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REVIEW

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Renal failure in liver disease

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Introduction

Patients with advanced liver disease commonly have reduced renal function, and in the terminal stages of their disease about 75 % percent develop oligoanuric renal failure [1]. Although it is always necessary to exclude a simple coincidence in cases of simultaneous renal and hepatic dysfunction, renal failure is frequently causally related to liver disease. This clinically important association may be subdivided into two broad categories (Table 1). First, combined liver and kidney disease may result from a common pathomechanism, which directly or indirectly affects both organs, including infectious, toxic, immunologic, or genetic causes. In many of these cases kidney disease develops gradually and is characterized by specific histopathology, but infectious or toxic causes may also lead to acute failure of both organs. Second, in advanced cirrhotic liver disease and less frequently in acute liver failure, renal function is often compromised as a secondary consequence of hepatic failure, independent of the etiology of liver disease. This secondary compromise of renal function has a complex pathophysiological background with at least three different components (Table 2). First, a reduction in renal blood flow, that may result from either a reduction in effective circulating blood volume or a more or less selective increase in renal vascular resistance. Second, an increment in renal tubular sodium reabsorption, which may reflect a physiological response to reduced renal blood flow, but may also be triggered independently of a reduction in renal perfusion by neural or humoral signals of hepatic origin. Third, in more advanced stages of renal dysfunction, an impairment of tubular function induced by ischemia, nephrotoxic agents, endotoxin, inflammatory mediators, and possibly also metabolites that accumulate during cholestasis. Depending upon which of these functional abnormalities predominate and the severity of the derangement, the clinical manifestation ranges from clinically inapparent renal hypoperfusion to different forms of acute renal failure including prerenal failure, acute tubular necrosis, and hepatorenal syndrome (HRS). The terms "HRS" is frequently used inappropriately and there is increasing agreement that it should be confined to a liver-specific type of functional kidney failure which should as far as possible be distinguished from other, nonspecific but more common forms of renal failure in patients with liver disease.

The onset and progression of secondary renal impairment in patients with advanced liver disease is usually

Table 1 Causes of simultaneous renal and hepatic failure

1. Common pathomechanisms (examples)
Infections (malaria, leptospirosis, septicemia, glomerulonephritis associated with hepatitis B and C)
Intoxications (paracetamol, carbon tetrachloride)
Immune mechanisms (connective tissue diseases)
Genetic disorders (polycystic disease, sickle cell anemia)
Protein deposition (amyloidosis)
2. Secondary renal failure (precipitating factors)
Prerenal failure (gastrointestinal hemorrhage, diarrhea, aggressive diuretic therapy, paracentesis)
Classical acute renal failure (renal ischemia, nephrotoxic agents, endotoxin, jaundice?)
Hepatorenal syndrome

Table 2 Pathomechanisms of secondary renal dysfunction in liver disease

1. Diminished renal perfusion
Secondary to reduced effective circulating volume
Secondary to renal vasoconstriction
2. Enhanced sodium reabsorption
Secondary to diminished renal perfusion
Independent of renal perfusion
3. Impairment of tubular function and structure
Secondary to severe impairment of renal perfusion (ischemia)
Secondary to nephrotoxic agents (e.g., aminoglycoside antibiotics, contrast media, nonsteroidal anti-inflammatory drugs), endotoxin, or a systemic inflammatory response
Secondary to substances accumulating in liver disease (bile acids, bilirubin?)

associated with a general worsening of their clinical status and frequently indicates progressive severity of liver disease. In addition, many metabolic complications of liver disease are compounded by the onset of uremia. Thus the coagulopathy of liver disease may be complicated by uremic inhibition of platelet function, the anemia of cirrhosis can be aggravated, and putative immunologic defects of uremia and liver failure may be additive. Moreover, the need for renal replacement therapy and associated forms of temporary vascular access may further increase hemodynamic instability and susceptibility to infections. Therefore, patients with combined renal and hepatic failure usually have to be treated on intensive care units (ICUs) and their management requires close collaboration between the physicians running the ICU, hepatologists, nephrologists, and transplant surgeons.

The following is a brief overview of the pathophysiological basis of secondary renal failure in patients with hepatic dysfunction, the differential diagnosis and the therapeutic options currently available.

Impact of liver disease on renal hemodynamics

Renal dysfunction in conjunction with chronic liver disease is noted almost exclusively in patients with ascites. A pathophysiological hallmark is a reduction of the "effective arterial blood volume" despite generally enhanced total extravascular fluid. This is considered to be due to (i) fluid loss into the peritoneal cavity and (ii) peripheral vasodilatation, in particular as a result of reduced vascular resistance in the splanchnic circulation [2, 3]. The reduction in effective arterial volume is thought to decrease renal blood flow and in particular blood flow to the renal cortex [4, 5] (Fig. 1). As a consequence of renal hypoperfusion and activation of the renin-angiotensin system via baroreceptors in afferent glomerular arterioles [6, 7] and partly due to additional mechanisms, such as increased sympathetic nervous activity [8], hepatorenal reflex mechanisms [9], and antidiuretic hormone secretion [10], sodium and water reabsorption in the kidney are enhanced. The resulting fluid retention maintains, and may increase, ascites formation.

Several theories have been proposed to explain the sequence of events underlying these complex pathomechanisms. While the traditional "underfilling hypothesis" proposed that a reduction in blood volume secondary to the intrahepatic blockade of hepatic blood flow is the initial step, subsequent investigations have shown that circulating blood volume is increased rather than reduced in cirrhotic patients and that sodium retention may precede the development of ascites. This led to an alternative "overflow theory" of ascites formation. However, a variety of features in cirrhotic patients cannot be satisfactorily explained on the basis of both concepts. It has therefore also been proposed that splanchnic arteriolar vasodilation secondary to portal hypertension is the initial event. Underfilling of the arterial vascular compartment, which is not due to a reduction in circulating blood volume but occurs because the vascular compartment is disproportionately enlarged, is considered as an intermediate step and renal sodium and water retention the final consequence ("peripheral arterial vasodilation hypothesis") [3, 11, 12].

Importantly, a reduction in cortical and total renal perfusion occurs long before a reduction in renal function becomes clinically apparent. This is in part due to the fact that in cirrhotic patients serum creatinine is not an accurate reflection of glomerular filtration rate (GFR). Because of frequently severe muscle wasting, the serum creatinine level is lower than would otherwise be the case for any given level of GFR and thus a rise above the "normal range" occurs particularly late during the course of progressive loss of renal function [13]. In addition, even when total glomerular filtration is still normal, renal cortical perfusion may already be impaired, as has been documented by isotope washout techniques [5]. Using duplex sonography, a reduction of renal perfusion can nowadays be easily assessed noninvasively [14, 15]. In a prospective study it has been demonstrated that more than 50 % of patients with normal serum creatinine levels but an elevated resistive index, as derived from Doppler waveform analysis, develop overt renal insufficiency within the following 2 years, as compared to only 6 % of patients with a normal resistive index [16]. This indicates that impaired renal perfusion renders the kidney susceptible to any further damage. Duplex sonography may therefore help to identify patients at particular risk of developing renal failure.

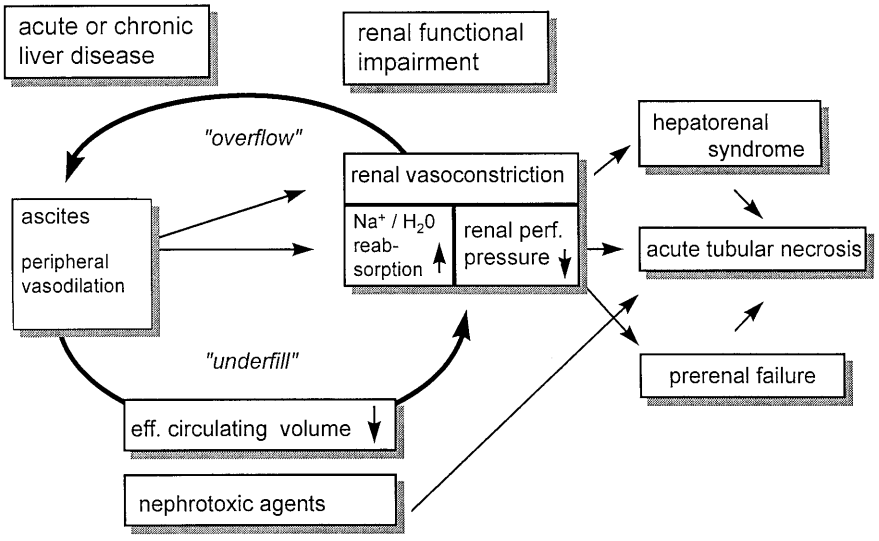

Fig. 1 Schematic presentation of different pathomechanisms and their interaction in the development of different types of renal failure in patients with advanced liver disease (see text for details)

Types of secondary renal failure in liver disease

Prerenal failure

The transition from clinically inapparent renal hypoperfusion to overt and frequently progressive impairment of kidney function can be triggered by a variety of clinical events and complications. Any cause of an incremental intravascular hypovolemia such as gastrointestinal bleeding, diarrhea, vomiting, increased ascites formation, or reduced sodium intake can aggravate renal hypoperfusion sufficiently to cause oliguria and renal failure. Iatrogenic events are also frequently responsible for volume contraction, such as when intensive diuretic therapy induces a diuresis that exceeds the rate of ascites mobilization [17], when volume depletion develops secondary to lactulose therapy, or when paracentesis is performed without intravascular volume replacement. Under all these conditions the reduction in effective circulating volume may lead to a further decrease in mean arterial pressure and thus also renal perfusion pressure. In addition, it is assumed that the autoregulatory mechanisms of renal blood flow and GFR, which normally ensure the stability of both parameters during changes in renal perfusion pressure, may be disturbed in chronic liver disease, which makes GFR more pressure dependent [18]. This results in an increased susceptibility of liver patients to the development of prerenal failure, a functional impairment of kidney function, which, by definition, is reversible after restoration of renal perfusion (Fig. 1). As a reflection of avid sodium reabsorption by functionally intact tubular cells in response to renal hypoperfusion, the urine is concentrated, the urinary sodium concentration in this case is usually low (< 10–20 mmol/l), and the urine-to-plasma creatinine ratio is high (Table 3). Since the reabsorption of filtered urea in the proximal tubule is linked to sodium reabsorption, this also results in a high plasma urea-to-plasma creatinine ratio.

Acute tubular necrosis

In the presence of severe and persistent renal hypoperfusion and other conditions, such as the use of nephrotoxic agents, in particular aminoglycoside antibiotics, contrast media, and nonsteroidal anti-inflammatory drugs, more severe impairment of renal function can develop that includes marked alterations in tubular function. Once this occurs, residual urine is less concentrated (urinary sodium > 40 mmol/l) and renal function becomes unresponsive to plasma volume expansion. This type of classical acute (intrarenal) failure is usually called “acute tubular necrosis” (ATN), although little evidence exists that significant portions of the kidney are in fact necrotic (Fig. 1, Table 3). Systemic infections can also trigger ATN, athough it is not yet understood how this occurs. Patients with jaundice generally appear to be at increased risk of developing ATN, and it has been postulated that bile constituents such as bile acids and bilirubin are nephrotoxic. The evidence in favor of this assumption is largely based on animal experiments and remains inconclusive, but jaundice may in many ways also aggravate the extrarenal factors that predispose to renal failure (reviewed in Bomzon et al. [19]).

Table 3 Differential diagnosis of renal failure in advanced liver disease

	Prerenal failure	Acute tubular necrosis	Hepatorenal syndrome	Primary nephropathy
Urine sodium	< 10 mmol/l	> 30 mmol/l	< 10 mmol/l	> 30 mmol/l
Urine-to-plasma creatinine ratio	> 30 : 1	< 20 : 1	> 30 : 1	< 20 : 1
Proteinuria	–	(+)	(+)	+/+++
Urine sediment	Normal	Casts, debris	Unremarkable	Variable
Ultrasound	Elevated resitive index	Elevated resitive index	Elevated resistive index	Elevated resistive index Reduced kidney size
History and course	Precipitating volume contraction	Volume contraction and/or nephrotoxic agents, septicemia	Advanced liver disease, usually tense ascites	Longstanding renal functional impairment
Effect of volume expansion	Return of renal function	–	–	–

Hepatorenal syndrome (HRS)

The term hepatorenal syndrome implies that the pathophysiology of this form of renal failure is different from other types of renal failure and more specific for the association with advanced liver disease. Extreme renal vasoconstriction is considered the most important characteristic of HRS [4, 5, 12, 18, 20, 21] (Fig. 1). It therefore resembles prerenal failure in that renal perfusion is markedly reduced, but more severely than in patients with acute oliguric renal failure who are not cirrhotic [22]. Moreover, HRS differs from prerenal azotemia in so far as renal hypoperfusion is not primarily due to a reduced blood supply to the kidneys but rather is attributable to intrarenal arterial and arteriolar vasoconstriction. A reduction in effective circulating volume and constriction of renal vessels, however, are two pathomechanisms (Table 2) that are not mutually exclusive, and diminished perfusion pressure probably plays a major role in inducing the increase in renal vascular resistance. Accordingly, there may be a gradual transition from circumstances in which renal function is dependent upon systemic hemodynamics (= prerenal failure) to a stage of predominantly renal vasoconstriction (= HRS), which is unresponsive to improvement in circulating blood volume [23] (Fig. 1, Table 3). It should be kept in mind, however, that these considerations are somewhat theoretical, since renal hemodynamics have not been determined in large patient series.

Although spontaneous recovery occurs only rarely [24], HRS is nevertheless a functional and principally reversible from of renal failure, as evidenced by its resolution when cadaveric kidneys from patients with HRS are transplanted into recipients with normal liver function [25] or, conversely, when liver transplantation is performed in patients with HRS [26–28]. Since no significant glomerular or tubular damage exists in HRS, significant proteinuria (> 500 mg/day) is usually absent and the urinary sediment is scanty (Table 3). As in prerenal failure, intact tubular function is reflected by a typically highly concentrated urine with a low sodium concentration (< 10 mmol/l). Nevertheless, using electron microscopy, some evidence of tubular damage can be demonstrated, even when urinary indices indicate functional renal failure [29]. Most investigators believe also that HRS can evolve into ATN [12, 21]. The most frequent setting is advanced alcoholic cirrhosis with ascites, but HRS is also associated with other causes of cirrhosis or severe acute hepatitis [11, 12, 18, 20, 21]. In many cirrhotic patients, HRS occurs after they enter hospital for one of several complications of severe liver disease. They may then experience a rapidly progressive reduction in GFR, often associated with oliguria, severe hyponatremia, and possibly also hyperkalemia. In others, the reduction in GFR may be more stable, with a moderate increase in serum creatinine and blood urea nitrogen persisting for weeks before progressive impairment of renal function occurs.

Despite much research the mechanisms underlying the renal vasoconstriction of HRS remain uncertain. Presumably, a variety of changes in vasoconstrictors and vasodilators in concert, rather than a single factor, are responsible for the proposed increase in renal vascular resistance. The many potential mediators that have been implicated in the pathogenesis of HRS include components of the renin-angiotensin system [6, 30], prostaglandins [31, 32], catecholamines [8, 33], endotoxin [34], and nitric oxide [35]. Recently, interest has focused on the role of endothelins (ETs) in HRS. These are peptides that are 21 amino acids long, which on a molar basis are the most potent vasoconstrictors so far identified and to which the renal vasculature is particularly sensitive. The first evidence of a potential role for ETs came from the observation that serum levels of ET-1 and ET-3 are elevated in patients with HRS – above those detectable in patients with other types of liver or kidney failure [36] and comparable to those causing a significant decrease in GFR in normal human vol-

Table 4 International Ascites Club's diagnostic criteria of hepatorenal syndrome [11]

Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
Low glomerular filtration rate, as indicated by a serum creatinine of > 1.5 mg/dl or a 24-h creatinine clearance < 40 ml/min.
Absence of shock, ongoinig bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss > 500 g/day for several days in patients with ascites without peripheral edema, or > 1000 g/day in patients with peripheral edema).
No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 l of isotonic saline.
Proteinuria < 500 mg/dl and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.
Additional criteria
Urine volume < 500 ml/day Urine sodium < 10 mEq/l Urine osmolality greater than plasma osmolality Urine red blood cells < 50 per high power field Serum sodium concentration < 130 mEq/l

unteers following infusion of ET [37]. More recently, preliminary evidence regarding the positive effect of treatment with an endothelin antagonist on renal blood flow and GFR was reported in three patients with HRS, suggesting a functional role for ETs in HRS [38].

Since the vasoconstrictors responsible for HRS are presumably at least in part produced within the kidney, the second important question besides the identity of these substances relates to the humoral and neural mechanisms inducing their generation. As maneuvers designed to lower portal venous pressure (see below) and lumbar sympathetic blockade can improve renal function in patients with HRS [39], hepatorenal reflex mechanisms seem to play an important role, but they remain poorly defined [9, 40].

Diagnosis of HRS

The pathophysiological mechanisms of HRS have not been entirely elucidated, the clinical criteria required to make the diagnosis also remain a matter of controversy, and distinguishing HRS from other types of kidney failure may be difficult [20]. Since renal hemodynamics are not routinely measurable, the diagnosis of HRS can only be made on indirect clinical rather than on precise pathophysiological grounds. The most recent definition of HRS was proposed by the International Ascites Club in 1996 (Table 4) [11] and suggests a more restrictive use of the term HRS as compared to a previous consensus statement that was formulated in Sassari in 1978 [41]. In particular, it is suggested that a diagnosis of HRS be entertained only when kidney function deteriorates in the absence of circulatory shock, ongoing bacterial infection, and recent treatment with nephrotoxic drugs, because under such conditions prerenal failure or classical acute renal failure (ATN) is more likely. It is also emphasized in this proposal that a prerenal component of renal failure should not only be excluded on the basis of clinical findings but that an active attempt to improve kidney function by increasing intravascular volume must fail before HRS can be diagnosed. By contrast, a low urinary sodium concentration is no longer considered a prerequisite (major criterion) for the diagnosis of HRS, which acknowledges that urinary sodium levels higher than 10 mmol/l have been reported in sporadic cases with otherwise well-documented HRS [42].

It is unlikely that this recent consensus statement will end the discussion about the appropriateness of using the term HRS, but it will hopefully contribute to a more standardized nomenclature, emphasizing in particular that the diagnosis of HRS is one of exclusion. The question remains, however, whether unresponsiveness to volume therapy always defines the presence of a separate nosological entity (HRS) or whether it may also indicate differences in the ability to improve renal hemodynamics by volume loading (see below).

Therapy of renal failure in liver disease

The best treatment of acute renal failure in liver disease is prevention with prompt attention to the contributory factors mentioned above. Moreover, although the causes for and types of kidney failure in liver disease are heterogeneous, no treatment options specific for these are yet available and therefore in all liver patients with manifest renal functional impairment the primary therapeutic goal must be to optimize renal blood supply and to minimize potential nephrotoxicity.

Intravascular volume expansion and supportive measures

Combined acute renal and hepatic failure usually requires management on intensive care or high dependency units, and initially should include the correction of any life-threatening abnormalities, such as hyperkalemia, hypoglycemia, severe acidosis, and coagulation disorders. Potential nephrotoxic drugs should be discontinued and in the absence of gross fluid overload the primary attempt to improve kidney function should include an interruption of diuretic therapy and judicious infusion of crystalloid or colloid solutions. However, although many patients directly respond to volume therapy by diuresis and a subsequent reduction in serum creatinine, the preexisting vasodilation of the entire hepatoportal vasculature frequently prevents a beneficial effect of volume loading on systemic and probably also renal hemodynamics. If diuresis does not improve, volume loading leads to further expansion of the extracellular volume, implying also the risk of respiratory failure. Monitoring of central venous, and in some patiens pulmonary artery occlusion pressures, may therefore be necessary. In fulminant hepatic failure, cerebral edema is the most common immediate cause of death and intracranial pressure monitoring should be considered in cases with advanced encephalopathy [43].

In view of the difficulties of improving renal hemodynamics by volume loading, strategies which aim to redistribute volume from the peritoneal cavity and the splanchnic vasculature toward the central vascular compartment rather than further expanding extracellular volume are particularly attractive. Although neck-out water immersion has been shown to be effective in this respect [44], the critical condition of the patients and the need for close medical monitoring render this approach unrealistic in most instances of simultaneous liver and kidney failure.

The use of vasopressin derivatives, such as ornipressin [45] and octapressin [46], which have little antidiuretic activity and lead to selective splanchnic vasoconstriction without causing renal vasoconstriction, has been suggested to reverse the maldistribution of blood volume and improve renal function. However, despite promising results reported by some investigators [45], this approach has not been generally adopted and others have not been able to confirm the beneficial effects on renal blood flow and GFR [47]. More recently, it was suggested that the combined administration of ornipressin plus plasma volume expansion with albumin improves renal function and normalizes hemodynamic changes in cirrhotic patients with HRS [48].

If oliguria persists after volume depletion has been corrected or excluded, vasoactive agents, such as dopamine with or without the addition of a loop diuretic, may also be justified in an attempt to improve diuresis and renal function, but controlled data about the efficacy of these drugs under these conditions are lacking [49].

Renal replacement therapy

When renal failure is severe or progressive and measures to improve renal function have been unsuccessful, consideration must be given to renal replacement therapy. The decision to commence dialysis or hemofiltration has to take into account that (i) in chronic liver disease, although not necessarily in fulminant acute hepatic failure, the occurrence of renal failure is usually a measure of the severity of liver damage (ii) in most cases recovery depends on the outcome of liver disease, and (iii) the outcome of HRS is usually fatal if liver function does not improve and transplantation is impossible. Therefore, if there is no realistic possibility of hepatic regeneration and a patient is not a candidate for liver transplantation, withholding renal replacement therapy in patients with HRS may be justified [12, 18, 21, 50, 51]. However, due to the inherent difficulties in making this diagnosis (see above) and to the possibility that using peritoneovenous or portosystemic shunts may, at least in selected cases, improve renal function (see below), a very careful evaluation and consideration of these options is mandatory before such a decision is made.

The most appropriate time to start renal replacement in patients in whom aggressive management is warranted and whether this therapy should be diffusive, convective, or both, has not been defined, but this holds true also for other instances of acute renal failure. Ultimate indications for commencing dialysis or hemofiltration include uncontrollable hyperkalemia, pulmonary edema, severe acidosis, and symptomatic uremia. However, if residual function is poor or absent, the development of these complications should not be awaited. The main procedures available for renal replacement therapy are intermittent hemodialysis, intermittent hemofiltration, continuous hemofiltration, and continuous hemodiafiltration. An intermittent technique with more rapid solute removal may be necessary for the initiation of therapy in cases of severe hyperkalemia or acidosis. On the other hand, in cases of severe and longstanding hyponatremia, rapid correction must be avoided given the risk of pontine and extrapontine myelinolysis [52]. Usually, continuous techniques are preferred for maintenance therapy, since they are associated with greater cardiovascular stability and allow a continuous and gradual fluid removal, which can be adapted to actual needs and the infusion volume required for drug therapy and nutritional support [53–55]. Importantly, in patients with combined acute renal and fulminant hepatic failure, continuous modes of renal replacement have also been shown to result in superior stability of intra-

cranial pressure [56]. Although replacement fluids for hemofiltration are usually lactate-buffered, bicarbonate-buffered solutions are available for patients with liver disease, in whom lactate metabolism is impaired. Combining diffusion and convection in hemodiafiltration can be more effective than continuous hemofiltration alone, but the latter also frequently provides sufficient clearance. Recent studies have initiated an intense debate about the biocompatibility of the membranes to be used in the treatment of acute renal failure in general [57, 58], and although the issue is not settled, it is probably advisable to use membranes which minimize blood-membrane interactions. Maintaining adequate anticoagulation to allow effective hemodialysis or hemofiltration may be difficult without significantly increasing the risk of bleeding. Standard unfractionated heparin remains the anticoagulant of choice in patients without significant risk factors for hemorrhage. Supplemental antithrombin III can decrease heparin requirement and platelet consumption. In patients with recent overt hemorrhage, alternative anticoagulation strategies have been proposed, including the use of low-molecular-weight heparin [59], "regional" heparinization whereby blood returning from the machine to the patient is infused with protamine sulfate and the use of prostacyclin [60]. Prostacyclin was shown to be superior to both unfractionated and low-molecular-weight heparin in reducing the number of bleeding episodes [61], but the efficacy and safety certainly also depend on individual experience in particular units.

Shunting procedures

A second category of treatment options in patients unresponsive to volume therapy implies the insertion of peritoneovenous or portosystemic shunts. These techniques, which were primarily developed for treatment of portal hypertension and refractory ascites, may improve renal function through both an increment in effective circulating volume and a reduction in portal venous pressure. Paracentesis alone, however, can, at most, transiently improve renal function [62]. Moreover, relieving the pressure on renal veins does not lead to a sustained improvement in renal function.

Peritoneovenous shunts

Following the introduction of the peritoneovenous (PV) shunt for the management of tense ascites by LeVeen and associates in 1974 [63], this technique has subsequently also been advocated as therapy for HRS [64]. However, despite widespread use of PV shunts for years, few reports exist of the reversal of well-documented HRS following shunt insertion (reviewed in Epstein [65]). Moreover, although PV shunts may improve and stabilize renal function in some patients [66, 67], they have so far not been shown to prolong survival significantly in patients with combined kidney and liver failure. In cirrhotic ascites in general, operative mortality rates up to 25 % have been reported, largely due to hepatic decompensation, disseminated intravascular coagulation, or septicemia [68, 69]. In view of these risks, the unproven benefit, and a high incidence of shunt occlusion [70], PV shunting cannot generally be recommended for treatment of renal failure.

Transjugular intrahepatic portosystemic shunt

Surgical side-to-side portacaval anastomosis provides another option in the treatment of refractory ascites, which can also improve renal function [67, 71]. However, a high perioperative mortality, the development of postoperative encephalopathy, and the compromise of subsequent liver transplant surgery limits the utility of this procedure [72] and has prompted the development of less invasive transjugular intrahepatic portosystemic shunts (TIPS) [73]. TIPS can be applied under conscious sedation through percutaneous puncture, usually of the right internal jugular vein. Following transhepatic cannulation of a branch of the portal venous system, a guidewire is introduced and manipulated into the main portal vein and, following subsequent dilatation of the tract between hepatic and portal veins, an expandable metallic stent is then deployed across this connection. Since 1990, when the first TIPS were implanted, this technique has generally been shown to be effective in most cases of refractory ascites, although many questions about the indication and mechanisms of response still remain unanswered. An interesting finding has been the progressive natriuresis seen in some patients after TIPS [74], and improvements in renal function after implanting TIPS have been documented in a number of case reports [75–77]. Further, in a series of 16 patients, diagnosed as having HRS according to the above-mentioned criteria [11], the majority (81 %) showed a rapid and sustained improvement of renal function with a fall in serum urea and creatinine, a doubling in creatinine clearance, and markedly increased natriuresis [78]. These observations suggest that TIPS may be a useful treatment option in otherwise uncorrectable renal failure, and more studies are urgently needed to evaluate this. Potential beneficial effects on renal function also have to be balanced against an increased risk for progressive hepatic encephalopathy.

Renal failure and liver transplantation

In many patients with endstage liver disease and accompanying renal failure, orthotopic liver transplantation remains the only long-term treatment option. Due to improvements in surgical techniques, immunosuppression, and increased practical experience, liver transplantation has been increasingly successful in recent years. Although improvement of renal function and the reversal HRS has been well documented [26–28], the impact of liver transplantation on kidney function is complex. The surgical procedure may at least temporarily impair renal function and the major immunosuppressives used (cyclosporine and tacrolimus) adversely affect renal function with a 30–50 % decline in GFR. Some centers therefore advocate a careful assessment of renal function prior to liver transplantation, using techniques more accurate than creatinine clearance (e. g., inulin clearance) to identify patients who may benefit from modification of the immunosuppressive protocol.

Not surprisingly, attempts to correlate posttransplant renal dysfunction with the preoperative course have demonstrated an increased association of renal impairment with preexisting renal failure [79]. However, out of a series of 59 liver transplant recipients with HRS, only 7 % were reported to require subsequent renal transplantation or continuation of dialysis for nonreturn of renal function [27]. In this study, 5-year patient survival was significantly lower in patients with pretransplant HRS than in patients without (60 vs 68 %), but this difference is certainly not of a magnitude that should influence the indication for transplantation. These data also imply that combined liver and kidney transplantation is not indicated in patiens with HRS or acute tubular necrosis and should be restricted to patients with well-documented renoparenchymal disease (reviewed in Gonwa and Wilkinson [80]).

Summary and conclusions

Progressive renal failure in cirrhosis and fulminant liver disease remains an adverse prognostic factor. Irrespective of the type of renal functional impairment which ranges form "prerenal failure" to "hepatorenal syndrome" and "acute tubular necrosis", renal hypoperfusion, as a consequence of either reduced perfusion pressure or increased renal vascular resistance, is an important pathomechanism. Awareness of the risk of renal failure and avoidance of nephrotoxic agents and of brisk reductions in effective circulating volume are important for prevention. Plasma volume expansion, on the other hand, is mandatory in trying to reverse incipient renal functional impairment. Pharmacological attempts to improve renal hemodynamics by lowering renal and increasing extrarenal vascular resistance have so far largely been disappointing. However, increasing knowledge about mediators and synthesis of specific agonists and antagonists, such as those against endothelin or antidiuretic hormone, may add promising treatment options in the near future. TIPS is another therapeutic tool of potential interest in the management of renal failure in liver disease which needs further evaluation. Renal replacement therapy, preferentially in the form of continuous procedures, may be life-saving in those patients awaiting liver transplantation or spontaneous recovery of their hepatic function.

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