Hepatopulmonary Syndrome and Portopulmonary Hypertension

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Opinion statement

- In patients with hepatopulmonary syndrome, supplemental oxygen and liver transplantation are the usual treatments of choice. Pharmacologic approaches have limited success in improving hypoxemia. Interventional radiology procedures may improve arterial hypoxemia in highly selected patients.
- In patients with portopulmonary hypertension, continuous infusion with intravenous epoprostenol (prostaglandin I₂) can significantly improve pulmonary hemodynamics. Outcome following liver transplantation is variable; increased cardiopulmonary mortality occurs in patients with moderate to severe pulmonary hypertension.

Introduction

The major pulmonary vascular consequences of chronic liver disease are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH). These are distinct clinical entities that occur in the setting of cirrhotic or noncirrhotic portal hypertension [1•]. HPS is characterized by arterial hypoxemia due to intrapulmonary vascular dilatation. PPH is defined as pulmonary arterial hypertension resulting from a spectrum of vascular occlusive and obliterative lesions. Specific diagnostic criteria for these syndromes have been proposed [2]. The pathophysiology causing hypoxemia (HPS) and pulmonary hypertension (PPH) is understood fairly well, but the specific mediators related to chronic liver dysfunction in humans have not been identified. Although these entities have been recognized for many years, their clinical importance has been magnified by the potential implications and expectations when these syndromes exist

in patients considered for orthotopic liver transplantation (OLT).

DIAGNOSIS

It is essential that screening and diagnostic studies be conducted for appropriate treatment and prognostic purposes. For example, not all patients with significant arterial hypoxemia have HPS; patients with concomitant chronic obstructive pulmonary disease may be hypoxemic, and no change in the partial arterial oxygen pressure (PaO₂) would be expected following successful OLT [3]. In addition, not all patients with significant pulmonary hypertension require pulmonary vasodilator therapy. Most patients with chronic liver disease have hyperdynamic circulatory states, which can result in increased pulmonary artery pressures and low calculated pulmonary vascular resistance [4]. Generally accepted diagnostic criteria are summarized in Table 1.

Table 1. Diagnostic criteria for hepatopulmonary syndrome and portopulmonary hypertension

Hepatopulmonary syndrome
Chronic liver disease*
PaO ₂ < 70 mm Hg or alveolar-arterial oxygen gradient > 20 mm Hg [†]
Intrapulmonary vascular dilatations [‡]
Portopulmonary hypertension
Portal hypertension
MPAP > 25 mm Hg
PCWP < 15 mm Hg
PVR > 120 dynes · s · cm ⁻⁵ §

*Intrapulmonary vascular dilatations have been demonstrated in the setting of acute liver failure.

[†]Measured on room air. Some investigators use an alveolar-arterial gradient of more than 15 mm Hg instead of 20 mm Hg.

[‡]Detected by contrast echocardiography, lung perfusion scanning, or pulmonary angiography.

§PVR = (MPAP–PCWP) × 80/CO. This criterion helps distinguish between increased pulmonary artery pressures associated with high-flow and hyperdynamic circulatory states (normal or decreased PVR) and vasoconstriction/vascular obliteration (increased PVR).

CO—cardiac output (L/min); MPAP—mean pulmonary artery pressure; PCWP—pulmonary capillary wedge pressure; PVR—pulmonary vascular resistance.

Treatment of hepatopulmonary syndrome

Pharmacologic treatment

- Spontaneous improvement in PaO₂ has been documented [5]. Case reports of PaO₂ improvement with the use of long-term, high-dose aspirin [6], oral almitrine bismesylate [7], indomethacin [8], and oral *Allium sativum* (garlic) [9•] have been published. Recently, improvement in oxygenation following acute administration of intravenous methylene blue in seven patients was reported [10]. The goal of these drug therapies is to improve ventilation-perfusion relationships (perhaps by inducing vasoconstriction), which could subsequently increase PaO₂.
- Supplemental oxygen consistently has provided improvement in PaO₂ and should not be underestimated as a treatment option at rest, exercise, and sleep in patients with HPS.

Supplemental oxygen

Standard procedure	Nasal cannula oxygen with a flow rate up to 5 L/min. Systems may be portable (liquid oxygen or small tanks) or stationary (tanks or concentrators). Patients with severe hypoxemia may require facemask high-flow oxygen (up to 40% inspired oxygen).
Contraindications	Smoking or open fires in the home.
Complications	Dryness of the nasal passages. Nonsmoking environment.
Special points	Hypoxemia and dyspnea may worsen in the standing position and with exercise or sleep. Increased supplemental oxygen may be needed in these situations.
Cost/cost-effectiveness	The majority of patients with HPS require oxygen 24 hours a day, and PaO ₂ is improved with low-flow oxygen (1 to 3 L/min). Insurance pays for most oxygen needs if PaO ₂ is less than 55 mm Hg or hemoglobin saturation is less than 88%. Cost is approximately \$300 to \$500 per month.

Interventional radiology procedures

- Interventional radiology is a limited but significant treatment option for treatment in highly selected patients. Coil embolotherapy [11•], transjugular intrahepatic portosystemic shunting (TIPS) [12–16], and balloon cavoplasty [17••] may have significant roles in patients with severe hypox-

emia. The role of TIPS to improve hypoxemia is controversial [16]. This procedure may temporarily enhance cardiac output (enhanced preload) and increase pulmonary artery pressures [18].

Coil embolotherapy

	The goal of coil embolotherapy is to occlude distinct arteriovenous communications that cause hypoxemia due to right-to-left intrapulmonary shunting.
Standard procedure	If discrete arteriovenous communications can be identified on pulmonary angiography, occlusion of the feeding pulmonary artery by metal Gianturco coils (Cook Group, Inc., Bloomington, IN) can obliterate the right-to-left anatomic shunt and redirect blood flow to normally perfused lung segments.
Contraindications	Bleeding diathesis (relative).
Complications	Pulmonary infarction, hemoptysis, chest pain.
Special points	The vast majority of patients with HPS do not have discrete lesions amenable to this procedure. Patients with a PaO ₂ less than 150 mm Hg while breathing 100% oxygen should be considered for pulmonary angiography and this procedure if arteriovenous communications are demonstrated.
Cost/cost-effectiveness	This procedure is approved by the US Food and Drug Administration (USFDA) and is covered by insurance. Dramatic improvements in PaO ₂ have been documented.

Transjugular intrahepatic portosystemic shunt

	The TIPS has been developed to reduce the degree of portal hypertension via nonsurgical placement of a shunt between the hepatic vein and portal vein. Assuming HPS is related to portal hypertension, this method has been proposed as a approach to improve hypoxemia.
Standard procedure	Creation of an artificial fistula with a vascular stent placed between branches of the hepatic veins and portal vein to reduce the degree of portal hypertension.
Contraindications	Severe pulmonary hypertension.
Complications	Worsening hyperdynamic circulation, (acutely) increased pulmonary artery pressures, high output cardiac failure.
Special points	Disagreement exists as to the effectiveness of this procedure to improve PaO ₂ . Cardiac output can increase immediately after TIPS and remain higher than baseline for up to 2 months postprocedure.
Cost/cost-effectiveness	This procedure is not USFDA-approved for the sole purpose of treating HPS. Its effectiveness in patients with this syndrome requires further study.

Balloon cavoplasty

	Cavoplasty is another method used to reduce the degree of portal hypertension in the specific situation in which an obstruction in the terminal portion of the inferior vena cava (superior to the hepatic veins) causes impaired venous return. Such obstruction causes hepatic vein dilatation with increased wedged and free hepatic vein pressures, hepatomegaly, and portal hypertension.
Standard procedure	Inferior vena cava catheterization via the right femoral vein in patients with portal hypertension and inferior vena cava obstruction. Membranous obstruction of the inferior vena cava is dilated using a mitral valvuloplasty balloon (22 mm) in an attempt to increase venous flow to the right atrium.
Contraindications	Bleeding diathesis (relative).
Complications	None reported.
Special points	Consider in very unusual causes of Budd-Chiari syndrome in which the inferior vena cava is obstructed in association with portal hypertension. Improvement in PaO ₂ implies a role of portal hypertension in the pathogenesis of HPS.
Cost/cost-effectiveness	No data available.

Surgery

Orthotopic liver transplantation

Initially considered a contraindication to OLT, HPS is now considered by most centers to be an indication for OLT, especially in the pediatric age group. Complete resolution of the syndrome after OLT has been well documented in children and adults [19•,20]. Increased mortality following OLT has been associated with severe hypoxemia [19•]. Surgical ligation of a portosystemic shunt has improved symptoms of severe hypoxemia following liver transplantation and precluded the need for retransplantation [21].

Standard procedure Total hepatectomy with implantation of cadaveric or living, related graft.

Contraindications Advanced age, coronary artery disease, other major organ system failure, malignancy within 2 years.

Complications Respiratory failure due to worsening hypoxemia, ventilator dependence with tracheostomy, immunosuppression-related complications, and liver disease recurrence.

Special points Hepatopulmonary syndrome resolves in 62% to 82% of patients with successful OLT. Resolution of hypoxemia may take up to 15 months [19•,20]. The 90-day posttransplant mortality is 30% if the preoperative PaO₂ is less than 50 mm Hg [19•].

Cost/cost-effectiveness Hepatopulmonary syndrome is an established indication for OLT in children. It is an expensive procedure, with life-long immunosuppression required.

Emerging therapies

- Inhaled nitric oxide after liver transplant for HPS [22,23]. In addition to severe hypoxemia that is associated with HPS, immediate post-OLT management and pulmonary complications experienced in the intensive-care unit may result in worsening ventilation perfusion relationships. The use of inhaled nitric oxide paradoxically can improve the arterial oxygenation in some patients with fluid overload, atelectasis, and pneumonitis.

Treatment of portopulmonary hypertension

Pharmacologic treatment

Epoprostenol sodium

The most significant breakthrough in treating primary pulmonary hypertension has been due to epoprostenol, a synthetic prostacyclin (prostaglandin I₂). Prostacyclin is a naturally occurring potent pulmonary and systemic vasodilator synthesized in the pulmonary endothelium. In patients with primary pulmonary hypertension and portopulmonary hypertension, intravenous administration of epoprostenol has been shown to improve pulmonary hemodynamics acutely and long term [24•]. It may serve as a bridge to liver transplantation in selected patients [24•,25••,26]. Worsening splenomegaly and thrombocytopenia during treatment with epoprostenol in the setting of advance liver disease has been reported [27].

Standard dosage Epoprostenol is marketed under the name Flolan (GlaxoSmithKline, Research Triangle Park, NC). Flolan must be reconstituted using a sterile diluent. It is administered via a central line (Hickman catheter) and is infused 24 hours per day via a CADD pump (SIMS Deltec, Inc., St. Paul, Minnesota). The dosage begins at approximately 2 ng/kg/min and is titrated by symptoms, with dosages increased every 2 to 4 weeks in increments of approximately 1 to 2 ng/kg/min. Abrupt withdrawal should be avoided.

Contraindications Inability to handle the catheter maintenance, left ventricular dysfunction, pulmonary veno-occlusive disease.

Main drug interactions Should not be mixed with any other parenteral medications. Additional reduction in systemic blood pressure with other vasodilators.

Main side effects	Flushing, headache, nausea, vomiting, hypotension, myalgia, chest pain, dizziness, jaw pain, diarrhea. Catheter infection. Can worsen thrombocytopenia by unknown mechanisms.
Special points	There are two major pharmacologic actions: 1) direct pulmonary and systemic vasodilator, and 2) inhibition of platelet aggregation.
Cost/cost-effectiveness	Extremely expensive: \$100,000 per year. Significant improvement in the acute and long-term pulmonary hemodynamics has been documented in patients with primary pulmonary hypertension; many patients improve but do not have normalized pulmonary hemodynamics.

Surgery

Orthotopic liver transplantation

	Unlike liver transplantation for HPS, PPH is a relative contraindication to liver transplantation due to the significant cardiopulmonary mortality associated with OLT when pulmonary hypertension exists [28••]. The outcome in patients with PPH following OLT is quite variable, ranging from intraoperative death due to right-sided heart failure to resolution of pulmonary hypertension [29,30•,31–33]. To date, no transplant center has performed OLT for the sole purpose of treating PPH.
Standard procedure	Total hepatectomy and implantation of donor graft.
Contraindications	The severity of PPH is a relative contraindication to OLT. A mean pulmonary artery pressure less than 35 mm Hg has not been associated with cardiopulmonary-associated mortality after OLT. A cardiopulmonary-associated mortality of approximately 50% has been reported in untreated patients with mean pulmonary artery pressures of more than 35 mm Hg and pulmonary vascular resistances more than 250 dynes · s · cm ⁻⁵ [28••].
Complications	Right-sided heart failure intraoperatively or posttransplant is the greatest concern. Progressive thrombocytopenia after OLT may be associated with worsening pulmonary hypertension.
Special points	Preliminary data suggest that pretransplant administration of epoprostenol sodium may facilitate a safe liver transplant if the pulmonary hemodynamics can be improved and right-sided heart function is preserved prior to OLT. No studies have addressed the duration of epoprostenol use after OLT other than the belief that this medication should be weaned when possible. Some patients experience progression of pulmonary hypertension after successful OLT.
Cost/cost-effectiveness	An expensive procedure, as well as the expense of intravenous epoprostenol before and after transplant.

Emerging therapies

- There are a number of investigational pulmonary vasodilators with potential use in patients with PPH [34]. These medications include UT-15 (a subcutaneous analogue of prostacyclin), beraprost (an oral analogue of prostacyclin), bosentan (a nonspecific endothelin receptor antagonist), oral mononitrates [35], and inhaled nitric oxide [36–39]. UT-15 (United Therapeutics, Research Triangle Park, NC) is currently available under an open-label protocol for patients with PPH. Specific endothelin A receptor antagonists may be studied in the future.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Krowka MJ: **Hepatopulmonary syndrome versus portopulmonary hypertension: distinctions and dilemmas.** *Hepatology* 1997, 25:1282–1284.

A practical primer that clarifies the differences in diagnostic criteria, screening, and outcomes between these pulmonary vascular syndromes.

2. Krowka MJ: **Hepatopulmonary syndromes.** *Gut* 2000, 46:1–4.
3. Martinez G, Barabera JA, Navasa M, *et al.*: **Hepatopulmonary syndrome associated with cardiorespiratory disease.** *J Hepatol* 1999, 30:882–889.
4. 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, 71:543–551.
5. Saunders KB, Frenando SSD, Dalton HR, *et al.*: **Spontaneous improvement in a patient with hepatopulmonary syndrome assessed by serial exercise tests.** *Thorax* 1994, 49:725–727.
6. Song JY, Choi JY, Ko JT, *et al.*: **Long-term aspirin therapy for hepatopulmonary syndrome.** *Pediatrics* 1996, 97:917–920.
7. Krowka MJ, Cortese DA: **Severe hypoxemia associated with liver disease: Mayo Clinic experience and experimental use of almitrine bismesylate.** *Mayo Clin Proc* 1987, 62:164–173.
8. Shijo H, Sasaki H, Yuh K, *et al.*: **Effects of indomethacin on hepatogenic pulmonary angiodysplasia.** *Chest* 1991, 99:1027–1029.
9. Abrams GA, Fallon MB: **Treatment of hepatopulmonary syndrome with allium sativum (garlic).** *J Clin Gastroenterol* 1998, 27:232–235.

This group is conducting animal studies that may provide the first solid foundation for the future investigational treatments that improve hypoxemia due to HPS.

10. Schenk P, Madl C, Rezaie-Majd S, *et al.*: **Methylene blue improves hepatopulmonary syndrome.** *Ann Int Med* 2000, 133:701–706.
11. Poterucha JJ, Krowka MJ, Dickson ER, *et al.*: **Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy.** *Hepatology* 1995, 21:96–100.

This article demonstrates how embolotherapy dramatically can improve hypoxemia in patients with discrete arteriovenous communications.

12. Riegler JL, Lang KA, Johnson SP, *et al.*: **Transjugular intrahepatic portosystemic shunt improves oxygenation in hepatopulmonary syndrome.** *Gastroenterology* 1995, 109:978–983.
13. Allgaier HP, Haag K, Ochs A, *et al.*: **Hepatopulmonary syndrome: successful treatment by transjugular intrahepatic portosystemic stent-shunt (TIPS) [letter].** *J Hepatol* 1995, 23:102.

14. Selim KM, Akriviadis E, Zuckerman E, *et al.*: **Transjugular intrahepatic portosystemic shunt: a successful treatment for hepatopulmonary syndrome.** *Am J Gastroenterol* 1998, 93:455–458.

15. 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, 7:147–149.
16. Corley DA, Scharschmidt B, Bass N, *et al.*: **Lack of efficacy of TIPS for hepatopulmonary syndrome [letter].** *Gastroenterology* 1997, 113:728–731.

17. De BK, Sen S, Biswas PK, *et al.*: **Hepatopulmonary syndrome in inferior vena cava obstruction responding to cavoplasty.** *Gastroenterology* 2000, 118:192–196.

A report on special cases of HPS due to portal hypertension associated with inferior vena cava obstruction. Treatment with balloon dilatation cavoplasty obviated liver transplantation.

18. Colobato LA, Spahr L, Martinet JP, *et al.*: **Haemodynamic adaptation two months after transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients.** *Gut* 1999, 39:600–604.

19. 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.

The largest published series of patients with HPS ($n = 81$) who underwent liver transplantation.

20. 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, 67:712–717.
21. Spencer LT, Langham MR, Hoyer MH, *et al.*: **Resolution of hypoxemia in a liver transplant recipient after ligation of a portosystemic shunt.** *J Pediatr* 2000, 137:575–577.
22. Alexander J, Greenough A, Baker A, *et al.*: **Nitric oxide treatment of severe hypoxemia after liver transplantation in hepatopulmonary syndrome.** *Liver Transpl Surg* 1997, 3:54–55.
23. Durand PH, Baujard C, Grosse AL, *et al.*: **Reversal of hypoxemia by inhaled nitric oxide in children with severe hepatopulmonary syndrome, type I, during and after liver transplantation.** *Transplantation* 1998, 65:437–439.

24. Krowka MJ, Frantz RF, McGoon MD, *et al.*: **Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension.** *Hepatology* 1999, 30:641–648.

The largest single-institution series, demonstrating acute and long-term improvement in pulmonary hemodynamics with outpatient, continuous 24-hour infusion of epoprostenol in the setting of advance liver disease complicated by pulmonary hypertension.

- 25.●●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, 65:457–459.
The first published case that describes the successful use of epoprostenol to facilitate liver transplantation in the setting of moderate pulmonary hypertension.
26. Kahler CM, Grazidei I, Wiedermann CJ, *et al.*: **Successful use of continuous prostacyclin in a patient with severe portopulmonary hypertension.** *Wien Klin Wochenschr* 2000, 112:637–640.
27. Findlay JY, Plevak DJ, Krowka MJ, *et al.*: **Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension.** *Liver Transpl Surg* 1999, 5:362–365.
- 28.●●Krowka MJ, Plevak DJ, Findlay JY, *et al.*: **Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation.** *Liver Transpl* 2000, 6:443–450.
Specific pulmonary hemodynamic criteria are proposed for patients with PPH considered for OLT.
29. DeWolf AM, Scott VL, Gasior T, *et al.*: **Pulmonary hypertension and liver transplantation [letter].** *Anesthesiology* 1993, 78:213.
- 30.● Ramsay MAE, Simpson BR, Nguyen AT, *et al.*: **Severe pulmonary hypertension in liver transplant candidates.** *Liver Transpl Surg* 1997, 3:494–500.
Single-institution series describing the spectrum of outcome in PPH when OLT is undertaken.
31. Levy MT, Torzillo P, Bookallil M, *et al.*: **Case report: delayed resolution of severe pulmonary hypertension after isolated liver transplantation in a patient with cirrhosis.** *J Gastroenterol Hepatol* 1996, 11:734–737.
32. Scott V, DeWolf A, Kang Y, *et al.*: **Reversibility of pulmonary hypertension after liver transplantation: a case report.** *Transpl Proc* 1993, 2:1789–1790.
33. Mandell MS, Duke J: **Nitric oxide reduces pulmonary hypertension during hepatic transplantation.** *Anesthesiology* 1994, 81:1538–1542.
34. Krowka MJ: **Pulmonary hypertension: diagnostics and therapeutics.** *Mayo Clin Proc* 2000, 75:625–630.
35. Ribas J, Angrill J, Barbera JA, *et al.*: **Isosorbide-5 mononitrate in the treatment of pulmonary hypertension associated with portal hypertension.** *Eur Respir J* 1999, 13:210–212.
36. Findlay JY, Harrison BA, Plevak DJ, *et al.*: **Inhaled nitric oxide reduces pulmonary artery pressures in portopulmonary hypertension.** *Liver Transpl Surg* 1999, 5:381–388.
37. Ramsay MAE, Spikes C, East CA, *et al.*: **The perioperative management of portopulmonary hypertension with nitric oxide and epoprostenol.** *Anesthesiology* 1999, 90:299–301.
38. Tarquino M, Geggel RL, Strauss RS, *et al.*: **Treatment of pulmonary hypertension with inhaled nitric oxide during hepatic transplantation in an adolescent: reversibility of pulmonary hypertension after transplantation.** *Clin Pediatr* 1998, 37:505–510.
39. DeWolf AM, Scott V, Bjerke R, *et al.*: **Hemodynamic effects of inhaled nitric oxide in four patients with severe liver disease and pulmonary hypertension.** *Liver Transpl Surg* 1997, 3:549–597.