Pulmonary complications in liver disease

Pulmonary complications of liver disease are poorly understood and often identified late. Abnormalities of the pulmonary vasculature lead to two distinct complications, hepatopulmonary syndrome and portopulmonary hypertension, which differ in their clinical features and management. This article focuses on these two entities.

Chronic liver disease is a complex clinical condition that can lead to dysfunction of almost every organ, including brain, kidneys and the cardiovascular system. Pulmonary complications of liver disease are poorly understood and often identified at a very late stage. The most common respiratory problems in patients with liver disease are concomitant conditions such as asthma and chronic obstructive pulmonary disease, but certain liver conditions such as α1-antitrypsin deficiency, cystic fibrosis and sarcoidosis are associated with specific pulmonary problems. Ascites often causes diaphragmatic splinting and may also be associated with hepatic hydrothorax, while intercostal muscular wasting characteristic of end-stage liver disease leads to further respiratory compromise.

Patients with more advanced chronic liver disease may also develop abnormalities of the pulmonary vasculature, independent of cardiorespiratory disease, which underpin two distinct and specific pulmonary complications: hepatopulmonary syndrome and portopulmonary hypertension, which are the focus of this article.

Hepatopulmonary syndrome

Background and definition

The first description of this syndrome was probably that of Flückiger in 1884 of a woman with liver cirrhosis, cyanosis and digital clubbing. In 1956 Rydell and Hoffbauer studied lung necropsy specimens from patients with juvenile cirrhosis and hypoxaemia using plastic vascular casts. They demonstrated both pre-capillary and capillary vascular dilatation, as well as anatomical arteriovenous communication (Hoffbauer and Rydell, 1956). In 1966 Berthelot et al noted marked pulmonary vascular dilatation in an autopsy study in patients with liver cirrhosis. The term 'hepatopulmonary syndrome' was first coined by Kennedy and Knudson (1977) and has been used since to describe the triad of liver disease, intrapulmonary vascular dilatation and defective oxygenation.

The most common hepatic disorder leading to hepatopulmonary syndrome is cirrhosis, irrespective of aetiology. It is likely that hepatopulmonary syndrome is often missed, especially in the early stages. Data from tertiary referral and transplant centres suggest a prevalence of between 15 and 32% (including mild cases) (Schenk et al, 2002). It has also been reported in non-cirrhotic portal hypertension, Budd–Chiari syndrome, viral and ischaemic hepatitis and can even occur transiently in acute hepatitis.

The definition of hypoxaemia has varied in the past, which explains the variable reported prevalence, but this has been standardized following the recommendations of the European Respiratory Society Task Force (Rodriguez-Roisin et al, 2004). An alveolar–arterial oxygen gradient ≥15 mmHg (2 kPa) or a partial pressure of arterial oxygen (PaO_2) <80 mmHg (10.7 kPa) while breathing room air, with the patient at rest and in an erect position, usually sitting, is now the accepted definition. For patients older than 64 years, a alveolar–arterial oxygen gradient ≥20 mmHg (2.7 kPa) or a PaO_2 <70 mmHg (9.3 kPa) have been recommended. The diagnostic criteria for hepatopulmonary syndrome are shown in *Table 1*.

Clinical features, natural history and staging

The development of hepatopulmonary syndrome is associated with the onset of progressive dyspnoea, initially occurring on exertion, but later present at rest. The presence or severity of hepatopulmonary syndrome does not correlate with the severity of underlying chronic liver disease, assessed by the Child–Pugh classification or the Model for End-stage Liver Disease score and the condition can develop in mild liver disease (Krowka et al, 2000a; Swanson et al, 2005). Spider naevi, central cyanosis and finger clubbing are common features. Dyspnoea worsens in the upright position compared to the supine position (platypnoea) and the associated finding of orthodeoxia (a reduction of PaO_2

Table 1. Diagnostic criteria for hepatopulmonary syndrome

Liver disease and/or portal hypertension
Positive contrast-enhanced echocardiography (or >6% uptake in the brain with radionucleotide lung perfusion scanning)
$P_{A\text{-}a}O_2$* ≥15 mmHg (2 kPa) or PaO_2 <80 mmHg (10.7 kPa) while breathing room air. For patients older than 64 years $P_{A\text{-}a}O_2$ ≥20 mmHg (2.7 kPa) or a PaO_2 <70 mmHg (9.3 kPa)

*$P_{A\text{-}a}O_2 = F_iO_2 (P_{atm} - P_{H20}) - PaCO_2$/ respiratory exchange ratio – PaO_2
F_iO_2 = inspiratory oxygen fraction; PaO_2 = partial pressure of arterial oxygen; $P_{A\text{-}a}O_2$ = alveolar–arterial oxygen gradient; P_{atm} = atmospheric pressure; P_{H20} = partial pressure of water vapour at body temperature; $PaCO_2$ = partial pressure of arterial carbon dioxide; 1 mmHg = 0.133 kPa. From Rodriguez-Roisin et al (2004)

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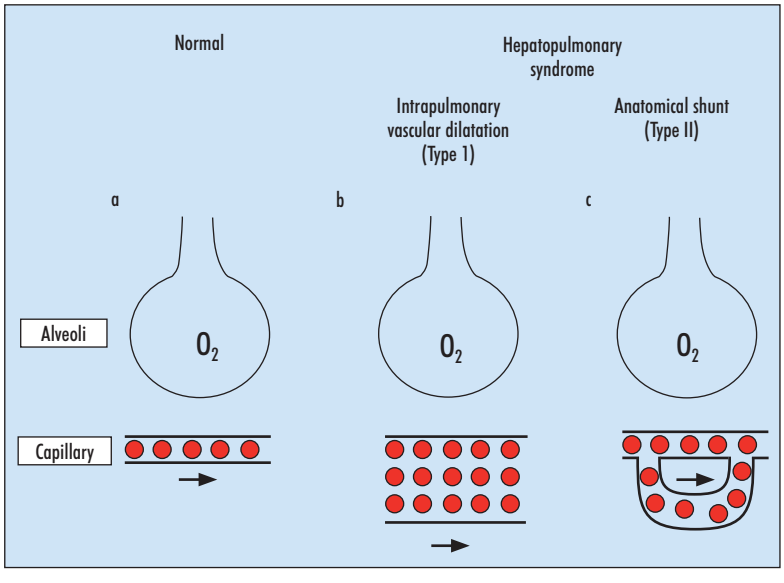
by ≥5% of baseline, or ≥4 mmHg (0.5 kPa) on changing position from supine to upright (Gomez et al, 2004)) is one of the hallmarks of hepatopulmonary syndrome.

Orthotopic liver transplantation has had a huge impact on survival following the development of hepatopulmonary syndrome, so studies of the natural history of hepatopulmonary syndrome have depended on patients who are not transplant candidates (because of age or comorbidity). The Mayo group showed a median survival of 24 months and a 5-year survival of 23% among 37 such patients; this contrasted with a control group, matched for age, severity and aetiology of liver disease, who also were not transplant candidates but who did not have hepatopulmonary syndrome, who had a median survival of 87 months and a 5-year survival of 63% (Swanson et al, 2005). These data support the view that the development of hepatopulmonary syndrome worsens the prognosis for patients with liver disease (Schiffer et al, 2006). The cause of death in a patient with hepatopulmonary syndrome is multifactorial and usually a consequence of complications of the associated liver disease. It is rare for patients with hepatopulmonary syndrome to die primarily of respiratory failure.

Table 2. Staging of severity of hepatopulmonary syndrome (with positive contrast-enhanced echocardiography and alveolar–arterial oxygen gradient ≥15 mmHg (2 kPa))

Stage	Partial pressure of arterial oxygen in mmHg (kPa)
Mild	≥80 (10.7)
Moderate	≥60 to <80 (≥8–<10.7)
Severe	≥50 to <60 (≥6.7–<8)
Very severe	<50 (6.7) or <300 (40) on 100% oxygen

Figure 1. Arrangement of alveolus and capillary in (a) normal lung, (b) type 1 hepatopulmonary syndrome (diffuse intrapulmonary vascular dilatation) and (c) type 2 hepatopulmonary syndrome (localized arteriovenous communications).



Staging of the severity of hepatopulmonary syndrome is important since this influences survival and therefore the timing and risk of orthotopic liver transplantation. The European Respiratory Society Task Force staging is widely accepted (*Table 2*) (Rodriguez-Roisin et al, 2004). Mild and moderate disease merit close follow up and severe hepatopulmonary syndrome (PaO_2 <60 mmHg or 8 kPa) is regarded as an indication of orthotopic liver transplantation. Very severe hepatopulmonary syndrome (PaO_2 <50 mmHg or 6.7 kPa, with a pulmonary shunt fraction of ≥20%), while still an indication for orthotopic liver transplantation, carries a high postoperative mortality (Arguedas et al, 2003) which may be prohibitive. In contrast to other anatomical intrapulmonary shunts, there is an active response in hepatopulmonary syndrome to the inhalation of 100% oxygen, with PaO_2 >300 mmHg (40 kPa) (Krowka et al, 2000a). This response is not seen in the very severe stages of hepatopulmonary syndrome (and also in the variant of hepatopulmonary syndrome where there are localized anatomical shunts, sometimes called type 2 hepatopulmonary syndrome).

Pathophysiology

The hallmark pathology underlying the development of hepatopulmonary syndrome is pre-capillary and capillary dilatation of the intrapulmonary vasculature (*Figure 1*). Pleural and pulmonary arteriovenous communications and portopulmonary anastomoses have also been noted (Berthelot et al, 1966). Wall thickness of capillaries and venules increases, vascular tone falls, with the impairment of hypoxic pulmonary vasoconstriction.

Mixed venous blood passes through dilated pulmonary capillaries and the intrapulmonary shunts too rapidly and too far from the alveolar membrane for effective oxygenation, leading to a ventilation–perfusion mismatch and shunting and consequently hypoxaemia. The relatively fixed pulmonary vascular tone is less able to accommodate gravitational blood flow changes in dependent alveolar units and resulting in orthodeoxia on change of position (Gomez et al, 2004). In advanced hepatopulmonary syndrome, alveolar–capillary diffusion impairment occurs, probably because of increased width of the alveolar–capillary interface. Pulmonary vascular remodelling may also contribute to the pathophysiology of hepatopulmonary syndrome.

Increased pulmonary production of nitric oxide, a potent vasodilator, has been implicated as central to the pathogenesis of hepatopulmonary syndrome. This is borne out by increased levels of exhaled nitric oxide in hepatopulmonary syndrome and normalization following orthotopic liver transplantation (Cremona et al, 1995). The exact mechanisms remain unclear, with studies based predominantly in bile-duct ligated rats. Endothelin-1, produced by the liver, possibly acts via the endothelin-B receptors to stimulate pulmonary vas-

cular endothelial nitric oxide synthase. Accumulation of pulmonary intravascular macrophages leads to enhanced expression and activity of inducible nitric oxide synthase and heme oxygenase-1, leading to overproduction of nitric oxide and carbon monoxide and resulting in vasodilatation (Zhang et al, 2003; Ling et al, 2004). Norfloxacin reduced macrophage accumulation and normalized inducible nitric oxide synthase activity in animal models, suggesting that gut translocation of bacteria in liver disease may stimulate pulmonary macrophage accumulation and contribute to the development of hepatopulmonary syndrome (Rabiller et al, 2002). Other animal studies have shown that the development of hepatopulmonary syndrome can be prevented by pentoxifylline (Sztrymf et al, 2004), an inhibitor of tumour necrosis factor-α, possibly by reducing angiogenesis (Zhang et al, 2009).

Investigations

The diagnosis of hepatopulmonary syndrome requires the demonstration of intrapulmonary vascular dilatation in addition to arterial gas exchange abnormalities in the presence of liver disease and/or portal hypertension.

Transthoracic contrast echocardiography

Transthoracic contrast echocardiography is the preferred screening test for intrapulmonary vascular dilatation (Krowka et al, 1990; Abrams et al, 1995). Agitated saline (8–9 ml containing micro-bubbles >10 μm in diameter) is injected intravenously while maintaining an apical four-chamber view on transthoracic echocardiography. Entry of micro-bubbles into the right heart is seen as 'opacification'. In the presence of normal lung vasculature, micro-bubbles are trapped in the capillaries (approximately 8–15 μm in diameter) and absorbed. With intrapulmonary vascular dilatation, some micro-bubbles pass through the lung vasculature and enter the left heart causing delayed opacification (three to six cardiac contractions after right heart opacification) (*Figure 2*). Left heart opacification within three cardiac contractions of right heart opacification suggests an intracardiac right-to-left shunt.

Radionucleotide lung perfusion scanning

Radionucleotide lung perfusion scanning uses technetium-99-labelled macro-aggregated albumin. Normally the material is trapped in the lungs, but in the presence of intrapulmonary vascular dilatation some escapes into the systemic circulation. An uptake ≥6% in the brain is the accepted level for diagnosis (Abrams et al, 1998). The advantages of this technique are that it is quantitative (giving a shunt fraction) and remains useful in those with intrinsic lung disease. However, there are problems with standardization of this technique between different centres, it is less sensitive than contrast echocardiography and the latter is the screening test of choice for intrapulmonary vascular dilatation.

Transoesophageal contrast echocardiography

Transoesophageal contrast echocardiography can exclude intracardiac shunts, but is invasive and is seldom used.

Pulmonary angiography

Pulmonary angiography can distinguish between the diffuse vascular pattern of typical (type 1) hepatopulmonary syndrome and the localized arteriovenous communications of type 2 hepatopulmonary syndrome (Krowka et al, 1993). It is an invasive procedure and is indicated only in severe hepatopulmonary syndrome (PaO_2 <60 mmHg or 8 kPa) where there is a poor response to inhalation of 100% oxygen and a chest computed tomography scan suggests an arteriovenous communication, amenable to embolization (Poterucha et al, 1995).

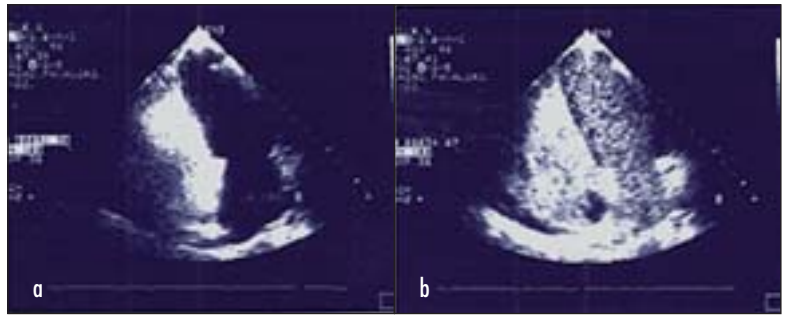
Treatment

There is no effective medical therapy for hepatopulmonary syndrome. Uncontrolled studies and anecdotal evidence suggest benefit with almitrine, antibiotics, indomethacin, somatostatin analogues, garlic preparations, pentoxifylline, nitric oxide inhibitors and methylene blue, but these and others are largely ineffective (Rodriguez-Roisin and Krowka, 2008; Tanikella et al, 2008). Long-term oxygen therapy provides symptomatic relief.

Other therapeutic modalities have been considered. Transjugular intrahepatic portosystemic shunt for hepatopulmonary syndrome remains controversial (Selim et al, 1998). Cavoplasty appears to reverse hepatopulmonary syndrome in Budd–Chiari syndrome with inferior vena cava obstruction (De et al, 2002). Coil embolization has been attempted in a case of hepatopulmonary syndrome with angiographic evidence of arteriovenous communications (Poterucha et al, 1995).

The only proven therapy for hepatopulmonary syndrome is orthotopic liver transplantation, which is indicated in patients with severe hepatopulmonary syndrome. Patients with very severe hepatopulmonary syndrome (PaO_2 <50 mmHg or 6.7 kPa, with a pulmonary

Figure 2. Transthoracic contrast echocardiography (apical four-chamber view). a. Immediately after injection of contrast (agitated saline), micro-bubbles enter the right heart and cause opacification. The left heart remains echo-free. b. Three to six cardiac contractions afterwards, a stream of micro-bubbles entering the left heart indicate the presence of intrapulmonary vascular dilatation (bottom).



shunt fraction of ≥20%) have a high postoperative mortality (Arguedas et al, 2003). Hepatopulmonary syndrome usually resolves completely following orthotopic liver transplantation, but this may take a year (Philit et al, 1997), possibly because of vascular remodelling.

Portopulmonary hypertension

Background and definition

Portopulmonary hypertension lies at the other end of the spectrum of pulmonary vascular complications of liver disease. It was first described in 1951 by Mantz and Craige and has now been defined as pulmonary arterial hypertension in the presence of portal hypertension with or without hepatic disease. It is a rare but severe condition affecting 3–8% of patients with advanced liver cirrhosis presenting to a transplant centre (Ramsay et al, 1997; Krowka et al, 2006). It has been reported in non-cirrhotic portal hypertension and, rarely, in liver disease in the absence of portal hypertension.

A moderate increase in mean pulmonary arterial pressure is often seen in patients with cirrhosis and portal hypertension, either as a result of increased cardiac output (despite reduced pulmonary vascular resistance) or of increased circulating blood volume (with increased mean pulmonary artery occlusion pressure). Less common is the development of moderate to severe pulmonary arterial hypertension caused by extensive vascular remodelling, a raised pulmonary vascular resistance and decreased mean pulmonary artery occlusion pressure. The latter category of pulmonary arterial hypertension has been described as portopulmonary hypertension and haemodynamic criteria based on right heart catheter studies define the condition (*Table 3*) (Rodriguez-Roisin et al, 2004). At the Third World Symposium in Venice in 2003, portopulmonary hypertension was reclassified as a unique entity within the modified World Health Organization group 1 category of pulmonary arterial hypertension (Simonneau et al, 2004).

Clinical features, natural history and staging

The clinical features of portopulmonary hypertension are non-specific and include fatigue, dyspnoea, chest pain, syncope and features of right heart failure (including ascites and peripheral oedema). Hypoxaemia is not a major feature and is milder than in hepatopulmonary syndrome (Swanson and Krowka, 2002). The clinical features of portopulmonary hypertension are often mistaken for those of the underlying liver disease itself, commonly leading to a late diagnosis. The risk factors for the development of portopulmonary hypertension are not clear, but data suggest the risk is increased in females and in those with autoimmune hepatitis, but reduced with hepatitis C virus infection (Kawut et al, 2008). The severity of portopulmonary hypertension does not correlate with the severity of associated liver disease or portal hypertension (Hadengue et al, 1991; Krowka et al, 2006).

Portopulmonary hypertension has a poor prognosis with mean and median survivals of 15 and 6 months respectively having been reported in the pre-orthotopic liver transplantation era (Robalino and Moodie, 1992). A single-centre study reported 58% mortality within a year of diagnosis of portopulmonary hypertension (Hadengue et al, 1991). The Mayo experience reports similar figures (Swanson et al, 2008). Patients not treated for pulmonary arterial hypertension and not receiving an orthotopic liver transplantation had a 5-year survival of 14%, with 54% dying within a year of diagnosis. Treatment of pulmonary arterial hypertension alone (without an orthotopic liver transplantation) improved the 5-year survival to 45%, with only 12% dying within a year. Causes of death seem to be distributed equally between liver related and cardiopulmonary.

Portopulmonary hypertension per se is not an indication for orthotopic liver transplantation, in contrast to hepatopulmonary syndrome. However, the presence of severe portopulmonary hypertension increases perioperative morbidity and mortality following orthotopic liver transplantation, highlighting the importance of staging severity. One system (*Table 4*) (Chemla et al, 2002), based on resting mean pulmonary arterial pressure, was recommended by the European Respiratory Society Task Force (Rodriguez-Roisin et al, 2004). Current data suggest an increased perioperative mortality of >50% following orthotopic liver transplantation in moderate to severe portopulmonary hypertension, but no such increase in mild portopulmonary hypertension (Krowka et al, 2000b).

Pathophysiology

The histological appearance of pulmonary vessels in portopulmonary hypertension is similar to that in other causes of pulmonary arterial hypertension, with endothe-

Table 3. Diagnostic criteria for portopulmonary hypertension

Portal hypertension, with or without liver disease
Mean pulmonary arterial pressure (MPAP) >25 mmHg at rest (30 mmHg during exercise)
Mean pulmonary artery occlusion pressure (MPAOP) <15 mmHg
Pulmonary vascular resistance (PVR)* >240 dyn/sec/cm^5 (or 3 mmHg/litre/min)†

* PVR (dyn/sec/cm^5) = 80 x (MPAP–MPAOP)/cardiac output (in litre/min). † Some previous studies have used a PVR cut-off of 120 dyn/sec/cm^5. From Rodriguez-Roisin et al (2004)

Table 4. Staging of severity of portopulmonary hypertension

Stage	Mean pulmonary arterial pressure at rest (mmHg)
Mild (early)	> 25 to < 35
Moderate	≥ 35 to < 45
Severe	≥ 45

lial proliferation, smooth muscle hypertrophy, intimal fibrosis, in situ thrombosis and plexiform arteriopathy. These changes, in conjunction with pulmonary vasoconstriction, obstruct pulmonary blood flow from the right ventricle to the lungs, with a consequent rise in mean pulmonary arterial pressure, pulmonary vascular resistance and pulmonary arterial hypertension (Budhiraja and Hassoun, 2003).

The underlying mechanisms responsible for the changes in the pulmonary vasculature are unclear. Portal hypertension leads to splanchnic vasodilatation, a hyperdynamic circulation, increased pulmonary blood flow and the generation of shear stress. Impaired hepatic detoxification and increased portopulmonary shunting of blood result in vasoactive substance imbalance (such as reduced prostacyclin and increased endothelin-1 and serotonin) and also increased delivery of bacterial toxins to the lung vasculature. Genetic variations in oestrogen signalling and cell growth regulators seem to be associated with portopulmonary hypertension (Roberts et al, 2009). It is probably a combination of shear stress, vasoconstrictor excess, pro-inflammatory substances, genetic susceptibility and other, as yet unrecognized, factors that result in vascular proliferation and remodelling leading ultimately to the pulmonary vascular changes of portopulmonary hypertension (Budhiraja and Hassoun, 2003).

Investigations

Right heart catheter study

Right heart catheter study is the gold-standard investigation for diagnosis of portopulmonary hypertension (Rodriguez-Roisin et al, 2004). Raised mean pulmonary arterial pressure and pulmonary vascular resistance with a low mean pulmonary artery occlusion pressure in portal hypertension, with or without liver disease, point to the diagnosis (*Table 3*). Staging of severity is also based on this haemodynamic study (*Table 4*). The main drawback is that it is invasive.

Transthoracic Doppler echocardiography

Non-invasive screening of orthotopic liver transplantation candidates for portopulmonary hypertension using transthoracic Doppler echocardiography has been proposed (Krowka et al, 2006). The tricuspid regurgitant jet can be used to calculate right ventricular systolic pressure. An echocardiographic right ventricular systolic pressure >50 mmHg can identify all patients with an mean pulmonary arterial pressure >35 mmHg (moderate–severe portopulmonary hypertension). The Mayo screening algorithm suggests that only these patients be investigated further with a right heart catheter study to help plan further management and prognostication. This second invasive testing is necessary, as 35% of patients with a right ventricular systolic pressure >50 mmHg do not fulfil the haemodynamic criteria of portopulmonary hypertension.

Acute vasodilator testing

Acute vasodilator testing is performed using intravenous prostacyclin or inhaled nitric oxide (Ricci et al, 2007). A positive test results in an acute decrease of mean pulmonary arterial pressure and pulmonary vascular resistance with unchanged or increased cardiac output. This is used to plan treatment in idiopathic pulmonary arterial hypertension. However, in portopulmonary hypertension the aim is to determine severity and therapeutic expectations, as there is no clinical relevance for using calcium-channel blockers, which are contraindicated in portal hypertension.

Serum biomarkers

The most promising serum biomarker is brain natriuretic peptide, which has been investigated extensively in idiopathic pulmonary arterial hypertension, but there are only scanty data for portopulmonary hypertension (Bernal et al, 2009).

Treatment

There are no large randomized controlled trials on the treatment of portopulmonary hypertension. However, untreated patients have a high mortality (Swanson et al, 2008). Medical management, with or without orthotopic liver transplantation, should be considered for all patients with portopulmonary hypertension, although the impact of medical management on those who are candidates for orthotopic liver transplantation is uncertain. At present, there are no guidelines and therapy is directed by clinical experience.

Medical management

Vasodilators, mainly prostaglandins, sildenafil and bosentan, have been used alone or in combination (Austin et al, 2008). They reverse vasoconstriction associated with portopulmonary hypertension, but have uncertain effects on the associated proliferative and fibrotic remodelling.

Epoprostenol, an analogue of endogenous prostacyclin, is a potent vasodilator, which also inhibits platelet aggregation and leads to clinical improvement in portopulmonary hypertension (Krowka et al, 1999). It does not, however, improve long-term survival (Fix et al, 2007). Because of its short half life, it must be infused continuously intravenously. It can also cause problems such as worsening splenomegaly and thrombocytopenia (Findlay et el, 1999). Treprostinil (subcutaneous) and iloprost (inhaled) are other analogues that have also been tried.

Bosentan is an oral endothelin-A and endothelin-B receptor antagonist used in idiopathic pulmonary arterial hypertension which can help in portopulmonary hypertension. However, it can be hepatotoxic, and should be used in advanced liver disease with caution. It has been used as part of combination therapy (Austin et al, 2008).

Sildenafil, a phosphodiesterase inhibitor that is generally well tolerated, has also been reported to be effective. It blocks the degradation of nitric oxide and may potentiate the action of prostacyclin. Uncontrolled studies suggest that monotherapy improves the haemodynamics of portopulmonary hypertension and may facilitate orthotopic liver transplantation in patients who otherwise would not have been candidates (Gough and White, 2009; Hemnes and Robbins, 2009).

Diuretics and digoxin have been tried cautiously. Beta-blockers worsen portopulmonary hypertension, while calcium-channel blockers worsen portal hypertension and are best avoided. Data on isosorbide-5-mononitrate and terlipressin are anecdotal and the role of inhaled nitric oxide is controversial. Transjugular intrahepatic portosystemic shunt is contraindicated, as it can worsen cardiac preload.

Liver transplantation

There are no accepted guidelines regarding pre-transplant medical management (which may be useful, according to some studies (Austin et al, 2008; Swanson et al, 2008; Gough and White, 2009; Hemnes and Robbins, 2009)) or the optimal timing of orthotopic liver transplantation. The 5-year survival of patients with portopulmonary hypertension who underwent orthotopic liver transplantation varies from 25 to 67%. One series reported 36% post-transplant mortality in moderate–severe portopulmonary hypertension patients (Krowka et al, 2004). According to another series, patients with a pre-transplant mean pulmonary arterial pressure of ≥50 mmHg had a 100% post-transplant mortality, those with an mean pulmonary arterial pressure of ≥35 but <50 mmHg and a pulmonary vascular resistance ≥250 dyn/sec/cm^5 had a mortality of >50%, but those with an mean pulmonary arterial pressure of <35 mmHg had no increase in mortality post transplant (Krowka et al, 2000b). Death resulted usually from cardiopulmonary compromise post transplant. Moderate–severe portopulmonary hypertension first detected in the operating room at the time of orthotopic liver transplantation carries a high mortality rate (Krowka et al, 2000b). This emphasizes the importance of pre-transplant screening with Doppler echocardiography and if indicated a right heart catheter study.

KEY POINTS

- Pulmonary vascular changes lead to significant complications in liver disease.
- Hepatopulmonary syndrome is characterized by vasodilatation and hypoxaemia.
- Orthotopic liver transplantation results in complete resolution of hepatopulmonary syndrome.
- Portopulmonary hypertension is characterized by vasoconstriction, increased pulmonary pressure and right heart strain.
- Orthotopic liver transplantation should be undertaken cautiously in portopulmonary hypertension.
- Pre-transplant screening for both is vital.

Conclusions

Hepatopulmonary syndrome and portopulmonary hypertension both result from pulmonary vascular changes in the setting of liver disease. Hepatopulmonary syndrome is characterized by vasodilatation and hypoxaemia and is an indication for orthotopic liver transplantation that results ultimately in complete resolution. Portopulmonary hypertension is characterized by vasoconstriction, increased pulmonary pressures and right heart strain. Orthotopic liver transplantation should be undertaken cautiously in moderate disease and is contraindicated in severe disease. Pre-transplant screening for both is vital. Future research will no doubt lead to a better understanding of both conditions and the development of more effective therapy. **BJHM**

Conflict of interest: none.

Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB (1995) Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology* **109:** 1283–8

Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallon MB (1998) Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. *Gastroenterology* **114:** 305–10

Arguedas MR, Abrams GA, Krowka MJ, Fallon MB (2003) Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* **37:** 192–7

Austin MJ, McDougall NI, Wendon JA et al (2008) Safety and efficacy of combined use of sildenafil, bosentan, and iloprost before and after liver transplantation in severe portopulmonary hypertension. *Liver Transpl* **14:** 287–91

Bernal V, Pascual I, Esquivias P et al (2009) N-terminal brain natriuretic peptide as a diagnostic test in cirrhotic patients with pulmonary arterial hypertension. *Transplant Proc* **41:** 987–8

Berthelot P, Walker JG, Sherlock S, Reid L (1966) Arterial changes in the lungs in cirrhosis of the liver--lung spider nevi. *N Engl J Med* **274:** 291–8

Budhiraja R, Hassoun PM (2003) Portopulmonary hypertension: a tale of two circulations. *Chest* **123:** 562–76

Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S (2002) Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J* **20:** 1314–31

Cremona G, Higenbottam TW, Mayoral V (1995) Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J* **8:** 1883–5

De BK, Sen S, Biswas PK et al (2002) Occurrence of hepatopulmonary syndrome in Budd-Chiari syndrome and the role of venous decompression. *Gastroenterology* **122:** 897–903

Findlay JY, Plevak DJ, Krowka MJ, Sack EM, Porayko MK (1999) Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension. *Liver Transpl Surg* **5:** 362–5

Fix OK, Bass NM, De Marco T, Merriman RB (2007) Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. *Liver Transpl* **13:** 875–85

Flückiger M (1884) Vorkommen von trommelschlägelförmigen Fingerendphalangen ohne chronische Veränderungen an den Lungen oder am Herzen. *Wien Med Wnschr* **34:** 1457

Gomez FP, Martinez-Palli G, Barbera JA, Roca J, Navasa M, Rodriguez-Roisin R (2004) Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. *Hepatology* **40:** 660–6

Gough MS, White RJ (2009) Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial hypertension. *Liver Transpl* **15:** 30–6

Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP (1991) Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* **100:** 520–8

Hemnes AR, Robbins IM (2009) Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. *Liver Transpl* **15:** 15–19
Hoffbauer FW, Rydell R (1956) Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am J Med* **21:** 450–60
Kawut SM, Krowka MJ, Trotter JF et al (2008) Clinical risk factors for portopulmonary hypertension. *Hepatology* **48:** 196–203
Kennedy TC, Knudson RJ (1977) Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. *Chest* **72:** 305–9
Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, Cortese DA (1990) Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates. Screening by two-dimensional contrast-enhanced echocardiography. *Chest* **97:** 1165–70
Krowka MJ, Dickson ER, Cortese DA (1993) Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* **104:** 515–21
Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH (1999) Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): A study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology* **30:** 641–8
Krowka MJ, Wiseman GA, Burnett OL et al (2000a) Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO(2) response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. *Chest* **118:** 615–24
Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA (2000b) Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl* **6:** 443–50
Krowka MJ, Mandell MS, Ramsay MA et al (2004) Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl* **10:** 174–82
Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH (2006) Portopulmonary hypertension: Results from a 10-year screening algorithm. *Hepatology* **44:** 1502–10
Ling Y, Zhang J, Luo B (2004) The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. *Hepatology* **39:** 1593–602
Mantz FA Jr, Craige E (1951) Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. *AMA Arch Pathol* **52:** 91–7
Philit F, Wiesendanger T, Gille D, Boillot O, Cordier JF (1997) Late resolution of hepatopulmonary syndrome after liver transplantation. *Respiration* **64:** 173–5
Poterucha JJ, Krowka MJ, Dickson ER, Cortese DA, Stanson AW, Krom RA (1995) Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy. *Hepatology* **21:** 96–100
Rabiller A, Nunes H, Lebrec D et al (2002) Prevention of gram-negative translocation reduces the severity of hepatopulmonary syndrome. *Am J Respir Crit Care Med* **166:** 514–17
Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB (1997) Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg* **3:** 494–500
Ricci GL, Melgosa MT, Burgos F et al (2007) Assessment of acute pulmonary vascular reactivity in portopulmonary hypertension. *Liver Transpl* **13:** 1506–14
Robalino BD, Moodie DS (1992) Primary pulmonary hypertension, then and now: 28 years of experience. *Cleve Clin J Med* **59:** 411–17
Roberts KE, Fallon MB, Krowka MJ et al (2009) Genetic risk factors for portopulmonary hypertension in patients with advanced liver disease. *Am J Respir Crit Care Med* **179:** 835–42
Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB (2004) Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J* **24:** 861–80
Rodriguez-Roisin R, Krowka MJ (2008) Hepatopulmonary syndrome--a liver-induced lung vascular disorder. *N Engl J Med* **358:** 2378–87
Schenk P, Fuhrmann V, Madl C et al (2002) Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. *Gut* **51:** 853–9
Schiffer E, Majno P, Mentha G et al (2006) Hepatopulmonary syndrome increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. *Am J Transplant* **6:** 1430–7
Selim KM, Akriviadis EA, Zuckerman E, Chen D, Reynolds TB (1998) Transjugular intrahepatic portosystemic shunt: a successful treatment for hepatopulmonary syndrome. *Am J Gastroenterol* **93:** 455–8
Simonneau G, Galie N, Rubin LJ et al (2004) Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* **43:** 5S–12S
Swanson KL, Krowka MJ (2002) Arterial oxygenation associated with portopulmonary hypertension. *Chest* **121:** 1869–75
Swanson KL, Wiesner RH, Krowka MJ (2005) Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology* **41:** 1122–9
Swanson KL, Wiesner RH, Nyberg SL, Rosen CB, Krowka MJ (2008) Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. *Am J Transplant* **8:** 2445–53
Sztrymf B, Rabiller A, Nunes H et al (2004) Prevention of hepatopulmonary syndrome and hyperdynamic state by pentoxifylline in cirrhotic rats. *Eur Respir J* **23:** 752–8
Tanikella R, Philips GM, Faulk DK, Kawut SM, Fallon MB (2008) Pilot study of pentoxifylline in hepatopulmonary syndrome. *Liver Transpl* **14:** 1199–203
Zhang J, Ling Y, Luo B et al (2003) Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. *Gastroenterology* **125**(5): 1441–51
Zhang J, Luo B, Tang L, Wang Y et al (2009) Pulmonary angiogenesis in a rat model of hepatopulmonary syndrome. *Gastroenterology* **136:** 1070–80