

Gut

Leading article

Hepatopulmonary syndromes

The lungs are “downstream” from the liver. The effects of venous blood (flow and constituents) arising in the liver and portal system and which subsequently traverses the pulmonary arterial and capillary system, seem to be quite subtle in the “normal” situation. Dysfunction of either the lungs or liver may dramatically alter this steady state condition and affect the other organ. For example, severe arterial pathology originating within the lungs, as seen in primary pulmonary hypertension, can have a profound “backflow” vascular impact on the normal liver, with resultant hepatic congestion and ascites. Alternatively, liver disorders causing portal hypertension (cirrhotic or non-cirrhotic) may result in a high flow, hyperdynamic circulatory state and an imbalance between vasoconstrictors, vasodilators, and other mediators metabolised or synthesised by the liver. The pulmonary consequences of hepatic dysfunction may have dramatic clinical relevance and have been considered hepatopulmonary syndromes. Such pathophysiologicals of recent interest are the focus of this article (table 1).

Pulmonary consequences

HEPATOPULMONARY SYNDROME

The triad of liver disease, arterial hypoxaemia, and intrapulmonary vascular dilatation has defined an entity commonly referred to as *the* hepatopulmonary syndrome.¹⁻³ In the original description by Rydell and Hoffbauer,⁴ lung necropsy specimens studied using plastic vascular casts contained both precapillary/capillary dilatations and distinct anatomic arteriovenous communications which caused severe hypoxaemia in the setting of chronic liver disease (juvenile cirrhosis). Subsequent investigations using the multiple inert gas elimination techniques (MIGET) and 100% inspired oxygen, have shown that hypoxaemia results from low ventilation to perfusion ratios (ventilation with excess perfusion) in the case of the precapillary/capillary dilatations, and anatomic shunting (perfusion with no ventilation) in the case of direct arteriovenous communications.¹ Therefore, the response to supplemental inspired oxygen, which includes near nor-

malisation of P_{aO_2} while breathing 100% oxygen, is quite variable and depends on the relative contributions of these vascular abnormalities. It is inappropriate to characterise all cases of hepatopulmonary syndrome as “intrapulmonary shunting”. By definition, “shunts” within the lungs (either anatomical or physiological) result in essentially no improvement on administration of 100% inspired oxygen.²

Diagnostic criteria for hepatopulmonary syndrome are summarised in the box.¹⁻³ Pulmonary vascular dilatation can be demonstrated non-invasively by contrast echocardiography or lung perfusion scanning with technetium labelled macroaggregated albumin (^{99m}TcMAA).^{3,5} Transoesophageal imaging is more sensitive, but is less practical than transthoracic views. Lung perfusion scanning permits quantification of the degree of vascular dilatation and may assist in distinguishing vascular from non-vascular reasons for hypoxaemia. In 20–30% of patients with hepatopulmonary syndrome, additional pulmonary problems coexist.⁶ Pulmonary angiography should be reserved for patients with severe hypoxaemia and a poor response to 100% inspired oxygen ($P_{aO_2} < 300$ mm Hg at the Mayo Clinic) in whom vascular embolotherapy to obliterate the arteriovenous communications (and eliminate the anatomic shunting) may be a therapeutic option.

Although medical treatments have been disappointing, there is no question that liver transplantation may result in the complete resolution of this syndrome. Indeed, the existence of this syndrome is an indication for liver transplantation in many centres, especially in the paediatric age group.⁷ Mortality, however, remains high (16–38% within one year) and seems to be greatest in patients with a pretransplant $P_{aO_2} < 50$ mm Hg and ^{99m}TcMAA lung perfusion scans with brain uptake $> 30\%$ (normal $< 5\%$).^{7,8}

The pulmonary vascular changes which occur after successful liver transplantation (cadaveric or living related) suggest a slow remodelling process as opposed to a simple acute reversal of vasodilatation. Syndrome resolution frequently requires up to 15 months post-transplant and discrete macroscopic arteriovenous communications may not improve after transplantation.⁷

The speculation that effluent from hepatic veins (as opposed to simply the existence of portal hypertension) holds the ultimate key to identifying vascular mediators in this syndrome is fuelled by the striking similarity and reversibility of pulmonary vascular consequences which occur in up to 25% of paediatric congenital heart operations for tricuspid atresia.^{9,10} Pulmonary angiography characteristic of the vascular patterns seen in hepatopul-

Abbreviation used in this article: ^{99m}TcMAA, technetium labelled macroaggregated albumin.

Table 1 Pulmonary consequence of advanced liver disease

Condition	Predominant clinicopathological findings
Hepatopulmonary syndrome	Pulmonary vascular dilatations causing varying degrees of hypoxaemia
Portopulmonary hypertension	Pulmonary vasoconstriction/obliteration with eventual right heart failure
α_1 -antitrypsin deficiency	Panacinar emphysema resulting in expiratory airflow obstruction
Hepatic hydrothorax	Transudative pleural effusions with subsequent lung atelectasis

Specific diagnostic criteria for hepatopulmonary syndrome and portopulmonary hypertension

HEPATOPULMONARY SYNDROME

- Chronic liver disease*
- $\text{Pao}_2 < 70$ mm Hg or alveolar–arterial oxygen gradient > 20 mm Hg†
- Intrapulmonary vascular dilatations

PORTOPULMONARY HYPERTENSION

- Portal hypertension
- Mean pulmonary artery pressure (MPAP) > 25 mm Hg
- Capillary wedge pressure (PCWP) < 15 mm Hg
- Pulmonary vascular resistance (PVR) > 120 dynes.s.cm⁻⁵‡

*Portal hypertension (cirrhotic or non-cirrhotic) has been reported in most cases.

†Some investigators use an alveolar–arterial oxygen gradient > 15 mm Hg.¹

‡PVR = (MPAP–PCWP)/CO. This criterion helps to discern increased pulmonary artery pressures from high flow/hyperdynamic circulatory states (low PVR) caused by vasoconstriction (high PVR).²

monary syndrome are indistinguishable from images obtained months after the creation of cavopulmonary surgical connections to improve pulmonary blood flow.¹⁰ Pathological specimens of such lesions have increased numbers of vessels abutting alveoli, as well as thin walled structures with patchy endothelium. The possibility of angiogenesis associated with vascular dilatation is suggested by these findings.^{10, 11} Remarkably, the surgical inclusion of hepatic vein flow into the vascular circuit, thereby allowing hepatic vein effluent to feed directly into the pulmonary arterial bed, has resulted in complete resolution of hypoxaemia and pulmonary angiographic abnormalities.^{9, 10} To date, the specific vascular mediators in hepatopulmonary syndrome (or paediatric cases of congenital heart disease) have not been identified. A common bile duct ligation rat model for hepatopulmonary syndrome has been developed and increased pulmonary endothelial nitric oxide synthase activities seem to correlate with vascular dilatation and oxygen abnormalities.¹²

PORTOPULMONARY HYPERTENSION

It is now recognised that increased pulmonary arterial pressures (defined as mean pulmonary artery pressure > 25 mm Hg via right heart catheterisation) may occur in up to 20% of patients with advanced liver disease and portal hypertension.¹³ The aetiology is related to a complex association among the hyperdynamic, high flow circulatory state, excess central volume, and non-embolic pulmonary vasoconstriction/obliteration.² The term portopulmonary hypertension should be reserved for the latter process, which is rare ($< 4\%$).¹³ Pathological findings range from medial and intimal hypertrophy (reversible?) to endothelial proliferation with plexogenic/thrombotic/fibrotic change (irreversible?) and are indistinguishable from histopathology documented in patients with primary pulmonary hypertension.¹⁴ In situ development of organised clot and platelet aggregates may be seen and probably result from impaired flow.

Diagnostic criteria are derived from the National Institutes of Health criteria for the diagnosis of primary pulmonary hypertension and are based on right heart catheterisation measurements (box).^{15, 16} Although pathologically similar to primary pulmonary hypertension, portopulmonary hypertension, unlike the former, is associated with greatly increased cardiac output.¹⁷

Screening for portopulmonary hypertension is conducted by chest radiography, electrocardiography and, most importantly, transthoracic Doppler echocardiography to estimate pulmonary artery systolic pressure. (Note that the definition of pulmonary hypertension is based on mean pulmonary artery pressure.) By measuring the abnormal regurgitant tricuspid systolic peak velocity and using a modified Bernoulli equation, a pressure gradient between the right ventricle and right atrium can be calculated and summed with an estimate of right atrial pressure to provide a right ventricular systolic pressure (RVsys).¹ This closely approximates the pulmonary artery systolic pressure (PA_{sys}) in most cases. RVsys > 50 mm Hg (normal < 30 mm Hg) strongly suggests the existence of portopulmonary hypertension and such patients require further study by right heart catheterisation in order to characterise their haemodynamic profile accurately. Roughly 85% of such patients will have increased pulmonary vascular resistance; 15% will have increased pulmonary pressures simply owing to the high flow state with normal or low pulmonary vascular resistance (unpublished Mayo Clinic data).

As opposed to limited medical treatment options in hepatopulmonary syndrome, the use of intravenous epoprostenol, a prostaglandin (PGI₂) analogue with potent pulmonary arterial vasodilatation effects and antiplatelet aggregating activity, is encouraging.^{18–20} Clinically important acute and long term reductions in mean pulmonary artery pressure and pulmonary vascular resistance (with a subsequent increase in cardiac output) have been reported with epoprostenol use.²⁰ However, potential worsening of thrombocytopenia and progressive splenomegaly may occur in some patients; the reasons for such events require careful additional study.²¹

Regarding liver transplantation in patients with portopulmonary hypertension, the lessons and expectations from studies of patients with hepatopulmonary syndrome have not been similar. Intraoperative death, postoperative death, unchanged or worsening pulmonary hypertension after transplantation with progressive right heart failure, and de novo development of severe pulmonary hypertension post-transplant have been reported.^{2, 22} Retrospective data derived from 44 patients reported in 19 studies indicate that mean pulmonary artery pressure > 35 mm Hg with a pulmonary vascular resistance > 250 dynes.s.cm⁻⁵ is associated with a post-transplant mortality greater than 40% (Krowka MJ, unpublished data). The characterisation of a pulmonary haemodynamic profile with specified treatment which will result in successful liver transplantation and favourable outcome of portopulmonary hypertension is still a clinical challenge.

A recent immunopathological investigation has demonstrated the relative deficiency of prostacyclin synthase in pulmonary vascular specimens obtained from patients with severe pulmonary hypertension and portal hypertension.²³ Pulmonary endothelium nitric oxide synthase deficiency was not shown. Intuitively, the universal existence of portal hypertension in such patients suggests that a key liver metabolic function(s) is lacking which at least initiates the spectrum of pulmonary vascular pathology in the setting of a high flow state.

α_1 -ANTITRYPSIN DEFICIENCY

Lung dysfunction (panacinar emphysema, bronchiectasis, airway inflammation) resulting from severe α_1 -antitrypsin deficiency (< 800 mg/l; normal 1200–2200) in essence represents the pulmonary vascular consequence of a liver disorder.^{24, 25} Abnormal α_1 protein synthesis evolves from a single point gene mutation located on chromosome 14 (over 75 abnormal alleles exist), which is co-dominantly expressed in the hepatocyte. Owing to subsequent

abnormal α_1 protein folding, accumulation within hepatocytes occurs, resulting in impaired venous release. Therefore, the circulating concentrations of the α_1 protein, which acts as a proteinase inhibitor, entering the pulmonary and bronchial circulations are low and a measurable deficiency exists.²⁴ Lung dysfunction is strongly correlated with the severity of the deficiency which, in turn, is related to certain allele combinations. The most common and significant pulmonary manifestations are associated with the Z or S alleles, especially in the ZZ or SZ phenotypes.²⁵

The most dramatic pulmonary presentation is evolution of bullous emphysema with severe expiratory airflow obstruction predominantly affecting the lung bases (greatest blood flow) caused by the imbalance between the protective α_1 protein (90% of which is synthesised in the liver) and neutrophil elastase derived from leucocytes. Such an imbalance allows chronic destruction of the supporting elastic tissue which tethers open the small airways. Smoking significantly accelerates the pulmonary insult.²⁵ Combined hepatic and pulmonary manifestations of severe α_1 deficiency in the same patient are rare, but do occur. With prolonged survival of patients with severe α_1 deficiency, the potential development of hepatocellular carcinoma should be considered.²⁴

In selected patients with progressive deterioration of lung function, augmentation therapy with weekly intravenous α_1 protein (Prolastin) from pooled donors at a dose of 60 mg/kg, may slow the rate of decline in lung function as measured by forced expiratory volume in one second-FEV₁.^{25, 26} Augmentation therapy has no role in the treatment of hepatocyte abnormalities or cirrhosis associated with α_1 deficiency. In theory liver transplantation with normalisation of α_1 serum concentrations should halt the progression in lung dysfunction resulting from this deficiency.

HEPATIC HYDROTHORAX

In addition to the previous pulmonary insults which arise via the venous vascular pathway from the liver through the lungs, compression of the lungs may occur as a result of the accumulation of fluid within the thorax or more precisely the pleural space.²⁷ Such unilateral or bilateral pleural effusions develop in less than 10% of patients and directly result from the physiology which causes ascites, hence the term hepatic hydrothorax. Such pleural effusions are transudates (low protein, low lactate dehydrogenase relative to serum) and rarely evolve in the absence of clinical ascites. Most cases are associated with effusions occupying less than 50% of the pleural space, but complete opacification of a hemithorax with impaired filling of the right side of the heart can occur.²⁷

Negative pleural space pressure generated with inspiration and positive peritoneal space pressure facilitates the peritoneal to pleural space flow of fluid via small diaphragmatic defects. Clinically significant dyspnea and hypoxaemia may result, the latter developing if the underlying lung becomes atelectatic and physiological shunting occurs (perfusion without ventilation).²⁸ The pleural space may become infected and require chest tube drainage in the setting of subacute bacterial peritonitis; prognosis in such patients is poor.²⁷ Pleural fluid should be sampled and analysed in the setting of hepatocellular carcinoma, pain, or fever.

Medical treatment of hepatic hydrothorax focuses on aggressive diuretic therapy to reduce the volume of ascites. Transjugular intrahepatic portosystemic shunting may greatly reduce the need for repeat thoracenteses in symptomatic patients with refractory ascites.^{29, 30} Successful obliteration of the pleural space via chest tube

pleurodesis or thoracoscopic repair of diaphragmatic defects has been reported in highly selected patients; increasing ascites following such procedures should be expected.²⁷ Refractory hepatic hydrothorax caused by uncontrollable ascites is considered an indication for liver transplantation.

Questions and future directions

Current questions of hepatopulmonary interest derived from clinical experiences include the following:

- What hepatic mediators are necessary to maintain a normal pulmonary vascular physiology?
- If portopulmonary hypertension exists, what haemodynamic and clinical criteria are associated with successful transplant? Under what conditions can that syndrome be reversed?
- Will liver transplantation or hepatic gene therapy prevent the progression of emphysema resulting from severe α_1 -antitrypsin deficiency?

The problems described earlier, the evolution of new liver diseases and their treatments, and findings following liver transplantation will continue to result in challenging clinical liver–lung relations. Much will be gained for patients and investigators if we integrate the genetic, physiological, and immunological expertise of both hepatologists and pulmonologists.

M J KROWKA

Divisions of Pulmonary and Critical Care Medicine, and Gastroenterology and Hepatology, Mayo Clinic and Mayo Foundation, 200 First Street SW, Mayo Clinic E18, Rochester, MN 55905, USA
email: krowka@mayo.edu

- 1 Herve P, Lebrec D, Brenot F, *et al.* Pulmonary vascular disorders in portal hypertension. *Eur Respir J* 1998;11:1153–66.
- 2 Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension: distinctions and dilemmas. *Hepatology* 1997;25:1282–4.
- 3 Abrams GA, Nanda NC, Dubovsky EV, *et al.* Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. *Gastroenterology* 1998;114:305–10.
- 4 Rydell R, Hoffbauer FW. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am J Med* 1956;21:450–9.
- 5 Whyte MKB, Hughes JMB, Peters AM, *et al.* Analysis of right to left shunt in hepatopulmonary syndrome. *J Hepatol* 1998;29:85–93.
- 6 Martinez G, Barbera JA, Navasa M, *et al.* Hepatopulmonary syndrome associated with cardiorespiratory disease. *J Hepatol* 1999;30:882–9.
- 7 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;72:44–52.
- 8 Egawa H, Kasahara M, Inomata Y, *et al.* Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. *Transplantation* 1999;67:712–17.
- 9 Srivasta D, Preminger T, Lock JE, *et al.* Hepatic venous return and the development of pulmonary arteriovenous malformations in congenital heart disease. *Circulation* 1995;92:1217–22.
- 10 Duncan BS, Kneebone JM, Chi EY, *et al.* A detailed histologic analysis of pulmonary arteriovenous malformations in children with cyanotic congenital heart disease. *J Thorac Cardiovasc Surg* 1999;117:931–8.
- 11 Clement B, Musso O, Lietard J, *et al.* Homeostatic control of angiogenesis: a newly identified function of the liver? *Hepatology* 1999;29:621–3.
- 12 Fallon MB, Abrams GA, Luo B, *et al.* The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. *Gastroenterology* 1997;113:606–14.
- 13 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.
- 14 Edwards BS, Weir EK, Edwards WD, *et al.* Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol* 1987;10:1233–8.
- 15 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;17:492–8.
- 16 Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987;107:216–23.
- 17 Kuo PC, Plotkin JS, Johnson LB, *et al.* Distinctive features of portopulmonary hypertension. *Chest* 1997;112:980–6.
- 18 Kuo PC, Johnson LB, Plotkin JS, *et al.* Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation* 1997;63:604–6.
- 19 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;65:457–9.
- 20 Krowka MJ, Frantz RF, McGoon MD, *et al.* Improvement in pulmonary hemodynamics with intravenous epoprostenol: a study of 15 patients with portopulmonary hypertension. *Hepatology* 1999;25:641–8.

- 21 Findlay JY, Plevak DJ, Krowka MJ, *et al.* Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension. *Liver Transplant Surg* 1999;5:362-5.
- 22 Ramsay MAE, Simpson BR, Nguyen AT, *et al.* Severe pulmonary hypertension in liver transplant candidates. *Liver Transplant Surg* 1997;3:494-9.
- 23 Tudor RM, Cool CD, Geraci MW, *et al.* Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;159:1925-32.
- 24 Mahadeva R, Lomas DA. Alpha₁-antitrypsin deficiency, cirrhosis and emphysema. *Thorax* 1998;53:501-5.
- 25 Alpha₁-Antitrypsin Deficiency Registry Study Group. Survival and FEV₁ decline in individuals with severe deficiency of alpha₁-antitrypsin. *Am J Respir Crit Care Med* 1998;158:49-59.
- 26 Wencker M, Banik N, Buhl R, *et al.* Long-term treatment of alpha₁-antitrypsin deficiency related pulmonary emphysema with human alpha₁-antitrypsin. *Eur Respir J* 1998;11:428-33.
- 27 Lazardis PP, Kamath PR, Krowka MJ. Hepatic hydrothorax. *Am J Med* 1999;107:262-7.
- 28 Agusti AGN, Cardus J, Roca J, *et al.* Ventilation perfusion mismatch in patients with pleural effusion. *Am J Respir Crit Care Med* 1997;156:1205-9.
- 29 Jeffries MA, Kazanjian S, Wilson M, *et al.* Transjugular intrahepatic portosystemic shunts and liver transplantation in patients with refractory hepatic hydrothorax. *Liver Transplant Surg* 1998;4:416-23.
- 30 Gordon FD, Anastopoulos HT, Crenshaw W, *et al.* The successful treatment of symptomatic, refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt. *Hepatology* 1997;25:1366-9.