

Review

The hepatorenal syndrome

Introduction

The hepatorenal syndrome (HRS) is defined as the development of renal failure in patients with severe liver disease (acute or chronic) in the absence of any other identifiable cause of renal pathology. It is diagnosed following exclusion of other causes of renal failure in patients with liver disease such as hypovolaemia, drug nephrotoxicity, sepsis, or glomerulonephritis. A similar syndrome may also occur in the setting of acute liver failure.

DIAGNOSTIC CRITERIA

The International Ascites Club (1996) group defined the diagnostic criteria for hepatorenal syndrome¹ and these are listed in table 1.

Two patterns of HRS are observed in clinical practice and these were defined by the International Ascites club.¹

- *Type 1 hepatorenal syndrome* is an acute form of HRS in which renal failure occurs spontaneously in patients with severe liver disease and is rapidly progressive. It is characterised by marked reduction of renal function, as defined by doubling of the initial serum creatinine to a level greater than 225 µM, or a 50% reduction in initial 24 hour creatinine clearance to <20 ml/min within two weeks. The development of type 1 HRS has a poor prognosis with 80% mortality at two weeks.² Renal function may recover spontaneously following improvement in liver function.² This is most frequently observed in acute liver failure or alcoholic hepatitis, or following acute decompensation on a background of cirrhosis. These patients are usually jaundiced with a significant coagulopathy. Death often results from a combination of hepatic and renal failure or variceal bleeding.
- *Type 2 hepatorenal syndrome* usually occurs in patients with diuretic resistant ascites. Renal failure has a slow course, in which it may deteriorate over months. It is associated with a poor prognosis³ although the survival time is longer than that of patients with type 1 HRS.

EPIDEMIOLOGY

HRS occurs in about 4% of patients admitted with decompensated cirrhosis, the cumulative probability being 18% at one year, increasing to 39% at five years.² Retrospective studies indicate that HRS is present in ~17% of patients admitted to hospital with ascites and in >50% of cirrhotics

Table 1 Major criteria for a diagnosis of hepatorenal syndrome

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| (1) Chronic or acute liver disease with advanced hepatic failure and portal hypertension |
| (2) Low GFR, as indicated by serum creatinine >225 µM or creatinine clearance <40 ml/min |
| (3) Absence of shock, ongoing bacterial infection, or recent treatment with nephrotoxic drugs. Absence of excessive fluid losses (including gastrointestinal bleeding) |
| (4) No sustained improvement in renal function following expansion with 1.5 litres of isotonic saline |
| (5) Proteinuria <0.5 g/day, and no ultrasonographic evidence of renal tract disease |
| Additional criteria NOT required for diagnosis but commonly present |
| (1) Urine volume <500 ml/day |
| (2) Urine sodium <10 mM |
| (3) Urine osmolality >plasma osmolality |
| (4) Urine RBC <50 per high per field |
| (5) Serum sodium <130 mM |

GFR, glomerular filtration rate; RBC, red blood cells.

dying from liver failure.³ The most frequent cause of renal failure in cirrhosis is spontaneous bacterial peritonitis (SBP). Approximately 30% of patients with SBP develop renal failure.⁴

There is still some contention as to whether patients who develop renal failure following the treatment of complications of liver diseases such as sepsis or bleeding should be classified as having HRS. Many authors include patients with “*successfully treated*” SBP or other precipitants as having HRS and yet there are many patients who develop renal failure spontaneously and who have no objective criteria for a precipitating event other than progressive liver failure (for example, alcoholic hepatitis or acute liver failure). In the future it may be useful to subdivide HRS type 1 into two categories—that is, those with and those without a precipitant event—but this will require further international consensus.

PATHOPHYSIOLOGY

The hallmarks of HRS are reversible renal vasoconstriction and mild systemic hypotension.⁵ The kidneys are structurally normal and at least in the early part of the syndrome, tubular function is intact, as reflected by avid sodium retention and oliguria. Moreover, kidneys from patients with HRS transplanted into a patient with end stage renal failure and a healthy liver resumed normal function.⁶

The cause of renal vasoconstriction is unknown but may involve both increased vasoconstrictor and decreased vasodilator factors acting on the renal circulation.⁷ There are three factors predominantly involved in its pathogenesis. These are:

- (1) Haemodynamic changes that decrease renal perfusion pressure.
- (2) Stimulated renal sympathetic nervous system.
- (3) Increased synthesis of humoral and renal vasoactive mediators.

The emphasis of each of the three pathogenic pathways probably varies from patient to patient, and between the acute (type 1) and chronic (type 2) forms of the syndrome. Each of these pathways are interrelated and in practice the pathophysiology of this process is more complicated. However, this outline provides a simple framework with which to understand the mechanisms involved.

Haemodynamic changes

Systemic vasodilatation of varying severity is the predominant haemodynamic abnormality in portal hypertension or acute liver failure, and accounts for several important complications.⁸ Vasodilatation increases regional blood flow to the splanchnic circulation and a compensatory increase in cardiac output. This leads to a fall in mean arterial pressure and reflex activation of the sympathetic

Abbreviations used in this paper: HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; RBF, renal blood flow; GFR, glomerular filtration rate; NO, nitric oxide; TNF, tumour necrosis factor; RAAS, renin-angiotensin-aldosterone system; NSAIDs, non-steroidal anti-inflammatory drugs; TIPS, transjugular intrahepatic portosystemic stent shunt; ET-1, endothelin 1; TXA₂, thromboxane A₂; MARS, molecular adsorbent recirculating system; OLT, orthotopic liver transplantation.

nervous system.⁸ Several studies have consistently shown a progressive decrease in mean arterial pressure with hepatic decompensation, with the lowest values (typically 60–65 mm Hg) observed in patients with HRS.⁹ Prognostic studies in patients with cirrhosis have shown that arterial pressure is one of the best predictors of survival in patients with cirrhosis and ascites,¹⁰ with low arterial pressure being associated with a poor prognosis and increased risk of developing HRS.¹¹

It is a common misconception that modest reductions in blood pressure are insignificant in humans, and that renal autoregulation exists to prevent fluctuations in renal blood flow (RBF). However, autoregulation of the renal circulation ensures a stable RBF during changes in renal perfusion pressure above 70–75 mm Hg.^{12–14} Below this pressure, RBF is directly proportional to perfusion pressure. Patients developing HRS have an activated sympathetic system, and increased synthesis of several renal vasoconstrictors. Several studies have shown that these cause a rightward shift in the autoregulatory curve,¹⁵ making RBF much more pressure dependent. Thus even modest decreases in mean blood pressure may result in a marked fall in RBF. Understanding this important principle is essential in targeting pressor treatment. As a result, there is an interest in drugs which increase blood pressure, and over the years all have been reported to increase urine output, sodium excretion, or glomerular filtration rate (GFR) with variable success in patients with severe liver disease and HRS.^{16–21}

The presence of modest arterial hypotension raises the question about its cause. It is well established that severe liver disease is characterised by an increase in cardiac output and plasma volume, and decreased peripheral vascular resistance^{22–23} due to peripheral vasodilatation. Studies in animals and humans with cirrhosis indicate that the splanchnic circulation is the main vascular bed responsible for vasodilatation but cutaneous and muscular vascular dilatation may also contribute to the reduction in systemic vascular resistance.^{9 24–28}

There is general acceptance that vascular reactivity is impaired in cirrhosis as isolated vessels have impaired responsiveness to vascular agonists. Ultimately, several mediators, either singly or in concert (nitric oxide (NO), prostacyclin, glucagon, or altered K⁺ channel activation) may be responsible for decreased vascular reactivity or opening of these anatomical shunts. Plasma levels of many endogenous vasodilators, as well as vasoconstrictors, are elevated in liver failure. More than one mediator may be involved, and several potential mediators have been proposed and include the following.

Nitric oxide

NO is synthesised by several cell types, including endothelial and vascular smooth muscle cells, and causes vasorelaxation.²⁹ NO synthesis may be induced by shear stress or in response to endotoxin related cytokine expression.^{30–34} The observation that many patients with decompensated cirrhosis have circulating endotoxaemia is thought to increase NO synthesis in cirrhosis. Studies in patients with decompensated cirrhosis show increased plasma nitrite/nitrate indicative of increased NO production.³⁵ Pharmacological studies using isolated vascular rings or the mesenteric vasculature have shown decreased vascular reactivity to several agonists, and inhibition of NO synthase fully or partially restores or partially restores vascular responsiveness.^{36–37} Likewise, studies *in vivo* have shown that inhibition of NO synthesis reverses some of the systemic and splanchnic circulatory changes in animal models or patients with liver disease.^{38–39} This hyporeactivity is also endothelium dependent.⁴⁰ Finally, NO reduces

resistance in the collateral portal circulation in animals with portal hypertension.^{41–42} While there was much enthusiasm for a primary role of NO in peripheral vasodilatation, there is still considerable controversy as to the importance of NO in the hyperdynamic circulation of cirrhosis.³²

Prostacyclin

Prostacyclin is a systemic vasodilator. Its secretion might be stimulated by shear stress in the arterial system.^{30–32} Urinary excretion of both systemic and renal metabolites of prostacyclin are high in decompensated cirrhosis, and plasma levels (undetectable by available analytical methods) are presumably elevated.^{43–44} Nevertheless, administration of indomethacin to cirrhotic patients increases systemic vascular resistance as well as pressor sensitivities to angiotensin II, suggesting that prostacyclin may have a facultative role in the vasodilatation of cirrhosis.⁴⁵

Potassium channels

There are three major types of potassium channels which control the flux of potassium from the intracellular to the extracellular environment. The ATP sensitive potassium channels are opened during low ATP:ADP ratios, or by agonist induced activation of G protein dependent pathways. The second type is the delayed rectifier channel opened by membrane depolarisation, and the third type is the calcium activated potassium channel, which is activated by increases in intracellular calcium and in a similar manner to that for ATP dependent potassium channels. Activation of potassium channels can cause vasodilatation due to hyperpolarisation of vascular smooth muscle cells. Potentially important activators include tissue hypoxia, prostacyclin, neuropeptides, and NO. Using potassium channel blockers and activators, Moreau *et al* found good evidence that activation of potassium channels is important in the vasodilatation of cirrhosis.^{46–48} Based on studies with potassium and calcium channel modifiers, Moreau and Lebrec have proposed that there is impairment of G protein dependent transduction pathways.⁴⁸ This hypothesis is based on the observation that hyporeactivity of vessels is not associated with downregulation of receptors, and reactivity to Bay K 8644 (which increases intracellular calcium) is normal. The central role of potassium channels in vascular tone makes it likely that potassium channels are important but whether there is a fundamental abnormality of function in a particular type of potassium channel is unknown

Endotoxaemia and cytokines

Endotoxin levels are usually elevated in patients with decompensated liver disease and more so in patients with HRS. This is believed to be due to increased bacterial translocation and portosystemic shunting.^{49–52} Inflammatory response to infection, as estimated by levels of cytokines in plasma or ascitic fluid, is increased in cirrhotic patients leading to circulatory dysfunction and concomitant renal impairment and increased mortality. Endotoxaemia may cause splanchnic vasodilatation, possibly mediated by cytokine induction and increased NO synthesis. Infusion of lipopolysaccharide into animals causes complement activation, accumulation of neutrophils in the liver, and renal dysfunction. There are increased circulating levels of several cytokines, including tumour necrosis factor (TNF) and interleukin 6, in patients with alcoholic hepatitis and HRS.^{53–54} Recent studies have shown that the vasodilatation observed in the partial portal vein ligated rat model is blocked by anti-TNF antibodies, *N*-acetylcysteine,⁵⁵ and inhibitors of tyrosine kinase, each of which may act on cytokine dependent pathways.^{56–57}

Table 2 Consequences of systemic vasodilatation

- Activation of the sympathetic nervous system
- Activation of the renin-angiotensin-aldosterone system
- Increased vasopressin release
- Increased renal production of vasodilatory prostanoids

Glucagon

Plasma glucagon levels are elevated in cirrhosis. Glucagon causes desensitisation of the mesenteric circulation to catecholamines and angiotensin II, and causes vasodilatation at pharmacological doses.⁵⁸ Glucagon also elevates intracellular cAMP and this may act synergistically with endothelin to induce NO synthase, and thus NO release by vascular smooth muscle cells.⁵⁹ Hence glucagon may enhance NO production in cirrhosis.

SECONDARY CONSEQUENCES OF SYSTEMIC VASODILATATION

The normal homeostatic response to vasodilatation is activation of several neurohumoral response mechanisms, primarily aimed at maintenance of arterial pressure. These responses are summarised in table 2:

Although activation of these neurohumoral mechanisms help to maintain blood pressure, some also induce renal vasoconstriction. This is not surprising as the renal vascular bed normally receives 25% of cardiac output and is an important regulatory pivot of blood pressure. By altering the normal renal autoregulatory response, they by necessity contribute to decreased RBF observed in HRS.

Renin-angiotensin-aldosterone system (RAAS)

The RAAS is stimulated in 50–80% of patients with decompensated cirrhosis, and is further activated in patients with HRS.^{22 57 60 61} Increased levels of angiotensin II protect renal function by selective vasoconstriction of the efferent glomerular arterioles. Although RBF⁶² may fall, GFR is preserved due to an increased filtration fraction. In cirrhosis, inhibition of the RAAS by either angiotensin II antagonists or angiotensin converting enzyme inhibitors (for example, captopril) may cause marked hypotension and a decrease in GFR^{63–67} and conversely, infusion of angiotensin II in cirrhosis improves GFR in some patients.⁶² Angiotensin II helps to maintain vascular tone in patients with advanced liver disease but has no role in healthy controls or patients with compensated cirrhosis. A recent finding that losartan (an angiotensin II receptor antagonist) decreases portal pressure in patients with cirrhosis and portal hypertension^{68–70} together with the vascular dependence on angiotensin II in severe cirrhosis, indicates that this mediator contributes to vascular dysfunction in cirrhosis.

Antidiuretic hormone

Antidiuretic hormone or vasopressin levels are elevated due to non-osmolar stimulation, despite the frequent presence of hyponatraemia.^{71 72} Vasopressin causes vasoconstriction through V₁ receptors and renal tubular water retention through V₂ receptors in the medullary collecting ducts. This increases volume expansion by water retention and helps maintain arterial pressure. Inhibition of V₁ receptors in cirrhotic rats causes profound hypotension.⁷³ Vasopressin however preferentially causes splanchnic rather than renal vasoconstriction.

Prostaglandins

Renal prostaglandins play an important role in the preservation of renal function in all situations, such as dehydration, congestive cardiac failure, shock, or decompensated liver disease, with elevated plasma levels of renin, angiotensin, noradrenaline, or vasopressin. In liver disease,

urinary excretion of prostaglandin E₂ and prostacyclin metabolites (6-oxo-PGF_{1α}) are usually increased.^{44 74–78} The mechanism for increased synthesis is unknown but is likely to be secondary to increased levels of several vasoconstrictors which induce prostaglandin formation *in vitro* or *in vivo*. Administration of cyclooxygenase inhibitors (non-steroidal anti-inflammatory drugs (NSAIDs)) to patients with ascites frequently causes renal failure, and this usually reverses on cessation of NSAIDs⁷⁸ (see fig 1).⁷⁹ It has been suggested that HRS is caused by a deficiency in renal prostaglandin E₂ and prostacyclin⁷⁸ as urinary excretion of prostaglandin E₂ and the prostacyclin metabolite 6-oxo-PGF_{1α} are decreased in HRS compared with patients with ascites alone. Other studies however have shown that synthesis of prostacyclin is actually increased but urinary excretion of its metabolite is decreased by the presence of renal failure.⁴⁴ The importance of each of these compensatory mechanisms is indicated by the fact that inhibition or antagonism of their actions frequently has adverse effects on systemic or renal function. Thus although they may contribute to some or many of the renal haemodynamic changes, the overall result of their activation tends to be beneficial.

The sympathetic nervous system

The sympathetic nervous system is highly activated in patients with HRS and causes renal vasoconstriction and increases sodium retention.^{80–83} Several studies have shown that there is increased secretion of catecholamines in the renal and splanchnic vascular beds.^{84–86}

The importance of hepatorenal innervation has been recognised since the 1980s. Kostreva and colleagues⁸⁷ observed that an increase in intrahepatic pressure resulted in greater efferent renal sympathoadrenergic activity. Vasoconstriction of the afferent arterioles of the kidney led to a reduction in renal plasma flow and GFR and to increased reabsorption of tubular sodium and water. Hepatic denervation was effective in delaying, but not preventing, the increased tubular reabsorption of sodium in portal hypertension, and Levy and Wexler⁸⁸ discovered that the onset of ascites formation was delayed in dogs with bile duct ligation following hepatic denervation. This concept has been reintroduced by Lang and colleagues⁸⁹ who observed that infusion of glutamine into the internal jugular vein had no effect on renal function whereas it caused a significant decrease in both GFR and RBF when infused into the portal vein. The mechanism is postulated to be secondary to hepatocyte swelling and activation of the renal sympathetic nervous system as no effect was seen in those animals with renal denervation. In support of this concept in humans, studies by Jalan *et al* have shown that acute occlusion of the transjugular intrahepatic portosystemic shunt (TIPS) is associated with an acute reduction in RBF in patients with cirrhosis.⁹⁰ In another study, temporary lumbar sympathectomy with local anaesthesia increased GFR in five of eight cirrhotic patients with HRS,⁹¹ suggesting that increased renal sympathetic nervous activity decreased GFR in some patients.

Humoral and renal vasoactive mediators

It is unlikely that development of HRS is purely a consequence of renal vasoconstriction. If one examines the relationship between RBF and the presence of HRS or hepatic decompensation with or without ascites, there is considerable overlap of RBF between these groups (fig 2).⁹²

The observation that two patients may have a comparable decrease in RBF and yet have either HRS or “near normal renal function” suggests that other factors must be involved which decrease the filtration fraction. The glomeruli within the kidney are dynamic structures,

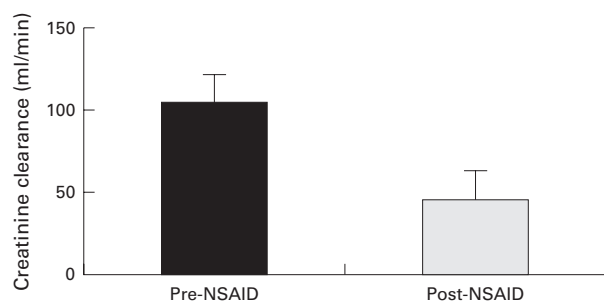


Figure 1 Administration of indomethacin, a non-steroidal anti-inflammatory drug (NSAID), to patients with cirrhosis AND ascites, caused a significant reduction in renal plasma flow (not shown) and glomerular filtration rate, as assessed by creatinine clearance (adapted from Boyer and colleagues⁷⁹).

invaginated with mesangial cells which may contract in response to several agonists and thus reduce the surface area available for glomerular filtration (fig 2). Many studies have now shown that there is increased synthesis of several vasoactive mediators, which although renal vasoconstrictors in their own right, also have the important added effect of causing mesangial cell contraction, thence lowering the glomerular capillary ultrafiltration coefficient (K_f) and thus the filtration fraction. Such factors involved may include the following.

Endothelin

This 21 amino acid peptide is a potent renal vasoconstrictor and a potent agonist of mesangial cell contraction. Endothelin 1 (ET-1) concentrations are increased in HRS and correlate with creatinine clearance in decompensated liver disease.⁹³⁻⁹⁵ Brensing and colleagues⁹⁶ noted a reduction in portal ET-1 levels after TIPS placement while systemic levels remained unchanged. Both observations indicate that local ET-1 formation may be more relevant in kidney dysfunction in HRS than circulating ET-1. The cause of increased plasma ET-1 concentrations is unknown. Volume expansion or upright tilt fails to increase plasma endothelin in cirrhotics⁹⁷ and there appears to be no correlation with circulating endotoxins.⁹⁸ Whether tissue hypoxia or oxidant stress dependent pathways are important are unknown. Increased lipid peroxidation is known to occur in HRS,⁹⁹ and certain products of lipid peroxidation, namely oxidised low density lipoprotein and F_2 isoprostanes, have been shown to induce ET-1 synthesis in vitro,¹⁰⁰

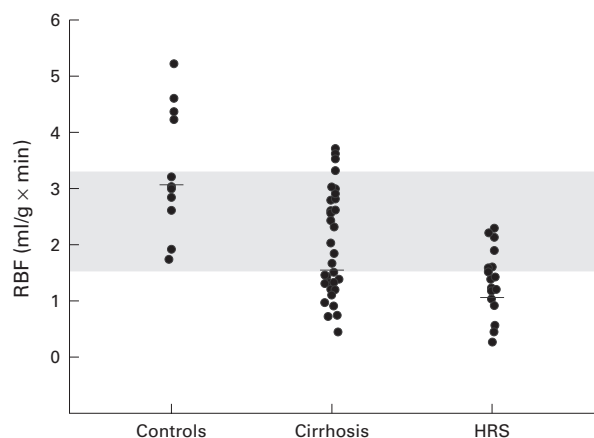


Figure 2 Measurement of renal blood flow (RBF) by 133 -xenon washout shows that RBF is decreased in cirrhosis and further decreased in patients with hepatorenal syndrome (HRS). However, as is evident in the shaded area, there is a considerable overlap in RBF values between normal, cirrhotic, and HRS patients (adapted from Ring-Larsen H. Renal blood flow in relation to systemic and portal haemodynamics and liver function. *Scand J Clin Lab Invest* 1977;37:635-42).

but whether this is responsible for increased plasma ET-1 concentrations is unknown.

Cysteinyl leukotrienes

Leukotrienes C_4 and D_4 are produced by inflammatory cells of the myeloid series, and their synthesis by the isolated kidney has been demonstrated.¹⁰¹ They are both potent renal vasoconstrictors and cause contraction of mesangial cells in vitro. Endotoxaemia, activation of complement, or various cytokines may stimulate their synthesis. There is good evidence that systemic and probably renal synthesis of cysteinyl leukotrienes is increased in HRS. Urinary leukotriene E_4 is markedly elevated as well as N -acetyl LTE_4 in HRS.¹⁰²⁻¹⁰⁴ Plasma concentrations are too low to have a direct effect on the renal circulation but renal leukotriene synthesis may be an important modulator of renal function in HRS.

Thromboxane A_2

Thromboxane A_2 (TXA_2) production is stimulated by renal ischaemia and causes both vasoconstriction and mesangial cell contraction. It has been suggested that the balance between vasodilatory prostaglandins and thromboxane A_2 may critically favour vasoconstriction.¹⁰⁵⁻¹⁰⁶ However, many of the early studies used urinary excretion of prostaglandin metabolites as markers of renal production, and failed to control for renal function or the severity of liver disease. It is now known that TXB_2 excretion should be corrected for renal function, and when this is done it has been shown that urinary TXB_2 excretion correlates with the severity of liver disease, rather than the presence or absence of renal failure. Furthermore, inhibition of TXA_2 synthesis with dazoxiben does not improve renal function.¹⁰⁶

F_2 isoprostanes

The F_2 isoprostanes are formed by lipid peroxidation. One of the major F_2 isoprostanes formed in vivo, namely 8-iso- PGF_2 , is a potent renal vasoconstrictor. We have observed increased synthesis of the F_2 isoprostanes in patients with HRS indicative of increased lipid peroxidation.⁹⁹ Whether F_2 isoprostanes themselves are important mediators of renal vasoconstriction in HRS is unknown. However, synthesis of several mediators implicated in the pathogenesis of HRS are regulated through products of lipid peroxidation or through redox changes in signalling pathways. Thus the development of oxidant stress may be important as the final pathway leading to increased synthesis of many of the mediators discussed above.

Management of the hepatorenal syndrome

PREVENTION

The following measures may decrease the incidence of renal failure or HRS in patients with liver disease.

Prophylaxis against bacterial infections

Bacterial infections occur in ~50% of patients with variceal haemorrhage, and antibiotic prophylaxis improves survival by ~10%. Patients who have had a previous episode of SBP have a 68%¹⁰⁷ chance of recurrent infection at one year, and this carries a 33% chance of developing renal failure.¹⁰⁸ As bacterial infections are an important cause of renal dysfunction in cirrhotic patients, prophylaxis with antibiotics is recommended in two clinical settings, namely variceal bleeding and a history of previous SBP.

Volume expansion

To prevent the development of renal failure in patients who develop SBP, it is now recommended that these patients should be given plasma volume expansion with 20% albumin (1-1.5 g/kg over 1-3 days) at diagnosis to prevent circulatory dysfunction, renal impairment, and mortality.¹⁰⁹

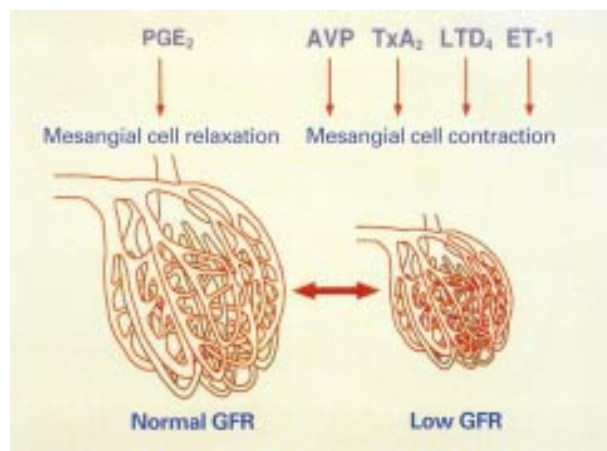


Figure 3 The glomeruli within the kidney are dynamic structures, invaginated with mesangial cells which express actin. These contractile cells control the surface area of glomeruli available for filtration. The cells contract in response to certain agonists such as endothelin 1 (ET-1), thromboxane A₂ (TXA₂), arginine vasopressin (AVP), or leukotriene D₄ (LTD₄). Vasodilatory prostaglandins such prostaglandin E₂ (PGE₂) can cause relaxation of mesangial cells.

Use of salt poor albumin as fluid replacement in patients undergoing large volume paracentesis (8 g for each litre of ascitic fluid removed) is known to prevent paracentesis induced circulatory dysfunction.^{110–112}

Judicious use of diuretics

Identifying the lowest effective dose of a diuretic for any individual patient is important, as diuretic induced renal impairment occurs in ~20% of patients with ascites. It develops when the rate of diuresis exceeds the rate of ascites reabsorption, leading to intravascular volume depletion. Diuretic induced renal impairment is usually moderate and rapidly reversible following diuretic withdrawal.

Avoid use of nephrotoxic drugs

Patients with cirrhosis and ascites are predisposed to develop acute tubular necrosis during use of aminoglycosides, with renal failure occurring in ~33% of patients compared with 3–5% in the general population.¹¹³ Another important cause of renal failure is the use of NSAIDs. These drugs inhibit formation of intrarenal prostaglandins causing a marked decline in renal function and Na⁺/H₂O₂ excretion in cirrhotic patients with ascites (fig 1).

Treatment of hepatorenal syndrome

INITIAL MANAGEMENT

- Optimal fluid management: renal function rarely recovers in the absence of hepatic recovery. The key goal in the management of these patients is to exclude reversible or treatable lesions (mainly hypovolaemia), and to support the patient until liver recovery (for example, from alcoholic hepatitis), hepatic regeneration (acute liver disease), or liver transplantation. The treatment of HRS is directed towards reversing the haemodynamic changes induced by reduced renal perfusion pressure, stimulated sympathetic nervous system, and increased synthesis of humoral and renal vasoconstrictor factors.
- In cirrhotic patients, renal insufficiency is frequently secondary to hypovolaemia (diuretics or gastrointestinal bleeding), NSAIDs, or sepsis. Precipitating factors should be recognised and treated, and nephrotoxic drugs discontinued.
- All patients should be challenged with up to 1.5 litres of fluid such as human albumin solution or normal saline to assess the renal response as many patients with

subclinical hypovolaemia will respond to this simple measure. This should be done with careful monitoring to avoid fluid overload. In practice, fluid overload is not usually a problem as patients with severe liver disease act as “fluid sumps” and their vasculature adapts to accommodate the extra fluid. This has been confirmed by Hadengue *et al* who described increased venous compliance following fluid challenge in advanced cirrhosis.¹¹⁴ Two recent studies have shown that prolonged treatment of patients with HRS (two weeks) with albumin and systemic vasoconstrictors (ornipressin¹¹⁵ or terlipressin¹¹⁶) resulted in an improvement in renal function in HRS.

- Evidence of sepsis should be sought by blood, ascitic, cannulae, and urine culture, and non-nephrotoxic broad spectrum antibiotics commenced, regardless of evidence of sepsis, as an undiagnosed delay in effective treatment of infection may increase mortality. In advanced cirrhosis, endotoxins and cytokines play increasingly important roles in advancing the hyperdynamic circulation and worsening renal function.¹¹⁷

OPTIMISATION OF RENAL HAEMODYNAMICS

Optimise blood pressure

If mean arterial pressure is low (<70 mm Hg), it should be increased to approximately 85–90 mm Hg or until urine output improves by infusing a vasopressor drug. Vasopressin, ornipressin, terlipressin, or noradrenaline infusion have all been used with some success.^{23 62 118} On physiological grounds it seems sensible to use either ornipressin or terlipressin as firstline.

Paracentesis

Drainage of tense ascites may temporarily improve renal haemodynamics and renal function by decreasing renal venous pressure. There may be a modest fall in blood pressure following paracentesis. There is no evidence to support this approach although it seems logical on the basis of published data. The fall in renal perfusion pressure due to decreased arterial pressure may of course counteract any beneficial effect and should therefore be counterbalanced by pressor support, as necessary.

Pharmacological treatment

All of the drugs that have been investigated in HRS have one overriding aim—to increase RBF. This has been either indirectly, by splanchnic vasoconstriction, or directly using renal vasodilators. One of the principle difficulties has been the lack of agents which act purely on the splanchnic circulation. Drugs which “spill over” into the systemic circulation may actually exacerbate the intense renal vasoconstriction already present. Currently, there is significant enthusiasm for vasoconstrictor agents in HRS. However, the numbers of patients studied has been small, mortality remains high, and there have been no randomised placebo controlled trials. This clearly needs to be addressed but is limited to the relative rarity of pure HRS patients without confounding variables such as sepsis and gastrointestinal bleeding. An important aspect of these reports is the need for a pressor response to these agents as well as return of abnormal renal function after cessation of vasoconstrictor therapy. HRS is effectively a marker of poor hepatic function, and these agents are probably best utilised as a bridge to further improvement in liver function, either following cessation of alcohol or liver transplantation. Thus the decision to use vasoconstrictor agents for HRS should be based on whether the patient is a realistic transplant candidate or if not, whether liver function might improve. Patients who do not satisfy these criteria will be treated unnecessarily, merely prolonging the

process of dying, at a time when palliative care would be more appropriate.

Dopamine. Dopamine was the first drug used due its vasodilator effect when given in subpressor doses. Dopamine is frequently prescribed to patients with renal impairment, and yet no studies have ever shown any convincing benefit.^{119 120} It is our impression that occasionally (<5% of the time) a patient responds with an increase in urine output. It is therefore our practice to give a 12 hour trial of dopamine and stop treatment if there is no improvement in urine output.

Ornipressin. Ornipressin is a vasopressin analogue that preferentially causes vasoconstriction of the splanchnic vasculature thus increasing blood and renal perfusion pressure. These effects are reflected by a commensurate decrease in plasma renin and angiotensin, and improved renal clearance and sodium excretion.¹²¹ In 1996, Salo and colleagues¹²⁰ studied 20 patients with hepatorenal syndrome. A two hour infusion of ornipressin at 6 IU/h in 11 patients resulted in a significant fall in plasma renin and a rise in blood pressure. In the same 11 patients, addition of dopamine with ornipressin had no further benefit. In the second part of their protocol performed on a further five patients, intravenous infusion of noradrenaline plus prostacyclin failed to increase renal perfusion or glomerular filtration rate, and actually reduced urinary volume and sodium excretion. In 1998, Guevara and colleagues¹¹⁵ also examined the role of ornipressin in the management of HRS. Two protocols were employed: each was performed in a group of eight patients. Using a combination of ornipressin and albumin infusion, they observed that prolonged administration of the combination resulted in an increase in mean arterial pressure and normalisation of renal function. These improvements were reflected by a marked fall in plasma renin activity, plasma aldosterone, noradrenaline concentrations, and an increase in atrial natriuretic peptide. HRS did not recur after cessation of therapy in patients who finished the 15 day treatment despite a rebound increase in the activity of systemic vasoconstrictor factors. However, this treatment had significant complications. Four patients had to stop therapy after six days because of serious side effects, including ischaemic colitis, an infarcted tongue, asymptomatic ventricular extrasystoles, and bacteraemia due to a urinary tract infection.

Terlipressin. Terlipressin (glypressin) is a synthetic analogue of vasopressin with intrinsic vasoconstrictor activity. It is slowly cleaved in vivo into vasopressin by enzymatic cleavage of the triglycyl residue. It has the advantage over vasopressin of a longer biological half life allowing administration as a four hourly bolus. Hadengue and colleagues¹²² showed that two day terlipressin administration (2 mg/day) increased blood pressure, GFR, and urine output in nine patients with type 1 HRS in a placebo controlled crossover study. No side effects were reported. These results were also confirmed by Uriz *et al* who showed that longer term administration of terlipressin with albumin for two weeks reversed HRS in seven of nine patients.¹¹⁶

Midodrine and octreotide. Octreotide is a long acting analogue of somatostatin which has a variable effect on splanchnic haemodynamics. Midodrine is a sympathomimetic drug. Data on its use in HRS are limited to a recent publication by Angeli and colleagues¹²³ and a series from Kaffy and colleagues.²¹ Angeli and colleagues¹²³ demonstrated that combined long term administration of midodrine, an oral α adrenergic agent, and octreotide, led to improvement in renal function. After 20 days of treatment with midodrine and octreotide, an impressive improvement in renal plasma flow, GFR, and urinary

sodium excretion was observed. This was accompanied by a significant reduction in plasma renin activity, plasma vasopressin, and plasma glucagon. No side effects were observed.

Misoprostol. Misoprostol, a synthetic analogue of prostaglandin E₁, was examined by Fevery *et al* in 1990¹²⁴ in four patients with HRS at a dose of 0.4 mg four times daily, orally. All four patients responded with diuresis and a fall in creatinine although only two patients had natriuresis. In a larger study by Gines and colleagues,¹²⁵ nine patients with renal impairment with or without hyponatraemia but not fulfilling the criteria for HRS, were given 0.2 mg misoprostol four times daily for four days. No changes in GFR (59 (11) *v* 54 (11) ml/min), sodium excretion (4.0 (1.3) *v* 4.1 (2) μ Eq/min), or free water clearance (2.4 (0.8) *v* 2.1 (0.9) ml/min) were observed. An infusion of prostaglandin E₂ in a similar group of nine patients had a similarly disappointing lack of effect on GFR and sodium excretion, and decreased free water clearance.

Endothelin antagonists. Endothelin, a potent endogenous vasoconstrictor, is increased in patients with HRS.¹²⁶ The role of an ET_A antagonist BQ123 was examined in a preliminary study of three cirrhotic patients with HRS by Soper and colleagues.¹²⁷ Consecutive 10, 25, and 100 nmol/min infusions of BQ123 were given for 60 minutes. All three patients showed a dose-response improvement in inulin and para-amino hippuric acid clearance, approaching 100% at the highest dose. All three patients subsequently died.

N-Acetylcysteine. There has been one series of 12 patients (nine of whom had alcoholic cirrhosis) with HRS where N-acetylcysteine was given intravenously for five days. This treatment was well tolerated with no side effects. At baseline, following aggressive fluid replacement, mean creatinine clearance was 24 (3) ml/min, rising to 43 (4) ml/min following five days of therapy. This was associated with an increase in urine output, and a significant increase in sodium excretion from 1.2 (0.5) to 1.8 (0.6) mmol/h ($p < 0.05$). High survival values of 67% (8/12) at one month and 58% (7/12) at three months were observed. This included two patients who underwent successful liver transplantation after improvement in renal function.¹²⁸

RENAL SUPPORT

Renal support should only be given when there is a clear goal of management and potential outcome. Thus renal support should only be offered where there is a realistic possibility of hepatic regeneration, hepatic recovery, or liver transplantation. Renal support otherwise merely prolongs the dying process. Renal support is generally given as continuous haemofiltration. Intermittent haemodialysis causes marked haemodynamic instability in some patients. The molecular adsorbent recirculating system (MARS) is a modified dialysis method using albumin containing dialysate that is recirculated and perfused online through charcoal and anion exchanger columns. MARS enables the elective removal of albumin bound substances. Mitzner and colleagues,¹²⁹ in a randomised controlled trial, compared standard therapy consisting of volume expansion, dopamine, and haemodynamic filtration versus the same plus extracorporeal albumin dialysis. They found a significant improvement in standard liver and kidney test function in the MARS group. Mortality rates were 100% in the control group and 62.5% in the MARS group at day 7. Further studies are underway.

Surgical manoeuvres, TIPS, and liver transplantation

There are few case reports of TIPS in patients with HRS and results are mixed. Some patients have a delayed

response (after four weeks) with improvement in renal function, and some worsen. In other words, patients can do very well if they survive the procedure but some develop significant complications, particularly when the patient has a Child Pugh score for severity of liver disease greater than 12. Only prospective randomised studies can resolve this issue. However, the largest series show improvement in renal function in most patients with type 2 HRS. The German series¹⁵⁰ had six of 16 patients with type 1 syndrome. Three month survival was 75%. Recently, long term follow up of this group with a larger cohort (median follow up two years) has been published.⁹⁶ Thirty one patients with HRS received TIPS (14 patients with HRS type 1, 17 with HRS type 2). Following TIPS, total survival rates at three and 12 months were 63% and 39%, respectively. These results are encouraging but controlled trials are required to confirm improvement in prognosis. TIPS could serve as a bridge to liver transplantation allowing kidney function to recover and clinical status to improve.

The only effective and permanent treatment for HRS is orthotopic liver transplantation (OLT). Gonwa *et al* compared survival following OLT of 56 patients with HRS with 513 controls (non HRS). They observed one and four year survival rates of 71% and 60%, respectively, for HRS patients, and 83% and 70% for non-HRS patients.¹³¹ The same retrospective study also considered the long term evolution of renal function following OLT for both groups of patients. Both cyclosporin and FK506 (used following OLT) also impaired renal function. As a consequence, in 407 non-HRS patients, GFR decreased from 94 to 60 ml/min at one year following transplantation. In 34 patients with HRS, GFR increased from 14 to 44 ml/min at one year following transplantation.¹³ Preoperative and postoperative morbidity in HRS patients was higher. Dialysis was required in 32% of HRS patients prior to OLT and 10% remained on dialysis following transplantation. Overall mean post-transplant hospital stay was 42 days for patients with HRS compared with 27 days for those without HRS.¹³¹ Hence it seems clear that eligible patients with HRS can safely benefit from liver replacement at the price of increased time spent in hospital and modest impact on long term survival.¹³²

Conclusion

The hepatorenal syndrome is a syndrome of functional renal failure due to end stage liver disease. It is caused by impaired renal perfusion pressure, stimulation of the renal sympathetic nervous system, and production of mediators causing mesangial contraction and reduced filtration fraction. Patients with HRS should be treated by supportive measures (blood pressure support and antibiotics), and haemofiltration of dialysis only given if recovery of liver function is likely, either spontaneously or following liver transplantation.

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