

Hepatopulmonary Syndrome: An Overview

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ABSTRACT

The hepatopulmonary syndrome is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the setting of liver disease. This clinical syndrome has three components: liver disease, pulmonary vascular dilatation, and a defect in oxygenation. Its occurrence has been described in up to 32% of cirrhotic candidates for liver transplantation. The key event in its pathogenesis is the development of intrapulmonary vascular dilatation (IPVD). Even though the clinical symptoms used to identify HPS seem obvious, there is no consensus on strict definitions for each diagnostic criterion. Liver transplantation is considered to be the definitive treatment of hepatopulmonary syndrome with often successful reversal of hypoxemia, however other treatments have been tested. The aim of this review was to review the pathogenesis, current diagnostic criteria and treatment of hepatopulmonary syndrome.

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Key words: Cirrhosis; Hepatopulmonary syndrome; Intrapulmonary vascular dilatation; Liver transplantation

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DEFINITION

The hepatopulmonary syndrome (HPS) is characterized by an oxygenation defect induced by pulmonary vascular dilatation in the setting of liver cirrhosis or portal hypertension. The clinical of HPS is characterized by triad of an oxygenation defect, intrapulmonary

vascular dilatation (IPVD), and liver disease. The oxygenation defect involves a widened age-corrected alveolar-arterial oxygen gradient ($P[A-a]O_2$) on room air, with or without hypoxemia^[1]. The oxygenation defect in HPS is defined as $P[A-a]O_2 \geq 15$ mm Hg while breathing room air, at sea level. For individuals older than 65 years, $P[A-a]O_2 \geq 20$ mm Hg is considered abnormal. Calculation of $P[A-a]O_2$ is one of the most sensitive approaches for the detection of early arterial deoxygenation because $P[A-a]O_2$ can increase before arterial oxygen tension (PaO_2) itself becomes abnormally low^[1].

PATHOGENESIS

The most common hepatic disorder leading to HPS is liver cirrhosis, irrespective of etiology. However, HPS may also present in patients in the absence of portal hypertension (acute and chronic hepatitis) or portal hypertension without cirrhosis (nodular regenerative hyperplasia, congenital hepatic fibrosis)^[2].

The key event in the pathogenesis of HPS is believed to involve a number of factors. Together, these factors lead to IPVD and oxygenation abnormalities in patients with liver disease (liver cirrhosis and portal hypertension)^[3,4]. A potent vasodilator, nitric oxide (NO), has been linked to these vascular changes because increased intrapulmonary levels of NO were seen in cirrhotic patients with HPS^[5]. There has also been documentation of subsequent normalization of NO levels after liver transplantation (LT), accompanied by resolution of HPS^[6]. Imbalance in the endothelin receptor response, pulmonary microvascular remodelling, and genetic predisposition is thought to lead to IPVD^[7]. In cases of liver cirrhosis there was an increase in endotoxin levels in the plasma, and the number of Gram-negative colonies in the mesenteric lymph nodes was closely associated with increased plasma levels of ET-1, NO and TNF- α , as well as rises in NO and ET-1 levels in the lung homogenate. This suggests that this organ may also be a source of ET-1, along with the liver, or that intestinal endotoxemia may irritate the Kupffer cells that release TNF- α , thereby either directly or indirectly inducing the production of ET-1^[8].

Experimental findings regarding the roles of ET-1, TNF- α and intestinal endotoxemia in the development of IPVD in the pulmonary microvasculature may contribute towards understanding the physiopathology of HPS in humans and allow the use of new treatments in the future^[1,4].

The major defect that underlies HPS is hypoxemia secondary to IPVD associated with pulmonary AVS (pulmonary arteriovenous shunting). AVS occurs through the dilated pulmonary capillaries^[9]. Hypoxia occurs as a result of inability of oxygen to diffuse through the markedly dilated lung capillaries. The unique striking pathological feature of hepatopulmonary syndrome is gross dilatation of the pulmonary precapillary and capillary vessels to 15 to 100 μm in diameter when the patient is at rest ($n=8-15 \mu\text{m}$), coupled with an absolute increase in the number of dilated vessels visualized by means of injection at autopsy^[10]. Pleural spider nevi also contribute to AVS^[11]. Capillary vasodilatation is most pronounced at the lung bases; thus, explaining orthodeoxia and platypnea associated with HPS. Pulmonary vasodilatation leads to increased pulmonary blood flow and an increase in cardiac output; an event that causes elevated perfusion ventilation mismatch (VQ mismatch) and AV shunts^[12,13]. VQ mismatch appears to be a major event in the pathogenesis of hypoxemia in HPS as a result of extensive pulmonary vasodilatation, a decrease in V/Q ratio in alveolar-capillary units and resultant low PO_2 and O_2 content of blood leaving the lungs. Air trapping and poor ventilation in dependent parts of the lungs may present clinically as closing volume exceeding functional residual capacity. Decreased ventilation from air trapping leads to further V/Q mismatched in the dependent parts of the lungs. Lowered V/Q ratio results in elevated $\Delta(A-a) \text{O}_2$ correctable only by 100% oxygen inhalation. However hypoxemia caused by larger AV shunts does not respond to inhalation of 100% oxygen. A significant proportion of patients with HPS and advanced liver disease show diffusion impairment associated with decreased DLCO without concomitant increase of $\Delta(A-a) \text{O}_2$. This phenomenon explains the higher sensitivity of DLCO over $\Delta(A-a) \text{O}_2$ in the detection of pulmonary vasodilatation^[14-16].

NATURAL HISTORY

Data from liver-transplantation centers indicate that the prevalence of the hepatopulmonary syndrome, including that involving mild stages, ranges from 5 to 32%^[17]. The prognosis associated with HPS is poor. A prospective study of 27 patients with HPS showed that the presence of HPS is a major independent risk factor for the survival of patients with cirrhosis^[18]. In this study the median survival time in cirrhotic patients with HPS was 10.6 months compared to 40.8 months in cirrhotic patients without HPS. At an observation period of 2.5 years the mortality rate for HPS patients was approximately 63%. The leading cause of death was hemorrhagic shock secondary to gastrointestinal bleeding. In a retrospective study of 22 patients with HPS, the mortality rate was 41% after a mean time of 2.5 years after diagnosis^[19]. The degree of arterial hypoxemia appears to influence survival. Swanson and colleagues demonstrated in a case-control study involving 61 HPS patients that long-term survival for HPS patients is worse in the subgroup with lower baseline PaO_2 ($\leq 50 \text{ mmHg}$)^[20]. The majority of patients with HPS develop progressive IPVD and worsening gas exchange over time, and spontaneous improvement is rare. The PaO_2 declined in 85% of patients over time, with an average decline of 5 mm Hg per year in a small cohort study of HPS patients^[20]. HPS is associated with an increase risk of death, worse functional status, and quality of life in patients evaluated for OLT^[21].

CLINICAL PRESENTATION

The clinical features of HPS are typically pulmonary manifestations. Dyspnea is the most common complaint and can be insidious in presentation. Platypnea defined as dyspnea exacerbated by sitting

up and improved with lying down is a clinical feature of HPS. Orthodeoxia, defined as arterial deoxygenation accentuated in the upright position versus the supine position often accompanies platypnea and is highly specific for HPS in the context of chronic liver disease^[22]. Both of these clinical features are attributed to the predominance of the IPVD in the lung bases and the increased blood flow through these regions when assuming the upright position^[23]. However, dyspnea is a nonspecific finding that is common in patients with advanced liver diseases because of the range of hepatic complications such as anemia, ascites, fluid retention and muscle wasting. There are no signs, symptoms, or hallmarks of the hepatopulmonary syndrome on physical examination. However, the presence of spider nevi, digital clubbing, cyanosis, and severe hypoxemia (partial pressure of oxygen, $<60 \text{ mm Hg}$) strongly suggests hepatopulmonary syndrome^[1].

DIAGNOSIS

Exclusion of other contributing cardiopulmonary causes such as pulmonary atelectasis, ascites, chronic obstructive pulmonary disease, and hepatic hydrothorax is mandatory when evaluate hypoxemic cirrhotic patient. A careful history and physical examination aids in the consideration of alternative diagnoses of Dyspnea. A definitive diagnosis of HPS can be made by demonstration of pulmonary vasodilatation associated with functional arteriovenous shunting. The most common tools are contrast echocardiography and technetium-99m-labelled (99mTc) macroaggregated albumin perfusion scanning. Contrast echocardiography is the most sensitive test to demonstrate intrapulmonary shunting. It is done using intravenous injections of agitated saline or indocyanine green to produced bubbles of at least 15 microns in diameter. Normally these microbubbles are trapped in the pulmonary vasculature and absorbed. In intracardiac right to left shunts, these microbubbles are seen in the left heart within the first three cardiac cycles^[24]. In hepatopulmonary syndrome, because of intrapulmonary shunting, the bubbles are seen in the left heart after the third heart beat, usually between the third and sixth heart beat. Studies have shown that transesophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting^[25]. Contrast echocardiography is the preferred method for diagnosing IPVD because of its greater sensitivity, in comparison with 99mTcMAA, and its ability to rule out intra-heart communication^[26], which is responsible for false-positive results^[27]. In normal situations, the contrast particles, which vary in diameter depending on the type of contrast used, are impacted in pulmonary capillaries of normal diameter. They are then physiologically absorbed by the alveoli and do not appear in the left atrium^[1].

There are however a number of limitations of contrast-enhanced echocardiography. It cannot quantify the shunting. It cannot differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication. Although contrast echocardiography is highly sensitive for HPS, it lacks specificity^[28]. In patients with concomitant intrinsic lung diseases, contrast echocardiography is a less useful investigation to detect HPS.

To overcome the disadvantages of low specificity of contrast echocardiography, 99mTechnetium macroaggregated albumin (Tc-99m MAA) lung perfusion scan is used. Under normal conditions, 99mTc albumin macroaggregates that exceed 20 μm in diameter are almost completely trapped in the pulmonary circulation. In the presence of a cardiac right to left shunt or intrapulmonary vascular dilatation the uptake of 99mTc macroaggregated albumin can be documented in other organs such as the brain or the spleen. This

technique has been used for the diagnosis of hepatopulmonary syndrome and for the quantification of the magnitude of shunting^[29].

The majority of studies suggest that arterial gas analysis is essential, beginning at the first consultation for cirrhotic patients who are candidates for liver transplantation. Furthermore, arterial blood analysis is recommended as a screening test for investigating HPS, which should be pursued in cases with high P[A-a]O₂ or hypoxemia^[30,31]. P[A-a]O₂, in which PaCO₂ is included as a component, has proven to be more sensitive than PaO₂ alone for diagnosing HPS^[1,32]. After the management guidelines for HPS were published, in which P[A-a]O₂ ≥ 15 mmHg in liver disease patients with IPVD was deemed sufficient for confirmation of HPS, it was suggested that PaO₂ should no longer be a separate diagnostic criterion and should also become part of the classification of the syndrome, with prognostic significance^[1,33]. HPS may therefore be classified as mild in cases of PaO₂ ≥ 80 mmHg, moderate in cases of PaO₂ < 80 mmHg or ≥ 60 mmHg, severe in cases of PaO₂ < 60 mmHg or ≥ 50 mmHg and very severe in cases of PaO₂ < 50 mmHg^[1].

Pulmonary angiography is an invasive procedure that can delineate the appearance of the pulmonary vasculature. It is reserved for those patients who have a poor response to 100% oxygen, demonstrated by an increase in the PaO₂ to less than 300 mmHg^[34]. Pulmonary angiographic study in HPS patients demonstrated two angiographic patterns: type I, or diffuse, and type II, or focal^[35]. The type I pattern was subdivided into a "minimal" pattern, characterized by normal vessels or fine diffuse spidery arterial vascular abnormalities, and an "advanced" pattern, with a diffuse spongy or blotchy appearance. The type II pattern, more infrequent, consisted of focal arteriovenous communications. Patients with "advanced" type I and type II patterns may exhibit a poor response to oxygen breathing (Pa,O₂ < 300 mmHg). Under these circumstances, the latter subset of patients may be considered for vascular embolisation, as type II lesions are not reversible and the patients may be at risk of cerebral embolism and/or abscess^[34,36,37]. Type I lesions can also be successfully embolised with subsequent marked increases in Pa,O₂, as shown in a case report^[38].

Two newer diagnostic modalities for assessing HPS are high-resolution chest computerized tomography (CT) and evaluation of pulmonary blood transit time. The degree of pulmonary microvascular dilation observed on chest CT shows good correlation with the severity of gas exchange abnormalities in patients with HPS. It also helps in quantification of intrapulmonary vasodilatation^[39].

Pulmonary transit time of erythrocytes, by using echocardiographic analysis of human serum albumin air microbubble complexes, also correlated with gas exchange abnormalities in a small group of patients with HPS^[40]. These two modalities should be tested further in large-scale studies to explore their potential in diagnosis of HPS.

TREATMENT

Currently, no effective medical therapies for the hepatopulmonary syndrome exist, and liver transplantation is the only successful treatment^[41]. Theoretically, the ideal treatment of hepatopulmonary syndrome would consist of a drug or any other means to reverse intrapulmonary vascular dilatation. Unfortunately, this therapeutic goal cannot be fully achieved in most patients with currently available treatments. Increased production of nitric oxide is a potential target, but this approach has not been established as routine. Diets containing low amounts of L arginine, the substrate of nitric oxide synthase have provided no long standing benefit. Intravenous infusion of methylene blue, an inhibitor of guanylate

cyclase, which mediates the intracellular effects of nitric oxide, causes pulmonary vasoconstriction and reduction of hypoxaemia in patients with hepatopulmonary syndrome^[42]. Reduction of the portal pressure seems to be an effective approach, which is supported by several reports of transjugular portosystemic shunting that have led to the correction of hypoxaemia although this procedure might not be successful in all patients^[43-46].

Novel treatment options are being explored and include antibiotics that aim to reduce enteral bacteria translocation. Experimental models in common-bile-duct-ligated rats suggest that the use of antibiotics to decrease bacterial translocation in the bowel is effective in preventing the development of hepatopulmonary syndrome^[47]. Several therapeutic trials in HPS have shown poor results such as somatostatin analogues, cyclooxygenase inhibitors, and immunosuppressive agents such as corticosteroids and cyclophosphamide^[48]. Almitrine bismesylate a selective pulmonary vasoconstrictor has achieved anecdotal success^[49]. Inhaled prostanoid iloprost could improve quality of life in patients with HPS waiting for (orthotopic liver transplantation) and post-surgery until the resolution of the hypoxemia^[50]. A small study using garlic powder capsules (*Allium sativum*) daily for a minimum of 6 months resulted in a modest improvement in arterial oxygenation in 6 out of 15 patients with HPS^[51]. The only definitive treatment for HPS is orthotopic liver transplantation. The data to support this is incontrovertible although the mechanism of how the pulmonary vasculature is remodeled after transplantation is not clearly understood. What is known is that at least 85% of all cases of patients with HPS undergoing liver transplantation experience either significant improvement or complete resolution in hypoxemia^[52]. This resolution however may take time and in some cases. It may take over a year^[53]. Unfortunately the mortality after liver transplantation is significantly increased in HPS patients with a 1-year survival rate of 71% noted in one cohort study^[54]. Survival is worse for those patients with more severe hypoxemia and significant intrapulmonary shunting. The understanding that orthotopic liver transplantation provides the best and often completed management of HPS has revolutionized the therapeutic approach to this unique disease entity. No longer is hypoxemia in such patients considered a relative contraindication for transplantation. In fact the degree of hypoxemia is considered critical in the consideration for liver transplantation. The ERS Task Force on Pulmonary-Hepatic Vascular Disorders recommends as a firm indication for orthotopic liver transplantation if PaO₂ ≥ 50- < 60 mmHg and consideration of orthotopic liver transplantation on an individual basis if PaO₂ < 50 mmHg^[1].

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