The hepatorenal syndrome

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1. The hepatorenal syndrome is the development of renal failure in patients with severe liver disease in the absence of any identifiable renal pathology.
2. Decreased glomerular filtration is caused by a reduction in both renal blood flow and the renal filtration fraction. These changes arise as a consequence of a fall in mean arterial pressure due to systemic vasodilatation, activation of the sympathetic nervous system causing renal vasoconstriction, and increased synthesis of several vasoactive mediators, which together modulate both renal blood flow and the glomerular capillary ultrafiltration coefficient, and hence filtration fraction.
3. Patients with liver disease developing renal failure should have hypovolaemia excluded by volume challenge, and all nephrotoxic drugs including diuretics should be stopped. Broad-spectrum antibiotics should be given for subclinical infection, which may be a treatable precipitant of renal failure in cirrhosis. Renal perfusion should be optimized by ensuring that the blood pressure and systemic haemodynamics are adequate, and that if renal venous pressure is elevated, due to tense ascites, it is alleviated.
4. The prognosis of hepatorenal syndrome is poor with a > 90% mortality. However, patients can and do recover from the hepatorenal syndrome, but only if there is a significant improvement of their liver function, or if they undergo liver transplantation.

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 [1]. It is diagnosed after exclusion of other causes of renal failure in patients with liver disease such as hypovolaemia, drug nephrotoxicity, sepsis or glomerulonephritis. The diagnosis of the HRS, however, is not dependent on the presence of a low urine sodium or high urine/plasma osmolality [2], and this was agreed at the recent symposium on redefining HRS and refractory ascites [3]. The diagnostic criteria agreed are shown in Table 1. Urinary protein should be less than 500 mg/day, which helps to distinguish it from glomerulonephritis, and the urinary sediment is normal or 'near normal'. Urine indices in the early stages typically show a urine sodium below 10 mmol/l, a fractional sodium of < 1, a urine/plasma osmolality of > 1 and a urine/plasma creatinine ratio of > 10, and HRS is sometimes referred to as functional renal failure, indicative of preserved tubular function. Functional renal failure (as one form of HRS) may evolve into acute tubular necrosis [4–6]. Indeed electron microscopy studies have shown evidence of acute tubular necrosis, even when the urinary indices indicate functional renal failure [7]. In practical terms it is important to distinguish it from the other causes of renal failure, such as dehydration, sepsis and use of nephrotoxic drugs.

Table 1. Major diagnostic criteria used to define HRS. The additional criteria relate to factors that are commonly present, but are not required for the diagnosis. These criteria are explained in more detail in [3].

Major criteria
1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
2. Low GFR as indicated by serum creatinine < 1.5 mg/dl or creatinine clearance < 40 ml/min.
3. Absence of shock, ongoing bacterial infection and 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
1. Urine volume < 500 ml/day
2. Urine sodium < 10 mmol/l
3. Urine osmolality < plasma osmolality
4. Urine red blood count < 50 per high per field
5. Serum sodium < 130 mmol/l

Key words: ascites, cirrhosis, hepatorenal syndrome, portal hypertension, renal blood flow.

Abbreviations: GFR, glomerular filtration rate; HRS, hepatorenal syndrome; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drugs; OLT, orthotopic liver transplantation; PG, prostaglandin; E2; RAAS, renin–angiotensin–aldosterone system; SSN, sympathetic nervous system; TIPSS, transjugular intrahepatic portosystemic shunt; TXA2, thromboxane A2; LTE4, leukotriene E4.

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Two patterns of the HRS are commonly observed in clinical practice. Firstly there is an acute form, now termed type 1 HRS, in which renal failure occurs spontaneously, with rapid onset and progressive renal failure. This is defined as an increase in plasma creatinine to $>200\,\mu\text{M}$, or a decrease in creatinine clearance to $<20\,\text{ml/min}$ [3]. This is most frequently observed in acute liver failure or alcoholic hepatitis, or after acute decompensation on a background of cirrhosis. These patients usually have marked icterus and a significant coagulopathy. Secondly, there is a more chronic form (now termed type 2 HRS) in which there is significant renal impairment, and in which renal function staggers towards improvement or deterioration over weeks or months. These patients frequently have refractory ascites, and jaundice may be mild.

The pathogenesis of the HRS is multifactorial. There are three factors predominantly involved in its aetiology.

**FACTORs INVOLVED IN THE PATHOGENESIS OF HRS**

1. Haemodynamic changes causing reduced renal perfusion pressure.
2. Stimulated sympathetic nervous system (SNS).
3. Increased synthesis of humoral and renal vasoactive mediators.

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

The prognosis of the HRS is poor with a mortality of 80–95% depending on aetiology. Survival and recovery of renal function is generally dependent on improvement of liver function due to recovery from the liver insult, effective hepatic regeneration or liver transplantation.

**PATHOGENESIS OF THE HEPATORENAL SYNDROME**

**A. Haemodynamic changes**

Autoregulation of the renal circulation ensures a stable renal blood flow during changes of renal perfusion pressure (i.e. mean arterial pressure minus renal venous pressure). This normally operates above a mean pressure of $70–75\,\text{mmHg}$ [8–10] (Fig. 1), and below this level, renal blood flow decreases in direct proportion to perfusion pressure. However, patients developing the HRS have an activated sympathetic system and increased synthesis of several renal vasoconstrictors, and animal studies have shown that this causes a right-ward shift in the autoregulatory curve [11], making renal blood flow more pressure dependent. Thus, as shown in Fig. 1, even modest decreases in mean arterial pressure may result in a marked fall in renal blood flow.

Several studies have consistently shown a progressive decrease in mean arterial pressure with hepatic decompensation, with the lowest values (typically 60–65 mmHg) observed in patients with the HRS [12]). A recent study by Gines et al. [13] demonstrated that the presence of a reduced mean arterial pressure in decompensated cirrhotics is a risk factor for the development of HRS [13]. Renal venous pressure (normally less than 5 mmHg), may be significantly increased in the presence of tense ascites or as a consequence of cirrhosis itself [14–17], and this coupled with decreased arterial pressure will cause a further decrease in renal blood flow. The importance of arterial blood pressure has been demonstrated conclusively in several studies. Infusion of various agonists which increase blood pressure have all been reported to increase urine output, sodium excretion or glomerular filtration rate (GFR) with variable success [18, 19].

The presence of modest arterial hypotension raises the question about its cause. It is well established that severe liver disease is characterized by an increase in cardiac output and plasma volume and decreased peripheral vascular resistance [20, 21] due to peripheral vasodilatation. This is mainly limited to either the splanchnic circulation or that supplying skin and muscular tissue [12, 22, 23]. While some studies have shown increased peripheral blood flow to the limbs [12], other studies do not support these findings [23]. Clinically, patients with severe liver failure and type 1 HRS have warm peripheries, and I would be surprised if total limb flow was normal or reduced. The primary mechanism is unknown.
Splanchnic vasodilatation is partly related to portal hypertension and the opening of portosystemic shunts, and minor arteriovenous fistulas [24, 25] and portovenous shunts within the human cirrhotic liver have recently been described [26]. Thus vasodilatation in cirrhosis is partly related to this shunting of blood from the systemic to the venous circulation. There is general acceptance that vascular reactivity is impaired in cirrhosis since isolated vessels have impaired responsiveness to vascular agonists. Ultimately several mediators, either singly or in concert, may be responsible for the decreased vascular reactivity or the opening of these anatomical shunts. Plasma levels of many endogenous vasodilators, as well as vasoconstrictors, are elevated in liver failure. In view of the multiple interactions between various vasoactive substances, the search for ‘the’ primary vasodilator is extremely difficult. More than one mediator may be involved, and several potential mediators have been proposed and include those described below.

Nitric oxide. Nitric oxide (NO) is synthesized by several cell types, including endothelial and vascular smooth muscle cells, and causes vasorelaxation [27]. NO synthesis may be induced by shear stress, or in response to endothotoxin-related cytokine expression [24, 28–30]. The observation that many patients with decompensated cirrhosis have circulating endotoxaemia provides the missing link. Studies in patients with decompensated cirrhosis show increased plasma nitrite or nitrate, indicative of increased NO production [31]. Pharmacological studies using isolated vascular rings or the mesenteric vasculature have shown decreased vascular reactivity to several agonists, and inhibition of NO synthase restores or partially restores vascular responsiveness [32, 33]. Likewise studies in vivo have shown that inhibition of NO synthesis reverses the systemic and splanchnic circulatory changes in animal models and patients [34, 35]. 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 [28].

Glucagon. Plasma glucagon levels are elevated in cirrhosis. Glucagon causes desensitization of the mesenteric circulation to catecholamines and angiotensin II, and causes vasodilatation at pharmacological doses [36]. Glucagon also elevates intracellular cyclic AMP. Recent studies have shown that raised cyclic AMP acts synergistically with endotoxin to induce NO synthase, and thus NO release by vascular smooth muscle cells [37]. Thus glucagon may enhance NO production in cirrhosis. Whether the therapeutic use of catecholamines to elevate blood pressure, which also elevate cyclic AMP, further enhances NO production when endotoxia is present is unknown and warrants further study.

Prostacyclin. Prostacyclin is a systemic vasodilator. Its secretion might be stimulated by shear stress of the splanchnic arterioles [28, 30]. 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 [38, 39]. Calculations, based on the known levels of exogenous prostacyclin required to cause vasodilatation in man, suggest that plasma levels are too low (by a factor of 100) to cause significant systemic vasodilatation [39]. Nevertheless, administration of non-steroidal anti-inflammatory drugs (NSAIDs) to cirrhotic patients causes haemodynamic changes, suggesting that prostacyclin may have a facultative role in the vasodilatation of cirrhosis [40].

Potassium channels. There are three major types of potassium channel 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 depolarization, 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 hyperpolarization of vascular smooth muscle cells. Potentially important activators include tissue hypoxia, prostacyclin, neuropeptides and NO. Using potassium-channel blockers and activators, Moreau et al. [41–43] have found good evidence that activation of potassium channels is important in the vasodilatation of cirrhosis. Based on studies with potassium and calcium channel modifiers, Moreau and Lebrec [43] have proposed that there is an impairment of G-protein-dependent transduction pathways. This hypothesis is based on the observation that hyperreactivity of vessels is not associated with down-regulation of receptors, and reactivity to Bay K 8644 (which increases intracellular calcium) is normal.

Endotoxaemia and cytokines. Endotoxin levels are usually elevated in patients with decompensated liver disease and more so in patients with the HRS. This is believed to be due to increased bacterial displacement and portosystemic shunting [44–47]. Endotoxaemia may cause splanchnic vasodilatation, possibly mediated by cytokine induction and increased NO synthesis. Infusion of lipopolysaccharide into animals causes complement activation, an accumulation of neutrophils in the liver (if given intraperitoneally) and renal dysfunction. The renal dysfunction that occurs can be blocked by both leukotriene and thromboxane antagonists. There are increased circulating levels of several cytokines, including tumour necrosis factor and interleukin-6, particularly in patients with alcoholic hepatitis and HRS [48, 49]. Recent studies in the rat have shown that the systemic vasodilatation observed in the partial portal vein ligated model is blocked by antitumour necrosis factor antibodies [50].
Adenosine. Adenosine induces splanchnic vasodilatation [51], and can induce renal vasoconstriction [52]. Administration of dipyridamole, which enhances the action of endogenous adenosine by inhibiting uptake and degradation, to patients with cirrhosis decreases renal blood flow [53].

Splanchnic circulation. The splanchnic circulation in cirrhosis develops chronically, and splenic blood flow increases with the opening up of various portosystemic shunts. Given the physiological basis of systemic vascular resistance (i.e. systemic vascular resistance is proportional to mean arterial pressure divided by cardiac output), then any mechanism which increases cardiac output, with the sustenance of a normal arterial pressure, is bound to decrease systemic vascular resistance. Thus the development of portosystemic collaterals, and secondary increase of arterial blood flow, will lower vascular resistance. While it is tempting to speculate that in cirrhosis a point is reached when compensation cannot be maintained, and thus arterial pressure falls, the argument is less applicable to the degeneration that occurs in acute liver failure or acute alcoholic hepatitis. It should be noted that portal hypertension can occur acutely, or be exacerbated in such circumstances, and whether this causes the acute development of collaterals sufficient to cause the systemic vasodilatation as observed is unknown [54].

What are the secondary consequences of systemic vasodilatation?

The normal homeostatic response to vasodilatation is the activation of several neuro-humoral response mechanisms, primarily aimed at the maintenance of arterial pressure, and should generally be considered beneficial rather than adversarial. These responses may be summarized as: activation of the SNS (see below); activation of the renin–angiotensin–aldosterone system (RAAS); increased vasopressin release; and increased renal production of vasodilatory prostanooids.

Although activation of these neurohumoral mechanisms is essential in maintaining homeostasis, some also induce renal vasoconstriction. This is not surprising, since 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 the decreased renal blood flow observed in the HRS.

The RAAS is stimulated in 50–80% of patients with decompensated cirrhosis, and is further elevated in patients with the HRS [21, 55, 56]. Increased levels of angiotensin II protect renal function by selective vasoconstriction of the efferent glomerular arterioles. Although renal blood flow may fall, GFR is preserved due to an increased filtration fraction [57]. In cirrhosis, inhibition of the RAAS by either saralasin or angiotensin-converting-enzyme inhibitors (e.g. captopril) causes marked hypertension and decreases GFR [58–62], whereas infusion of angiotensin II in cirrhosis has been shown to improve glomerular filtration in some patients [57], presumably in part because of increased arterial pressure.

Anti-diuretic hormone or vasopressin levels are elevated due to non-osmolar stimulation, despite the frequent presence of hyponatraemia [63, 64]. 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 to maintain arterial pressure. Inhibition of V1-receptors in cirrhotic rats causes profound hypotension [65]. Vasopressin, however, preferentially causes splanchnic rather than renal vasoconstriction. Glypressin or octapressin induces reversion of the hyperdynamic circulation, reduces plasma angiotensin and catecholamine levels and increases diuresis and natriuresis [66–68].

Renal prostaglandins play an important role in the preservation of renal function in all situations with elevated plasma levels of renin, angiotensin, noradrenaline or vasopressin, such as dehydration, congestive cardiac failure, shock or decompensated liver disease. In the latter situation urinary excretion of prostaglandin E2 (PGE2) and prostacyclin metabolites (6-oxo-PGF1α) are usually increased [39, 69–73]. The mechanism for increased synthesis is unknown, but is likely to be secondary to the increased levels of the vasoconstrictors, many of which have been shown to cause prostaglandin formation in vitro or in vivo. Administration of cyclooxygenase inhibitors (NSAIDs) to patients with ascites frequently causes renal failure, and this usually reverses on cessation of NSAID treatment [71, 74]. Some workers have suggested that HRS is caused by a deficiency of renal PGE2 and prostacyclin [71], since urinary excretion of PGE2 and the prostacyclin metabolite 6-oxo-PGF1α are low compared with patients with ascites but preserved renal function. 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 (Fig. 2). To investigate the ratio of urinary prostacyclin metabolites to thromboxane A2 (TXA2), a plot of the ratio of these two metabolites in patients with HRS was compared with those with ascites and those with severe liver failure (but who did not develop HRS), and is shown in Fig. 3. Post-mortem immunohistochemical studies have shown that prostaglandin endoperoxide synthase is markedly decreased in medullary collecting tubules of patients with the HRS as compared with patients with liver failure but normal renal function [75]. There have been no further histochemical studies to confirm this, and the mechanism is unknown.

The importance of each of these compensatory mechanisms is indicated by the fact that inhibition
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Fig. 2. Synthesis of prostacyclin is increased but urinary excretion of its metabolite is decreased by the presence of renal failure. Urinary excretion of TXB₂ (○), and 6-oxo-PGF₁α (△) were markedly elevated in a single patient with alcoholic hepatitis, and fell rapidly during the development of HRS in parallel with creatinine clearance (●) (left panel). This strongly suggests that urinary excretion of these metabolites should be corrected for creatinine clearance. After correction for creatinine clearance, urinary excretion of 6-oxo-PGF₁α was markedly elevated compared with other groups (right panel). The groups studied included normal controls (N), compensated liver disease (CLD), ascites (Asc), severe hepatitis (SH), HRS and chronic renal failure (CRF). From [39], reproduced with permission from the publisher.

or antagonism of their actions frequently causes either adverse systemic and/or adverse renal effects. Thus, although they may contribute to some or many of the renal haemodynamic changes, the overall result of their activation tends to be beneficial.

B. The sympathetic nervous system

The SNS is highly activated in patients with the HRS [76-79]. The elevation of plasma catecholamines in the HRS is due to increased secretion, and studies exploiting differences across vascular beds demonstrate increased secretion in the renal and splanchnic vascular beds [80-82]. The sympathetic axis can be stimulated by three different mechanisms: (1) pressure receptors in response to hypotension in the aortic arch and carotid glomus, and volume receptors in response to hypovolaemia in the atria; (2) non-volume-dependent hepatic baroreceptors; and (3) secondary to metabolic changes (c.f. secretion in response to hypoglycaemia).

All three of these mechanisms may be active in the HRS, although with the current available data it is impossible to state which predominates.

The importance of the hepatorenal innervation has been recognized since the 1980’s. Kostreva et al. [83] found that increased intra-hepatic pressure is associated with increased efferent renal SNS activity, and Levy and Wexler [84] 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 et al. [85], 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 renal blood flow when infused into the portal vein. The mechanism is unknown but is postulated to be due to hepatocyte swelling. This effect seemed to be mediated via the renal nervous system, since no effect was seen in those animals in which the renal nerves had been severed. In support

Fig. 3. Individual ratio of 6-oxo-PGF₁α to TXB₂ plotted for each patient to determine whether there was an altered ratio in patients with the HRS. The data were obtained from [39]. The ratio was essentially the same in each group, with a tendency for it to be increased rather than decreased in the HRS. The groups studied included normal controls (N), compensated liver disease (CLD), ascites (Asc), severe hepatitis (SH), HRS and chronic renal failure (CRF). The data in this format has not previously been published.
of this concept in man, recent studies by Jalan et al. [113] have shown that acute occlusion of the transjugular intrahepatic portosystemic shunt (TIPSS) is associated with an acute reduction of renal blood flow in patients with cirrhosis [113]. In another study, temporary lumbar sympathectomy with local anaesthesia increased GFR in five of eight cirrhotic patients with HRS [86].

Activation of the renal SNS causes vasoconstriction of the afferent renal arterioles, with a decrease in renal plasma flow and GFR, and sodium retention. This may also activate renin secretion (via \( \beta \)-receptors) causing further salt retention. Finally, as discussed above, activation of the SNS makes renal blood flow more pressure dependent. Systemic administration of \( \beta \)-blockers induces variable responses in cirrhotic patients [87–89], but has not been tried in the HRS. \( \alpha \)-Adrenergic blockade induces arterial hypotension, impairing renal perfusion. In contrast, administration of noradrenaline usually results in improvement of renal function in the HRS, probably secondary to improved arterial pressure [57].

**C. Humoral and renal vasoactive mediators**

It is unlikely that the development of the HRS is purely a consequence of renal vasoconstriction. If one examines the relationship between renal blood flow and the presence of HRS or hepatic decompensation with or without ascites, there is considerable cross-over in the renal blood flow between these groups [90]. Likewise, a recent study [91] has shown that the presence of an elevated 'resistive index', as determined by duplex doppler ultrasonography, indicative of renal vasoconstriction, was a predictor of the development of HRS in patients awaiting liver transplantation. While other studies [92] support the concept of a 'renal blood flow dependent mechanism', we have independently observed a marked decrease in renal blood flow in cirrhotic subjects with preserved renal function using intravascular doppler probes (K. Moore, J. Wendon and R. Williams, unpublished work), supporting the findings of Ring-Larsen et al. [90]. The observation that two patients may have a comparable decrease in renal blood flow, and yet have either renal failure 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, invaginated with mesangial cells, which may contract in response to several agonists and thus reduce the surface area available for glomerular filtration. 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 \( (K_t) \), and thus the filtration fraction. Such factors involved may include the following.

**Endothelin.** This 21 amino acid peptide is a potent vasoconstrictor with preferential renal vasoconstriction, and a potent agonist of mesangial cell contraction. Endothelin-1 concentrations are increased in the HRS and correlate with creatinine clearance in decompensated liver disease [93–95]. Moreover, the plasma levels observed by Moore et al. [95] are comparable with those causing a significant decrease in GFR in normal human volunteers after infusion of endothelin-1 [96]. The cause of increased plasma concentrations is unknown. Volume expansion or upright tilt fails to increase plasma endothelin in cirrhotic patients [97], and there appears to be no correlation with circulating endotoxins [98]. Whether tissue hypoxia or oxidant stress-dependent pathways are important is unknown. Increased lipid peroxidation is known to occur in HRS [99], and certain products of lipid peroxidation, namely oxidized low-density lipoproteins, have been shown to induce endothelin-1 synthesis *in vitro* [100], but whether this is involved aetiologically is unknown.

**Cysteinyl leukotrienes.** Leukotrienes \( \text{C}_4 \) and \( \text{D}_4 \) 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*. Their synthesis may be stimulated by endotoxaemia, activation of complement, or various cytokines. There is good evidence that systemic and probably renal synthesis of cysteinyl leukotrienes are increased in the HRS. Urinary leukotriene \( \text{E}_4 \) (\( \text{LTE}_4 \)) is markedly elevated, as is \( N \)-acetyl \( \text{LTE}_4 \) (probably a renal product of leukotriene biosynthesis), in HRS [102–104] (Fig. 4). Estimated plasma levels are too low to cause direct effects on the renal circulation, but renal leukotriene synthesis might be an important modulator of renal function in the HRS.

**Thromboxane \( \text{A}_2 \).** \( \text{TXA}_2 \) production is stimulated by renal ischaemia and causes both vasoconstriction and mesangial cell contraction. It has been suggested that the balance between vasodilatatory prostaglandins and \( \text{TXA}_2 \) might 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. When one takes a comparable group of patients with severe liver disease, but in whom renal failure does not develop, and analyses the urinary excretion of \( \text{TXA}_2 \) and prostacyclin metabolites, one finds equally increased metabolite levels of prostacyclin and \( \text{TXA}_2 \), when corrected for GFR in patients with HRS, compared with those with severe liver failure, but well-preserved renal function [39] (Figs. 2 and 4). Furthermore, inhibition of \( \text{TXA}_2 \) synthesis with dazoxiben does not improve renal function [106]. Such studies do not exclude a role...
for thromboxane, but clearly question its legitimacy as a prime candidate.

**F₂-isoprostanes.** The F₂-isoprostanes are formed by lipid peroxidation. One of the major F₂-isoprostanes formed in vivo, namely 8-iso-PGF₂ₐ, is a potent renal vasoconstrictor. We have observed increased synthesis of the F₂-isoprostanes in patients with the HRS, indicative of increased lipid peroxidation [99]. Whether the F₂-isoprostanes themselves are important mediators of renal vasoconstriction in the HRS is unknown. However, the synthesis of several mediators implicated in the pathogenesis of HRS are regulated through products of lipid peroxidation or through redox changes secondary to oxidant stress. 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: A PERSONAL APPROACH**

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 (e.g. from alcoholic hepatitis), hepatic regeneration (acute liver disease), or until liver transplantation.

**A. Initial management**

In cirrhotic patients, renal insufficiency is frequently secondary to hypovolaemia (diuretics or gastro-intestinal bleeding), non steroidal anti-inflammatory drugs or sepsis. Precipitating factors should be recognized and treated, and nephrotoxic drugs discontinued.

All patients should be challenged with up to 1.5 litres of colloid, such as human albumin solution, to assess the renal response. Whereas the recent article defining the criteria for HRS [3] recommended using saline, my preference is to use colloid where available. This should be done with careful monitoring to avoid fluid overload. In practice, fluid overload is not usually a problem, since patients with severe liver disease act as 'fluid sumps' and their vasculature adapts to accommodate the extra fluid. This has been scientifically demonstrated by Hadengue et al. [107] who demonstrated increased venous compliance after fluid challenge in advanced cirrhosis.

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.

**B. Optimization of renal haemodynamics**

It is important to maximize renal blood flow. **Optimization of blood pressure.** Mean arterial pressure should be maximized to >75 mmHg. Vasopressin, ornipressin (a vasopressin analogue) or noradrenaline infusion have all been used with some success [18–20]. Physiologically it seems sensible to use either ornipressin or vasopressin first line.

**Paracentesis.** Drainage of tense ascites may temporarily improve renal haemodynamics and renal func-
tion by decreasing the renal venous pressure. There may be a modest fall in blood pressure after paracentesis.

**Dopamine.** Low-dose dopamine infusion improves renal blood flow, but in the two small studies published, in cirrhosis with or without HRS there was no improvement in GFR [108–110], and only one study has shown any improvement in GFR in cirrhosis [110]. Prolonged use may increase catabolism, and if there is no discernible response within 24 h it should be discontinued.

**C. 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.

**D. Surgical manoeuvres and liver transplantation**

There is no role for the LeVeen shunt in HRS [111], and there has been only one study on lumbar sympathectomy [86]. TIPSS has been reported to improve renal function in patients with refractory ascites, but only after a 4 week interval [113], and anecdotal reports have suggested that renal function can improve in patients with the HRS. Recent studies have also shown that temporary occlusion of the TIPSS by a balloon catheter causes a sudden reduction in renal blood flow, consistent with the concept of a hepatorenal reflex arc [113].

The only effective and permanent treatment for the HRS is orthotopic liver transplantation (OLT). Iwatsuki et al [114] reported on three patients with the HRS with rapid and full recovery of the renal function after OLT [114]. In a recent report, comparing survival following OLT of 56 patients with HRS with 513 patients without HRS, only a tendency towards impaired survival was noted, with a 1- and 4-year survival of 71% and 60% for HRS patients, and 83% and 70% respectively for non-HRS patients [115]. The same retrospective study also considered the long-term evolution of renal function after OLT for both groups of patients. Both cyclosporine and FK506 (used following OLT) also impair renal function. As a consequence, in 407 non-HRS patients, GFR decreased from 94.1 to 59.8 ml/min at 1 year after transplantation. In 34 patients with HRS, GFR increased from 14.1 to 44 ml/min at 1 year after transplantation. GFR remained significantly lower in previous HRS patients until 4 years after transplantation [10]. Although there was only a tendency towards impaired survival in patients with HRS after OLT, the pre-operative and post-operative morbidity was much higher. Dialysis was given to 32% of HRS patients before OLT, and 10% remained on dialysis after transplantation [115].

**Potential future therapies**

Any process which interferes with the normal homeostatic responses (i.e. increased sympathetic activation, increased RAAS etc.) are unlikely to succeed, and may actually worsen clinical parameters. How do we reconcile the sometimes rapid recovery from HRS after liver transplantation with some of the pathways that have been described? Firstly, the process of liver transplantation involves the physical severing of the hepatorenal reflex pathways, and in patients in whom activation of the SNS is an important component one would expect a rapid effect. Likewise there is aggressive management of the circulatory disturbances (namely poor renal perfusion) during liver transplantation, and clinical studies have shown that increasing the renal perfusion improves renal function transiently in HRS. A well-functioning graft will improve host defence against the multitude of insults that enhance activation of synthesis of many of the circulatory mediators responsible for renal decompensation. Future work must concentrate on those mechanisms that are pathological, such as increased cytokine production, possibly as a consequence of circulating endotoxins or oxidant stress. We have recently described increased plasma concentrations of F2-isoprostanes, which indicate increased lipid peroxidation, and thence oxidant stress in patients with the HRS [99]. Recent publications demonstrating the role of oxidant-stress-dependent pathways on gene expression of a variety of cytokines suggest that this may be an important pathway in these patients. These mechanisms seem to be primarily deleterious. Therapeutic agents are coming on-line which may help us in the future, but for the present we must concentrate on supporting the patient until good Providence or liver transplantation.

**CONCLUSION**

The HRS 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 SNS and production of mediators, causing mesangial contraction and reduced filtration fraction. Patients with the HRS should be treated by supportive measures (blood pressure support and antibiotics), and haemofiltration of dialysis should only be given if recovery of liver function is likely, either spontaneously or after liver transplantation.

**ACKNOWLEDGMENT**

K.M is an MRC Senior Fellow, supported by the MRC, UK.
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