Review : hepatopulmonary syndrome and portopulmonary hypertension

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Introduction

There are several causes of pulmonary dysfunction in patients with cirrhosis and portal hypertension. On the one hand, some reflect involvement of both lung and liver in systemic disease processes. On the other hand, patients with cirrhosis and portal hypertension are at increased risk for developing specific abnormalities of pulmonary mechanics, haemodynamics and ventilation-perfusion matching (Table I) (1-4). This review focuses on two clinically important pulmonary vascular complications : the *portopulmonary hypertension* (PPHTN) and the *hepatopulmonary syndrome* (HPS). Their pathophysiology, histology, clinical presentation, diagnosis and treatment will be discussed. Haemodynamic alterations in cirrhosis and portal hypertension are first summarized.

Table I. — **Pulmonary manifestations in chronic liver disease**

- Systemic diseases affecting both lung and liver :
  - autoimmune hepatitis
  - cystic fibrosis
  - α1-antitrypsin deficiency
  - sarcoidosis
  - primary biliary cirrhosis
- drug toxicity Hepatopulmonary syndrome
- Portopulmonary hypertension
- Hepatic hydrothorax and ascites (restrictive lung defect)

Haemodynamic changes in cirrhosis and portal hypertension (5-8)

Portal hypertension in cirrhosis results initially from an increase in intrahepatic vascular resistance. Despite the formation of portosystemic collaterals, portal hypertension persists mainly because of an increase in portal venous flow that is in turn secondary to *splanchnic arteriolar vasodilation* (low vascular tone and decreased responsiveness to vasoconstrictors). This vasodilation is not only confined to the splanchnic circulation but is also noticed in the systemic circulation. Its exact cause is unknown, but much attention has been focused on the identification of possible humoral vasoactive mediators. On the one hand, endogenous vasodilators of splanchnic origin (such as glucagon) normally present in portal blood and cleared by the liver, may escape hepatic removal as a result of portosystemic shunting and/or impaired hepatocellular metabolism. On the other hand, an increased production of vasodilators (such as nitric oxide) within the hepatic or splanchnic vascular endothelium may be involved. A *hyperdynamic circulatory state* with an increased cardiac output, a decreased systemic vascular resistance (SVR), a decreased pulmonary vascular resistance (PVR) and an increased splanchnic blood flow, is present in 30-50% of cirrhotics. The arterial vasodilation in the splanchnic and systemic circulation results in an arterial hypotension and a decrease in the effective circulating volume, followed by a series of neurohormonal reactions (stimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone axis and the vasopressin secretion), sodium and water retention and finally an increased total blood volume. These reactions, together with a decrease in the cardiac afterload (due to arterial dilation), result in an increased cardiac output. Compared with healthy subjects, cirrhotic patients with portal hypertension have a lower median PVR but a much wider range of PVR values, extending from the very low levels seen in HPS to the high levels in PPHTN.

Portopulmonary hypertension

Definition, pathophysiology and prevalence

PPHTN is defined as an elevated mean pulmonary artery pressure (mPAP) (> 25 mm Hg at rest) with an elevated PVR (> 120 dynes.s.cm-5) and a normal pulmonary capillary wedge pressure (PCWP) (< 15 mm Hg) occurring in patients with portal hypertension (9). It is classified as a form of *secondary pulmonary hypertension.*

A mild increase in mPAP is not uncommon (about 20%) in patients with advanced liver disease and portal hypertension (10) : a high blood flow (hyperdynamic circulation) and/or a volume phenomenon (elevated intravascular volume) associated with possible cardiac manifestations of cirrhosis (left ventricular dysfunction) may be responsible (11,12) ; in these cases, PVR is near normal. Rarely, a more pronounced increase in mPAP with an elevated PVR and a normal PCWP is observed,

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the pulmonary hypertension being due to a non-embolic local vasoconstriction/obliteration (9). Only this type of pulmonary hypertension should be regarded "PPHTN". Its *prevalence* is about 2% in patients with portal hypertension and cirrhosis (13) and 3.5 – 8.5% in those being evaluated for orthotopic liver transplantation (OLT) (10,14-16). PPHTN has been subjectively subcategorized as mild, moderate or severe based upon mean or systolic pulmonary artery pressures. However, the values vary between authors and say nothing about the also important right heart anatomy and functional capacity (17).

Histology

The three major patterns of *pulmonary arteriopathy* are : 1) isolated medial hypertrophy ; 2) medial hypertrophy and concentric laminar intimal fibrosis, sometimes with plexiform lesions (end-stage insult with enlargement and destruction of the vessel wall with a plexus of proliferating microvessels, myofibroblasts and smooth muscle cells ; complex thin-walled channels may occur distal to this lesion) ; 3) medial hypertrophy with eccentric and concentric nonlaminar fibrosis, which are believed to result from in situ microthrombosis. This spectrum of pathological changes occurs in a patchy fashion within the same lung and is indistinguishable from that observed in primary pulmonary hypertension (PPH) (5,11,18,19) ; other histological patterns of PPH (pulmonary veno-occlusive disease, capillary haemangiomatosis) have not been reported in PPHTN. Pathological changes correlate poorly with cardiopulmonary haemodynamics : a high mPAP can be associated with (potentially reversible) isolated medial hypertrophy, a lower mPAP with (presumably fixed) plexogenic arteriopathy.

Etiology and relationship between liver disease, portal hypertension and PPHTN

The exact etiology of PPHTN is still obscure although several hypotheses have been proposed.

As in PPH, there may be a *genetic predisposition.* Recently, the gene for familial PPH has been assigned to chromosome 2q31-32 (20). Probably, some patients with PPHTN also have a mutation at this (or another) locus.

Several stimuli in predisponed patients with portal hypertension and cirrhosis may then trigger or influence the development of pulmonary hypertension. The presence of portosystemic shunts may allow *vasoconstrictors, cytokines or growth factors* normally cleared by the liver, to gain access to the pulmonary circulation resulting in local vasoconstriction and arteriopathy. Serotonin, IL-1, hepatocyte growth factor and vascular endothelial growth factor have been identified as being of possible relevance (5). As in PPH, an altered function of the *pulmonary vascular endothelium* may be important (21). A relative deficiency of prostacyclin synthase was seen in pulmonary vascular specimens of patients with severe pulmonary and portal hypertension, suggesting that a diminished activity of prostacyclin contributes to the pathogenesis of PPHTN (22). *Portal hypertension* rather than liver disease seems to be the key factor for the development of PPHTN : PPHTN has been reported both in patients with pre- or post sinusoidal and in patients with sinusoidal portal hypertension (5,13,23, 24) ; the risk of developing pulmonary hypertension increases with the duration of portal hypertension ; the diagnosis of portal hypertension mostly precedes that of pulmonary hypertension ; the severity of liver failure in cirrhotics is not correlated with the level of PVR (13). Earlier reports suggest a higher prevalence of PPHTN in patients with a *surgical portosystemic shunt,* but a more recent analysis reported similar values of mPAP or PVR as well as a later occurrence of PPHTN in patients with a surgical shunt compared with those without one. Surgical shunting may not to be a major risk factor, but may rather allow patients to escape variceal bleeding or ascites, live longer and remain longer exposed to other and more important risk factors (13). Studies couldn't support the idea that *chronic embolization* of microthrombi from the portal to the pulmonary circulation may cause PPHTN (25).

Diagnosis

Symptoms of dyspnoea on exertion or at rest, oedema, fatigue, syncope, haemoptysis or chest pain in patients with portal hypertension may suggest PPHTN. In one study, 60% of patients with PPHTN were asymptomatic at the time of evaluation (13). *Physical examination* can reveal signs of right heart failure, with splitting of the second heart sound with enhancement of the pulmonary component, a murmur of tricuspid regurgitation and peripheral oedema. Unfortunately, in the setting of cirrhosis and portal hypertension many of these symptoms and signs may be attributed purely to liver dysfunction. *Electrocardiography, chest radiography, arterial blood gases* and (most importantly) *transthoracic Doppler echocardiography* are non-invasive screening tests and help to exclude other secondary causes of pulmonary hypertension. Most patients with PPHTN have a right ventricular hypertrophy, right axis deviation or right branch block on the electrocardiogram. Chest radiography can demonstrate right heart dilation with prominent central pulmonary arteries and exclude parenchymal lung diseases. An arterial blood gas shows minimal hypoxemia and hypocapnia with chronic respiratory alkalosis : patients with PPHTN have an accentuation of the chronic respiratory alkalosis seen in PPH, and an increased alveolar-arterial oxygen (A-a O2) gradient in comparison with patients with liver disease alone (26). If right heart pressures reach high levels, right-to-left intracardiac shunting can develop through atrial septal defects or a patent foramen ovale and result in severe hypoxemia (27). Echocardiography with doppler rules

out intrinsic cardiac causes of pulmonary hypertension and evaluates the right heart, searching for possible right ventricular hypertrophy and elevated pressures, dilation of the right heart and paradoxical septal movement ; it can estimate the systolic pulmonary artery pressure in the presence of a tricuspid regurgitant jet. In a series of OLT patients, the combination of a suspicious blood gas and an abnormal echocardiography as a screening regimen for PPHTN was associated with a positive and negative predictive value of respectively 96% and 100% (17).

In case of positive screening test results, *pulmonary function tests* should be done to exclude significant parenchymal or airway disorders ; patients with severe pulmonary hypertension may have a mild restrictive pattern or a low diffusion capacity. A *ventilation-perfusion lung scan* is required to rule out thromboembolic disease ; pulmonary arteriography is useful when the scan is inconclusive (21).

Ultimately, *right heart catheterization* has to confirm the diagnosis of PPHTN : PPHTN patients show a typical haemodynamic profile with features of both PPH and cirrhosis : an elevated mPAP and PVR with normal PCWP, together with an increased cardiac output and a decreased SVR (26). Catheterization also determines the degree of pulmonary hypertension, excludes intrinsic cardiac causes of pulmonary hypertension and tests pulmonary vascular reactivity on vasodilators (intravenous prostacyclin or adenosine, inhaled nitric oxide) in order to discern reversible (medial hypertrophy) from irreversible PPHTN (intimal, plexogenic, thrombotic changes). A positive response to a vasodilator test is characterized by a reduction in mPAP and PVR (> 20%) and by an increase in cardiac output, with maintenance of systemic arterial pressure and oxygen saturation (28). Failure to achieve a good response suggests the disease has become fixed and may be a poor prognostic sign.

Differential diagnosis

Other causes of *secondary pulmonary hypertension* must be excluded, such as cardiac diseases (valvular, left heart or some congenital heart disease), chronic thromboembolic disease, other lung diseases (restrictive or obstructive lung disease, sleep apnoea syndrome), collagen vascular diseases (lupus, scleroderma, rheumatoid arthritis, vasculitis), appetite suppressants, toxic oils, HIV-1, schistosomiasis and cocaine inhalation (11,21, 29).

Survival and natural history

Little is known about the clinical course or the predictors of clinical deterioration. It is still unclear if all prognostic variables predictive of survival in PPH (right atrial pressure, mPAP, cardiac output, response to vasodilators, mixed venous oxygen saturation, New York Heart Association class) apply to patients with PPHTN (18,21,29). Mortality is frequent because of the combined severity of pulmonary hypertension (right heart failure and arhythmia) and hepatic dysfunction. In the absence of any intervention, an American study demonstrated a 6-month mortality of 50% and a mean survival period after diagnosis of 15 months (25).

Treatment

Supplemental *oxygen* is of benefit in patients with hypoxemia. *Diuretics* are useful in reducing excessive preload in case of right heart failure. Medications that can aggravate pulmonary hypertension should be avoided. Discontinuation of b-blocker therapy, often used in the prevention of variceal bleeding, should be considered because of its potential myocardial depressive and pulmonary vasoconstrictive effect (27). Trials in PPH patients suggest a better survival for those treated with *anticoagulation* (21,29) ; no such trials have been done in PPHTN.

Currently, no medical therapy has been able to lower efficiently the mPAP and alter outcome in patients with PPHTN. However, especially epoprostenol and perhaps also nitric oxide (NO) are promising substances (30-37). *Oral vasodilators* (mostly calcium-channel blockers) do improve survival, symptoms and haemodynamics in PPH patients with a positive vasodilator challenge (21,29,38) ; there are no trials in PPHTN. Chronic *intravenous epoprostenol* (*prostacyclin*) improves survival, haemodynamics and exercise tolerance in patients with severe PPH, independently of the response to a vasodilator challenge (21,29,39). It is hypothesized that besides a pulmonary vasodilating activity, epoprostenol has a favorable long-term effect on inhibiting platelet aggregation and on vascular remodeling. In PPHTN, intravenous epoprostenol may be useful to achieve stability or reversal of pulmonary haemodynamics in patients awaiting or undergoing OLT. Three small case series reported a significant improvement in symptoms and cardiopulmonary haemodynamics after acute and long-term use of epoprostenol in patients with PPHTN (30,31,36), and a successful OLT of a patient with "severe" PPHTN treated perioperatively with epoprostenol was performed (32). Progressive splenomegaly with hypersplenism may occur in PPHTN patients treated by chronic epoprostenol (40). *Inhaled NO* crosses the alveolar membrane and relaxes vascular smooth muscle cells. Its value in the treatment of PPHTN, i.e. in the intraoperative therapy of pulmonary hypertension during OLT, is still unclear. In a small series, 5 of 6 patients responded to inhalation of NO with a decrease in mPAP and PVR of greater than 10% (37) ; a case report described an intraoperative response to NO in a patient with "severe" PPHTN undergoing a successful OLT (33). In another small group however, NO was unable to give any significant effect on pulmonary hypertension prior to OLT (34). Finally, a successful OLT was performed in a patient treated perioperatively with NO and epoprostenol (35).

Classically, most transplant centres have considered the presence of PPHTN in cirrhotics to be a contraindication to *liver transplantation*. An increased intra- and postoperative morbidity and mortality (especially right heart failure) as well as an unchanged or worsening or de novo development of pulmonary hypertension after transplantation have been reported (11,15). However, with recent observations and an increased surgical, anaesthetic and critical care expertise, the absolute contraindication to OLT nowadays has to be questioned. Studies demonstrated similar morbidity and mortality rates after OLT in patients with "mild or moderate" PPHTN compared with those without PPHTN (10,14, 15). Several case reports and series have now reported a resolution or improvement of (even "severe") pulmonary hypertension after OLT (11,41,42). In a review of the literature, 7 of 10 PPHTN liver transplant recipients demonstrated improved or normalized pulmonary pressures within 6 months after OLT (17). Finally, epoprostenol and NO may become useful in the OLT management in order to decide for OLT candidacy, to control pulmonary hypertension perioperatively and to improve survival.

Further studies must try to characterize a cardiopulmonary haemodynamic profile (with special attention to the degree of pulmonary hypertension and functional state of the right heart) with a specified treatment which will result in successful OLT and favourable outcome of PPHTN. To date, studies indicate that patients with "mild to moderate" PPHTN may have a transplantation risk similar to patients without PPHTN (10,14,15) ; however, these studies are retrospective and the definition of "mild to moderate" lacks conformity. There is no consensus concerning the therapy of patients with "moderate to severe" PPHTN, who carry a poor outcome (15) ; perioperative pulmonary vasodilation (epoprostenol and/or NO) or multiorgan transplantation (heart and/or lung and/or liver) must be considered individually. Currently at the Mayo Clinic, a mPAP > 35 mm Hg, a PVR > 300 dynes.s.cm-5 and a cardiac output < 8 L/min without any pre-transplant vasodilator therapy, are considered as high risk for post-transplant mortality (more than 40%)(9) ; if an acute or chronic vasodilator therapy successfully improves such haemodynamics, multiorgan transplantation may be considered (11).

Hepatopulmonary syndrome (HPS)

Definition, pathophysiology and incidence

HPS is a triad of *chronic liver disease*, abnormal pulmonary gas exchange resulting ultimately in profound arterial hypoxemia (PaO2 < 70 mm Hg or increased A-a O2 gradient > 20 mm Hg while breathing room air) and intrapulmonary vascular dilations (9).

The frequency of *gas exchange abnormalities* in cirrhotics has not been clearly established. Studies of patients referred for OLT indicate that 40-69% have an increased A-a O2 gradient and 9-29% a decreased PaO2 in the absence of cardiopulmonary diseases (43). It has to be stated that quite often hypoxemia associated with liver disease is multifactorial and not only a consequence of HPS. Other reasons for hypoxemia are more frequent and often result in a mild hypoxemia, such as hypoalbuminemia (interstitial pulmonary oedema), ascites or pleural effusion (restrictive defect). However, severe hypoxemia (PaO2 < 50 mm Hg) is most likely because of HPS.

Intrapulmonary vascular abnormalities are the distinctive feature of HPS and take essentially two forms (5,11,43-46). In the first form, the *precapillary and capillary dilation*, hypoxemia results from a "diffusion-perfusion defect". The capillary adjacent to normal alveoli, is dilated to such an extent (> 8 μm in diameter) that it prevents oxygen molecules from diffusing completely to the centre of the capillary to oxygenate the haemoglobin. An impaired hypoxic vasoconstriction in cirrhotic patients with portal hypertension together with a reduction of the capillary transit time (and the available time for oxygen diffusion) due to the hyperdynamic circulation, high cardiac output and elevated pulmonary blood flow, enhances ventilation-perfusion mismatching and hypoxemia ("ventilation with excess perfusion"). Administration of 100% inspired oxygen provides enough driving pressure to overcome partially this defect and to realise a rise in PaO2. In the second form, the venous pulmonary blood bypasses the capillary-alveoli interface via *direct arteriovenous channels* (anatomic shunt) and remains poorly oxygenated ("perfusion with no ventilation") ; breathing 100% oxygen has little effect on PaO2. The exact *prevalence* of HPS is unclear. Studies in patients with end-stage liver disease identified pulmonary vascular dilations in 13 - 47% using contrast echocardiography, but this was only in half of the cases associated with hypoxemia as seen in "true" HPS ; the other half can be considered to have a "forme fruste" of HPS (43,44).

Histology

The most common findings are the (pre)capillary dilations, with the large arteriovenous channels being less frequent. Both vascular abnormalities predominate in the middle to lower lung fields which explains the worsening of hypoxemia in an upright position. Other structural changes include pleural spider naevi and portopulmonary vein anastomoses, which are not believed to contribute greatly to the hypoxemia (5,43,44).

Etiology and the relation between liver disease, portal hypertension and HPS

The exact mechanism underlying the intrapulmonary vasodilation is still unsettled. *Portal hypertension* seems to play a crucial role since HPS has been reported both in patients with pre- or postsinusoidal and in patients with sinusoidal portal hypertension, but never in patients

without it. All HPS patients have a hyperdynamic circulation. The severity of HPS may parallel *the severity of hepatic failure* with a gradual decrease in PVR, the development of pulmonary vascular dilations and ultimately a loss of pulmonary vasoreactivity : hypoxemic cirrhotics have higher Child-Pugh scores than non-hypoxemic cirrhotics, and pulmonary hypoxic vasoconstriction and PVR are more decreased in severe cirrhotic patients. However, not all studies confirm both parallelisms and gas exchange abnormalities may antedate the diagnosis of liver dysfunction or worsen despite stable liver function (43,45).

The pathogenesis of HPS probably involves an *imbalance* between *vasoconstrictors* and *vasodilators* with increased production or insufficient hepatic clearance of vasodilators (e.g. glucagon, NO), increased sensitivity of the pulmonary endothelium to a vasodilating hepatic factor or lack of sensitivity to a vasoconstrictor emanating from a healthy liver (e.g. endothelin-1). An imbalance between hepatic factors *inhibiting* or *stimulating pulmonary vascular cell growth* (e.g. vascular endothelial or hepatic growth factor) may also play a role (5,11, 43,44). The specific vascular mediators of HPS have not yet been identified. *NO* is an important mediator of systemic and splanchnic haemodynamical changes in cirrhosis and portal hypertension. An elevated pulmonary NO production may be involved in gas exchange abnormalities and pulmonary haemodynamics in cirrhotics with HPS (5,43,44,47) : increased concentrations of exhaled NO were found in these patients ; after OLT, there was a correlation between the decrease or normalization of exhaled NO and the improvement in oxygenation (6,48,49) ; oxygenation improved after administration of a NO inhibitor (methylene blue) (50,51).

An animal model of HPS (rats with common bile duct ligation-induced cirrhosis) has been developed and may further clarify the pathogenesis (52). Observations in this model indicate that the development of portal hypertension and a hyperdynamic circulation alone is not enough to cause pulmonary vasodilations. They also support the role of NO : pulmonary endothelial NO synthase levels are increased and correlate with alterations in gas exchange, and an enhanced basal pulmonary artery NO activity is present with a NO-mediated impairment in the response to a vasoconstrictor (53). Other observations in the animal model suggest that *endothelin-1* produced in the liver during hepatic injury may serve as an endocrine mediator of the pulmonary vasodilation by modulating pulmonary endothelial NO synthase (54,55). Finally, the increase in pulmonary capillary size and density in these rats suggests that the pathogenesis of HPS also could result from an increased *angiogenesis*. The presence of cutaneous and pleural spider naevi in patients with HPS lends support to this possibility.

Probably, effluent from hepatic veins (as opposed to simply the existence of portal hypertension) holds the ultimate key to identifying vascular mediators in HPS. This is supported by observations in patients with congenital heart disease associated with diversion of normal hepatic venous blood from the pulmonary circulation (56,57). These patients developed pulmonary vascular abnormalities indistinguishable from those seen in HPS ; however, redirection of hepatic venous flow to the pulmonary vascular bed resulted in the resolution of hypoxemia and vascular abnormalities. It seems that the pulmonary bed needs a (yet unknown) "hepatic factor" contained in normal hepatic venous blood to control its vascular tone and angiogenesis.

Diagnosis

The principal *symptoms* are dyspnoea at rest or on exertion (in 18-67%) and platypnoea, defined as dyspnoea induced by the upright position (in 22-88%) (43). *Physical findings* include spider naevi, clubbing and cyanosis. Impaired oxygenation varies on an *arterial blood gas* from a mild increase in the A-a O2 gradient to a severe decrease in PaO2. The A-a O2 gradient is a more sensitive indicator of impaired oxygen exchange than PaO2. In a retrospective study, 60% of patients had a PaO2 < 60 mm Hg (45). Orthodeoxia, defined as arterial deoxygenation accentuated in an upright position (PaO2 decrease > 3 mmHg), is a characteristic finding present in most patients. The PaO2 response to administration of 100% oxygen is variable and depends on the relative contributions of the two forms of pulmonary vascular abnormalities (9). It can give an idea of the magnitude and form of the intrapulmonary shunting. Most patients respond poorly to 100% oxygen (PaO2 < 300 mm Hg).

Most intrinsic pulmonary diseases of sufficient severity to cause hypoxemia, will be detected by radiographies and pulmonary function tests. In HPS, *pulmonary function testing* should be normal except for a reduction of the corrected diffusion capacity. A *chest radiography* may show a reticular nodular pattern at the base of both lungs ; peripheral pulmonary vascular dilations and an abnormally large number of visible terminal branches may be seen on *thoracic computer tomography* (5,43,44, 58,59).

The final diagnosis of HPS is made by a contrast-enhanced echocardiography or a technetium-99 albumin macroaggregate body scan, which are able to non-invasively identify pulmonary vascular dilations (60). *Contrast-enhanced echocardiography* utilizes peripheral intravenous injection of agitated saline or indocyanine green to produce microbubbles of at least 10-15 μm in diameter. Normally, the bubbles are trapped and absorbed in the pulmonary capillaries and do not reach the left heart. However, in patients with intrapulmonary vascular dilations and direct arteriovenous communications, the bubbles do appear in the left atrium within four to six heartbeats after their appearance in the right heart. This intrapulmonary shunting can be differentiated from intra-cardiac right-to-left shunting where bubbles appear

in the left heart within three heartbeats. Contrast-enhanced echocardiography provides semi-quantification of the shunting (left ventricular opacification). Transoesophageal contrast echocardiography (TEE) is more sensitive than transthoracic contrast echocardiography (TTE) and gives a better correlation between the degree of intrapulmonary shunting and gas exchange abnormalities (61,62).

In a *technetium-99 albumin macroaggregate body scan (lung perfusion scanning)*, the albumin macroaggregates (> 20 μm in diameter) are normally trapped in the pulmonary vasculature. In case of an intrapulmonary or intracardiac shunt, the labelled albumin that escapes from the pulmonary vascular bed is taken up by the brain, kidneys and liver. This method is unable to distinguish intracardiac from intrapulmonary shunting. In HPS, it permits quantification of the degree of vascular dilation (e.g. by calculating the ratio of systemic to total body radioactivity). Lung perfusion scanning is less sensitive than contrast echocardiography (TTE). However, a contrast echocardiography lacks specificity since many cirrhotics with a positive echocardiography result have normal arterial blood gases and therefore do not fulfil all criteria of HPS (they may represent a "forme fruste"). In contrast, a positive lung scan in cirrhotics is very specific for the presence of moderate to severe HPS (60,63).

On *pulmonary angiography*, two patterns of intrapulmonary dilations exist (44,45). A type I (diffuse) pattern is subdivided in a "minimal" (normal vessels or finely diffuse spidery vascular abnormalities) and an "advanced" pattern (diffuse spongy of blotchy appearance), and corresponds to the (pre)capillary vasodilation form of HPS. The main goal of an angiography in HPS is the detection of the infrequent type II (focal) pattern : it corresponds to direct arteriovenous communications and should be considered for embolization in specific cases (9,44,64).

In conclusion, contrast-TTE or (preferably) TEE should be used as screening test for HPS in patients with a PaO2 < 70 mm Hg or an A-a O2 gradient > 20 mm Hg. A positive contrast-TTE or TEE in a patient without intrinsic bronchopulmonary diseases strongly suggests HPS. If the patient has an intrinsic bronchopulmonary disease, a lung scan should be performed : if the lung scan result is positive, it indicates that HPS is contributing significantly to the observed hypoxemia ; a negative scan suggests that HPS is relatively less important in causing the hypoxemia (60,63). Patients with severe hypoxemia and a poor response to 100% oxygen (PaO2 < 300 mm Hg) should undergo a pulmonary angiography to exclude a direct arteriovenous communication (9,44,64).

Survival and natural history

The clinical course of HPS is poorly characterized. Progressive hypoxemia has been observed despite a stable hepatic function . A retrospective study documented an overall mortality of 41%, occurring a mean of 2.5 years after diagnosis ; the cause of death was often non-pulmonary (variceal bleeding, renal failure and sepsis)(45).

Treatment

A variety of medical agents such as almitrine, indomethacin, tamoxifen, b-blockers, sympathomimetics, plasma exchange, methylene blue and somatostatin analogue have been used in the treatment of HPS without substantial improvement in outcome (5,43-45,58). In a pilot trial, *garlic* powder improved oxygenation and symptoms in 40% of patients ; its mechanism of action is unknown (65). Surprisingly, some reports demonstrated that inhaled *NO* can improve arterial oxygenation during and after OLT in some HPS patients (66,67). This may be explained by a redistribution of pulmonary blood flow from the non-ventilated to the ventilated lung units accessible to NO, resulting in a locally improved ventilation-perfusion matching which outweighs the harmful effects of further pulmonary vascular dilation. PaO2 measurement while breathing room air and 100% oxygen is useful to assess which patients require *supplemental oxygen*. Pulmonary angiography is recommended in case of a poor response to 100% oxygen since it may show arteriovenous communications amenable to *vascular embolization*.

A *transjugular intrahepatic portosystemic shunt* (TIPS) will lower portal hypertension which is postulated to play a key role in the pathogenesis of HPS. Three reports demonstrated improved gas exchange after TIPS (68-70) as opposed to a fourth one (71). Further prospective studies need to clarify the role of TIPS in treating HPS. Severe hypoxemia due to HPS was once considered an absolute contraindication to *liver transplantation* due to the perioperative deaths associated with hypoxemia. However, there are now many reports and series of even severe HPS patients who survived OLT with resolution and normalization of oxygenation in the majority of cases (11,43,44,58,64,72,73). HPS resolution often requires up to 15 months post-transplant (64,73). Based upon these observations, upon the important mortality of an untreated HPS and upon the ineffective medical therapy, HPS has become an accepted indication for OLT in many centres (9,44,46,58,64). Timing for OLT is controversial. It seems logical that progressive deterioration of hypoxemia is an indication irrespective of the Child-Pugh class ; maybe the existence of the syndrome itself should be an early indication (9,44,46). Further analyses are needed to determine the factors that predict favorable timing for OLT and also reversibility of HPS postoperatively. In a review of reported cases of OLT in HPS, improvement or normalization of hypoxemia occurred in 82% of transplant recipients within 15 months after transplantation ; 16% died within 3 months ; a pretransplantation PaO2 < 50 mmHg while breathing room air was associated with

Table II. — **Distinctions between HPS and PPHTN**

	HPS	PPHTN
Causes	Sinusoidal or pre-/post sinusoidal portal hypertension	Sinusoidal or pre-/post sinusoidal portal hypertension
Pathology	Precapillary and capillary vascular dilations (type I) Direct arteriovenous communications (type II)	Obstructive arteriopathy
Clinical symptoms	Progressive dyspnoea Frequent cyanosis Frequent clubbing Frequent spider naevi	Progressive dyspnoea Chest pain (near) Syncope Enhanced pulmonary component of the second heart sound
PaO2	Hypoxemia frequently severe Orthodeoxia common	Hypoxemia usually minimal
Chest X-ray	Usually normal	Cardiomegaly ; hilar enlargement
Contrast echo	Delayed, positive microbubble opacification in left atrium (universal finding) Normal right ventricle	Immediate positive microbubble opacification if patent foramen ovale or atrial septal defect (rare) Dilated and hypertrophic right ventricle
99 Tc lung scan	> 5% uptake brain	No unusual brain uptake
Pulmonary angio	Normal or "spongy/blotchy" arterial aspect (type I) Discrete arteriovenous communication (type II)	Large main pulmonary arteries ; distal arterial prunning
Right heart catheterization	Normal or low pulmonary vascular resistance	Elevated pulmonary vascular resistance (> 120 dyne.s.cm-5) ; Normal pulmonary capillary wedge pressure (< 15 mm Hg)

a higher mortality rate (30%) ; successful tranplantation did occur and morbidity rates were minimal when a pre-operative PaO2 response to 100% inspired oxygen was at least moderate (PaO2 > 400 mm Hg) (64). In a recent study, patients with larger shunts as measured by a lung scan (brain uptake > 30%, normal < 5%) appeared unlikely to benefit from a transplantation (74). Also, patients with profound hypoxemia and a poor response to 100% oxygen should not proceed to OLT without first performing a pulmonary angiography to exclude direct arteriovenous shunts.

Summary (Table II)

The hepatopulmonary syndrome and portopulmonary hypertension are two important pulmonary vascular consequences of advanced liver disease causing portal hypertension. The pathogenesis of both diseases has not yet been clarified but may involve an imbalance between vasoconstrictors, vasodilators and other mediators metabolised or synthesized by the liver, subsequently affecting the lung. The hepatopulmonary syndrome is characterized by intrapulmonary vasodilation and gas exchange impairment with finally severe hypoxemia. Currently, there is no medication with proven benefit. Liver transplantation or vascular embolization of anatomic arteriovenous shunts can be curative treatments. Portopulmonary hypertension is characterized by pulmonary hypertension and an increased pulmonary vascular resistance, occurring in the setting of portal hypertension. Haemodynamic compromise with right heart failure may develop. Nitric oxide and/or epoprostenol seem to be promising medications. Liver transplantation result is uncertain, but the use of nitric oxide and/or epoprostenol may help to ameliorate results. A multicenter database on portopulmonary hypertension and hepatopulmonary syndrome (administered by Krowka et al. at the Mayo Clinic) may elucidate remaining questions.

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