Symptoms and Syndromes

17 Hepatorenal syndrome

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► ***Coexistence of liver and kidney disease is a frequent clinical event.*** • Reports in the literature date back more than 100 years (F. Th. Frerichs, 1861; K. W. H. Nothnagel, 1874; P. J. Moebius, 1877; A. Weil, 1886). • In 1863 A. Flint noted the coexistence of cirrhosis with ascites and oliguria, although autopsy revealed the kidneys to be normal. • In animal experiments, M. Pawlow (1893) was able to show the occurrence of albuminuria after placement of a portacaval anastomosis. Jaundice mainly developed parallel to renal damage. Richardière (1890) coined the term "hépatonéphrite" to describe this clinical picture. (44) • In 1911 both P. Clairmont et al. and F. Steinthal reported for the first time on renal failure with fatal outcome following surgery on the bile ducts for obstructive jaundice. This renal failure in biliary obstruction was described by F. C. Helwig et al. in 1932 as *"liver-kidney syndrome"*. (25) • However, the coexistence of cirrhosis and the hepatorenal syndrome was first published by R. Hecker et al. in 1956. (24)

The term **"hepatorenal syndrome"** was introduced by P. Merklen in 1916 and taken up by W. Nonnenbruch in 1939. (39) The following description is still largely accepted today: *"A combination of anatomically defined liver disease with a sometimes severe restriction in the function of the kidneys, which display few, if any, morphological changes. Liver disease can be the outcome of hepatocellular damage of any type, i. e. it may be toxic or infectious and originate from cirrhosis or cancer."*

1 Definition

The hepatorenal syndrome (HRS) is a functional, oliguric, progressive and in principle reversible circulation-related kidney failure occurring in severe liver disease and portal hypertension as well as increasing liver insufficiency or in the setting of acute liver failure − assuming there are indeed no other causes of the renal insufficiency.

► This syndrome is, in fact, a prerenal kidney failure − *yet without response to an adjustment of the effective plasma volume,* i. e. expansion of the intravasal volume does not influence the renal function. • This functional renal failure is due to extreme intrarenal vasoconstriction and reduced perfusion in the area of the renal cortex, whereby the blood supply to the medullary parts of the kidney is largely normal. The extrarenal circulation is undisturbed (arterial vascular resistance and vascular filling as well as cardiac output are normal). • In cases of cirrhosis, systemic vasodilation becomes increasingly prevalent, together with hyperdynamic circulatory disturbance. • In clinical terms, the ultimate outcome is a reduced glomerular filtration rate, pronounced sodium and water retention with oliguria and excretion of practically sodium-free urine − without or with only slight (< 500 mg/dl) proteinuria.

2 Pathogenesis

The frequent **coexistence** of the *hepatorenal syndrome*, *ascites* and/or *hepatic encephalopathy* suggests that similar pathogenetic mechanisms are responsible for these three intricate developments in liver cirrhosis.

2.1 Biochemical factors

The numerous biochemical substances that may be considered regarding hepatic encephalopathy or ascites have been outlined in detail. (s. tabs. 15.2; 16.5) • Similarly, an extensive synopsis of pathogenetically effective biochemical factors can also be drawn up for HRS. All of them ultimately interfere − directly or indirectly − with the renal retention of sodium (= ascites) and water retention (= hyponatraemia) as well as the balance between vasodilation and vasoconstriction. RAAS and SNS are markedly activated; secretion of ADH is increased. (5, 26, 30, 36, 56, 58) (s. tab. 17.1) • Vasodilative factors under discussion include bilirubin, bile acids, nitric oxide (NO), false neurotransmitters, calcitonin peptide (23) and platelet-activating factor (PAF). In more recent studies, far higher plasma values of the vasoconstrictor leukotrienes (C4 and D4) (37) and endothelin 1 and 3 (36) were detected.

Biochemical factors	Liver	Plasma	Kidneys/Urine
Aldosterone breakdown	↓		
Angiotensin II breakdown	↓		
Angiotensinogen synthesis	↓		
Endotoxin breakdown	↓		
Kininogen synthesis	↓		
Renin breakdown	↓		
Vasopressin breakdown	↓		
Aldosterone		↑	
Angiotensin II		↑	
Antidiuretic hormone (ADH)		↑	
Calcitonin peptide (23)		↑	
Endothelin 2 and 3 (36)		↑	
Endotoxin		↑	
Leukotriene C_4 and D_4 (37)		↑	
Noradrenaline		↑	
Renin (56)		↑	
Vasopressin		↑	
Atrial natriuretic factor (ANF)		↓	
Bradykinin (56)		↓	
Kallikrein		↓	
Aldosterone			↑
Angiotensin II			↑
Bradykinin			↑
Endothelin			↑
Leukotriene E_4			↑
Prostacyclin			↑
Prostaglandin E_2 (58)			↑
Renin			↑
Thromboxane A_2 (58)			↑

Tab. 17.1: Synopsis of the activity of biochemical factors in the liver, plasma and kidneys or urine relating to the hepatorenal syndrome (with some references)

2.2 Haemodynamic factors

The hepatorenal syndrome is characterized by pronounced vasoconstriction of the renal cortex with tortuosity and narrowing of the interlobular and arcuate arteries. The blood supply to the renal cortex may be almost totally interrupted; at the same time, the blood flow is diverted into areas containing cortical vessels near the medulla. The renal medulla is, however, supplied with blood in a regular way, thus allowing the nephrons to function normally. The insufficient blood supply to the renal cortex is aggravated by intrarenal arteriovenous shunts, leading to rapid changes in haemodynamics. This instability in renal perfusion is possibly due to reduced synthesis of angiotensinogen in the liver. Disturbances in the renal blood supply can proceed continuously through the non-azotaemic and azotaemic stages to the oliguric final phase. • The **functional nature** of renal vasoconstriction was also shown by the fact that the ischaemia of the renal cortex, which had been ascertained by selective angiography in vivo, was not evident in the postmortem evaluation of the kidney. Indeed, the cortical vascular network had fully regained its normal structure. • Increased levels of *neuropeptide Y* were found in HRS. This is related to circulatory dysfunction as well as to stimulation of the sympathetic nervous system (SNS) and may contribute to renal vasoconstriction. • *The pathogenesis of renal vasoconstriction is thus multifactorial.* (5, 26, 30, 46, 48, 49)

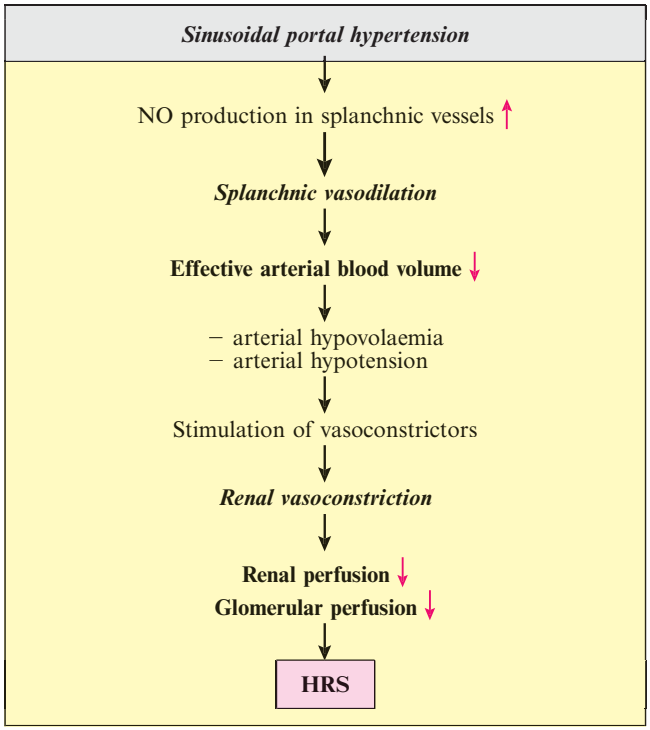

Fig. 17.1: Hypothetic pathogenesis of the hepatorenal syndrome in cirrhosis

3 Clinical aspects

In liver cirrhosis, the hepatorenal syndrome is nearly always (> 80%) accompanied by ascites. HRS is most common in alcoholic cirrhosis. In some 75% of cases, hepatic encephalopathy is found at the same time, and jaundice is evident in about 40% of cases. HRS occurred in 18% of all cirrhotic patients with ascites within one year and in 32% within five years. (20, 47)

Histological findings are minimal in HRS. No constant or specific changes are known. In most cases, histology is either completely normal, or only minor degenerative changes of the tubuli and glomeruli are present. • Nevertheless, with a severe and protracted course of disease, the occurrence of acute tubular necroses can become more pronounced, resulting in end-stage renal failure.

3.1 Risks and predictive factors

Many risk situations trigger HRS, and various predictive factors make it possible to ascertain the development of HRS in non-azotaemic patients with cirrhosis and ascites. Often the cause is not directly recognizable (e. g. undisclosed alcohol abuse, environmental noxae). Typical liver function parameters do not help to anticipate the development of HRS. (11, 18, 49, 55) (s. tab. 17.2)

Risk factors
Alcohol abuse
Cholestasis
Electrolyte imbalance
Excessive diuresis
Gastrointestinal bleeding
Increased intra-abdominal pressure (tense ascites!)
Inexpert paracentesis
Infections
Nephrotoxic drugs
Nonsteroidal antirheumatics
Poor nutritional status
Previous episodes of ascites
Spontaneous bacterial peritonitis
Surgical therapy
Predictive factors
Creatinine ↗
Glomerular filtration ↘
Natriuresis ↘
Plasma osmolality ↘
Potassium ↘, (↗)
Renin activity ↗
Urea ↗
Urine osmolality ↗

Tab. 17.2: Risk and predictive factors in patients with cirrhosis and ascites regarding the development of HRS

3.2 Courses of disease

There are **three ways** in which the hepatorenal syndrome can become manifest:

1. **Type I (acute HRS):** rapid elevation of creatinine (> 2.5 mg/dl), reduction of 24-hour creatinine clearance (< 20 ml/min), oliguria (< 500 ml/day) and natriuria (< 10 mmol/l) as well as jaundice, hypoprothrombinaemia,

hypalbuminaemia and encephalopathy − but no proteinuria. • All courses of disease which do not correspond to type I are assigned to one of the other two types;

2. **Type II (chronic HRS):** slow course of this complicated condition, renal function is more stable, reduction of 24-hour creatinine clearance (<40 ml/min). This (most frequent) form is often long-standing, although only slightly increased creatinine values in the serum (>1.5 mg/dl) and natriuria (<20 mmol/l) are clinically detectable. Type II is frequently accompanied by a diuretic-resistent ascites;

3. **Acutely exacerbated chronic HRS.**

3.3 Diagnosis

Subjective factors suggestive of HRS are unknown or uncharacteristic. The clinical picture is influenced by the underlying liver disease. (s. tab. 17.3)

1. Liver cirrhosis, especially in
   - − alcoholic cirrhosis
   - − ascites and diuretic therapy
   - − hepatic encephalopathy
   - − oesophagogastrointestinal bleeding
2. Acute liver failure
3. Acute viral hepatitis (31, 40)
4. Primary liver cell carcinoma (34)
5. Liver metastases (45)
6. Hemihepatectomy
7. Acute fatty liver of pregnancy

Tab. 17.3: Severe liver diseases with the occurrence of a hepatorenal syndrome (with some references)

Oliguria: The diagnosis is initially based on the principal symptom of oliguria (urine volume <500 ml/day). When setting up a differential diagnosis, the classification of oliguria is facilitated by a *probationary volume replenishment* (1500 ml of 0.9% NaCl solution or 5% human albumin). A clear improvement in or normalization of urine excretion achieved in this way is evidence *against* the hepatorenal syndrome and *in favour of* prerenal kidney failure. (s. tab. 17.4)

Azotaemia: This condition develops progressively with increasing creatinine and urea, pointing to a drop in the glomerular filtration rate (GFR) and renal blood flow. The quotient of creatinine in the urine and plasma is high (>40) and that of urea-N in the urine and plasma is elevated (>8). There is a reduction in creatinine clearance within 24 hours to <40 ml/min. The serum value of urea displays a disproportionate increase (urea-N/creatinine ratio >20), since the tubular reabsorptive capacity with respect to urea depends on diuresis (maximum 2 ml/min). In the hepatorenal syndrome, the minimal urinary flow gives rise to a longer tubular period of contact with greater tubular reabsorption of urea.

Criteria	Hepatorenal syndrome	Acute kidney failure	Prerenal kidney insufficiency
Specific weight	>1,030	1,020	>1,030
Oliguria (<500 ml/day)	+	+	+
Azotaemia	+	+	+
$Urine_{osm}$ (mosm/kg)	> 500	< 350	> 500
$Urine_{Na}$ (mmol/l)	< 10	> 30	< 20
$Urine_{osm}/P_{osm}$	> 1.3	< 1.1	> 1.3
$Urine_{urea}/P_{urea}$	> 8	< 3	> 8
$Urine_{creat.}/P_{creat.}$	> 30	< 20	< 30
Fe_{Na} (%)	< 1	> 1.5	< 1

Tab. 17.4: Urine findings for the differential diagnostic definition of the hepatorenal syndrome − provided that there has been no previous diuretic therapy. • Generally, however, this has proved necessary, which could be a reason for the considerable differences in the factors and figures reported in the literature

Urine: In general, the sediment in the urine is normal. Proteinuria or erythrocyturia are not characteristic of the hepatorenal syndrome. • The *excretion of sodium* in the urine is lower than 10 mmol/day, with a fractional excretion of sodium of <1%. For this reason, there is increased renal retention of water. • *Urine osmolality* is greater than plasma osmolality, which results in a quotient of >1.3. With increasing severity of the hepatorenal syndrome and transition of the penultimate phase, the urine becomes iso-osmotic with an osmolality quotient of 1 or <1. (18, 38, 48, 49, 55) (s. tab. 17.4)

Hyponatraemia: *Reduced free water clearance* is characteristic. It is the cause of hyponatraemia (serum sodium <130 mmol/l), which is often in evidence − this can be precipitated by an increased intake of free water (elevated sodium level in the presence of excessive water). This dilutional hyponatraemia is a sign of a reduced serum osmolality (<280 mosm/kg). (4)

Gastrin: In liver cirrhosis, elevated gastrin values in the serum, due to restricted excretion of gastrin in the urine and/or reduced gastrin inactivation in the liver, are suggestive of the hepatorenal syndrome.

Resistance index: A rise in the resistance index of the kidneys and a reduction in renal perfusion as shown by *Doppler sonography* provide an early diagnosis before renal dysfunction is clinically evident. (42) • *Colour-encoded sonography* has proved useful in determining renal haemodynamics (which deteriorates when the patient is in an upright position).

3.4 Differential diagnosis

The diagnosis of the hepatorenal syndrome calls for the exclusion of prerenal, renal or postrenal kidney insufficiency. (s. tabs. 17.4, 17.6) • *The presence of disease in the liver and kidney in the sense of a pseudohepatorenal syndrome must also be ruled out.* (s. tab. 17.5)

3.4.1 Pseudohepatorenal syndrome

Numerous diseases can impair both liver and kidneys at the same time. Each individual case reflects different levels of damage and severity, the liver and kidneys being affected to varying degrees. The prognosis is determined by this wide scope of variability. Simultaneously occurring diseases of the liver and kidneys are subsumed under the term **pseudohepatorenal syndrome** (H.O. Conn, 1973). (s. tab. 17.5)

1. **Circulatory disorders**
   - Cardiac insufficiency
   - Shock
2. **Congenital malformations**
   - Congenital liver fibrosis
   - Cystic liver and cystic kidney
3. **Experimental**
   - Choline deficiency

   etc.
4. **Infections**
   - Legionnaire's disease
   - Leptospirosis
   - Malaria
   - Sepsis
   - Viral hepatitis
   - Yellow fever
5. **Intoxications**
   - Burns
   - Chemicals
     - carbon tetrachloride
     - chrome, lead, arsenic, mercury
     - copper sulphate
     - trichloroethylene, methanol
   - Endotoxins
   - Hyperthermia
   - Mycotoxins
   - Snake venoms
   - Waterhouse-Friderichsen syndrome
6. **Medicaments**
   - Halothane
   - Iproniazid
   - Methoxyflurane
   - Paracetamol
   - Sulphonamide
   - Tetracycline
7. **Metabolic diseases**
   - Acute intermittent porphyria
   - Amyloidosis
   - Diabetes mellitus
   - Eclampsia
   - Glycogenosis I
   - Haemochromatosis
   - Reye's syndrome
   - Sickle-cell anaemia
   - Tyrosinaemia, oxalosis
   - Wilson's disease
8. **Systemic diseases**
   - Lupus erythematosus
   - Periarteritis nodosa
   - Rheumatoid arthritis
   - Sarcoidosis
9. **Tumours**
   - Hypernephroma
   - Metastases

Tab. 17.5: Coexistent disease of the liver and kidneys (comorbidity), so-called pseudohepatorenal syndrome (H.O. Conn, 1973)

3.4.2 Prerenal kidney insufficiency

Dehydration with diminished volume (bleeding, large water losses, diuretic therapy, paracentesis, intravasal volume shifting) can lead to prerenal azotaemia. Typically, renal function normalizes again when fluid intake is increased, *i.e. in contrast to the hepatorenal syndrome, the intravasal volume can be influenced by therapy.*

3.4.3 Primary kidney diseases

Initially, it is important to rule out primary kidney diseases, including all glomerular, interstitial and vascular forms, as well as acute tubular necrosis resulting, for example, from nephrotoxins, sepsis, hypoxia or shock. In severe or protracted kidney disease, various chemical findings can point to liver involvement (as suggested by a rise in GPT, GOT, GDH and AP or by impaired liver function). These pathological laboratory parameters are also reflected in cellular or canalicular forms of impairment. The treatment of primary kidney diseases (e.g. with immunosuppressives, cyclosporin) may give rise to liver damage, which can be ascertained morphologically and in laboratory investigations.

3.4.4 Secondary kidney diseases

In various diseases of the liver and biliary ducts, with or without jaundice, a wide range of secondary kidney diseases can occur. They differ greatly in their degree of severity and their prognosis and can cause considerable **difficulties** in the drawing up of a **differential diagnosis.** (49) (s. tab. 17.6)

Glomerular kidney diseases
1. Impaired renal function with acute viral hepatitis 2. Immune complex nephritis with chronic HBV and HCV infection 3. Glomerulosclerosis with cirrhosis – mesangial form – IgA nephropathy – membranous proliferative form
Tubular kidney diseases
1. Renal tubular acidosis – distal form (type I) – distal and proximal form (type II) 2. Acute tubular necrosis (acute kidney failure) 3. Biliary nephrosis

Tab. 17.6: Forms of secondary kidney damage in the course of hepatobiliary diseases

Mild renal dysfunction in the form of clinically non-significant proteinuria and erythrocyturia in acute viral hepatitis subsides once the acute viral hepatitis has been cured. Occasionally, serum creatinine levels may be slightly raised. Histologically, small deposits of immune complexes can be found in the glomeruli.

Immune complex nephritis is generally caused by the deposition of circulating immune complexes in the glomeruli, mostly in chronic viral hepatitis B and C (men are affected four times as often as women). Proteinuria and haematuria are in evidence, together with the retention of substances usually eliminated in the urine. A nephrotic syndrome possibly leading to renal insufficiency with hypertension may develop. Treatment of this perimembranous glomerulonephritis with interferon alpha has proved beneficial.

Glomerulosclerosis can be shown histologically in some 50−95% of patients with liver cirrhosis. The course of glomerulosclerosis may take *three different forms:* (*1.*) mesangial form with thickening of the mesangial matrix and basal membrane of the capillaries, (*2.*) glomerulosclerosis with glomerular deposition mainly of IgA (= IgA nephropathy), and (*3.*) membranous proliferous form with obvious cellular proliferation and additional glomerular deposition of IgA. As a rule, proteinuria and erythrocyturia are only minimal. Up to now, treatment has not been possible − and is usually not required. (s. tab. 17.6)

Renal tubular acidosis in liver cirrhosis is due to an inadequate concentration of sodium ions on the distal tubuli (type I). As a result, the secretion of hydrogen ions is reduced. This is attributed to cellular immune processes as well as to toxic effects such as copper or bile acids. (s. tab. 17.6)

Acute tubular necrosis can occur in the course of a hepatobiliary disease. In an aetiopathogenetical context, hypoxia, hypotension, nephrotoxins and so far undefined biochemical substances are deemed responsible. The outcome is a disruption in the reabsorption of sodium and water; the urine is less concentrated (isosthenuria). There is a greater excretion of sodium (>30 mEq/l) and of beta-2 microglobulin in the urine. Acute, yet in principle reversible renal failure can develop. Therapy thus consists of bridging the phase of insufficiency temporarily by dialysis.

Biliary nephrosis in its acute form reveals swellings of the tubular cells and bilirubin renal casts under histological investigation. This is due to elevated concentrations of bilirubin and bile acids in the serum. The kidneys show a marked sensitivity to oxygen deficiency, with the danger of acute kidney failure. That explains the relatively frequent occurrence of renal insufficiency in diseases of the extrahepatic bile ducts, in obstructive jaundice or following bile duct surgery. (s. tab. 17.6)

Hepatorenal syndrome: After exclusion of these differential diagnostic possibilities in liver diseases with renal symptoms, the likely diagnosis is hepatorenal syndrome. In the case of a severe and protracted course, this functional impairment of the kidneys can progress to true, acute renal failure, even with tubular necrosis.

3.5 Prognosis

The prognosis of HRS, especially type 1, is poor with a **lethality rate** of 87−98%. The survival time amounts to 1.7−2.6 weeks. (19) Death results from acute renal failure or complications of cirrhosis, such as gastrointestinal bleeding or hepatic coma. Patients with HRS type II have a better prognosis (6−12 months). Spontaneous **reversibility** of the hepatorenal syndrome has been demonstrated following a decisive improvement in liver function − yet it can only be rarely expected (in 3−5% or 2−13% of cases). With the spontaneous regression of portal ascites, the impaired renal function is generally improved. Liver transplantation likewise led to a normalization of renal function (12, 28) − just as the kidneys of a patient with hepatorenal syndrome functioned normally again following transplantation into a patient with a healthy liver (M. H. Koppel et al., 1969). (5, 6, 11, 18, 19, 20, 39, 47, 55)

4 Prophylaxis and therapy

Prophylactic measures with regard to the hepatorenal syndrome are of decisive and vital importance. It must be borne in mind that the *water balance is extremely sensitive in cirrhotic patients.* The cause can almost always be found in an enormous iatrogenic intervention in the volumetric balance (aggressive diuresis, imbalance in the tapping of ascitic fluid, excessive restriction of fluid). For this reason, it is important to avoid all substances which could worsen renal function (e.g. nonsteroidal antirheumatics, aminoglycoside antibiotics) and all measures which could lead to a reduction in the effective plasma volume. Furthermore, care should be taken to apply the principles of prophylaxis and therapy for hepatic encephalopathy (s. p. 285) and ascites (s. p. 310). Spontaneous bacterial peritonitis should be treated at an early stage. (s. p. 309) • The most significant prophylaxis and therapy target is to decrease the tonus in the efferent vessel of the glomerule.

4.1 Maintaining homoeostasis

The *electrolyte balance* and *acid-base balance* should be restored in careful coordination with the renal function. In **hyponatraemia,** either the fluid intake should be reduced to 700−1,000 ml/day or a combination of a hypertonic salt solution (3%) and a loop diuretic should be administered intravenously. (s. p. 314) Likewise, an attempt can be made using a combination of diuretics and urea diuresis. Generally, sodium and water intake should be restricted. It is imperative to achieve an even volumetric balance, possibly supported by the cautious intake of fluid.

4.2 Improvement of liver function

To date, there is no effective therapy for the hepatorenal syndrome. Therapeutic possibilities are very limited due to the loss of function of two vital organs, liver and kidneys. The ideal goal would be to improve liver function, since clear improvement in the condition of the diseased liver has always preceded the reversibility of the hepatorenal syndrome. • Even if there is only a slight chance of improving liver function, certain biochemically justifiable and pharmacologically plausible procedures can indeed be implemented in serious cases of disease: (*1.*) *optimal nutrition*, (*2.*) *substitution measures* (e. g. multivitamins, trace elements, branched-chain amino acids, essential phospholipids), and (*3.*) *supportive therapy programme* (reducing endotoxinaemia by means of lactulose, influencing the synthesis of urea by means of ornithine aspartate, etc.). (5, 7, 9, 48, 57)

4.3 Conservative treatment

The overriding aim of therapy is to increase renal blood flow. This can be achieved either indirectly through

splanchnic vasoconstriction or directly by encouraging renal vasodilation. Hereby, certain problems arise concerning substances which spill over into the splanchnic circulation, causing splanchnic vasoconstriction and at the same time exacerbating the renal vasoconstriction already present. (5−7, 10, 18, 20, 30, 38, 47, 55, 57)

Many investigations have focused on the efficacy of conservative treatment for improving both systemic and renal haemodynamics or for suppressing the activated hormone systems. • The complexity of the pathogenesis of the hepatorenal syndrome, which varies in each individual case, explains the differences in impact of the substances used. For this reason, there are pathogenetic grounds for the simultaneous application of the pharmacological possibilities mentioned.

Optimal **fluid management** is necessary. Fluid overload must be avoided. Measurement of the central venous pressure is important.

Attempts at treatment through **"head-out" water immersion** (M. Epstein et al., 1976) can be deemed relatively effective and, above all, low in risk, provided such a measure is feasible with a seriously ill patient. This simple method increases the central blood volume (= redirecting extracellular fluid to the vascular system). There is a significant rise in the volume of the urine and in natriuresis − although one must also reckon with a number of non-responders when applying this method.

A **lumbar blockade** of the sympathetic nervous system is a methodologically simple procedure, practically free from complications, which has proved to be effective in individual cases. (53)

Intravenous application of sodium-free **albumin** and/or 10% **mannitol** can be successful, possibly with the additional administration of low-dose *diuretics* (such as xipamide, torasemide), whereby due attention should be paid to renal function. Diuretics or aldosterone antagonists may only be used if the indication is precise and all risks have been considered.

Thought can be given to i.v. application of low-dosed **dopamine** (100 mg/12 hr or < 5 µg/kg BW/hr). This vasodilator was able to improve the angiographic appearance of the renal cortical vasculature and the cortical blood flow. No change was seen in GFR or urine output. Dopamine alone cannot be recommended. (quot. 6, 21, 38)

Ornipressin is a vasopressin analogue that primarily leads to vasoconstriction of the splanchnic vasculature. The first report outlining its use was compiled in 1985 by K. Lenz et al. (33) Dosage was 25 IU/12 hr or 6 IU/4 hr. The outcome was a fall in renal vascular resistance and an improvement in the glomerular filtration rate. (21; quot. 6, 10, 38) • The combined administration of *ornipressin* (2−6 IU/hr) and *albumin* (20−60 g/day) for a period of two weeks (with intensive care monitoring!) has led to remarkable therapeutic success. (22)

Terlipressin (2 mg/day, multiple doses) was likewise successfully administered over a temporary period. No side effects were reported. Terlipressin produced an improvement of renal function in 70−75% of cases and an increased survival in patients with type 1 HRS. (2, 11, 38, 52) • *Terlipressin* (0.5−2.0 mg/4 hr, i.v.) plus *albumin* (20−40 g/day) (18, 54) or plus *hydroxyethyl starch* (500 ml/day) appears to be an effective form of treatment for HRS. (15)

The combined application of **midodrine** and **octreotide** (i.e. an α-adrenergic agonist as a vasoconstrictor plus a substance inhibiting the release of endogenous vasodilators such as glucagon) led to an improvement in both GFR and natriuresis. (3)

Therapeutic attempts using **angiotensin II / noradrenalin** (first described by R. Ames et al. in 1965) or ACE inhibitors, sympathicomimetic agents and α- as well as β-receptor blockers yielded no (or only brief) success. • The combined i.v. application of noradrenalin (0.5−3.0 mg/day) plus albumin and furosemide shows a remarkable improvement in type 1 HRS. (13)

A therapeutic effect has been achieved by administering **N-acetylcysteine** (150 mg/kg BW for 2 hours and subsequently 100 mg/kg BW for 5 days). (27)

Likewise, reports have been published on the positive effect of **misoprostol,** a synthetic prostaglandin$_{E1}$, after oral administration (4 × 0.4 mg/day) (16) or with intra-arterial application.

A few isolated reports are available on the elimination of renal vasoconstriction, particularly using **ANP** (atrial natriuretic peptide) with its pronounced diuretic and natriuretic effects.

Treatment with **branched-chain amino acids** led to a reduction in azotaemia and creatinine as well as an increase in natriuresis. (9)

4.4 Invasive therapy

The infaust prognosis of the hepatorenal syndrome and the short space of time preceding its fatal outcome not only call for the swift and concurrent use of multiple conservative measures, but also make invasive therapy worth considering. Here, too, any decision with regard to therapy must initially focus on the clinical difficulties relating to the respective underlying disease.

Haemodialysis may be indicated after the condition has passed from functional renal failure to true renal insufficiency. Discussion should also centre on dialysis as a possible way to bridge the phase of renal insufficiency

or to gain time for the liver function to improve and allow the hepatorenal syndrome to become reversible. (29) • **Peritoneal dialysis** achieved temporary success in treating azotaemia and hyponatraemia, but the lethality rate could not be reduced. Nevertheless, some cases of successful treatment were observed. (43)

PVS: There are many reports on experience made with peritoneovenous shunts (s. p. 317), the positive tenor of which justifies its incorporation when planning therapy for the hepatorenal syndrome with marked ascites. (14, 17, 29, 41)

TIPS: In its function as a portacaval side-to-side shunt (s. pp 267, 320, 899), TIPS has also proved to be successful in the treatment of HRS. The survival rate after 18 months was 35%, whereas only 10% of non-shunted patients survived 3 months. (8) However, patients with type I HRS and those with bilirubin levels of 15 mg/dl or higher as well as patients with a Child-Turcotte-Pugh score greater than 12 have a low response rate to TIPS and a high mortality rate.

MARS: A new therapeutic option that could improve renal function and prolong survival, especially in risk patients to TIPS, can be found in the molecular adsorbent recirculating system (MARS). It represents a cell-free liver dialysis technique and enables the selective removal of albumin-bound substances using an albumin-enriched dialysate fluid. Significant improvements for different biochemical and clinical parameters as well as a 30-day prolongation of survival were reported. (35) (s. p. 390)

Portacaval shunt: In some cases, the placement of a portacaval shunt (side-to-side) resulted in the restoration of normal renal function. (50, 51)

Liver transplantation: Where the hepatorenal syndrome occurs, consideration should understandably be given to liver transplantation in view of increasing liver insufficiency. (s. p. 903) With suitable cases, this intervention proved efficacious. (12, 20, 28, 32) In severe forms of HRS and with inadequate response to conservative therapy, the indication for liver transplantation should be reviewed without further delay. The feasibility of surgical intervention will largely depend on whether the phase of hepatic and renal insufficiency can be bridged − with as favourable clinical findings as possible and perhaps supported by suitable invasive measures − until transplantation is carried out. Three-year and four-year survival rates were both given as 65.7%. (20)

Support systems: Artificial renal and liver support systems may also be considered in order to bridge the period of time until liver transplantation is performed. (1)

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