Symptoms and Syndromes

18 Hepatopulmonary syndrome

18 Hepatopulmonary syndrome

► 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. (49) 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.** (43) Since then, there have been many reports on the detection of arteriovenous anastomoses in the lungs (further details in references 6, 7, 25). 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, 50) • The term **hepatopulmonary syndrome** was used by T.C. Kennedy et al. (1977) 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 observed 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, 32, 51, 52, 56) • Intrapulmonary vasodilations could be ascertained in 13–47% of liver transplant candidates. (27) In about 50% of all cirrhotic patients, a decline in the diffusion capacity for carbon monoxide was detected. (24) About 30% of cirrhotic patients showed no (physiological) reduction in pulmonary vasoconstriction under conditions of hypoxia. The prevalence of HPS in cirrhotic patients varies between 4% and 19%. It occurs more frequently in patients with cirrhosis than with extrahepatic portal venous obstruction. (21, 45)

3 Causes and pathogenesis

In theory, there are **three causes** for the occurrence 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 are associated with HPS. Transient HPS in acute viral hepatitis A and B has recently been reported. (17, 38) (s. tab. 18.1)

α_1-antitrypsin deficiency	Liver cirrhosis
Biliary atresia	Nodular regenerative hyperplasia (9)
Budd-Chiari syndrome (13)	Peliosis hepatis (8)
Chronic active hepatitis	Postsurgical shunt (22)
Chronic hepatic allograft rejection	Primary biliary cirrhosis
Congenital cystic fibrosis (20)	Schistosomiasis
Fulminant liver failure (55)	Tyrosinaemia
Inf. vena cava obstruction (12)	Wilson's disease

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

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 have been presented as a review. (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 hepatopulmonary syndrome (= lower pulmonary vascular resistance). NO concentration is increased in the expired air of patients with HPS. (11, 53) 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,