Recent Advances in Hepatopulmonary Syndrome

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Hepatopulmonary syndrome is defined as the clinical triad of advanced liver disease, arterial deoxygenation and intrapulmonary vascular dilatation. Its pathogenesis is not completely understood. Excessive pulmonary nitric oxide production seems to be one of the factors that contribute to the intrapulmonary vascular dilatation. Other mediators such as endothelin-1 and the heme oxygenase-1/carbon monoxide system have recently been found to be important contributors. The major clinical manifestations are arterial hypoxemia, clubbed fingers and spider nevi. Orthodeoxia is the characteristic clinical feature. Contrast-enhanced echocardiography is the preferred screening test. 99mTechnetium macroaggregated albumin (Tc-99m MAA) lung perfusion scan can further specify the diagnosis of hepatopulmonary syndrome and quantify the magnitude of shunting. No clearly effective medical treatments have been found. Although liver transplantation seems feasible to reverse this situation, it is associated with increased postoperative morbidity and mortality. A preoperative arterial oxygen tension of 50 mmHg or less and Tc-99m MAA shunt fractions of 20% or more are strong predictors of postoperative mortality that can be used to stratify patients with better outcome. [J Chin Med Assoc 2005;68(11):500–505]

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Introduction

Hypoxemia is a common clinical manifestation in patients with liver cirrhosis. It may result from the common cardiopulmonary diseases such as pneumonia, chronic obstructive pulmonary disease, congestive heart failure and pulmonary edema. A relationship between cirrhotic liver and lung was first described by Fluckiger1 in 1884 based on the observation of a woman with cirrhosis, cyanosis and clubbed digits. Several authors have since confirmed this finding. In 1977, Kennedy and Knudson coined the term “hepatopulmonary syndrome” to describe this entity.2 This article reviews the clinical features as well as the current understanding of the pathogenesis and clinical management of hepatopulmonary syndrome.

Definition and Demographics

Hepatopulmonary syndrome (HPS) is characterized by the triad of advanced liver disease, arterial hypoxemia (arterial oxygen tension, PaO2 < 70 mmHg or alveolar-arterial oxygen gradient > 20 mmHg at room air), and intrapulmonary vascular dilatation.3–5 The prevalence in the setting of cirrhosis ranges from 4% to 17%.6–8 The correlation between the severity of liver disease and the existence of HPS remains controversial. One prevailing concept is that the development of intrapulmonary vascular dilatation is related to the progression of liver dysfunction and correlates with systemic vasodilatation and hyperdynamic circulation.9 In a prospective study, Vachiery et al10 suggested that cirrhotic patients with HPS were characterized by a higher Child-Pugh’s score and a higher hepatic venous
pressure gradient. However, other studies did not support this finding. There may be factors other than the severity of liver disease that are important for the development of HPS.

Pathogenesis

The exact pathogenesis of HPS is not completely understood. Common bile duct ligation (CBDL) in rat is the only recognized model for the study of HPS. It is interesting to note that in the animal model of partial portal vein ligation (a model of portal hypertension but without cirrhosis), in which the rats develop a similar degree of portal hypertension and hyperdynamic circulation as CBDL rats, there is no detectable alteration of the pulmonary vasculature. Therefore, it is possible that both hepatic injury and portal hypertension are required for the development of HPS.

Castro and Krowka proposed that an imbalance between vasoconstrictors and vasodilators in the pulmonary vasculature contributed to the pathogenesis of HPS. The most extensively investigated vasodilator is nitric oxide (NO). Increased levels of exhaled nitrite and nitrate, the metabolites of NO, are found in patients with HPS; levels return to normal after liver transplantation, with normalization of oxygen saturation. In rats that develop HPS, the level of endothelial NO synthase (eNOS) protein is increased in the region of pulmonary small alveolar vessels, and there is an increase in basal NOS activity. An NO-mediated decreased response to vasoconstrictors in the intralobar pulmonary arteries has also been observed. Moreover, there is a positive correlation between the extent of the increase in pulmonary eNOS expression and the severity of gas exchange abnormalities in HPS. Even though no significant change in the level of inducible NO synthase (iNOS) has been found, there might be a slight, difficult-to-detect, increase in iNOS level. The role of iNOS in HPS cannot be completely ruled out.

In addition to NO, other vasoactive substances have also been suggested to play a role in the development of HPS. Increased hepatic expression and plasma levels of endothelin-1 (ET-1) have been observed in both experimental and human cirrhosis. Luo et al reported that increased ET-1 production correlated with intrapulmonary molecular and gas exchange abnormalities, and suggested that ET-1 may contribute to the pathogenesis of HPS. Thereafter, the same group of investigators also found increased endothelin B (ET\textsubscript{B}) receptor expression in the pulmonary vasculature from cirrhotic animals. It is known that ET-1 may exert an autocrine vasodilatory effect by increasing eNOS activity and subsequent NO production via the ET\textsubscript{B} receptors on vascular endothelial cells. Accordingly, Luo et al suggested that, in response to the increased circulating ET-1 level in cirrhosis, an increase in pulmonary vascular ET\textsubscript{B} receptors may result in increased eNOS activity and NO production, with subsequent intrapulmonary vasodilatation. The factors that contribute to increased ET\textsubscript{B} receptor expression in pulmonary vasculature in cirrhotics have not been completely established. Hyperdynamic circulation-related increase in pulmonary blood flow with a flow-mediated alteration in vascular ET\textsubscript{B} receptor expression may play a role. Other factors such as increased cytokine production, particularly of interleukin-1β, and hypoxia that are known to alter in cirrhosis may also modulate intrapulmonary ET\textsubscript{B} receptor expression.

Carbon monoxide (CO) is another vasoactive substance that has recently been evaluated for its role in the pathogenesis of HPS. CO can cause vasodilatation by the cyclic guanosine monophosphate (cGMP) independent pathway, possibly by directly activating K\textsubscript{Ca} channels. CO is generated during the degradation of heme by heme oxygenase (HO), which has constitutive and inducible isoforms. HO-1 is an inducible protein that is expressed in a number of cell types in the lung, most notably alveolar, bronchial epithelium and inflammatory cells, including macrophages. Increased NO production in cirrhosis has been shown to induce upregulation of intrapulmonary HO-1 expression, which may be involved in the pathogenesis of HPS. Zhang et al reported that increased CO production induced by pulmonary HO-1 overexpression in cirrhotic rats may contribute to the progression of HPS. They also suggested that the increase in pulmonary HO-1 protein may be caused by the accumulation of intravascular macrophages in the early stage after bile duct ligation when cirrhosis and hemodynamic changes have not completely developed. Thereafter, increased CO production can be observed with the development of HPS to worsen gas exchange. However, the mechanism of macrophage accumulation in the pulmonary vasculature is not understood. Increased circulating tumor necrosis factor α may be an important triggering factor.

Clinical Manifestations

Since intrapulmonary vascular dilatation leads to ventilation-perfusion mismatch, the major clinical manifestation of HPS is impaired oxygenation, which
varies from a mild increase in the alveolar-arterial oxygen gradient to severe arterial hypoxemia. As the vascular abnormalities predominate in the middle to lower lung fields,\textsuperscript{34} gravitational effects may increase the blood flow to worsen the ventilation-perfusion mismatch and, finally, result in a deterioration in arterial oxygenation when in the upright position.\textsuperscript{34} Orthodeoxia, defined as arterial deoxygenation accentuated in the upright position versus the supine position, is a characteristic feature of HPS. A cutoff value for orthodeoxia is defined by a $\text{PaO}_2$ decrease of 5% or more, or 4 mmHg or more from the supine to upright position.\textsuperscript{34} Its reported prevalence ranges from 20% to 80% in patients with HPS.\textsuperscript{12,35} Krowka and Cortese\textsuperscript{36} found that the mean drop in $\text{PaO}_2$ was 12 mmHg when patients stood from the supine position.

Clubbed fingers are common, and the presence of spider nevi has been suggested as one of the most sensitive clinical markers. In cirrhotic patients with portal hypertension, spider nevi, clubbed fingers and hypoxemia are highly suggestive of HPS.

**Diagnosis**

Several causes other than HPS may be involved in cirrhosis presenting with hypoxemia, such as intrinsic cardiopulmonary abnormalities, pulmonary atelectasis, pneumonia, ascites, pulmonary edema or hepatic hydrothorax. In cirrhotic patients with clinical symptoms and arterial blood gas compatible with hypoxemia, a chest film must first be taken to rule out reversible conditions. Pulmonary function test should be performed to rule out the common intrinsic pulmonary disorders such as chronic obstructive pulmonary disease. HPS should be suspected in patients who have persistent hypoxia after a normal chest film or after optimal treatment of the underlying conditions.

Contrast enhanced echocardiography is the preferred screening test for HPS.\textsuperscript{3,8} It uses agitated saline or indocyanine green to produce microbubbles at least 15 $\mu$m in diameter that are then injected intravenously. Under normal circumstances, these microbubbles are trapped in the pulmonary microvasculature and then absorbed. In patients with intracardiac or intrapulmonary shunts, these microbubbles are seen in the left heart. Differentiation between intracardiac and intrapulmonary shunting is based on the timing of when these bubbles are found in the left heart. In intracardiac right-to-left shunts, these bubbles appear in the left heart in 10 heartbeats after they appear in the right heart. In intrapulmonary shunts, these bubbles appear in 4–6 heartbeats. A recent study by Vedrinne et al\textsuperscript{17} revealed that transesophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting. However, there are several shortcomings of contrast enhanced echocardiography. First, it cannot quantify the shunting. Second, it cannot differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication. Third, even though contrast echocardiography is highly sensitive for HPS, it lacks specificity. A proportion of cirrhotic patients with positive results on contrast echocardiography have normal arterial blood gas and do not fulfill the diagnostic criteria for HPS.\textsuperscript{8,37} Lastly, in patients with concomitant intrinsic lung diseases, the contribution of HPS to arterial desaturation cannot be defined by contrast echocardiography.

In order to overcome the disadvantages of contrast echocardiography, the role of $^{99m}$technetium macroaggregated albumin (Tc-99m MAA) lung perfusion scan in diagnosing HPS was assessed. The albumin macroaggregates are more than 20 $\mu$m in diameter. Under normal circumstances, they are entrapped in the pulmonary vasculature. In patients with intracardiac or intrapulmonary shunts, these albumin macroaggregates can escape the pulmonary vasculature and be taken up by other organs. In normal healthy patients, less than 5% of isotope can be quantified in the brain. In HPS patients, the fraction is more than 6%. In a cohort study, Tc-99m MAA lung perfusion scan identified all cirrhotic patients with HPS who presented with moderate to severe hypoxemia, and yielded negative results in those without HPS and in all non-cirrhotic hypoxic patients with intrinsic lung disease.\textsuperscript{11} Accordingly, Tc-99m MAA scan may be useful for the diagnosis of HPS. In cirrhotic patients with concomitant intrinsic pulmonary disorders, the fraction of Tc-99m MAA scan can define the significance of the HPS in clinical hypoxemia. That study also showed an inverse correlation between the magnitude of the shunt fraction and arterial oxygen saturation. The major disadvantage of Tc-99m MAA scan is that it cannot differentiate intracardiac from intrapulmonary shunting. The shunt fraction of Tc-99m MAA scan also does not correlate with the response of $\text{PaO}_2$ after 100% oxygen is supplied.

Pulmonary angiography is an invasive procedure that can show the appearance of the pulmonary vasculature. A pulmonary arteriography study in patients with HPS revealed 2 vascular patterns,\textsuperscript{36} the type I or diffuse pattern and the type II or focal pattern. The minimal diffuse type I pattern is characterized by the presence of normal vessels or
finely diffuse spidery vascular abnormalities. The advanced type I pattern is characterized by a diffuse spongy or blotchy appearance. The type II pattern is a less frequent finding. Patients with advanced type I or type II patterns show a poor response to 100% oxygen. Due to the focal involvement of the pulmonary vasculature and poor treatment response, patients with a type II pattern should be considered for embolization therapy. Pulmonary angiography should, because of its invasiveness, only be reserved for patients with HPS who respond poorly to 100% inspired oxygen and in whom vascular embolotherapy can be performed at the same time to obliterate the arteriovenous communications.

### Treatment and Prognosis

As the major clinical manifestation of HPS is arterial hypoxemia, supplying oxygen is the first line of therapy. Similar to oxygen therapy in patients with chronic obstructive pulmonary disease, long-term oxygen supply prolongs survival in patients with HPS. In patients with poor response to 100% oxygen, pulmonary angiography with embolization therapy is an alternative.

Several medical treatments including almitrine bismesylate, indomethacin, tamoxifen, somatostatin analogues, sympathomimetics, β-blockers, methylene blue and plasma exchange have been used in the treatment of HPS with disappointing results. In a retrospective analysis in 22 patients with HPS, the mortality rate was approximately 41% after a mean follow-up of 2.5 years. A prospective study on the prognostic significance of HPS showed that HPS is an independent predictor of survival, and mortality correlates with HPS severity. As the presence of HPS independently worsens the prognosis of cirrhotic patients, its presence should influence clinical management. If patients are on the waiting list for liver transplantation, the presence of HPS should be combined with the MELD (model for end-stage liver disease) score to accelerate the process for liver transplantation.

A retrospective study by Krowka et al. reported an improvement or normalization of hypoxemia in about 80% of patients after liver transplantation. A prospective study by Battaglia et al. also demonstrated resolution of intrapulmonary shunting in patients with HPS after liver transplantation. It is thus considered that HPS may be reversed after liver transplantation. The pulmonary vascular changes after successful transplantation show a slow remodeling process that may take a long time for symptom relief. It has been found that the lower the preoperative PaO2, the longer the time to decrease the alveolar-arterial pressure gradient and to improve arterial oxygenation. However, retrospective data show that there is a higher mortality rate after liver transplantation in patients with HPS than in those without HPS. Unique postoperative complications in patients with HPS have been described, which include pulmonary hypertension, embolic cerebral hemorrhage and postoperative deterioration in oxygenation. These unique postoperative complications, along with delayed resolution of hypoxemia, are implicated in the higher mortality rate. For patients with severe preoperative hypoxemia (PaO2 ≤ 50 mmHg) and significant intrapulmonary shunting (Tc-99m MAA shunt fraction ≥ 20%), the mortality rate may increase further after liver transplantation.

### References

1. Fluckiger M. Vorkommen von trommelschlägelförmigen fingerendphalangen ohne chronische veränderungen an der lungen oder am herzen. Wien Med Wschr 1884;34:1457.


