Refresher Course

Hepatopulmonary Syndrome

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Definition

Hepatopulmonary syndrome (HPS) is present when an individual with advanced liver disease develops dilatation of the pulmonary microcirculation and hypoxemia[1-5].

Incidence

The HPS prevalence has been found to be 18% in candidates for liver transplantation[6]. The disorders associated with HPS are hepatic cirrhosis, primary biliary cirrhosis, chronic active hepatitis, fulminant hepatic failure, chronic hepatic allograft rejection, nodular regenerative hyperplasia, and congenital hepatic fibrosis[2].

Clinical Feature

Most patients with HPS initially present with signs or symptoms related to their liver disease and portal hypertension such as jaundice, ascites or gastrointestinal bleeding[7]. The physical signs most closely linked to HPS in liver patients include cyanosis, digital clubbing, dyspnea (platypnea is dyspnea induced by the upright position and relived by recumbency, orthodeoxia is arterial deoxygenation accentuated in the upright position and relieved by recumbency) and cutaneous spider nevi. The HPS consists of the following triad: portal hypertension associated with advanced chronic liver disease, alteration in pulmonary gas exchange, expressed by an increase in the alveolar-arterial oxygen pressure difference [$P(A\text{-}a)O_2$] > 15 mm Hg while breathing room air, and evidence of intrapulmonary vascular dilatation (IPVD) or an intrapulmonary shunt[1,3,4].

Pathologic finding

The anatomic substrate explains the gas exchange abnormities. Vascular dilatation is produced at capillary and precapillary levels, with diameters reaching 500 micron and overt arteriovenous communications. Dilatation and communications are localized to the lung bases because of the effect of gravity[8,9].

Pathophysiology

The mechanism though which these changes occur seems to be related to the balance between pulmonary vasodilator and vasoconstrictor substances. In the presence of portal hypertension and liver disease, a detour of substances that are normally cleared and inactivated at the hepatic level would take place in the pulmonary circulation. The hemodynamic disturbances probably result from excess production or decreased metabolism of one or more of these vasodilating substances derived from endothelial cells or the gastrointestinal tract. Among the vasodilator substances are nitric oxide, arterial natriuretic factor, prostaglandin E_1 prostaglandin I_2, leukotrienes, platelet-activating factor, substance P, glucagon, calcitonin and vasoactive intestinal peptide[10,11]. Among the vasoconstrictor substances are endothelin, serothenin, cytokines (Interleukin1and 6), vascular growth endothelial factor, hepatocytic growth factor, tyrosine, and thromboxane A_2[12].

Mechanism of hypoxemia in HPS

The theory focuses on the physiologic impact of dilated gas-exchange vessels. Gas exchanging vessels may be increased in diameter five or ten times. This leads to layering of erythrocytes and a substantial increase in the diffusion distance for oxygen. Consequently erythrocytes in the center of the capillary may fail to fully equilibrate with alveolar gas before reaching the venous circulation. In addition, patients with cirrhosis commonly develop high cardiac outputs with diminished systemic and pulmonary vascular resistance[13,14]. When pure oxygen is breathed, however, the driving force for O_2 diffusion is often sufficient to overwhelm these limitations in gas transfer.

Three type of mechanism are responsible. The first mechanism is oxygen diffusion alteration termed "diffusion-perfusion disorder. In this mechanism, marked vascular dilatation causes the oxygen molecules to take longer to diffuse to the red blood

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cells located in the center of the flow. The second mechanism proposed is the right-to-left shunt caused by the anatomic alteration. This shunt is accompanied by loss of hypoxic vasoconstriction. The third mechanism is the alteration in the ventilation-perfusion ratio (increased perfusion with preserved ventilation).

Diagnosis

Based on the demonstration of severe chronic liver disease with portal hypertension or portal hypertension without liver disease, alteration in gas exchange and evidence of IPVD. Intrapulmonary vascular alteration can be demonstrated by three methods

1. Contrast echocardiography has become the most widely used test to demonstrate the presence of IPVD. The technique consists of a peripheral venous injection of an agitated saline solution, which produces bubbles measuring 60 to 150 microns in diameter. When injected into normal subjects, the air bubbles opacify the right heart chambers and are then trapped and resorbed in precapillary vessels. In a patient with HPS, however, some of the bubbles pass though the pulmonary capillaries and become visible in the left heart after three to six cardiac cycle. This "delayed opacification" of the left-sided chambers is specific for intrapulmonary shunting. When an intracardiac shunt exists, bubbles appear in the left heart within just one or two cardiac cycles "early opacification".

2. A technique to determine intrapulmonary vascular alteration is a perfusion body scan with Technetium 99m macroaggregated albumin (Tc 99m MAA). Tc 99m MAA is given by intravenous injection, which then travels to the right side of the heart and subsequently the pulmonary circulation. Tc 99m MAA has a diameter > 15 microns and normally remains trapped in the pulmonary vasculature. In patients with an intracardiac or intrapulmonary shunt, labelled albumin is taken up by the liver, brain and kidney (Figure 1), allowing the extent of the shunt to be quantified by means of the ratio between lung

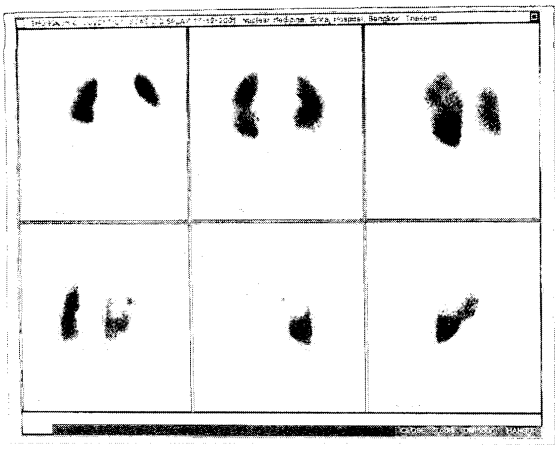

Figure 1A. A fifty-four year old Thai female presented with upper GI bleeding, cyanosis and dyspnea. She is known to have alcoholic cirrhosis and portal hypertension with hepatopulmonary syndrome as evidence by esophageal varices, hypersplee-nism, ascites, spider nevi, and palmar erythema. The $P(A\text{-}a)O_2 = 92.20$ mm Hg (> 15 mm Hg). Imaging of the lung reveals non uniform distribution of radioactivity in both lungs.

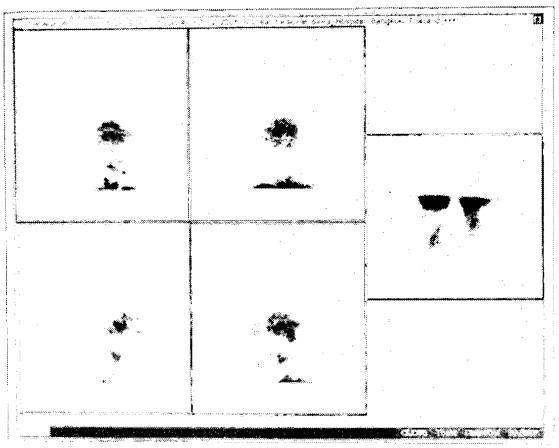

Figure 1B. Imaging of the skull and posterior abdomen in the same patient of Figure 1A. shows the IPVD or intrapulmonary shunt, demonstrate by perfusion lung scan showing abnormal activity in the brain and kidneys.

and brain radioactivity. However, this method does not allow differentiation between an intracardiac and an intrapulmonary shunt.

3. Pulmonary angiography is a method for discerning IPVD. Two patterns have been described, type I or "diffuse" has been subdivided into minimal and advanced. Type II or "focal" shows arteriovenous malfomations. Patients with advanced type I and type II respond poorly to the 100% oxygen test.

Echocardiography may have superior sensitivity, distinguishes intrapulmonary from intracardiac shunting, and permits the exclusion of pulmonary hypertension. Pulmonary arteriography may demonstrate IPVD, but it is more invasive and less sensitive than either contrast echocardiography or radionuclide perfusion scanning.

Treatment

Patients who present with a $PaO_2 < 55$ mm Hg or $PaO_2 > 55$ mm Hg accompanied by manifestations of polycythemia, cor pulmonale or cognitive impairment should be subjected to the 100% oxygen test If the test results show a $PaO_2 > 500$ mm Hg and the hypoxia is corrected with ambulatory oxygen therapy, then these patients benefit clinically from this treatment. However, if the 100% oxygen test gives a value < 150 mm Hg, the patients should undergo pulmonary angiography to determine the existence of a type II pattern and may eventually benefit from therapeutic embolization[4,10,15]. Intrapulmonary shunting and arterial oxygenation improve substantially in most patients with HPS after orthotopic liver transplantation. Krowka and colleagues[16] have compiled a comprehensive review of the transplantation experience in HPS. Over 80% of patients demonstrated an improvement in or resolution of the syndrome by 15 months after liver transplantation. It is recommended that patients with advanced liver disease be transplanted before their arterial oxygen tension falls below 50 mm Hg in room air.

Summary

HPS is a triad of portal hypertension with or without liver disease, with a gas exchange disorder, and IPVD. The most frequent anatomic substrate is precapillary or capillary pulmonary vascular dilatation. Clinical manifestation included progressive dyspnea, spider nevi, clubbing, platypnea and cyanosis. Impairment of pulmonary function is demonstrated by an increase in $P(A\text{-}a)O_2$ >15 mmHg, hypoxemia, hypocapnia, orthodeoxia. Contrast echocardiography is the method of choice to demonstrate IVPD. Tc 99m MAA is taken up by the liver, brain and kidney. Pulmonary angiography shows two radiographic patterns in the hepatopulmonary syndrome; a diffuse and a localized pattern. Pulmonary vascular resistance is commonly low, cardiac output is usually high, and the oxygen arteriovenous difference decreased. There is a relationship between the severity of liver disease and the development of HPS, which can be corrected by liver transplantation.

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Comment

Two pulmonary abnormalities can be seen in association with chronic liver disease. One is hepatopulmonary syndrome and the other is portopulmonary hypertension. The former is associated with intrapulmonary vascular dilatation resulting in hypoxemia. The latter is caused by abnormal pulmonary vasoconstriction. The former, as presented by the author, is generally cured or improved by liver transplantation. It is by itself not an indication or contraindication for liver transplantation. Postopulmonary hypertension is contraindicated for transplantaion because the patient will develop acute right heart failure at the time of liver reperfusion leading to liver congestion and graft failure.

In term of liver transplantation, we used to perform formal pulmonary function test including diffusion capacity of CO in every transplant candidate. Results have little impact on plan of treatment. We now order pulmonary function test selectively.

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