Hepatopulmonary Syndrome

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Introduction

There are two distinct pulmonary vascular consequences of hepatic disorders: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) (1). HPS is characterized by arterial hypoxemia caused by intrapulmonary vascular dilatations, whereas POPH is a pulmonary hypertension syndrome with vascular obstruction and increased resistance to pulmonary arterial flow due to varying degrees of pulmonary endothelial/smooth muscle proliferation, vasoconstriction and in-situ thrombosis. Both have serious implications for liver transplantation (LT) and reflect quite different associated genetics, histopathologies and clinical courses. This review includes key papers and selected advances since 2008 in understanding HPS pathogenesis and implications for the liver transplant candidate. A comprehensive review of HPS literature through 2007 was recently published in the New England Journal of Medicine (1).

The clinical triad of 1) portal hypertension; 2) hypoxemia; and 3) pulmonary vascular dilatations characterizes the clinical picture of HPS (1). Consensus diagnostic criteria suggested by the European Respiratory Society (ERS)/European Association for Study of
the Liver (EASL) Task Force are shown in Table 1 (1). It is important to review the liver-lung pathophysiology that underlies the development of this syndrome as new understandings and potential therapeutic interventions are evolving.

**Table 1.** Diagnostic Criteria for HPS.

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<td>1) Liver disease (usually portal hypertension with or without cirrhosis);</td>
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<td>2) A-a oxygen gradient &gt; 15 mmHg (20 mm Hg of age if age &gt; 64)*</td>
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<td>3) Pulmonary vascular dilatation documented by:</td>
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<td>a) &quot;positive&quot; delayed, contrast-enhanced echocardiography with left heart detection of microbubbles ≥ 4 cardiac cycles after right heart opacification of microbubbles.</td>
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<td>b) brain uptake &gt; 6% following ⁹⁹mTc macroaggregated albumin (MAA) lung perfusion scanning.</td>
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*A-a oxygen gradient (1) = \text{FIO}_2(P_{atm}-47)-(\text{PaCO}_2/8) – \text{PaO}_2 |

where \text{FIO}_2 = inspired alveolar oxygen fraction  
\text{P}_{atm}=atmospheric pressure  
\text{PaCO}_2=arterial carbon dioxide tension

**Note:** It is commonly accepted that \text{PaO}_2 < 80 mm Hg define HPS when A-a gradient can not be calculated at sea level. In addition, normal \text{PaO}_2 at higher altitude is affected by barometric pressure. Hence, arterial hypoxemia in Denver Colorado (~5,000 feet) would have a lower estimated threshold of < 65 mmHg.

**Background**

As a result of factors that cause portal hypertension (with or without cirrhosis; adults or children), splanchnic and systemic vascular tone is impaired, resulting in a hyperdynamic circulatory state with increased cardiac output and decreased system vascular resistance (2). In this setting, the pulmonary vascular bed experiences vascular dilatation changes
that range from the subtle (documented, but with no obvious clinical presentation) to the debilitating (severe arterial hypoxemia requiring supplemental oxygen). Such pulmonary vascular bed abnormalities can be of two distinct types: diffuse, microscopic precapillary and capillary dilatations, and discrete, macroscopic arteriovenous communications that may resemble classic pulmonary arteriovenous malformations (1). The diffuse pattern is by far the most common. These vascular abnormalities may lead to ventilation-perfusion mismatch (excess perfusion for given ventilation), oxygen diffusion-perfusion limitation (oxygen molecules not totally traversing through deoxygenated blood due the size of the dilatations) and anatomic right to left shunts (vascular structures that bypass normal alveoli-capillary interface) (Figure 1).

**Figure 1.** Schematic showing the a) normal relationship between the alveoli and the pulmonary capillary bed; b) abnormal pulmonary vascular communications between pulmonary arteries and pulmonary veins in HPS ( taken from ref 2 with permission).
The clinical presentation includes exertional dyspnea, clubbing, cyanosis, spider angiomas and worsening of dyspnea as a patient moves from the supine to standing position (platypnea) (1). Chest radiograph abnormalities may be subtle in both patterns and mimic interstitial lung disease in the diffuse situation. Chest CT scanning can identify the discrete lesions that are most commonly seen in the periphery and lung bases. There appears to be no gender, race or hepatic disease relationship with HPS (3).

In the recent prospective study conducted through the Pulmonary Vascular Complication of Liver Disease study group (PVCLD), 33% of 218 patients (72 with HPS/146 matched controls) screened from 7 clinical centers had fulfilled established diagnostic criteria for HPS (3). However, approximately 46% of liver transplant candidate controls in that study had documented pulmonary vascular dilatation by contrast echocardiography without arterial oxygenation abnormality as measured by the alveolar-arterial oxygen gradient.

**Arterial Hypoxemia**

Screening for hypoxemia is commonly accomplished by finger pulse oximetry (4). Hemoglobin saturation < 92% in the sitting position should trigger further arterial blood gas (ABG) measurements, keeping in mind oxygenation may worsen with the standing position (orthodeoxia), with exercise and during sleep. Although the arterial partial pressure of oxygen (PaO₂) measured from a radial artery stick is the usual measure to quantify hypoxemia, oxygenation characterized by the calculated alveolar-arterial (Aa) oxygen gradient is more accurate since it takes into account age, altitude effects (barometric pressure, assumed alveolar oxygen levels), and PaCO₂, all of which ultimately effect PaO₂. Therefore, it is generally accepted for clinical and research purposes that an ABG derived Aa oxygen gradient > 15 mmHg is abnormal (> 20 mmHg if age > 64) and in circumstances where that can not be accurately determined, PaO₂ < 80 mmHg is considered abnormal. Although not specific for HPS, PaO₂ frequently worsens as the patient moves from the supine to standing position (orthodeoxia), with exercise and during sleep (1, 2). Inspired supplemental oxygen via nasal cannula (up to 5 liters/min)
usually improves oxygenation and symptoms. Despite severe hypoxemia (PaO₂ < 50 mmHg), patients may have near-normalization of PaO₂ (> 500 mm Hg) while breathing 100% inspired oxygen (by sealed mouthpiece and nose clips). Such a result favors the existence of perfusion-diffusion limitation (seen in diffuse lesions), as opposed to true anatomic shunting (seen in discrete lesions).

Prognosis (5-year survival) is worse in the setting of Childs C liver disease, as well as with the severity of hypoxemia (5). It is well-documented that up to 30% of HPS patients may have other reasons for hypoxemia that includes hepatic hydrothorax, interstitial lung disease and chronic obstructive lung disease due to smoking (1). In such cases the use of lung perfusion scanning (see below) can help quantify the degree of hypoxemia due to HPS, since all other conditions mentioned will not be associated with brain uptake of radiolabeled albumen (see below). Such distinction may be important in deciding how hypoxemia may be affected by liver transplantation.

**Imaging**

The existence of pulmonary vascular dilatations can be determined using either contrast enhanced transthoracic echocardiography (qualitatively) or ⁹⁹m Tc macroaggregated albumin (⁹⁹mTc MAA) lung perfusion scanning with brain uptake imaging (quantitatively). (Figure 2) (1). The abnormal passage of agitated-saline microbubbles (echocardiography) or radiolabeled albumen (lung perfusion scan) through the pulmonary capillary bed after peripheral vein injection documents the existence of intrapulmonary vascular dilatations which characterize HPS. Normal caliber pulmonary capillaries (diameter < 8 um) do not allow passage of the microbubbles or albumen aggregates (usually > 20 um in size).
Figure 2. Imaging methods for detecting pulmonary vascular dilatations in HPS. A) contrast enhanced transthoracic echocardiography showing opacification of left heart chambers > 4 cardiac cycles after microbubbles appeared in the right heart.; b) abnormal radionuclide uptake over the brain quantified by calculating the geometric mean of uptake from the left side and right side of the brain.

Transthoracic contrast-echocardiography is more sensitive than lung perfusion scanning in detecting pulmonary vascular dilatations (1). In situations where transthoracic contrast-echocardiography remains equivocal for the observation of abnormal opacification in the left atrium following peripheral administration of agitated saline, a transesophageal echocardiography study can distinguish between microbubbles entering the left atrium versus microbubbles entering into the left atrium from the pulmonary veins. Lung perfusion scanning can not discern intracardiac from intrapulmonary shunting (1).
Pulmonary angiography is not necessary in most cases, but should be considered in the setting of severe hypoxemia (PaO$_2$ < 50 mmHg) breathing room air when there exists a poor response to 100% inspired oxygen (PaO$_2$ < 300 mmHg) (1). The goal of angiography is to document discrete arteriovenous communications (usually > 5 mm in diameter) that could be embolized. Such embolization has resulted in significant improvement in oxygenation (1).

**Pathogenesis**

Results from the PVCLD study group and animal studies (a common bile duct-ligated rat model) suggest that the pathogenesis of HPS may involve genetic disposition, an imbalance of pulmonary vascular endothelin A and B receptors, nitric oxide mediated vasodilatation and strong evidence for a neovascularization (angiogenesis) component of pulmonary vessels (3, 6-8). Based on the PVCLD study of 72 HPS and 146 control patients, 4 genes (associated with vascular structure) derived from single nucleotide polymorphism analyses appear to have a relationship to HPS: angiopoietin, endostatin, TIE-1 and endoglin (3). An overexpression of endothelin B receptors (whose role is to facilitate vasodilation and clearance of circulating endothelin-1) has been documented in the animal model of HPS (6). The implication for human HPS is unclear at this point. As a suspected mediator to induce vasodilatation, increased levels of exhaled nitric oxide (NO) have been documented in cirrhosis with the highest levels noted in HPS. But, human interventions using L-NAME (a nonselective inhibitor of nitric oxide synthetase)-induced reductions in exhaled NO have not resulted in improved arterial oxygenation (1, 7). In addition, the occurrence of angiogenesis in the HPS animal model has recently been documented (8). These findings support human observations of increased numbers of dilated vessels abutting normal alveoli in autopsy specimens taken from HPS patients (1). The role of selected genes, their protein products, circulating growth factors and circulating endothelial progenitor cells are currently being prospectively studied by the PVCLD group.
**Treatments**

There are no proven pharmacologic treatment options in HPS that have resulted in sustained improvements in arterial oxygenation (1). Transjugular intrahepatic portosystemic shunting (TIPS) has resulted in variable effects on arterial oxygenation based upon single case reports and, as such, is not considered a reliable or preferred long-term treatment. Although rare, the hypoxemia of HPS associated with noncirrhotic portal hypertension, may significantly improve following interventional radiology approaches. Balloon cavoplasty has improved oxygenation in selected cases of hepatic vein and inferior vena cava obstruction due to Budd-Chiari syndrome (1). Inferior vena cava stenting has dramatically improved oxygenation in the type 2 Abernethy malformation (the side to side communication between the portal vein and inferior vena cava) (9). The mechanism of improvement is probably due to redirecting flow back into the portal vein through the normal hepatic tissues. The use of inhaled prostacyclin to “steal” venous blood from the dilated pulmonary vessels, redirecting flow to areas of better ventilation-perfusion matching, can acutely improve arterial oxygenation and warrants further investigation (10).

**Liver Transplantation**

HPS occurs in up to 33% of liver transplant candidates with no specific relationship to the cause or severity of liver disease as determined by either the Child Turcotte Pugh classification or Model for End Stage Liver Disease (MELD) score (3). Once considered as an absolute contraindication for liver transplantation, HPS is now considered to an indication for LT in appropriate circumstances due to the extensive documentation for complete resolution of HPS and long-term survival with successful LT in both the pediatric and adult age groups (12, 14, 16). However, post-LT morbidity and mortality is not trivial (11-14, 16).

There are no unique preoperative preparations or intraoperative concerns when attempting LT in patients with HPS, other than to insure adequate oxygenation. Recently, transjugular intrahepatic shunting (TIPS) has been reported to facilitate LT in HPS, but the routine use of TIPS to consistently improve oxygenation due to HPS has not been
espoused (17). No intraoperative deaths directly related to the inability to adequately oxygenate HPS patients during the surgical procedure have been reported. The immediate post-LT intensive care management can be complicated by further deterioration in arterial oxygenation due to atelectasis, fluid administration, transfusion-related pulmonary effects and aspiration. The use of inhaled nitric oxide, trendelenburg positioning and high frequency ventilation can facilitate better ventilation-perfusion matching post-LT in selected circumstances and improve $\text{PaO}_2$ (16). Post-LT ECMO has been successfully used in complicated pediatric HPS cases (18).

Patients with severe hypoxemia ($\text{PaO}_2 < 50 \text{ mm Hg}$) may indeed have good long-term outcomes, but are more likely to require prolonged intensive care unit management (11, 16). The severity of pre-LT hypoxemia correlates directly with the length of time needed for HPS resolution post-LT (12). The time for hypoxemia resolution is usually measured in terms of months, not days.

All-cause post-LT mortality has ranged from 5-67% at various post-LT times depending upon the series. Which patients are at highest risk for LT? Severity of hypoxemia ($\text{PaO}_2 < 50 \text{ mm Hg}$) and increased brain uptake (> 30%) after lung perfusion scanning correlate with worse post-LT survival (11, 12, 14). The role of hypoxemia in transplant hospitalization deaths, as well as post-hospitalization morbidity and mortality, is difficult to discern from the existing literature. However, biliary and vascular complications seem to predominate and conceivably could be related to tissue hypoxia, thus contributing to such complications (11, 16).

Long-term survivals following LT in HPS patients are encouraging. In the published Mayo Clinic experience of 61 HPS patients, 5-year survival of all patients was 23% if LT was not accomplished (n=37); 76% 5-year survival was noted for those who underwent LT (n=24) (Figure 3) (14). Unpublished analysis of an additional 44 HPS patients seen at the Mayo Clinic since that publication (a total cohort of n=105 HPS patients followed up to 300 months; 23 additional patients who underwent transplant), has documented a 5-year post-LT survival of 80% versus 35% survival for those not undergoing LT (19).
Centers experienced in managing HPS patients have reported excellent post-LT survivals even in the setting of severe hypoxemia (PaO$_2$ < 50 mm Hg) (16), however, post-LT morbidity may be significant as mentioned earlier (16). Finally, it is important to note that living-donor LT (with reduced hepatic mass) can result in total resolution of HPS and excellent survival (11, 16).

**Figure 3.** Survival curves of HPS patients managed at the Mayo Clinic. Significant 5-year survival difference between patients who received liver transplant (76%) and those not transplanted (23%). No difference in baseline PaO$_2$ noted between the two groups.

Current practice guidelines in the United States suggest that all patients considered for LT should have arterial blood gases measured in the sitting position at rest (20). Patients with age-related abnormal alveolar-arterial oxygen gradients or PaO$_2$ < 80 mmHg should be screened for HPS by contrast-enhanced transthoracic echocardiography. Higher priority for LT (MELD exception) can be granted in the US if the PaO$_2$ is less than 60 mm Hg, in attempts to improve morbidity and reduce post-LT mortality associated with
severe arterial hypoxemia (20). The goal of progressive higher priority has not been to necessarily reduce wait-list time mortality, but rather to dramatically improve short and long-term post-LT clinical course.

References.


**Questions**

1. HPS is not characterized by or associated with:
   - a) hypoxemia
   - b) pulmonary vascular dilatation
   - c) orthodeoxia
   - d) pulmonary artery hypertension

2. HPS is most commonly documented in hepatic patients with
   - a) portal hypertension
   - b) hepatocellular carcinoma
   - c) acute hepatitis
   - d) acute liver failure

3. HPS is a consequence of liver disorders that
   - a) are diagnosed in adults only
   - b) are only seen in Caucasians
   - c) may be complicated by COPD
   - d) predominantly affect females

4. The pediatric age group
   - a) is less affected by HPS than adults
   - b) experiences a much more severe form of HPS than adults
   - c) seldom totally resolves HPS after liver transplantation
   - d) frequently experiences total resolution of HPS after liver transplantation

5. The following treatment has been shown to completely resolve HPS
   - a) prednisone
   - b) ciprofloxacin
c) TIPS
d) surgical splenorenal shunt
e) living-donor liver transplantation

6. Liver transplantation in the setting of HPS
   a) has been complicated by intraoperative death due to hypoxemia
   b) should not be attempted if \( \text{PaO}_2 \) is less than 50 mmHg
   c) has increased post-transplant hospital mortality
   d) frequently results in long-term mechanical ventilation post-transplant

7. One animal model finding implicated in the pathophysiology of HPS is
   a) increased pulmonary endothelin A receptor expression
   b) decreased pulmonary endothelin B receptor expression
   c) excess of endothelial prostacyclin synthase
   d) evidence of angiogenesis

8. The following are well-documented additional findings in HPS with the exception of
   a) COPD
   b) pulmonary fibrosis
   c) pulmonary emboli
   d) hepatic hydrothorax

9. The image of choice to qualitatively demonstrate pulmonary vascular dilatation is
   a) Contrast-enhanced transthoracic echocardiography
   b) Contrast-enhanced transesophageal echocardiography
   c) \( ^{99m} \text{Tc} \) macroaggregated lung perfusion scan
   d) Pulmonary angiography

10. Arterial blood gas results obtained in severe HPS usually show
    a) \( \text{PaO}_2 \) < 50 mmHg breathing 100% oxygen
    b) \( \text{PaO}_2 \) < 50 mmHg breathing room air
    c) A-a gradient < 15 mmHg
    d) \( \text{PaCO}_2 \) > 50 mm Hg

11. Contrast-transesophageal echocardiography will demonstrate the following in HPS
    a) microbubbles passing backward from the right ventricle to the right atrium
b) right to left shunt at the atrial level  
c) left to right shunt at the atrial level  
d) microbubbles emanating from the pulmonary veins into the left atrium

12 The following nuclear medicine study can quantify the severity of HPS  
a) Sulfur colloid liver-spleen scan  
b) Ventilation-perfusion lung scan  
c) Lung perfusion scan with brain uptake  
d) Lung perfusion scan with liver uptake

13. Pulmonary angiography  
a) must be accomplished before liver transplantation when HPS is suspected  
b) is the diagnostic procedure of choice to prove HPS  
c) frequently detects pulmonary emboli in patients with HPS  
d) effectively improves hypoxemia if discrete HPS lesion are embolized  
e) effectively improves hypoxemia if diffuse HPS lesion are embolized.

14. 5-year survival in the setting of HPS is best characterized by the following:  
a) similar to lung transplant, approximately 40-50% following liver transplant  
b) does *not* depend on the severity of hypoxemia  
c) worse if living-donor transplant is attempted  
d) optimal if combined heart-lung-liver transplant is accomplished  
e) 23% survival if liver transplant *not* accomplished

*Correct answers:* 1)d  2)a  3)c  4)d  5)e  6)c  7)d  8)  9)a  10)b  11)d  12)c  13)d  14)e