Symptoms and Syndromes

18 Hepatopulmonary syndrome

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► Recognition of a hepatopulmonary syndrome goes back over one hundred years (1884) to the detection of the **triad:** *cyanosis*, *clubbed fingers* and *liver cirrhosis*. (18). The same constellation of findings was described by A. GILBERT et al. in 1895 in juvenile patients suffering from hypertrophic biliary cirrhosis. • Reports on **hypertrophic osteoarthropathy** were published by A.A. HIJMANS VAN DEN BERGH in 1901. • A.M. SNELL detected **hypoxaemia** in chronic liver patients for the first time in 1935. (52) A right shift of the dissociation curve of oxyhaemoglobin was ascertained by A. KEYS et al. in 1938. In the course of acute progressive liver failure, R. RYDELL et al. (1956) also observed hypoxaemia; at autopsy, this patient showed intrapulmonary **arteriovenous shunts.** (45) Since then, there have been many reports on the detection of arteriovenous anastomoses in the lungs (further details in references 6, 7, 23). These arteriovenous shunts had already been attributed to vasoactive substances. The development of clubbed fingers was deemed to be the result of arteriovenous anastomoses in the tips of the fingers and the impact of reduced ferritin. (35, 53) • The term **hepatopulmonary syndrome** was used by T.C. KENNEDY et al. (1977) (26) and likewise by L.S. ERIKSON et al. (1989) to describe the correlation between hypoxaemia and liver cirrhosis.

1 Definition

The hepatopulmonary syndrome (HPS) is defined as a disorder in pulmonary gas exchange (= mismatch of ventilation and perfusion) due to intrapulmonary vasodilations (= reduction of pulmonary vascular resistance) in cases of chronic liver disease or acute liver failure. • Other criteria must also be met: (*1.*) ruling out of underlying pulmonary or cardiac disease, (*2.*) increase in the alveolar-capillary oxygen gradient (> 20 mm Hg) without or with hypoxaemia (< 70 mm Hg partial oxygen tension) with a clear drop of the O_2 value when changing from the supine to the upright body position, and (*3.*) detection of intrapulmonary vasodilations and/or a.-v. shunts.

2 Epidemiology

Hypoxaemia (p_aO_2 < 70 mm Hg) is found in 45–69% of patients suffering from cirrhosis or liver insufficiency. Only rarely has severe hypoxaemia been demonstrated (p_aO_2 < 50 mm Hg). (6, 31, 55, 58) • Intrapulmonary vasodilations could be ascertained in 13–47% of liver transplant candidates. (25) In about 50% of cirrhotic patients, a decline in the diffusion capacity for carbon monoxide was detected. (22) Some 30% of cases showed no (physiological) reduction in pulmonary vasoconstriction in hypoxia. The prevalence of HPS in cirrhosis varies between 4% and 19%. It occurs more frequently in patients with cirrhosis than with extrahepatic portal venous obstruction. (5, 20, 47)

3 Causes and pathogenesis

In theory, there are **three causes** of HPS (since hypoventilation is not deemed a possible cause): (*1.*) arteriovenous shunts, (*2.*) disturbed alveolocapillary oxygen diffusion in terms of impaired diffusion-perfusion, and (*3.*) mismatches between ventilation and perfusion. Consequently, there are numerous liver diseases which can be associated with HPS. (s. tab. 18.1)

Acute viral hepatitis (17, 40)	Liver cirrhosis
α_1-antitrypsin deficiency	Nodular regenerative hyperplasia (9)
Biliary atresia	Peliosis hepatis (8)
Budd-Chiari syndrome (13)	Postsurgical shunt (21)
Chronic active hepatitis (54)	Primary biliary cirrhosis
Chronic hepatic allograft rejection	Schistosomiasis
Congenital cystic fibrosis (19)	Tyrosinaemia
Fulminant liver failure (57)	Wilson's disease
Inf. vena cava obstruction (12)	

Tab. 18.1: Liver diseases associated with the hepatopulmonary syndrome (with some references). • Portal hypertension is considered to be an essential factor in the pathogenesis of HPS.

The existence of *portal hypertension* is probably the decisive factor in the development of HPS. The pathophysiological principles of HPS and the change in haemodynamics in cirrhotic patients were presented as a review in 1973. (6) A marked *pulmonary vasodilation* due to vasodilative substances is deemed to be the essential causative factor of HPS (K.R. REISMANN, 1956).

3.1 Vasodilation

Endotoxin is capable of inducing nitric oxide synthetases in the vascular endothelia of the liver and lung. *Nitric oxide* (NO) is a powerful **vasodilator** (through activation of guanylate cyclase) and is identical to the endothelium-derived relaxing factor (EDRF). An increase in NO in the vascular endothelia of cirrhotic patients is deemed to be one of the causative factors in the development of a hyperdynamic circulatory condition (= lower peripheral resistance), yet also of the hepatopulmonary syndrome (= lower pulmonary vascular resistance). NO concentration is increased in the expired air of patients with HPS. (5, 11) Animal experiments likewise suggested endothelial nitric oxide synthetase as being another causative factor. (16) In the same way, elevated values of glucagon, histamine, VIP, prostacyclin, calcitonin, substance P, atrial natriuretic factor and platelet-activating factor are considered to be vasodilators in the pulmonary vascular system. • Animal models of HPS showed that an increase of ET-1 production in

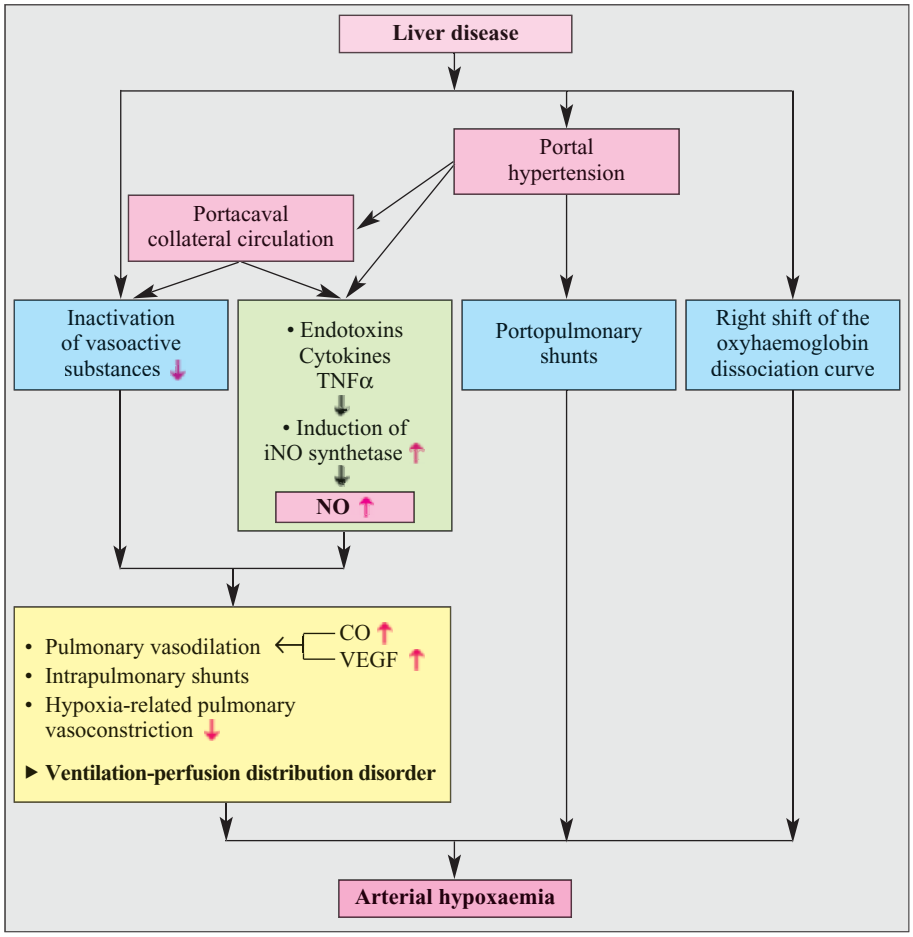

Fig. 18.1: Possible mechanisms in the pathogenesis of the hepatopulmonary syndrome. (VEGF = vascular endothelial growth factor, iNOS = inducible nitric oxide synthetase, TNF = tumour necrosis factor)

the liver correlates with both pulmonary nitric oxide synthase levels and pulmonary dysfunction. (5, 37, 59) In patients with liver cirrhosis, a markedly increased serum value of the vasoconstrictor ET-1 was demonstrated. Therefore it may be assumed that pronounced endothelinaemia leads to a modulation of NO production, which results in extensive intrapulmonary vasodilation. • *In cirrhosis, a decrease in the pulmonary vascular resistance with formation of intrapulmonary shunts occurs more frequently than pulmonary hypertension; the reason for these different modes of reaction is unknown.*

3.2 Shunt formations

The assumption that **a.-v. shunts** play a causative role in HPS is founded on (*1.*) the presence of very small intrapulmonary a.-v. shunts in the lung parenchyma and on the pleura (= *pleural spider naevi*) at autopsy (7), (*2.*) dilation of the capillary and precapillary intrapulmonary vessels, particularly in the basal lung region, and (as a very rare finding) (*3.*) isolated links detected between the branches of the portal vein and the pulmonary vessels. • These a.-v. anastomoses are mainly **functional shunts.** They are found in about 50% of cirrhotic patients. Given a normal width of the lung capillaries (8−15 µm), precapillary vascular dilations can attain a diameter of 15−150 (−500) µm. This is reversible. HPS (probably only type 1) can therefore completely recede after liver transplantation − analogous to the hepatorenal syndrome. It remains uncertain, however, whether the vascular changes imply dilated capillaries or opened a.-v. anastomoses. • **Anatomic shunts,** which may be intrapulmonary and portopulmonary as well as pleural, are rare. In terms of haemodynamics, they have no noteworthy effect. (5, 9, 23, 24, 33, 44, 56, 57) (s. fig. 18.1)

3.3 Impairment in diffusion and perfusion

The pathogenesis of HPS has not yet been fully clarified. Presumably, however, substances with vasodilator activity can bypass the liver through collateral vessels, thus effecting vasodilation of the pulmonary vessels. There is oxygen desaturation of the erythrocytes flowing centrally through the dilated vessels (= increased distance from vessel wall to vessel centre). Moreover, insufficient oxygen saturation of the erythrocytes is induced by a hyperdynamic circulatory state (= reduced blood-oxygen contact time) − giving rise to a **diffusion-perfusion defect.** As a result, inadequately oxygenated or non-arterialized blood reaches the pulmonary veins, leading to hypoxaemia. (22, 58) (s. fig. 18.1)

3.4 Ventilation-perfusion distribution disorder

In poorly ventilated lung areas, perfusion is diminished (= *von Euler-Liljestrand reflex*). This reflex is impaired in liver cirrhosis. The decrease in or loss of hypoxia-induced pulmonary vasoconstriction leads to the greater perfusion of poorly ventilated lung areas; this results in an increase in the intrapulmonary shunt volume and thus in a ventilation-perfusion distribution disorder with hypoxaemia. (15, 22, 31, 33, 56, 58) (s. fig. 18.1)

A particular pathophysiological finding with HPS is a **right shift of the oxyhaemoglobin dissociation curve.** The cause of this diminished affinity of haemoglobin for oxygen is assumed to be the greater concentration of 2,3-diphosphoglycerate found in erythrocytes. This results in arterial hypoxaemia.

4 Clinical aspects

In most HPS patients, pulmonary discomfort or findings generally remain absent for a long period; the p_aO_2 is still within the normal range (>80 mm Hg). Some patients, however, display *dyspnoea* at an early stage.

HPS becomes manifest three to seven years after the development of portacaval and/or splenorenal collateral vessels. In a more or less rapidly progressing course of disease, *cyanosis* develops with even more pronounced *hypoxaemia* (p_aO_2 < 70 mm Hg). Both hypoxaemia and dyspnoea generally worsen in an upright position (see below) due to increased cardiac output with shortened pulmonary transit time. Patients with distinct *spider naevi* show more severe pulmonary disorders than those where this skin stigma of liver disease is absent or only developed to a minor degree. Frequently, signs of respiratory *alkalosis* due to hyperventilation are found. There is a decreased diffusing capacity for CO_2. • Some 85–90% of HPS patients show *platypnoea* (= clear improvement of dyspnoea when the body position is changed from the vertical to the horizontal) and/or *orthodeoxia* (= decrease in p_aO_2 of >3 mm Hg upon assuming an upright body position); it is usually accompanied by aggravated dyspnoea. (42) Orthodeoxia is diagnosed by blood gas analysis or pulse oximetry in both the recumbent and the standing position. The cause of platypnoea and orthodeoxia is the reinforced perfusion of the dilated pulmonary vessels in the poorly ventilated basal lung areas in an upright body position. This leads to a rise in shunt volume and hence to a deterioration of the ventilation-perfusion disorder. • *Hour-glass nails* and *drumstick fingers* are frequently observed. (s. fig. 4.19) • There might even be a connection with the formation of *oesophageal varices.* (10) • Patients with functional shunts and impaired diffusion and perfusion present significantly better values regarding the arterial O_2 partial pressure upon *inspiration of 100% O_2*; patients with anatomic shunts show no improvement. • Tachycardia, higher cardiac output and lower values of mean arterial pressure and peripheral vascular resistance point to a *hyperdynamic circulation*. There is always a risk of *bacterial infection* with a corresponding deterioration in prognosis. (6, 9, 20, 27, 33, 38, 47)

The *ECG* is regular. The *chest radiograph* usually shows reinforced basal, interstitial vascular markings (bilateral, basilar, nodular or reticulonodular opacities). (36) *Spirography* yields normal volumes and expiratory resistance. (32) • The detection of intrapulmonary shunts is effected by *scintigraphy* (^{99m}Tc-labelled macro-aggregated albumin). Tracer particles with a diameter of 20–60 µm are not retained in the lung capillaries, but are directly passed on through shunts and pulmonary vasodilations (positive = >3–6 heart beats) to the brain, liver, kidney and other organs. (2, 38) • By means of contrast-medium *echocardiography* (generally using oxypolygelatine solution), it is also possible to identify intrapulmonary shunts. This procedure is deemed to be the screening method for the diagnosis of HPS, prior to the occurrence of alterations in blood gas. (3, 38) • *Angiography* produces normal or reduced pressure values in the pulmonary artery, diminished pulmonary vascular resistance and increased cardiac output; a net-like dilated vascular system is visible. • The ventilation-perfusion status in the lung can be defined exactly by means of the *multiple inert gas elimination technique* (MIGET). At the same time, it is possible to differentiate between intrapulmonary shunts and vasodilations.

One can differentiate between **two distinct patterns** of HPS, whereby type 2 is only very rarely detectable (49):

Type 1: Using angiography, minor to pronounced vasodilations of speckled or sponge-like appearance may be demonstrated. Additionally, spider-like vascular ramifications are identifiable. Depending on the extent of the vasodilations, marked or only slight improvement in hypoxaemia is observed in patients following administration of 100% oxygen. Liver transplantation is the most successful approach in the treatment of type 1. With a good response to the administration of 100% oxygen, regression of HPS is to be expected after OLT.

Type 2: As a rule, only slight vascular changes resembling a.-v. shunts or vascular malformations are identified using angiography. No hypervascularization is found. There is no real improvement in hypoxaemia following administration of 100% oxygen. Liver transplantation is often unsuccessful regarding HPS. • In the individual case, embolization may be indicated.

5 Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (hour-glass nails, clubbed fingers) (s. fig. 4.19), which has been known since 1884, is not caused by hypoxia, as has been assumed up

to now. (18) The cause is to be found in the intrapulmonary arteriovenous shunts: from the venous limb of the pulmonary vessels, megakaryocytes and thrombocyte aggregates pass directly through the shunts into the arterial limb and hence (unfiltered, uncatabolized or not inactivated) into the circulation. These (and possibly other) substances are deposited in the acra; they effect the release of the platelet-derived growth factor. The PDGF induces nail bed oedema (= *hour-glass nails*) and an increase in collagen synthesis by activating the fibroblasts (= *drumstick fingers*). (14, 35, 53)

6 Therapy

Up to now, there is no satisfactory drug therapy for HPS available. Spontaneous improvement of HPS after recovery from an underlying liver disease has been reported. Often HPS has deteriorated despite stable liver function. Improvements in HPS with the help of various substances, for which a certain therapeutic effect was considered plausible, were only achieved in individual cases and for just a limited time. (27, 33, 38)

► By administering *100% oxygen* (as long-term oxygen therapy), a higher and nearly normal partial oxygen pressure can be achieved in the dilated pulmonary vessels (albeit only in some of the patients and just temporarily). • Intravenous application of *prostaglandin* F_{2a} has produced some improvement in hypoxaemia. With the help of *antibiotic therapy* (e.g. norfloxacin), which led to a reduction in bacterial endotoxins in the intestines, it was possible to improve the arterial hypoxaemia considerably. (4) *Indomethacin*, or a combination of indomethacin and PGF (51), has likewise been effective. By administering *allium sativum* (garlic) for a period of several months, a significant improvement in arterial O_2 saturation could be achieved. (1) Only isolated cases involving treatment with *methylene blue* (= inhibitor of NO-related guanylate cyclase) have been reported. (43, 46) In HPS due to multifocular nodular hyperplasia, *glucocorticoids* and *cyclophosphamides* have been successful. (9) *Somatostatin antagonist*, *NO antagonist* and *almitrine bimesylate* have proved ineffective.

► *Implantation of a TIPS* has brought about a clear improvement in cases of hypoxaemia, probably due to a decrease in endotoxinaemia and the resulting reduction in the formation of nitric oxide. There was a rise in pulmonary perfusion together with a marked decrease in pulmonary vascular resistance. Consequently, placement of a TIPS would serve to bridge the period of time until a liver transplantation can be carried out. (30, 33, 41, 50)

Liver transplantation: Like the hepatorenal syndrome (s. p. 336), HPS (probably only type 1) is, in principle, reversible after transplantation of the liver. The postoperative prognosis depends on the severity of hypoxaemia prior to transplantation (postoperative lethality is < 5% if preoperative hypoxaemia is > 50 mm Hg). An increase in arterial pO_2 when the patient is inhaling 100% O_2 in a horizontal position is a good prognostic sign for transplantation. It was possible to demonstrate improvement and normalization regarding arterial blood gas values and intrapulmonary shunt volumes as well as restoration of the responsive capacity of the von Euler-Liljestrand reflex. HPS may prove reversible within a few days of liver transplantation. However, other studies have shown that the process of recovery can last much longer (2–18 months). (5, 15, 28–30, 33, 34, 48) • *Embolization* may be indicated in the individual case of arteriovenous fistulas. (27, 33, 38)

7 Portopulmonary hypertension

This clinical picture was described for the first time in 1951 by F. Mantz et al. (70) and confirmed in 1983 by P.J. McDonnell et al. • Portopulmonary hypertension (PPH) is defined as a secondary form of pulmonary hypertension with portal hypertension (or as hypertension in combination with liver disease). Frequency in patients with cirrhosis is given as 2–4%, in patients in an advanced stage of cirrhosis (e.g. presenting for liver transplantation) as 5–10% of cases.

7.1 Definition, morphology and diagnosis

Definition: Characteristic criteria of PPH include (*1.*) elevated pulmonary artery pressure (> 25 mm Hg), (*2.*) increased pulmonary vascular resistance (> 120 dyne/sec/cm^{-5}), and (*3.*) normal pulmonary capillary wedge pressure (< 15 mm Hg). An elevated transpulmonary gradient (mean pulmonary artery pressure/pulmonary capillary wedge pressure = > 10 mm Hg) is likewise used as a diagnostic criterion. (67, 75) • *The presence of portal hypertension is considered as a prerequisite for the development of PPH.*

► The main difference between PPH and HPS is to be seen in the fact that the latter reveals an impaired gas exchange with hypoxaemia and a reduction in pulmonary vascular resistance due to vasodilation. The coexistence of these two pathological conditions (*vasodilation* on the one hand and *vasoconstriction* on the other hand) has recently become documented more often. Any illnesses which lead to pulmonary hypertension must be ruled out as part of the differential diagnosis.

Morphology: PPH is characterized by anatomically fixed pulmonary vasoconstriction. Vascular changes are brought about by (*1.*) vasoconstriction, (*2.*) structural remodelling of the pulmonary arteries (intimal fibroelastosis, hyperplasia of the media), and (*3.*) formation of microthrombi. Endothelial dysfunction may also arise due to shear stress, resulting from hypercirculation and/or autoimmune processes. In the further course of HPP,

there is a proliferation of capillaries, followed by angioma-like changes with fibrinoid necroses of the arterial wall (= *plexogenic arteriopathy*). These findings are disseminated unevenly throughout the lungs. Thus the histological changes of PPH are similar to those of primary pulmonary hypertension. (73) • Remarkably, the combined occurrence of the primary antiphospholipid syndrome and PPH with anticardiolipin antibodies and microthrombi was observed. (61)

Diagnosis: Clinical symptoms of PPH can appear approximately five years after the diagnosis of portal hypertension. Initially, patients have no complaints regarding PPH. In the further course, however, effort dyspnoea, syncope and chest pains may occur. Occasionally, haemoptysis is observed. There is no cyanosis. Additional findings include a loud P_2 heart sound, systolic murmur (mostly right parasternal in the fifth ICS), prominent central pulmonary arteries on the chest roentgenogram and changes in the ECG (right ventricular hypertrophy, right axis deviation, right bundle branch block). • An initial diagnosis can be made using Doppler echocardiography. This proved to be an excellent screening test for identifying all patients with PPH before they presented for liver transplantation. (62) Respiratory alkalosis on room air arterial blood gas can be used as an adjunctive screening test, whereby exaggerated values are indicative of PPH. (68) The scintigraphy index with ^{99m}TMAA is $<6\%$. Diagnosis is established using right heart catheterization, which is regarded as the "gold standard".

7.2 Endothelin and ET-receptor antagonist

Endothelin-1 was first isolated in 1988 by M. Yanagisawa et al. from endothelial cells as a peptide comprising 21 amino acids linked through two sulphide bridges. In 1989 the same team discovered two further isoforms, endothelin-2 and endothelin-3, also in endothelial cells and smooth muscle cells. These endothelins closely resemble the cardiotoxic poison sarafotoxin, a potent vasoconstrictor toxin found in the Israeli mole viper. Endothelin-1 (ET) is the most important isoform in humans. The two ET receptors, ETA and ETB, can be detected on smooth muscle cells, in especially high densities in the pulmonary and coronary vessels, and produce intense vasoconstriction (T. Sakurai et al., 1992). ETB receptors are likewise found in large numbers on endothelial cells. Activated under normal physiological conditions, they stimulate the release of vasodilatory substances (e. g. NO, prostacycline). Vasoconstriction is predominant under pathological conditions. Some results have shown that ETB receptors are upregulated in certain diseases, such as liver cirrhosis. (75). ET has a low plasma concentration and a short half-life of 4−7 minutes. It therefore acts as a local hormone rather than a circulating endocrine hormone. Apart from immediately producing vasoconstriction (ET is one of the strongest and slowest-acting endogenous vasoconstrictors), it stimulates numerous medium and long-term pathophysiological effects. (71, 76) (s. p. 300) (s. tab. 18.2)

Bosentan was first described as an ETA/ETB receptor antagonist by S.M. Gardiner et al. in 1994. These two receptors are features of the intense vasoconstrictory as well as the proliferative and profibrotic effects of ET. Pharmacological characterization was carried out in 1994 by M. Clozel et al. and in 1999 by S. Roux et al.

The effects of bosentan have since been confirmed in numerous studies, and this substance was approved for use in the treatment of pulmonary arterial hypertension (WHO classes III and IV) in 2001. (63, 64, 72) • This dual ET receptor antagonist shows a number of important properties. (s. tab. 18.3)

Acute effects	• inflammation • platelet aggregation • stimulation of RAAS • stimulation of sympathetic nervous system • vasoconstriction • volume retention
Chronic effects	− cell proliferation − fibrosis − mitogenic effects − neuroendocrine activation − stimulation of growth factors

Tab. 18.2: Biological effects of endothelin

Antifibrotic effects
Antihypertrophic effects
Antiinflammatory effects
Buffering of other neurohormonal systems
Reduction in vascular resistance

Tab. 18.3: Main properties of bosentan

7.3 Prognosis and therapy

Prognosis: Prognosis is poor. The patients die as a result of liver insufficiency, right heart failure and/or various infectious diseases. The mean survival period after diagnosis was 15 months, with a six-month mortality of 50%. Mild forms can, however, exist without propression for several years.

Therapy: So far, no effective therapy is known. *Inhaled nitric oxide* as a specific pulmonary vasodilator may be useful perioperatively regarding liver transplantation. In several studies, the use of nitric oxide and *calcium channel blockers* only proved successful in single cases, and then just for a limited time. • *Epoprostenol* (prostacyclin)

is a potent vasodilator with a short half-life (3−5 min), so that a permanent supply is required; this is made possible with the help of an indwelling i.v. catheter attached to a continuous pump. (66) A significant reduction in pulmonary hypertension could be achieved following a five-month period of application (8 ng/kg BW/min). (65) Further studies have also shown an improvement in haemodynamics and exercise tolerance as well as prolonged survival in patients with PPH. The application of *iloprost* (an inhaled analog of prostacyclin) was encouraging. It was also shown that long-term administration of epoprostenol led to a remodelling of the right ventricle. • Depending on the underlying liver disease, the use of *anticoagulants* may be indicated. The newly developed endothelin-receptor antagonist *bosentan* has also proved successful in the treatment of arterial pulmonary hypertension. (63, 64, 72) As a last resort, a combination of bosentan and epoprostenol (or other prostanoids) can be recommended. As yet, there have only been isolated cases involving the use of bosentan in PPH. The phosphodiesterase-5 inhibitor *sildenafil* improved the haemodynamics significantly. In the meantime, PPH is no longer considered to be an absolute contraindication for *liver transplantation*. The indication is given in cases involving a mild or moderate course of the disease. (60, 69, 74) A well-functioning right ventricle is a prerequisite for liver transplantation. In severe cases, liver-lung transplantation may be discussed.

References:

Hepatopulmonary syndrome

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