MINIREVIEWS

Hepatopulmonary syndrome: An update

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Abstract

Hepatopulmonary syndrome (HPS) is characterized by defects in oxygenation caused by intra-pulmonary vasodilation occurring because of chronic liver disease, portal hypertension, or congenital portosystemic shunts. Clinical implications of portal hypertension are very well-known, however, awareness of its effect on multiple organs such as the lungs are less known. The presence of HPS in chronic liver disease is associated with increased mortality. Medical therapies available for HPS have not been proven effective and definitive treatment for HPS is mainly liver transplantation (LT). LT improves mortality for patients with HPS drastically. This article provides a review on the definition, clinical presentation, diagnosis, and management of HPS.

Key Words: Hepatopulmonary syndrome; Chronic liver disease; Hypoxemia; Intrapulmonary vasodilatation; Liver failure

Core Tip: Hepatopulmonary syndrome (HPS) is a progressive disease, the presence of which in cirrhotic patients worsens their prognosis. Patients with HPS have an increase rate of mortality compared to those without HPS when matched for severity of liver disease, age, sex, and liver transplantation (LT). HPS should be identified in all patients with chronic liver disease and supportive management should be provided until definitive treatment, *e.g.*, LT could be done.

INTRODUCTION

HPS is a progressive disease associated with worsen prognosis in patients with chronic liver disease. Patients with HPS have an increase rate of mortality compared to those without HPS when matched for severity of liver disease, age, sex, and liver transplantation (LT)[1]. Hepatopulmonary syndrome (HPS) was first described in 1884 by Fluckiger based on observation in a woman with cyanosis, clubbing, and cirrhosis. Later, HPS was coined in 1977 after multiple post-mortem studies showing pulmonary vascular dilation in cirrhotic patients. These studies showed marked peripheral dilation of pulmonary arteries at precapillary and capillary levels, without any obvious lung parenchymal disease. These studies were also remarkable for multiple pleural spider naevi[2].

DEFINITION

HPS is defined as hypoxemia due to pulmonary vascular dilation in the setting of liver disease with or without portal hypertension. Definition and staging of HPS are shown in Table 1 and Table 2.

INCIDENCE/PREVALENCE

HPS has been reported in 5%-35% of patients with end-stage liver disease[3,4]. Studies have shown the presence of HPS in various liver etiologies including cirrhosis, non-cirrhotic portal fibrosis, and extra-hepatic portal vein obstruction[5,6]. Studies showed an increasing prevalence of intrapulmonary shunt in patients with increased severity of cirrhotic disease such as pretransplant patients with Child-Pugh Class C when compared with class A or B[7]. It has also been found to be associated with liver disease severity assessed by MELD score[3].

PATHOPHYSIOLOGY

Chronic liver disease can lead to hypoxemia due to a variety of underlying pathologies. Thus, it is imperative to differentiate between them. For example, HPS is caused by pulmonary vasodilation in the setting of liver disease whereas Portopulmonary hypertension, which is very similar in clinical presentation, is defined by pulmonary vasoconstriction causing hypoxemia due to resultant pulmonary hypertension.

The hypoxemia associated with HPS is secondary ventilation-perfusion mismatch caused mainly by diffusion defect in the dilated pulmonary bed: (1) Increased blood flow through the intra-pulmonary vasodilatation (IPVD) through the well-ventilated alveoli results in the passage of mixed venous blood in the pulmonary veins; and (2) Diffusion of oxygen is limited through the dilated pulmonary vessels due to their increased diameters resulting in disequilibrium. Supplemental oxygen increases the partial pressure of oxygen by providing the driving pressure for the oxygen to diffuse across the dilated vessels. Thus, IPVDs act as physiologic shunts more than anatomic shunts as oxygenation improves with external supplementation[8].

The unique pathological feature of HPS is dilatation of pulmonary precapillary and capillary vessels (15-100 μm diameter) along with an absolute increase in the number of dilated vessels. Paraumbilical vein and hepatic artery diameters are significant larger in cirrhotic patients with HPS compared to non-HPS[9]. Lungs and pleural spider nevi are the terms used when these vessels are noted in the lungs and along the pleural surface. Intrahepatic vasculature changes which were reported in HPS include thrombosis in intrahepatic portal venules, fibrous septa with vessels proliferation, and

Table 1 Hepatopulmonary syndrome definition

Index	
Oxygenation	PaO2 < 80 mmHg or A-a gradient (corrected for age) > 15 mmHg or 20 mmHg if age > 64 years while breathing room air
Intrapulmonary vasodilation	Confirmed by contrast-enhance echocardiography or lung perfusion scanning showing brain shunt fraction > 6%
Liver disease	Cirrhosis and/or portal hypertension

Table 2 Staging based on severity of hepatopulmonary syndrome

Stage	Partial pressure of oxygen (mmHg) on room air
Mild	≥ 80
Moderate	≥ 60 to < 80
Severe	≥ 50 to < 60
Very severe	< 50 on room air or < 300 while breathing 100% oxygen

centrilobular venous thickening[9]. Doppler ultrasonography in HPS reveals hepato-jugular flow and portal blood flow of less than 10 cm/s[9].

The underlying pathophysiology is not fully proven, however, is thought to be caused by loss of pulmonary capillary vessel tone and inhibition of pulmonary vasoconstrictors. Enhanced production of nitric oxide (NO) is the major factor for pulmonary vasodilatation. NO is produced by the action of NO synthase on l-arginine. NO synthase had three isoforms of which endothelial NO synthase (eNOS) produced by pulmonary endothelial cells is the major source of NO production[10].

In experimental rat models of HPS with common bile duct ligation, proliferating cholangiocytes produces endothelin-1 (ET-1) which activates pulmonary vascular endothelin-B (ETB) receptor which in turn mediates eNOS activation and pulmonary macrophages accumulation. These animal models also showed overall increased expression of ETB receptors and increased circulation of ET-1[11,12].

In humans with HPS, exhaled NO is elevated which is a result of pulmonary vascular production and it normalizes after LT[13,14]. Acute administration of methylene blue, an inhibitor of NOS, transiently improves oxygenation[15].

Bacterial translocation from the gut in the setting of portal hypertension results in pulmonary vascular macrophages has been proposed as a mechanism causing pulmonary vasodilatation[16,17]. A study shows the decrease in this bacterial translo-cation by norfloxacin and thus, decreasing the severity of HPS[18]. Heme-oxygenase-derived carbon monoxide and tumor necrosis factor-alpha are also observed to contribute to pulmonary vasodilatation and angiogenesis[19,20].

CLINICAL PRESENTATION

Dyspnea on exertion or rest is the most common presenting symptom of HPS. However, dyspnea is very non-specific given it can be present in chronic liver disease due to ascites, volume overload, anemia, or muscle weakness. The presence of platypnea and orthodeoxia are specific for HPS, but not pathognomonic. Platypnea means dyspnea in an upright position which is relieved in the supine position. Orthodeoxia refers to a decrease in partial pressure of oxygen by greater than 4 mmHg or a decrease in oxygen saturation by more than 5% from a supine to upright position [21]. Both platypnea and orthodeoxia are attributed to the ventilation-perfusion mismatch.

Physical signs such as the presence of spider nevi, clubbing, cyanosis along hypoxia are strongly suggestive of HPS. Of these signs, patients with the chronic liver disease having spider nevi have a higher prevalence of HPS compared to those without spider nevi[22].

DIAGNOSIS

Patients with chronic liver disease who has dyspnea, or signs of clubbing, cyanosis, spider nevi should undergo screening and evaluation for HPS. All patients who are candidates for LT are also screened for HPS. Evaluation of HPS includes assessment of hypoxemia and intrapulmonary vasodilation. Exhaled NO is found to be higher in HPS than non-HPS patients which may help with the diagnosis.

ASSESSMENT FOR HYPOXEMIA

Pulse oximetry is used for screening purposes in chronic liver diseases to assess for HPS. All the patients with oxygen saturation < 96% should further undergo arterial blood gas analysis (ABG) to evaluate for underlying hypoxemia[23]. ABG should be drawn in the upright position to evaluate for orthodeoxia. A-a gradient > 15 mmHg or PaO$_2$ < 80 mmHg is used for evaluation of hypoxemia. A-a gradient is more reliable than the partial pressure of oxygen as it accounts for hyperventilation, which is common in chronic liver disease[24].

The establishment of hypoxemia alone is not enough for the diagnosis of HPS, as it can be seen in other diseases such as Porto-pulmonary hypertension. Diagnosis requires confirmation of intrapulmonary vasodilation.

ASSESSMENT FOR INTRAPULMONARY VASCULAR DILATATIONS

Transthoracic contrast echocardiography (TTCE) is first-line diagnostic tool for IPVDs. IPVDs create a shut wherein 5%-6% of the cardiac output gets shunted. TTCE is performed by injecting the agitated saline into the venous system during the echocardiogram. Agitated saline leads to the formation of bubbles in the right atrium which is then filtered by the pulmonary capillary bed. Pulmonary capillary diameter varies from 8 to 15 μm which does not allow the passage of the microbubbles. The presence of intra-cardiac or intra-pulmonary shunt leads to visualization of microbubbles/contrast in the left heart chambers. The timing of the appearance of these bubbles in the left atrium varies with heart rate, cardiac output, and shunt size. With the intra-pulmonary shunt, the microbubbles or opacification of the left atrium occurs in three to six cardiac cycles after their first appearance in the right atrium. Whereas with the intra-cardiac shunt, this opacification of the left atrium is visualized within the first three cardiac cycles after its first appearance in the right atrium. Thus, TTCE is a sensitive tool for the diagnosis of pulmonary shunt[25].

Transesophageal echocardiography is a more specific alternative to TTCE, however, is generally avoided due to the high risk associated with bleeding from esophageal varices in this patient population[26].

Technetium-99m-labeled macro aggregated albumin is also filtered by the pulmonary capillary bed and can be used to measure shunt fraction by identifying its uptake in the brain and/or kidneys. Under normal circumstances, macro aggregated albumin should not pass the pulmonary capillary bed. However, in presence of right-to-left shunt, the radionuclide is taken up by the brain and kidneys and the percentage uptake can be used to quantify the shunt. In contrast to TTCE, this method does not distinguish between intra-pulmonary and intra-cardiac shunts[27].

Contrast pulmonary angiography is rarely used to visualize the IPVD due to the invasive nature of this procedure. It is generally indicated in patients with suspicion for pulmonary arteriovenous malformations, which rarely occurs in HPS[28]. Contrast-enhanced triple phase multi-detector computed tomography abdominal portosystemic shunts of more than 10 mm in diameter[9].

MANAGEMENT

LT

The only definitive management for HPS is LT. All the patients with the partial pressure of oxygen less than 60 mmHg should be evaluated for LT. Mortality is significantly higher in patients with HPS who do not undergo LT compared to those who undergo LT. A study showed 78% mortality in HPS patients who did not undergo LT compared to 21% mortality in patients who underwent LT[29]. Thus,

patients with HPS are given higher priority for liver transplants compared to other factors. LT has been shown to improve oxygenation and shunt within the first year of transplant[30,31]. A retrospective study with 74 patients showed improvement in PaO_2 from 89% to 94% and a decrease in A-a gradient from 16 to 8 mmHg after transplantation, without significant change in DLCO[32]. A study showed a 76% 5-year survival rate in HPS who underwent LT, which is similar to liver transplant patients without HPS[33].

Oxygen supplementation

All the patients with mild to moderate HPS should be evaluated every 3 to 6 mo with ABG. All patients with oxygen saturation less than 89% or partial pressure of oxygen less than 55 mmHg at rest, exercise and while sleep should be provided supplemental oxygen.

Investigational therapies

Pentoxifylline, a tumor necrosis factor-alpha inhibitor, vasodilator with anti-angiogenesis, showed variable results in oxygenation improvement in HPS[34-36]. Early-stage HPS patients seem to have a favorable outcome, while patients with advanced-stage HPS had unimproved oxygenation and difficulty tolerating pentoxi-fylline due to gastrointestinal adverse effects. Randomized placebo-controlled trial is needed to prove its result.

Garlic, has allicin which is a potent vasodilator and anti-angiogenesis. It shows significant improvement in gas exchange in small studies, which include one randomized controlled trial[37,38]. Large trials are still required to prove its benefit. Inhaled NO, a vasodilator, showed an improvement of PaO_2 in a recent physiologic study even though prior findings were contradicting[39,40]. Vascular dilatations, pulmonary capillary arteriovenous communication, and blood flow shunting in HPS are thought to be more prominent in lower lung zones due to gravitation and the vasodilators use in HPS are believed to be more potent in upper and mid lung zones. Therefore, ventilation-perfusion mismatch decreased.

Methylene blue causes vasoconstriction by inhibiting NO and may also decrease angiogenesis. It has shown some benefits in improving oxygenation; however, no randomized clinical trial is available to support its use[15]. Another agent that has been shown to reduce pulmonary NO is N(G)-nitro-L-arginine methyl ester. However, it didn't improve arterial oxygenation or ventilation-perfusion mismatch[41].

Sorafenib is a tyrosine kinase inhibitor that can reduce angiogenesis. It significantly decreased alveolar-arterial oxygen gradient in rat model but failed to show benefit in patients with HPS in a randomized-controlled trial[42]. Octreotide, a somatostatin analogue that can inhibit angiogenesis, also showed no benefit in HPS patients in few studies[43].

Mycophenolate mofetil only showed benefit in one case report[44]. Norfloxacin decreases bacterial translocation and reveals benefit in an animal study and a human case report but not in a randomized controlled trial[45]. Other medications including iloprost (vasodilator), paroxetine (NO synthase inhibitor), almitrine bismesylate (pulmonary vasoconstrictor) have been tried without any clear benefit. Letrozole is undergoing an ongoing phase two trial.

The transjugular intrahepatic portosystemic shunt has been proposed to decrease portal hypertension in HPS. A small prospective study showed improvement in gas exchanged, but limited data are available[46,47]. Few case reports regarding embolization of pulmonary vasodilatation have shown improvement in oxygen[28]. All these studies do not have clear establish benefits.

CONCLUSION

All the patients with chronic liver disease with dyspnea should be screened for HPS using ABG. There is no definitive proven treatment plan for HPS except LT. Thus, all patients with HPS should undergo expedited evaluation of LT.

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