues and has potent and long-lasting vasodilatory activity. Plasma levels of adrenomedullin were found to be increased in cirrhotic patients and were inversely correlated with arterial pressure, GFR, renal plasma flow, and creatinine clearance [29, 30]. The pathophysiological role of adrenomedullin in the development of HRS is not clear.

Norepinephrine

The relation of renal vasoconstriction and increased sympathetic activity to cirrhosis and HRS has been shown by increased levels of circulating norepinephrine [31] and increased release of norepinephrine in neuroeffector junctions [32]. Furthermore, it has also been indicated that plasma norepinephrine levels, mean arterial pressure, urinary sodium excretion, and GFR are better predictors of survival than markers routinely used to assess hepatic function in cirrhotic patients [33, 34]. The mechanisms of renal vasoconstriction have not yet been fully elucidated in the development of renal failure in patients with HRS [35, 36].

Endothelin 1

Endothelin 1 concentrations were significantly increased in HRS and well correlated with GFR in decompensated liver disease in several studies [37–39]. After infusion of the endothelin antagonist BQ123, all patients with HRS showed a dose-related increase in both GFR and renal plasma blood flow [40]. In contrast to this finding, there was no correlation between endothelin 1 and renal vasoconstriction assessed by duplex ultrasonography [41], suggesting that endothelin 1 may not be the only pressor agent responsible for renal vasoconstriction in HRS. Thus, the cause of increased plasma endothelin 1 levels needs to be investigated in further studies.

F_2-Isoprostanes

Increased synthesis of F_2-isoprostanes, the products of lipid peroxidation, in patients with HRS was found to be indicative of increased lipid peroxidation [42, 43]. In a recent study in patients who were given a continuous infusion of the antioxidant N-acetylcysteine for 5 days, creatinine clearance was approximately doubled without any change in liver function or systemic hemodynamics [44]. F_2-Isoprostanes should be further investigated to confirm if they are important mediators of renal vasoconstriction in HRS.

Cytokines

Recent studies have implicated increased circulating levels of several cytokines, including tumor necrosis factor (TNF) and interleukin-6 (IL-6), in patients with HRS. According to related studies, inflammatory response to infection, as estimated by increased levels of cytokines in plasma or ascitic fluid, leads to circulatory dysfunction and concomitant renal impairment and increased mortality [45–47]. Studies have shown that vasodilation was observed in cirrhotic rats with portal hypertension on administration of anti-TNF antibodies, N-acetylcysteine and inhibitors of tyrosine kinase [48–50].

Renin-angiotensin-aldosterone (RAA) system

The RAA system is activated in most patients with decompensated cirrhosis and is further induced in patients with HRS [51–56]. Increased plasma renin release followed by an increase in angiotensin II formation was found in refractory ascites and HRS, indicating a role of RAA in the development of HRS [57]. Angiotensin II helps to maintain vascular tone in patients with advanced liver disease, but has no role in healthy controls or patients with compensated cirrhosis, suggesting that this mediator contributes to vascular dysfunction in cirrhosis [58].

Antidiuretic hormone (ADH)

ADH or vasopressin causes vasoconstriction through V_1 receptors and renal tubular water retention through V_2 receptors in the medullary collecting ducts. This increases volume expansion by water retention and helps maintain arterial pressure. Inhibition of V_1 receptors in cirrhotic rats causes profound hypotension. Vasopressin preferentially causes splanchnic rather than renal vasoconstriction [59].

Vasopressin analogues (ornipressin and terlipressin) are used in HRS treatment for their vasoconstrictor effects. Administration of these drugs in combination with albumin improves arterial underfilling and renal function. Ornipressin is very effective in HRS treatment, but it is not widely used because it has serious ischemic complications such as ischemic colitis and myocardial ischemia [60]. Terlipressin (triglycyl-lysine vasopressin) is cleaved in vivo by endothelial peptidases, releasing the active lysine-vasopressin. Treatment with terlipressin caused a significant decrease in serum creatinine concentrations, an increase in arterial pressure, and suppression of the renin aldosterone system in HRS patients [61]. It is the most commonly used drug in HRS therapy because it has fewer side effects and a prolonged duration of action [62].

Diagnosis

The diagnosis of HRS is based on major criteria for both clinical and laboratory aspects defined by the International Ascites Club in 1996 [2]. Minor criteria are not necessary for the diagnosis of HRS, but these criteria are frequently present in HRS patients (Table 2).

Table 2 Definition of hepatorenal syndrome.

Major criteria
1. Chronic or acute liver disease with liver failure and portal hypertension
2. Low glomerular filtration rate as indicated by serum creatinine >1.5 mg/dL (133 μmol/L) or a creatinine clearance <40 mL/min
3. Absence of shock, ongoing bacterial infection, or recent treatment with nephrotoxic drugs; absence of excessive fluid loss (including gastrointestinal loss)
4. No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
5. Proteinuria of <500 mg/day
6. No ultrasonagraphic evidence of obstructive uropathy or parenchymal renal disease
Minor criteria
1. Urine volume <500 mL/day
2. Urine sodium <10 mmol/day
3. Urine osmolality >plasma osmolality
4. Urine red blood cell count <50 per high-power field
5. Serum sodium <130 mmol/L

Adapted from Arroyo et al. [2].

Use of diagnostic tests for differential diagnosis

HRS may only be diagnosed after eliminating other potential causes of acute renal failure. Although chronic liver disease is easily diagnosed, diagnosis of the cause of renal failure may not be as easy. Prerenal causes of acute renal failure in patients with cirrhosis are gastrointestinal and renal fluid losses, hemorrhage, shock, sepsis, congestive heart failure, NSAID use and HRS [63]. Intrinsic causes include glomerulonephritis, interstitial nephritis and acute tubular necrosis (ATN), with postrenal causes due to the obstruction of urinary flow tract [63].

The differential diagnosis of HRS includes all these renal diseases. Generally, HRS is assumed to be a prerenal disease and distinguishing this condition from other disorders is clinically important because of the marked difference in prognosis. ATN and other causes of prerenal diseases are generally reversible, but prognosis is poor in HRS [64, 65].

Watt et al. reported that 40% of patients with advanced liver disease and renal failure are mistakenly diagnosed as having HRS, suggesting that many physicians are unaware of the criteria that exist for defining HRS [7]. Some conditions that should be considered that affect both the liver and the kidney are Weil's disease and malaria.

Renal failure is common in cirrhotic patients with sepsis unrelated to spontaneous bacterial peritonitis and is associated with arterial underfilling and renal vasoconstriction [66]. Therefore, diagnosis of HRS should always be ruled out with cultures, leukocyte count and C-reactive protein. The diagnosis of HRS can only be made if renal failure persists after complete resolution of the infection.

No laboratory test can firmly establish a diagnosis of HRS, which is mainly based on the absence of any specific cause of renal failure [1]. Laboratory and ultrasonographic tests based on non-invasive techniques are being investigated as possible diagnostic approaches.

Platt et al. prospectively studied the prognostic impact of renal duplex sonography in 180 cirrhotic patients with normal renal function at the time of first examination. They concluded that renal Doppler ultrasonography non-invasively identified a subgroup of non-azotemic cirrhotic patients at significantly higher risk for renal dysfunction or HRS [67].

Despite intensive studies of non-invasive sonographic techniques, routine laboratory tests are still commonly used. Urinary examinations, plasma creatinine and blood urea nitrogen (BUN) assays and estimation of GFR are the most popular diagnostic tools. In addition, bacterial cultures of blood, ascites, and urine should be evaluated in all patients with HRS to identify occult infection before antibiotic therapy.

Plasma and urinary electrolytes and osmolality should be assessed in all patients to rule out other causes of renal failure when possible, because of their importance as minor diagnostic criteria [2]. Some of these parameters are discussed in detail below.

Urinary examination

Urinanalysis may give valuable diagnostic information regarding HRS. Examination of urinary sediment is necessary, especially for the differential diagnosis of HRS from the other types of renal failure, such as the typical occurrence of pigmented granular casts and tubular epithelial cells alone or in casts in ATN and the red cell casts in glomerulonephritis [68–70]. Proteinuria, which is a major component of the diagnostic criteria, is typically mild and does not exceed 0.5 g/day in HRS [2].

Tubular function is usually well preserved at the time when HRS develops, but prolonged renal hypoperfusion caused by progressive circulatory dysfunction may eventually result in acute tubular necrosis by increasing sensitivity to other factors, such as radiographic contrast agents, nephrotoxic antibiotics, hemorrhage, endotoxemia, or any other cause of medullary hypoxia [71].

HRS can be difficult to distinguish clinically from acute tubular necrosis and other types of acute and chronic renal failure that may be handled in different ways [72]. Most HRS patient have low urinary sodium (<10 mmol/L) and high urinary osmolality because of preserved tubular function and activation of tubular reabsorption of sodium. Some HRS patients also show high urinary sodium (>10 mmol/L) and low urinary osmalality, as in ATN [2]. However, few cirrhotic patients with ATN have low urinary sodium (<10 mmol/L) and high urine osmolality [2] (Table 3). Therefore, urinary sodium and osmolality are not considered major criteria for the diagnosis of HRS.

Measurement of the fractional excretion of sodium (FENa) has been recommended as a useful clinical tool in evaluating acute renal failure. FENa has been shown

Table 3 Urinary parameters in different types of acute renal failure.

	Urine osmolality, mOsm/kg	Urine sodium, mmol/L	Fractional sodium excretion, %
Prerenal failure	>500	<20	<1
Intrinsic renal failure			
Tubular necrosis	<350	>40	>1
Acute interstitial nephritis	<350	>40	>1
Acute glomerulonephritis	>500	<20	<1
Postrenal failure	<350	>40	>1

Adapted from Moreau and Lebrec [72].

to be a reliable discriminatory test between prerenal failure and ATN [2, 74] (Table 3). However, some patients with ATN have FENa of <1% [73]. In addition to this finding, some cases of prerenal failure, including HRS, have FENa of >1% [73]. For these reasons, limited sensitivity of this parameter may make the interpretation of FENa difficult in this setting.

Assay of plasma urea and creatinine levels

Both urea and creatinine production may be highly reduced because of liver disease, reduced muscle mass and protein-meat intake. BUN tends to be variable in these patients. If urea production is markedly reduced, it may be lower than expected. The intense sodium avidity in this clinical setting can also raise BUN by accelerating sodium and water and eventually passive urea reabsorption in the proximal tubule [74].

Although plasma creatinine is one of the major diagnostic criteria, there is still controversy over the diagnostic value of this test. In advanced liver disease, because of muscle wasting and the insufficient conversion of creatine to creatinine, the net effect is a plasma creatinine concentration that appears to be within the normal range, which leads to false values for creatinine clearance [64, 75].

Estimation of GFR

In HRS, the reduction in GFR is often masked clinically. Estimation of GFR by creatinine clearance will tend to overestimate the true GFR owing to increased tubular secretion of creatinine [64] or reduced production because of muscle wasting and incomplete urine collection [64, 76]. In addition, because of the marked discrepancy between serum creatinine and GFR, this approach is not a valid parameter for assessing renal function in advanced cirrhosis [64, 77, 78].

Exogenously administered substances such as inulin or other radioisotopic agents can reflect GFR more precisely. However, these determinations are more invasive, requiring continuous intravenous infusion and urine sampling with a bladder catheter. These diagnostic limitations in identifying the true GFR have stimulated investigators to find more convenient and non-invasive techniques to assess the degree of renal conditions [67, 79, 80].

Cystatin C

Cystatin C is a non-glycosylated, basic protein of low molecular mass (13 kDa) that is a member of the cystatin superfamily of cysteine protease inhibitors. Cystatin C consists of 120 amino acids and is a new marker of GFR produced at a constant rate in all nucleated cells [81, 82]. Its production is independent of gender and muscle mass [83]. Since the first discovery of these beneficial features, it has been suggested as a better marker of GFR than creatinine [84–88]. Reference ranges for cystatin C in children [89], adults [90] and the elderly [91] have already been determined.

Rosenthal et al. showed in a study of 226 patients with various nephropathies (53 patients with glomerular and 26 patients with tubular impairment) that cystatin C and creatinine did not significantly differ with regard to efficacy. However, the efficacy of cystatin C as a screening test was superior to creatinine, with higher overall sensitivity and a higher negative predictive value [79]. In a recent study, Gerbes et al., who identified separate cutoff concentrations for each of three analytes, reported a differential diagnostic advantage of cystatin C over creatinine and urea in patients with cirrhosis [92]. In these patients, they found that serum cystatin C concentrations were significantly correlated with impaired renal function (creatinine clearance 40–69 mL/min) compared with patients with creatinine clearance >70 mL/min. The difference between these groups was less pronounced for serum creatinine and was not significant for serum urea concentrations. Subgroup analysis for various nephropathies indicated that neither glomerular nor tubular impairment led to different cystatin C efficacy [79]. We previously demonstrated that in patients with HRS, neither serum creatinine nor creatinine clearance were good indicators of HRS, because the mean value for creatinine clearance was higher than Tc-DTPA clearance, and there was no correlation between these two parameters ($r=0.059$). In addition, the mean serum creatinine was within the normal range, whereas the mean Tc-DTPA clearance level was below the normal range. However, we found significant correlation between cystatin C and Tc-DTPA. Thus, we suggest that serum cystatin C assay, which shows good analytical performance, could replace or at least be added to creatinine measurement for GFR assessment in patients with cirrhosis [93]. Orlando et al.

found that creatinine, which showed sensitivity of only 23%, failed to detect reduced renal function, whereas cystatin C exhibited good diagnostic sensitivity of 88% [80].

Conclusions

This article summarizes the literature on the current definition, suggested pathogenetic mechanisms and the role of laboratory assessment in the differential diagnosis of HRS from other causes of renal disease that may arise during hepatic cirrhosis and some diseases affecting both liver and kidney. It should be remembered that the main theory suggested for the pathogenesis of HRS is the arterial vasodilation hypothesis of portal hypertension, ending in type 1 and type 2 HRS, but there is no consensus supporting either mechanism as a solid theory for the initiation of HRS pathogenesis to date. Thus, discussion of the humoral modulators originating from experimental models, as well as clinical data, is critical in supporting either mechanism. Response to volume loading is useful in the differentiation of pre-renal failure from other forms of acute renal failure, but HRS rarely responds to volume loading, and even though a careful follow-up may lead to timely diagnosis of HRS, the treatment still does not yield positive progress. Finally, even though it is beyond the scope of this article to set criteria for the differential diagnosis of HRS, tests to identify etiologies underlying other causes of renal failure should be sufficient to differentiate renal failure due to hepatic disease accompanied by portal hypertension and ascites, given as a definition of HRS.

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