The hepatopulmonary syndrome

David T. Palma, Michael B. Fallon*

University of Alabama at Birmingham Liver Center, MCLM 290, 1918, University Boulevard, Birmingham, AL 35294, USA

1. Background

Respiratory symptoms are exceedingly common in patients who have chronic liver disease with estimates ranging as high as 50–70% of patients complaining of shortness of breath [1]. The differential diagnosis of dyspnea is extensive in such patients and numerous causes should be considered. Over the last 15 years, pulmonary vascular abnormalities have been increasingly recognized as important clinical entities that influence survival and liver transplant candidacy in affected patients. The most common such abnormality, the hepatopulmonary syndrome (HPS), occurs when intrapulmonary vasodilatation impairs arterial oxygenation. This syndrome is now recognized as many as 15–20% of patients undergoing evaluation for orthotopic liver transplantation (OLT) [2]. The presence of HPS increases mortality in the setting of cirrhosis and may influence the frequency and severity of complications of portal hypertension [3]. The purpose of this review is to provide an update on HPS, including the pathophysiology and clinical features, and to provide guidelines for diagnosis and treatment.

2. Definition

HPS is classically defined by a widened alveolar-arterial oxygen gradient (AaPO2) on room air (>15 mmHg, or >20 mmHg in patients >64 years of age) with or without hypoxemia resulting from intrapulmonary vasodilation in the presence of hepatic dysfunction or portal hypertension [4–7]. From a practical vantage point, identifying patients with PaO2 <70 mmHg is useful for recognizing those with clinically significant HPS. Early studies emphasized that the exclusion of all other causes of cardiopulmonary dysfunction was required to establish the diagnosis of HPS [7]. However, it is now evident that HPS may coexist with other cardiopulmonary abnormalities [8,9] and contribute significantly to gas exchange abnormalities in this setting. In addition, the AaPO2 normally increases with age and varies significantly even in healthy adults. Therefore, using values above the 95% confidence interval for the age-corrected AaPO2 is appropriate to avoid over-diagnosis of HPS [10].

3. Pathophysiology

3.1. Mechanisms in humans

A fundamental question regarding pathogenesis in HPS is whether the mechanisms of vascular alterations in the lung are similar to those involved in the systemic and splanchnic alterations in the hyperdynamic circulatory state of cirrhosis. HPS is found most commonly in the setting of cirrhosis and appears to occur across the spectrum of etiologies of liver disease [5,11,12]. However, whether the presence or severity of intrapulmonary vasodilatation and HPS correlate with the severity of underlying liver disease is controversial and studies have found HPS more commonly in both less and more advanced cirrhosis [5,11–14]. Recently, HPS has also been recognized in patients with portal hypertension in the absence of cirrhosis (portal vein thrombosis, nodular regenerative hyperplasia,
congenital hepatic fibrosis and Budd–Chiari syndrome) [15–18] and has been reported in the setting of acute and chronic hepatitis in the absence of portal hypertension [19,20]. These findings support that advanced liver disease is not required for HPS to develop and that the pathophysiologic events occurring in the pulmonary microvasculature of patients with HPS are unique relative to the systemic and splanchnic circulations.

The pathogenetic hallmark of HPS is microvascular dilatation within the pulmonary arterial circulation. These changes may result from decreased pre-capillary arteriolar tone alone or could involve additional mechanisms such as angiogenesis, remodelling, and vasculogenesis, which have been recently suggested [21]. In human HPS, the vasodilatation is assumed to result from excessive vascular production of vasodilators, particularly nitric oxide (NO). This has been based on the observation that exhaled NO levels, a measure of pulmonary production, are increased in cirrhotic patients with HPS and normalize after OLT [22–24], as HPS resolves. In addition, a case report revealed that acute inhibition of NO production or action with \( \text{N}^\text{G} \)-nitro-L-arginine methyl ester (L-NAME) or cyclic GMP inhibitor methylene blue, respectively, transiently improves HPS [25–27]. However, a recent study found that administration of inhaled L-NAME did not acutely improve intrapulmonary vasodilatation [21], raising the possibility that factors other than NOS-derived NO effects on vascular tone contribute to HPS.

The exact mechanisms of increased endogenous NO production and its relationship to the presence of portal hypertension, the hyperdynamic circulation and the degree of liver injury remain uncertain. In addition, whether other mediators such as heme oxygenase-derived carbon monoxide [28] might contribute to intrapulmonary vasodilatation and explain the lack of improvement of HPS with NO inhibition in some patients has not yet been established.

3.2. Mechanisms in experimental HPS

Chronic common bile duct ligation (CBDL) in the rat is the only established model that reproduces the physiologic features of human HPS [29,30] (Fig. 1). It is unique among rodent models of cirrhosis and/or portal hypertension in that other commonly used models such as thioacetamide-induced cirrhosis and partial portal vein ligation do not result in the development of HPS [31]. Early studies in CBDL animals focused on the vasoconstrictor role of eicosanoids and on an

![Fig. 1. Potential mechanisms and treatments in experimental HPS](see text for details).
increase in intravascular macrophage-like cells [32,33]. Subsequent work identified increased pulmonary vascular endothelial nitric oxide synthase (eNOS) as a major source of pulmonary NO production [34-36] and demonstrated that the administration of intravenous L-NAME improved hypoxemia after CBDL [37]. Further studies have revealed that increased hepatic production of endothelin-1 (ET-1) with release into the circulation is an important mechanism for triggering the increase in pulmonary eNOS and the onset of vasodilatation after CBDL [35,38]. This effect may be driven by a shear stress-mediated increase in pulmonary vascular endothelial endothelin B (ETB) receptor expression which enhances endothelial NO production by ET-1 [39]. Accordingly, administration of a selective ETB receptor antagonist to CBDL animals decreases pulmonary endothelial eNOS and ETB receptor levels and significantly improves HPS [40]. Recent data support that biliary epithelium is an important source of hepatic ET-1 production after CBDL and may explain the unique susceptibility of CBDL animals to HPS [41,42].

As experimental HPS progresses, there is a steady accumulation of intravascular macrophages. These cells transiently produce inducible nitric oxide synthase (iNOS) [36,37] and progressively produce heme oxygenase 1 (HO-1) [36,43]. These events contribute to further vasodilatation through production of iNOS-derived NO and HO-1-derived carbon monoxide (CO). Accordingly, HO inhibition improves experimental HPS. In addition, prolonged treatment of CBDL animals beginning at the time of ligation with norfloxacin to inhibit bacterial translocation and tumor necrosis factor-alpha (TNF-α) production decreases macrophage accumulation and prevents the transient increase in iNOS [44], supporting that TNF-α contributes to macrophage accumulation. Further, pentoxifylline, a non-specific phosphodiesterase inhibitor that increases intracellular cAMP levels and also inhibits TNF-α production in macrophages [45], given over a similar time frame can prevent the onset or decrease the severity of HPS [46]. Both of these agents initiated at the onset of liver injury influence the development of the hyperdynamic state and may modify ETB receptor expression and endothelin related signaling events in the pulmonary microvasculature.

Findings to date in the CBDL model suggest that a sequence of events related in part to increased vascular shear stress and to hepatic ET-1 production may trigger the onset of experimental HPS. The observation that hepatic and plasma ET-1 levels increase within 1 week after CBDL [42] suggests that hepatic ET-1 production and release may occur with relatively modest degrees of bile duct proliferation. The finding that macrophages accumulate in the pulmonary microvasculature and may be influenced by TNF-α inhibition supports that these cells may also contribute to vasodilatation. Fig. 1 includes potential therapeutic targets for treatment in HPS based on experimental data.

4. Clinical manifestations

The clinical features of HPS typically involve respiratory complaints and findings associated with chronic liver disease. The insidious onset of dyspnea, particularly on exertion, is the most common complaint but is non-specific. Platypnea (shortness of breath exacerbated by sitting up and improved by lying supine) and orthodeoxia (hypoxemia exacerbated in the upright position) are classically described and result from a gravitational increase in blood flow through dilated vessels in the lung bases [47]. While orthodeoxia has been observed in a variety of conditions, including post-pneumonectomy, recurrent pulmonary thromboemboli, and atrial septal defects (such as patent foramen ovale), it is highly specific for HPS in the setting of liver disease [48]. The sensitivity of orthodeoxia for HPS is relatively low, but increases in cases of severe HPS [49,50]. Cough is not a common finding in HPS. Spider angiomata are commonly reported in HPS but are frequently seen in cirrhotic patients without HPS. One study observed that patients with these cutaneous lesions had more pulmonary vasodilatation and higher alveolar-arterial oxygen gradients than those without vascular spiders (AaPO2: 20 mmHg versus 8 mmHg) [51]. Finally, clubbing and distal cyanosis, when present in the setting of liver disease or portal hypertension, should raise suspicion for HPS [2].

5. Diagnosis

The diagnostic features of HPS include evidence of liver disease or portal hypertension, an elevated age-adjusted alveolar-arterial oxygen gradient (AaPO2), and evidence of intrapulmonary vasodilatation. In the presence of coexisting cardiac or pulmonary disease, establishing a diagnosis of HPS can be difficult. Fig. 2 presents an algorithm for the diagnosis of HPS. A logical evaluation of dyspnea in the patient with liver disease or portal hypertension begins with a careful history and physical examination. Such an evaluation may lead the clinician to consider alternate, more common diagnoses such as COPD, CHF or myocardial ischemia. However, if the common causes of dyspnea can be excluded, and particularly if platypnea or digital clubbing is present, further evaluation for HPS is warranted.
5.1. Assessment of arterial oxygenation

In patients with liver disease found to have dyspnea or clubbing, or in those undergoing transplant evaluation, pulse oximetry is a simple, non-invasive screening test for hypoxemia and a decreased SpO\textsubscript{2} should lead to arterial blood gas (ABG) analysis. However, caution must be exercised in interpreting a “normal” SpO\textsubscript{2} as pulse oximetry may overestimate SaO\textsubscript{2} in nearly one-half of patients with cirrhosis [52]. Therefore, to reliably detect hypoxemia ABG analysis should be considered when the SpO\textsubscript{2} values are 97% or less. In addition, if hypoxemia or HPS is strongly suspected based on history and physical exam, arterial blood gas analysis should be performed while breathing room air regardless of pulse oximetry. In HPS, ABGs reveal an elevated age-adjusted A\textsubscript{a}PO\textsubscript{2} with or without hypoxemia. The expected upper limit of normal for room-air A\textsubscript{a}PO\textsubscript{2} at a given age (>95% confidence interval) can be calculated using the following equation: A\textsubscript{a}PO\textsubscript{2} = [0.26 age – 0.43] + 10 [10].

If gas exchange abnormalities are detected, chest radiography and pulmonary function tests are performed to evaluate for the presence of other pulmonary abnormalities. Since cardiopulmonary disorders unrelated to liver disease or those related to ascites are more common than HPS, treating these abnormalities prior to further evaluation for HPS is reasonable in the absence of significant hypoxemia (PaO\textsubscript{2} <70 mmHg).

The ERS Task Force has proposed a classification system that uses arterial oxygen tension (PaO\textsubscript{2}) to stage the severity of HPS. According to this system, a PaO\textsubscript{2} <50 mmHg indicates very severe HPS, a PaO\textsubscript{2} >50 and <60 mmHg suggests severe HPS, and a PaO\textsubscript{2} ≥60 and <80 mmHg corresponds with moderate HPS [4]. Staging the severity of HPS is important as a means of predicting survival [13,53], and determining the timing and risks of orthotopic liver transplantation [3,6,53].

5.2. Contrast echocardiography

If hepatopulmonary syndrome is suspected, transthoracic microbubble contrast echocardiography is the preferred screening test for intrapulmonary vasodilatation [12]. Contrast echocardiography is performed by injecting agitated saline intravenously during normal transthoracic echocardiography, producing microbubbles that are visualized by sonography. This bolus opacifies the right ventricle within seconds and in the absence of right-to-left shunting, bubbles are absorbed in the lungs. If an intra-cardiac shunt is present, contrast agent enters the left ventricle within three heart beats (early shunting). If intrapulmonary shunting characteristic of hepatopulmonary syndrome is present, the left ventricle opacifies at least three heart beats after the right (delayed shunting). While up to 40% of patients with cirrhosis have a positive contrast echocardiogram [12], only a subset of these patients

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**Fig. 2.** Diagnosis of HPS (see text for details). [This figure appears in colour on the web.]
have sufficient vasodilatation to cause abnormal gas exchange and fulfill criteria for hepatopulmonary syndrome. If a patient with liver disease or portal hypertension and hypoxemia has a positive contrast echocardiogram in the absence of significant cardiopulmonary disease, the diagnosis of hepatopulmonary syndrome has been established. A semi-quantitative scoring system for assessing intrapulmonary shunting during contrast echocardiography has been developed, though it remains unclear whether the degree of shunting correlates with the degree of gas exchange abnormalities [54].

5.3. Macroaggregated albumin scan

In hypoxemic patients with both intrapulmonary vasodilatation and intrinsic cardiopulmonary disease, the technetium-labeled macroaggregated albumin scan (MAA scan) may be useful in defining the contribution of HPS to gas exchange abnormalities. In this test, radiolabeled aggregates of albumin measuring approximately 20 μm in diameter are infused into the venous system. Ordinarily, particles of this size become trapped in the pulmonary microvasculature and scintigraphy reveals nearly complete uptake in the lungs. In the presence of significant intrapulmonary shunting, a fraction of the macroaggregated albumin passes through the lungs and into the systemic circulation. Scintigraphy then also reveals uptake in other organs in addition to the lung, allowing the calculation of the shunt fraction. In one study, the MAA scan was positive only in patients with HPS and a PaO₂ < 60 mmHg and not in COPD patients with a similar degree of hypoxemia [8]. However, the MAA scan is less sensitive than contrast echocardiogram and may be most useful in determining whether HPS contributes to hypoxemia in patients with concomitant obstructive pulmonary disease.

5.4. Pulmonary function studies

While abnormal pulmonary function studies are frequently observed in HPS, these findings are of low specificity [55]. In the absence of concomitant obstructive or restrictive lung disease, measurements of total lung capacity and expiratory flow rates in HPS patients are generally normal. Diffusion impairment is commonly seen in HPS [55]. In one study, the diffusing capacity for carbon monoxide (DₕCO) was less than 80% of the predicted value in 15 of 18 patients with HPS [49]. However, the presence of decreased DₕCO with normal spirometry is not specific for HPS, and is routinely observed in patients with early interstitial lung disease, vasculocclusive disease, and profound anemia [56].

5.5. Other diagnostic techniques

Pulmonary angiography is expensive and invasive and has a low sensitivity for detecting intrapulmonary vasodilatation. Therefore, it is not routinely utilized in the diagnosis of HPS. High-resolution chest computed tomography (CT) and evaluation of pulmonary blood transit time are newer diagnostic modalities for assessing HPS. In one study, the degree of pulmonary microvascular dilatation observed on chest CT correlated with the severity of gas exchange abnormalities in a small cohort of patients with HPS, suggesting that quantitation of intrapulmonary vasodilatation was possible [57]. In another study, pulmonary transit time of erythrocytes, measured by echocardiographic analysis of human serum albumin-air microbubble complexes through the heart, also correlated with gas exchange abnormalities in a small group of patients with HPS [58]. Whether these techniques have diagnostic utility for HPS remains to be determined.

6. Natural history and prognosis

The natural history of hepatopulmonary syndrome is incompletely characterized. Most patients appear to develop progressive intrapulmonary vasodilatation and worsening gas exchange over time [49,59] and spontaneous improvement is rare [60]. A recent prospective study has evaluated the natural history of HPS in a cohort of 111 patients with cirrhosis of whom 27 (24%) had HPS [3]. The median survival among patients with HPS was significantly shorter (10.6 months) compared to patients without HPS (40.8 months). Mortality remained higher in those with HPS after adjusting for severity of underlying liver disease and after excluding patients who underwent liver transplantation during follow-up. The causes of death in patients with HPS were mainly due to complications of hepatocellular dysfunction and portal hypertension and correlated with the severity of hypoxemia in HPS. These data raises the possibility that the presence of HPS may be an important factor that influences the progression of liver disease and the risk of complications related to portal hypertension. Finally, even modest hypoxemia related to HPS may worsen during sleep based on the observation that nocturnal oxygen saturation decreased in a small cohort of non-HPS cirrhotic patients [61].

Mortality after liver transplantation also appears to be higher in patients with HPS compared to those without HPS. The utility of the severity of HPS as a predictor of outcome after liver transplantation has been prospectively evaluated in a cohort of 24 patients with cirrhosis and HPS [53]. The authors found that
mortality after liver transplantation was markedly increased in severe HPS, in part due to the development of unique post-operative complications recognized in HPS patients [62,63]. A preoperative PaO\textsubscript{2} of \( \leq 50\) mmHg alone or in combination with a macroaggregated albumin shunt fraction \( \geq 20\% \) were the strongest predictors of post-operative mortality. These results support that the presence of HPS may adversely affect survival in patients with cirrhosis and that the post-transplant outcome worsens in proportion to the severity of HPS.

7. Treatment

7.1. Orthotopic liver transplantation

Liver transplantation is the only established effective therapy for HPS based upon the total resolution or significant improvement in gas exchange post-operatively in more than 85\% of reported patients [64]. However, the length of time for arterial hypoxemia to normalize after transplantation is variable and may be more than 1 year [65]. In addition, mortality is increased after transplantation in patients who have HPS compared with subjects who do not have HPS [64], and unique post-operative complications, including pulmonary hypertension [66], cerebral embolic hemorrhages [67], and immediate post-operative deoxygenation requiring prolonged mechanical ventilation [68], have been reported. Innovative approaches such as frequent body positioning [69] or inhaled NO [70,71] have been used to improve post-operative gas exchange. Further investigation focused on the peri-operative medical management of HPS patients is needed to optimize survival.

The observation that HPS increases mortality and that transplant outcomes may worsen in cases of advanced HPS has led to the policy in US centers of increasing priority for OLT in patients with HPS and significant hypoxemia [72]. While sufficient data exist to justify additional priority for patients with HPS [3,59], preliminary data on the current MELD exception have not found reduced pre-OLT survival in listed patients relative to those that did not receive MELD exception [73]. This underscores the need to standardize MELD exception criteria and to further characterize the progression of hypoxemia in HPS as well as the factors that influence mortality. These efforts are essential to optimize OLT outcomes in HPS and avoid biasing allocation to or away from these patients.

7.2. Oxygen supplementation

While no data exist regarding efficacy or cost-effectiveness, oxygen supplementation remains a mainstay of therapy for HPS patients with a PaO\textsubscript{2} \( \leq 60\) mmHg or with exercise-induced oxygen desaturation. This practice derives from the established benefits of oxygen therapy in other pulmonary disorders where hypoxemia occurs. Anecdotal evidence supports that enhancement of arterial oxygenation improves exercise tolerance and quality of life in hypoxemic patients with HPS. Since oxygen influences pulmonary blood flow and hypoxemia is well recognized to adversely affect hepatocyte function [74], oxygen supplementation is a low risk treatment option that may have important benefits.

7.3. Transjugular intrahepatic portosystemic shunt

Seven case reports evaluated the effects of transjugular intrahepatic portosystemic shunt (TIPS) on HPS in cirrhosis. Six found a degree of improvement in oxygenation. However, the short duration of follow-up in two cases [75] and the presence of co-existent hepatic hydrothorax in another [76] limit assessment of the utility of TIPS. In a fourth report, arterial oxygenation clearly improved by 20 mmHg 6 months after TIPS placement [77]. Significant intrapulmonary shunting, however, persisted based on radionuclide lung perfusion scanning, and the cardiac output increased after TIPS. These findings suggest that improved oxygenation may not have been caused by reversal of intrapulmonary vasodilatation. In the case reports of an 11-year-old girl with biliary atresia and a 46-year-old woman with presumed alcohol related cirrhosis, oxygenation and intrapulmonary shunting were improved and sustained over 8 months and 3 years, respectively, following TIPS placement [78,79]. There is a seventh report of failure of TIPS to improve oxygenation in one patient and identification of two patients where HPS developed in the setting of a functional TIPS [80]. Together, these findings document the considerable uncertainty regarding the utility of TIPS for HPS. TIPS should be considered an experimental treatment, and its use should be confined to the setting of clinical trials so that efficacy may be assessed.

7.4. Medical therapies

There are currently no effective medical therapies for HPS. Small uncontrolled studies have reported a lack of efficacy using sympathomimetic agents, somatostatin, almitrine, indomethacin, and plasma exchange [81]. Aspirin increased arterial oxygenation in two children who had HPS [82], and a case report [83] and subsequent open label trial [84] using garlic also suggested a beneficial effect. In the latter trial, garlic powder was administered for a minimum of 6 months. Six of 15 (40\%) patients who had HPS had improvements greater than 10 mmHg in the PaO\textsubscript{2}, and one subject had resolution
of hypoxemia (PaO$_2$: 46–80 mmHg) over a 1.5-year period. Acute infusion of methylene blue, a dye that inhibits the effect of NO on soluble guanylate cyclase, also transiently improved oxygenation in two reports comprising a total of eight patients [27,85]. Acute administration of inhaled L-NAME, to inhibit nitric oxide production, also transiently improved oxygenation in one patient (PaO$_2$: 52–70 mmHg), but failed to significantly alter oxygenation in another group of 10 patients [21,86]. Finally, a single case report suggests that norfloxacin also may have contributed to improvement in oxygen saturation in HPS [87]. These reports underscore the need to evaluate agents targeted at likely pathogenetic mechanisms in randomized multi-center trials to determine efficacy.

8. Summary

HPS occurs when pulmonary microvascular dilatation impairs arterial oxygenation in the setting of liver disease or portal hypertension. The syndrome is found in up to 15–20% of patients with cirrhosis and should be considered in any patient with chronic liver disease who develops dyspnea or hypoxemia. The presence of HPS increases mortality in the setting of cirrhosis and may influence the frequency and severity of complications of portal hypertension. The recognition in experimental models that a unique sequence of molecular alterations leads to endothelin-1 and TNF-α modulation of pulmonary microvascular tone may lead to the development of novel and effective medical therapies. Contrast echocardiography and standard cardiopulmonary testing are generally sufficient to make the diagnosis of HPS but further testing may be needed in patients that have both intrinsic cardiopulmonary disease and intrapulmonary vasodilatation. Treatment consists of supplemental oxygen and consideration of orthotopic liver transplantation if significant hypoxemia is present.

References


