Review

Hepatopulmonary syndrome

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Hepatopulmonary syndrome unveiled: Exploring pathogenesis, diagnostic approaches, and therapeutic strategies

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Abstract

Hepatopulmonary syndrome (HPS) is a pulmonary complication of liver cirrhosis that causes an oxygenation defect. Many patients are asymptomatic at diagnosis or may have non-specific symptoms such as dyspnea. Since the diagnostic criteria for HPS have been established, its prevalence has been better estimated. HPS is an important prognostic indicator for patients undergoing evaluation for liver transplant. The implementation of the Model for End-stage Liver Disease exception policy has improved the outcomes of HPS; however, the mortality remains high. Here, we discuss the pathophysiology, diagnostic criteria, and recent experimental studies in HPS.

Keywords: Cirrhosis; liver disease; liver transplant.

Introduction

Hepatopulmonary syndrome (HPS) is a pulmonary manifestation of liver disease characterized by pulmonary vasodilation, affecting the ventilation-perfusion ratio at the alveolar surface. Portal hypertension in patients with cirrhosis is due to increased vascular resistance in the portal circulation. This may result in an imbalance between vasodilation and vasoconstriction in the pulmonary vessels, leading to impaired oxygenation. Patients may not have respiratory symptoms, which leads to an underdiagnosis of the condition. Studies have shown that the presence of HPS increases mortality in patients with cirrhosis. A retrospective analysis conducted at a liver transplantation (LT) center revealed that individuals with HPS who did not undergo LT experienced a median survival of 24 months, with a 5-year survival rate of 23%. In comparison, control patients who did not undergo LT exhibited a median survival of 87 months, with a 5-year survival rate of 63%.[1] The prevalence of HPS has been estimated to be around 10–32% in patients with cirrhosis.[2] Before 2004, the diagnostic criteria for HPS were not well established. Specifically, the cutoff values for the alveolar-arterial gradient (A-a) and partial pressure of oxygen in the arterial blood (PaO_2) were not standardized; hence, the prevalence rates differed across multiple centers.[3] HPS can also be seen in patients with acute or chronic hepatitis without cirrhosis, as well as in the presence of portal hypertension without underlying liver disease.[4] Unfortunately, the only management for HPS is LT, and there is much need for exploration of further medical therapy. In this review, we will discuss the pathogenesis of HPS and the new experimental studies conducted to explore treatment modalities.

Pathogenesis

HPS occurs due to abnormal pulmonary microcirculation that leads to V/Q mismatch and diffusion impairment. Many experimental studies have helped to provide a better understanding of the disease process. There have been studies conducted on mice to induce cirrhosis via common bile duct (CBD) ligation and observe the development of hepatopulmonary shunts over time, which showed increased levels of vasodilatory peptides, namely nitric oxide and endothelin, in patients with HPS. Some experimental studies used mice models with portal vein ligation, which induces portal hypertension without causing cirrhosis.[5]

Endothelin-1 is a peptide produced by endothelial cells. It has been observed that its levels are elevated in patients with cirrhosis.[5] It causes vasoconstriction in the sinusoidal hepatic vasculature, resulting in portal hypertension. Experimental studies have shown that there is a selective upregulation of pulmonary endothelin-1A receptor in CBD ligation models. When endothelin-1 binds to endothelial receptors in pulmonary vessels, it causes vasodilation by activating the nitric oxide synthase pathway, and subsequently, hypoxemia worsens, and respiratory status declines over time.[6]

Patients with cirrhosis also have increased intestinal bacterial translocation due to underlying predisposing factors. The bacterial endotoxins and products are released into the bloodstream, reach the pulmonary circulation, and cause inflammation. Macrophages in pulmonary vasculature produce cytokines such as tumor necrosis factor-alpha (TNF-α) that further contribute to the inflammatory cascade.[7] In an experimental study conducted on mice models subjected to CBD ligation, the analysis revealed a significant increase in the expression of TNF-α and matrix metalloproteinase-9 (MMP-9) in the lungs compared to the control group.[8]

Pulmonary angiogenesis has also been described as a mechanism for HPS. In experimental studies, subjects with HPS have been found to have increased pulmonary expression of proangiogenic factors, including Von Willebrand Factor (vWF), endoglin, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), placental growth factors (PlGF), and others. It was observed that mice

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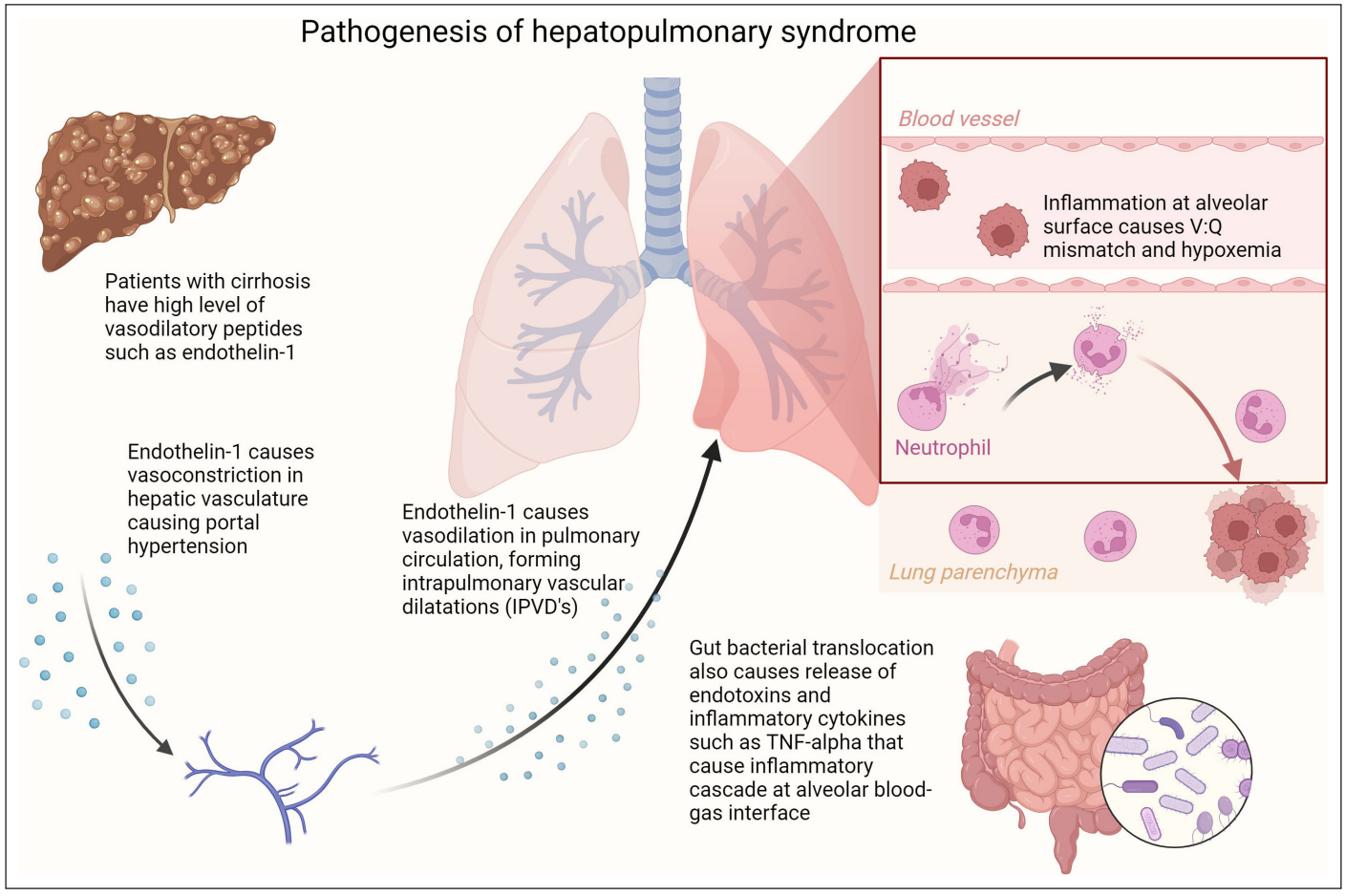

Figure 1. Understanding the pathogenesis and disease sequela of hepatopulmonary syndrome.

with CBD ligation who developed HPS had higher levels of CD68+ macrophages. In addition, activated CD68+ macrophages express nitric oxide synthase, VEGF, and PDGF, which contribute to the hemodynamic features observed in HPS (Fig. 1).[9]

Clinical Presentation

HPS stems from a right-to-left shunt phenomenon. It is most commonly seen in patients with cirrhosis and portal hypertension. However, it may occur in patients with acute hepatic inflammation, such as viral hepatitis or Budd-Chiari syndrome, as well as congenital or acquired vascular malformations. Interestingly, the presence or extent of HPS does not necessarily correlate with the severity of underlying cirrhosis or liver disease. As numerous patients with HPS may not exhibit symptoms, it is recommended to screen patients undergoing LT evaluation for HPS. A study conducted across various LT centers revealed that pulmonary vascular dilatations may be detected in as many as 80% of liver transplant candidates, even when hypoxia is not present.[10]

Pulmonary vascular dilation increases blood flow through the lungs and prevents adequate time for gas exchange to occur at the alveolar bed. Blood flow also bypasses the capillary bed due to low-resistance pulmonary vascular dilatation structures, resulting in a right-to-left shunt. The increased distance that the molecules must pass through further contributes to hypoxemia. This explains the abnormal diffusing capacity for carbon monoxide (DLCO) observed in HPS.[11]

HPS can be classified according to disease severity using PaO_2. HPS is categorized as mild with PaO_2 ≥80 mmHg, moderate when PaO_2 ≥60 and <80 mmHg, severe when PaO_2 ≥50 to <60 mmHg, and very severe when PaO_2 <50 mmHg.[3] The most common symptom observed in patients with HPS is dyspnea; however, it is a non-specific finding. Most HPS patients may also be asymptomatic, especially in the early phase of the disease. Patients may also experience orthopnea, although this symptom is rare.

The characteristic clinical signs observed in patients with HPS are platypnea (dyspnea worsening when moving from the supine to upright position) and orthodeoxia (>5% or >4 mmHg decrease in PaO_2 after changing from supine to upright position).[12] Dyspnea and clubbing are good clinical indicators in patients with HPS, with a reported positive predictive value of 75% for clubbing and negative predictive value of 75% for dyspnea.[13] Poor response to medical therapy, persistent dyspnea, and signs of cyanosis, such as digital clubbing on exam in cirrhotic patients, warrant further testing to rule out HPS.

HPS is a diagnosis of exclusion. Patients should also be assessed for underlying primary pulmonary disorders, such as chronic obstructive pulmonary disorder, asthma, or interstitial lung disease. Pulmonary function tests (PFT) are valuable in this regard. As there is no screening test, HPS is underdiagnosed in patients undergoing LT evaluation. Patients undergoing LT evaluation should be evaluated for HPS using the diagnostic criteria mentioned below.

Table 1. The severity of Hepatopulmonary syndrome (HPS) is assessed based on the levels of arterial oxygen tension (PaO_2)

Stage	PaO_2 level
Mild	PaO_2 ≥80 mm Hg with A-aO_2 ≥15 mm Hg while breathing room air.
Moderate	PaO_2 ≥60 mm Hg to <80 mm Hg with A-aO_2 ≥15 mm Hg while breathing room air.
Severe	PaO_2 ≥50 mm Hg to <60 mm Hg with A-aO_2 ≥15 mm Hg while breathing room air.
Very severe	PaO_2 <50 mm Hg with A-aO_2 ≥15 mm Hg while breathing room air Or PaO_2 <300 mm Hg while breathing 100% oxygen.

Diagnosis

The classic triad for HPS is the presence of chronic liver disease, evidence of alveolar gas exchange abnormalities, and the presence of intrapulmonary vascular dilatation. Intrapulmonary vascular dilatations (IPVD) are low-resistance vascular structures connecting the pulmonary artery to the pulmonary vein, bypassing the capillary bed where gas exchange occurs in the alveoli. Diagnostic criteria for HPS require identification of IPVD via transthoracic echocardiogram with a saline bubble study. This procedure involves the injection of a small volume of saline with microbubbles into a peripheral vein. In the absence of a shunt, these bubbles should only be observed in the right heart. Microbubbles in the left heart indicate the presence of a right-to-left shunt. The number of cardiac cycles it takes for the microbubbles to appear in the left heart helps to differentiate between intracardiac versus IPVD. The delayed appearance of microbubbles in the left heart (after three or more cardiac cycles) is diagnostic for IPVD.[14,15] The advantage of obtaining an echocardiogram is that it is a quick, minimally invasive, and inexpensive technique. Transesophageal echocardiogram may be more sensitive for identifying IPVD; however, the endoscopic procedure increases the risk of trauma-related complications and is a relative contraindication in patients with esophageal varices.[16] Pulmonary angiography helps to identify two different disease patterns of HPS. Type I, which is more commonly seen, is associated with diffuse pulmonary vasodilation, and Type II is associated with focal pulmonary intravascular dilatations. However, angiography is an invasive technique, with little impact on management, and it is not routinely performed for diagnosis.

Alveolar gas exchange impairment is defined as PaO_2 <80 mmHg or P(A-a)O_2 gradient based on the European Respiratory Task Force guidelines.[17] Arterial blood gas samples obtained in the supine position compared to sitting are more sensitive in detecting HPS.[18] PFTs show preserved Forced Expiratory Volume in one second to forced vital capacity (FEV1/FVC) ratio with decreased DLCO; however, this is nonspecific and is not diagnostic for HPS. Similarly, pulse oximetry is not a good screening tool to identify patients with ventilation/perfusion (V/Q) mismatch. There have been recent studies to identify biomarkers that help differentiate patients with cirrhosis with HPS from those without HPS. Vascular cell adhesion molecule (VCAM), von Willebrand factor (vWF), and angiotensin I levels are elevated in patients with HPS; however, none of these biomarkers have high sensitivity or specificity, which limits their utility.[19]

Portopulmonary hypertension (PPH) is another cause of hypoxemia in patients with cirrhosis. It is characterized by pulmonary arterial hypertension in the setting of portal hypertension. The diagnosis is made by an echocardiogram, followed by right heart catheterization when systolic pulmonary artery pressure is greater than 30 mmHg. The criteria for diagnosing PPH are based on evidence of pulmonary hypertension by pulmonary artery catheter measurements (mean pulmonary arterial pressure ≥25 mmHg) with a normal left ventricular end-diastolic pressure in the presence of signs of portal hypertension on ultrasound or other imaging modalities.[20] Right heart catheterization is not routinely done for the diagnosis of HPS. In cases where elevated right ventricular systolic pressure (RVSP) is observed on the transthoracic echocardiogram, it is reasonable to proceed with right heart catheterization to assess right heart pressure. This approach helps in ruling out portopulmonary hypertension (Table 1).

Management

HPS in patients with cirrhosis has been shown to worsen mortality in post-transplant patients.[1] There are no adequate pharmacological therapies for HPS, and the mainstay of treatment is LT. However, over recent years, understanding pathogenesis has tremendously helped in giving clues for potential targets for medical management. There is a need for novel pharmacological therapies for HPS to slow the progression of the disease for patients who are not candidates for LT or are awaiting LT. In rats with cirrhosis, decreasing levels of TNF-alpha has been shown to decrease the right-to-left shunt and improve hypoxemia.[21] In the setting of HPS, as there is a high level of inflammatory cells, particularly CD68+ macrophages, targeting these cells has shown improvement in experimental studies.[22] More human studies are needed to determine the efficacy of anti-inflammatory drugs such as diosmin in cirrhotic patients with HPS. An experimental study of human lung sections of 10 deceased patients with cirrhosis reported increased levels of CD68+ macrophages in autopsies.[23] However, there have been no human trials to demonstrate the efficacy of anti-inflammatory agents in HPS.

The important mechanism identified for HPS is angiogenesis. Anti-VEGF medications are another potential therapy to target pro-angiogenesis factors. A tyrosine-kinase inhibitor, sorafenib, has improved the morphological findings and symptoms of HPS in animal models.[23] However, a multicenter randomized controlled trial conducted in a small cohort of patients with HPS comparing sorafenib and placebo did not show any significant difference in the PaO_2, six-minute walk test, or symptoms. Patients in the intervention arm reported significant side effects, including diarrhea and alopecia, which caused a few patients to withdraw from the study.[24]

The current management focuses on treating the underlying hypoxemia with supplemental oxygen. As discussed above, hypoxemia is caused by right-to-left shunting, diffusion impairment, and V/Q mismatch. Supplemental 100% oxygen may correct hypoxemia in some cases where diffusion impairment is playing a major role. However, it has a minor effect in correcting hypoxemia where there is significant right-to-left shunting. Embolization of pulmonary vascular dilations can be done for palliation but does not have any mortality benefit.

Prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors have shown benefit in patients with idiopathic pulmonary hypertension and pulmonary hypertension associated with connective tissue disorders. Bosentan, a dual non-selective endothelin receptor antagonist, has shown improvement in the hemodynamic and functional capacity of patients with PPH.[25] However, these drugs have not been well studied in the HPS population.

In light of the potential involvement of TNF in the pathogenesis of HPS, pentoxifylline has been experimented on in a limited number of HPS patients. Unfortunately, the trial did not demonstrate an improvement in arterial oxygenation.[26] Moreover, the treatment was poorly tolerated, with only one patient managing to complete the study protocol, thereby complicating the interpretation of the results. Interestingly, there have also been two pilot studies that showed a positive effect of garlic on dyspnea and oxygenation in HPS patients, although the mechanism of action remains unknown. However, it is noteworthy that no randomized controlled studies involving garlic for HPS have been published.[27]

Currently, the only definitive management for HPS is LT. However, there have been studies exploring the role of transjugular intrahepatic portosystemic shunts (TIPS) procedures in HPS patients. These studies demonstrated that the procedure could reduce symptoms by increasing oxygen saturation (sO_2), decreasing the alveolar-arterial oxygen gradient ($A–aPO_2$), and redistributing blood flow. In a recent study, 81 patients with HPS underwent the TIPS procedure, and results showed that post-procedure portal vein pressure reduced significantly compared to baseline, which may potentially reverse the pathophysiology involved in HPS.[27] There is a need to explore clear guidelines or consensus regarding the optimal location for establishing the portal vein bypass–whether in the main portal vein or its branches. Currently, the clinical application of TIPS relies solely on the experience and safety considerations of the procedure.

Previously, HPS was a contraindication for LT due to perceived poor post-transplant outcomes. However, case reports and case series showed improvement in the oxygenation of patients with HPS post-LT. This led to an evolution in the LT criteria guidelines over the years. The Model for End-stage Liver Disease (MELD) exception for HPS was formally added in 2006 via the MELD Exception Study Group Conference. Interestingly, there has been no correlation noted in the degree of arterial hypoxemia and the severity of liver disease.[1] LT has been shown to improve arterial hypoxemia in patients within 6 to 12 months.[28] Patients with HPS who have hypoxemia are prioritized on the LT list, regardless of the severity of cirrhosis. This is because they are at high risk for the progression of hypoxemic respiratory failure. After the implementation of the MELD exception, data about survival rates in adult patients with HPS who underwent LT remains controversial. Patients with severe hypoxemia who have PaO_2 <50 mmHg have a high risk of complications and death post-LT.[29] A recent systematic review showed that after the implementation of the MELD exception policy for HPS, the mortality and oxygenation in patients with HPS have improved after LT.[30,31]

Conclusion

HPS is a serious complication of portal hypertension and cirrhosis. Over the past decade, numerous experimental studies have been conducted, contributing significantly to our understanding of the pathogenesis of HPS. The standardization of diagnostic criteria aided in identifying more patients with HPS, as many patients are asymptomatic. Screening LT candidates for the presence of HPS using the established diagnostic criteria is critical. There is a need for large-scale studies at multiple LT centers to establish the prevalence of the condition. Currently, LT is the only intervention that has been shown to improve outcomes in patients with HPS. There are several experimental studies underway in the hope of identifying medical therapy for HPS, which may provide a therapeutic bridge for patients who are awaiting LT. More prospective studies comparing the survival and quality of life outcomes in pre-transplant and post-transplant patients are needed to help identify high-risk HPS patients who should be prioritized on the LT list.

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