

## Review

# Portopulmonary hypertension and hepatopulmonary syndrome

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**The clinically and pathophysiologically distinct entities of portopulmonary hypertension and hepatopulmonary syndrome occur in a substantial proportion of patients who have advanced liver disease of different causes. These disorders are notoriously underdiagnosed, but they have a substantial impact on survival and require focused treatment. Abnormal intrapulmonary vascular dilatation, the hallmark of hepatopulmonary syndrome, can cause profound hypoxaemia that can be very difficult to treat. By contrast, portopulmonary hypertension results from excessive pulmonary vasoconstriction and vascular remodelling that eventually leads to right-heart failure. Insights into the pathogenesis of these syndromes have led to novel therapeutic approaches. However, in severely affected patients, effective treatment remains a difficult task. In selected patients, liver transplantation represents the only treatment option, but the decision to do isolated liver transplantation is particularly challenging in patients who have severe pulmonary disease involvement. Data from several centres have contributed to provide criteria that allow improved prediction of which patients may, or may not, benefit from liver transplantation alone.**

Cardiopulmonary abnormalities are present in most patients who have advanced liver disease. A combination of pulmonary and hepatic risk factors can lead to the synchronous existence of liver and lung disease, as seen in combined alcohol, drug, and nicotine consumption. Malnutrition because of advanced cirrhosis can lead to immunosuppression, which puts these patients at risk of infectious pulmonary complications. Most notably, pneumonia accounts for 20–40% of the serious infections encountered in patients with alcohol-related liver disease.<sup>1</sup> Large amounts of ascites or pleural effusions resulting from advanced portal hypertension compromise the lung mechanically, and frequently cause severe dyspnoea.<sup>2,3</sup> Furthermore, specific diseases affecting the liver and the lung, including  $\alpha$ -1 antitrypsin deficiency or cystic fibrosis, alter the function of these organs' systems in some patients.

Besides these well-recognised disorders, two distinct pulmonary syndromes deserve special attention when dealing with patients with chronic liver disease: portopulmonary hypertension and hepatopulmonary syndrome. These two syndromes seem pathogenetically linked to the presence of portal hypertension, but their pathophysiological mechanisms clearly differ. The development of portopulmonary hypertension or the hepatopulmonary syndrome has major clinical and prognostic implications and requires specific treatment considerations. In this review, we provide a detailed summary of the epidemiology, pathophysiology, diagnosis, and treatment of portopulmonary hypertension and hepatopulmonary syndrome.

## Portopulmonary hypertension

Haemodynamically, portopulmonary hypertension is defined by the presence of the following features in patients with portal hypertension: raised pulmonary arterial pressure (mean pressure determined by right-heart catheterisation of >25 mm Hg at rest and >30 mm Hg during exercise);<sup>4</sup> raised pulmonary vascular resistance (>240 dyne s<sup>-1</sup> cm<sup>-5</sup>) in the presence of a pulmonary arterial occlusion pressure; or a left-ventricular end-diastolic pressure of less than 15 mm Hg. According to the current WHO classification, portopulmonary hypertension is no longer classified as secondary pulmonary hypertension but as pulmonary arterial hypertension associated with liver disease or portal hypertension.<sup>4</sup>

Reports on the incidence of pulmonary hypertension in patients with liver disease vary greatly. In autopsy studies, pulmonary vascular changes consistent with the presence of pulmonary hypertension have been reported in 0.7% of patients with cirrhosis.<sup>5</sup> By use of various diagnostic criteria, 2–10% of cirrhotic patients have been estimated in clinical studies to be at risk of developing pulmonary hypertension.<sup>6–9</sup> In selected patients who have advanced liver disease, especially those assessed or referred for liver transplantation, pulmonary hypertension occurs in up to 16%.<sup>10,11</sup> Although these observations seem to suggest that portopulmonary hypertension is a complication affecting mainly patients with advanced liver disease, no clear relation between the severity of hepatic dysfunction or raised portal venous pressure and the severity of pulmonary hypertension has been conclusively shown.<sup>7</sup>

## Search strategy

We did an unrestricted MEDLINE search with use of the key words “porto-pulmonary hypertension”, “pulmonary hypertension and liver”, “pulmonary hypertension and cirrhosis”, and “hepatopulmonary syndrome”. For papers we deemed relevant for this review, we did a secondary search with the “related-articles” option in MEDLINE. We selected retrieved reports on the basis of their scientific merit and relevance for this review.

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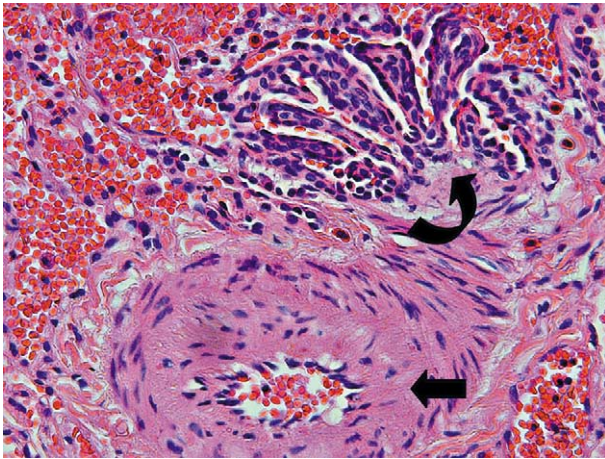


Figure 1: **Histological sample from lungs of patient with severe portopulmonary hypertension**

Pulmonary artery wall shows striking intimal and medial thickening (straight arrow) and outspread channel-like structures forming plexiform lesions are present (curved arrow), a hallmark of proliferative pulmonary vasculopathy. Figure provided by and reproduced with permission of Peer Flemming.

The development of severe pulmonary hypertension in patients who have cirrhosis is an ominous prognostic sign. Nevertheless, the reported survival rates vary substantially. In an analysis of 78 patients with portopulmonary hypertension who had a mean pulmonary arterial pressure of 59 mm Hg (SD 19), the median survival was 6 months and the 5-year survival was less than 10%.<sup>12</sup> By contrast, Hervé and colleagues<sup>9</sup> reported an actuarial 5-year survival of 50% in 39 patients with portopulmonary hypertension who had similar haemodynamics.

### Pathogenesis

The development of portopulmonary hypertension seems to be independent of the cause of portal hypertension. Although most patients with portopulmonary hypertension have cirrhosis as the underlying disease, the syndrome has been described in patients with portal hypertension due to non-hepatic causes, such as portal venous thrombosis in the absence of chronic hepatic disease.<sup>13</sup> Thus, portal hypertension seems to be the required driving force of pulmonary hypertension.

The mechanisms by which portal hypertension causes pulmonary hypertension remain incompletely understood. A hyperdynamic circulation state seems to be present in almost all patients who have portopulmonary hypertension in the early stages of disease. However, high cardiac output and hyperdynamic circulation is a hallmark of almost all patients with advanced liver disease who develop portal hypertension. Several factors are presumed to lead to this feature, including splanchnic volume overload and bowel-wall congestion, leading to the release of endotoxins and cytokines into the splanchnic circulation. High cardiac output in turn delivers an increased amount of shear stress on the pulmonary circulation, which responds in several ways: the maintenance of an adequate pulmonary vascular resistance will prevent development of any syndrome; and abnormal pulmonary vascular dilatation will lead to an abnormally decreased vascular resistance and hepatopulmonary syndrome. By contrast, increased vascular resistance caused by vasoconstriction and progressive pulmonary vascular remodelling due to proliferation of pulmonary arterial endothelial cells and smooth-muscle cells will result in pulmonary

hypertension. In these two cases, portopulmonary hypertension and the hepatopulmonary syndrome, changes in vascular resistance are caused partly by variations in the vessel tone but probably more so by pulmonary vascular remodelling.

The presence of a high cardiac output can result in a mild degree of pulmonary hypertension in the presence of a normal or near-normal pulmonary vascular resistance, which might have led to the overestimation of the incidence of portopulmonary hypertension in some case series.<sup>14</sup> The individual factors at the cellular and molecular levels that determine the direction of the outlined vascular response have still to be elucidated but seem to vary in association with the stage of the disease.

Portopulmonary hypertension remains of mild to moderate severity in most patients, and vasoconstriction and medial hypertrophy of the pulmonary arteries are the dominant features of pulmonary hypertension.<sup>15,16</sup> However, in an unknown proportion of patients, mild or moderate portopulmonary hypertension progresses to severe disease, and becomes a clinically apparent complication in chronic liver disease or portal hypertension. Histologically, proliferative pulmonary arteriopathy with obliteration of the vessel lumen by endothelial cells and smooth-muscle cells and with formation of plexiform lesions indistinguishable from those seen in primary pulmonary hypertension is the hallmark of this disorder (figure 1).<sup>16,17</sup>

In contrast to patients who have mild to moderate pulmonary hypertension, those who progress might show rapid clinical worsening that leads to right-heart failure. The factors involved in the development of proliferative vasculopathy have yet to be identified. One such candidate might be mutations in the bone morphogenetic protein receptor type 2, a member of the transforming growth factor receptor family, which has been linked to proliferative pulmonary vasculopathy and has been detected in patients with familial and sporadic primary pulmonary hypertension,<sup>18–20</sup> but has not yet been described in patients with portopulmonary hypertension. Mutations in ALK-1, another member of the transforming growth factor receptor family, have been linked specifically to pulmonary hypertension in patients with hereditary haemorrhagic telangiectasia.<sup>21</sup> Other, as yet unidentified, genetic factors are also likely to contribute to the development of proliferative pulmonary vasculopathy in patients with severe portopulmonary hypertension since the underlying pathophysiological abnormalities are present in almost all patients and only a few develop pulmonary hypertension.

### Symptoms and diagnosis

The most common presenting symptom in patients with pulmonary hypertension, irrespective of its cause, is progressive dyspnoea on exertion.<sup>12</sup> Other symptoms such as fatigue, palpitations, syncope, or chest pain are less frequent. Physical findings indicating pulmonary hypertension are generally subtle and may be completely absent. The most common findings are an accentuated pulmonary component of the second heart sound and a systolic murmur, indicating tricuspid regurgitation. Extended jugular veins, oedema, and ascites can be signs of either decompensated cirrhosis or overt right-heart failure.

The diagnosis of portopulmonary hypertension requires raised pulmonary arterial pressure and resistance combined with the exclusion of other causes of pulmonary hypertension. Electrocardiography, radiography, or pulmonary-function testing can provide some clues as to

|  | Normal  | Mild       | Moderate     | Severe  |
|--|---------|------------|--------------|---------|
| NYHA class   | –       | I, II      | II, III      | III, IV |
| Mean pulmonary arterial pressure (mm Hg)                               | 15–24   | 25–34      | 35–44        | >45     |
| Cardiac index (L min <sup>-1</sup> m <sup>-2</sup> )                   | 2.5–4.0 | >2.5       | >2.5         | <2.0    |
| Pulmonary vascular resistance (dyne s <sup>-1</sup> cm <sup>-5</sup> ) | <240*   | 240–500    | 500–800      | >800    |
| Right arterial pressure (mm Hg)  | 0–5     | 0–5        | 5–8          | >8      |
| Prognosis  | –       | Favourable | Questionable | Poor    |
| Specific treatment required†   | –       | No         | Questionable | Yes     |
| Reversibility after liver transplantation                              | –       | Yes        | Questionable | No      |

NYHA=New York Heart Association. Not all factors indicate same degree of severity in individual patients; distinction between mild, moderate, and severe portopulmonary hypertension must be based on combination of several factors viewed in clinical context. \*Some workers deem pulmonary vascular rate 120 dyne s<sup>-1</sup> cm<sup>-5</sup> upper limit of normal in patients with liver disease. †Specific treatment—ie, intravenous epoprostenol, other prostanoids, or endothelin-receptor antagonists in highly selected cases—may be necessary in patients with mild to moderate portopulmonary hypertension who require liver transplantation or other major surgery.

### Criteria to distinguish between mild, moderate, and severe portopulmonary hypertension

the presence of pulmonary hypertension, but in most cases, echocardiography provides the first, and mostly accurate, sign leading to the diagnosis.<sup>22–24</sup> If uncertainty remains, pulmonary hypertension can be conclusively shown—or ruled out—by right-heart catheterisation.<sup>25</sup> The presence of pulmonary hypertension in a patient with cirrhosis and portal hypertension per se is not sufficient to establish the diagnosis of portopulmonary hypertension. Other common causes of pulmonary hypertension, especially left-heart disease, valvular heart disease, interstitial or obstructive lung disease, sleep-related breathing disorders, and chronic thromboembolism, must be excluded first.

When the diagnosis of portopulmonary hypertension has been established, differentiation between mild, moderate, and severe pulmonary arterial hypertension is helpful for prognostic and treatment considerations. There is no universally accepted definition on which this distinction is routinely based, but for practical use cardiac output is better suited for classification than the magnitude of pulmonary arterial pressure. In mild to moderate portopulmonary hypertension, normal or high cardiac output is present and the pulmonary vascular resistance is only slightly raised. However, in severe portopulmonary hypertension cardiac output is reduced and pulmonary vascular resistance is strikingly raised (table).

### Management

Patients who have mild portopulmonary hypertension frequently have no symptoms and signs of pulmonary vascular disease. In these patients, specific treatment of pulmonary hypertension is not generally required. However, regular follow-up examinations, including biannual to annual echocardiographic examinations, are advisable to monitor the potential progression of pulmonary disease. Even mild to moderate portopulmonary hypertension can pose a notable threat to patients in special situations, such as those in whom major surgery is necessary. The attending physicians for such patients should be experienced in the management of liver disease and pulmonary hypertension.

Severe portopulmonary hypertension has a poor prognosis.<sup>9,12</sup> Specific treatment is available but is burdensome, expensive, and risky. Decisions about treatment should, therefore, be made on an individual basis, taking into account the severity of the underlying liver disease, accompanying risk factors, continuing alcohol or drug abuse, and the patient's adherence to treatment.

### Anticoagulation

Anticoagulation is recommended in patients who have primary pulmonary hypertension because it can slow

disease progression.<sup>26,27</sup> Efficacy and safety of oral anticoagulants in patients with portopulmonary hypertension have not yet been assessed in trials. Many such patients do not receive anticoagulants because of an increased risk of haemorrhagic complications, especially if there is a history of bleeding from oesophageal or gastric varices. In addition, the failure of liver synthesis leads to low concentrations of coagulation factors and to abnormal global coagulation studies. In such patients the intrinsic anticoagulation secondary to hepatic synthetic failure may render anticoagulation in principle expendable. However, from the limited data available, whether anticoagulation should be recommended for patients with severe portopulmonary hypertension is impossible to judge.

### Pharmacotherapy

Intravenous epoprostenol is the best-studied drug in patients with portopulmonary hypertension. Although the efficacy and safety of epoprostenol in such patients has never been addressed in randomised controlled trials, strong evidence from several open-label studies shows that this drug given intravenously improves haemodynamics and exercise capacity in patients with portopulmonary hypertension.<sup>15,28,29</sup> However, preliminary data from the Mayo Clinic suggest that intravenous epoprostenol does not improve long-term survival.<sup>30</sup> This treatment option has major drawbacks. Continuous intravenous epoprostenol administration requires permanent central venous access and uninterrupted infusion of the drug. Central venous access and the delivery system are prone to serious complications resulting from infection or pump failure.<sup>31,32</sup> Therefore, patients must adhere strictly to the recommendations for treatment and handling of the delivery system. For these reasons, continuous intravenous epoprostenol treatment should not be used in patients with continuing excessive alcohol intake or illicit drug use.

Other prostanoids have become available for the treatment of pulmonary arterial hypertension that can be administered orally,<sup>33</sup> subcutaneously,<sup>34</sup> or by inhalation,<sup>35,36</sup> and, therefore, have a more favourable safety profile than intravenous epoprostenol. However, experience with aerosolised iloprost, oral beraprost sodium, or treprostinil in portopulmonary hypertension is still anecdotal and large trials assessing their safety and efficacy for this indication are needed.

The endothelin system might be a potential target in portopulmonary hypertension. Plasma endothelin-1 concentrations are substantially higher in patients with portopulmonary hypertension than in healthy controls and patients with cirrhosis but no pulmonary hypertension.<sup>11</sup> The dual endothelin-receptor antagonist bosentan can be administered orally and has beneficial effects on haemodynamics and exercise capacity in patients with

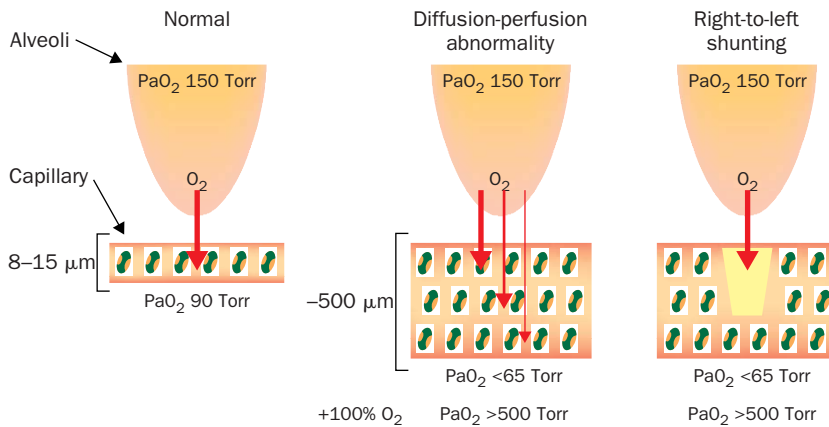


Figure 2: **Pathophysiology of hypoxaemia in hepatopulmonary syndrome**

Abnormal intrapulmonary vascular dilatation in combination with increased pulmonary blood flow leads to diffusion-perfusion disturbance and arterial hypoxaemia, correctable by oxygen supplementation. Most severe intrapulmonary vascular dilatation or formation of arteriovenous malformations causes right-to-left shunting only partially correctable by oxygen administration.

primary pulmonary hypertension and pulmonary arterial hypertension associated with systemic sclerosis.<sup>37,38</sup>

Patients with liver disease were excluded from the initial clinical trials because of safety concerns about the hepatotoxic potential of bosentan and other endothelin-receptor antagonists under clinical investigation. A rise in aminotransferase activity is seen in 10–15% of patients receiving bosentan.<sup>38</sup> A mechanism by which bosentan might cause liver injury is impairment of the activity of bile-salt transporters, leading to hepatocellular bile-salt accumulation.<sup>39</sup> Whether additional as yet unidentified mechanisms also contribute to liver toxic effects is unclear.

So far, no case of severe liver injury has been associated with bosentan use. However, two cases of severe liver injury, one of them fatal, have been associated with sitaxsentan, a novel selective inhibitor of type-A endothelin receptors.<sup>40</sup> Despite the shortage of controlled data, approval of bosentan by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products includes patients with portopulmonary hypertension, provided liver function is not severely impaired (Child-Pugh classes B and C). Preliminary unpublished experiences from several centres suggest that bosentan is safe and effective in selected patients with portopulmonary hypertension, but a high degree of caution is prudent in this group of patients until further investigations have addressed the safety and efficacy of this approach. For the time being, the use of bosentan in patients with portopulmonary hypertension should be restricted to highly experienced centres.

Sildenafil, a phosphodiesterase-5 inhibitor, is another novel and promising substance for the treatment of pulmonary hypertension,<sup>41,42</sup> but controlled data and reported experiences in patients with portopulmonary hypertension are not yet available.

### Liver transplantation

Liver transplantation requires special consideration, and is likely to be beneficial only in a selected cohort of patients with portopulmonary hypertension. The presence of pulmonary hypertension of any severity increases the perioperative and long-term risks of liver transplantation.<sup>43</sup> Clinical assessment protocols before liver transplantation should, therefore, specifically include a screening algorithm for portopulmonary hypertension in suspected cases, as outlined above. In addition, patients with proven

portopulmonary hypertension are better managed in transplant centres that have specific experience with this complication of advanced liver disease. Given this approach, liver transplantation generally has a good outcome in patients with mild to moderate portopulmonary hypertension.<sup>6,10</sup>

Mild to moderate pulmonary hypertension, signified by a high cardiac output in cirrhotic patients, is frequently reversible after liver transplantation,<sup>6,44–47</sup> but severe pulmonary hypertension is not<sup>48</sup> and has been associated with high mortality after this intervention.<sup>49,50</sup> In such patients, specific pulmonary vasodilator treatment followed by liver transplantation might be necessary to improve transplant outcome.<sup>28,51</sup> Severe portopulmonary

hypertension poses a pulmonary risk for liver-transplant candidates but also leads to a compromised perfusion of the liver graft. After liver-transplantation, congestion of the hepatic veins due to decreased right-ventricular function carries a notable risk of primary graft dysfunction. In highly selected cases, combined liver and lung transplantation or even heart-lung-liver transplantation might have to be considered.<sup>52,53</sup>

### Hepatopulmonary syndrome

The reported frequency of hepatopulmonary syndrome in patients with liver disease is between 4% and 29%.<sup>14,54–57</sup> The differing incidence is primarily due to heterogeneity of the applied diagnostic criteria. This syndrome is a well-defined cause of hypoxaemia in patients who have liver disease due to abnormal intrapulmonary vascular dilatation, which results in an excess perfusion for a given state of ventilation. This complication is characterised by anatomical shunting and a diffusion-perfusion abnormality (figure 2).<sup>14,58–60</sup> Thus, abnormal pulmonary vascular dilatation plays a central part in the hepatopulmonary syndrome, whereas abnormal vasoconstriction and obliterative vascular remodelling are the key features of portopulmonary hypertension. In fact, in one case report, development of portopulmonary hypertension in a patient who originally had hepatopulmonary syndrome seemed to lead to the correction of hypoxaemia.<sup>61</sup>

As with portopulmonary hypertension, hepatopulmonary syndrome occurs mostly in patients who have established cirrhosis and portal hypertension. The association between the severity of liver disease and the degree of hypoxaemia is slight, but the risk seems to be highest in Child C patients.<sup>54,62,63</sup> The cause of liver disease leading to portal hypertension does not seem to affect the development of the hepatopulmonary syndrome, which is evident from reports of a hepatopulmonary syndrome in patients with prehepatic portal hypertension in the absence of chronic liver disease,<sup>55,64</sup> in Budd-Chiari syndrome,<sup>65</sup> and even in patients with acute or chronic inflammatory liver disease without evidence of cirrhosis or portal hypertension.<sup>66–68</sup> The prognosis of the hepatopulmonary syndrome is poor and mortality rates of 41% within a mean observation period of 2.5 years have been reported.<sup>69</sup>

### Pathogenesis

From a pathophysiological point of view, hepatopulmonary syndrome is almost exactly the opposite

of portopulmonary hypertension. Evidence is growing rapidly that abnormal intrapulmonary vascular dilatation is linked to portal hypertension, which in itself leads to altered bowel perfusion and an increased rate of enteral translocation of gram-negative bacteria and endotoxin. This process in turn stimulates the release of vasoactive mediators, which include tumour necrosis factor  $\alpha$ , haem-oxygenase-derived carbon monoxide, and nitric oxide.<sup>70-72</sup> Experimental and clinical data suggest that increased production of nitric oxide in the lung plays a central part in the pathogenesis of the hepatopulmonary syndrome.<sup>73-77</sup> Increased concentrations of exhaled nitric oxide are positively correlated with the increase of alveolar-arterial oxygen difference.<sup>78</sup> The constitutive and the inducible isoforms of nitric-oxide synthase have been implicated in this process.<sup>70,74-77</sup> In addition, the endothelin system, especially abnormal activation and increased expression of endothelial type B endothelin receptors, has been implicated in the pathogenesis of the hepatopulmonary syndrome. In patients who have pulmonary hypertension, endothelin predominantly exerts vasoconstrictive and mitogenic effects due to activation of type A and type B endothelin receptors on pulmonary arterial smooth-muscle cells.<sup>79-81</sup> By contrast, in experimental models of the hepatopulmonary syndrome, the expression of endothelial type B endothelin receptors is strikingly increased and is linked to the increased production of nitric oxide by endothelial cells (figure 3).<sup>82-84</sup>

Histological examination reveals dilated intrapulmonary arterioles and capillaries and dilated vascular channels between pulmonary arteries and veins. The latter structures have been described as vascular spider naevi on the pleura and exhibit features of vasculogenesis.<sup>85</sup>

A typical, albeit not universal, finding in hepatopulmonary syndrome is orthodeoxia—ie, arterial deoxygenation improving in recumbency—which leads to the debilitating clinical symptom of orthodeoxia-platypnoea (hypoxaemia and dyspnoea induced or worsened in the upright position). This phenomenon is explained by the worsening of diffusion-perfusion matching and an increase of the shunt fraction in the upright position because of increased perfusion of the lower lobes.<sup>14</sup>

### Symptoms and diagnosis

Patients with hepatopulmonary syndrome complain of progressive dyspnoea and can become increasingly cyanotic. Some patients develop clubbing, and cutaneous telangiectasias (spider angiomas) are typically seen in high numbers.<sup>60</sup> In some instances, systemic arterioembolisation causing severe complications such as stroke, cerebral haemorrhage or brain abscess may occur.<sup>54,86</sup> Physical examination might reveal evidence of liver

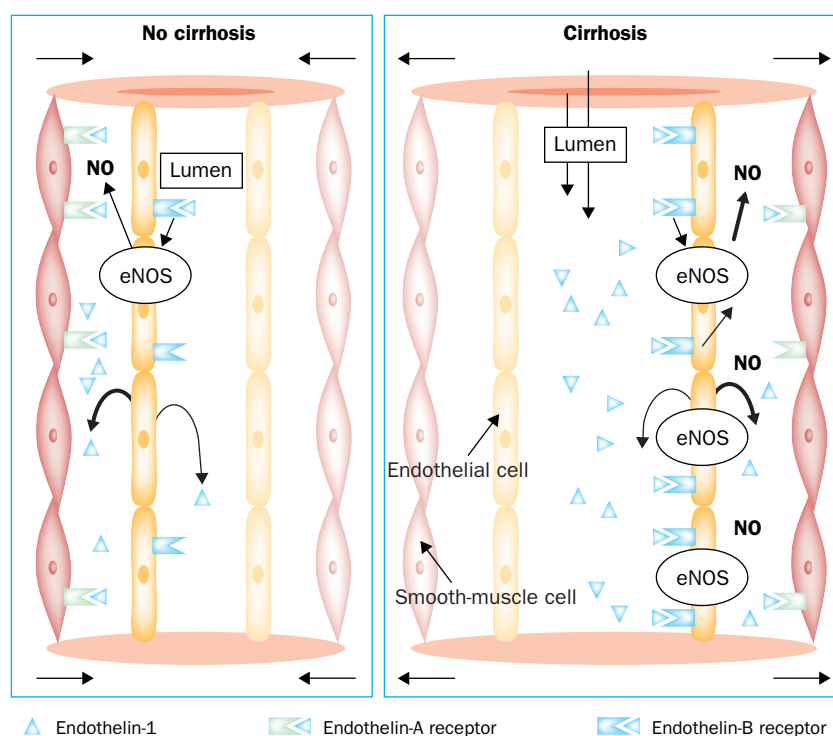


Figure 3: Schematic illustrating hypothesis underlying pulmonary-vessel dilatation in hepatopulmonary syndrome

NO=nitric oxide. eNOS=endothelial nitric oxide synthase. Left panel: In absence of cirrhosis and portal hypertension, endothelin-1 is secreted, mainly abluminally, where it activates vasoconstrictive endothelin type A receptors on smooth-muscle cells and contributes to maintenance of adequate vascular tone. Under physiological conditions, lumenally secreted endothelin is rapidly cleared from circulation after binding to endothelial type B endothelin receptors, which stimulates production of NO, partly antagonising vasoconstrictive effects of endothelin. Right panel: In presence of portal hypertension, hepatic production occurs of endothelin-1 and expression of endothelial type B receptors, but no type A receptors increase in pulmonary vasculature. Signalling via endothelially expressed endothelin B receptor leads to increased NO production by eNOS, with the overall effect of pulmonary vascular dilatation, which is pathognomonic of hepatopulmonary syndrome.

disease, but findings in the lungs and the heart are generally normal unless coexisting disease is present. The condition of many patients who have hepatopulmonary syndrome rapidly worsens even in the presence of stable hepatic synthesis, detoxification function, and degree of portal hypertension.

Since hypoxaemia is a prerequisite of the fully established hepatopulmonary syndrome, every diagnostic approach should begin with the documentation of hypoxaemia at rest by means of arterial or capillary blood-gas analysis. An arterial partial pressure of oxygen lower than 8.65 kPa is a good cut off to show a decreased value.<sup>54</sup> Since orthodeoxia is a typical finding in the hepatopulmonary syndrome, blood-gas analyses should be obtained with the patient in erect and supine positions. Blood-gas analysis is also useful while the patient is breathing 100% oxygen to assess the amount of right-to-left shunting.

Pulmonary function testing may show a low diffusion capacity for carbon monoxide. However, this finding is not a prerequisite for the diagnosis of the hepatopulmonary syndrome.<sup>56,87</sup>

In all patients who have chronic liver disease and hypoxaemia, the diagnosis of hepatopulmonary syndrome requires documentation of intrapulmonary vascular dilatation. The most common tools are contrast echocardiography and technetium-99m-labelled (<sup>99m</sup>Tc) macroaggregated albumin perfusion scanning. By contrast echocardiography, agitated saline or gelatine contrast medium is visualised in the left atrium between three and six heart cycles after intravenous injection, when shunts

typical of the hepatopulmonary syndrome are present.<sup>88</sup> However, an immediate appearance of echo contrast material in the left atrium suggests the presence of a cardiac right-to-left shunt that is an important differential diagnosis.<sup>89</sup> An alternative to contrast echocardiography is scintigraphic perfusion scanning. Under normal conditions, <sup>99m</sup>Tc albumin macroaggregates that exceed 20 µm in diameter are almost completely trapped in the pulmonary circulation. In the presence of a cardiac right-to-left shunt or intrapulmonary vascular dilatation the uptake of <sup>99m</sup>Tc macroaggregated albumin can be documented in other organs such as the brain or the spleen. This technique has been used for the diagnosis of hepatopulmonary syndrome and for the quantification of the magnitude of shunting.<sup>62</sup>

Pulmonary angiography is not a standard diagnostic tool in patients who have hepatopulmonary syndrome. However, in patients with a poor response to oxygen administration, which suggests substantial right-to-left shunting, pulmonary angiography can be done to identify focal arteriovenous malformations that may be amenable to embolisation.<sup>90</sup>

### Management

The treatment of hepatopulmonary syndrome includes the correction of hypoxaemia by administration of oxygen. However, in severe cases and the presence of right-to-left shunting, hypoxaemia might not be fully correctable.

Theoretically, the ideal treatment of hepatopulmonary syndrome would consist of a drug or any other means to reverse of intrapulmonary vascular dilatation. Unfortunately, this therapeutic goal cannot be fully achieved in most patients with the currently available treatments. Increased production of nitric oxide is a potential target, but this approach has not been established as routine. Diets containing low amounts of L-arginine, the substrate of nitric oxide synthase have provided no long-standing benefit. Intravenous infusion of methylene blue, an inhibitor of guanylate cyclase, which mediates the intracellular effects of nitric oxide, causes pulmonary vasoconstriction and reduction of hypoxaemia in patients with hepatopulmonary syndrome.<sup>91</sup> In addition, a case report showed increased oxygenation with inhaled N(G)-nitro-L-arginine methyl ester in one patient.<sup>92</sup> These observations support the notion that increased production of nitric oxide is involved in the pathogenesis of hepatopulmonary syndrome, but long-term application of methylene blue or N(G)-nitro-L-arginine methyl ester have not attained a practical role in treating the hepatopulmonary syndrome.<sup>93</sup> The concept of therapeutic nitric-oxide inhibition might become clinically more useful when specific inhibitors of the various isoenzymes of nitric oxide synthases have been developed.

The focus is, therefore, on strategies aimed at improving portal hypertension, which is the underlying pathophysiological problem leading to the hepatopulmonary syndrome. Reduction of the portal pressure seems to be an effective approach, which is supported by several reports of transjugular portosystemic shunting that have led to the correction of hypoxaemia,<sup>94-97</sup> although this procedure might not be successful in all patients.<sup>98</sup> Transjugular portosystemic shunting is not currently an established routine procedure for hepatopulmonary syndrome.

In our experience, pharmacological means of lowering portal venous pressure, such as β-adrenergic-receptor blockers and nitrates, which constitute the standard of care in chronic portal hypertension, exert no beneficial

effect on oxygenation in patients with hepatopulmonary syndrome.

Novel treatment options are being explored and include antibiotics that aim to reduce enteral bacteria translocation. Experimental models in common-bile-duct-ligated rats suggest that the use of antibiotics to decrease bacterial translocation in the bowel is effective in preventing the development of hepatopulmonary syndrome,<sup>99</sup> but whether this approach has reproducible and long-standing clinical effects remains to be shown.

In patients with progressive and refractory hypoxaemia, liver transplantation is the treatment of choice since it can correct all the discussed abnormalities secondary to the correction of the underlying hepatic disease. Severe hypoxaemia is a strong risk factor for increased mortality after liver transplantation,<sup>100,101</sup> but complete resolution after this procedure is well documented. Improvement in oxygenation might, however, take several months or even years.<sup>44,101-104</sup>

### Future perspectives

Although portopulmonary hypertension and the hepatopulmonary syndrome are associated with the same underlying diseases, they have distinct pathophysiological backgrounds. The rapidly increasing knowledge of pulmonary vascular tone regulation and vascular remodelling, including the identification of genes that increase the risk of developing pulmonary vascular disease, will eventually lead to a specifically targeted treatment approach. The treatment of portopulmonary hypertension has been largely based on the latest advances in the treatment of other forms of pulmonary arterial hypertension, but studies are now needed that are tailored specifically to analyse specifically patients who have portopulmonary hypertension. This requirement is particularly true for new substances such as endothelin-receptor antagonists and phosphodiesterase inhibitors. For theoretical reasons, endothelin-receptor antagonists, especially those which specifically block type B endothelin receptors, might also be useful in hepatopulmonary syndrome, but this remains to be studied. The same is true for various selective inhibitors of nitric-oxide-synthase isoforms, which are currently being developed. Experiences with liver transplantation teach us that the hepatopulmonary syndrome is completely reversible in most patients, which opens one currently available perspective for successful treatment.

#### Conflict of interest statement

M M Hoepfer has served as consultant for and has received speaker's fees from Schering, Pfizer, and Actelion, who produce substances that are mentioned in the paper. C P Strassburg and M J Krowka have no personal or financial relationship to report that causes a conflict of interest in writing this review.

#### References

- 1 Rolando N, Harvey F, Brahm J, et al. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology* 1990; **11**: 49-53.
- 2 Alberts WM, Salem AJ, Solomon DA, Boyce G. Hepatic hydrothorax: cause and management. *Arch Intern Med* 1991; **151**: 2383-88.
- 3 Hanson CA, Ritter AB, Duran W, Laviertes MH. Ascites: its effect upon static inflation of the respiratory system. *Am Rev Respir Dis* 1990; **142**: 39-42.
- 4 Rich S. Primary pulmonary hypertension: executive summary from the world symposium on primary pulmonary hypertension 1998. Geneva: World Health Organization, 1998.
- 5 McDonnell PJ, Towe PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? *Am Rev Respir Dis* 1983; **127**: 437-41.
- 6 Taura P, Garcia-Valdecasas JC, Beltran J, et al. Moderate primary pulmonary hypertension in patients undergoing liver transplantation. *Cardiovasc Anesth* 1996; **83**: 675-80.

- 7 Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991; **100**: 520–28.
- 8 Castro M, Krowka MJ, Schroeder DR, et al. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. *Mayo Clin Proc* 1996; **71**: 543–51.
- 9 Herve P, Lebrec D, Brenot F, et al. Pulmonary vascular disorders in portal hypertension. *Eur Respir J* 1998; **11**: 1153–66.
- 10 Plevak D, Krowka M, Rettke S, Dunn W, Southorn P. Successful liver transplantation in patients with mild to moderate pulmonary hypertension. *Transplant Proc* 1993; **25**: 1840.
- 11 Benjaminov FS, Prentice M, Sniderman KW, Siu S, Liu P, Wong F. Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *Gut* 2003; **52**: 1355–62.
- 12 Robalino BD, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. *J Am Coll Cardiol* 1991; **17**: 492–98.
- 13 Budhiraja R, Hassoun PM. Portopulmonary hypertension: a tale of two circulations. *Chest* 2003; **123**: 562–76.
- 14 Naeije R. Hepatopulmonary syndrome and portopulmonary hypertension. *Swiss Med Wkly* 2003; **133**: 163–69.
- 15 Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology* 1999; **30**: 641–48.
- 16 Edwards BS, Weir EK, Edwards WD, Ludwig J, Dykoski RK, Edwards JE. Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol* 1987; **10**: 1233–38.
- 17 Jamison BM, Michel RP. Different distribution of plexiform lesions in primary and secondary pulmonary hypertension. *Hum Pathol* 1995; **26**: 987–93.
- 18 Deng Z, Morse JH, Slager S, et al. Familial primary pulmonary hypertension (Gene PPH-1) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet* 2000; **67**: 737–44.
- 19 Thomson JR, Machado RD, Pauciulo MW, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF- $\beta$  family. *J Med Genet* 2000; **37**: 741–45.
- 20 Machado RD, Pauciulo MW, Thomson JR, et al. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. *Am J Hum Genet* 2001; **68**: 92–102.
- 21 Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic teleangiectasia. *N Engl J Med* 2001; **345**: 325–34.
- 22 Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl* 2000; **6**: 453–58.
- 23 Torregrosa M, Genesca J, Gonzalez A, et al. Role of Doppler echocardiography in the assessment of portopulmonary hypertension in liver transplantation candidates. *Transplantation* 2001; **71**: 572–74.
- 24 Auletta M, Oliviero U, Iasiuolo L, Scherillo G, Antonello S. Pulmonary hypertension associated with liver cirrhosis: an echocardiographic study. *Angiology* 2000; **51**: 1013–20.
- 25 Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology* 2003; **37**: 401–09.
- 26 Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984; **70**: 580–87.
- 27 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327**: 76–81.
- 28 Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation* 1997; **63**: 604–06.
- 29 Plotkin JS, Kuo PC, Rubin LJ, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. *Transplantation* 1998; **65**: 457–59.
- 30 Swanson KL, McGoon MD, Krowka MJ. Survival in patients with portopulmonary hypertension. *Am J Respir Crit Care Med* 2003; **167**: A693.
- 31 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106**: 1477–82.
- 32 Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; **40**: 780–88.
- 33 Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; **39**: 1496–502.
- 34 Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; **165**: 800–04.
- 35 Hooper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; **342**: 1866–70.
- 36 Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; **347**: 322–29.
- 37 Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; **358**: 1119–23.
- 38 Rubin LJ, Roux S. Bosentan: a dual endothelin receptor antagonist. *Expert Opin Investig Drugs* 2002; **11**: 991–1002.
- 39 Fattinger K, Funk C, Pantze M, et al. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* 2001; **69**: 223–31.
- 40 Barst RJ, Rich S, Widlitz A, Horn EM, McLaughlin V, McFarlin J. Clinical efficacy of sitaxsentan, an endothelin- $\alpha$  receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. *Chest* 2002; **121**: 1860–68.
- 41 Lodato RF. Viagra for impotence of pulmonary vasodilator therapy. *Am J Respir Crit Care Med* 2001; **163**: 312–13.
- 42 Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; **42**: 158–64.
- 43 De Wolf AM, Scott VL, Gasior T, Kang Y. Pulmonary hypertension and liver transplantation. *Anesthesiology* 1993; **78**: 213–14.
- 44 Levy MT, Torzillo P, Bookallil M, Sheil AG, McCaughan GW. Case report: delayed resolution of severe pulmonary hypertension after isolated liver transplantation in a patient with cirrhosis. *J Gastroenterol Hepatol* 1996; **11**: 734–37.
- 45 Schott R, Chaouat A, Launoy A, Pottecher T, Weitzenblum E. Improvement of pulmonary hypertension after liver transplantation. *Chest* 1999; **115**: 1748–49.
- 46 Koneru B, Ahmed S, Weisse AB, Grant GP, McKim KA. Resolution of pulmonary hypertension of cirrhosis after liver transplantation. *Transplantation* 1994; **58**: 1133–35.
- 47 Scott A, De Wolf A, Kang Y, et al. Reversibility of pulmonary hypertension after liver transplantation: a case report. *Transplant Proc* 1993; **25**: 1789–90.
- 48 Rafanan AL, Maurer J, Mehta AC, Schilz R. Progressive portopulmonary hypertension after liver transplantation treated with epoprostenol. *Chest* 2000; **118**: 1497–500.
- 49 Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg* 1997; **3**: 494–500.
- 50 Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl* 2000; **6**: 443–50.
- 51 Kuo PC, Plotkin JS, Gaine SP, et al. Portopulmonary hypertension and the liver transplant candidate. *Transplantation* 1999; **67**: 1087–93.
- 52 Dennis CM, McNeil KD, Dunning J, et al. Heart-lung-liver transplantation. *J Heart Lung Transplant* 1996; **15**: 536–38.
- 53 Wallwork J, Williams R, Calne RY. Transplantation of liver, heart, and lungs for primary biliary cirrhosis and primary pulmonary hypertension. *Lancet* 1987; **2**: 182–85.
- 54 Schenk P, Fuhrmann V, Madl C, et al. Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. *Gut* 2002; **51**: 853–59.
- 55 Gupta D, Vijaya DR, Gupta R, et al. Prevalence of hepatopulmonary syndrome in cirrhosis and extrahepatic portal venous obstruction. *Am J Gastroenterol* 2001; **96**: 3395–99.
- 56 Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol* 2001; **34**: 651–57.
- 57 Lange PA, Stoller JK. The hepatopulmonary syndrome. *Ann Intern Med* 1995; **122**: 521–29.
- 58 Whyte MK, Hughes JM, Peters AM, Ussov W, Patel S, Burroughs AK. Analysis of intrapulmonary right to left shunt in the hepatopulmonary syndrome. *J Hepatol* 1998; **29**: 85–93.

- 59 Edell ES, Cortese DA, Krowka MJ, Rehder K. Severe hypoxemia and liver disease. *Am Rev Respir Dis* 1989; **140**: 1631–35.
- 60 Rodriguez-Roisin R, Roca J, Agustí AG, Mastai R, Wagner PD, Bosch J. Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. *Am Rev Respir Dis* 1987; **135**: 1085–92.
- 61 Mal H, Burgiere O, Durand F, Fartoukh M, Cohen-Solal A, Fournier M. Pulmonary hypertension following hepatopulmonary syndrome in a patient with cirrhosis. *J Hepatol* 1999; **31**: 360–64.
- 62 Krowka MJ, Wiseman GA, Burnett OL, et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO<sub>2</sub> response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. *Chest* 2000; **118**: 615–24.
- 63 Vachieri F, Moreau R, Hadengue A, et al. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. *J Hepatol* 1997; **27**: 492–95.
- 64 De BK, Sen S, Biswas PK, Sanyal R, Jundar DM, Biswas J. Hepatopulmonary syndrome in inferior vena cava obstruction responding to cavoplasty. *Gastroenterology* 2000; **118**: 192–96.
- 65 De BK, Sen S, Biswas PK, et al. Occurrence of hepatopulmonary syndrome in Budd-Chiari syndrome and the role of venous decompression. *Gastroenterology* 2002; **122**: 897–903.
- 66 Avendano CE, Flume PA, Baliga P, Lewin DN, Strange C, Reuben A. Hepatopulmonary syndrome occurring after orthotopic liver transplantation. *Liver Transpl* 2001; **7**: 1081–84.
- 67 Regev A, Yeshurun M, Rodriguez M, et al. Transient hepatopulmonary syndrome in a patient with acute hepatitis A. *J Viral Hepat* 2001; **8**: 83–86.
- 68 Teuber G, Teupe C, Dietrich CF, Caspary WF, Buhl R, Zeuzem S. Pulmonary dysfunction in non-cirrhotic patients with chronic viral hepatitis. *Eur J Intern Med* 2002; **13**: 311–18.
- 69 Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome: clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* 1993; **104**: 515–21.
- 70 Nunes H, Lebec D, Mazmanian M, et al. Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. *Am J Respir Crit Care Med* 2001; **164**: 879–85.
- 71 Carter EP, Hartsfield CL, Miyazono M, Jakkula M, Morris KG Jr, McMurtry IF. Regulation of heme oxygenase-1 by nitric oxide during hepatopulmonary syndrome. *Am J Physiol Lung Cell Mol Physiol* 2002; **283**: L346–53.
- 72 Strassburg CP. Shock liver. *Best Pract Res Clin Gastroenterol* 2003; **17**: 369–81.
- 73 Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; **337**: 776–78.
- 74 Fallon MB, Abrams GA, Luo B, Hou Z, Dai J, Ku DD. The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. *Gastroenterology* 1997; **113**: 606–14.
- 75 Liu L, Zhang M, Luo B, Abrams GA, Fallon MB. Biliary cyst fluid from common bile duct-ligated rats stimulates endothelial nitric oxide synthase in pulmonary artery endothelial cells: a potential role in hepatopulmonary syndrome. *Hepatology* 2001; **33**: 722–27.
- 76 Rolla G, Brussino L, Colagrande P, et al. Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation. *Ann Intern Med* 1998; **129**: 375–78.
- 77 Schroeder RA, Ewing CA, Sitzmann JV, Kuo PC. Pulmonary expression of iNOS and HO-1 protein is upregulated in a rat model of prehepatic portal hypertension. *Dig Dis Sci* 2000; **45**: 2405–10.
- 78 Rolla G, Brussino L, Colagrande P, et al. Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. *Hepatology* 1997; **26**: 842–47.
- 79 Ooi H, Colucci WS, Givertz MM. Endothelin mediates increased pulmonary vascular tone in patients with heart failure: demonstration by direct intrapulmonary infusion of sitaxsentan. *Circulation* 2002; **106**: 1618–21.
- 80 Giaid A, Yanagisawa M, Langleben Dea. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; **328**: 1732–39.
- 81 Davie N, Haleen SJ, Upton PD, et al. ET(A) and ET(B) receptors modulate the proliferation of human pulmonary artery smooth muscle cells. *Am J Respir Crit Care Med* 2002; **165**: 398–405.
- 82 Luo B, Abrams GA, Fallon MB. Endothelin-1 in the rat bile duct ligation model of hepatopulmonary syndrome: correlation with pulmonary dysfunction. *J Hepatol* 1998; **29**: 571–78.
- 83 Luo B, Liu L, Tang L, et al. Increased pulmonary vascular endothelin B receptor expression and responsiveness to endothelin-1 in cirrhotic and portal hypertensive rats: a potential mechanism in experimental hepatopulmonary syndrome. *J Hepatol* 2003; **38**: 556–63.
- 84 Zhang M, Luo B, Chen SJ, Abrams GA, Fallon MB. Endothelin-1 stimulation of endothelial nitric oxide synthase in the pathogenesis of hepatopulmonary syndrome. *Am J Physiol* 1999; **277**: G944–52.
- 85 Schraufnagel DE, Kay JM. Structural and pathologic changes in the lung vasculature in chronic liver disease. *Clin Chest Med* 1996; **17**: 1–15.
- 86 Abrams GA, Rose K, Fallon MB, et al. Hepatopulmonary syndrome and venous emboli causing intracerebral hemorrhages after liver transplantation: a case report. *Transplantation* 1999; **68**: 1809–11.
- 87 Agustí AG, Roca J, Bosch J, Rodriguez-Roisin R. The lung in patients with cirrhosis. *J Hepatol* 1990; **10**: 251–57.
- 88 Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, Cortese DA. Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates: screening by two-dimensional contrast-enhanced echocardiography. *Chest* 1990; **97**: 1165–70.
- 89 Raffy O, Sleiman C, Vachieri F, et al. Refractory hypoxemia during liver cirrhosis. Hepatopulmonary syndrome or “primary” pulmonary hypertension? *Am J Respir Crit Care Med* 1996; **153**: 1169–71.
- 90 Castro M, Krowka MJ. Hepatopulmonary syndrome: a pulmonary vascular complication of liver disease. *Clin Chest Med* 1996; **17**: 35–48.
- 91 Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; **133**: 701–06.
- 92 Brussino L, Bucca C, Morello M, Scappaticci E, Mauro M, Rolla G. Effect on dyspnoea and hypoxaemia of inhaled N(G)-nitro-L-arginine methyl ester in hepatopulmonary syndrome. *Lancet* 2003; **362**: 43–44.
- 93 Fallon MB. Methylene blue and cirrhosis: pathophysiologic insights, therapeutic dilemmas. *Ann Intern Med* 2000; **133**: 738–40.
- 94 Lasch HM, Fried MW, Zacks SL, et al. Use of transjugular intrahepatic portosystemic shunt as a bridge to liver transplantation in a patient with severe hepatopulmonary syndrome. *Liver Transpl* 2001; **7**: 147–49.
- 95 Paramesh AS, Husain SZ, Shneider B, et al. Improvement of hepatopulmonary syndrome after transjugular intrahepatic portosystemic shunting: case report and review of literature. *Pediatr Transplant* 2003; **7**: 157–62.
- 96 Riegler JL, Lang KA, Johnson SP, Westerman JH. Transjugular intrahepatic portosystemic shunt improves oxygenation in hepatopulmonary syndrome. *Gastroenterology* 1995; **109**: 978–83.
- 97 Allgaier HP, Haag K, Ochs A, et al. Hepato-pulmonary syndrome: successful treatment by transjugular intrahepatic portosystemic shunt (TIPS). *J Hepatol* 1995; **23**: 102.
- 98 Corley DA, Schar Schmidt B, Bass N, Somberg K, Gold W, Sonnenberg K. Lack of efficacy of TIPS for hepatopulmonary syndrome. *Gastroenterology* 1997; **113**: 728–30.
- 99 Rabiller A, Nunes H, Lebec D, et al. Prevention of gram-negative translocation reduces the severity of hepatopulmonary syndrome. *Am J Respir Crit Care Med* 2002; **166**: 514–17.
- 100 Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* 2003; **37**: 192–97.
- 101 Krowka MJ, Porayko MK, Plevak DJ, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc* 1997; **72**: 44–53.
- 102 Collisson EA, Nourmand H, Fraiman MH, et al. Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl* 2002; **8**: 925–31.
- 103 Philit F, Wiesendanger T, Gille D, Boillot O, Cordier JF. Late resolution of hepatopulmonary syndrome after liver transplantation. *Respiration* 1997; **64**: 173–75.
- 104 Taille C, Cadranet J, Bellocq A, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation* 2003; **75**: 1482–89.