A Tale of Two Circulations: the Pulmonary Vascular Complications of Portal Hypertension

Sonja D. Bartolome, MD

Associate Professor, Pulmonary and Critical Care Medicine

Director, Abdominal Transplant Critical Care

Associate Director, Pulmonary Hypertension Program

University of Texas Southwestern Medical Center

Dallas, TX 75390

Phone 214-645-9578

Fax 214-645-6272

Email: Sonja.Bartolome@UTSouthwestern.edu

This is to acknowledge that Sonja Bartolome, MD has disclosed that she does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Bartolome will not be discussing off label uses in her program.

Sonja Bartolome, MD

Associate Professor

Pulmonary and Critical Care Medicine

Interests: Dr. Bartolome's clinical and clinical research interests lie in pulmonary vascular disease including pulmonary arterial hypertension of all causes, hepatopulmoanry syndrome and thromboembolic disease. She has particular interests in pulmonary vascular disorders associated with liver disease.

Purpose and Overview – The purpose of this talk is to review the current data regarding two pulmonary vascular disorders associated with liver disease, portopulmonary hypertension (POPH) and hepatopulmonary syndrome (HPS). POPH is a progressive small vessel pulmonary arteriopathy which develops in a small percentage of patients with portal hypertension, eventually resulting in right ventricular failure and death. A small percentage of patients may be curable with liver transplantation, but the they also are at increased risk for perioperative death. The ideal patient selection for liver transplantation in patients with POPH is an active area of research. In contrast, HPS is a pulmonary vascular disorder characterized by intrapulmonary vasodilation that causes intrapulmonary shunting and hypoxemia in patients with portal hypertension. HPS is associated with increased mortality in patients with liver disease and is considered an indication for liver transplantation.

Education Objectives:

At the end of this presentation, attendees will be able to:

1. Describe the 3 common hemodynamic alterations in patients with liver disease
2. Describe the clinical presentation of patients with portopulmonary hypertension
3. Identify the available therapies for patients with portopulmonary hypertension
4. Describe the clinical presentation of patients with hepatopulmonary syndrome
5. Determine the diagnostic approach to patients with hepatopulmonary syndrome

Introduction

Intra-abdominal pathology may have distant effects on the pulmonary vascular bed, the pulmonary parenchyma or the pleural space. This paper will review the pulmonary vascular complications of liver disease by discussing the pathology, epidemiology, clinical features and management of these pulmonary complications.

Pulmonary Vascular Complications of Hepatic Disease

Portopulmonary Hypertension

Portopulmonary Hypertension (POPH) is simply defined as pulmonary artery hypertension that occurs in the setting of liver disease, or more specifically, portal hypertension.

Epidemiology and Pathogenesis

Approximately 2-6% of patients with decompensated liver disease will develop POPH. [1-3] Based upon multi-center case-control data, autoimmune hepatitis and female gender are risk factors for the development of POPH; therefore the role of hormonal and immunologic influences on the pulmonary vasculature in these patients is being studied.[4,5]

At the protein level, patients with POPH have measureable alterations in pulmonary vasoactive substances. Prostacyclin is a potent pulmonary vasodilator in addition to its antithrombotic and antiproliferative properties, and is decreased in the lungs of patients with pulmonary hypertension. In 1999, Tuder et al. confirmed that patients with POPH had a loss of endothelial prostacyclin synthase expression compared with normal controls.[6] Endothelin-1, a pro-proliferative and vasoconstrictive agent implicated in the pathophysiology of other types of PH, has also been demonstrated to be increased in the circulation of patients with POPH.[7]

Histologically, POPH appears to be very similar to other types of pulmonary arterial hypertension (PAH). It is a pre-capillary pulmonary arteriopathy involving multiple layers of the vessel: specifically, smooth muscle hypertrophy, adventitial proliferation, and endothelial cell proliferation. Additionally, the plexiform lesions characteristic of other types of pulmonary hypertension have been demonstrated in patients with POPH (**Figure 1**). [8]

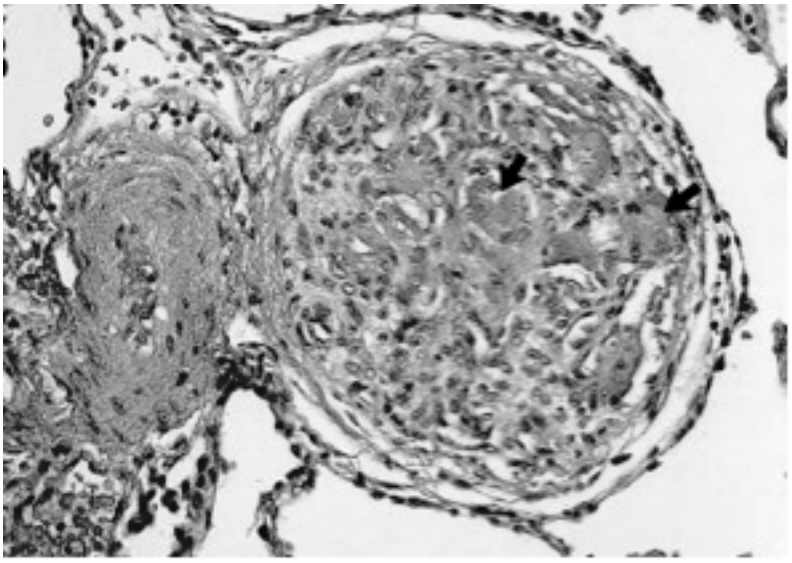

Figure 1 -- Autopsy specimen from a 55 yo female with cryptogenic cirrhosis and portopulmonary hypertension, showing the plexiform lesion common in pulmonary arterial hypertension. Adapted with permission from Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. Liver Transpl 2000;6:241-2.

These changes in the microvasculature produce a system with increased resistance and low capacitance, in sharp contrast to the normal pulmonary vascular physiology of a "low-pressure, high flow state." Thus, this altered physiology presents an increased workload to the right ventricle. Early in the disease process, the right ventricle (RV) hypertrophies, therefore increasing its stroke volume. But over time these changes become maladaptive and the right ventricle dilates and becomes dysfunctional. At this stage the patient presents with progressive right ventricular failure. This clinical course is similar to other types of PAH, justifying its placement in Group 1 in the World Health Organization (WHO) Classification system **(TABLE 1)**. [9] However, the concomitant presence of end-stage liver disease with fluid retention, hypoalbuminemia, coagulopathy, renal dysfunction, and gastrointestinal bleeding complicates the clinical management of POPH patients.

TABLE 1 – WHO Classification of PH

Group I Pulmonary Arterial Hypertension

- Idiopathic
- Hereditary
- Associated with:
  - Collagen vascular disease
  - Congenital heart disease
  - Human immunodeficiency virus
  - Drugs or toxins
  - Portal Hypertension
  - Chronic hemolytic anemia
  - Schistosomiasis

Group II Pulmonary Venous Hypertension

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Group III PH associated with respiratory disease/hypoxia

- Chronic Obstructive Pulmonary Disease
- Interstitial Lung Disease
- Sleep Disordered Breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude

Group IV Chronic Thromboembolic PH

Group V PH with unclear/multifactorial mechanism

Clinical Features

Patients with POPH may present with complaints of fatigue and dyspnea with exertion, which later progress to include signs and symptoms of right ventricular failure, such as jugular venous distension, lower extremity edema, pre-syncope and syncope. [10] This diagnosis can be particularly elusive in the cirrhotic patient, who may have edema from portal hypertension and a spectrum of hemodynamic disturbances.

For this reason, the diagnostic workup must be performed carefully to avoid a misdiagnosis of POPH. The most common hemodynamic derangement in patients with liver disease is not pulmonary arterial hypertension, but rather a vasodilated, high cardiac output state induced by splanchnic vasodilation.[3] In these patients, hemodynamics are characterized by increased mean pulmonary artery pressure (mPAP), high cardiac output (CO), low pulmonary capillary wedge pressure (PCWP) and reduced pulmonary vascular resistance (PVR). These individuals do not have small vessel arteriopathy, but rather increased pressure resulting from high flow through the pulmonary circulation. This hemodynamic pattern is evident in approximately 35% of liver transplant candidates and is not associated with a poor outcome. [3] A second abnormal hemodynamic profile present in the patient with liver disease involves volume overload or diastolic dysfunction. In these patients, pulmonary pressures may be elevated, but also CO and PCWP are increased, with a resulting low PVR, indicating pulmonary *venous* hypertension from elevated left heart filling pressures rather than small vessel pulmonary arteriopathy. Finally, POPH patients have an elevated pulmonary artery pressure, a normal PCWP, a high PVR, and a high, normal, or low CO (depending on the degree of resultant right ventricular failure and liver disease). (**TABLE 2**) Not infrequently, patients may present with a *combination* of the above hemodynamic profiles, for example, POPH with volume overload.. In this case, an increased transpulmonary gradient (TPG = mPAP – PCWP > 12 mmHg) can suggest the existence of combined volume overload and pulmonary arteriopathy. To characterize such complexity, many have suggested the hemodynamic definition of POPH be expanded to include mPAP >25, TPG >12, and a PVR greater than 3 Wood units.

TABLE 2 – HEMODYNAMIC PATTERNS IN PATIENTS with Liver Disease

	mPAP	CO	PCWP	PVR	TPG
High cardiac output and vasodilated	↑	↑↑	↓	↓↓	N ↑
Fluid overload or diastolic dysfunction	↑	N ↑	↑↑	N	N
POPH	↑↑	∩	N	↑	↑

Table 2 –

mPAP - mean pulmonary artery pressure (normal < 25mmHg)

PCWP - pulmonary capillary wedge pressure (normal < 15mmHg)

CO - cardiac output (normal 4-6 l/min)

PVR - pulmonary vascular resistance (normal < 3 wood units: (mPAP-PWCP)/CO)

TPG - transpulmonary gradient (normal < 12: mPAP-PCWP)

N – normal

Diagnosis

To make the diagnosis of POPH, measured evidence for portal hypertension (with an increased hepatic vein free pressure to wedge gradient) or clinical evidence of portal hypertension must be present. The diagnosis of POPH is often first suggested by an echocardiogram, but echocardiography is confounded by the above-mentioned hemodynamic changes associated with cirrhosis.[11] Therefore, an echocardiographically estimated peak PA pressure greater than 50 mmHg or signs of significant right ventricular dysfunction should trigger the confirmatory right heart catheterization. A screening series at the Mayo Clinic determined that this threshold was 100% sensitive in finding all cases of POPH while minimizing unnecessary invasive testing on patients with cirrhosis, who often have a hyperdynamic circulation. [3]

Clinical Course

Patients with POPH appear to have poorer outcomes when compared to patients with other types of PAH. The French registry recorded the outcome of 154 patients with POPH and included both treated and untreated subjects with follow-up data recording 68% 5-year survival.

Multivariate analysis identified advanced Childs-Pugh Scores (B and C) and lower cardiac index as independent risk factors for mortality.[12] The REVEAL registry for pulmonary artery hypertension is an ongoing multi-center observational study and has recorded the outcomes of 174 patients with POPH, the largest cohort to date. Analysis of these data showed that POPH patients had poorer survival and all-cause hospitalization rates when compared to patients with idiopathic and familial PAH. This outcome occurred despite more favorable initial hemodynamic profiles in the POPH group. [13] (**FIGURE 2)** Further, when this data was analyzed to create a risk score for 1-year mortality for all patients presenting with PAH, POPH as the etiology of PH emerged as a risk factor for 1-year mortality with a hazard ratio of 3.6. [14]

FIGURE 2

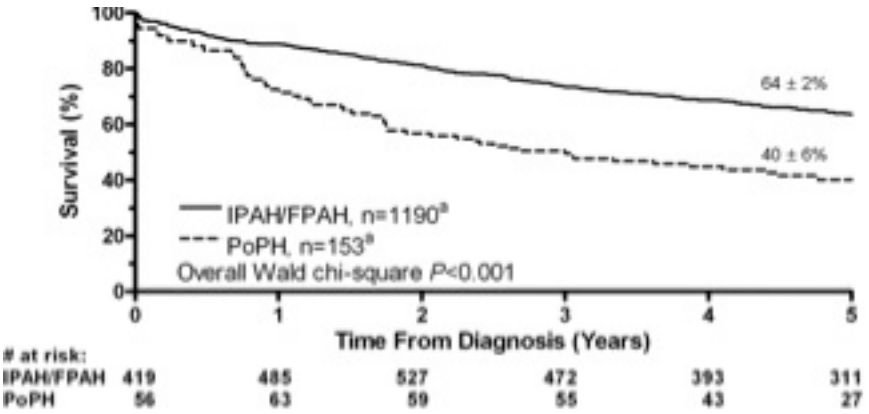

Figure 2 --
Five-year survival from time of diagnosis of POPH versus IPAH/FPAH. Data from REVEAL registry. Only patients enrolled within 5 years of diagnosis were included in the 5 years survival from diagnosis curve. Reprinted with permission from CHEST 2012; 141(4):905-915

Management

Portopulmonary hypertension is classified as WHO Group I PAH, and therefore amenable to the use of FDA-approved drugs for this group of patients. However POPH was excluded from clinical trials for these agents. Specific data for the treatment of POPH is limited to case series and single center studies as summarized below.

Endothelin Antagonists

The endothelin antagonists bosentan and ambrisentan are established treatments for WHO Group I PAH. Endothelin is a pulmonary vasoconstrictor and proproliferative agent, and its antagonism has been shown to improve exercise capacity and hemodynamics in patients with PAH. Data in POPH specifically are limited. Bosentan is a dual endothelin receptor antagonist (ET_A and ET_B) and POPH patients treated with this agent have shown improvements in exercise capacity and survival in small, single center, uncontrolled, observational trials.[15,16] The use of

bosentan has been limited in this population of patients due to its well-described hepatotoxicity in a minority of patients (approximately 10%) with PAH but no underlying liver disease. This hepatotoxicity is likely related to its inhibition of a bile salt transporter, and is reversible with drug discontinuation. [17] Ambrisentan is a selective ET_A antagonist, also FDA approved for the treatment of WHO group I PAH. Hepatotoxicity has not been reported with this agent. A single center uncontrolled, observational trial of ambrisentan in POPH from the Mayo Clinic reported a significant improvement in mPAP and PVR with treatment and no hepatotoxic events. [18]

Phosphodiesterase Type 5 Inhibitors

Two phosphodiesterase Type 5 inhibitors, sildenafil and tadalafil, are currently FDA approved for the treatment of WHO group I pulmonary hypertension. These agents are vasodilate the pulmonary vascular bed by inhibiting the breakdown of cyclic GMP and work within the nitric oxide pathway. Small, uncontrolled observational trials reveal that sildenafil treatment for POPH increases 6 minute walk test distance and lowers N-terminal prohormone of brain natriuretic peptide levels, both of which correlate with better prognoses in patients with PAH. [19] The reported hemodynamic response has been mixed, with one observational trial reporting an improved pulmonary vascular resistance in 3/5 patients at one year [20] and another showing an improved pulmonary vascular resistance in all patients (n=9) at a follow up time varying between 95 and 282 days. [21]

Prostacyclins

Prostacyclin analogues are key agents in the treatment of PAH and considered by many to be the agent of choice for the "sickest" patients with PAH. These agents must be given in either continuous subcutaneous, continuous intravenous, or intermittently inhaled form. The current FDA approved prostacyclins for intravenous use are epoprostenol and treprostinil. Treprostinil is also available in subcutaneous infusion and inhaled form. In the United States, iloprost is available only in the inhaled form, although it is given intravenously in Europe. Uncontrolled, single center series have consistently demonstrated that prostacyclin infusions result in significant improvements in mean PAP, CO and PVR in patients with POPH.[22-24] Further, prostacyclin infusions have been successfully used to improve hemodynamics in patients with POPH to the degree that liver transplantation can be safely pursued.[24-27] Less data exist to support the use of inhalational prostacyclins for POPH, and although iloprost has been shown to acutely improve hemodynamics, long-term effects are less certain.[28]

Liver Transplantation

The history of liver transplantation in the setting of POPH is one of controversy. In early experiences, the diagnosis of POPH was made in the operating room at the time of liver transplantation. Such patients were neither treated for their disease, nor under the care of a medical team familiar with critical care of the POPH patient. Not surprisingly, intraoperative death from decompensated right ventricular failure was not infrequent.[29] Long-term outcome was also affected, and those with severe pulmonary hypertension (systolic PAP >60) had a 9-month post-transplant survival of 58%.[30] Because of these data, severe POPH was considered a contraindication to liver transplantation. With experience and the advent of newer treatment modalities for PAH, centers began to report not only successful liver transplants in patients with POPH, but also at times, regression of the POPH after liver transplantation. [31,32] In 2006, Baylor

Medical Center reported eight sequential cases of severe POPH who were treated with IV epoprostenol. Of those eight, seven had significant hemodynamic improvement with epoprostenol. Six of those seven were listed for liver transplantation, and four of those listed were successfully transplanted. Of those transplanted, survival was 100% at 5 years. [26,32] Further, a retrospective right heart catheterization screening analysis published from the Mayo clinic documented the lowest 5-year survival in POPH patients who were neither transplanted nor treated for PH (15%), and the highest 5-year survival (64%) in those both treated for pulmonary hypertension and transplanted.[33]

Because of the initial poor experiences with POPH patients undergoing liver transplantation, retrospective studies sought to identify risk factors for perioperative mortality. These series have suggested that if a patient has a mean PA pressure of <35 and normal right ventricular function, perioperative mortality approaches those without portopulmonary hypertension. However, if the patient's mean PA pressure is > 50 mm Hg at the time of transplant, mortality approaches 100%. [29,31,34] Because there is a role for liver transplantation in selected patients with POPH, the United Network for Organ Sharing (UNOS) has allowed for upgrade points in the model for end-stage liver disease (MELD) system for POPH patients who meet criteria, to expedite liver transplantation. The MELD system prioritizes liver transplantation for the sickest patients with liver disease, and the exception system allows extra points for those patients whose mortality risk is not reflected in their MELD score. The guidelines currently state that if a patient has a confirmed diagnosis of POPH (using mPAP, PVR and TPG), and they are treated with pulmonary vasodilator therapy to attain mPAP <35 and PVR <5 wood units, they are eligible for a MELD exception to 22 points, with an increase in their MELD by 10% every 3 months until they are transplanted. Liver transplantation in such patients should be performed at a center experienced with pulmonary vascular disease, as the perioperative course may be complicated. Even in patients without POPH, there is a well-described "reperfusion syndrome" at the time of allograft reperfusion, which may cause an acute elevation in both cardiac output and pulmonary artery pressure, and induce acute decompensated right ventricular failure in the patient with underlying POPH. [35,36] The use of intraoperative prostacyclin infusions, inhaled nitric oxide, or intravenous milrinone has been reported in this emergent setting, with mixed results. [37,38]

Limited data exists regarding the clinical course of POPH after liver transplantation. POPH progression, stability, improvement and resolution have all been reported. In most cases, patients are able to wean from their prostacyclin infusion over a period of months, but some remain on oral pulmonary vasodilators. (**FIGURE 3)** Available data suggests that 40-50% of patients may be able to be weaned from all pulmonary vasodilators given enough time.[24-26]

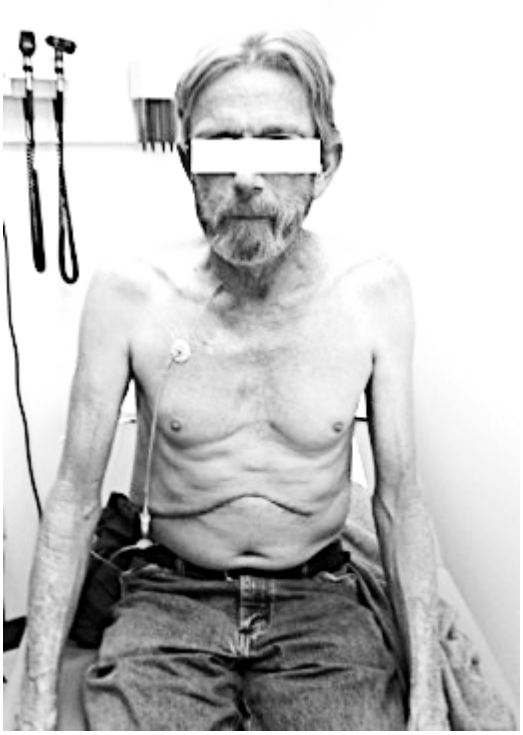

Figure 3– Patient 3 months s/p liver transplantation with POPH. Note central catheter with prostacyclin pump attached and healing abdominal incision. Photo courtesy of Juan Arenas, MD.

Summary

POPH is an uncommon complication of liver disease, characterized by a progressive pulmonary arteriopathy and resulting in right ventricular failure and death. Patients with POPH appear to have an increased mortality versus patients with similar levels of liver disease or with other types of pulmonary hypertension. The exact timing for, and optimal use of pulmonary vasomodulators in this disease is unclear, but patients do exhibit improved hemodynamics and exercise capacity through specific PAH therapy. The role of liver transplantation for these patients is arguable, but LT may be performed in carefully selected patients and may cure not only their liver disease but also their POPH.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is a liver-induced pulmonary vascular disorder characterized by a widened alveolar-arterial oxygen gradient. This gradient is the result of intrapulmonary vasodilation (IPVD) in the presence of hepatic disease or portal hypertension. Clinically, IPVD can occur with or without overt hypoxemia, depending on the severity of the

disease. HPS increases mortality in patients with liver disease, is without specific therapy, and is completely curable with liver transplantation. Therefore, unlike POPH, the presence of significant HPS is considered an indication for liver transplantation.

Epidemiology and Pathogenesis

The prevalence of HPS is reported as 4-32% in cohorts of cirrhotic patients undergoing liver transplant (LT) evaluation. [39,40] The pathogenesis of hepatopulmonary syndrome is poorly understood, but is thought to involve angiogenesis, as well as inadequate synthesis or metabolism of pulmonary vasoactive substances such as nitric oxide, prostaglandins, vasoactive intestinal peptide, endothelin, calcitonin, glucagon, substance P, and atrial natriuretic factor by the impaired liver. [41-43] Nitric oxide has long been implicated in the pathophysiology of HPS, given its known pulmonary vasodilatory effects.[44-48] Endothelin has also been implicated in the pathophysiology of HPS. Although endothelin is often thought of as a vasoconstricting agent, and its inhibition is a common therapy for pulmonary hypertension, endothelin's actions vary widely by the receptor to which it attaches. When endothelin-1 (ET-1) binds to the ET_A receptor, the effect is pulmonary vasoconstriction. But, when ET-1 attaches to the ET_B receptor, it enhances the activity of endothelial nitric oxide synthase and causes pulmonary vasodilation. In an experimental model of HPS, the ET_B receptor has been demonstrated to be up-regulated, and in these animal models, the experimental HPS was reversed by ET_B receptor blockade.[49,50]

Whatever the underlying mechanism, patients develop IPVD that causes a ventilation-perfusion (V/Q) mismatch and diffusion limitation to oxygenation by the increase in vascular diameter. The normal pulmonary capillary is 8-15 μm in diameter but in HPS, capillaries can dilate to 15-100 μm in diameter. Because of this alteration in the normal structure of the alveolar-capillary units, inhaled oxygen does not reach the center of the blood vessel and some blood returns to the left heart still de-oxygenated.

Clinical Features

Most HPS patients present with symptoms of chronic liver disease, and a minority (18% in one trial) present with dyspnea as their primary symptom.[48] Therefore, a high index of suspicion should be maintained to make a timely diagnosis. Patients may complain of platypnea (dyspnea with standing) or have the physical examination finding of orthodeoxia, which is defined as a PaO_2 decrease of 5% or 4mmHg upon standing. This sign/symptom combination is attributed to the increases in IPVD in the lung bases, and therefore increased V/Q mismatch in the standing position. Although this sign/symptom combination is well described in HPS, it is neither a common finding (occurs in 25% of patients) nor is it pathognomonic for HPS as it also has been noted in patients with atrial septal defects, post-pneumonectomy and post-pulmonary emboli.[51] On physical examination, patients with HPS may present with spider angiomata, digital clubbing and peripheral cyanosis. [39] The chest radiograph is often normal but may reveal bibasilar increased interstitial markings which may reflect vascular dilation in the bases.[52] Pulmonary function testing often reveals reduced diffusion capacity for carbon monoxide, out of proportion to other pulmonary function abnormalities.[53]

HPS has been recorded in patients with both acute and chronic liver disease. Most commonly it is described in cirrhotics, but HPS has also been documented in the setting of noncirrhotic

portal hypertension, and acute and chronic hepatitis.[48,54] The severity of the HPS does not correlate with the severity of the liver disease.

Diagnosis

The diagnosis of HPS requires the presence of: 1) cirrhosis or portal hypertension, 2) a widened age-corrected alveolar-arterial gradient (>15mmHg), and 3) demonstration of IVPD on a bubble-contrast transthoracic echocardiogram. Bubble contrast enhanced TTE is the most sensitive test for the detection of IPVD. However, TTE is a qualitative exam whereby saline is agitated and then injected into a peripheral vein. This agitation of saline causes microbubbles that are at least 15 μm in diameter. In normal physiology, as these microbubbles encounter the pulmonary capillary bed they are trapped and absorbed. However, if IPVD is present, these bubbles traverse the pulmonary capillaries and appear in the left atrium approximately 3-6 cardiac cycles after their injection. TTE can also identify intracardiac shunt in which case, the bubbles will appear in the left atrium in within 3 cardiac cycles. [55] IPVD may also be detected by technetium labeled macroaggregated albumin lung perfusion scanning. (^{99m} TcMAA). In this exam ^{99m} TcMAA is injected intravenously and uptake is then measured in the lungs and over the brain. In the absence of intrapulmonary or intracardiac shunt, the tracer will be trapped in the pulmonary circulation and very little will be observed on brain imaging. A fractional uptake >5% is considered abnormal. MAA scanning does allow quantification of the shunt, but cannot differentiate between intracardiac shunt and IPVD. One additional advantage of the ^{99m} TcMAA scan is that it is specific for HPS even in the presence of intrinsic lung disease, and therefore may help quantify hypoxemia from HPS versus that related to pulmonary parenchymal disease if both are present. However, ^{99m} TcMAA scanning is less sensitive than TTE for the presence of HPS and has correlated poorly with the degree of hypoxemia in several clinical trials. [55]

Arterial blood gases that quantify PaO2 and alveolar-arteriolar gradient (A-a)O_2 for HPS should be obtained with the patient at rest, breathing room air and in a sitting position. Due to changes of V/Q matching with positional changes in the disease, and a propensity for increased IPVD in the lung bases, patients' hypoxemia may worsen with standing and improve in the supine position. The European Respiratory Society Task Force published guidelines in 2004 suggesting that HPS be sub-classified by severity based on levels of hypoxemia: PaO_2 >80mmHg = mild, PaO_2 <80 to ≥60mmHg = moderate, PaO_2 < 60 to ≥ 50mmHg = severe, and PaO_2 < 50mmHg = very severe. [56]

Pulse oximetry is a noninvasive screening method for HPS and can prompt arterial blood gas analysis. A prospective study of pulse oximetry in cirrhotic patients determined that a threshold of SpO_2 of <96% was 100% sensitive and 88% specific in detecting patients with HPS and a PaO_2 <70 mmHg. This threshold resulted in ABG testing in 14% of the cohort.[57]

Clinical Course

The presence of significant HPS decreases exercise capacity, impairs quality of life and increases mortality compared to peers with similar severity of liver disease. [58] Further, the majority of patients will progress over time with an average decline in their resting PaO_2 of 5 mmHg/year. [59] In one multi-center prospective cohort, patients with HPS had a doubling of the risk for death, compared with patients without HPS, despite no differences in rates of listing for LT, performance of LT, age, sex or race. [58] Because of these statistics, screening programs have

been instituted at many institutions at the time of liver transplant evaluation. With the advent of this screening, a population of patients has been identified with IPVD via screening contrast-enhanced echocardiography but no hypoxemia. These patients may not share the poor prognosis of the hypoxemic patients described above.[60]

Management

There is no medical therapy proven to improve patients with HPS. Many agents have been tried unsuccessfully, including norfloxacin, beta-blockade, nitric oxide inhibitors, nitric oxide, glucocorticoids, cyclooxygenase inhibitors, indomethacin, somatostatin, cyclophosphamide, and plasma exchange.[61] Pentoxifylline is a phosphodiesterase-4 inhibitor that interferes with TNFα synthesis and has had some success in animal models of HPS. A recent pilot study in ten children determined that after 3 months of treatment there was a significant increase in PaO_2 (>10mmHg in all patients) and this treatment effect disappeared 3 months after drug discontinuation. However, there was a 40% drug discontinuation rate due to side effects in this small trial. [62] An earlier pilot study of pentoxifylline in adults showed no significant change in PaO2 and the drug was poorly tolerated due to gastrointestinal toxicity. [63] Supplemental oxygen is often administered and can ameliorate the symptoms of hypoxemia.

Liver Transplantation

Liver transplantation is the only proven therapy to resolve HPS. Long-term follow up reveals significant improvement or resolution of HPS in 85% of patients who underwent LT. [64-66] The time for oxygenation improvement is variable and may take up to 1 year or longer. Hypoxemia due to HPS can complicate the postoperative course for LT and a preoperative PaO_2 of <50 and MAA shunt fraction ≥ 20% has been associated with an increased postoperative mortality in an early prospective study.[67] However, a recent study has countered this data and suggests that LT can be safely performed for patients with HPS, even for those with severe hypoxemia. [68,69] Because of the increased mortality associated with HPS, and the favorable outcome with LT, the United Network for Organ Sharing (UNOS) has instituted a MELD exception guideline for these patients. This guideline states that if the diagnosis of HPS is confirmed with bubble contrast echocardiography and the patient's PaO_2 is less than 60 mmHg, an application for MELD upgrade may be submitted with the local RRB. This upgrade will increase the patient's MELD score to 22, regardless of the level of liver disease, with an increase by 10% every three months until liver transplantation. [70]

Summary

HPS is a liver-induced pulmonary vascular disorder characterized by intrapulmonary vascular dilation that results in a V/Q mismatch and diffusion limitation for oxygenation. There is no known medical treatment, and patients with this syndrome have a poorer prognosis than that offered by their liver disease alone. HPS is an indication for and is curable by liver transplantation.

References

1. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology.* Feb 2003;37(2):401-409.

2. Castro M, Krowka MJ, Schroeder DR, et al. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. *Mayo Clin Proc.* Jun 1996;71(6):543-551.

3. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: Results from a 10-year screening algorithm. *Hepatology.* Dec 2006;44(6):1502-1510.

4. Roberts KE, Fallon MB, Krowka MJ, et al. Genetic risk factors for portopulmonary hypertension in patients with advanced liver disease. *Am J Respir Crit Care Med.* May 1 2009;179(9):835-842.

5. Roberts KE, Fallon MB, Krowka MJ, et al. Serotonin transporter polymorphisms in patients with portopulmonary hypertension. *Chest.* Jun 2009;135(6):1470-1475.

6. Tuder 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.* Jun 1999;159(6):1925-1932.

7. Benjaminov FS, Prentice M, Sniderman KW, Siu S, Liu P, Wong F. Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *Gut.* Sep 2003;52(9):1355-1362.

8. Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. *Liver Transpl.* Mar 2000;6(2):241-242.

9. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology.* Jun 30 2009;54(1 Suppl):S43-54.

10. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* Aug 1987;107(2):216-223.

11. Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl.* Jul 2000;6(4):453-458.

12. Le Pavec J, Souza R, Herve P, et al. Portopulmonary hypertension: survival and prognostic factors. *Am J Respir Crit Care Med.* Sep 15 2008;178(6):637-643.

13. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. *Chest.* Apr 2012;141(4):906-915.

14. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation.* Jul 13 2010;122(2):164-172.

15. Hoeper MM, Seyfarth HJ, Hoeffken G, et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. *Eur Respir J.* Dec 2007;30(6):1096-1102.

16. Hoeper MM, Halank M, Marx C, et al. Bosentan therapy for portopulmonary hypertension. *Eur Respir J.* Mar 2005;25(3):502-508.

17. 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.* Apr 2001;69(4):223-231.

18. Cartin-Ceba R, Swanson K, Iyer V, Wiesner RH, Krowka MJ. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. *Chest.* Jan 2011;139(1):109-114.

19. Reichenberger F, Voswinckel R, Steveling E, et al. Sildenafil treatment for portopulmonary hypertension. *Eur Respir J.* Sep 2006;28(3):563-567.

20. Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. *Liver Transpl.* Jan 2009;15(1):15-19.

21. Gough MS, White RJ. Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial hypertension. *Liver Transpl.* Jan 2009;15(1):30-36.

22. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation.* Feb 27 1997;63(4):604-606.

23. 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.* Sep 1999;30(3):641-648.

24. Fix OK, Bass NM, De Marco T, Merriman RB. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. *Liver Transpl.* Jun 2007;13(6):875-885.

25. Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* May 2007;7(5):1258-1264.

26. Sussman N, Kaza V, Barshes N, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* Sep 2006;6(9):2177-2182.

27. Sakai T, Planinsic RM, Mathier MA, de Vera ME, Venkataramanan R. Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease. *Transplant international : official journal of the European Society for Organ Transplantation.* May 2009;22(5):554-561.

28. Melgosa MT, Ricci GL, Garcia-Pagan JC, et al. Acute and long-term effects of inhaled iloprost in portopulmonary hypertension. *Liver Transpl.* Mar 2010;16(3):348-356.

29. 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.* Jul 2000;6(4):443-450.

30. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver transplantation and surgery : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society.* Sep 1997;3(5):494-500.

31. Starkel P, Vera A, Gunson B, Mutimer D. Outcome of liver transplantation for patients with pulmonary hypertension. *Liver Transpl.* Apr 2002;8(4):382-388.

32. Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. *Liver Transpl.* Aug 2012;18(8):881-891.

33. Swanson KL, Wiesner RH, Nyberg SL, Rosen CB, Krowka MJ. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* Nov 2008;8(11):2445-2453.

34. Martinez-Palli G, Taura P, Balust J, Beltran J, Zavala E, Garcia-Valdecasas JC. Liver transplantation in high-risk patients: hepatopulmonary syndrome and portopulmonary hypertension. *Transplant Proc.* Nov 2005;37(9):3861-3864.

35. Ramsay M. Portopulmonary hypertension and right heart failure in patients with cirrhosis. *Curr Opin Anaesthesiol.* Apr 2010;23(2):145-150.

36. Fukazawa K, Pretto EA, Jr. Poor outcome following aborted orthotopic liver transplantation due to severe porto-pulmonary hypertension. *Journal of hepato-biliary-pancreatic sciences.* Jul 2010;17(4):505-508.

37. Fukazawa K, Poliac LC, Pretto EA. Rapid assessment and safe management of severe pulmonary hypertension with milrinone during orthotopic liver transplantation. *Clinical transplantation.* Jul-Aug 2010;24(4):515-519.

38. Molmenti EP, Ramsay M, Ramsay K, et al. Epoprostenol and nitric oxide therapy for severe pulmonary hypertension in liver transplantation. *Transplant Proc.* Feb-Mar 2001;33(1-2):1332.

39. Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol.* May 2001;34(5):651-657.

40. Schenk P, Schoniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Muller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology.* Oct 2003;125(4):1042-1052.

41. Bruix J, Bosch J, Kravetz D, Mastai R, Rodes J. Effects of prostaglandin inhibition on systemic and hepatic hemodynamics in patients with cirrhosis of the liver. *Gastroenterology.* Feb 1985;88(2):430-435.

42. Pizcueta P, Pique JM, Fernandez M, et al. Modulation of the hyperdynamic circulation of cirrhotic rats by nitric oxide inhibition. *Gastroenterology.* Dec 1992;103(6):1909-1915.

43. 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.* May 2003;38(5):556-563.

44. Rolla G, Brussino L, Colagrande P, et al. Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. *Hepatology.* Oct 1997;26(4):842-847.

45. Delclaux C, Mahut B, Zerah-Lancner F, et al. Increased nitric oxide output from alveolar origin during liver cirrhosis versus bronchial source during asthma. *Am J Respir Crit Care Med.* Feb 1 2002;165(3):332-337.

46. 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.* Jul 5 2003;362(9377):43-44.

47. Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med.* Nov 7 2000;133(9):701-706.

48. Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. *Chest.* Aug 1993;104(2):515-521.

49. Zhang J, Ling Y, Tang L, Luo B, Pollock DM, Fallon MB. Attenuation of experimental hepatopulmonary syndrome in endothelin B receptor-deficient rats. *Am J Physiol Gastrointest Liver Physiol.* Apr 2009;296(4):G704-708.

50. Ling Y, Zhang J, Luo B, et al. The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. *Hepatology.* Jun 2004;39(6):1593-1602.

51. Seward JB, Hayes DL, Smith HC, et al. Platypnea-orthodeoxia: clinical profile, diagnostic workup, management, and report of seven cases. *Mayo Clin Proc.* Apr 1984;59(4):221-231.

52. McAdams HP, Erasmus J, Crockett R, Mitchell J, Godwin JD, McDermott VG. The hepatopulmonary syndrome: radiologic findings in 10 patients. *AJR Am J Roentgenol.* Jun 1996;166(6):1379-1385.

53. Deibert P, Allgaier HP, Loesch S, et al. Hepatopulmonary syndrome in patients with chronic liver disease: role of pulse oximetry. *BMC Gastroenterol.* 2006;6:15.

54. Babbs C, Warnes TW, Haboubi NY. Non-cirrhotic portal hypertension with hypoxaemia. *Gut.* Jan 1988;29(1):129-131.

55. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology.* Oct 1995;109(4):1283-1288.

56. Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J.* Nov 2004;24(5):861-880.

57. Arguedas MR, Singh H, Faulk DK, Fallon MB. Utility of pulse oximetry screening for hepatopulmonary syndrome. *Clin Gastroenterol Hepatol.* Jun 2007;5(6):749-754.

58. Fallon MB, Krowka MJ, Brown RS, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology.* Oct 2008;135(4):1168-1175.

59. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology.* May 2005;41(5):1122-1129.

60. Tanikella R, Kochar, R, Kawut SM, Machicai VI. Intrapulmonary vasodilitation and survival in liver transplant candidates (Abstract). *Hepatology.* 2010(52 (S1)).

61. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. *N Engl J Med.* May 29 2008;358(22):2378-2387.

62. Kianifar HR, Khalesi M, Mahmoodi E, Afzal Aghaei M. Pentoxifylline in hepatopulmonary syndrome. *World J Gastroenterol.* Sep 21 2012;18(35):4912-4916.

63. Tanikella R, Philips GM, Faulk DK, Kawut SM, Fallon MB. Pilot study of pentoxifylline in hepatopulmonary syndrome. *Liver Transpl.* Aug 2008;14(8):1199-1203.

64. Krowka MJ, Mandell MS, Ramsay MA, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl.* Feb 2004;10(2):174-182.

65. 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.* Jan 1997;72(1):44-53.

66. Taille C, Cadranel J, Bellocq A, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation.* May 15 2003;75(9):1482-1489; discussion 1446-1487.

67. 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.* Jan 2003;37(1):192-197.

68. Iyer VN, Swanson KL, Cartin-Ceba R, et al. Hepatopulmonary syndrome: Favorable outcomes in the MELD exception era. *Hepatology.* Sep 19 2012.

69. Gupta S, Castel H, Rao RV, et al. Improved survival after liver transplantation in patients with hepatopulmonary syndrome. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* Feb 2010;10(2):354-363.

70. OPTN. Policy 3.6.4.5.1December 13, 2012.