Nicolae Testemitanu State University of Medicine and Pharmacy
Department of Internal Medicine,
Discipline of Internal Medicine – Clinical synthesis

Lilia Vlasov

Innovative approaches in pathophysiology and management of hepatorenal syndrome

Chisinau • 2015

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Authors:

Lilia Vlasov associate professor, MD, PhD

References:

Natalia Capros professor, MD, PhD

Larisa Rotaru associate professor, MD, PhD

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List of abbreviations

AASLD	American Association for the Study of the Liver
ALF	acute liver failure
AGL	alpha-glucosidase
ALP	alkaline phosphatase
DH	antidiuretic hormone
ATN	acute tubular necrosis
AKI	Acute kidney injury
AKIN	acute kidney injury network
ARF	acute renal failure
BP	blood pressure
CO	cardiac output
CLKT	combined liver-kidney-transplant
EASL	European Association for the Study of the Liver
eNOS	endothelial NO synthase
ET	endothelin
EDV	end-diastolic velocity
ETA	endothelin A
ETB	endothelin B
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
HRS	hepatorenal syndrome
HSCs	hepatic stellate cells
IAC	International Ascites Club
IL	interleukin
KDOQI	Kidney Disease Outcome Quality Initiative
LC	liver cirrhosis

LDH	lactate dehydrogenase
LSEC	liver sinusoidal endothelial cell
LRA	left renal artery
MARS	molecular adsorbents recirculating system
MELD	model of end-stage liver disease
NAG	N-acetyl-beta-D-glucosaminidase
NE	norepinephrine
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drugs
LT	liver transplantation
PG	prostaglandin
PGE_2	prostaglandin E2
PI	pulsatility index
PGI_2	prostacyclin
PSV	peak systolic velocity
RAAS	renin-angiotensin-aldosterone-system
RAs	renal arteries
RRA	right renal artery
RBF	renal blood flow
RI	resistive index
SBP	spontaneous bacterial peritonitis
SEC	sinusoidal endothelial cells
SNS	sympathetic nervous system
SMA	superior mesenteric artery
TIPS	transjugular intrahepatic portosystemic shunt
TNF	α-tumor necrosis factor alpha
TXA_2	thromboxane A_2

Chapter I. Primary hepatic disorder with secondary renal dysfunction

The interrelation of liver disease and kidney involvement

Chronic liver diseases are amongst the top leading causes of death in Europe as well as in other areas of the world and are characterized by unrelenting progression of liver inflammation and fibrosis. Advanced liver cirrhosis leads to a complex syndrome of chronic liver failure which involves many different organs besides the liver, including the brain, heart and systemic circulation, adrenal glands, lungs and kidneys. Renal dysfunction is common in patients with acute and chronic liver disease. The presence of renal failure in this group of patients significantly affects mortality. Renal and liver dysfunctions are often present together, either as a part of multiorgan failure in a critically ill patient, or as a result of failure of each organ independently. It can be identified in which liver and renal dysfunction coexist; diseases simultaneously involving the liver and the kidney, or a primary hepatic disorder with secondary renal dysfunction, or vice versa.

Impaired glomerular filtration plays a major role in the pathophysiology of a large number of complications seen in patients suffering from liver diseases. Azotemia is found in 30% of patients with liver cirrhosis (LC) and ascites. Acute renal failure can be caused by nonspecific infection in 32%, renal parenchymal disease in 24%, hypovolemic shock in 22%, acute tubular necrosis (ATN) in 11%, hepatorenal syndrome (HRS) in 8% , acute renal failure (ARF) from drug toxicity in 3% [99]. The mortality as a result of renal complications is significantly higher, ranging from 50 to 70% in ATN and 75 - 100% in HRS [88.152]. The probability of the occurrence of HRS in patients with hepatic cirrhosis and ascites in 1 and 5 years is 18% and 39% respectively, with mortality approaching 100% in type I HRS without specific therapy.

The interrelation of liver disease and kidney involvement has aroused great interest over the years. In 1969 Ritz et al. detected the decrease in renal function in 13 (42%) from 31 patients with acute liver failure. Wilkinson S. et al. observed impaired renal function in 53% among 160 patients with cirrhosis. Epstein et al. performed renal angiography in patients with HRS and indicated the absence of blood flow in renal cortex.

Koppel et al. demonstrated the functionality and reversibility of hepatorenal syndrom in 1969 after cadaveric kidney transplantation from

patients with LC to patients with end-stage renal failure. Reversibility of HRS was demonstrated after liver transplantation, too.

A recent study has revealed that hepatorenal syndrome is the third most common cause of admission to hospital in the intensive care unit among 420 patients with cirrhosis, and was only surpassed by upper digestive hemorrhage and encephalopathy. Mortality occurred within one to five years in 69% to 77% of all these patients. Mortality occurred within 30 days in 92% of the cases presenting all three of these risk factors and in 11% of the cases without any of the above risk factors.

In conclusion, major renal events involving both the liver and kidney are an unfavorable prognostic factor for cirrhotic patients with significant social and medical costs and a high rate of morbidity and mortality. Minor degrees of renal dysfunction are associated with an increased risk in patients with pre-existing liver disease. This recommendations reviews our current knowledge, as well as future perspectives on the management of circulatory and renal dysfunction in liver cirrhosis.

Definition of hepatorenal syndrome

Hepatorenal syndrome is a unique form of severe functional kidney failure due to intense renal vasoconstriction that develops in patients with hepatic cirrhosis in the absence of significant histological abnormalities of the kidneys.

During the 19th century, Frerichs and Flint made the original description of renal function disturbances in liver disease. They described oliguria in patients with chronic liver disease in the absence of proteinuria and linked the abnormalities in renal function. In the 1950s, the clinical description of HRS by Sherlock, Popper, and Vessin emphasized the functional nature of the syndrome and the coexistence of systemic circulatory abnormalities. Further studies in the following two decades demonstrated that renal failure occurred because of vasoconstriction of the renal circulation and intense systemic arteriolar vasodilatation. The definition of HRS was first proposed in 1999 and afterward modified in 2007. In the previous definition, the existence of bacterial infection exclude the diagnosis of HRS, whereas in the most recent definition, HRS is resulting in reduced systemic vascular resistance and arterial hypotension.

Hepatorenal syndrom is a form of acute kidney injury (AKI) that develops only in patients with advanced liver cirrhosis or fulminant hepatic failure and it is common in cirrhotic patients with ascites. The definition of acute kidney

injury proposed by the Acute Kidney Injury Network (AKIN) for kidney failure developing in the general population of hospitalized patients has been suggested to kidney failure that occurs in patients with LC. Early studiers of patients with HRS characterized two types of renal failure, named functional renal failure and acute tubular necrosis. Whether these two forms of acute renal failure represent distinct entities or opposite ends of a clinical spectrum is still unclear. Various new concepts have emerged since the initial diagnostic criteria and definition of HRS was published. These include better understanding of the pathophysiological mechanisms involved in HRS, identification of bacterial infection (especially spontaneous bacterial peritonitis) as the most important HRS precipitating event, recognition that insufficient cardiac output plays a important role in the occurrence of HRS and evidence that renal failure can be reversed with pharmacotherapy. In the most recent definition, HRS may be diagnosed in the presence of an infection, except if there is septic shock.

Therefore, it seems reasonable to keep the term of HRS for the unique form of kidney failure of functional origin, with preserved tubular function.

Types of hepatorenal syndrome

Intermediate forms of HRS occur commonly in acute liver failure or chronic liver disease and two main patterns of HRS can be identified:

Type 1 HRS - rapidly progressive, where serum creatinine doubles in two weeks 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 or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/minute in less than two weeks. It is associated with the development of oliguria, encephalopathy and marked hyperbilirubinemia.

Type 1 HRS usually occurs in close temporal relationship to a precipitating event, mainly spontaneous bacterial peritonitis. Other infections and noninfectious events (such as viral, alcoholic, toxic or ischemic hepatitis superimposed on cirrhosis; gastrointestinal bleeding; and major surgical procedures) are less frequently associated with HRS. However, in some patients with type 1 HRS, a precipitating event cannot be identified. Episodes of spontaneous bacteremia owing to translocation of bacteria from the intestinal lumen into the systemic circulation, as well as translocation of bacterial endotoxins, are frequent in patients with liver cirrhosis, and may act as precipitating factors.

Most patients with type 1 HRS had severe liver cirrhosis characterized by a MELD score ≥ 20 or Child Pugh score ≥12. The syndrome is frequently diagnosed in acute fulminant hepatic failure or alcoholic hepatitis. Jaundice and coagulopathy, bleeding from esophageal veins is frequently present. Patients with severe alcoholic hepatitis have a higher probability of association of sepsis in the case of type 1 HRS installation and high rate of mortality, eloquently demonstrated by a study conducted on a group of 195 patients. In the absence of liver transplantation (LT), the mean survival rate of patients with HRS type 1 is about two weeks, most patients with a fatal end within 2-3 months from the establishment of the diagnosis. There was an average survival rate of 2.7 months in 91 patients with type 1 HRS in a retrospective study of cirrhotic patients with HRS in 24 medical centers in Europe,

Type 2 HRS is slowly progressive, this state was described later and despite the otherwise typical signs of hepatorenal failure, it is quite stable. It is characterized by impairment in renal function (serum creatinine - 415 μmol/l) that does not have a rapidly progressive course and does not meet the criteria of type 1 HRS. The typical clinical self-evidence of Type 2 HRS is the presence of refractory ascites in patients with liver cirrhosis due to a poor response to diuretics (furosemide and spironolactone) and avid sodium retention. The median survival after onset of type 2 HRS is 6 months. Type 2 HRS is associated with stable or slowly progressive kidney failure and has a better prognosis than HRS type 1.

Alessandria C. et al. studied 105 patients with HRS and liver cirrhosis, 41 patients with type 1 HRS and 64 - with type 2 and concluded that patients with HRS type 1 have a more severe hepatic and renal impairment, hemodynamic disturbances with lower blood pressure and a high activity of vasoconstrictor factors than those with SHR type 2. In patients with type 1 SHR the survival rate was one month and the average survival of type 2 SHR before liver transplantation was about 6 months.

Certainly, these definitions are only applicable to those patients with moderately acute liver failure, as those with hyperacute liver failure develop progressive renal impairment over a matter of days and are likely to have an element of acute tubular necrosis in addition to functional renal failure.

The difference in prognosis between the two types of HRS is essential as the median survival of type 1 is about 2 weeks while that of type 2 1 is generally around 4-6 months. Type 1 HRS is often induced by the occurrence of a precipitating stimulus. As we earlier emphasized, the important factors are

infections (e.g., urinary tract infections and infections of the biliary or intestinal tract) but the most important thing is the development of a spontaneous bacterial peritonitis Almost one third of patients with spontaneous bacterial peritonitis develop a form of renal failure, which in most cases fits the diagnostic criteria of type 1 HRS. With an emphasis on recent diagnostic and therapeutic advances, Munoz S defined type 3 and type 4 of HRS in 2008.

Type 3 HRS 85% of end-stage cirrhotics have intrinsic renal disease on renal biopsy. Patients with obstructive renal disease, diabetic nephropathy or chronic glomerulonephritis can develop HRS due to a precipitating event or worsening liver failure. Chronic glomerulonephritis should be confirmed by renal biopsy.

Type 4 HRS More than half of patients with acute liver failure develop HRS, although the frequency varies depending on the ALF etiology The pathophysiology of HRS in ALF is not fully elucidated and it is believed to be similar to that established for HRS occurring in cirrhosis.

Incidence of hepatorenal syndrome

The incidence of hepatorenal syndrome is variable. In patients with liver cirrhosis hospitalized with ascites HRS occurs in about 10% with the probability of developing in ranges between 8-20% per year and increases to 40% at 5 years of disease evolution. In 1993 prior to the introduction of International Ascies Club (IAC) criteria, Gines et al. reported that HRS had an incidence of 18% in one year and 39% in five years in patients with liver cirrhosis and ascites.

Actually, a retrospective study in 229 patients with liver cirrhosis demonstrated the presence of HRS in 18% after a year of decompensation and in 39% in five years. On the other hand, in 263 patients with LC investigated in two clinics of Spain during 41 months, only 8% of patients were diagnosed with HRS. In a 2010 study using the diagnostic IAC criteria, Montoliu et al. evaluated the incidence of functional renal impairment in 263 cirrhotic patients with ascites. The authors found that 49% of patients developed functional renal impairment during 41 months. The annual incidence of HRS was 7.6% (type 1 = 7, type 2 = 13). According to other studies, HRS was a third cause, which led to hospital intensive care admission of 420 patients with upper gastric bleeding and hepatic encephalopathy. Patients with primary biliary cirrhosis, however, have a lower incidence of HRS. Recent data indicate a much lower incidence of HRS (11%) after 5 years of evolution in decompensated cirrhosis.

HRS occurs almost exclusively in patients with ascites. The occurrence probability in patients having LC and ascites for more than 5 years reaches 40%. Besides the above-mentioned prognostic factors, ascitic patients with a small liver, esophageal varicose veins and an unbalanced diet have a higher risk of HRS. Dilution hyponatremia, tachycardia and arterial hypotension are warning signs, too.

Lately, the prevalence of HRS ranged last years from 13 to 45.8%. Salerno et al. conducted a prospective study of 253 consecutive patients with liver cirrhosis and renal impairment admitted to 21 Italian hospitals. The prevalence of HRS was 45.8% (30% type 1 and 15.8% type 2). Martin-Llahi et al. studied 562 patients with cirrhosis and renal impairment admitted to a single institution and found HRS prevalence of 13%. A study by Thabut et al. of 100 consecutive patients with liver cirrhosis and renal impairment admitted to five French hospitals found HRS prevalence of 27%.

In almost half of the HRS cases, one or more precipitating factors can be identified, which can be - bacterial infections (57%), gastrointestinal hemorrhage (36%) and therapeutic paracentesis (7%).

Chapter II. The pathophysiology of renal dysfunction in liver cirrhosis

The consequence of dysfunctions in the systemic arterial circulation and precipitating factors of HRS

The relationship between liver disease, portal hypertension and abnormalities in renal circulation is discuss in detail in many clinical cases. It is established that mechanisms leading to portal hypertension involve a passive increase in intrahepatic resistance due to fibrosis and increased portal blood flow due to vasodilation of splanchnic arteries.In this context, there is a small decrease in systemic vascular resistance as a result of splanchnic arterial vasodilation. The effect of the decrease in systemic resistance in arterial pressure is balanced by increased cardiac output, so that arterial pressure and effective arterial blood volume are maintained at normal levels.

In the presence of decompensated liver cirrhosis patients are usually symptomatic and have already developed some complications of the disease, the reduction in systemic vascular resistance is marked and cannot be compensated by further increases in cardiac output; therefore, underfilling of the arterial circulation develops, there being a disarrangement between the intravascular blood volume and a very enlarged intravascular arterial circulation. This condition is known as effective arterial hypovolemia. Hypovolemia unloads the high-pressure baroreceptors in the carotid body and aortic arch with compensatory activation of the sympathetic nerves system (SNS), the renin-angiotensin-aldosterone system (RAAS) and nonosmotic release of vasopressin. This results in a hyperdynamic circulation with increased cardiac output (CO), decreased systemic vascular resistance, hypotension, and vasoconstriction of the renal vessels.

With liver cirrhosis progression, further splanchnic vasodilation occurs. In addition, studies on animals and humans with cirrhosis consistently demonstrate that the splanchnic circulation is the main vascular bed responsible for the peripheral vasodilation, especially in advanced liver disease. The vasodilation of the splanchnic arterial circulation is due to an increased production and activity of vasodilator factors, particularly nitric oxide, carbon monoxide and endogenous cannabinoids.

In addition, in advanced stages of liver cirrhosis the vasodilation of the splanchnic arteries increases due to progressive bacterial translocation and enhanced synthesis of vasodilator factors in the intravascular blood volume and

a very enlarged intravascular arterial circulation. Therefore, a vicious cycle that favors more systemic vasodilation and subsequent renal vasoconstriction is created.

Although this hypothesis provides a rational explanation to the hemodynamic changes that take place in cirrhosis and HRS, it has not been tested in human studies. However, the markedly reduced systemic vascular resistance despite elevated norepinephrine, renin, and aldosterone levels is well documented and is compatible with peripheral vasodilation. Studies by Fernandez-Seara and others demonstrated that the degree of hepatic decompensation directly correlates with the degree of hyperdynamic circulation and inversely correlates with the arterial blood pressure (BP) noted in patients with HRS.

Finally, the improvement in the hemodynamic and neurohormonal parameters and reversal of HRS with systemic vasoconstrictor administration, provide an additional support to the peripheral vasodilation role in renal hypoperfusion and vasoconstriction. It becomes curious, then, to ask why renal vasoconstriction persists despite the presence of systemic vasodilation. Iwao et al. demonstrated that with liver disease progression and before the development of HRS, femoral artery blood flow decreases, whereas mesenteric blood flow continues to rise. Importantly, Fernandez-Seara et al. showed a correlation between the reduced femoral blood flow and the renal blood flow (RBF) in patients with decompensated cirrhosis, including patients with HRS. Similar correlation is also noted between the cerebral, upper extremities blood flows and the RBF.

These findings suggest that at an early stage, both the splanchnic and the peripheral circulations are vasodilated and contribute to the genesis of the hyperdynamic circulation. With liver cirrhosis progression, the splanchnic circulation becomes the primary vascular bed responsible for the maintenance of the hyperdynamic state, with subsequent stimulation of the vasoconstrictor agents leading to vasoconstriction of extrasplanchnic vascular beds, including the kidney. The activation of vasoconstrictor systems assist in preserving effective arterial blood volume and arterial pressure, but they strongly influence kidney function, particularly retention of sodium and salt-free water. As a consequence, ascites and edema develop, as well as hypervolemic hyponatremia (Figure 1).

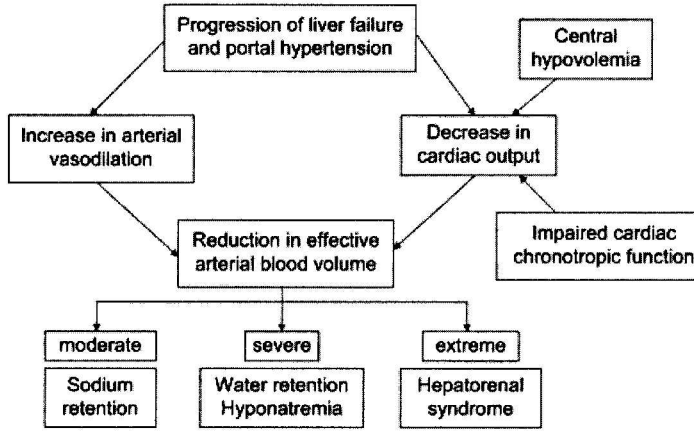

Fig. 2.1 Dysfunctions in the systemic arterial circulation in HRS (Munoz S. Medical Clinics of North America. July 2008. Volume 92, Issue 4, p. 813–837).

The parameters associated with a higher risk of HRS, physiological and hemodynamic changes with their consequences in different stages of cirrhosis are summarized in tables 2.1 and 2.2 (Das K A. Hepato-Renal Syndrome: A Complication of Advanced Chronic Liver Disease with Portal Hypertension. Journal of Gastroenterology and Hepatology Research 2013; 2(8): 709-718).

Tables 2.1 Predictors of HRS development

Previous episodes of ascites
Poor nutritional status
Moderate increase in BUN and/or S. Creatinine
Serm Na<130 mEq/L
Urine Na<10 mEq/L
Plasma renin activity>4 ng/mL/hour
Mean Arterial Pressure <85 mm Hg
Low water excretion (<3 mL/min) after water load
Plasma norepine phrine>500 pg/mL
Esophageal Varices
MELD score

Tables 2.2 Hemodynamic changes during different stages of cirrhosis

	Compensated Cirrhosis	Diuretic responsive ascites	Diuretic resistant ascites	HRS
Splancnic/systemic vasodilatation	Normal/+	+	++	+++
Effective circulating volume	Normal	–	– –	– – –
Renin, Aldosterone, Vasopressin, Norepinephrine	Normal	+	++	+ + +
Renal sodium retention/plasma volume	+	++	+++	++++
Renal vasoconstriction	Normal	Normal	++	++++

Basically, a high risk of hepatorenal failure must be expected in patients with liver cirrhosis and ascites, with an indication of dilution hyponatremia, with tachycardia and mean <85 mm Hg arterial pressure.

In type 1 HRS, a precipitating factor is identified in 70 to 100% of patients with HRS. This factors include bacterial infections, large-volume paracentesis without albumin infusion, gastrointestinal bleeding and acute alcoholic hepatitis.

In 20%-30% of cases patients with SBP develop HRS despite appropriate treatment of infection. Similarly, large-volume paracentesis without albumin expansion precipitates type 1 HRS in 15% of cases, and 25% of patients who present with acute alcoholic hepatitis eventually develop HRS.

In type 2 HRS and in some patients with type 1 HRS, no precipitating factor can be identified. The mechanism of renal failure in these cases is unclear, but it seems to be related to severe failure of compensatory mechanisms of liver disease that aim to maintain adequate renal perfusion. The main precipitating factors of HRS are illustrated in Figure 2.2

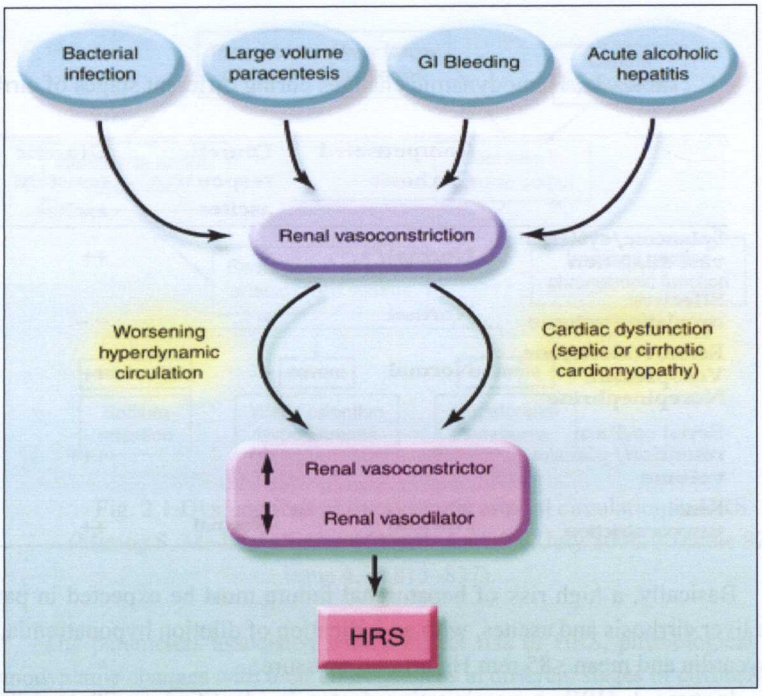

Fig. 2.2 Precipitating factors in HRS (Hani M. Wadei, Martin L. Mai, Hepatorenal Syndrome: Pathophysiology and Management CJASN September 2006 vol. 1 no. 5 p.1066-1079)

A precipitating factor can lead to HRS in different ways. Navasa et al. suggested that renal failure in SBP is due to cytokine-induced aggravation of circulatory dysfunction and exacerbation of renal hypoperfusion creates an intrarenal vicious cycle that favors more renal vasoconstrictor release and impairs renal vasodilator synthesis. This vicious cycle eventually will progress to HRS even if the underlying precipitating event has been corrected. In type 2 HRS and in some patients with type 1 HRS, no precipitating factor can be identified. In these cases the mechanism of renal failure is unclear, but it seems to be related to severe failure of compensatory mechanisms of liver disease that aim to maintain adequate renal perfusion.

In our study a total of 114 patients with liver cirrhosis were investigated. In 23 selected patients with HRS we assessed the precipitating factors of this syndrome, too (Figure 2.3).

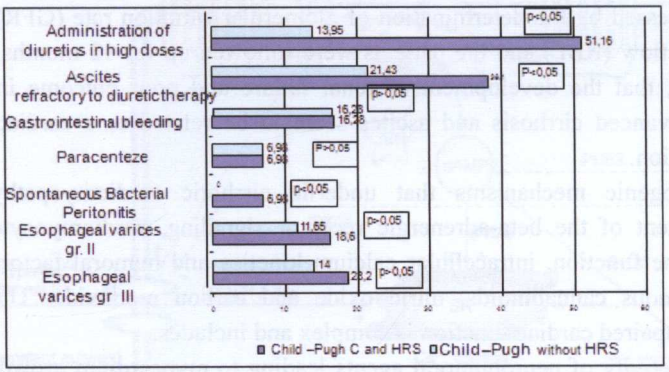

Fig. 2.3 Precipitating factors of HRS

We concluded that in our cirrhotic patients the most frequent precipitating factors of HRS were gastrointestinal bleeding and presence of refractory ascites.

Cardiac dysfunction in hepatorenal syndrome

Liver cirrhosis is known to be associated with numerous cardiovascular abnormalities. The characteristic features of the hyperdynamic state of advanced liver disease is increased heart rate and cardiac output (CO). Despite this increased baseline cardiac output, patients with cirrhosis show an attenuated systolic and diastolic function. These abnormalities have been termed cirrhotic cardiomyopathy. The concept was confirmed by studies that demonstrated decreased cardiac function in cirrhotic animals. In humans, Bernardi et al. evaluated cardiac function in 22 nonalcoholic patients with cirrhosis and demonstrated impaired myocardial contractility both at rest and on exercise that correlated with the degree of cirrhosis. Similarly, diastolic dysfunction is documented in patients with cirrhosis, the degree of which parallels the degree of liver dysfunction. Elevated plasma natriuretic peptide level that has been observed in some patients with liver cirrhosis can explain cardiac dysfunction despite reduced central venous pressure. In the study of 52 decompensated patients with liver cirrhosis, natriuretic peptide level correlated with the Child-Pugh score and the ventricular wall thickness. Recent studies of

Kraq et al. suggest that cardiac dysfunction precedes the development of the hepatorenal syndrome. In the follow-up study of 24 patients with cirrhosis and ascites, cardiac function was investigated by gated myocardial perfusion imaging for the assessment of cardiac index and cardiac volumes. The renal function was assessed by the determination of glomerular filtration rate (GFR) and renal blood flow (RBF) and the patients were followed up for 12 months. They concluded, that the development of renal failure and poor outcome in patients with advanced cirrhosis and ascites seem to be related to a cardiac systolic dysfunction.

The pathogenic mechanisms that underlie cirrhotic cardiomyopathy include impairment of the beta-adrenergic receptor signaling, cardiomyocyte plasma membrane function, intracellular calcium kinetics and humoral factors such as endogenous cannabinoids, nitric oxide and carbon monoxide. The mechanism of impaired cardiac function is complex and includes:

1) Hyperactivity of neurohumoral agents leading to myocardium growth and fibrosis with disturbed relaxation;
2) Defect in cardiac β-adrenergic receptor signaling, increase in endocannabinoid activity
3) Repressing effect of circulating cytokines, including nitric oxide, IL-1 (interleichina-1) and TNF-α on ventricular function and myocyte apoptosis.

The complex interplay between different signaling pathways determines the contractile behavior of cardiomyocytes. Increased activity of inhibitory pathways such as tumor necrosis factor, nitric oxide and carbon monoxide in the cirrhotic heart lead to increased cyclic GMP levels, which exert a negative inotropic effect. Increased cannabinoid receptor 1 signaling also contributes to the depressed contractility of cirrhotic heart through inhibitory G proteins. (Figure 2.4).

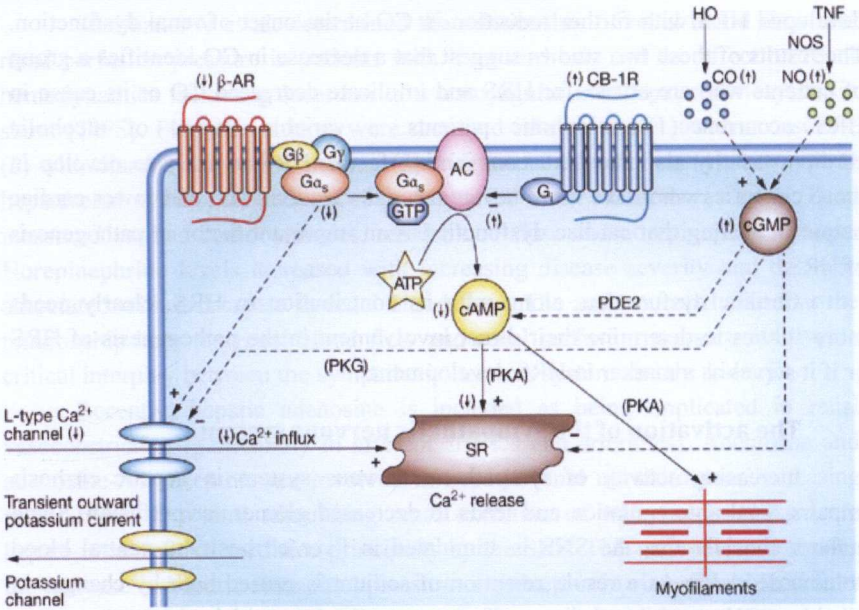

Fig 2.4 Intracellular signaling pathways of cirrhotic cardiomyopathy Seyed A Gaskari, Therapy Insight: cirrhotic cardiomyopathy. Clinical Practice Gastroenterology & Hepatology (07/2006; 3(6): p. 329-37).

Cirrhotic cardiomyopathy is believed to contribute to cardiac dysfunction that can be observed in patients with transjugular intrahepatic portosystemic stent-shunt insertion and liver transplantation. Insufficient cardiac contractile function may also play a role in the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis.

The role of cardiac dysfunction in HRS was recently studied by Ruiz-del-Arbol et al. who demonstrated reduction in CO at the time of diagnosis of spontaneous bacterial peritonitis without a change in systemic vascular resistance in patients who had cirrhosis and subsequently developed HRS. Further CO decreased after elimination of infection in the HRS group patients but not in those without renal failure. The same group of researchers studied systemic and hepatic hemodynamics of 66 patients with liver cirrhosis and ascites and normal serum creatinine with repeat assessments in 27 patients who developed HRS. At baseline, arterial BP and CO were significantly lower whereas RAAS and SNS activity were significantly higher in the group that

developed HRS with further reduction in CO at the onset of renal dysfunction. The results of these two studies suggest that a decrease in CO identifies a group of patients who are at risk for HRS and implicate decreased CO or its cause in HRS occurrence. In alcoholic patients, a variable degree of alcoholic cardiomyopathy also can be a contributing factor. HRS is likely to develop in those cirrhotics who have more severe arterial vasodilatation and lower cardiac output indicating that cardiac dysfunction is an important factor in pathogenesis of HRS.

Cardiac dysfunction, along with its contribution to HRS, clearly needs more studies to determine their direct involvement in the pathogenesis of HRS or if it serves as a marker in HRS development.

The activation of the sympathetic nervous system

Increasing activity of sympathetic nervous system in hepatic cirrhosis impairs renal autoregulation and leads to decreased glomerular perfusion. Some authors consider that the SNS is stimulated in liver cirrhosis by central blood volume decrease. As a result, retention of sodium is caused both by changes in renal haemodynamics and direct effects on renal tubes, which play an important role in the installation and development of ascites.

However, several studies do not find any direct correlation between urinary norepinephrine and excretion of sodium in patients with cirrhosis and ascites. The administration of clonidine (inhibitor of SNS) to 64 patients with LC favored a rapid increase in diuresis, but it did not affect the excretion of sodium. Clonidine decreased the amount of serum norepinephrine in renal and mesenteric blood flow, thus contributing to the reduction of sympathetic renal vasoconstriction and increased glomerular filtration.

Kostreva et al. observed that increasing intrahepatic pressure by vena cava ligation in anesthetized dogs results in high renal sympathomimetic activity. This reflex persists despite carotid sinus denervation, bilateral cervical vagotomy, and phrenectomy and abolishes only after sectioning of the anterior hepatic nerves. Further studies by Levy and Wexler demonstrated delayed sodium retention and ascites formation in cirrhotic dogs after hepatic denervation. Similarly, Lang et al. showed reduction in GFR and renal blood flow (RBF) after inducing hepatocyte swelling using an intramesenteric glutamine infusion. Severing the renal, hepatic or spinal nerves abolishes this response.

Stadlbauer V et al. determined the relationship of renal blood flow and renal perfusion pressure in patients with liver cirrhosis and the effect on renal hemodynamics following insertion of a transjugular intrahepatic portosystemic shunt (TIPS). Fifty-six patients were recruited into groups (1) with no ascites, (2) with diuretic-responsive ascites, (3) with intractable ascites, (4) with type II hepatorenal syndrome, and (5) requiring a TIPS for refractory ascites. They measured cardiac hemodynamics, renal blood flow and norepinephrine levels. Norepinephrine levels increased with increasing disease severity and this was associated with a decrease in renal blood flow. The authors concluded that the relationship between renal blood flow and renal perfusion pressure involves a critical interplay between the sympathetic nervous system and the kidney.

Recently, hepatic adenosine is included as being implicated in renal vasoconstriction (particularly in afferent arteries and arterioles). Adenosine and adenosine-A1 receptors are involved in hepatic renal ultrafiltration, increasing portal blood flow and stimulating renal excretion of water and sodium by a hepato-renal reflex - mediated principally by the SNS. This reflex is activated by the increase in hepatic sinusoidal pressure or reduction in sinusoidal blood flow leading to decreased renal blood flow and thereby may contribute to HRS as well. A similar splenorenal reflex also is observed in animal models with portal hypertension. This concept is supported in humans and comes from the studies by Jalan et al, who demonstrated acute reduction in RBF in a patient with liver cirrhosis after acute TIPS occlusion. In another study, lumbar sympathectomy increased GFR in five patients with HRS and GFR <25 ml/min but not in three others with GFR >25 ml/min, suggesting that renal sympathetic nerve activity contributes to renal vasoconstriction in a selected group of patients with HRS.

Anyway, the current evidence is lacking a primary role for hepatorenal or splenorenal reflex in HRS in humans. Still, the renal sympathetic system may play a contributory role in HRS in patients with liver cirrhosis. Some authors consider hepato-renal reflex as one of the key factors in the pathophysiology of renal hemodynamic disturbances in LC. In this respect, the study of sympathetic activity (plasma noradrenaline) is still welcome.

The role of nitric oxide in the pathophysiology of hepatic cirrhosis

As renal ultrafiltration superimposes between patients who have cirrhosis with and without HRS, other factors involved in the regulation of intrarenal hemodynamics and glomerular filtration rate are incriminated to HRS. These factors include vasoactive agents that affect both the systemic and the renal circulation as nitric oxide (NO), tumor necrosis factor alpha (TNF-α), endothelin, endotoxin, glucagon, and intrarenal vasodilating prostaglandins.

As a systemic agents, NO has gained large attention. Nitric oxide is a hydrophobic gas, which diffuses freely through cell membranes and may have autocrine and paracrine effects at distances up to 100 mm. It is produced by enzyme nitric oxide synthase (ONS), with three well known isoforms. Each of the three isoforms of nitric oxide is generated as a by-product of the conversion of arginine to citrulline. Isoforms are the isoform n-ONS and e-ONS from endothelial cells responding to physical and biochemical stimuli, causing the elevation of NO level and the increase of intracellular calcium concentration. I-NOS, whose expression is induced by cytokines in macrophages and other cell types, do not influence the cytoplasm calcium concentration and has a low enzyme activity compared with the other two isoforms. In the vascular bed, nitric oxide produced by e-NOS endothelial cells is a determinant of resting vascular tone. In healthy liver, e-NOS is a predominant form secreted by sinusoidal endothelial cells and it is involved in maintainance of blood flow and capillary sinusoidal tone. In cirrhotic liver, although e-NOS levels appeared to be low, high levels of endothelial cells derived caveolin-1 inhibitory protein e-NOS, while decreasing calmodulin (which plays a role in contraction).

Increased nitric oxide synthesis has been implicated in the development of this state of vasodilation and pulmonary dysfunction including increased exhaled NO concentrations. NO(x) correlated with portal pressure and hemodynamic indicators of vasodilatation, but not with exhaled NO concentrations.

However, the relations of these abnormalities to the hemodynamic changes remain unclear. Supplementary, NO production is increased in liver cirrhosis as a result of regulation of endothelial NO synthase (eNOS) activity due to increased stress in the splanchnic and systemic circulation as well as endotoxin-mediated eNOS activation. Increased NOS activity has also been demonstrated. In animal models, NO is responsible for the reduced pressor effect of endogenous vasoconstrictors in the splanchnic circulation.. Moreover,

inhibition of NO synthesis corrects circulatory abnormalities and reverses neurohormonal changes in cirrhotic rats.

In humans, inhibition of NOS activity in patients with cirrhosis and ascites decreases blood flow and increased vascular resistance. Similarly, acute NOS inhibition increases systemic vascular resistance in patients with decompensated cirrhosis and decreases plasma renin activity and urinary prostaglandin E2 excretion.

Patients with cirrhosis and ascites have higher NO plasma concentrations than normal individuals or those with compensated cirrhosis and high serum NO level correlates with high plasma RAAS activity and antidiuretic hormone levels as well as low urinary sodium excretion.

The concentration of NO is higher in portal venous plasma than in peripheral venous plasma, suggesting increased splanchnic production of NO. Although there is enthusiasm for a role of NO in peripheral vasodilation, it is still unclear about whether NO is the primary factor in the genesis and maintenance of the hyperdynamic circulation.

In addition, the vasodilating effect of NO is expected to antagonize renal vasoconstriction; however, in HRS, renal vasoconstriction progresses despite elevated NO levels. The explanation of this is not clear, but Lluch et al. suggested that in decompensated liver failure the increase in the plasma level of asymmetric dimethylarginine, a natural eNOS inhibitor may antagonize the elevated NO level and promote renal vasoconstriction in HRS.

In response to increased portal pressure, raised levels of vasodilators, such as nitric oxide, cause subsequent vasodilatation and nitric oxide overproduction causes arterial wall thinning, which may also contribute to sustained vasodilatation (Figure 2.5).

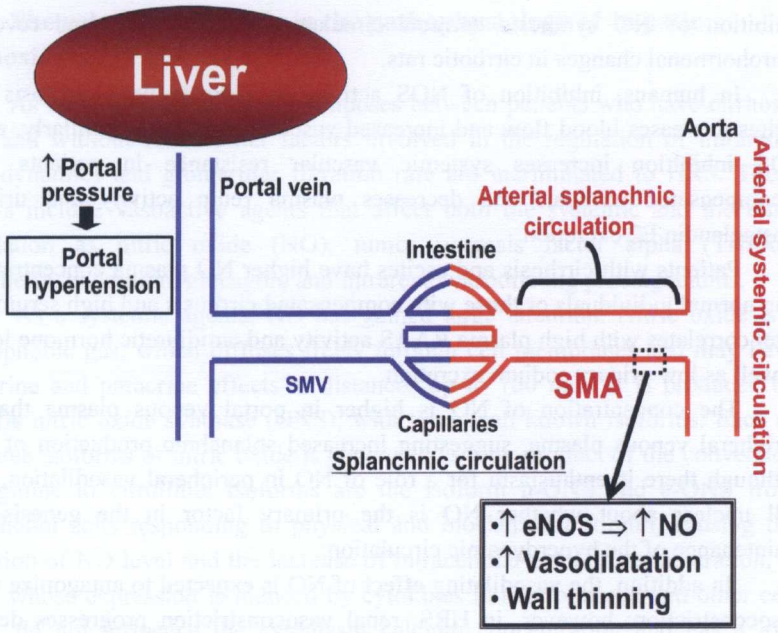

Fig. 2.5 Nitric oxide overproduction in liver cirrhosis (Yasuko Iwakiri. Endothelial dysfunction in the regulation of portal hypertension. Liver Int. 2012 Feb; 32(2) p.199–213).

An increased production of nitric oxide is likely to play a major role in the development and maintenance of splanchnic arterial vasodilation in liver cirrhosis. Moreover, in experimental cirrhosis the normalization of the overproduction of nitric oxide is associated with an improvement in renal and circulatory function and reduction of ascites. Unfortunately, the inhibitors of the nitric oxide system were withdrawn from development because of important side effects in patients with septic shock. In contrast to the splanchnic and systemic circulation in which there is overproduction of nitric oxide, in the intrahepatic circulation the production of nitric oxide is markedly decreased, which may be a factor contributing to an increased intrahepatic vascular resistance and portal hypertension. Therefore, the hypothesis was offered that increasing NO in the intrahepatic circulation could have beneficial effects on portal pressure. Attempts to decrease portal hypertension by the selective delivery of nitric oxide to the liver were promising in experimental portal hypertension but failed in human cirrhosis.

Impact of endothelial dysfunction on hepatic cirrhosis and HRS

The liver sinusoidal endothelium is a very specialized and phenotypically differentiated endothelium.

Sinusoidal endothelial cells (SEC) have unique and distinct characteristics from any other vascular endothelial cells for their sieve-like fenestrae on the cell surface and lack of basement membrane.

Being the first contact of hepatic blood circulation, fenestrae structure is quite important for selecting molecules and substances that enter the liver and exchange between the sinusoidal lumen and the space of Disse. Because of the fenestrae and lack of basement membranes, circulating lymphocytes can also contact hepatocytes directly. Sinusoidal endothelial cells play important roles in the regulation of intrahepatic vascular tone. Vasoactive substances released from SECs diffuse to hepatic stellate cells (HSCs) and cause their relaxation or constriction.

Thus SECs produce a wide variety of vasoactive substances and regulate the blood flow in the sinusoidal microcirculation. Substances such as endothelin-1 (ET-1), angiotensin II, norepinephrine, prostaglandin F2, thromboxane A2 (TXA2), and thrombin can trigger HSCs contraction

In contrast, vasoactive substances such as acetylcholine, vasointestinal peptide, NO, carbon monoxide (CO), prostaglandin E2, and adrenomedullin are known to relax HSCs. Among these vasoactive agents, ET-1 and NO have been recognized as important regulators in the sinusoidal microcirculation. Endothelin-1 has dual vasoactive effects, mediating vasoconstriction through binding to endothelin A(ETA) receptors located on HSCs and causing HSCs contraction. In contrast, vasodilatation is induced by endothelin B (ETB) receptors by stimulating eNOS activity through the activation of protein kinase B (Figure 2.6).

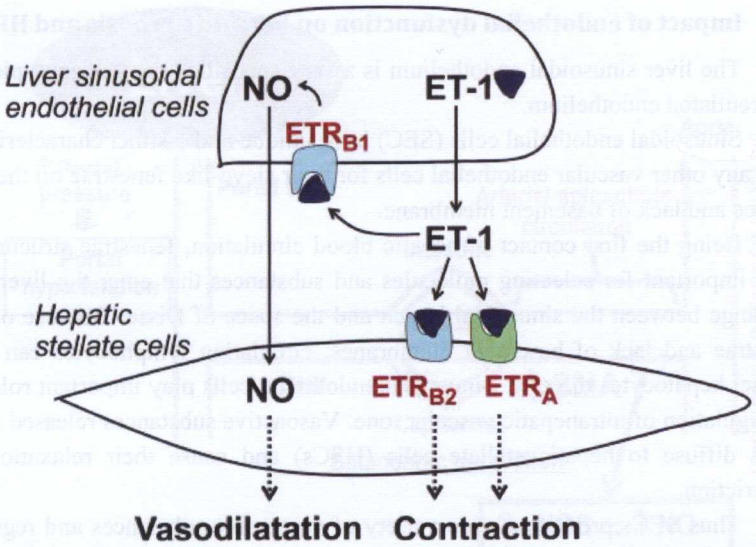

Fig. 2.6 Endothelin-1 (ET-1) mediation of both vasodilatation and vasoconstriction through ET-1 receptors (Yasuko Iwakiri. Endothelial dysfunction in the regulation of portal hypertension. Int. 2012 Feb (2): p.199–213).

In addition, it has been demonstrated that the disappearance of the normal filtration barrier in cirrhotic livers results in an impaired bidirectional exchange between the sinusoidal blood and parenchymal cells. As a consequence, defenestration and capillarization of the sinusoidal endothelium may therefore be a major contributor to hepatic failure in cirrhosis and elevated ET-1 values contributes to portal hypertension (Figure 2.7). Studies on patients with liver cirrhosis or on experimental models of cirrhosis have shown that all forms of cirrhosis are characterized by a defenestrated sinusoidal endothelium and the absence of subendothelial basement membrane.

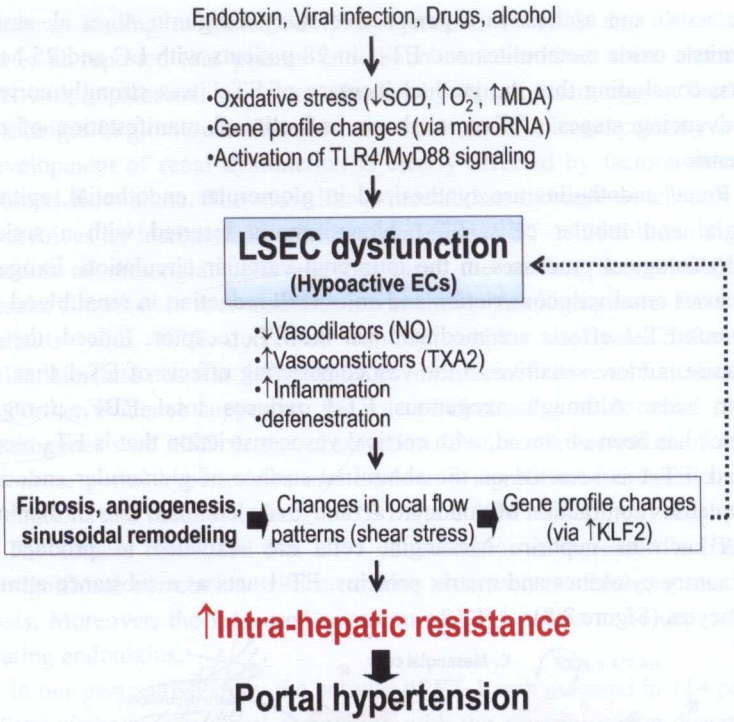

Fig. 2.7 Liver sinusoidal endothelial cell (LSEC) dysfunction in intrahepatic and sinusoidal circulation (Yasuko Iwakiri. Endothelial dysfunction in the regulation of portal hypertension. Liver Int. 2012 Feb (2): p.199–213).

In a recent study ET-1 receptors were localized in the endothelium of liver sinusoids by immunoperoxidase monolayer assay method. Liver sinusoids were examined by scanning electron microscopy after injecting to the rat an endothelin receptor antagonist BQ-123 for 10 minutes. After the infusion of antagonist BQ-123 to the rats a decrease in portal pressure was observed, thus demonstrating the action of ET-1 on liver microcirculation through its receptors. Besides, elevated levels of ET-1 are interacting with hepatic stellate cells by activation of proteinkinase and a rapid increase in intracellular free calcium coupled with cell contraction.

As already reported, endothelial dysfunction correlates significantly with the severity of liver disease. S. Pribilov et al. demonstrated on a group of 45 patients with LC Child-Pugh class B and C without hypertension, heart failure and obesity has revealed hypersecretion of ET-1 in cirrhotic patients with Child-

Pugh class C and ascites. In a perspective study Curgunlu A. et al. assessed serum nitric oxide metabolites and ET-1 in 28 patients with LC and 25 healthy subjects, concluding that the gradual increase of ET-1 was strongly correlated with advancing stages of liver cirrhosis and clinical manifestation of portal hypertension.

Renal endothelins are synthesized in glomerular endothelial, epithelial, mesangial and tubular cells. ET-1 bioactivity is inserted with a series of pathophysiological processes in the intrarenal vascular circulation. Exogenous ET-1 causes renal vasoconstriction and an overall reduction in renal blood flow. Exogenous ET-1 effects are mediated via the ET_A receptor. Indeed, the renal vasculature is more sensitive to the vasoconstricting effects of ET-1 than other vascular beds. Although exogenous ET-1 reduces total RBF, a regional difference has been observed, with cortical vasoconstriction that is ET_A receptor mediated. ET-1 is secreted on the abluminal surface of glomerular endothelial cells. It causes contraction of podocyte actin cytoskeleton and loss of diaphragm proteins such as nephrin. Mesangial cells are activated to produce pro-inflammatory cytokines and matrix proteins. ET-1 acts as a substance attractant to monocytes (Figure 2.8).

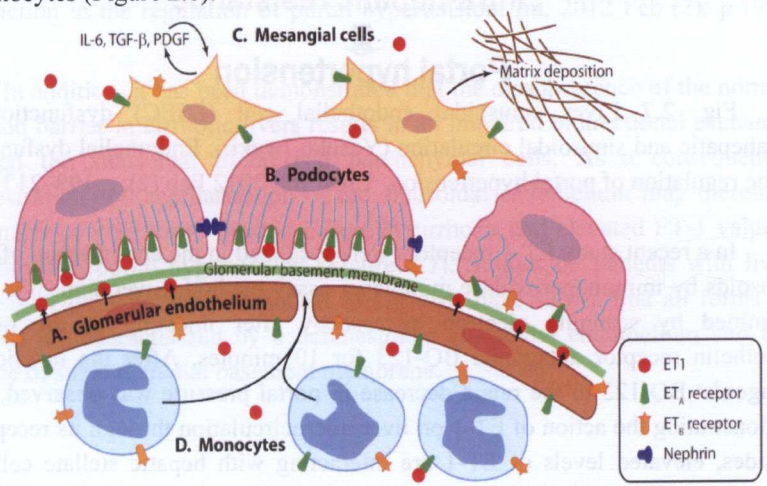

Fig. 2. 8 ET-1 effects on the glomerulus (Br J Pharmacol. 2012 Oct; 167.4: p.720–731).

The hepatic vascular bed of cirrhotic patients with HRS also exhibits endothelial dysfunction. Renal ET-1 production is increased in most causes of renal and hepatic injury and strongly intercalated with HRS. However, the

mechanisms leading to increased ET-1 synthesis in HRS are still unknow. Moore et al. reported that plasma endothelin concentrations were elevated in patients with hepatorenal syndrome. Studies by Ring-Larsen suggest that many of the changes in glomerular filtration rate occur at the microcirculatory level as the development of renal dysfunction is clearly affected by factors other than renal blood flow alone. The most likely mechanism through which this could occur involves an increased formation of vasoactive ET-1. Endothelin 1 causes contraction of mesangial cells and decreases the surface area available for glomerular filtration. In recent studies it was shown that high plasma ET-1 levels in patients with HRS decreased rapidly within one week after liver transplantation and this was followed by an improvement in renal function.

Further evidence supporting the role of circulating or autocrine ET-1 in the pathogenesis of HRS is the observation, that acute occlusion of a TIPS causes acute portal hypertension and leads to a significant increase in arterial concentrations and renal synthesis of ET-1 and a 40% reduction in renal plasma flow. The authors concluded that ET-1 concentration is increased in HRS and has a significant correlation with creatinine clearance in decompensated liver cirrhosis. Moreover, the increased secretion of ET-1 seems to be dependent of circulating endotoxins.

In our perspective study the activity of ET-1 was assessed in 114 patients with liver cirrhosis, the direct correlation with the severity of the disease was established and serum level of ET-1 was significantly higher in 23 patients with Child-Pugh class C and SHR compared with Child-Pugh class A patients ($p < 0.001$).

We found an extremely elevated levels of ET-1 in patients with HRS (15.57 pg / ml) as compared with those without HRS in Child-Pugh class C ($p < 0.05$) and as compared with Child-Pugh class A ($p < 0.001$). Our results show that alterations of circulating Endothelin-1 do not occur in all cirrhotic patients. Elevated plasma levels of ET-1 are only detectable in patients with more severe hepatic failure as compared with control patients. We established that high activity of ET-1, the most potent vasoconstrictor is a consequence of hemodynamic disorders occurred in the advanced phase of liver cirrhosis and HRS (Figure 2.9).

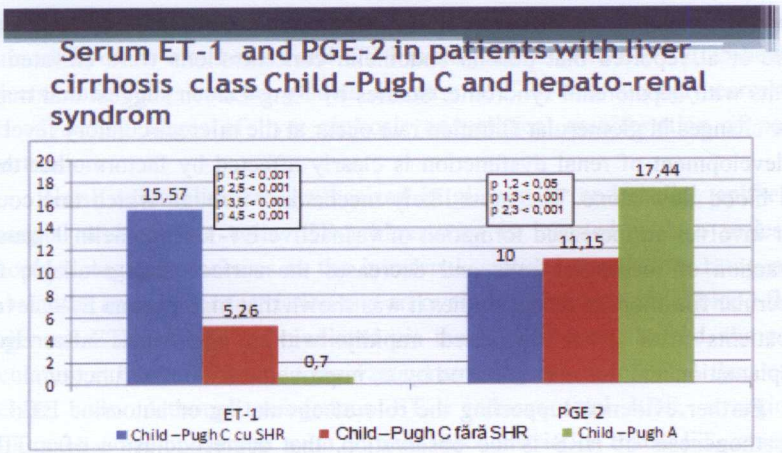

Fig. 2.9 Activity of ET-1 and PGE in patients with Child-Pugh class C and in Child-Pugh class C liver cirrhosis and HRS

This suggests that endothelial dysfunction is a significant pathogenic event in the course of severe complications that occur in cirrhotic patients. In keeping with this concept, correction of endothelial dysfunction is associated with an improvement in prognosis of HRS and therefore, it is considered a useful therapeutic target.

Involvement of renal prostaglandins in pathogenesis of HRS

Intrarenal prostaglandins (PG) play an important role in endogenous renal protection. Prostaglandins are classified as autocoids because, unlike true hormones, they are produced in minute amounts and have a local action. They are also referred to as eicosanoids because their structure is based on a 20-carbon fatty acid. Vasodilator prostaglandins are I not of so much important to maintain normal renal function as to preserve it during the ischemic situations.

Phospholipase A_2 is stimulated by ischemia, norepinephrine, and angiotensin II and cleaves arachidonic acid from its bond with membrane phospholipid. Cyclooxygenase acts on arachidonic acid to form cyclic endoperoxides (PGG_2 and PGH_2). Action of isomerase and prostacyclin synthetase form vasodilator prostaglandins PGD_2, PGE_2, and PGI_2 (prostacyclin), which decrease the actions of the renin-angiotensin system on the kidneys and protect against ischemic stress (Figure 2.10).

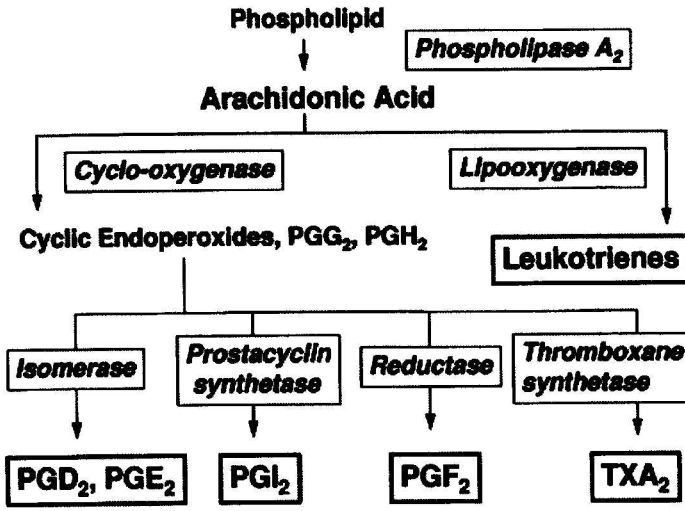

Figure 2.10 Synthesis of renal prostaglandins (Dunn MJ, Greely HP, Valtin H, et al. Prostaglandins and the kidney - Renal Physiology. Eur J. Clin Invest 5:311–318, 1975).

Important vasodilator renal prostaglandins are PGD_2, PGE_2 and PGI_2 (prostacyclin). Additionally, they oppose the actions of norepinephrine and angiotensin II and block distal tubule sodium reabsorption. Prostaglandins may be particularly important in decreasing the vasoconstrictor activity of angiotensin II on the afferent arteriole and glomerular mesangial cells. Production of prostaglandins promotes renal vasodilation, maintains intrarenal hemodynamics and enhances sodium and water excretion. Under hypoxic or ischemic conditions, cyclic endoperoxides undergo reduction to the vasoconstrictor PGF_2, which acts on thromboxane receptors. Endotoxin increases the activity of leukocyte lipooxygenase and thromboxane synthetase. Leukotrienes (especially C_4 and D_4) and thromboxane (TXA_2) induce renal vasoconstriction and contribute to vasomotor HRS.

Evidence accumulated during the past few years suggests that in decompensated cirrhosis, renal function is dependent of renal prostaglandin synthesis. Inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs induces acute reversible reductions of renal blood flow and

glomerular filtration rate. Furthermore, it has been documented that renal synthesis of vasodilator prostaglandins, such as prostaglandin E2(PGE2) and prostacyclin, is augmented in those patients with preserved renal function, while a spontaneous development of renal failure is accompanied by reductions in urinary prostaglandins. This derangements in renal prostaglandin production are associated with dramatic decrease in GFR and reduce natriuretic response of furosemide and spironolactone in patients with CH and ascites contributing to the development of hepatorenal syndrome.

In addition, immunohistochemical studies demonstrate reduced cyclooxygenase staining in renal medullary tissue of patients with HRS, whereas the enzyme is detected in kidneys of patients with other causes of acute renal failure. Factors that are associated with reduced prostaglandin production in HRS are unknown, but intense renal vasoconstriction may contribute to reduced prostaglandin synthesis. Conversely, systemic prostaglandin infusion in patients with HRS improve renal function, suggesting that decreased prostaglandin production is not the unique player in HRS. Natriuretic effects of PGE-2 is evident. Body immersion in water up to the neck in patients with decompensated liver disease causes a significant natriuresis, increased GFR and increased the urinary excretion of PGE-2 about three times. Rincon-Sanchez A. et al. evaluated the effect of infusion of PGE-2 on liver and kidney function in experimental cirrhosis models. Cirrhotic rats were exposed to a dose of carbon tetrachloride for eight weeks. Intramuscular injection of PGE-2 decreased acute phase of inflammation mediatores (acidglicoprotein Alpha-1, fibrinogen, Apo-A1M RNA-protein) in serum and improve liver and kidney function.

Bradykinin and other kinins are also synthesized in the kidney and their vasodilator effect contributes to a decreased reabsorbtion of sodium. The kidney is rich in tissue kallikrein located in the proximal and distal segments of the nephron. The natriuretic effect of the kallikrein-kinin system suggests that this system is more involved in the reabsorption of sodium and water than in modulation of glomerular filtration. Recent scientific evidence confirms the important role of renin in the kallikrein-kinin system activation, suppression of renin production is associated with reduced urinary excretion of kinins. Bradykinin activates phospholipase, which contributes to increased activity of prostaglandins and indirectly promotes increased secretion of NO. From this point of view, the decrease in the synthesis of kinin also contributes to the retention of sodium in liver cirrhosis. Plasma levels of other vasodilators like glucagon, carbon monoxide, prostacyclins, endogenous opiates, adrenomedullin,

substance-P, and calcitonin gene-related peptide are also elevated in HRS. PGE-2 and calcitonin gene-related peptide is a potent vasodilator, and circulating levels of both are increased in patients with alcoholic cirrhosis with ascites but not in controls patients or cirrhotic patients without ascites.

Derivatives of arachidonic acid that induce vasoconstriction may be important in pathologic state, too. Thromboxane (TXA_2) is derived from cyclic endoperoxides by the action of thromboxane syntheses. It induces vasoconstriction and platelet aggregation and it causes mesangial cell contraction in the kidney. Renal levels of thromboxane are increased in experimental acute renal failure and sepsis. In animal experiments, the administration of a specific thromboxane synthetase inhibitor prevents the deterioration in renal function induced by injection of endotoxin.

The vasodilators agents described before enter the systemic circulation through the portosystemic shunts, that are present in portal hypertension leading to systemic vasodilatation in later stages and contributing to the development of HRS. This syndrome is likely to develop in cirrhotic patients with more severe arterial vasodilatation. In our study in 23 patients with liver cirrhosis, ascites and HRS serum concentrations of PGE-2 were significantly reduced as comparied with Child-Pugh class A ($p < 0.001$) and as comparied with cirrhotics from Child-Pugh class C without HRS (($p < 0.05$) (figure 8).

In conclusion, local renal vasodilators such as prostaglandins are initially able to counterbalance the effects of the neurohormonal vasoconstrictor systems. Ultimately, this becomes inadequate, as renal vasoconstrictor tone predominates. The final result of this process is a severe decline in renal blood flow leading to reduced glomerular filtration rate and the development of HRS.

Chapter III. Diagnostic criteria of HRS

Due to the lack of specific biochemical or radiologic markers, the diagnosis of HRS is based on criteria to exclude other causes of renal impairment that may be found in liver cirrhosis. The criteria defined by the International Ascites Club (by Arroyo V, et al, 1996) are listed as follows:

Major criteria:

Chronic or acute liver disease with severe hepatic insufficiency and portal hypertension.

Reduced glomerular filtration rate, defined as serum creatinine > 1.5 mg / dL or lower creatinine clearance <40 ml / min.

Exclusion of the shock, bacterial infections, fluid losse, treatment with nephrotoxic drugs (nonsteroidal anti-inflammatory, aminoglycosides, etc.).

Exclusion of excessive fluid loss in the digestive system (vomiting or diarrhea) or renal function (weight loss over 500 g/day for several days, in patients with liver cirrhosis and ascites, edema).

Improves renal function (serum creatinine falls below 1.5 mg / dl, creatinine clearance 24 hours does not increase above 40 ml / min) after discontinuation of the diuretic and given 1500 ml of solution.

Proteinuria <500 mg / 24 hours, indicating the absence of sonographic criteria obstructive or parenchymal renal disease.

Minor criteria:

Diuresis <500 ml / 24 hours.

Urinary sodium <10 mEq / l.

Urinary osmolality> plasma osmolarity.

Urinary red blood cells <50 / field.

Serum sodium <130 mEq / l.

New diagnostic criteria of HRS

Due to the non-specific additional criteria (they can be found in patients with acute tubular necrosis and may be absent in patients with SHR and hyperbilirubinemia) these criteria were conflicting for the diagnosis of SHR.

In 2007, in town San Francisco at the 56th meeting of the American Association for the study of Liver Diseases and the International Ascites Club to reach a consensus, criteria for diagnosis of SHR were reviewed (Table 3.1).

Table 3.1 New diagnostic Criteria of HRS (after Salerno F, et al, 2007)

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

The main differences between the new diagnostic criteria and those developed in 1996 are:

1. Creatinine clearance was excluded from the diagnostic criteria. Creatinine clearance is considered suboptimal diagnostic criteria compared with serum creatinine due to urine sampling errors common in practice, which may lead to a high proportion of false positive diagnoses.
2. Renal failure occurs in patients with cirrhosis and bacterial infections in the absence of septic shock sould be considered SHR. Pharmacological treatment (albumin vasoconstrictor agents) of SHR should be initiated without waiting for complete resolution of infection.
3. The absence of hypovolemia (indicated by a lack of improvement in renal function after expansion of plasma volume with saline solution or albumin) can be used as an additional diagnostic criteria.

The actuality of these diagnostic criteria will also include minor changes regarding the role of infections and plasma expansion prior to the diagnosis of HRS.

Markers of glomerular filtration rate in patients with liver cirrhosis

There are several aspects that need to be mentioned in diagnosis of HRS. Early detection is crucial. It should be noted that, although serum creatinine has a high specificity for detecting GFR, its sensitivity is low. When traditionally measured by the Cockcroft-Gault GFR was low even at normal or slightly reduced serum creatinine. This finding was attributed to a low production of endogenous creatinine, resulting in malnutrition and reduced muscle mass, commonly seen in patients with liver cirrhosis. The sensitivity of 24-hour creatinine clearance for measuring GFR is greater than the sensitivity of serum creatinine, but it may give an overestimation and therefore careful 24-hour urine collection is needed. This is also frequently impaired, since such patients are mostly oliguric.

In 68 nonazotemic cirrhotic patients with uncomplicated cirrhosis, the evidence for renal dysfunction was detected in nearly two thirds, including 21 patients with a creatinine clearance of 50 to 80 mL/min and 25 patients with a creatinine clearance less than 50 mL/min. Detection of renal insufficiency is clinically important because there is an associated substantial increase in mortality. With a mean follow-up of 180 days, the mortality rate was 24% in patients with a creatinine clearance of 50 to 80 mL/min and 36% in those with a creatinine clearance of less than 50 mL/min, as compared with 9% in those with normal renal function. It is also important to mention that HRS patients may present acute tubular necrosis because of intense vasoconstriction that leads to ischemia. About one third of cirrhotic patients with spontaneous bacterial peritonitis also develop renal insufficiency and one third of such cases recover after treating SBP with appropriate antibiotic therapy. Therefore, SBP needs to be excluded in HRS even if there are no symptoms of SBP.

Clinical diagnosis of renal failure in patients with cirrhosis might also alternatively be based on blood urea nitrogen levels. However, both serum creatinine and blood urea nitrogen levels are poor markers of GFR. The use of other measures of GFR, such as levels of serum cystatin C, should needs to be explored in these patients. Current studies argue that for the correct assessment of GFR (if is less than <50 ml / min), serum bilirubin should not exceed 20 mmol / l. For this reason the perfect markers of GFR have to be completely filtered in the glomerulus, it is neither reabsorbed nor secreted by the renal tubules. Inulin is such a substance and it is believed to be the gold standard in determining GFR. In a performed study, which included a group of 306 patients

with LC and ascites glomerular filtration was estimated using both inulin clearance and creatinine clearance. Sensitivity to calculate GFR <80 ml / min was 51% for creatinine clearance and 74% for inulin clearance. However, due to technically complicated problems laboratory determination of inulin clearance is less used in clinical practice, only in 11%. The markers used for GFR assessment can be mannitol, sorbitol, vitamin B-12 labeled with the radioactive cobalt, but these techniques are complicated, costly, time-consuming and have potential side-effects. Actually, protease inhibitor - cystatin C is widely studied as a potential sensitive marker of GFR. Cystatin C, is a low-molecular-weight protein and is produced throughout the body by all cells that contain a nucleus and is found in a variety of body fluids, including the blood. It is produced and filtered from the blood by the kidneys. Compared to creatinine, the production of cystatin C is much less influenced by a person's age, gender, and size, hyperbilirubinemia, hemolysis.

Therefore, cystatin C has been shown to represent a potentially superior marker of the glomerular filtration rate compared with creatinine clearance. Cystatin C was first described in 1961 as a trace protein together with other ones in the cerebrospinal fluid and in the urine of patients with renal failure. Grubb and Löfberg firstly reported its amino acid sequence. They noticed it was increased in patients with advanced renal failure. It was first proposed as a measure of glomerular filtration rate by Grubb and coworkers in 1985. Being interested in this issue, Rogne N. et al. evaluated GFR by determining the clearance of inulin and creatinine in 148 patients with decompensated ethyl LC. The difference between creatinine clearance compared with that of inulin was 22 ± 20 mL / min per 1.73 m2, and the authors concluded that creatinine clearance remains a plausible index of GFR. Recent studies suggest that in patients with advanced liver cirrhosis GFR should be interpreted with caution However, the use of serum creatinine and cystatin C was found very effective in accurately reflecting the glomerular filtration in a study reported in the July 5, 2012 in issue of the New England Journal of Medicine.

Chapter IV. Differential diagnosis of HRS

Renal dysfunction in the context of liver cirrhosis

As we discussed before due to the absence of recognized biomarkers, the diagnosis of HRS is based on a combination of clinical and laboratory criteria. Acute tubular necrosis, prerenal failure due to volume depletion, and chronic glomerulonephritis in patients with hepatitis B or C can be found in patients with advanced liver cirrhosis. Gastrointestinal fluid lose as a result of vomiting or diarrhea or kidney fluid lose occur in all patients with cirrhosis and kidney failure. If renal failure is secondary to volume depletion, it will improve quickly after volume repletion and treatment of the underlying cause.

In patients with septic shock, HRS sometimes is mistakenly diagnosed if indicators of infection (such as cell count in ascitic fluid) are not carefully considered because low arterial pressure of sepsis may erroneously be attributed to arterial hypotension of HRS. Unfortunately, treatment with nonsteroidal anti-inflammatory drugs is another relatively common reason for acute kidney failure in patients with liver cirrhosis and ascites. Clinically, this condition is identical to HRS. Before making a diagnosis of HRS, it is vital clinicians to exclude the treatment with nonsteroidal anti-inflammatory drugs. Patients with cirrhosis who have been treated with aminoglycosides are also at increased risk of developing kidney failure. In addition, they may develop kidney failure because of glomerulonephritis and patients with cirrhosis due to nonalcoholic steatohepatitis have a high incidence of chronic kidney disease, too. In cases of chronic glomerulonephritis, proteinuria and hematuria usually are present and may be confirmed by kidney biopsy. The key step in diagnosing HRS is to exclude the possibility of kidney failure secondary to these conditions (Figure 4.1).

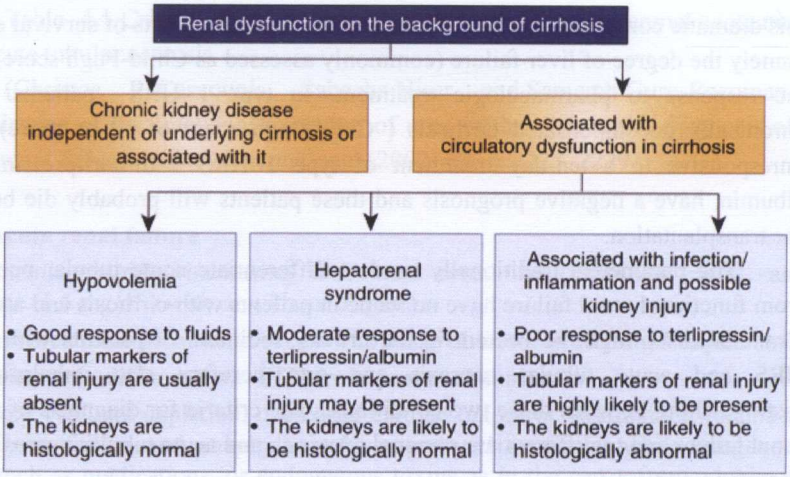

Fig 4.1 Differential diagnosis of renal dysfunction in live cirrhosis (Adebayo D et al. Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. Kidney International 2015. 87, p. 509–515).

Only a minority of patients with liver cirrhosis and elevated serum creatinine fulfills the criteria of hepatorenal syndrome. One prospective study found that in a transplant center, 40% of patients with cirrhosis and kidney failure had HRS, followed by renal parenchymal disease in 23% and drug-induced kidney failure in 19% of patients.

However, depending on the selection of patients in referring hospitals, these data will probably differ among different centers. It is crucial to distinguish between patients with hepatorenal syndrome and those with other causes of renal impairment not only for clinical management, but also for proper prognostic appraisal of patients with cirrhosis and kidney failure The presence of type 1 HRS has been shown to be an independent predictor of survival in these patients, even if the MELD score (which also reflects kidney function) is included. Patients with type 1 HRS have a worse prognosis than their respective MELD score would predict, which is of major importance in the context of priority listing for transplantation.

On the other hand, in terms of prognosis, the diagnosis of type 2 HRS is probably less relevant since these patients have a similar prognosis as liver cirrhotic patients with other causes of kidney impairment. Data of the largest retrospective multicenter analysis on HRS type 1 suggest that in patients with

this dramatic complication of cirrhosis, two major determinants of survival exist, namely the degree of liver failure (commonly assessed as Child-Pugh score) and the response to pharmacologic treatment. In type 1 HRS patients with chronically decompensated cirrhosis (Child-Pugh score of 12 or more) and unresponsive to a ten-day treatment of type 1 HRS with terlipressin and albumin, have a negative prognosis and these patients will probably die before the transplantation.

The parameters traditionally used to differentiate acute tubular necrosis from functional renal failure have no value in patients with cirrhosis and ascites. Granular casts might be present in the urinary sediment of patients with both HRS and acute tubular necrosis and are therefore also unhelpful in distinguishing between these two conditions. The criteria for diagnosis of acute renal failure and to differentiate prerenal azotemia and acute tubular necrosis are shown in Table 4.1.

Table 4.1 Criteria for diagnosis of acute renal failure - prerenal azotemia and acute tubular necrosis

(Christos P. Carvounis, Sabeeha Nisar and Samerah Guro-Razuman. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. Kidney International (2002) 62. p.2223–2229).

A. Acute renal failure

1. Azotemia—rapidly increasing BUN and creatinine (BUN>30 mg/dL and creatinine>1.5 mg/dL) with or without oliguria.

2. Serum creatinine increase in excess of 0.5 mg/dL in the preceding 2 days.

B. Criteria to differentiate ATN from prerenal azotemia

1. History (volume depletion, decreased cardiac output or vasodilation related to sepsis, liver failure and anaphylaxis favor prerenal azotemia, while exogenous toxins such as medications, or endogenous toxins as in the case of myoglobin, or even prolonged renal hypoperfusion that became unresponsive to appropriate corrective measures or to high dose of loop diuretics).

2. Physical examination (blood pressure, heart rate, orthostatic changes, cardiac sounds, pulmonary findings, presence of ascites or leg edema).

3. Findings of the urine analysis (urinary sediment undetected in prerenal failure, presence of muddy brown granular casts in patients with ATN). Response to therapy also was recorded.

4. Urinary indices evaluated at the time of consultation are:

—Urinary sodium (U_{Na}): U_{Na} <15 mEq/L favors prerenal failure, while a value higher than 20 is consistent with ATN.

—Urinary to plasma creatinine ratio (U/P_{Cr}). U/P_{Cr}>20 is consistent with prerenal while levels <15 suggest ATN.

—Fractional excretion of sodium (FE_{Na}). FE_{Na} <1% is suggestive of prerenal azotemia, while levels>1% indicate the presence of ATN.

—Urinary sodium/potassium ratio (U_{Na}/K; a reflection of prerenal conditions with associated hyperaldosteronism). If U_{Na}/K is less than $^1/_4$, this favors prerenal azotemia.

The key step in diagnosing HRS is to exclude the possibility of kidney failure secondary to these conditions,

It is necessary to emphasize, that renal failure secondary to liver dysfunction is generally functional in nature and occurs in the absence of significant alterations in renal histology (prerenal). However, intrinsic renal abnormalities can also complicate acute or chronic liver disease (intrinsic renal

failure). Obstructive uropathy that leads to postrenal acute renal failure only develops in chronic liver disease (papillary necrosis in alcoholic liver disease, bleeding in the urinary tract due to severe coagulopathy). ARF in patients with cirrhosis frequently accompanies complications such as bacterial peritonitis or other sepsis, excessive diuretic therapy, administration of nephrotoxic drugs or contrast agents. The course of renal response to fluid challenge or vasoconstrictor therapy can also help differentiate causes of acute azotemia in liver disease (Table 4.2).

Table 4.2 Differential diagnosis of ARF in advanced liver disease

(Miller TR, Anderson RJ, Linas SL, et al: Urinary diagnostic indices in acute renal failure. Annals of Internal Medicine 1978.89(1):p. 47–50).

Indices	**Prerenal failure**	**Intrinsic renal failure**	**HRS**
Urine sodium	< 10	> 30	< 10
U/P creat	> 30:1	< 20:1	> 30:1
U/Posm	UO > PO	UO = PO	UO > PO
Urine sediment	Normal	Casts, cellular debris	Unremarkable
History disease	Profound volume	Volume contraction	Advanced liver disease
Clinical course (renal response)	Contraction	Nephrotoxic agent sepsis	Tense ascites
Fluid challenge	+	-	-
Vasoconstriction	+ -	-	+

Urine indices are useful theoretical tools for differential diagnosis of the three principal causes of ARF in liver disease. However, in reality apart from urinary sediments these are often not clear assessed.

Chapter V. Early detection of hepatorenal syndrome

Potential predictors of HRS

Several studies have been performed to investigate potential predictors of HRS. Gines et al., in a study of 234 patients, identified 16 variables that may be useful as predictors of HRS. The variables included hepatomegaly, esophageal varices, history of ascites, nutritional status, GFR, blood urea nitrogen, serum sodium and potassium, plasma renin activity, plasma noradrenaline, serum and urinary osmolality, urinary sodium excretion, free water clearance after a water load and mean arterial pressure. However, only three independent variables, absence of hepatomegaly, high plasma renin activity, and low serum sodium, were found to be predictive of HRS on multivariate analysis.

In a study of 263 patients, Montoliu et al. found that older age, high baseline serum creatinine, and high Child-Pugh score were independent predictors of HRS in multivariate analysis. These variables may reflect alonger duration of liver disease and a greater severity of liver and renal impairment. In a study of 180 patients with nonazotemic liver disease Platt et al. reported that the resistive index (RI) of the intrarenal arteries on Doppler ultrasound predicted the development of renal dysfunction, including HRS.

HRS does not have any specific clinical features. Its physical manifestations broadly reflect the underlying advanced liver disease, renal impairment and present circulatory abnormalities. Clinical findings of advanced liver disease include hepatomegaly, ascites, stigmata of portal hypertension (e.g., gastroesophageal varices, caput medusa, hepatic encephalopathy, etc.), jaundice, pruritus, coagulopathy, gynaecomastia, finger clubbing, palmar erythema, spider naevi, and constitutional disturbances such as weakness, fatigue, anorexia, and poor nutritional status. Patients with type 1 HRS are affected more severely than patients with type 2 HRS. Acute oliguria is typically present in type 1 HRS, while urine output shows a more gradual decline in type 2 HRS.

Circulatory disturbances include hyperdynamic circulation and reduced systemic vascular resistance. This may be manifested clinically as low blood pressure, low jugular venous pressure, tachycardia, bounding pulse. The following laboratory findings are suggestive of HRS: elevated plasma renin

activity, elevated plasma noradrenaline activity, hyponatraemia, hyperkalaemia, elevated blood urea nitrogen, decreased plasma osmolality, elevated urinary osmolality, and decreased urinary sodium excretion. Serum abnormalities that reflect the severity of liver disease include hyperbilirubinemia, hypoalbuminemia, and prolonged prothrombin time.

Markers of tubular damage in patients with liver cirrhosis and HRS

As mentioned above, the assessment of serum creatinine concentration in renal dysfunction of liver cirrhosis could be not sufficiently formative. Recently, novel biomarkers for diagnosing tubular damage in patients with liver cirrhosis and HRS are in quest. Several studies have demonstrated the utility of early measurement of urinary enzymes for predicting the severity and clinical outcomes of HRS. It is allowable that profound renovascular constriction may cause subclinical tubular damage in at least a subset of nephrons, not detectable by urinary sodium, which is not sensitive enough to identify mild tubular epithelial damage.

The kidney has a numerous group of enzymes located primarily in the nephron. Low concentrations of enzymes are normally found in urine as a result of pinocytosis in epithelial cells of the proximal tubules. Increased cell membrane permeability causes excessive amount of enzymes in urine, which in turn determines the extent and location of damage in the glomerular and tubular segments of the nephron. Although in human urine were detected around 50 enzymes, several of them are used for diagnostic purposes. Urinary lysosomal hydrolytic enzyme- N-acetyl-β-glicosaminidaza (NAG) is released by lysosomes from the cytoplasm of epithelial cells in the renal proximal convoluted tubules. Gamma-glutamyltransferase, (GTP), alkaline phosphatase (ALF) are released by lysosomes from the cytoplasm of epithelial cells in the renal proximal tubule, too, and demonstrates a high activity in certain clinical states, being eliminated in tubular fluid. Alpha-glucosidase (AGL) is another enzyme is localized in the cytoplasm of epithelial cells of the brush border membrane of renal proximal tubule cells and its excessive secretion in urine was reported. Similarly, increased number of cytoplasmic enzymes - lactate dehydrogenase and glutamate dehydrogenase, synthesized in mitochondria determine renal tubular epithelial cell cytolysis. The presence of high molecular weight enzyme – pseudocholinesterase (PCE) in urine (it is absent in the urine

of healthy subjects) indicates a decrease in selectivity and increased permeability of the glomerular basement membrane of the kydney. Undoubtedly, an excessive amount of enzymes in urine is determined by impaired renal cell membranes and an intense enzymatic activity in certain clinical states. Multiple studies relate to the determination of urinary enzymes, especially NAG as an indicator of early renal tubular injury in hypertensive patients, in diabetic nephropathy, chronic pyelonephritis, as markers of nephrotoxic drugs, etc.

Further evidence supporting the hypothesis that renal dysfunction in cirrhotic patients is more than just functional renal failure and that tubular injury occurs derive from studies that have shown that markers of tubular injury are elevated in some patients with renal dysfunction in liver cirrhosis. Rector et al. observed an increase in urinary beta-2-microglobulin, which is an indicator of tubular function in cirrhotic patients with presumed HRS compared with control subjects. Neutrophil gelatinase–associated lipocalin is a protein produced the renal tubules, which is unregulated after renal tubular injury. Patients diagnosed with HRS were shown to have significantly higher plasma and urinary neutrophil gelatinase–associated lipocalin levels compared with stable cirrhotic patients. In addition, neutrophil gelatinase–associated lipocalin was identified as a predictor of mortality in patients with HRS. Urinary levels of β2-microglobulin are useful in the diagnosis of aminoglycoside nephrotoxicity, too. β2-microglobulin is filtered by the glomerulus and almost completely reabsorbed in the proximal tubule. In patients with acute tubular necrosis owing to aminoglycosides, necrosis in proximal tubules results in a marked increase of β2-microglobulin concentration in urine.

Furthermore, in the later stages of liver cirrhosis, there was evidence of hydropic degeneration of the proximal and distal tubules. Similarly, an animal study, involving a rat model of cirrhosis treated with lipopolysaccharide (which is clinically similar to a patient with renal dysfunction associated with infection), showed evidence of tubular vacuolar degeneration in the proximal tubules, and this was associated with sloughing of tubular cells. There was also an increase of caspase-3 signifying tubular cell apoptosis. It is recognized that apoptosis of tubular cells by inflammatory cytokines occurs in renal dysfunction associated with endotoxemia and AKI. A similar pathophysiology may underlie infection and inflammation-associated renal dysfunction in cirrhotic patients. These observations suggest that immunologic mechanisms are important in mediating a renal injury and that hemodynamic factors do not operate in isolation. The

value of other urinary biomarkers, such as γ-glutamyltranspeptidase, transaminases, neutrophil gelatinase-associated lipocalin, liver-type fatty acid binding protein, IL-18 and hepatitis A virus cellular receptor 1 in the differential diagnosis between type 1 HRS and acute tubular necrosis has not been assessed.

Determination of urinary enzymes in patients with liver cirrhosis as a diagnostic tool in the control of renal impairment was studied over the years. Gatta A., Amodio P et al. observed an increased activity of enzyme GTP, alpha-glucosidase and beta-2-microglobulin from tubular cells in 93 patients with liver cirrhosis, particularly in those with a significant reduction of GFR. Solis-Herruzo J. et al. assessed the importance of urinary enzymes as markers of early renal impact in 32 patients with LC, 12 of them with HRS, concluding that high values of GTP, alkaline phosphatase, beta-galactosidase suggest that they have a high risk of developing renal complications and have a low life expectancy. Amakasu H. et al. studied enzyme activity of N-acetyl-beta-glucosaminidase in patients with liver cirrhosis. The enzyme output of 32 patients was compared and urinary NAG values were higher in patients with liver cirrhosis Child-Pugh class C than in patients with Child-Pugh class A and class B, especially in 8 patients with ARI. In 1994 the further studies of Bruno C. et al. suggested that the highest average enzymuria occured in decompensated cirrhosis as compared with the control group ($p < 0.01$).

Some urinary enzymes (NAG, lysozyme) considered to be sufficiently sensitive and reliable markers of renal tubular damage were controlled in 20 patients with cirrhosis of the liver and in 20 healthy control subjects. The results, stated as mean +/- SD, showed a statistically very significant increase ($p < 0.01$) of NAG and lysozyme in cirrhotics.

A number of imposing recent studies concluded that some urinary enzymes are sufficiently sensitive and reliable markers of renal damage in patients with LC. An impressive study that was carried out by Liang A et al. Assessed the activity of urinary NAG in 201 hospitalized patients with prerenal ARF genesis. The presence of elevated NAG in the early stages of the ARF, including 42% of patients with liver cirrhosis was established. Furthermore, this increase of NAG could be at least in part related with the severity of clinical condition. Based on these results, we concluded that in subjects with liver cirrhosis the urinary dosage of NAG and lysozyme is a bloodless method to show an early renal damage. Recently Lisowska-Myjak B has classified acute kidney injury markers into several groups: enzymes of tubular nephrotelium - FTA, IIGTP, alanine aminopeptidase, glutathione transferase isoenzyme, NAG,

enzymes with small molecular weight- alpha-1-microglobulin, beta-2 microglobulin, neutrophil gelatinase-associated lipocalin (NGAL), cytokines and chemokine (growth-regulated protein alpha, IL-18) and renal tubular structural proteins- F-Actin, Na^+/H^+-exchanger izoform 3 protein. In summary, this results show, that the analysis of urinary enzyme patterns may be a helpful adjunct for differential diagnosis of ARI in liver cirrhosis.

In our study enzyme activities were assayed in three hour morning samples after gel filtration of urine in 23 cirrhotic patients with HRS. Activities were related to time volume, and to urinary creatinine concentration. Patients with HRS type II had a significantly higher excretion of alkaline phosphatase and GTP ($p<0.05$) as compared with HRS type I and as compared with patients with Child-Pugh A score ($p<0,01$), ($p<0,001$). N-acetyl-beta-glucosaminidase, AGL , PCE enzyme activity ware significantly higher in type I and type II HRS as compared with with patients with Child-Pugh A score. ($p <0,01$) (Table 5.1).

Table 5.1 Urinary enzyme activity in patients with HRS Type I and II

Values	HRS type I	HRS type II	Child –Pugh A cass	$p_{1,2}$	$p_{1,3}$	$p_{2,3}$
	$M_1 \pm m_1$	$M_2 \pm m_2$	$M_3 \pm m_3$			
Urinary FTA (nmol/s mmol creat)	1513,82±276,89	2640,22±489,44	307,21,0±21,41	**	***	***
Urinary γ-GTP (nmol/s mmol creat)	1264,52±88,17	1199,01±90,46	266,7 ± 29,87	**	****	****
Urinary NAG (pmol/s mmol creat)	11,74±1,85	15,27±1,35	1,15±0,20	*	****	****
Urinary PCE (nmol/s mmol creat)	7,66±1,36	5,76 ± 0,95	0,66±0,06	*	****	****
Urinary AGN (pmol/s mmol creat)	123,25±6,62	149,11± 16,37	36,94±2,71	*	****	****

Note: * $p>0,05$ ** $p<0,05$ *** $p<0,01$ **** $p<0,001$

In summary, these results show, that the analysis of urinary enzyme patterns may be a helpful adjunct for differential diagnosis of different types of ARI in liver cirrhosis.

Diagnostic value of Renal Duplex Doppler Ultrasonography

Doppler ultrasonography of renal arteries (RA) as an alternative and noninvasive method was applied earlier to evaluate the incidence of renovascular disease and the diagnosis of kidney transplant rejection in the 1980s. Doppler ultrasound provides one of the most successful images of renal arteries, its sensitivity is 85% as compared with CT angiography of renal arteries (95%) and magnetic resonance angiography (90%). A high finesse diagnostic classification was possible due to duplex and color coding particular installation, which allowed a more accurate interpretation of ultrasound morphology. Doppler signal is a graphical expression of all wave frequencies reflected from a moving structure. It is received by the transducer in the form of a spectrum, indicating with respect to time, frequency, and intensity of the flow. Attention to the technique is important to ensure accurate examination results, including selecting a transducer that is appropriate for the patient's body habitus, optimizing color Doppler parameters. .

The greatest peak systolic velocities should be recorded on the proximal portion of renal arteries and near the hilum. An effort should be made to search for accessory renal arteries. When visualized, peak systolic velocities should be recorded as described above. An appropriate angle-corrected spectral waveform of the abdominal aorta at the level of the renal arteries should be recorded. The aortic peak systolic velocity is used to calculate the ratio of the peak systolic velocity in the renal artery to the aorta. Renal artery stent evaluation should include recording a peak systolic velocity in the proximal renal artery (if possible), within the stent, and distally to the stent (if possible).

The evaluation of the renal hemodynamics in patients with liver cirrhosis is based mainly on the index of resistance of the intrarenal arteries. Renal vasoconstriction has been documented in several groups of cirrhotic patients on the base of increased resistive index (RI). Renal dysfunction developed in 55% of patients with an elevated RI at baseline, including 6% of patients with a normal RI. HRS developed in 26% of patients with elevated baseline RI and in 1% of patients with normal baseline RI. Patients who kept developing HRS had

higher baseline RIs (0.77) than patients without HRS renal impairment (0.72) or patients with preserved normal renal function (0.65,).

The RI may be regarded as a barometer of the intrarenal vascular tone and this is elevated in HRS due to increased vasoconstrictor activity. In patients with refractory ascites, as well as in subjects with serum creatinine within the normal range, increased RI seems to be correlated with a higher risk of subsequent deterioration in renal function. The detailed investigation of the renal blood flow in real time is a challenge for the investigators. Joel f. Platt et col. studed with renal Doppler ultrasonography 180 patients who had liver disease without azotemia. Vascular waveform analysis indicated an increase in resistive index in 42% of cirrhotic patients, kidney dysfunction subsequently developed in 55%, as compared with only 6% of those with a normal resistive index.

HRS occurred in 26% of those with an elevated resistive index, as compared with only 1% of those with normal values. In cirrhotic patients with renal failure, the resistive index correlates with the glomerular filtration rate, arterial pressure, plasma renin activity and free water clearance and has a sensitivity rate and specificity rate for the detection of renal failure of 71% and 80%, respectively. The RI may be regarded as a barometer of the intrarenal vascular tone and this is elevated in HRS due to increased vasoconstrictor activity.

D. Popov, R. Krasteva, et al. evaluated and compared the changes of liver and renal Doppler Abdominal Ultrasound (US) parameters in 67 patients with liver cirrhosis according to the degree of liver disease. The deviations of renal Doppler US parameters were also related in patients with liver cirrhosis, as well as deviations in serum urea and creatinine levels. The resistive index increases progressively from normal values in control patients (0.53) to higher values in cirrhotic patients with ascites, renal Doppler US parameters correlate with the severity and complications of liver cirrhosis.

Götzberger M. et al. performed Renal Duplex Doppler Ultrasonography in 81 cirrhotic patients and 75 healthy subjects. They found significantly higher values of RI in patients with ascites compared with those without ascites - RI (0.74 vs. 0.67, $p < 0.01$) and those without ascites as compared with the control group (RI 0.67 vs. 0.62, $p < 0.01$). As a result, in 48% of patients with decompensated liver cirrhosis and normal values of serum creatinine renal RI was increased more than 0.70. Fouad Y. study presented similar occurrence of high values of RI and pulsatility index (PI) in 60 patients with Child-Pugh class C, especially in patients with refractory ascites and 15 patients with HRS.

In our study we evaluated and compared Renal Doppler US parameters in 114 patients with liver cirrhosis (including 24 patients with HRS) according to the degree of liver disease. Abdominal ultrasound (US) and renal Doppler US, were made and interpreted by the same investigator according to standard protocol. Intrarenal arteries, segmental branch were evaluated by Color Doppler US. The mean values of the parameters for each kidney were obtained from the measurement of the waveforms of both, right and left renal areas.

We evaluated the following intrarenal blood flow Doppler parameters (m/sec): RA peak systolic velocity (RA-PSV), RA minimal end diastolic velocity (RA-EDV), RA mean velocity (RA-MnV), RA resistance index (RA-RI = RA-PSV − RA-EDV/RA-PSV), and RA pulsatility index (RA-PI = RA-PSV − RA-EDV/RA-MnV).

All intrarenal blood flow Doppler parameters except right and left RA peak systolic velocity showed significant differences between Child-Pugh class A, B, and C. In addition, we also found a significant relationship between Child's score and right and left RA minimal end diastolic velocity, right and left RA resistance and RA pulsatility indices.

The deviations of renal Doppler US parameters were also related with the complications of liver cirrhosis, as well as serum urea and creatinine levels. Resistive index and pulsatility index were significantly elevated in group of cirrhotics with Child -Pugh class B ($p < 0.05$) and Child -Pugh class C ($p < 0.001$) as compared with healthy subjects and Child-Pugh class A ($p < 0.001$), (Figure 11,12).

Our results show, renal Doppler US parameters correlate with the severity and complications of liver cirrhosis. The resistive index increases progressively from normal values in control patients (0.63) to higher values in non-ascitic cirrhotic patients (0.72) and those with ascites. Compared with those with Child--Pugh class A, values of RI are also higher in Child--Pugh class B and C cirrhotic patients. Therefore, abnormal values may help identify high-risk patients.

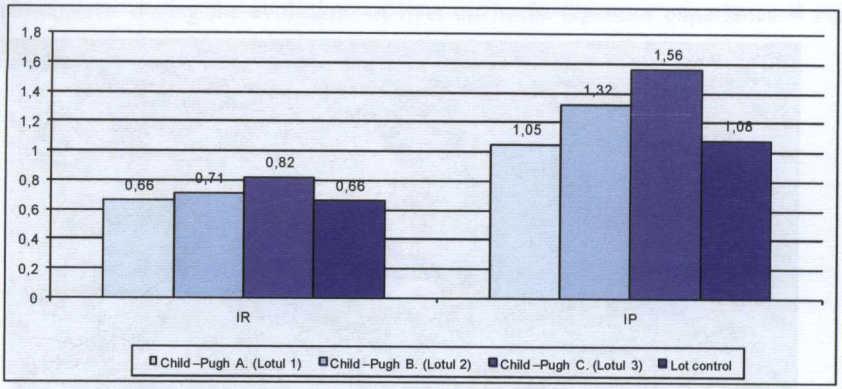

Fig. 5.1 Renal Doppler US parameters in patients with liver cirrhosis according to Child-Pugh classification.

In our study all intrarenal blood flow Doppler parameters except RA peak systolic velocity show a significant association with the severity of liver cirrhosis, evaluated by Child's scores.

Most of these parameters also correlate with the presence of esophageal varices and ascites, as well as with the severity of liver cirrhosis.

Clasa Child-Pugh C

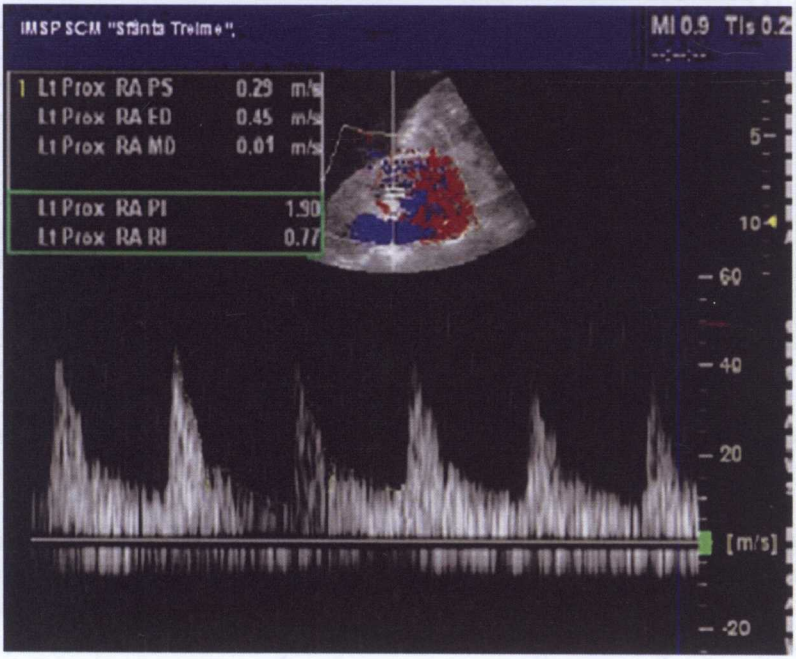

Fig. 5.2 Color Dupler US of renal arteries in patient with liver cirrhosis Child-Pugh class C.

Renal artery Doppler US parameters may be useful to identifying patients with high risk for developing impaired renal function at an early stage. On the other hand, there is no evidence that Doppler US helps differentiate cirrhotic patients with impaired renal function related only to vasoconstriction from patients with both vasoconstriction and intrinsic kidney damage.

The values of renal Doppler US parameters also depend on many factors. The application of diuretics leads to an elevation in the impedance indices of the intrarenal arteries.

Paracentesis and albumin infusion are followed by a significant decrease in renal RI. Due to that, renal artery Doppler US may help to clarify the impact of therapeutic intervention on renal hemodynamics. The therapy with beta-blockers and diuretics may interfere with the renal blood flow.

We strongly recommend Doppler US of renal artery as a part of follow up of these patients because of dynamic deviations of renal Doppler US parameters during the evolution of liver cirrhosis. Operator experience is also important before this method can be recommended for routine use.

Chapter VI. Management and current therapeutic strategies in HRS

Management and treatment of type 1 HRS

In the management of patients with HRS, the main objective is to minimize kidney failure in order to provide a successful tranzit to liver transplantation. Patient have to be admited to the hospital - ideally to intensive care unit. If there are signs of renal failure, first of all, the causative factors have to be eliminated and treated. Discontinuation of nephrotoxic medicens, treatment of a suspect bacterial infection, including spontaneous bacterial peritonitis with focus on gram-negative flora, arrest of bleeding in gastrointestinal tract and adequate compensation for loss of liquids. Discontinuation of nonsteroidal antiinflamatory drugs, caution in administration 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 is the partial evacuation of tension ascites accompanied by a consistent compensation for albumin.

As in HRS laboratory findings are similar to those of prerenal uremia, attempts have been made to treat this syndrome by hypovolemia correction. Earlier, a physiological solution or Dextran has been administered, which is unfortunately inappropriate in this case. Nevertheless, human albumin has proven to be the most suitable. Human albumin is used for expansion of circulatory blood volume and has been shown to reduce successfully the incidence of type 1 HRS. When used for the treatment of HRS, it has shown better results when administrated in combination therapy as it amplifies the effect of other pharmacologic therapies in the treatment of HRS. Adequate hypovolemia correction is required before, as well as during, the subsequent treatment with medicaments, but aggressive hypovolemia substitution must be avoided (risk of cerebral oedema) - fluid restriction is more suitable. Albumin is now the basis of the HRS therapy in combination with vasoconstrictors.

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 splanchnic arterial vasodilation and inadequate cardiac output, which implies an extreme

overactivation of the endogenous systemic vasoconstrictor systems- RAAS, SNS and nonosmotic release of vasopressin. This means that the final aim of the therapeutic approach is to reduce severe renal arterial vasoconstriction.

In an effort to reduce intrarenal vascular resistance the first group of drugs used for this indication was prostaglandins. They were used to be recommended, but have not shown any demonstrable improvement in renal function. Formerly, dopamine was tested in a small to medium dose to treat HRS 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.

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 in the treatment of HRS. This analogues act on the V1 receptors in the splanchnic vasculature, causing a greater vasoconstrictive effects in the mesenteric circulation than in the renal or other vascular systems.

Vasoconstriction of an extremely dilated splanchnic arterial bed subsequently improves arterial underfilling, reduces the activity of the endogenous vasoconstrictor systems and increases kidney perfusion. In retrospective studies it has been demonstrated that prolonged use of an ornipressin, terlipressin or α-agonist vasoconstrictor (midodrine plus octreotide, noradrenaline alone) in association with human albumin is capable of recovering renal function in 40%-60% of patients with type 1 HRS. In time, the use of ornipressin was stoped because of its high rate of ischemic side effects.

Most published data concern the use of intravenous terlipressin. Results of recent randomized controlled studies and systematic reviews indicate that treatment with terlipressin together with albumin is associated with marked improvements of kidney function in approximately 40% to 50% of patients and this vasoconstrictor therapy improves survival in type I HRS. The treatment is typically started with intravenously administration with 1 mg/4-6 hours and the dose is increased up to a maximum of 2 mg/4-6 hours in three days if there is no response to therapy (defined as a reduction of serum creatinine level > 25% of the pretreatment values). In responders, the goal is to achieve the lowest levels of serum creatinine. The treatment is stopped when there is no further reduction of creatinine. In nonresponders, if there is no decrease in serum creatinine or if its level increases, treatment should be stopped after three to four days of the

maximum dose of terlipressin. If the reduction in serum creatinine is very slow, the treatment can be maintained as long as the serum creatinine level decreases and there are no side effects of therapy. Recent studies suggest that the administration of terlipressin as a continuous intravenous infusion may improve its efficacy and decrease adverse effects. The incidence of ischemic side effects is approximately 10%. The recurrence of HRS after this therapy occurs in less than 15% of patients. The treatment is usually applied for 5 to 15 days. It is unlikely that vasoconstrictor drugs to improve survival beyond the short term. A multicentre randomised controlled trial comparing terlipressin and albumin with albumin alone in 46 patients with HRS showed improved renal function in the former group (43.5% versus 8.7%,), but no survival advantage in either group in three months (27% versus 19%,). A second multicentre randomised controlled trial in 56 patients with HRS type I comparing terlipressin with placebo and albumin found similar survival in both groups in 180 days (42.9% versus 37.5%,).

Albumin infusions start at a priming dose of 1 g/kg of body weight, followed by 20-40 g daily. Central venous pressure should be monitored and in patients who respond to this therapy, treatment is continued until serum creatinine levels normalize (<133 μmol/l). Intravenous albumin, apart from being a volume expander, also has anti-oxidant, ligand binding, anti inflammatory and other beneficial metabolic effects. When infused alone albumin has not shown any benefit in terms of reversal of HRS. In some patients who do not respond to terlipressin and albumin treatment, the mechanism of renal failure might be an underlying intrarenal disease (for example, acute tubular necrosis) rather than HRS.

The alternative treatments to terlipressin include noradrenaline and Alpha-adrenergic receptor agonists Midodrine and Norepinephrine. They have been also used in HRS type I because of their low cost and wide availability.

Midodrine and octreotide: 7.5 mg of midodrine orally 3 times daily (increased to 12.5 mg three times a day if needed) and 100 μg of octreotide subcutaneously 3 times daily (increased to 200 μg 3 times a day if needed).The duration of treatment depends on the level of serum creatinine. A relatively large retrospective study evaluated the effects of treatment with octreotide plus midodrine on kidney function and 1-month survival in 87 patients with type 1HRS versus a control group (21 subjects). A significantly higher proportion of patients treated with octreotide plus albumin showed a sustained reduction in serum creatinine in comparison with the control subjects. (40%

versus 10%,) and the 1- month mortality rate was significantly lower (43% versus 71%). Another recent study also analyzed the effects by combination of octreotide and midodrine plus albumin on kidney function and survival in 75 patients with type 1 or 2 HRS as compared with 87 with control subjects.

The number of treated patients with midodrine and octreotide is still limited and the studies are retrospective. Therefore, large randomized comparative trials with this vasoconstrictors are needed.

Administering of a continuous intravenous infusion of noradrenaline appears to be effective for the treatment of type 1 HRS, although the number of treated patients is relatively small. A recent randomized trial compared the safety and efficacy of treatment with terlipressin versus noradrenaline for patients with HRS. Approximately 40% of the patients responded to the treatment in both groups and the adverse effect profiles were similar in all patients. Therefore, noradrenaline seems to be as effective and safe as terlipressin for the treatment of HRS.

In HRS type 1 Norepinephrine 0.5–3 mg/hour as a continuous intravenous infusion aimes to increase the mean arterial pressure by 10 mm Hg. The treatment is continued until the serum creatinine level decreases below 1.5 mg/dL. 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 than to terlipressin. Other treatment alternatives, with a similar effect on circulatory parameters, may include alpha-adrenergic agonists. In comparison with terlipressin their advantage is a lower price, but they seem to be less effective than terlipressin.

There is a category of patients with HRS who will not respond to vasonstrictors and will need alternative therapy. It is important to be aware of this fact, especially to identify them from those who wait for liver transplant. A recent meta-analysis of clinical trials showed that the pooled rate of patients with HRS recurrence after terlipressin therapy was 0.52. Predictors of response were assessed in 39 cirrhotics with type 1 HRS treated with terlipressin plus albumin. Multivariate analysis showed that baseline serum bilirubin <10 mg/dL (indicating less severe liver disease) predicted HRS reversal. Another multicenter randomized placebo controlled study of terlipressin in HRS1 found that only those with baseline serum creatinine level <5.6 mg/dL and treatment duration of > three days of terlipressin achieved HRS recurrence. Therefore, severe renal or hepatic dysfunction and lack of improved hemodynamics in first three days of treatment are not likely to respond to vasoconstrictors.

To sum up the role of vasoconstrictors in HRS, we conclude that they can reverse HRS but large, randomized and controlled trials are still needed.

The role for transjugular intrahepatic portosystemic shunts

Reduction of portal pressure by portocaval shunt is a alternative therapy in HRS typel. Transjugular intrahepatic portosystemic shunts (TIPS) involves the insertion of an intrahepatic stent that connects the portal vein to the hepatic vein. This shunts portal blood into the systemic circulation, which reduces the portal pressure and increases the systemic venous return. In turn, this treats the arterial underfilling and the overactivity of the RAAS and SNS. Several case reports suggested the effect of intrahepatic portosystemic shunts in the reversal of HRS.

Brensinget et al. analyzed the role of TIPS in four studies which included a total of 31 patients who underwent TIPS (14 patients type 1 HRS, and 17 patients, type 2 HRS), and ten were excluded due to advanced liver disease. The renal function showed a gradual improvement within two weeks after TIPS. Overall survival following TIPS was 81% in three months, 71% at six months, 48% in 12 months, and 35% in 18 months. In contrast, seven of the ten non - TIPS patients died within three months. The authors concluded that TIPS could provide a survival benefit in well-selected HRS patients. Guevara et al. assessed the effects of TIPS on renal function and the vasoactive systems and found improved renal function in 6 of 7 patients with type 1 HRS. The serum creatinine fell from 5 ± 0.8 to 1.8 ± 0.4 mg/dL within 30 day time. Reduced activity of the RAAS and SNS was manifested by a reduction in serum renin, aldosterone, and norepinephrine levels.

Testino et al. did TIPS in nine patients with type 1 HRS and acute alcohol-related hepatitis which resulted in a improvement of renal function (decreased serum creatinine and blood urea nitrogen and increased urine volumes). Wong et al. evaluated the combination of medical therapy (midodrine, octreotide, and albumin) and TIPS in type 1 HRS. They observed that serum creatinine decreased to < 135 μmol/L in ten patients in three days after this followed medical therapy. Half of the responders underwent TIPS and showed recovery of ascites with normalization of renal function and serum renin and aldosterone within 12 month period. Three pilot studies have evaluated transjugular intrahepatic portosystemic shunting in patients with type 1 HRS and relatively preserved hepatic function (Child-Pugh score <12). These studies

showed recurrence of HRS and survival for more than three months in ~50% of patients. Hepatic encephalopathy was a common event following the procedure, but it generally responded well to medical therapy.

However, most of the cases of HRS, are usually not good candidates for TIPS due to high Child-Pugh score, encephalopathy or cardiac dysfunction and need to survive before undertaking liver transplant. ADQI work group recommends that TIPS should not be used as the first line treatment for type 1 HRS due to insufficient data. Nevertheless, TIPS insertion could be an alternative treatment for type 1 HRS in patients who cannot take or are unresponsive to combined terlipressin and albumin perfusion.

Renal replacement therapy

Hemodialysis, hemofiltration (arteriovenous or venovenous) and extracorporeal albumin dialysis are other alternative treatment modalities in type 1 HRS.

The traditional point of view is that dialysis is unproductive in hepatorenal syndrome, except when used as a bridge to liver transplantation. In patients with preexisting liver disease and acute renal failure (including, but not limited to, hepatorenal syndrome) that requires dialysis, the relative risk of dying is increased substantially in those with thrombocytopenia, hepatic encephalopathy or an elevated prothrombin time. In the absence of these features, the one year survival is 38% Extracorporeal liver support has been a much studied subject throughout the last 50 years. The Molecular Adsorbent Recirculating System (MARS) is based on the concept of albumin dialysis and allows for the removal of protein-bound as well as water-soluble toxins. Besides its role as a sufficient volume expander human serum albumin is an important cleaner for molecules with pathophysiological relevance in liver failure. Albumin dialysis enables the selective regeneration of patient's albumin resulting in an increase of albumin binding capacity.

Clinically, an improvement of central and local hemodynamics as well as liver, brain and kidney functions were observed. Thus, the treatment with MARS can contribute to reversibility of HRS and bridge patients to liver transplantation. Today, albumin dialysis MARS is among the best studied liver support methods. It appears as a valuable therapeutic tool for the treatment of various complications of liver failure, especially hemodynamic instability and hepatic encephalopathy.

Three large, randomized, controlled trials have been performed.–In the first study, albumin dialysis with the MARS system was safe and more effective than the standard medical therapy in the management of patients with grade III-IV hepatic encephalopathy. Most of these patients had severe HRS._ The other two trials compared standard medical therapy with albumin dialysis, one using MARS in patients with type 1 HRS, and the other using Fractionated plasma separation and adsorption system Prometheus in patients with type 1 and type 2 HRS._ A statistically significant beneficial effect of MARS albumin dialysis on hepatic encephalopathy was observed. In the trial of Prometheus albumin dialysis, no effect on survival was observed in the group as a whole, but a significant improvement in survival was observed in patients with type 1 HRS. Studies that reported MARS use for HRS treatment, show that, in comparison with hemodialysis, MARS is better with regard to sodium, creatinine and bilirubin levels and prothrombin time. Further studies are in need to help define the optimal patient selection and technical process parameters such as session length and frequency of treatment.

Lumbar sympathectomy has also been proposed as a surgical option for HRS treatment. In a small report on eight patients, Solis-Herruzo suggested that sympathetic block might improve renal function in cirrhotics with HRS, particularly among those with more impaired GFR. In this study, five patients presented GFR below 25 mL/min, and in these cases sympathetic block induced a significant increase in GFR, and effective renal plasma flow and a decrease in plasma rennin activity. Further research is ongoing in this area.

In conclusion, the first line of therapy in HRS type I is steel the use of vasoconstrictors combined with albumin. Patients with partial or no response to vasoconstrictors may be treated with TIPS. If there are contraindications to TIPS, extracorporeal albumin dialysis (ECAD) could be used in the setting of prospective trials. The use of vasoconstrictors plus albumin and TIPS in corresponding patients is an interesting idea deserving further investigation.

A proposed actual algorithm of management of type 1 HRS is shown in Figure 6.1.

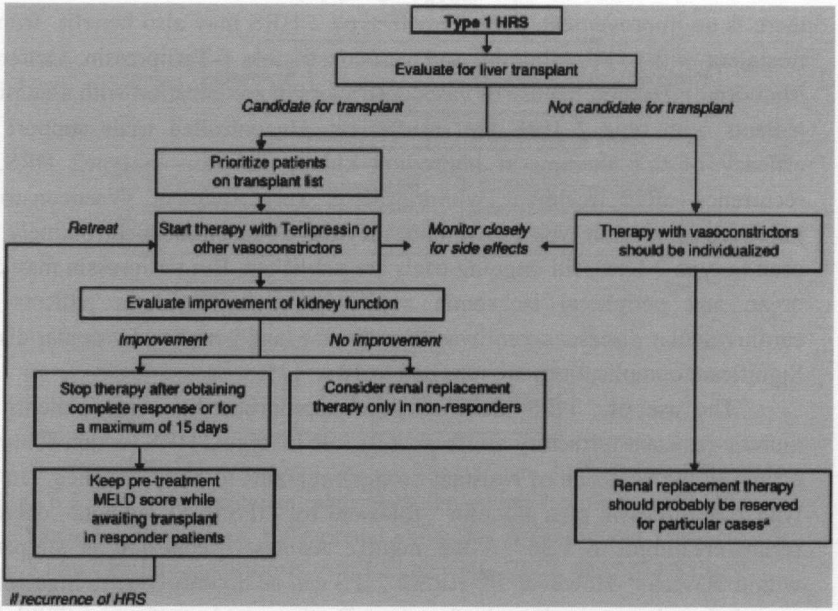

Fig. 6.1 Proposed treatment algorithm for patients with type 1 HRS (Cláudia Fagundes, Pere Ginès. Hepatorenal Syndrome A Severe, but Treatable, Cause of Kidney Failure in Cirrhosis. Am J Kidney Dis. 2012;59(6):874-885).

Treatment of Type 2 HRS

A practical and basic approach to suspected cases of HRS type 2 will be:
1) Discontinuation of diuretics;
2) Volume expansion;
3) Avoidance of nephrotoxic drugs.

Patients with type 2 HRS are usually treated by repeated large-volume paracentesis. Up to the head submergence in water has proved to be an interesting and valuable model for study the pathogenesis and treatment of resistant ascites in type 2 HRS. In patients with ascites, head-out water immersion increases central blood volume and promotes marked natriuresis and diuresis, with two- to three-fold increases in urine volume and urine sodium excretion.

Plasma levels and urinary excretion of norepinephrine decrease and generally there is a prompt increase in atrial natriuretic factor level. Thus, if facilities are available, the hemodynamic response to immersion is favorable. If there is no improvement, patients with type 2 HRS may also benefit from the treatment with IV Albumin, and vasoconstrictors (Terlipressin, Octreotide, Midodrine). Data on the use of vasoconstrictors in combination with albumin for patients with type 2 HRS are insufficient. Uncontrolled trials support the efficacy of this therapy in improving kidney function in type2 HRS, but recurrence after treatment withdrawal is very frequent. Vasoconstrictors improves survival in type 1 HRS and they can be recommended routinely to be used in type 2 HRS, till ongoing trials are published. But terlipressin may cause organ and peripheral ischaemia and is contraindicated in patients with cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Significant complications are reported in 10 to 12%.

The use of TIPS alone may be appropriate for some patients with diuretic-resistant refractory ascites, but its role in type 2 HRS (which commonly occurs in the presence of resistant ascites), remains to be established. In HRS type 2 terlipressin plus albumin followed by TIPS in 11 patients decreased serum creatinine to 1.36 +/- 0.3 mg/dL. Ascites disappeared in all patients within 2 weeks. However, in HRS 2 TIPS can be doubtful due to high MELD, encephalopathy or cardiac dysfunction. Testino et al. performed TIPS in 18 patients with type 2 HRS and refractory ascites that were awaiting for liver transplantation. The study found that TIPS improved the renal function and led to complete elimination of ascites in eight patients and partial elimination of ascites in ten patients. The authors suggested that TIPS may be used as transient phase before transplantation.

One current option is combined therapy with Shehuang Paste, a traditional Chinese medicine with colonic dialysis in treating patients with refractory cirrhotic ascites complicated with azotemia. It has been reported to be beneficial in reducing the long-term incidence of HRS.

A proposed algorithm of management of type 2 HRS is shown in figure 6.2

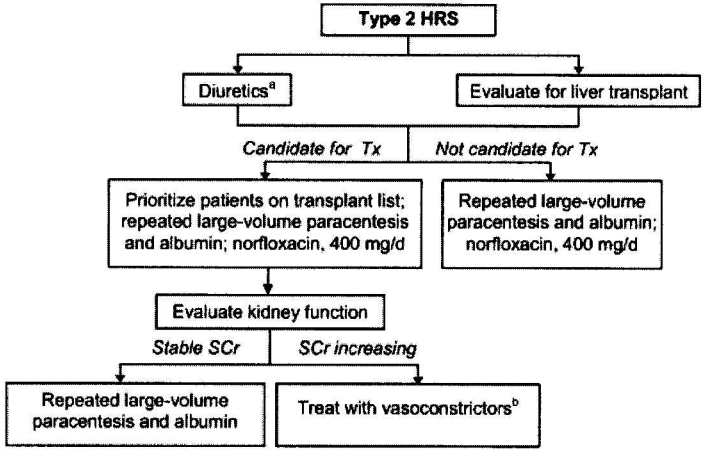

Fig. 6.2 Proposed treatment algorithm for patients with type 2 HRS (Cláudia Fagundes, Pere Ginès. Hepatorenal Syndrome A Severe, but Treatable, Cause of Kidney Failure in Cirrhosis. Am J Kidney Dis. 2012;59(6):874-885).

Liver transplantation

As early in the 1970s, Iwatsuki et al showed that HRS patients recovered renal function after liver transplantation confirming the functional nature of the kidney dysfunction. Liver transplantations eliminate the three central factors leading to pathogenesis of HRS - liver dysfunction, portal hypertension and hemodynamic anomalies in decompensated cirrhosis. When successful, full recovery from functional renal failure can be expected. However, HRS patients present greater morbidity and mortality with lower survival rates. One- and two-year survival rates in non-HRS patients were 87.2% and 82.1%, respectively. The one- and two-year survival rate for the HRS patients was 76.6% (p> 0.005). A transplant recipients with HRS had a significantly decreased five year survival rate compared with those without hepatorenal syndrome. A pretransplant treatment of HRS is logical and may improve survival . But longer stays in the intensive care unit, longer hospitalizations and more dialysis sessions can be required. Thus, early transplantation remains the best course whenever possible.

In those with chronic renal failure a combined liver-kidney-transplant (CLKT) may be indicated. This is a difficult issue that needs clear indications as

irreversible renal failure or progressively worsening renal dysfunction. But at present, liver transplant alone is considered preferential because postoperative outcome in CLKD is not so effective compared to liver transplant alone. If renal failure progresses after liver transplant, then kidney transplant may be indicated.

Management of HRS according to guidelines of international Societies

The most recent guidelines, published in 2010 by the European Association for the Study of the Liver (EASL), recommend terlipressin (1 mg/4-6 h as IV bolus) together with albumin as first-line treatment for patients with type 1 HRS. Modifications of the dose are guided by changes in serum creatinine concentration; if serum creatinine level decreases by at least 25% after three days of treatment, the dose is maintained, and if not, the dose is increased to 2 mg/4-6 h. If there is a recurrence at any time after treatment discontinuation, patients should be retreated with terlipressin and albumin. Alternatives to terlipressin are noradrenaline and midodrine plus octreotide, both in combination with albumin, yet information about efficacy is very limited. Main contraindications to vasoconstrictor drugs are severe cardiovascular diseases.

The use of TIPS is not recommended and should be used only in patients not responding to vasoconstrictors who fulfill criteria for kidney support. As far as patients who are candidates for transplant is concerned, EASL guidelines recommend the treatment of HRS with vasoconstrictors before a liver transplant. Moreover, liver transplant alone is appropriate, with combined liver-kidney transplant reserved for only patients who have been on renal replacement therapy for more than 6-8 weeks. Although the guidelines state that vasoconstrictor therapy is effective for the treatment of type 2 HRS, no specific recommendation is made to treat these patients due to limited data.

The AASLD (American Association for the Study of the Liver) guidelines published in 2009 recommend that patients with type 1HRS to be treated with midodrine and octreotide together with albumin. It should be noted that terlipressin is not available in the United States. These guidelines also emphasize that patients who are candidates for liver transplant should be referred immediately to transplant centers because of their low survival expectancy.

Chapter VII. Long term outlook for hepatorenal syndrome

Prevention of HRS

SBP and severe Acute Alcoholic Hepatitis are known to trigger HRS typel. HRS can be prevented in patients with cirrhosis and SBP by administration of intravenous albumin (an initial 1.5 g/kg infusion followed by a further infusion of 1 g/kg in 48 h). This treatment achieved substantial reductions in type 1 HRS, in-hospital mortality and 3-month mortality versus standard care (10% versus 33%, 10% versus 29% and 22% versus 41%, respectively). IV Albumin plus Cefotaxime markedly reduced HRS type 1 when compared with Cefotaxime alone (10% *vs* 33%). In another study, which investigated oral norfloxacin as primary prophylaxis of SBP in patients with ascites and severe liver failure, patients to whom the antibiotic was administrated had a significantly lower rates of both SBP and type 1 HRS at one year than patients who did not receive the antibiotic (7% versus 61% and 28% versus 41%, respectively). Survival at three months and one year was also significantly higher in patients who received norfloxacin, versus 62% and 48%, respectively in those who were not. Alternative oral antibiotics are ciprofloxacin and trimethoprim-sulfamethoxazole. In severe Alcoholic Hepatitis administration of Pentoxyfyllin 400 mg (TNF inhibitor) reduced the occurrence of type 1 HRS when compared to placebo (8% *vs* 35%) and a reduction in in-hospital mortality. In the future, vasoconstrictors may be included in studies to prevent HRS in cirrhotic patients.

Conclusions

- The pathophysiology of renal dysfunction in cirrhosis and the treatment of ascites and related conditions like hepatorenal syndrome have been a problem of major interest during the last two decades. Many aspects of these problems remain unclear and will continue to be an important issue as clinical and fundamental research in hepatology and nephrology.
- To prevent HRS we must identify the circumstances associated with a high risk of developing of HRS and avoiding or promptly managing the precipitating factors.
- Current scientific research is focused on the identification of novel diagnostic biomarkers of HRS. The renal artery resistive index assessed by Duplex Doppler Ultrasonography in the follow-up of patients with liver cirrhosis. The assessment of urinary enzymes in order to predict the severity and clinical outcomes of HRS are promising markers. Additionally, the activity of urinary enzyme patterns may be a helpful adjunct for differential diagnosis of ARI in liver cirrhosis.
- Recent evidence has shown that vasoconstrictor agents are effective and serve as a bridge to LT. Large randomized controlled trials are required to determine which treatment modality is most effective to improve survival rates along with its dose and duration of treatment.
- The modalities of treatments other than vasoconstrictors and albumin continues in order to be recommended for the recurrence of HRS in the near future. Elevated levels of serum PGE and ET-1 in decompensated cirrhosis can be triggers of HRS and a therapeutic option. Drugs like misoprostol, which is a synthetic drug similar to prostaglandin E1, endothelin 1 antagonists, which inhibit the powerful vasoconstriction of endothelium may be useful in treating HRS.
- Alternative therapies such as transjugular intrahepatic portosystemic shunt and extracorporeal albumin dialysis have given encouraging results but practical experience is extremely limited. Actually, to perform liver transplantation in patients with liver cirrhosis and ascites before HRS develops is preferential.

Further recommendations

1. Nephrologist

The importance of a nephrologist in the multidisciplinary management of patients with HRS cannot be overemphasized. Nephrologists assist hepatologists and liver transplant surgeons in the management of these critically ill patients.

Despite the fact that no controlled studies evaluating the role of dialysis have been performed, most of dialyze centers have to waitlist patients with HRS and dialyze them. Continuous arteriovenous or venovenous hemofiltration has to be used also.

Variations of hemodialysis include the molecular adsorbent recirculating system.

If transplantation is not available, hemodialysis probably will continue to be performed for patients on the waiting list.

2. Interventional radiologist

The use of TIPS in the treatment of HRS has yet to be established. Due to its ability to reduce portal hypertension in patients with variceal bleeding and refractory ascites, its role in HRS seemed logical. The role of TIPS in the treatment of HRS remains investigational because of the lack of prospective studies and the wellknown risks of the procedure.

3. Surgical care

Peritoneovenous shunting leads to plasma volume expansion and improvement of circulatory function and has been used predominantly for the treatment of refractory ascites. This may be important for patients with type 2 HRS, who often develop refractory ascites and are not candidates for liver transplantation. Peritoneovenous shunt is not used in type 1 HRS. No description on the surgical treatment of HRS is complete without a brief review of the role of portacaval shunts, particularly with the introduction of TIPS. Despite the theoretical benefit of improving portal hypertension and evolution of HRS with a portosystemic shunt, only a few scattered case reports have shown some benefit. Currently, no indication for portacaval shunts exists in this setting.

4. Liver transplantation

Liver transplantation is the ideal treatment of HRS but is limited by the availability of donors. Patients with HRS have a higher risk of postoperative morbidity, early mortality, and longer hospitalization. As renal dysfunction is common in the first few days following transplantation, avoiding nephrotoxic immunosuppressant generally is recommended until recovery of renal function. Long-term survival rates are excellent, with the three year survival rate in approximately 60%. This is only slightly lower than 70-80% survival rate of transplant recipients without HRS and is markedly better than the survival rate of patients with HRS and without transplant.

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