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Hepatopulmonary Syndrome and Portopulmonary Hypertension : what's new ?

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Abstract

Hepatopulmonary syndrome (HPS) is found in 4-47% of patients with cirrhosis and is characterized by intrapulmonary vascular dilatations especially in the basal parts of the lung. Liver injury and/or portal hypertension trigger the release of endothelin-1, TNF-α, cytokines and mediate vascular shear stress and release of nitric oxide and carbon monoxide, all contributing to intrapulmonary vasodilation.

Severe HPS increases mortality (30%) after liver transplantation, especially if Pa O_2 is below 50 mmHg. The diagnosis is made by calculating the alveolar-arterial oxygen gradient and by performing a contrast echocardiography. Medical therapy fails and the only long-term treatment available is liver transplantation. More than 85% experience significant improvement or complete resolution in hypoxaemia, but this may take more than 1 year.

Portopulmonary hypertension (PPHT) occurs in 2-8% of the patients with cirrhosis. Imbalance between vasodilating (decreased pulmonary expression of eNOS and prostacyclin I_2) and vasoconstrictive agents (increased expression of ET-1 and angiotensin 1) may be responsible for misguided angiogenesis and pulmonary hypertension. The diagnosis is made by performing an echocardiography and a right heart catheterisation when systolic pulmonary artery pressure is higher than 30 mmHg on echocardiography. Although prostacyclin analogues are efficacious, adverse effects in terms of safety, tolerability and drug delivery occur. Bosentan is probably the therapy of choice for patients with PPHT because it decreases pulmonary but can also diminish portal hypertension. Sildenafil, a phosphodiesterase-5 inhibitor is used for idiopathic pulmonary hypertension, however, it should be used cautiously in patients with portal hypertension as it may increase portal hypertension by splanchnic vasodilation. (Acta gastroenterol. belg., **2006**, 69, **203-209**).

Review

Introduction

Respiratory syndromes are common in patients presenting with liver disease and might be associated with a specific liver disease (e.g. sarcoidosis, alpha1-antitrypsin deficiency, mucoviscidosis) or associated with chronic liver disease and /or portal hypertension such as hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax and restrictive lung disease secondary to massive ascites.

In this review we will only discuss hepatopulmonary syndrome and portopulmonary hypertension.

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is the consequence of intrapulmonary vascular dilations occurring in a subgroup of patients with cirrhosis and/or portal hypertension (1).

HPS is characterised by the clinical triad of :

- liver disease and/or portal hypertension
- widened alveolar-arterial oxygen (A-a) O_2 gradient while breathing room air
- intrapulmonary vascular dilations (capillary, precapillary, arterio-venous malformations) especially in the basal parts of the lung

Prevalence and natural history

The prevalence of HPS in patients with chronic liver disease ranges between 4% and 47% depending on methods and diagnostic criteria used (2,3). HPS is probably a progressive disease, however, there is no clear relationship between severity of hepatic dysfunction and severity of hypoxaemia and shunting. Patients with HPS have a higher Child-Pugh score and Model of End-Stage Liver Disease score. Over time, HPS will alter quality of life and survival in these patients (2).

Pathogenesis of HPS

The causes of HPS are unknown, but are generally believed to involve an imbalance between vasoconstrictors and vasodilators, and/or between hepatic factors inhibiting and stimulating vascular growth.

Liver injury triggers the release of endothelin (ET)-1 from activated hepatic stellate cells and from biliary epithelium (4,5). On the other hand, cirrhosis and portal hypertension mediate vascular shear stress and may cause bacterial translocation from the gut, leading to endotoxaemia with release of cytokines (6,7). Both ET-1 and endotoxaemia cause an up-regulation of tumour necrosis factor (TNF)-α (8).

Under normal conditions, ET-1 has a paracrine function, released from endothelial cells to the abluminal side of the cell, where it targets ET_A-receptors on vascular smooth muscle cells and causes vasoconstriction (9). To a lesser degree, ET-1 released into the vascular lumen targets ET_B-receptors on the endothelial cell and triggers nitric oxide (NO) production, which counterbalances the

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vasoconstrictive effects (9). After common bile duct ligation and in cirrhosis, ET-1 produced by the liver may reach the pulmonary circulation and preferentially interact with pulmonary endothelial ET_B-receptors. In this setting, it acts as an endocrine vasodilator by enhancing endothelial NO production and intrapulmonary vasodilation (9). Recently, increased levels of pulmonary vascular ET_B-receptors have been described in animals with cirrhosis and portal hypertension (3, 10). This correlates with the previously observed susceptibility to ET-1-mediated increase in pulmonary endothelial nitric oxide synthase (eNOS) and NO production *in vitro* and *in vivo* (4).

Under influence of TNF-α, macrophages accumulate in the pulmonary vascular lumen and produce NO from inducible NOS and carbon monoxide (CO) from haeme-oxygenase-1, all contributing to intrapulmonary vasodilation (8,11,12).

Oestradiol and progesterone levels are also higher in patients with HPS than in those without HPS (13).

Increased concentrations of exhaled NO and plasma carboxyhaemoglobin levels have been found in patients with HPS compared with patients without HPS (14-16). In these patients there was a significant correlation between carboxyhaemoglobin, exhaled NO and (A-a) O_2 gradient.

Taken together, these studies suggest that local production of NO and CO in the lung may play an important role in HPS.

Pathogenesis of hypoxaemia in HPS

The pathogenesis of hypoxaemia in patients with HPS is caused by 3 gas exchange abnormalities (1) :

– intrapulmonary shunting
– ventilation – perfusion mismatch
– diffusion-perfusion impairment

a. Intrapulmonary shunting

Intrapulmonary vascular dilations (IPVDs) with diameters ranging from 15 to 500 μm are probably the major cause of the typical characteristics of HPS and hypoxaemia. Failure to clear pulmonary vasodilators by the diseased liver ; production of pulmonary vasodilators by the liver and inhibition of pulmonary vasoconstrictors in response to hypoxaemia, are probably the most important factors leading to IVPD.

b. Ventilation – perfusion mismatch

The IPVDs result in right-to-left shunts, failure of hypoxic pulmonary vasoconstriction and over-perfusion of low ventilated units especially in the basal parts of the lung leading to hypoxaemia.

c. Diffusion-perfusion impairment (Fig. 1)

Because the enlarged diameter of the intrapulmonary capillaries, oxygen molecules of the adjacent alveoli can not reach the centre of the dilated vessel which leads to non-oxygenated haemoglobin in red blood cells at the centre of the venous blood stream despite a normal oxygen pressure in the alveolus, resulting in hypoxaemia (Alveolus a in figure 1) (17). When alveolar oxygen is increased, it provides enough driving pressure for the oxygen molecules to diffuse in the dilated blood vessel, improving oxygenation (Alveolus b in figure 1).

Increased cardiac output associated with liver cirrhosis further limits the oxygenation, because it reduces the erythrocyte transit time through the lung vasculature and the amount of time available for the oxygenation of haemoglobin.

Clinical manifestations

Clinical manifestations are dyspnoea and platypnea (shortness of breath exacerbated by sitting up and improved by lying supine) (18). Because the vascular abnormalities predominate in the middle lobe to lower lobes, where gravitational effects result in an increase in blood flow, worsening of hypoxaemia can occur in upright position and is called orthodeoxia due to increased shunting and ventilation/perfusion mismatching (18).

Spider angiomata are markers of IPVD and are associated with an enlarged alveolar-arterial oxygen gradient. Clubbing and distal cyanosis can also occur.

Lung function examination reveals normal lung volumes and expiratory flow rates but the diffusion capacity for CO (DLCO) is impaired (18).

Diagnosis of HPS

Arterial hypoxaemia is arbitrarily defined as a PaO_2 lower than 70 mmHg. In the diagnostic criteria for HPS however, a widened alveolar-arterial partial oxygen pressure gradient (A-a) O_2 of more than 20 mmHg, is sufficient to indicate the presence of gas exchange abnormalities (17,18). The diagnosis is thus made by calculating the age-adjusted (A-a) O_2 gradient > 20 mmHg by performing an arterial blood gas.

(A-a) O_2 gradient = [(760 mmHg-47mmHg) × FiO_2 – $PaCO_2$/R] - PaO_2.

R is defined as the respiratory quotient (R = 0.8) and Fi O_2 as the fraction of oxygen inspired (21% in room air). Measuring PaO_2 alone may underestimate the true degree of the oxygenation abnormality because of hyperventilation, which is common in patients with cirrhosis. The (A-a) O_2 gradient is more accurate because it includes the determination of $PaCO_2$, which is low as a result of hyperventilation (17,18).

Contrast enhanced echocardiography by injecting agitated saline intravenously can confirm the diagnosis of HPS. The microbubbles opacify the right ventricle and are normally absorbed by the lungs. Contrast agent enters the left atrium within 3 heartbeats if an intracardiac shunt is present, while intrapulmonary shunting opacifies the LV at least after 3 to 6 heart beats (delayed shunting). Trans-oesophageal echocardiography can

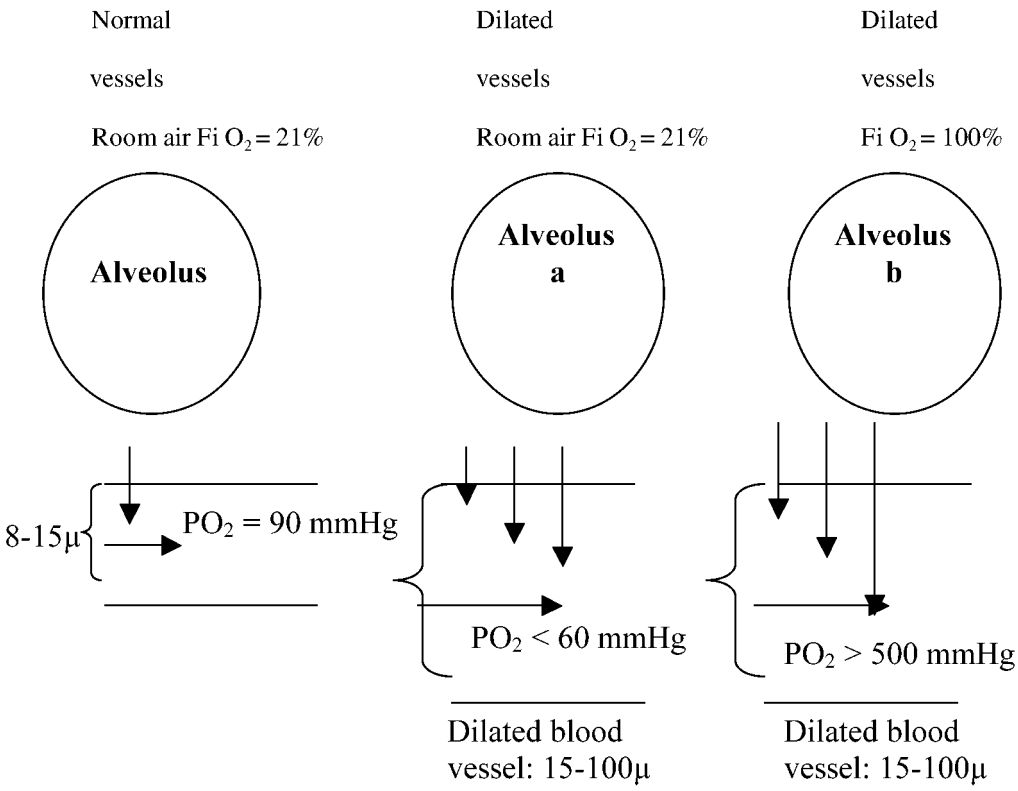

Fig. 1. — Diffusion / perfusion impairment

even better visualise directly the bubbles in the pulmonary veins and left atrium (18,19).

To quantify the shunt fraction one can perform a technetium 99m-labelled macro-aggregate (20 µm particles) albumin scan. These particles are normally trapped in the lung, but when intracardiac or intrapulmonary shunts are present these particles are also taken up in the brain and kidneys. The percentage shunting = [brain uptake + kidney uptake] / total uptake (18).

The 100% oxygenation test can also measure the right-to-left shunt fraction. The patient should wear a nose clip and breath 100% oxygen through a tight fitting mouth piece or mask for 20 minutes. A PaO_2 of less than 150 mmHg suggests a high shunt fraction (18).

Pulmonary angiography can distinguish 2 different radiological patterns of HPS : type 1 is characterised by diffuse, spider like vascular abnormalities ; type 2 is characterised by localised arteriovenous communications and is associated with a poor response to extra oxygen supply (18).

Recently, it has been shown that high resolution computed tomography of the lungs can also contribute to the diagnosis of arteriovenous communications (20).

Treatment of HPS

Cirrhotic patients with HPS have a higher mortality (RR > 2) than patients without HPS, regardless of the Child-Pugh score, age and kidney function (2). Medical therapy fails and the only long-term treatment available is liver transplantation (18,21).

Medical therapy (methylene blue, garlic, nitric oxide synthase inhibitors, octreotide, propranolol, almitrine bismesylate) is disappointing and none can be recommended at this time. Treatments with pentoxifylline (inhibits TNF-α) and norfloxacin (inhibits bacterial translocation) in rats with HPS showed promising results (18,21).

Angiography can be used to treat large type 2 lesions with occlusion of the arteriovenous communications by using coils (18,21).

Liver transplantation is nowadays indicated for patients with a HPS. Severe HPS increases post liver transplant mortality (30%) especially if PaO_2 is below 50 mmHg. More than 85% experience significant improvement or complete resolution in hypoxaemia, but this may take more than 1 year (2-14 months) (18,21,22).

Portopulmonary hypertension

Definition

Pulmonary arterial hypertension in association with portal hypertension and in the absence of other causes of pulmonary hypertension (such as cardiac valve disease, schistosomiasis, toxins, HIV, pulmonary embolism and appetite suppressants) is called porto-pulmonary hypertension (PPHT) (23). Initially described in 1951 by

Mantz and Craige, PPHT has been increasingly recognised especially with the progression of liver transplantation as treatment for end stage liver disease (24).

The prevalence of PPHT varies between 2% (25) in patients with cirrhosis to 8.5% in candidates for liver transplantation (26,27). The prevalence of primary pulmonary hypertension in the normal population is 1-2 cases per million (23). Although hepatopulmonary syndrome and PPHT are two distinct diseases, they can exceptionally be present in the same patient (28-30).

Pathology

Histologically, PPHT is similar to that seen in primary pulmonary hypertension, but there is no evidence for veno-occlusive disease or recurrent thromboembolism (31,32). PPHT is characterized by the proliferation of the vascular endothelium and smooth muscle cells (intima proliferation and media hypertrophy), leading to thickening of the pulmonary arteriolar wall and the formation of plexiform lesions that occlude the vessel. This vascular remodelling increases pulmonary vascular resistance, resulting in right ventricle hypertrophy, dilatation and failure (31).

Pathogenesis of PPHT

Tuder et al demonstrated that small and medium-sized hypertensive pulmonary vessels with mild and severe remodelling have a decreased expression of prostacyclin synthase when compared with normal vessels. Prostacyclin is a powerful vasodilator and inhibits platelet adhesion and cell growth (33). The expression of eNOS is significantly decreased in the endothelium of pulmonary arteries with severe morphologic abnormalities in primary and secondary pulmonary hypertension. The decrease in eNOS is inversely correlated with increased pulmonary vascular resistance (34).

Giaid et al showed increased ET-1 expression in lung vascular endothelial cells in patients with pulmonary hypertension (34). Endogenous ET-1 contributes to the development of pulmonary hypertension in rats exposed to chronic hypoxia (35). There is a strong correlation between ET-1 and big-ET-1 plasma levels and the severity of pulmonary hypertension (36). In patients with pulmonary hypertension there is also an increased expression of tromboxane A2 and angiotensin-1, both leading to pulmonary vasoconstriction (37).

Taken together, these considerations suggest that a down-regulation of the endothelium-derived relaxing and antiproliferative factors (e.g. NO, prostacyclin) and an up-regulation of the endothelium-derived vasoconstrictors and mitogenic factors (e.g. ET-1, tromboxane A2, angiotensin 1) contribute to pulmonary hypertension (37).

Other pathophysiological mechanisms such as mutations in the serotonine gene promoters and TGF-beta regulation, pulmonary endothelial injury by shear stress and autoimmune factors and down regulation or abnormal closure of potassium channels, may all lead to vasoconstriction and vascular remodelling. However, there is only small literature available about the pathogenesis of PPHT (1,37).

Symptoms and clinical signs of PPHT

The most common symptoms of PPHT are fatigue, chest pain, syncope, haemoptysis and dyspnoea on exertion. However, 60% of patients are asymptomatic at the time of diagnosis (38).

Clinical predictors of PPHT in patients undergoing liver transplantation are systemic arterial hypertension (systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg), loud pulmonary component of the second heart sound, jugular vein distension, lower limb oedema, right ventricle dilatation, right ventricle hypertrophy and systolic pulmonary artery pressure of more than 30-40 mmHg on echocardiography (37,39).

Diagnosis of PPHT

The diagnosis of PPHT can already been suggested on chest X-ray (prominent pulmonary artery, dilated right atrium and ventricle) and on electrocardiogram (right ventricle hypertrophy, right bundle branch block, right atrium hypertrophy) (37).

The ideal diagnostic screening test should be sensitive and specific, cost-effective and minimally invasive for the patient. Doppler echocardiography is a useful non-invasive tool to ascertain or rule out PPHT, but right heart catheterisation remains the "gold standard" for the diagnosis of PPHT (40,41). A prospective study compared Doppler-echocardiography and right heart catheterisation under the same conditions at the time of evaluation for liver transplantation (42). A cut-off value for the systolic pulmonary artery pressure (PAPs) of 30 mmHg was taken at echocardiography to make the diagnosis of pulmonary hypertension (42). The results were compared with those on right heart catheterisation. Echocardiography had an accuracy of 96% ; sensitivity of 100% ; specificity of 96% ; a positive predictive value of 59% but a negative predictive value of 100% (42). This means that if no pulmonary hypertension is discovered on echocardiography that there is none on right heart catheterisation. On the other hand, if PAPs is more than 30 mmHg, one should perform a right heart catheterisation to confirm the diagnosis (42).

Pulmonary hypertension is diagnosed on right heart catheterisation when mean pulmonary artery pressure (MPAP) is more than 25 mmHg, pulmonary capillary wedge pressure (PCWP) lower than 15 mmHg and pulmonary vascular resistance (PVR) more than 240 dynes.s.cm^{-5} (1).

Prognosis of PPHT

The prognosis of patients with PPHT is poor, with a mean survival of 15 months and a 6-months survival of

50% without liver transplantation (37,38). The presence of PPHT is associated with a much higher peri- and postoperative morbidity and mortality during and after liver transplantation. When MPAP is > 50 mmHg mortality is 100%, while mortality is 50% when MPAP is between 35 and 50 mmHg. No increased mortality was reported when MPAP is below 35 mmHg (43,44). The operative risk is high when MPAP > 35 mmHg, cardiac output lower than 8 L/min and a PVR of > 250 dynes.s.cm^{-5} (43).

Treatment of PPHT

Many of the treatment options have been extrapolated from idiopathic pulmonary hypertension. There are no clinical predictors for response to vasodilators. The vessels are probably still vasoreactive in an early stage and than PPHT can be reversible (37). However, in later stages, structural changes occur in the pulmonary vessels leading to non-reactive vessels, and perhaps at that time pulmonary hypertension is not reversible anymore. A vasodilator treatment in pulmonary hypertension should always be installed in a hospital and even best in a catheterisation room, because each individual response is different and may result in hypotension, worsening of gas exchange and may even lead to death (45,46).

Inhalation of NO is a pulmonary vasodilator, however, the use in PPHT is controversial. NO can be used in patients with minimal PPHT during reperfusion at liver transplantation (47-51).

Calcium channel blockers increase survival in patients with primary pulmonary hypertension, however, its effects in patients with PPHT is not known and should not be used at this moment (52,53).

Prostacyclines and its analogues (e.g. epoprostenol, iloprost, treprostinyl, beraprost) are important pulmonary vasodilators with an antiproliferatif and antiplatelet effects (54,55). Epoprostenol is given intravenously (IV), which can cause catheter related complications such as sepsis and thromboembolisms. Stopping the IV infusion may cause rebound pulmonary hypertension leading to right heart failure and death. Epoprostenol results in better pulmonary (decrease in pulmonary vascular resistance, mean pulmonary artery pressure) and cardiac hemodynamics (increase in cardiac output) in patients with moderate to severe PPHT (54). Epoprostenol however, can induce a decrease in hepatic function and increases portal hypertension with aggravation of hypersplenism (54,56). Inhalation of iloprost 6 to 12 times a day showed a diminution of the pulmonary artery pressure. Recently, the subcutaneous use of the analogue treprostinyl has been approved by the US Food and Drug Administration for the treatment of pulmonary hypertension (57). Also beraprost orally can be used in pulmonary hypertension (58).

Phosphodiesterase inhibitors prevent the degradation of cyclic guanosine and adenosine monophosphate (cGMP and cAMP). Thus more cGMP and cAMP are present in blood vessels resulting in vasodilation. Phosphodiesterase (PDE) inhibitor type V (e.g. sildenafil) has been used for the treatment of idiopathic- but also of porto-pulmonary hypertension (37,59). PDE-5 inhibitors mediate relaxation and inhibit growth of pulmonary vascular smooth muscle cells (59). However, as PDE-5 receptors are also present in the splanchnic vascular bed, it may happen that sildenafil causes a splanchnic vasodilation and increases portal hypertension. This has been confirmed in rats with cirrhosis, and should be tested in patients with portal hypertension before using it widely in patients with PPHT (60).

Recently, oral endothelin A + B receptor antagonists such as bosentan, have been explored in the treatment of pulmonary hypertension and showed an amelioration in pulmonary and cardiac hemodynamics (37). Bosentan is probably the therapy of choice for patients with pulmonary hypertension, because it is easy to administer orally, results in improved symptoms, increase of six minutes walking distance, cardiac index and decrease in pulmonary vascular resistance (61). However, bosentan may have other beneficial effects by decreasing portal hypertension, as ET-1 is involved in increasing intrahepatic resistance (62). Unfortunately, hepatic venous pressure gradients were seldom measured and only some case reports of patients with PPHT describe a decrease of portal HT, but studies evaluating pulmonary HT and portal HT are underway. We should be aware that endothelin antagonists can increase liver tests.

Liver transplantation is a good option for PPHT certainly in patients with reversible pulmonary hypertension (37). The diagnosis of PPHT must be made preoperatively during the evaluation of candidacy for liver transplantation and pharmacological treatment should be instituted before transplantation (42,43,63). If it is impossible to lower the MPAP below 40-50 mmHg during the transplant procedure, any significant hemodynamic change, such as observed during reperfusion, may result in right ventricle failure and cardiac arrest. As already mentioned, the mortality risk during and after transplantation is very high if the mean pulmonary artery pressure exceeds 50 mmHg (37,43). Amelioration of pulmonary artery pressure has been described after liver transplantation, however, other cases of recurrence or aggravation have been seen (42,64,65,66). A combined liver-heart-lung transplantation can be considered in patients with fixed pulmonary hypertension, however, clear guidelines can not be given as few information is available about such cases (37,67).

Conclusion

New developments are made in the pathogenesis of the HPS. Liver injury and/or portal hypertension trigger the release of ET-1, TNF-α, cytokines and mediate vascular shear stress. In experimental HPS, ET_B receptors are up-regulated in the endothelial wall of the pul-

monary vessels and activate under influence of hepatic ET-1, eNOS producing NO. Under influence of TNF-α, macrophages accumulate in the pulmonary vascular bed and produce NO from iNOS and CO from haeme-oxygenase-1, all contributing to intrapulmonary vasodilation. Despite this new ideas in pathophysiology, treatment for HPS remains disappointing and liver transplantation is the best option in some cases.

PPHT is a severe complication of portal hypertension and end stage liver disease, with a high morbidity and mortality peri- and postoperatively after liver transplantation. Although prostacyclin analogues are efficacious, adverse effects in terms of safety, tolerability and drug delivery occur. Bosentan is probably the therapy of choice for patients with pulmonary hypertension, because it is easy to administer orally, results in improved symptoms and pulmonary and cardiac hemodynamics. As ET-1 is involved in increasing intrahepatic resistance, bosentan may also decrease portal hypertension. Careful pre- and postoperative management of these patients and increasing surgical and anaesthetic expertise make liver transplantation possible in patients with PPHT. Probably patients with a fixed PPHT will not exhibit regression of pulmonary hypertension after liver transplantation.

Future Research proposals

The better knowledge of the pathophysiology of hepatopulmonary syndrome will probably increase therapeutic options in these patients in the next coming years. Local pulmonary vasoconstrictors, ET_B receptor antagonists or inhibitors of TNF alfa, eNOS and haeme-oxygenase 1 are molecules with possible potential benefit. Most of them have already been studied in animals, however human studies are lacking.

In the case of portopulmonary hypertension, there is little information about the pathophysiology and the relation with liver failure and portal hypertension. Why in one patient with cirrhosis, PPHT develops and in the other HPS is actually unknown. At this stage, more animal experiments should be performed to elucidate this problem. However, despite the lack of knowledge on pathophysiology, treatment of PPHT is available as a result of studies in primary pulmonary hypertension.

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