Symptoms and Syndromes

14 Portal hypertension

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► Aristoteles (384–322 BC) first described the portal vein within the venous system. Herophilos (ca. 300–250 BC) was the first to recognize the portal vein system and its importance as the discharge zone for all resorbent intestinal veins. (s. pp 6, 7) • A description of the portal vein system with its intrahepatic branches and separate bloodstream was given by Galenus (129–199 AD). (s. p. 8) • The independence of the portal vein circulation from the overall blood circulation was demonstrated by F. Glisson (1597–1677). (s. p. 10)

► In 1905 the **cause** of portal hypertension was regarded by R. Kretz as being the mechanical constriction of the hepatic veins resulting in a shunt between the arterial and venous circulation. • The term **portal hypertension syndrome** was defined by A. Gilbert and M. Villaret (1906) and taken to encompass ascites, opsiuria, splenic tumour, haemorrhoids, gastrointestinal bleeding and the development of hepatofugal collaterals. The underlying disease consisted of cirrhosis and portal vein thrombosis. (38) • **Measurement of portal venous pressure** was taken by L. M. Rousselot in 1936. Pressure measurement by puncturing oesophageal varices was first performed by P. Allison (1951). A. Paton et al. (1953) reported on the indirect determination of portal venous pressure with the aid of hepatic venous pressure measurements. A correlation between pressure in the portal vein and pressure in the splenic vein was established by M. Atkinson and S. Sherlock (1954).

1 Definition

A persistent pressure elevation of >12 mmHg in the portal vein circulation, dilation of the portal vein to >13 mm or an increase in the portal pressure gradient of >7 mmHg (difference between the pressure of the portal vein and that of the inferior vena cava) is termed portal hypertension. At pressure values of more than 20 mmHg, collaterals generally develop. • *Portal hypertension is regarded as a systemic disease which affects a number of organ systems.*

2 Pathogenesis

The portal vein is 5–8 cm long with a diameter of 1.2 ± 0.2 (or 0.97) cm. The portal venous pressure is 3–7 (–12) mmHg. It is dependent on several *criteria*: posture, intra-abdominal pressure (e. g. coughing, compression), respiratory phase, Valsalva's manoeuvre and a number of biochemical mediators. (18)

Hepatic circulation: About 70–75% of the hepatic circulation (1,500 ± 300 ml/min, or 1.4–1.5 ml/min/1.73 m^2 body surface) pass through the portal vein (25–30% via the hepatic artery). Hepatic circulation increases after the ingestion of food, but decreases by about 30% after physical exertion as a result of sympatheticotonia. The oxygen content of portal venous blood is lower than that of arterial blood, but is significantly higher than in the rest of the venous system. The portal vein supplies about 10–12 ml O_2/min × 100 g, i. e. 50–60% of the liver's oxygen requirement. The liver is very adaptable in this respect and balances an increased or decreased oxygen supply by decreasing or increasing oxygen extraction (by almost 100%) from the portal and arterial blood. (5, 11, 81, 91) (s. pp 852, 860, 864)

Hepatic blood flow: In addition to the autoregulation of the arterial hepatic system, the hepatic blood flow is mainly regulated via neural (sympathetic) stimulation and the effects of hormones, mediators or pharmaceuticals. • Agents such as α-agonists, histamine, serotonin, noradrenaline, endothelin and angiotensin have a constrictive effect on the portal venous system. A vasodilatory effect on the arterial system is brought about by β-agonists, nitric oxide (NO) (46, 110), glucagon, prostaglandins, pentagastrin, adenosin, etc. • Under pathological conditions (e. g. lowered response to vasoconstrictors), individual factors of these biochemical regulation systems may be present to a greater or lesser extent and thereby lead to pathophysiological mechanisms. This also applies to the action of endotoxins with regard to an elevation of the portal pressure. • **Ito cells** are key targets for vasodilators: they regulate the hepatic microcirculation. (110)

Hepatic resistance: Various areas of resistance can regulate the circulation of blood in the liver: (*1.*) arterioles of the hepatic artery, (*2.*) arterioles in the region of the splanchnic vessels, (*3.*) presinusoidal portal venules, (*4.*) sinusoids and postsinusoidal sections of vessels, and (*5.*) portosystemic collaterals.

Forward-flow hypothesis: When hepatic resistance is constant, increased blood supply causes an elevation of the portal pressure. • **Backward-flow hypothesis:** This primarily requires an increase in hepatic vascular resistance. The subsequently reduced circulation of blood in the liver is compensated by increased circulation in the splanchnic vessels.

The portal hypertensive syndrome is caused by (*1.*) increased resistance in the portohepatic circulation, (*2.*) an increase in the splanchnic vein blood supply, or both.

► The *rise in vascular resistance* is the decisive factor and, in most cases, even the sole cause. It may be *func-*

tional and *reversible* as well as *structural* and *irreversible*. Blood flow correlates directly with vessel diameter to the 4th power, i.e. small radial changes cause large changes in vessel resistance. An increase in the blood supply leads to portal hypertension and/or respective clinical sequelae. The persistent disturbance in biochemical mechanisms which regulate the blood circulation in the liver and the impact of pathological substances may also have pathogenic effects. (21, 57, 67, 110, 119) (s. fig. 14.1)

Despite the development of *portosystemic collaterals*, which ought to lead to a fall in portal hypertension, the *hyperdynamic circulation* accompanied by splanchnic vasodilation (= increased cardiac output, decreased systemic vascular resistance, hypervolaemia, systemic arteriolar vasodilation) maintains portal hypertension in both the splanchnic and systemic vascular systems. (11, 42, 81) The hyperdynamic circulation is either the cause or the result of portal hypertension – or both. Arterial blood pressure is normal or slightly decreased.

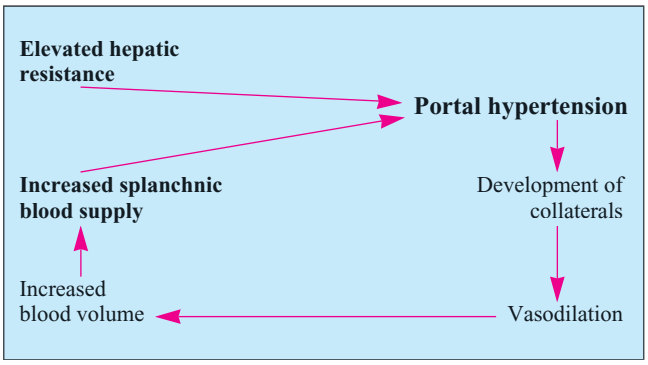

Fig. 14.1: Pathogenesis of portal hypertension

3 Forms and aetiology

Portal hypertension is classified according to the *localization* of the flow resistance. Increases in pressure in the portal vein system are rapidly transferred to the preceding vascular sections, since the portal vein does not have any venous valves. Depending on whether its localization lies before, within or beyond the liver, portal hypertension is broken down into *prehepatic, intrahepatic* and *posthepatic blocks*. The intrahepatic form is further subdivided into a presinusoidal, sinusoidal and postsinusoidal rise in resistance. Underlying *morphology* allows distinction between cirrhotic and non-cirrhotic portal hypertension. • Sometimes the aetiology is unknown (= *idiopathic, non-cirrhotic portal hypertension*). (33, 64, 66, 94, 107, 131, 133, 146, 150) (s. tab. 14.1)

3.1 Prehepatic portal hypertension

Prehepatic (non-parenchymatous) portal hypertension develops (*1.*) as a result of an increase in the portal blood supply in the form of hyperkinetic hypertension, or (*2.*) due to occlusion of the portal vein or its trunks. The frequency is 10–20%. The liver is morphologically normal, but diminished in size. Its function is not impaired. The reduced afferent portovenous flow is compensated by arterial perfusion of the liver. Ascites occurs only rarely. There are a variety of known causes for this portal block form. (s. tab. 14.2) (s. figs. 14.4, 14.5)

Phylogenetically, the portal vein is derived from several fused embryonic vessel components. Malformation can lead to *atresia* or *hypoplasia* of the portal vein and cause portal hypertension in newborns. (92, 150)

Non-parenchymatous portal hypertension
1. *Prehepatic portal hypertension*
2. *Intrahepatic portal hypertension*
   a. presinusoidal block

Parenchymatous portal hypertension
   b. sinusoidal block
   c. postsinusoidal block
3. *Posthepatic portal hypertension*

Tab. 14.1: Forms and localization of portal hypertension

Congenital or postnatal
1. Arterioportal fistulas
   = *hyperkinetic hypertension*
2. Atresia or hypoplasia of the portal vein
3. Thrombosis of the portal vein
   – encroachment of the postnatally obliterated umbilical vein on the portal vein
   – infection of the umbilical vein with phlebitis of the portal vein
4. Cruveilhier-von Baumgarten disease
5. Cavernous transformation of the portal vein

Acquired
1. Thrombophlebitis or thrombosis of the portal vein
2. Compression of the portal vein
3. Cavernous transformation of the portal vein
4. Arterioportal fistulas
   = *hyperkinetic hypertension*
5. Compression or thrombosis of the splenic vein
   = *segmental portal hypertension*

Tab. 14.2: Forms and causes of prehepatic portal hypertension

3.1.1 Cavernous transformation

The most common cause of prehepatic portal hypertension in early childhood is cavernous transformation, a primary angiomatous malformation of the portal vein (H. Breining et al., 1968; C. Marks, 1973). • In adults, septic diseases (appendicitis, pancreatitis, cholecystitis, etc.) and traumas are deemed responsible, since they trigger a slow occlusion of the portal vein (H. W. Clatsworthy, 1974). Myeloproliferative syndromes, hepatic tumours

and cirrhosis are also possible causative factors. • This transformation consists of a spongy convolute of paraportal, tendril-like interlaced vascular structures in place of a single portal vein, mainly in the area of the hepatoduodenal ligament. Symptoms are abdominal pain, haematemesis, splenomegaly and oesophageal varices. Diagnosis is based on US and CT. A cavernous transformation of the portal vein usually appears sonographically as a string of bead-like varicose collaterals in the hepatoduodenal ligament. (9, 10, 122) (s. p. 861)

3.1.2 Cruveilhier-von Baumgarten disease

The **Cruveilhier-von Baumgarten disease** develops when postnatal occlusion of the umbilical vein is absent (P. von Baumgarten, 1907). An open, dilated umbilical vein connects the left portal vein with the systemic venous circulation in the navel area. This collateral vein has a diameter of > 3 mm and a hepatofugal flow of > 5 cm/sec. Sonography shows an echofree tubular structure. In addition to the persistence (and, in most cases, malformation) of the umbilical vein, a hypoplastic portal vein system is found. The resulting hypoplasia of the liver and its vessels culminates in portal hypertension. Typical of this condition are the massive varicose collaterals between the portal vein and the abdominal wall veins in the form of a Medusa's head (s. p. 91), a continual venous hum below the xiphoid ("bruit de diable" or "humming-top murmur") (s. p. 92), and splenomegaly. (s. p. 221) • In the **Cruveilhier-von Baumgarten syndrome,** the postnatally closed umbilical vein in the region of the round ligament is recanalized due to portal hypertension; thus the blood from the left portal branch is drained caudally. As a consequence of haemodynamically effective "shunting", flow values of > 10 cm/sec can be measured.

3.1.3 Arterioportal fistulas

Hyperkinetic hypertension in the prehepatic portal vein system is caused by arterioportal fistulae with resulting increased blood flow. About 150 cases of such aneurysmal anomalies are known from the literature. (3) They occur more frequently, however, after abdominal traumas or iatrogenic interventions (e. g. liver biopsy, cholangiography, arteriography) and in the presence of malignant liver tumours. They are found mainly in the proximity of the splenic artery or mesenteric vessels. Arterial flow into the low-pressure portal region is unaffected. Oesophageal varices, splenomegaly and, in some cases, ascites develop very rapidly despite a "healthy liver" (no abnormal clinical or laboratory findings). This is followed by the subsequent development of secondary thrombosis of the portal vein as a result of fibromuscular hyperplasia of the intima and fibrosis in the portal area (= *hepatoportal sclerosis*). Clinically, a "machinery murmur" in the abdomen is discernible on auscultation. Diagnosis can be made with the aid of duplex sonography or radiological procedures.

3.1.4 Portal vein thrombosis

The most frequent cause of prehepatic portal hypertension in adults is portal vein thrombosis. Sonography displays the fresh thrombus as a hypoechoic structure in the initially dilated portal vein. (83, 95, 135) The blood flow (during the reversal phase from a hepatopetal to a hepatofugal flow) slows down due to liver cirrhosis, and this is deemed the causative factor in over 30% of cases of portal vein thrombosis. The liver function is greatly restricted. Ascites is often observed and proves difficult to treat. The presence of thrombophilia is seen as a predisposing factor. • Other causes are: thromboembolism (87), abdominal operations, traumas (63), pregnancy, collagenoses, portography, polycythaemia vera, osteomyelosclerosis, Budd-Chiari syndrome, primary hepatocellular carcinoma, hepatic echinococcus cysts (99). Septic processes (e. g. umbilical vein infection in newborns, appendicitis, diverticulitis, pancreatitis, colitis) play a major role. Tuberculosis is a rare cause. (113) (s. tab. 39.5) The severity of the clinical picture of portal vein thrombosis depends on how quickly and extensively the obstruction develops. Rapid occlusion, due to the haemorrhagic infarction of the intestine, leads to extreme abdominal pain, haematemesis, melaena, haemorrhagic shock, and ultimately death. When the obstruction is more gradual, splenomegaly develops rapidly together with paraportal collateral vessels which function as intrahepatic portal branches (= cavernous transformation), thus permitting partial compensation. With normal WHVP (= wedged hepatic vein pressure), there is a rise in intrasplenic pressure. (s. tab. 14.9) Diagnosis is possible using duplex sonography, splenoportography or modern radiological methods. Disorders of liver function are only apparent at a later stage. *Hepatoportal sclerosis* may develop. (s. p. 862)

3.1.5 Segmental portal hypertension

An increase in peripheral resistance following *thrombosis of the splenic vein* is termed segmental portal hypertension. Bleeding from gastric fundus varices is frequently found. Due to the intact liver function, bleeding from the upper gastrointestinal tract is better tolerated. Parasplenic variceal convolutes can be visualized by means of colour-encoded duplex sonography. As a rule, ascites does not occur. Pressure in the enlarged spleen is greatly elevated. The WHVP remains unchanged even with normal portal pressure. For this reason, a shunt operation is contraindicated in cases of bleeding from oesophageal or gastric fundus varices owing to segmental portal hypertension. (39, 71, 76, 117)

3.2 Intrahepatic portal hypertension

Intrahepatic portal hypertension is caused by lesions which are easy to distinguish morphologically as well as pathogenetically and which occur in the following regions: (*1.*) presinusoidal veins of the intrahepatic peri-

portal triangles, (*2*.) liver sinusoids, and (*3*.) draining postsinusoidal veins. Pathogenic overlapping is possible, since some lesions affect both the presinusoidal and sinusoidal vascular sections simultaneously. Frequency is estimated at 70–80%. (s. figs. 14.4, 14.5)

3.2.1 Presinusoidal block

► The presinusoidal block is a form of non-parenchymatous portal hypertension. The WHVP is normal. There is no impairment of liver function until a later stage of the underlying disease has been reached. This type of block is caused by a congenital or acquired constriction of the lumen or by a reduction in portal venous branches within the periportal triangles. (s. tab. 14.3)

Fibrocystic liver diseases, which show an autosomal-recessive inheritance pattern, may hence cause a presinusoidal block within the clinical picture of *cholangiodysplasia*. Histological differentiation between cirrhosis and cholangiodysplastic pseudocirrhosis is very difficult. • *Congenital liver fibrosis* (D.N.S. Kerr et al., 1962), an autosomal recessive disease involving the kidneys, causes an increase in presinusoidal pressure due to increased vascular resistance. *Rendu-Osler-Weber disease* and *Gaucher's disease* should also be mentioned as forms of a congenital presinusoidal block, the portal hypertension here possibly also being of sinusoidal origin. (s. tab. 14.3)

Various infectious, toxic or immunological lesions lead to a presinusoidal block in adults. From a primary endothelial lesion, endophlebitis ensues. Rich in fibres and deficient in cells, it is ultimately responsible for the obliteration and even disappearance of the portal branches. • *Obliterative portal venopathy* (N.C. Nayak et al., 1969) with portal and periportal fibrosis and subsequent perisinusoidal sclerosis is referred to as *hepatoportal sclerosis* (W. P. Mikkelsen et al., 1965). This is a complex disorder involving splenomegaly, hypersplenism and portal hypertension, which has also been described as non-cirrhotic portal fibrosis (J.L. Boyer et al., 1967) or idiopathic portal hypertension (K. Okuda et al., 1982). (118) *Banti's syndrome* (8) probably fell into this group; this is, however, now an obsolete term. The WHVP and flow rates are normal and liver function is not affected. Cirrhosis may develop in cases of prolonged illness.

Thrombosis of small portal veins due to bacterial cholangitis with pericholangitis or to malignant and subsequently thrombotic processes can cause an increase in presinusoidal resistance.

Even in the early stage of *primary biliary cholangitis,* immunological or scar-related atrophy of the small portal veins is evident. (73) • In *primary sclerosing cholangitis*, these changes are only manifested once cirrhotic transformation has set in. (s. tab. 14.3)

The main cause of presinusoidal hypertension in the world is *schistosomiasis.* The eggs of the parasite are washed "embolically" into the portal veins. Thus portal hypertension is induced, whereby the rise in pressure correlates with the quantity of obstructing eggs. The WHVP is normal. In addition, a granulomatous foreign-body reaction occurs with immunologically induced eosinophilic infiltrations. This leads to pronounced portal-periportal fibrosis, in which the periportal triangles are distended with nodules and scars and incorporate the axis of the Rappaport acini (= *"pipe-stem fibrosis"*). (28, 108) (s. p. 509) (s. fig. 25.14)

Presinusoidal block
Congenital 1. Rendu-Osler-Weber disease 2. Gaucher's disease 3. Cholangiodysplasia or congenital liver fibrosis (microcystic liver), congenital polycystic disease
Acquired 1. Thrombosis of the portal venous branches (95, 135) 2. Aneurysmal dilatation of the portal vein (2) 3. Primary biliary cholangitis (73), primary sclerosing cholangitis 4. Sclerosing granulomas – schistosomiasis (28, 108) – sarcoidosis (70, 129, 134) – tuberculosis (113) 5. Toxically induced hepatoportal sclerosis/periportal fibrosis – arsenic (82, 89, 102, 105) – vinyl chloride monomers (13) – insecticides (particularly with copper sulphate) (105) – cytostatics (methotrexate, 6-mercaptopurine) (115) – immunostatic agents (azathioprine) (74) – cyanamide 6. Myeloproliferative syndromes (26, 75) 7. Collagenoses (24, 25, 54) 8. Haemoblastoses (e.g. mastocytosis) 9. Lymphoblastoses 10. Wilson's disease 11. Haemochromatosis 12. Malignant diseases 13. Liver adenoma 14. Nodular regenerative hyperplasia (86, 104, 124, 145) 15. Partial nodular transformation (116, 144) 16. Idiopathic (non-cirrhotic) presinusoidal block (146)

Tab. 14.3: Causes of elevated presinusoidal resistance in intrahepatic portal hypertension (with some references)

Both *liver adenomas* and *nodular regenerative hyperplasia* can cause a presinusoidal block due to distortion of the portal veins. • *Wilson's disease* leads to an overlapping of presinusoidal and sinusoidal portal hypertension. • In *alcoholic cirrhosis*, there is a similar overlap of the sinusoidal and postsinusoidal forms.

3.2.2 Sinusoidal block

► The sinusoidal block is attributed to various *pathogenic mechanisms*: (*1*.) compression of the sinusoids via hepatocellular storage of substances (e. g. steatosis), (*2*.) prolonged action of hepatotoxins with increasing collagen formation and fibrosis, (*3*.) disturbed passage in Disse's space (e. g. due to oedema), (*4*.) storage processes in the sinusoidal cells, (*5*.) influence of vaso-active substances on the sinusoids, and (*6*.) compression of the

sinusoids by the formation of nodules. Increased resistance thus comes from constriction or reduction of the sinusoidal vessels. The sinusoidal block is the most common cause of portal hypertension. It is ascribed to intrahepatic parenchymal hypertension of the portal vein. Hepatomegaly is nearly always present. (s. tabs. 14.1, 14.4, 14.9) (s. figs. 14.4, 14.5)

Sinusoidal block
1. Storage of substances – fatty liver – acute fatty liver in pregnancy – amyloidosis (153) – glycogenosis type III (79) – Gaucher's disease – Niemann-Pick disease (127) – α_1-antitrypsin deficiency 2. Hepatotoxins – alcoholic hepatitis – vitamin A (112) – vinyl chloride, methotrexate 3. Severe parenchymal loss – acute viral hepatitis (136) – acute liver failure (88) – malaria 4. Peliosis hepatitis 5. Chronic hepatitis (69) 6. Regenerative nodes in cirrhosis 7. Formation of nodes 8. Cirrhosis

Tab. 14.4: Causes of a sinusoidal block in intrahepatic portal hypertension (with some references)

Alcohol: With regard to hepatotoxins, by far the greatest importance must be attributed to alcohol. The development of alcohol-mediated portal hypertension is complex. The increasing accumulation of fat in the hepatic cells interferes with the microcirculation, since the sinusoids become both longer and narrower as a result of fatty degeneration of the hepatocytes. In cases of fatty liver, a greater microcirculation is observed in the arterioles at the same time. Stimulation of the Ito cells is an important pathogenic factor; it induces collagenization of the perisinusoidal reticular fibres. Scar areas develop around the central veins, with perivenous sclerosis and ultimately even further obliteration of these vessels.

Vitamin A intoxication: Prolonged and marked vitamin A intoxication leads to a substantial increase in individual Ito cells. This causes constriction of the sinusoids; accompanying fatty degeneration of the hepatocytes supports the obstructive effect. The Ito cells are responsible for perisinusoidal fibrosis. The liver surface is strikingly smooth despite marked portal hypertension (often with considerable oesophageal varices). (112) (s. figs. 14.2, 14.3)

Cirrhosis: Irrespective of its aetiopathogenesis, cirrhosis always leads to portal hypertension. In addition to the principal sinusoidal factors, it is also affected by presinusoidal mechanisms. In some cases, it is not always possible to assess the pathogenic significance of individual factors. The real cause of portal hypertension lies within the sinusoids. Because of the cirrhotic conversion of the liver and the regeneration of nodes, the portal veins are nearly always compressed, allowing hypertension to build up due to the vascular resistance. The sinusoids, thereby stiffened, trigger phlebectasia in their immediate vicinity, and a compensatory increased afferent arterial flow is produced. This can be easily detected because of muscular hyperplasia of the small arteries and the occurrence of shunts between the small arteries and portal veins.

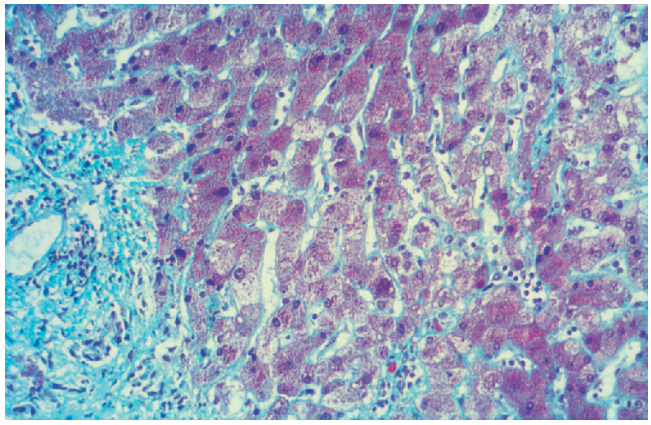

Fig. 14.2: Slight lobular inflammation. Periportal/perisinusoidal delicate fibrosis as a result of chronic vitamin A intoxication (same patient as in fig. 14.3) (Ladewig)

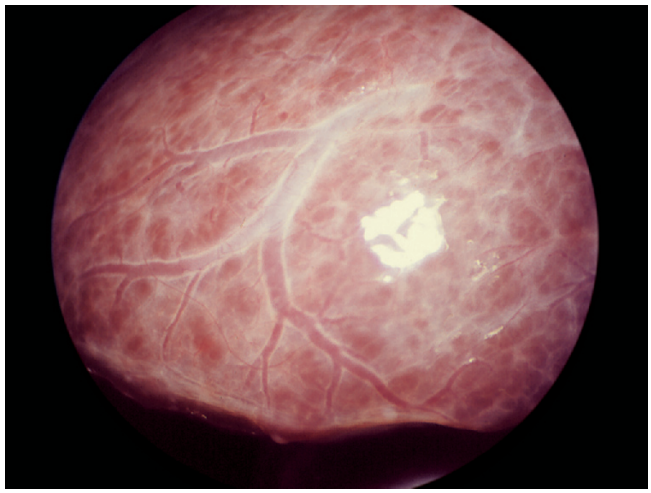

Fig. 14.3: "Smooth" cirrhosis with smooth surface and portal hypertension resulting from chronic vitamin A intoxication (same patient as in fig. 14.2)

3.2.3 Postsinusoidal block

► The postsinusoidal block is due to increased resistance in the hepatic veins and venules beyond the sinusoids. This block form is attributed to parenchymatous portal hypertension. (s. tabs. 14.1, 14.5, 14.9) (s. figs. 14.4, 14.5)

Liver cirrhosis is the most common cause of postsinusoidal portal hypertension. The greater resistance in this vascular zone is predominantly due to the expansive pressure caused by regenerative nodes on the small vein branches. An additional pathogenic factor is the elevated arterial blood flow to the liver. There is increasing evidence of arterioportal anastomoses. The arterial component of blood flowing to the liver can be raised by up to 80%. The blood flow from the splanchnic area is also higher. The internal pressure in the spleen and the WHVP rises in accordance with the respective stage of cirrhosis. Infiltration of portal fields, portal/periportal fibrosis and fibrous septa in cirrhosis leads to constriction and rarefaction of the portal venules and thus culminates in a presinusoidal block. For this reason, after the positioning of a portaca-

Postsinusoidal block

1. Liver cirrhosis (e.g. Wilson's disease, haemochromatosis)
2. Budd-Chiari syndrome
   - Stuart-Bras syndrome
     (veno-occlusive disease; radicular form)
     - pyrrolizidine alkaloids
     - cytostatic agents
     - immunosuppressants
     - contraceptives
     - anabolic agents
     - exposure to X-rays
     - thorotrast
   - Chiari's disease
     (obliterative hepatic endophlebitis; truncal form)
3. Alcoholic hepatitis
   Alcoholic central hyaline sclerosis
4. Partial nodular transformation of the liver (116, 145)

Tab. 14.5: Causes of a postsinusoidal block in intrahepatic portal hypertension (with some references)

val shunt, the WHVP is hardly (if at all) reduced. It is possible to ascertain the respective extent of a presinusoidal block by way of the splenosinusoidal pressure gradient.

Budd-Chiari syndrome is the term used for the clinical picture resulting from the occlusion of the hepatic veins. This occlusion may be acute or chronic, total or partial. Thrombosis of hepatic veins was first described in 1845 by G. Budd. In 1899 H. Chiari compiled all previously recorded observations and categorized them as an independent pathological entity. There are numerous causes: congenital anomalies of the hepatic veins, inflammatory diseases of the hepatic veins, localized or diffuse liver diseases, extrahepatic pathological processes, traumas, haematological or malignant diseases, pregnancy, myeloproliferative processes, etc. (s. p. 856)

Veno-occlusive disease (VOD) describes the occlusion of small hepatic veins and is defined as a *radicular form* of the Budd-Chiari syndrome. A variety of endotheliotoxic noxae, particularly phytotoxins, are responsible for this clinical picture. In 1951 reports were simultaneously published for the first time in South Africa (G. Selzer et al.) and Jamaica (K. R. Hill) dealing with this disease of the small venous branches, which results from chronic intoxication with pyrrolizidine alkaloids. (s. pp 562, 587) Similar morphological and clinical effects can also be caused by cytostatic agents (6-mercaptopurine, dacarbazine, thioguanine), azathioprine, contraceptives and exposure to X-rays. Since 1957, the term *Stuart-Bras syndrome* has also been used to describe the occlusion of the small hepatic veins. (s. p. 859)

Obliterative hepatic endophlebitis is also referred to as *Chiari's disease* and can be distinguished from the Budd-Chiari syndrome as its *truncal form*. It presents as primary, independent phlebitis of the large hepatic veins with secondary thrombosis. (s. tab. 14.5) In Chiari's disease, the hepatic veins are affected to differing degrees and at differing stages; this characterizes the clinical picture. Possible causes are rheumatic or paraneoplastic diseases and disorders of the immune system. Total occlusion of the hepatic veins has a dismal prognosis. Partial occlusion results in portal hypertension with hepatosplenomegaly, ascites and oesophageal varices.

Alcoholic hepatitis also leads to a postsinusoidal block following the deposition of alcoholic hyaline in the centrilobular zone, with perivenous fibrosis and subsequent occlusion of the small veins.

3.3 Posthepatic portal hypertension

In posthepatic portal hypertension (prevalence about 5%), the flow hindrance is in the region of the inferior vena cava or the right heart. Extrahepatic processes impede the efferent flow of venous blood from the hepatic veins. Parenchymatous portal venous hypertension develops with a simultaneous elevation of pressure in the femoral vein. Liver findings correspond to the truncal form of the Budd-Chiari syndrome. (s. tabs. 14.6, 14.9) (s. figs. 14.4, 14.5)

Heart
1. Right heart insufficiency
2. Constrictive pericarditis
3. Tricuspid valve incompetence
4. Idiopathic dilative cardiomyopathy

Inferior vena cava
1. Membranous obstruction
2. Anomaly
3. Thrombosis
4. Tumours
5. Nephrotic syndrome
6. Polycythaemia vera

Hepatic veins
1. Anomaly
2. Chiari's syndrome
3. Tumours
4. Amoebic abscess

Tab. 14.6: Causes of posthepatic portal hypertension

The most frequent **cause** of posthepatic portal hypertension is *right ventricular insufficiency.* The central venous pressure is transferred to the hepatic veins and the sinusoids. • *Constrictive pericarditis* leads to a state of pronounced posthepatic portal hypertension with the early development of ascites. • Severe *tricuspid valve incompetence* also culminates in this condition. • A *membranous obstruction* of the inferior vena cava was likewise described as a genetically determined cause of posthepatic portal hypertension (S. Yamamoto et al., 1968). Three variants can be distinguished by angiography, depending on the different ways in which the hepatic veins are involved or whether they are affected at all. • *Thrombosis* of the inferior vena cava can develop either from thrombosis of the pelvic veins or independently in the presence of predisposing factors.

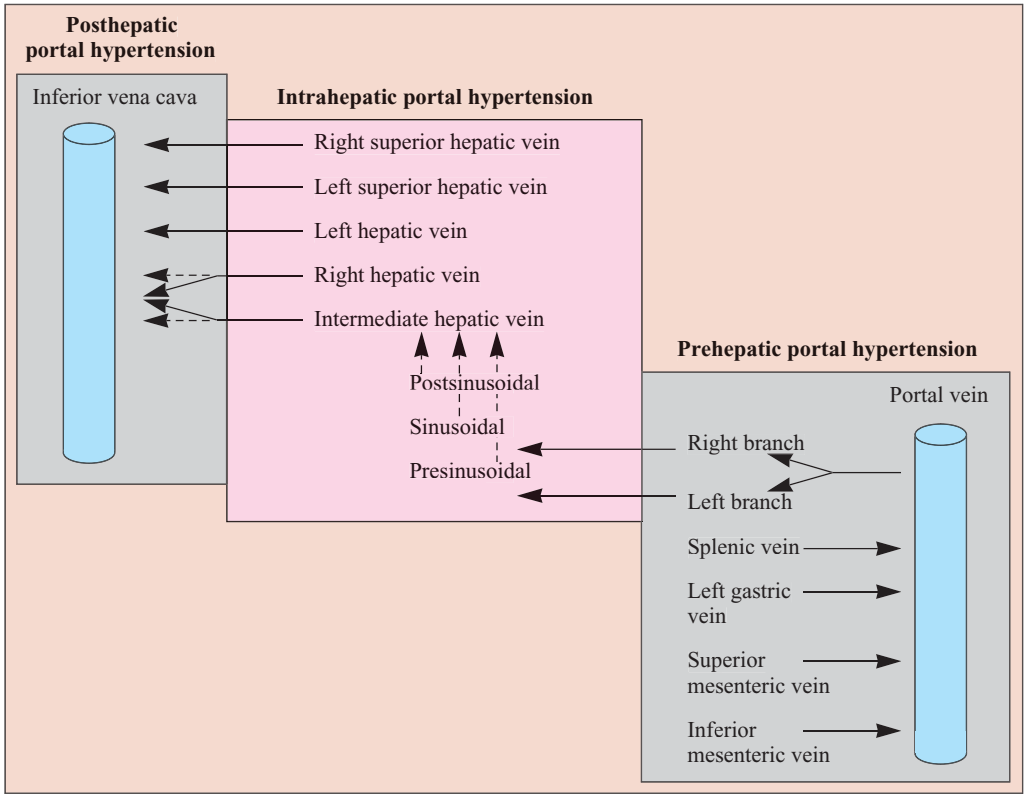

Fig. 14.4: Anatomical systematics of portal hypertension

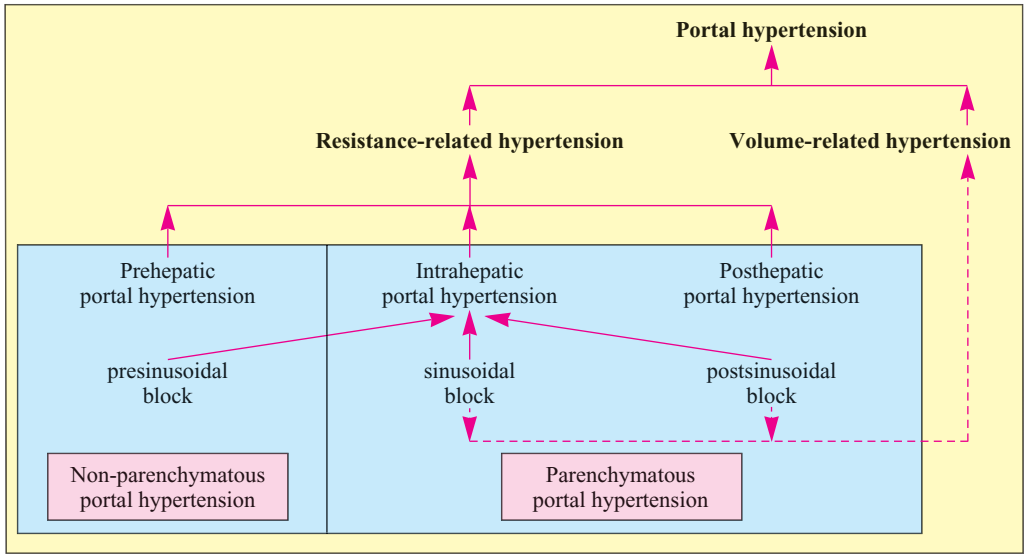

Fig. 14.5: Forms, localization and systematics of portal hypertension (resistance-related and volume-related hypertension can occur either as primary or secondary forms)

4 Diagnosis

Hypertension of the portal vein, with its numerous intrinsic or acquired causes, may not display any symptoms for several years. Portal hypertension itself is very often a concomitant symptom in a number of liver diseases. It can lead to severe or even fatal complications. For this reason, hepatological investigation frequently needs to explore (*1.*) the presence of portal hypertension, (*2.*) its aetiology, (*3.*) its severity, and (*4.*) potentially successful treatment of the underlying causes – in order to produce a favourable effect on the overall condition of the patient.

4.1 Anamnesis

Specific investigation of the patient's medical history can provide evidence of existing portal hypertension. The main ***anamnestic details*** given by the patient are related to various targeted questions:

- **existence of a liver disease**
- **existence of extrahepatic diseases**
- **alcohol abuse**
- **medication**
- **consumption of tea containing alkaloids**
- **tarry stools, haematemesis, bleeding tendency, thrombophilia**
- **visits to tropical regions (malaria, etc.)**
- **oedema, abdominal pain**

4.2 Clinical findings

In the physical examination, particular attention should be paid to a number of ***clinical findings***:

- **hepatomegaly or atrophic liver cirrhosis**
- **splenomegaly**
- **skin stigmata of liver diseases**
- **anorectal varices**
- **oedema or ascites**
- **epigastric pulsation**
- **congested neck veins**
- **venous patterns on the surface of the abdomen**
- **vessel sounds**
- **prolonged Q-T interval (151)**

4.3 Laboratory findings

Laboratory parameters are not suitable for detecting portal hypertension. Only *thrombopenia* (< 100,000/ mm^3) should be taken as evidence of a splenomegaly due to portal hypertension; decreased *haemoglobin values* can be seen as a sign of a continuous loss of blood. Testing for *occult blood* in faeces is obligatory when portal hypertension is suspected. Elevated *ammonia values* hint at an existing shunt circulation. *Cholinesterase* provides more information on the functioning of the liver, hence facilitating a prognosis.

4.4 Sonography

Sonography provides a reliable means of detecting splenomegaly, which is often, but not always present with portal hypertension. Normal spleen findings generally rule out this condition. The sonographically based suspicion of a particular liver disease should at the same time draw attention to the possible existence of portal hypertension. Nevertheless, diagnosis cannot simply be founded on the diameter of the portal vein, since the values obtained from healthy subjects and from patients with portal hypertension overlap. The blood flow sometimes slows down even when the portal vein is normal. Furthermore, the diameter of the portal vein (and also of the splenic vein) depends on the capacity of existing collaterals. (41, 78, 142, 149) (s. tab. 14.7)

Vaginal sonography revealed rectal varices in about 50% and pararectal varices in about 80% of cases. The varices had a diameter of 2.1 – 5.5 mm. (77)

Endoscopic sonography is ideally suited for displaying intramural and perimural oesophageal varices. (125) (s. fig. 19.6) Endoscopic colour Doppler sonography is another promising procedure, particularly for demonstrating a (still) evident variceal perfusion.

4.5 Doppler sonography

Valuable information on the haemodynamics in the portal vein system can be obtained with the aid of pulsed or colour-encoded Doppler sonography – predominantly by using a transducer with 3.5 MHz. • All forms of portal hypertension can also be classified and quantified in terms of severity. • A marked deceleration of the portal flow (< 10 cm/sec) together with evidence of portosystemic collateral vessels as well as a reversal of the portal blood flow (= hepatopetal to hepatofugal), which may also occur in the splenic vein, demonstrate a severe impediment in flow capacity. In the case of portal hypertension, a hepatofugal portal flow is found in 6 – 10% of patients. A dilation of the left gastric vein of > 6 mm points to the presence of oesophageal varices, since this vein is the main collateral vessel in such cases; evidence of high hepatofugal flow (more than 15 cm/sec) represents a distinct risk of variceal bleeding. (s. p. 133)

- Splenomegaly (> 4 × 7 × 11 cm) (s. p. 220)
- Dilation of the portal vein (> 13 mm)
- Dilation of the splenic vein (> 10 mm)
- Dilation of the ventricular coronary vein (> 6 mm)
- Restricted respiratory modulation of the vascular width of up to 3 mm (increase on inspiration and decrease on exspiration) regarding the portal vein and more particularly the splenic vein and the superior mesenteric vein. • Decrease in width of the lumen by more than 50% on exhalation = absence of portal hypertension
- Jump in calibre of the portal vein
- Reversal of flow in portal vessels
- Stasis of the gall bladder and gastric walls
- Visible evidence of collaterals
- Recanalization of the umbilical vein (s. fig. 6.7)
- Cavernous transformation of the portal vein

Tab. 14.7: Sonographic criteria in portal hypertension

The **Doppler effect** is produced by changes in wavelength due to the reflection of sound on moving particles (e. g. erythrocytes). Consequently, the *direction of flow* (away from or towards the sound source) as well as the *flow rate* in arterial and venous vessels can be determined. The *flow volume* is then calculated by additional sonographic measurement of the vessel diameter. It has been shown that the rate of flow is clearly dependent upon the respiratory activity, so that an increase in blood flow velocity can be determined with maximum exspiration as well as postprandially (normal value: 18 – 30 cm/sec). (30, 37)

Fibrous transformation in the structure of the liver leads to a **change in hepatic haemodynamics.** Stenosis in the region of the hepatic veins can be recognized by an increased flow rate. Yet, even in cases of marked liver fibrosis or cirrhosis, the *hepatopetal flow in the portal vein* may only be slightly lowered or even normal owing to the dilation of the portal vessels and the formation of collaterals. In cirrhosis, the arterial flow is greater than the portal flow, the rate of which is about 30% lower than in healthy persons. The *relative change (in %)* following stimulation by a ***standard test meal*** provides a more exact diagnosis of portal hypertension. Postprandial flow, due to digestive hyperaemia, may reach 40 cm/sec. (68, 72) In the case of a distinct reduction in the flow rate, the flow direction may be reversed (= *hepatopetal to hepatofugal*). Blood flow in the portal venous system is normally hepatopetal as opposed to pulsatile (or only slightly pulsatile) and follows an increased exspiration flow rate. • Undulating blood flow when inhaling (= hepatopetal) and exhaling (= hepatofugal) is evidence of portal hypertension. (11, 81, 91)

Congestion index (CI): This parameter is the most reliable indicator of portal hypertension. It relates the portal cross-sectional area to the portal blood flow rate. The CI ranks higher than the direct pressure level in the diagnostics of the portal system and the HVPG. These three techniques (in this order) are considered to be the *gold standard* in early diagnosis of portal hypertension. CI levels of >0.1 are associated with excessive portal pressure with >95% sensitivity and specificity. (85) Sonographic imaging of *cavernous transformation* in the portal vein usually shows beaded varicose collaterals in the hepatoduodenal ligament.

4.6 Endoscopy

► **Oesophagogastroscopy** is considered to be the diagnostic procedure of choice for the detection of oesophageal or gastric varices. This examination should always be extended to the antrum and the duodenum, since varices can also occur there. Endoscopy allows the detection of oesophageal varicosis at an early stage of development. It also enables an assessment to be made of the size and preferred localization of the varices as well as imaging the surface of these veins, where red spots or stripes are often found. Blackish-brown spots are due to intramucosal haemorrhage. (s. p. 263) With the aid of gastroscopy, it is also possible to identify *erosive gastropathy* caused by portal hypertension. (s. p. 265) • In combination with **coloscopy,** examination initially focuses on the presence of anorectal varices. Endoscopy of the colon frequently reveals the presence of erosive colopathy with mucosal findings similar to those in the stomach. In rare cases, colonic varices are present. • **Video capsule endoscopy** makes it possible to examine the small bowel in portal hypertension. (111)

Laparoscopy permits the very early detection of portal hypertension due to the dilation and meandering of the fine peritoneal, intestinal or gastric vessels. (93) (s. p. 163) (s. figs. 7.5; 14.6, 14.11, 14.12; 16.9)

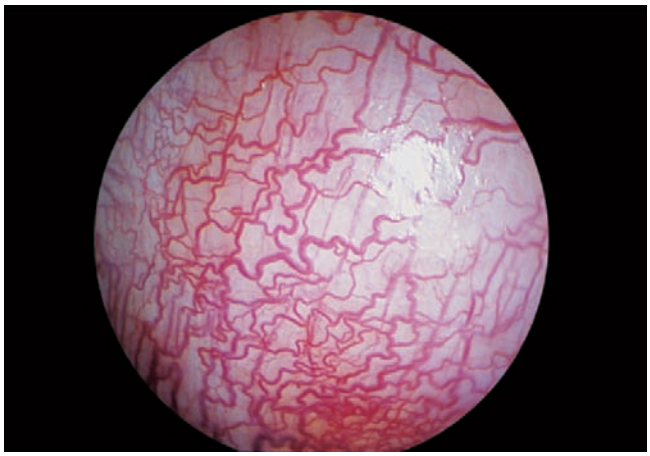

Fig. 14.6: Dilation and meandering of the fine peritoneal vessels in the initial stage of portal hypertension

4.7 Angiography

Splenoportographic procedures allow an accurate depiction of the portal vein and its afferent flow areas. Despite the development of new techniques, these methods are of importance in clarifying the cause of portal hypertension, and they are (still) deemed to be a prerequisite for operations aimed at reducing the pressure and volume in the portal venous circulation. Vessels with a diameter of <1 cm are unsuitable for long-term patency of a shunt. Direct and indirect procedures are available. (16, 31)

In the light of a possible shunt operation, it has become more important to obtain additional information on the arterial blood supply to the liver. As regards cirrhosis with portal hypertension, **arteriographic investigations** have shown that the more the blood flow through the liver increases, the more the portal blood flow is reduced. Thus the blood flow relationship through the liver can become almost completely reversed: as little as 20% via the portal vein and as much as 80% via the hepatic arteries. Evidence of haemodynamically active stenosis in the arteries supplying the liver therefore constitutes a contraindication for shunt operations.

Direct splenoportography is the most informative procedure for visualizing the portal vein system and its collaterals. Yet this technique is costly, time-consuming and high-risk. The injection of contrast medium into the spleen is carried out either percutaneously (sonography-guided) or, preferably, by laparoscopy. It is also possible to *measure the pressure* in the portal vein system. In addition, this method ensures access to the collaterals if *radiological obliteration* is planned. (s. p. 189)

Indirect splenoportography via the femoral artery is not only very important, but also low-risk. Using radiography, the arterial branches of the abdominal aorta initially become visible, followed by the spleen, the splenic vein and the portal vein together with its afferent veins and collaterals. This procedure provides **information** on: (*1.*) localization of vascular resistance-related hypertension, (*2.*) cause of portal hypertension (in individual cases), (*3.*) patency and diameter of the respective vessel, (*4.*) extent of collateral circulation, (*5.*) hepatopetal or hepatofugal direction of flow in the portal vein, and (*6.*) shunt capacity of the splenic vein or superior mesenteric vein. (s. p. 190)

Hepatic vein phlebography via the femoral vein and the inferior vena cava facilitates visualization of the hepatic veins; it is technically simple, practically risk-free and puts little strain on the patient.

Other procedures that can be applied are indirect mesentericoportography, transjugular or transhepatic splenoportography, umbilical portography (s. p. 190) and scintigraphic splenoportography.

4.8 CT and MRI

Additional examination with CT or spiral CT may be necessary with respect to certain diagnostic questions (e. g. retroperitoneal space, CT portography). This also applies to MRI (e. g. in pronounced obesity or meteorism). Thus MRI angiography is a valuable additional diagnostic procedure. (58, 80, 128, 143)

4.9 Carbon dioxide wedged venography

Injection of carbon dioxide into a catheter in the wedged hepatic venous position facilitates excellent venography of the hepatic venous and portal venous tree. (23)

4.10 Portal pressure measurement

Vein-occlusion pressure: It is possible to measure the vein-occlusion pressure by inserting a measuring catheter through the cubital or jugular vein into a hepatic vein. Measurement can be made as free hepatic venous pressure (FHVP), whereby hepatic venous blood flows around the measuring catheter, or as wedged hepatic venous pressure (WHVP), whereby occlusion of the hepatic vein is achieved by inserting the measuring catheter into a branch of the hepatic vein or by inflating the measuring catheter balloon. The WHVP correlates closely with the portal vein pressure. Its normal value is 7–12 mm Hg. • The FHVP corresponds to the intra-abdominal pressure, which is normally 3–11 mm Hg.

Hepatovenous pressure gradient: The difference between WHVP and FHVP is used to calculate the hepatovenous pressure gradient (HVPG). This is equivalent to the portal (= sinusoidal) venous pressure. The pressure difference between the portal vein and the inferior vena cava is 1–4 mm Hg. Pressure levels of ≥ 8 mm Hg result in the formation of collateral vessels or ascites. At 12 mm Hg and higher, bleeding of the oesophageal varices occurs. The HVPG can be an important prognostic factor in terms of survival in patients with bleeding oesophageal varices. (84, 100) The examination can be carried out on an outpatient basis; this takes about 15 minutes, whereby the length of exposure to radiation is < 2 minutes. Accordingly, it is possible to carry out follow-ups over a number of years. Normal WHVP values are 4–8 mm Hg. In cases of intrahepatic portal hypertension, particularly with liver cirrhosis, the WHVP corresponds to the directly measured portal venous pressure. In a prehepatic or presinusoidal block, the WHVP is normal. Posthepatic portal hypertension displays increased hepatic venous pressure. (s. tab. 14.9)

Morphological sequelae
1. Splenomegaly
2. Portacaval collateral circulation
3. Formation of hepatic lymphocysts
4. Portal hypertensive intestinal vasculopathy
– portal hypertensive gastropathy
– portal hypertensive colonopathy
Haemodynamic sequelae
1. Elevated cardiac output
2. Lowered peripheral resistance
3. Elevated heart rate
4. Lowered arterial blood pressure
Pathophysiological sequelae
1. Reduced detoxification of noxae
2. Impaired biotransformation
3. Coagulation disorders
4. Hepatopulmonary syndrome
5. Endocrine and metabolic disorders
6. Disposition to bacterial infections
7. Insufficiency of lymph drainage
8. Ascites

Tab. 14.8: Characteristic morphological, haemodynamic and pathophysiological sequelae of portal hypertension

5 Sequelae of portal hypertension

The **clinical picture** of portal hypertension can vary greatly, since it is either characterized by the respective underlying disease or the symptomatology of the latter is still prevalent. • Irrespective of their aetiology and pathogenesis, all forms of long-standing portal hypertension generally lead to the same **sequelae,** albeit of differing intensity. (s. tab. 14.8)

Depending on the localization of the portal resistance, differing portal and hepatic **pressure values** and clinical findings are obtained for the five forms of portal hypertension. In this way, it is possible to gain more information for differential diagnosis. (s. tab. 14.9)

5.1 Splenomegaly

Splenomegaly following portal haemostasis (s. fig. 14.7) leads to increased haemolysis as well as leukopenia and thrombopenia. The last two conditions can also result from the sequestration of blood in the enlarged spleen or from an inhibited function of the bone marrow. Generally, these haematological findings only normalize in about 25% of cases following splenectomy or a shunt operation. It should be noted that a normal-sized spleen does not exclude portal hypertension. (36) There is no close correlation between the severity of portal hypertension and the size of the spleen. Morphological analysis reveals a thickened capsule with a firm consistency and dark blood oozing from the surface. An increase in fibres mainly affecting the sinus walls is the principal morphological manifestation. Sinusoids are dilated and lined with thickened epithelium. In addition to this fibroadenia, hyperplasia of the RES ensues. Haemorrhages often develop adjacent to arterioles of a Malpighian corpuscle. Splenic infarction occurs frequently. (s. fig. 35.10) • Prolonged portal hypertension sometimes leads to the formation of **Gamna-Gandy nodules.** These are brown-yellow, siderin-laden fibrous nodules within the sinus, apparently caused by microhaemorrhaging. *(see chapter 11)*

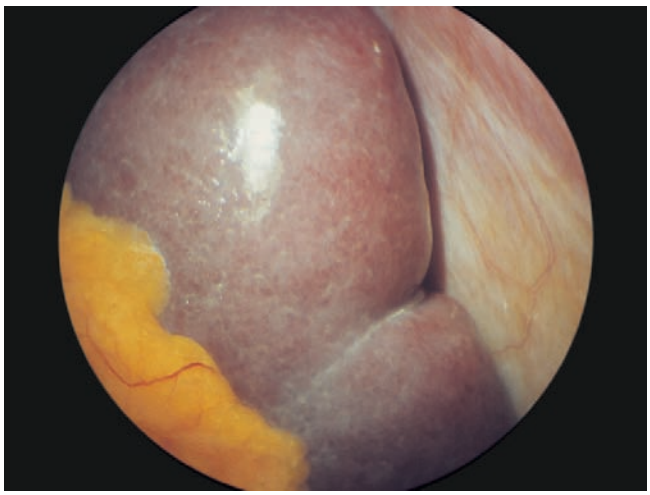

Fig. 14.7: Splenic tumour in portal hypertension following posthepatitic liver cirrhosis

Forms	Portal pressure	WHVP	Spleno-megaly	Oesophageal varices	Ascites
1. **Prehepatic portal hypertension**	↑	N	++	++	∅, (+)
2. **Intrahepatic portal hypertension**					
• presinusoidal	↑	N	+	++	(+)
• sinusoidal	↑	↑	++	+++	+++
• postsinusoidal	↑↑	↑↑	++	+++	+++
3. **Posthepatic portal hypertension**	↑	↑	+	++	++

Tab. 14.9: Haemodynamic and clinical findings in the 5 localized forms of portal hypertension (elevated hepatovenous pressure gradient = >9 mm Hg; increased risk of oesophageal varix bleeding = >12 mm Hg) (N = normal; ∅ = not present)

5.2 Portacaval collateral circulation

Portacaval collaterals represent the final stage of pressure-induced changes to the portal vessels. Initial *dilation* of the small portal vein branches is followed by the development of *meandering vessels*. This produces a compensating gain in vascular volume. In the long term, however, the thin-walled portal vessels are unable to withstand the elevated portal venous pressure. As a result, portacaval anastomoses form, which ultimately culminate in *varices* and frequently also in extensive *collateral circulation*. In addition to this, the portal vein itself can develop different degrees of ectasia. However, this reaction is generally accompanied by fibrosis and increased elasticity of the vessel wall. Portal hypertension leads to the dilation and reopening of veins which connect the portal vein system to the superior or inferior vena cava. Hence collateral circulation develops in the region of the oesophagus and gastric fundus as well as in the intestinal tract, retroperitoneum, lungs, spleen and kidneys, and at the anterior abdominal wall. (s. tab. 14.10) (s. figs. 7.5; 14.11, 14.12; 16.9)

Cranially draining collaterals
1. coronary gastric vein → azygous vein → short gastric veins → azygous vein
2. paraumbilical
3. portocoronary
4. portorenal
5. veins of Glisson's capsule, splenic capsule and diaphragm

Caudally draining collaterals
1. paraumbilical
2. gastrolienal
3. splenorenal
4. superior and inferior mesenteric veins → Retzius veins → ovarian/spermatic vein → haemorrhoidal venous plexus

Tab. 14.10: Possible formation of portacaval collaterals

5.2.1 Oesophageal and gastric varices

The collateral circulation described by H. Eppinger (1937) leading to the formation of oesophageal and fundic varices is still valid. (s. fig. 14.8) The hepatofugal blood flow of the portal vein passes through the coronary gastric vein to the perioesophageal venous plexus, which can form varices of the fornix or fundus. The blood is transported to the submucosal venous complex in the lower oesophagus. There are collaterals to the spleen via the short gastric veins. Anastomoses lead from the lower third of the oesophagus to the azygous and hemiazygous vein. In the central third of the oesophagus, a varicose venous plexus is formed due to stasis of the hepatopetal blood flow. From here, anastomoses run to the pericardial and intercostal veins as well as to the superior mediastinal and the diaphragmatic veins. These vessels conduct the blood to the azygous and hemiazygous veins, draining the entire blood flow into the superior vena cava. At the junction between the central and upper third of the oesophagus, the oesophageal varices disappear. This is a result of the balance of pressure with the right atrium created by the azygous vein. In line with the caudocranial blood flow, these oesophageal varices are also referred to as **"uphill" varices** (V. Buchtala, 1950) or as *type I varices*. The *pressure in the oesophageal varices* is temporarily raised by the ingestion of food and by an intra-abdominal increase in pressure (e.g. coughing, straining, lifting heavy loads). However, the pressure in the oesophageal varices is not raised in the head-down position. (35, 109, 123)

Oesophageal variceal pressure: The size of the oesophageal varices does not correlate with the magnitude of the portal venous pressure, but it does correlate with the oesophageal variceal pressure. This measurement is defined as the difference in pressure between the oesophageal lumen and the varix lumen. Measuring is done by fine-needle aspiration of a varix and the use of an extracorporeal pressure recorder. This technique is simple and reliable; it does not precipitate bleeding. Intravariceal pressure is a key factor in predicting variceal bleeding. (90) Measuring by way of a pressure sensor applied directly only yields valid results with large varices.

The **frequency,** localization and severity of oesophageal varices determine the life span of patients with portal hypertension. Oesophageal varices can be detected in about 80% of patients (i.e. some 20% of patients surprisingly do not present varices). In 90–95% of cases, the varices are located in the lower and central thirds of the oesophagus. The simultaneous occurrence of gastric fundic varices is only observed in 5–10% of patients. *Regression* of oesophageal varices (e.g. after alcohol abstinence) may occur.

The **radiographic detection** or **monitoring** of oesophageal varices using contrast medium is only carried out in rare

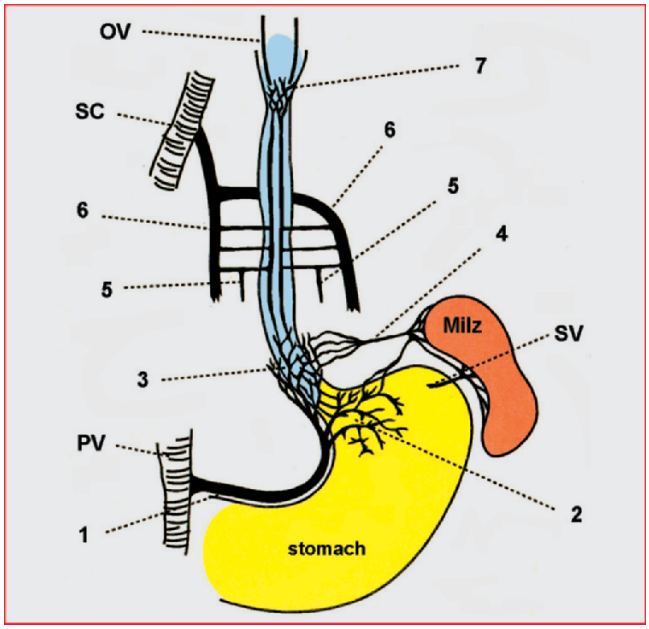

Fig. 14.8: Diagram showing the formation of oesophageal varices in portal hypertension (modified from H. Eppinger, 1937) • OV = oesophageal veins; SC = superior vena cava; SV = splenic vein; PV = portal vein; 1 = coronary gastric vein; 2 = perioesophageal venous plexus; 3 = submucous venous complex in the lower oesophagus; 4 = short gastric veins; 5 = hemiazygous vein; 6 = azygous vein; 7 = venous plexus of the central oesophagus

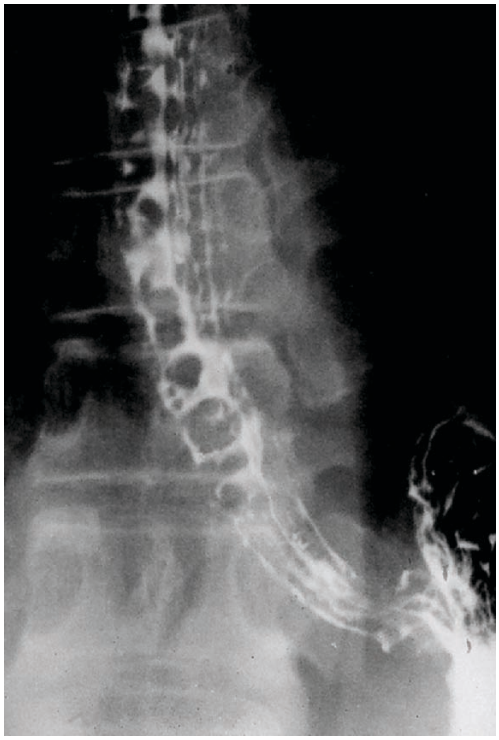

Fig. 14.9: Moderately dilated oesophagus with irregular surface. Numerous, differently sized filling defects as a result of varices

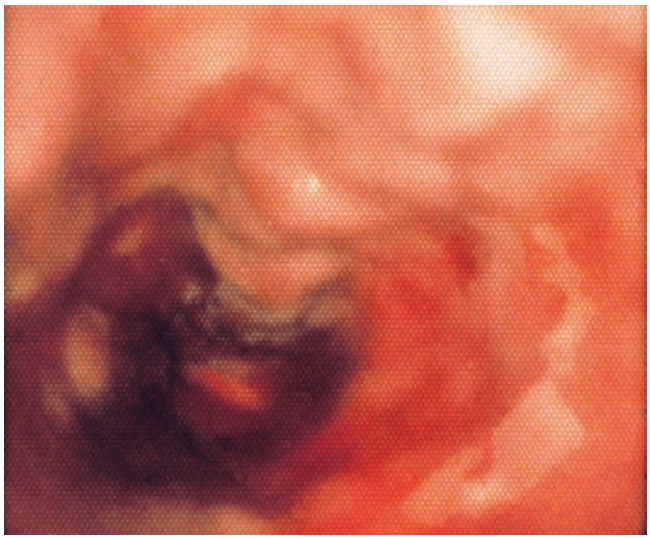

Fig. 14.10: Oesophagogastroscopy: pronounced varicosis (degree of severity III) in the lower third of the oesophagus

cases (after immobilizing the oesophagus by medication). During this procedure, the areas of the cardiac and fornix fundus should be carefully examined. (s. fig. 14.9)

The best method of detection is **oesophagogastroscopy.** (s. fig. 14.10) Localization, extent and severity of varices can be reliably determined with this method. (37, 121) The literature features a number of **staging schemes,** most of which have been developed empirically. (quot. 121) The main assessment *criteria* (with differing degrees of emphasis) are: length extension, vessel diameter, variations in diameter, number and colour of varices, mucosal changes (red spots, folding). Three-dimensional venous imaging (luminal prominence, length extension, diameter) can also be carried out. According to a well-accepted classification (1988), the criterion for stage I is defined as the possibility of depressing and squeezing out the varices, while stage II is characterized by the absence of this possibility. The circular enlargement of varices is defined as stage III. (s. tab. 19.6)

► **Downhill varices:** The downhill varices (B. Felson et al., 1964), which only occur in the proximal third of the oesophagus, are of both diagnostic and clinical significance. They were first described by M. Israelsky and H. Simchowitz in 1932. These varices do not result from portal hypertension, but are due to an elevation of pressure in the superior vena cava. This leads to a craniocaudal "downhill" blood flow. If there is an obstruction of the superior vena cava and/or the azygous vein, the blood flows from the head, neck and mediastinal region via the inferior thyroid vein and the mediastinal collateral veins into the oesophageal veins and via the coronary gastric veins (hepatopetally) into the portal vein (= *type II*). Causal factors are goitre or recurrent goitre (45–60%), mediastinal fibrosis and malignant tumours with mediastinal lymph nodes (25–35%).

Type IIa is characterized by the patency of the azygous vein. Varices are only found in the upper third of the oesophagus. Retrosternal goitre has proved to be the most frequent cause. A superior vena cava syndrome is generally not detectable. • *Type IIb* is produced by the additional occlusion of the azygous vein. The entire

blood volume must now be redirected to the inferior vena cava. • Although downhill oesophageal varices mainly occur in the upper third section, they often spread over the entire oesophagus in relation to the severity of the neck vein distension and the duration of the pathological condition. They are generally very pronounced and hence represent a genuine differential diagnosis of oesophageal varices in portal hypertension. The vertebral venous plexus and the thoracic veins are also used for drainage of the blood. • Bleeding from downhill oesophageal varices is rare, since (*1.*) there is a smaller blood volume with a lower pressure in the region of the superior vena cava, (*2.*) there is generally no coagulation disorder, and (*3.*) the mechanical burden in the upper oesophageal third is considerably lower. Bleeding is, however, quite possible in type IIb. • For this reason, *clarification of oesophageal varices* should always take into account the clinical picture of downhill oesophageal varices from the pathogenic and prognostic viewpoints. (27, 29)

5.2.2 Anorectal varices

Blood from the haemorrhoidal venous plexus passes via the azygous superior rectal vein into the inferior mesenteric vein and thereafter into the portal vein. By contrast, the paired middle rectal vein and inferior rectal vein discharge their blood via the iliac vein into the inferior vena cava. In portal hypertension, anorectal varices are found in the region of the rectum, the anal canal and the external anal region. • **Haemorrhoids** are distended and dislocated cavernous bodies in the rectum, which have no connection to the portal venous system. • Although haemorrhoids and anorectal varices are two different clinical pictures, it is quite possible for them to occur simultaneously. The frequency of anorectal varices (40–80%) is dependent upon the extent and duration of portal hypertension. The bleeding tendency is low (7–14%). However, there have also been reports of massive haemorrhages. (20, 40, 51, 61, 77, 97, 148) (s. tab. 14.10)

5.2.3 Intestinal varices

Varices occasionally occur in the stomach (114), duodenum (55, 140), small intestine, gall bladder (32, 78, 149) and colon (17, 40, 43, 62, 137) – excluding the transverse colon – as well as in the proximity of operative anastomoses or stomata. This generally involves collaterals between the branches of the inferior or superior mesenteric vein and small veins leading to the inferior vena cava. Colonic varices, which have not been detected endoscopically can be demonstrated by visceral angiography with a sensitivity of about 95%.

5.2.4 Abdominal wall varices

Pronounced anastomoses can develop between the mesenteric veins and the anterior abdominal wall. This is largely a result of spontaneous or postoperative adhesions (so-called *spontaneous Talma effect*). (s. figs. 7.5;

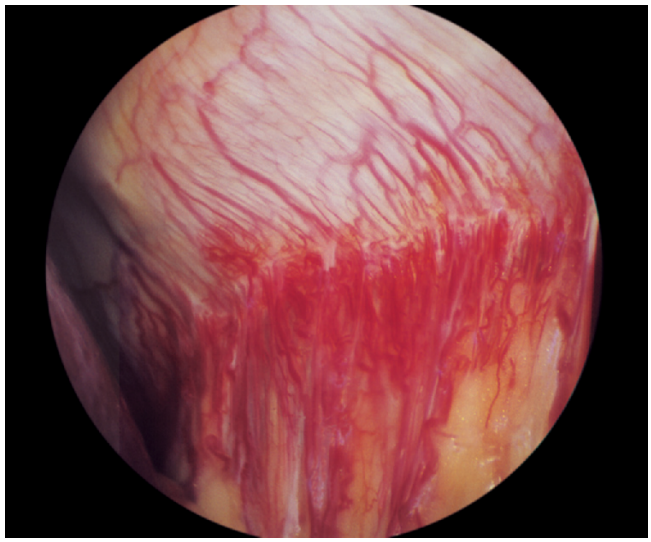

Fig. 14.11: Postoperative adhesions in the region of the abdominal wall with "spontaneous Talma effect" resulting from portal hypertension

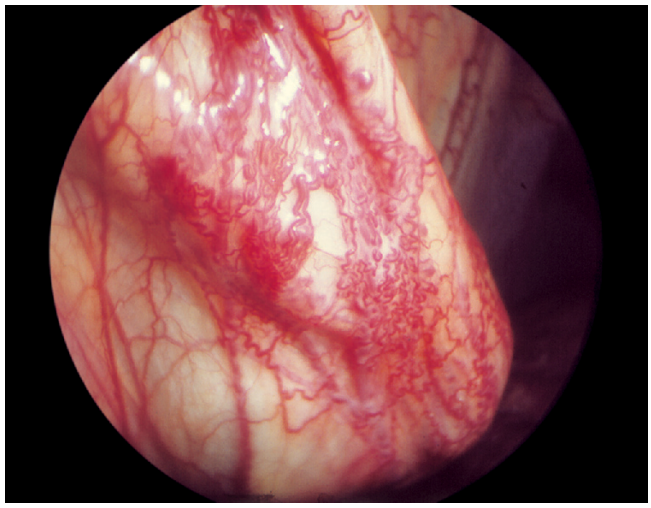

Fig. 14.12: Dilation and convolution of the small veins in the region of the round ligament (= teres) with recanalization of the umbilical vein resulting from portal hypertension (s. fig. 6.7)

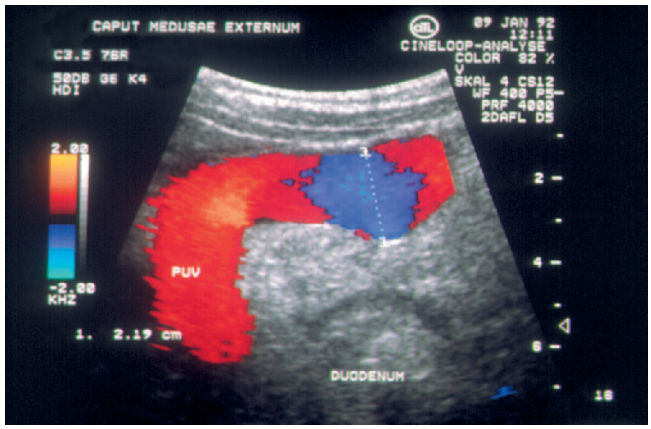

Fig. 14.13: External caput Medusae in liver cirrhosis. • The thick paraumbilical vein (diameter 2 cm) is shown subcutaneously at the exit of the vessel from Glisson's capsule. The colour-encoded vessel with a varicose enlargement at the exit point of the paraumbilical vein from Glisson's capsule is visible immediately below the ventral layers of the abdominal wall

14.11) Reopening of the umbilical vein in the round ligament (s. fig. 14.12) causes anastomoses to form with the epigastric veins in the anterior abdominal wall. (93) This can occasionally result in **caput Medusae:** radial, bluish, tortuous vessels, which are sometimes slightly raised and sometimes nodally varicose, leading from the navel to the abdominal wall. Generally, however, only a few larger collateral vessels are detectable as opposed to a complete caput Medusae. (s. p. 91) (s. fig. 14.13)

5.2.5 Retroperitoneal varices

There is a direct blood flow from the veins of the colon into the inferior vena cava via anastomoses with retroperitoneal veins.

5.2.6 Splenorenal varices

In about 5% of cases, blood passes through the short gastric veins to the splenic vein and then through other collateral veins to the left renal vein (= spontaneous splenorenal shunt).

5.2.7 Retzius' veins

Distally, the suprarenal veins and Retzius' veins provide a pathway into the inferior vena cava via the renal vein. Retzius' veins act as anastomoses between the portal vein branches in the intestinal and mesenteric regions and the branches of the inferior vena cava. (53)

5.2.8 Sappey's veins

Sappey's veins are located between the surface of the liver or spleen and the diaphragm. They are used for collateral circulation. Drainage takes place into the inferior vena cava.

5.2.9 Bronchial varices

Tracheobronchial varices with haemoptysis in alcoholic cirrhosis with portal hypertension were reported for the first time in 1994. (152)

5.2.10 Biliary varices

Biliary varices are defined by means of endosonography as serpiginous, anechoic vascular channels in and/or surrounding the extrahepatic biliary ducts as well as the gall bladder. (32, 59, 78, 98, 149) (s. p. 266)

5.2.11 Sublingual varices

Sublingual varices may be a rare source of expectorated blood in portal hypertension. (56)

5.3 Formation of hepatic lymphocysts

Particularly in intrahepatic portal hypertension, the portal vein system is relieved by an increase in hepatic lymph formation. The hepatic lymph flow is raised up to 7 ml/min (about 8 times the normal level), and the lymphatic pressure rises to 18 cm H_2O (normal value: 11.6 cm H_2O). The increase in lymphatic pressure leads to the formation of lymphocysts on the surface of the liver. Lymph, which is rich in albumin, is then able to drip from these lymphocysts into the abdominal cavity. (s. p. 297) (s. fig. 16.5)

5.4 Portal hypertensive vasculopathy

Endoscopic examination of the gastrointestinal tract often reveals erosion in the form of *portal hypertensive intestinal vasculopathy.* (48, 111, 138) These findings correlate with the degree of severity of portal hypertension. Intestinal erosion is generally the cause of a positive blood test in the faeces of patients with cirrhosis (= occult bleeding). In *portal hypertensive gastropathy* (frequency 20–30%), hyperaemic mucosa is in evidence due to dilation of the vessels and submucosal arteriovenous shunt formations. There is a mosaic-like pattern with small polygonal areas, surrounded by a whitish-yellow depressed border. Red marks (= lesions) signify a high risk of bleeding. These changes can usually be detected in the fundus, but may extend throughout the stomach. Hypoxaemia of the mucosa increases its susceptibility to aggressive elements. Numerous petechial lesions with punctiform deposits of haematinized blood are observed on the otherwise apparently intact gastric mucosa. (106, 130) Levels of prostaglandin E_2 in the mucosa are reduced. (147) (s. fig. 14.14)

About 10% of patients with cirrhosis have ulcers that bleed, whereas in 20–25% of cases, bleeding is caused by portal hypertensive gastropathy. (4, 6, 22, 34, 49, 101, 106, 120, 130, 132, 141) • Erosive vasculopathy can also be detected endoscopically in the region of the colon as *portal hypertensive colonopathy.* (12, 40, 62, 103, 126) Bleeding following vasculopathy of this kind requires local measures (e. g. laser), medication or shunting.

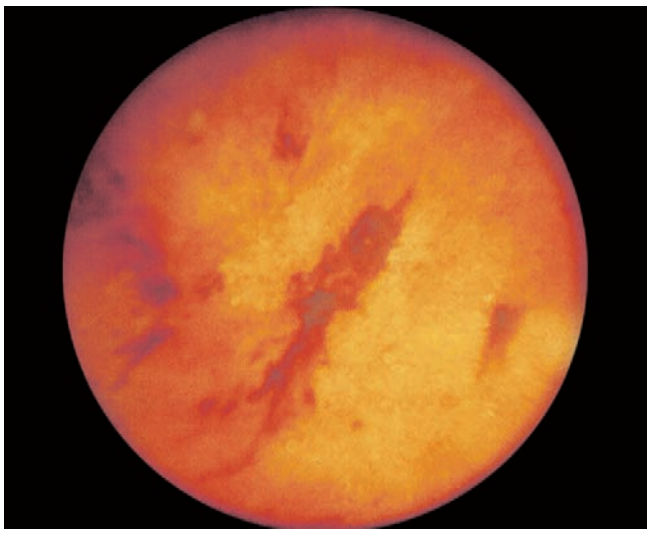

Fig. 14.14: Portal hypertensive gastropathy showing linear and patchy erosions

5.5 Pathophysiological sequelae

Portosystemic collaterals can divert up to 80% of the portal vein blood away from the liver. This initially results in haemodynamic disorders with subsequent (multifactorial) *hyperdynamic splanchnic circulation*. More and more varices develop around the bypasses in various venous areas, primarily in the form of oesophageal varices. Damage to the mucous membrane in the stomach and in the colon takes the form of hypertensive gastropathy/colopathy. Rechannelling of the umbilical vein leads to the Cruveilhier-von Baumgarten syndrome. (42) (s. tab. 14.8)

A grave consequence of collateral circulation is the reduced detoxification of exogenously administered noxae or endogenously produced toxins. This can lead to the development of latent, or eventually manifest, *hepatic encephalopathy* or neuropathy as well as to additional toxically mediated liver damage, or even liver insufficiency. • *Impairment of biotransformation* may cause unpredictable changes in the pharmacokinetics of medicaments or indeed trigger adverse drug reactions and interactions. (s. p. 57)

In addition to this, the occurrence of collateral circulation induces a protracted derangement of the numerous *RES functions*. (s. p. 69) As a result, the clearance capacities of activated coagulation products and inhibitors of the coagulation and fibrinolysis systems are reduced. Besides this, changes in the intrahepatic vascular architecture lead to a disorder of the portal microcirculation and trigger intravascular coagulation. (65) (s. p. 350) The increased RES activity results in hypergammaglobulinaemia and the subsequent inhibition of albumin synthesis. Inadequate elimination of endotoxins leads to endotoxinaemia with damage to the biological membranes, interference in hepatocellular metabolic processes, development of vasoactive substances, haemolysis, coagulopathy, etc.

Portosystemic collaterals also divert *hormones* past their target organ, the liver, with the result that they do not fully develop their activity (e. g. insulin, glucagon) or are not broken down and eliminated (e. g. aldosterone, steroids).

Portopulmonary hypertension (PPH) is defined as a secondary form of pulmonary hypertension in patients with portal hypertension. It is characterized by increased pulmonary vascular resistance in normal pulmonary capillary wedge pressure. Pulmonary hypertension typically features an anatomically fixed pulmonary vasoconstriction. The vascular changes depend on (*1*.) vasoconstriction, (*2*.) structural remodelling of the pulmonary arteries (fibroelastosis of the intima, hyperplasia of the media), and (*3*.) formation of microthrombi. Thus the histological changes are similar to those found in primary pulmonary hypertension. • Frequency of PPH in cirrhosis is 2−5%. Diagnosis is established using Doppler echocardiography and right heart catheterization. Prognosis is poor. In some patients, it was possible to improve the pulmonary blood flow by means of i.v. prostacyclin. (45, 104) *(see chapter 18)*

5.6 Portal biliopathy

Portal biliopathy as an entity was first described by S.K. Sarin et al. in 1992. This condition may be observed in portal hypertension, particularly in patients with extrahepatic portal vein obstruction. Such changes have also been reported, however, in a milder form in non-cirrhotic fibrosis, congenital hepatic fibrosis and cirrhosis.

The venous drainage of the common bile duct is guaranteed both by a paracholedochal *Petren's venous plexus* (T. Petren, 1932; quot. 19) and a pericholedochal *Saint's venous plexus* (J.A. Saint, 1961; quot. 19). The veins of these plexuses vary in size, but their diameter is usually no larger than 1 mm. • The development of portal hypertension leads to the opening of numerous collaterals. Likewise, the formation of varices in these plexuses may be observed. The first description of choledochal varices with subsequent compression of the common bile duct was given by A.H. Hunt in 1965. The same process causes collaterals around the gall bladder and the bile ducts.

The bile duct wall is thin and pliable, thus allowing protrusion of the varices into the lumen (a picture resembling oesophageal varices). This results in partial (and occasionally complete) bile duct obstruction, a condition which explains the usual clinical features: abdominal pain, recurrent fever, jaundice, increase of γGT and AP. It should be noted, however, that most patients are asymptomatic at onset and indeed for a long period after that. Development of choledocholithiasis is a frequent sequela. It is the cause of recurrent cholangitis, and subsequently of secondary biliary cirrhosis. Therefore, in patients with portal hypertension who show signs of biliary obstruction (clinical, biochemical, sonographical, cholangiographical), portal biliopathy may well be suspected. Sonography and MR cholangiography, if necessary ERC, are essential for establishing the diagnosis. (44)

Therapy: Asymptomatic patients do not need any treatment. With symptomatic patients, it is important to use therapeutic strategies which are directed towards the predominant symptoms. These include removal of gallstones by means of sphincterotomy (beware of varices!), antibiotics, placement of a stent, cholagogue agents, TIPS and surgical techniques. (19, 32, 59, 98, 149)

6 Therapy

The underlying cause of portal hypertension must first be found. Elimination of this cause (if possible) is even more important than treating the portal hypertension itself.

6.1 Conservative therapy

In cases of acute thrombosis, *fibrinolytic therapy* may occasionally be necessary.

Both vasodilators and vasoconstrictors can be used in the medicinal therapy of portal hypertension. However, the extensive literature available is limited almost exclusively to their use in treating oesophageal varix bleeding; less attention is paid to long-term therapy with the objective of lowering portal hypertension. The combination of β-blockers with, for example, nitrovasodilators, α-adrenergic antagonists or spironolactone leads to an additional decrease in the portal venous pressure. (7, 14, 33, 64, 119) (s. tab. 14.11)

Clonidine	=	α_2-adrenergic agonist
Isosorbide dinitrate	=	nitrovasodilator
Isosorbide-5-mononitrate	=	nitrovasodilator
Molsidomine	=	nitrovasodilator
Nadolol	=	β-blocker (nonselective)
Prazosin	=	α_1-adrenergic antagonist
Propranolol	=	β-blocker (nonselective)
Spironolactone	=	aldosterone antagonist
Terlipressin	=	vasopressin derivative

Tab. 14.11: Substances for lowering portal hypertension

Propranolol, which was used for the first time by D. Lebrec et al. in 1980, brings about an approx. 50% reduction in portal venous pressure in some two thirds of patients. Dosage is established in line with the slowing-down of the heart rate (to about 25% less than that of the initial value, but not below 55/min). Propranolol also appears suitable for preventing erosive gastropathy. (6) In cases of bleeding, intravenous administration of terlipressin should be considered. (s. p. 366)

Nadolol has also been shown to reduce portal venous pressure. Gradually increasing the dosage to 2 x 1 mg/day is usually sufficient. (1)

Clonidine is an α_2-adrenergic agonist which is used effectively in portal hypertension at an average dosage of 0.075−0.3 mg/day.

Prazosin belongs to the α_1-adrenergic antagonist group and can be administered in portal hypertension at an average dosage of 2−4 mg/day.

Molsidomine is a prodrug. This substance is especially effective due to the fact that no tolerance develops. It leads to a fall in portal pressure of up to 40%, even after long-term use. Administration of this substance (e. g. 2 x 8 mg/day) is therefore recommended. (52) (s. p. 366)

Spironolactone is used as the basic medication in liver cirrhosis. By means of this therapy (upwards of 50 mg/day), it is possible to achieve a reduction in pressure in the portal system of about the same magnitude as with propranolol. (1, 60) (s. p. 312)

Ascorbic acid as an antioxidant improved the endothelium dysfunction and reduced the elevated level of malondialdehyde in patients with cirrhosis. In addition, the postprandial increase in hepatic venous pressure gradient was reduced. (50)

Total *abstinence from alcohol* (an absolute "must") can have a long-lasting beneficial effect in lowering elevated portal pressure values.

▶ These recommendations regarding medication are limited by the respective pharmacological properties, interactions and unwanted side effects. Such factors must always be taken into account. Therapeutic expectations with regard to adequate and constant reduction in portal pressure should not be set too high. Nevertheless, every possibility to reduce elevated portal venous pressure should be exploited.

6.2 Invasive therapy

In systemic diseases, *splenectomy* has to be considered. A *shunt operation* may be indicated in haemorrhage-free intervals. A proven alternative to the operative shunt is the transjugular intrahepatic portosystemic stent shunt.

Transjugular intrahepatic portosystemic stent shunt (TIPS) is available as an invasive therapy for portal hypertension. This concept has now been methodologically standardized. The success rate is extremely high. By means of balloon-expanded stents, portal decompression can be adapted to the respective situation in every single patient. The Palmaz stent can be placed with an accuracy of one millimetre; its diameter can also be adjusted in millimetre increments. The Wall stent can be used as an alternative in individual cases. **Indications** for this therapy in portal hypertension, where there is a persisting danger of variceal bleeding, are: (*1*.) lack of success with all medication therapy, including repeated sclerotherapy, (*2*.) inoperability in terms of a shunt operation, (*3*.) when a liver transplantation is not feasible, and (*4*.) bridging the time gap before an indicated liver transplantation. However, in up to 50% of patients, the period from stenosis to stenting ranges from 6 to 24 months; the stent must therefore be monitored constantly. (15, 132, 139) (s. pp 314, 320, 368, 899)

Shunt operations: Surgical shunts are only to be considered in cases where iatrogenic refractory bleeding occurs after all forms of conservative therapy have failed. A therapeutic shunt is only justified in the form of a (delayed) emergency shunt following a massive haemorrhage or as an elective shunt following bleeding. Portosystemic anastomoses are carried out in the form of a complete shunt (i. e. without maintaining residual portal perfusion) or as an incomplete shunt (i. e. maintaining residual portal perfusion with only a slight fall in the portal pressure). Portacaval end-to-side anastomosis as

a complete shunt is technically the most simple and also the safest form, with the lowest risk; the thrombosis rate is less than 2%. (s. p. 370) A central total shunt is more successful in variceal bleeding or ascites (but there is a greater tendency for postoperative HE). A peripheral shunt reduces the tendency to bleed, but may cause deterioration of status in patients with ascites (however, HE is less frequent). A central shunt should not be carried out on patients who are scheduled to have a liver transplantation. There is no indication for prophylactic shunting or sclerosing of oesophageal varices before bleeding. (47, 96) (s. p. 870)

Liver transplantation not only removes the continued risk of variceal bleeding, but also eliminates the underlying liver disease causing portal hypertension. However, due to the scarcity of liver donors, limited financial resources and the life-long immunosuppression required, this major surgical intervention can only rarely be considered − perhaps in cases where a previous shunt operation or the creation of a TIPS was not possible. The survival rate for transplantation is higher than when recurrent bleeding is treated by repeated sclerotherapy (73% versus 17% after 4 years). The indication for transplantation (e. g. cirrhosis Child B or C) should be set as early as possible. (s. p. 903)

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