CHAPTER

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Hepatopulmonary Syndrome: A Clinical View

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Introduction

In 1884 Flückiger first described a woman with liver cirrhosis, cyanosis, and digital clubbing.[1] The term 'hepatopulmonary syndrome', the triad of liver disease, an increased alveolar-arterial gradient while breathing room air, and evidence of intrapulmonary vascular dilatations, was coined in 1977 by Kennedy and Knudson.[2] These vascular abnormalities predominate in the lower lung fields. As gravity induces increased blood flow to the lower lung fields hypoxemia is increased when changing from supine to upright position. Mild hypoxemia occurs in approximately one third of all patients with chronic liver disease and often is multifactorial,[3,4] because other cardiopulmonary abnormalities (e.g., pleural effusion, ascites) are common in these patients and may coexist with HPS. The special qualities of HPS are platypnea,[5] defined as dyspnea induced by the upright position and relieved by recumbency and orthodeoxia,[6] defined as arterial deoxygenation induced by the upright position and relieved by recumbency. Although these phenomena are not pathognomonic for HPS, they strongly suggest this diagnosis in the setting of liver dysfunction.[7]

Definition

HPS is a disease process with a triad of:

1. Liver disease / Portal hypertension.
2. Widespread intrapulmonary vasodilatation.
3. Gas exchange abnormality presenting with increased alveolar arterial oxygen gradient (ΔP (A-a)O2) while breathing room air, that results ultimately in hypoxemia.

The most common liver disease responsible for HPS is liver cirrhosis. Other liver diseases may contribute like Non cirrhotic portal hypertension, Extrahepatic portal vein obstruction, Chronic active hepatitis, Fulminant hepatic failure.

Prevalence

Studies on HPS report a wide range of prevalence of the disease which can be due to different patient groups and study designs. Usually it is reported to be between 9 and 29% of patients with liver disease.

Pathophysiology

Vasodilatation

Imbalance of vasodilator and vasoconstrictor agents favoring vasodilators. This could be due to Overproduction of the vasodilators from injured hepatobiliary system, Decrease in their clearance by the liver, Production of a vasoconstrictor inhibitor or Normal sensitivity of the pulmonary vessels to vasoconstrictors in response to hypoxemia is blunted in HPS. Numerous vasodilators are suspected but

nitric oxide (NO) is the most appreciated one. Other mediators include vaso-active intestinal peptide (VIP), calcitonin related peptide, glucagon, substance P and platelet activating factor.

Hypoxemia

The main pathophysiologic event underlying hypoxemia is widespread pulmonary precapillary and capillary vasodilatation. Pulmonary capillary diameter is normally about 8-15 micrometer (μm) and this could rise up to 500 μm in HPS. In addition, there is distinct arterio-venous (AV) malformations and direct AV communications. Pleural *spider angiomas* may also form. These changes lead to the following:

a. Ventilation perfusion (V/Q) mismatch: This hypoxemia is correctable by breathing 100% oxygen.

b. Right to left shunting of the blood: If numerous, they can give rise to severe hypoxemia unresponsive to breathing 100% oxygen.

c. Diffusion impairment: Excessive vasodilatation causes O_2 molecules not to reach the center of dilated capillaries readily. Increased cardiac out put and decreased transition time of blood through pulmonary vascular bed on the other hand impairs diffusion, this is called *diffusion-perfusion defect* or *alveolar capillary oxygen disequilibrium*.

d. Response to breathing 100% O_2: In response to breathing 100% oxygen if PaO_2 rose to levels ≥ 600 mmHg, shunting of blood is unlikely. If it failed to exceed 500 mmHg, shunt can't be ruled out and if it didn't rise to levels above 150-200 mmHg, shunt is most probably the main mechanism of hypoxemia.

Clinical Manifestations

Three Cs are important in the diagnosis of hepatopulmonary syndrome, these are cirrhosis, clubbing and cyanosis. More than 80% of patients present with symptoms and signs of liver disease. In less than 20%, the presenting symptoms and signs are related to lung disease. These include dyspnea, cyanosis, clubbing, platypnea and orthodeoxia. There is controversy on a correlation between the severity of liver disease and HPS. Some studies have shown that the severer the liver disease the severer the HPS, but others have failed to show so. Mortality is high among HPS patients and is reported to be around 40% within 2-3 years after presentation. Curious enough, the causes of mortality are most commonly non respiratory (e.g., GI bleeding, sepsis, renal failure).

Diagnosis

Diagnostic criteria for HPS are

1. Liver disease/ Portal hypertension, and
2. Gas exchange abnormality manifested by hypoxemia ($PaO_2 < 70$ mmHg) and/or ΔP (A-a) O2 > 20 mmHg due to widespread intrapulmonary vasodilatation, in the absence of any primary cardiopulmonary disease.

Diagnostic Procedures

a. Arterial blood gas analysis: Performed in the supine and sitting positions. Orthodeoxia

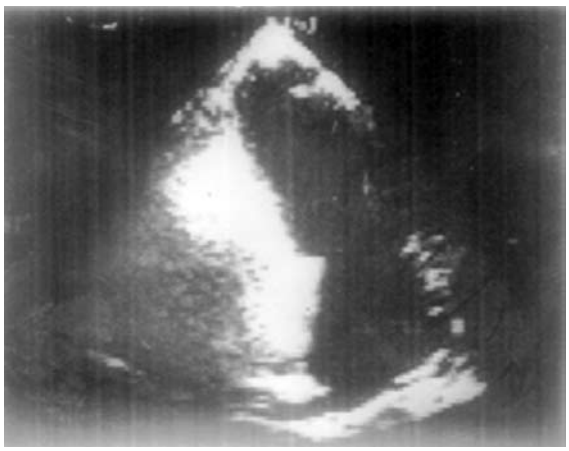
b. Chest X-ray and chest CT: are normal or show non-specific minor reticulonodular change in the base of the lungs *and /or dilatation of the peripheral pulmonary vasculature. Figure showing peripheral vasodilatation on chest CT.*

c. Pulmonary function tests: commonly show decreased diffusion ability of the lungs pointing to intrapulmonary vasodilatation.

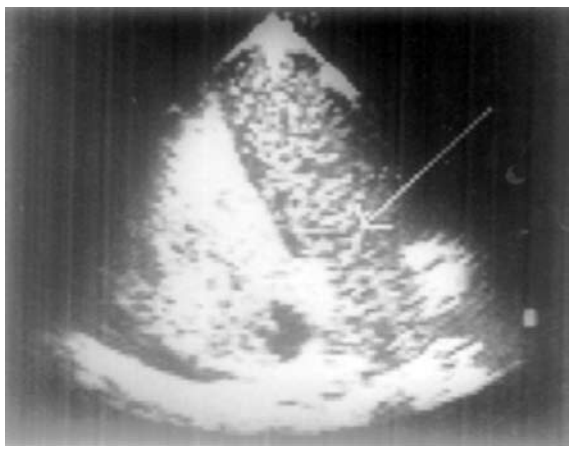
d. Two dimensional contrast enhanced echocardiography (CEEC):

This is the method of choice for diagnosing intrapulmonary vasodilatation and is the most sensitive procedure designed for this purpose. CEEC, however, lacks specificity in that in chronic liver disease the prevalence of pulmonary vasodilatation is about 20% by this method despite normal gas exchange status. In this study hand-agitated saline is

injected into venous circulation, This contrast is seen filling the right atrium then the right ventricle. If this saline bubbles appear in left atrium and left ventricle after 5 heart beats, this test is interpreted as Positive Bubble Test. Contrast enhanced trans-esophageal echocardiography is more sensitive than trans-thoracic echocardiography, and correlates more with gas exchange abnormality.



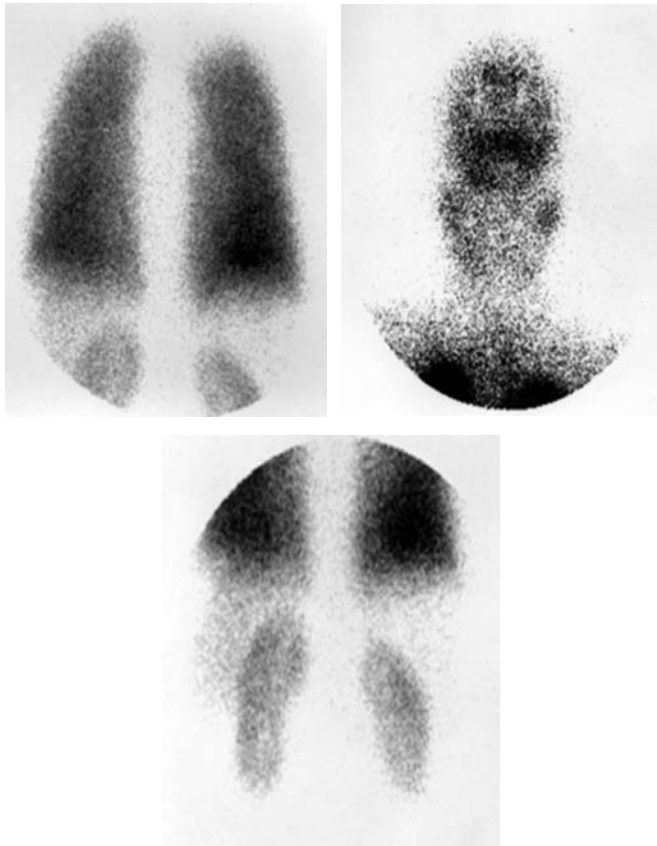
Negative echocardiogram showing no air bubbles in the left heart chambers



Positive echocardiogram showing air bubbles (arrow) in the heart chambers

e. Macro aggregated albumin scanning

Technetium 99m- labeled macroaggregated albumin is used. The estimated sensitivity of this method for diagnosing intrapulmonary vasodilatation is about 84% and its specificity is 100% (8,9). In addition, shunt fraction can be calculated by this procedure.



Technetium 99m macroaggregated albumin scanning reveals A) normal uptake of the radionuclide in the lungs. Uptake is also displayed in the B) brain and C) kidneys, suggesting a right to left shunt.

f. Pulmonary angiography: Two different angiographic patterns in HPS:

Type I: *more common*. There are minimal changes with diffuse spider like branches to more advanced changes with a blotchy, spongy appearance (the type that responds to breathing 100% oxygen).

Type II: *less common*. There are vascular lesions as vascular dilatations representing A-V communications (the type that responds poorly to breathing oxygen and liver transplantation is not as suitable as for type I vascular lesions).

g. Pulmonary artery catheterization: is not used commonly for diagnosing HPS.

Treatment

I. Medical therapy: There are currently no medications proved to have persistent, adequate or acceptable effect on HPS. The following are tried:

   a. *Almitrin bimesylate*: is a stimulator of arterial chemoreceptors (used in COPD).

   b. *Indomethacin* : To cause inhibition of prostaglandin production which has a putative role of vasodilatation.

   c. *Methylene blue*: Is a potent inhibitor of NO and its intracellular mediator, gunaylate cyclase and is potentially effective for treatment of HPS although transiently. It might be used in the post-operative period of liver transplantation in cases with transient hypoxemia, however its routine and long term use is not recommended yet.

II. Interventions other than liver transplantation

   a. Embolotherapy: It is recommended that pulmonary angiography be done for HPS patients who respond poorly to breathing 100% oxygen i.e., $PaO_2 < 150$-200 mmHg. If type II vascular lesions are diagnosed, embolotherapy with 22-coil spring devices must be tried.

   b. Portal decompression with transjugular intrahepatic portosystemic shunt (TIPS): There is controversy regarding the beneficial effects of this technic on HPS. Some studies confirmed the improvement of hypoxemia and others ruled out any usefulness of TIPS. More researches are needed undoubtfully.

III. Orthotopic Liver transplantation (OLT)

Previously, hypoxemia was considered as an absolute contraindication for OLT. Today the trend is to give a chance to this group of patients with the logic that HPS is a progressive and fatal disease and there isn't an effective therapy which could improve oxygenation significantly. The rate of improvement of HPS patients with type I vascular lesions undergoing OLT is about 80% , but is much less in those with type II lesions.

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