The Hepatopulmonary Syndrome

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Interactions between pulmonary gas exchange abnormalities and liver disease have been studied since 1884, when a case of cirrhosis, cyanosis, and clubbing was first described by Fluckinger[1] and dubbed the "hypoxia of cirrhosis." In 1977, Kennedy and Knudson[2] used the term *hepatopulmonary syndrome* (HPS) to describe a patient who developed dyspnea on exertion after portacaval shunting for complications of alcoholic cirrhosis.

HPS is defined clinically as the triad of chronic liver disease, abnormal pulmonary gas exchange with an increased alveolar-arterial oxygen gradient, and evidence of pulmonary vascular dilatations.[3] Although arterial oxygen abnormalities are common in patients with severe liver disease[4,5] and one study showed that up to 70% of patients with severe liver disease may be hypoxemic,[6] hypoxemia caused by HPS is relatively uncommon and its incidence is unknown. However, the clinical importance of HPS lies in its potential for profound hypoxemia that may be responsive to therapeutic interventions. Recently, the success of liver transplantation has renewed interest in HPS and in the pathophysiology of other liver and lung interactions.

This article discusses the pathophysiology and clinical presentation of HPS. Diagnosis and treatment are also presented.

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of HPS is unknown and remains the focus of intense research and debate. The most currently accepted hypothesis proposes a defect in the synthesis and metabolism of pulmonary vasoactive substances by the impaired liver.[7–9] Prostaglandins, nitric oxide, vasoactive intestinal peptide, calcitonin, glucagon, substance P, and atrial natriuretic factor have all been implicated but not proved.[7,10–15] This defect may lead to the formation of functional intrapulmonary vascular dilatations[12]—the major cause of hypoxemia and the defining feature of HPS.[8,9] These capillary and precapillary dilatations (also known as *hepatogenic pulmonary angiodysplasia*[9]) range from 15 to 500 µm in diameter and predominate in the middle and lower lung fields. Consequently, when a patient moves from a supine position to a standing position, blood flow to these fields increases and exacerbates the shunt and ensuing hypoxemia (ie, orthodeoxia).[16] Dilatations in the pleura have also been described, although the significance of this symptom in the development of hypoxemia is unclear.[17] The increased cardiac output and hyperdynamic circulation associated with liver disease reduces the transit time of blood in the lung vasculature; thus the time available for oxygen diffusion is reduced, which further contributes to the hypoxemia.[7,9,18]

Patients with HPS also experience a decreased arterial partial pressure of oxygen (PO_2) caused by the inability of oxygen molecules to diffuse to the center of the dilated pulmonary capillaries to oxygenate the hemoglobin in the erythrocytes.[19] However, increasing the alveolar PO_2 with supplemental oxygen may increase the blood arterial PO_2 and improve the hypoxemia (**Figure 1**).

HPS patients have been found to have decreased pulmonary vascular resistance and decreased hypoxic pulmonary vascular constriction.[3,6] However, the development of pulmonary hypertension in HPS patients has also been reported.[20]

PATHOLOGY

Several points must be considered when distinguishing HPS vascular dilatations from other abnormal pulmonary arteriovenous communications. First, although these dilatations are referred to as "shunts," this is a misnomer. HPS lesions respond to supplemental oxygen; therefore, the term "shunt" is technically incorrect. Second, some patients with intrapulmonary vascular dilatations do not develop hypoxemia, whereas other patients develop severe hypoxemia with minimal dilatations.[16] Third, the degree of intrapulmonary shunting is not directly associated with the degree of liver disease.[19] Fourth, the oxygenation can worsen over time without any concomitant decline in liver function.[21] Fifth, HPS dilatations do not have a tendency to bleed and result in pulmonary hemorrhage.[18] Finally, these lesions seem to be reversible with liver transplantation.[22,23]

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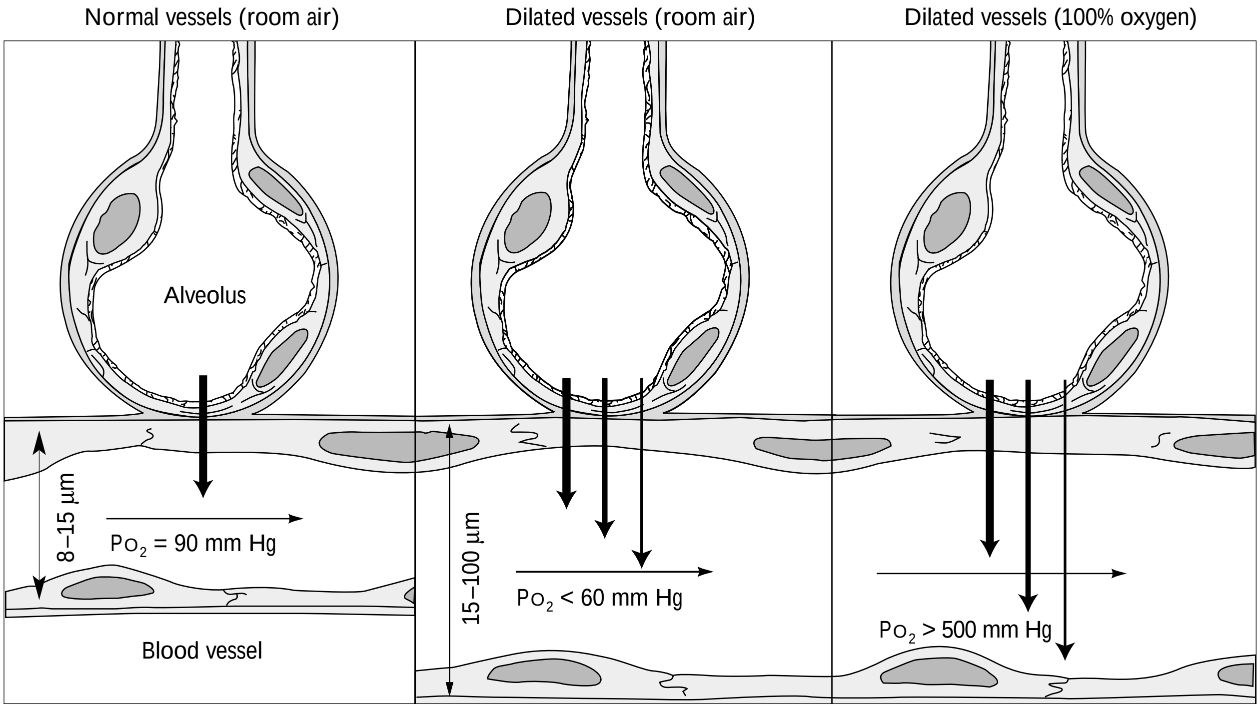

Figure 1. Illustration of precapillary pulmonary vascular dilatations. In the abnormal vessel, the oxygen molecules are not able to diffuse far enough to reach the center of the capillary, which reduces oxygenation of blood hemoglobin and leads to hypoxemia. This hypoxemia can be potentially overcome by increasing the arterial partial pressure of oxygen with supplemental oxygen. PO_2 = partial pressure of oxygen. Adapted with permission from Krowka MJ, Cortese DA: Severe hypoxemia associated with liver disease: Mayo Clinic experience and the experimental use of almitrine bismesylate. *Mayo Clin Proc* 1987;62:164–173.

Classification

The HPS vascular dilatations can be classified into two types.[24] Type I lesions, the more common of the two types, are characterized by a diffuse pattern that responds well to 100% oxygen. Type II lesions are more localized and discrete and have a poorer response to oxygen. The type I patient is more likely to benefit from liver transplantation, whereas the type II patient is a better candidate for coil-spring embolization.

CLINICAL PRESENTATION

Typically, patients with HPS initially present with signs and symptoms of liver disease. The most common respiratory symptom is exertional dyspnea. However, the time between the first presentation of dyspnea and a diagnosis of HPS may be quite prolonged. According to one study, the mean duration of respiratory symptoms until the diagnosis of HPS is 4.8 years.[18] Another well-described symptom is platypnea (ie, dyspnea accentuated by assumption of an upright position and relieved by assumption of a recumbent position); however, this symptom may not always be present. On physical examination, cyanosis, clubbing, spider nevi, and other signs of liver disease may be seen. Manifestations of a hyperdynamic circulation characterized by systemic vasodilatation and an increased cardiac output are common in patients with advanced liver disease and may also occur in patients with HPS.[3,7] Orthodeoxia (ie, hypoxemia exacerbated by an upright position) is not unique to patients with HPS but is highly suggestive of HPS in the characteristic clinical setting. Arterial hypoxemia of HPS may range from mild to severe and does not correlate with the severity of the underlying liver disease. A low diffusing capacity may also be revealed during diagnostic testing. Chest radiography, which is usually normal if no associated, underlying cardiopulmonary disease is present, often displays a bibasilar interstitial pattern that reflects the predominantly basal vascular dilatations (**Figure 2**). These findings are commonly misinterpreted as pulmonary vascular congestion or other interstitial lung disease.

NATURAL HISTORY

The natural history of HPS is not well described because of the lack of prospective data. The diagnosis of liver disease usually precedes the identification of respiratory symptoms by years. These patients usually die from nonpulmonary problems (eg, gastrointestinal bleeding, sepsis).[18] The development of hypoxemia portends a poor prognosis,[21] and the deterioration to death can be quite rapid. Remarkably, spontaneous resolution or improvement of the hypoxemia without intervention has been reported in some patients with HPS.[25]

DIAGNOSIS

Three imaging techniques can be used to confirm the presence of intrapulmonary vascular dilatations.

Contrast-Enhanced Echocardiography

Contrast-enhanced (microbubble) echocardiography provides delineation between the cardiac chambers and the pulmonary vasculature, and therefore, is the preferred initial screening test for HPS. The use of contrast-enhanced echocardiography for the diagnosis of vascular dilatations was first reported in 1981 by Hind and Wong.[26] The imaging technique involves the intravenous administration of indocyanine green dye or agitated saline that produces a stream of microbubbles 60 to 90 µm in diameter. Normally, the microbubbles, which are trapped, dissolved, and absorbed in the pulmonary capillaries (8 to 15 µm in diameter), opacify only the right heart chambers. In the presence of an intrapulmonary or intracardiac shunt, the microbubbles pass through the shunt and opacify the left heart chambers.[27]

After the microbubbles are first detected in the right heart chambers, the number of cardiac cycles necessary for the microbubbles to appear in the left heart chambers allows differentiation between intrapulmonary and intracardiac shunts. Typically, 1 to 3 cycles indicate an intracardiac shunt, whereas 4 to 6 cycles suggest an intrapulmonary shunt.

Contrast-enhanced echocardiography cannot differentiate between type I and type II HPS intrapulmonary dilatations. Therefore, a transesophageal approach, which visualizes areas of vascular dilatations in the lung lobes, may help to localize the major sites of dilatations by detecting contrast pulmonary veins that drain specific lung lobes.[18,28]

Perfusion Lung Scanning

Perfusion lung scanning is the second imaging technique used to detect intrapulmonary vascular dilatations.[29] Technetium 99m macroaggregated albumin measuring 20 µm in diameter is administered intravenously and is normally trapped in the pulmonary capillary bed. However, the presence of dilatations allows passage through the lung and into the systemic circulation. The technetium 99m macroaggregated albumin is then detected by scanning that reveals the uptake of radionuclide over the kidneys, the brain, or both (**Figure 3**). This technique cannot differentiate between intracardiac and intrapulmonary shunts.

Figure 2. Chest radiograph of a patient with hepatopulmonary syndrome displays a bibasilar interstitial pattern that reflects the basal predominance of vascular dilatations.

Pulmonary Angiography

Pulmonary angiography is the gold standard for imaging and localizing intrapulmonary dilatations in patients with HPS. Pulmonary angiography can also differentiate type I and type II HPS.[24] However, pulmonary angiography is the most invasive imaging technique, and therefore, the least frequently used. According to Mayo Clinic data,[30] pulmonary angiography is indicated in patients with an arterial Po_2 less than 150 mm Hg while on 100% inspired oxygen. Such patients have a greater likelihood of having discrete dilatations that are amenable to embolotherapy.[24] Angiography is also useful to exclude the rare cirrhosis-associated pulmonary hypertension, which is distinct from HPS and less amenable to correction by liver transplantation.[20]

TREATMENT

Medical and Symptomatic Therapy

Medical therapy for HPS has been disappointing. Trials of various therapeutic options (eg, somatostatin analogues, sympathomimetic agents, steroids, nonsteroidal anti-inflammatory drugs, β-adrenergic blockers,

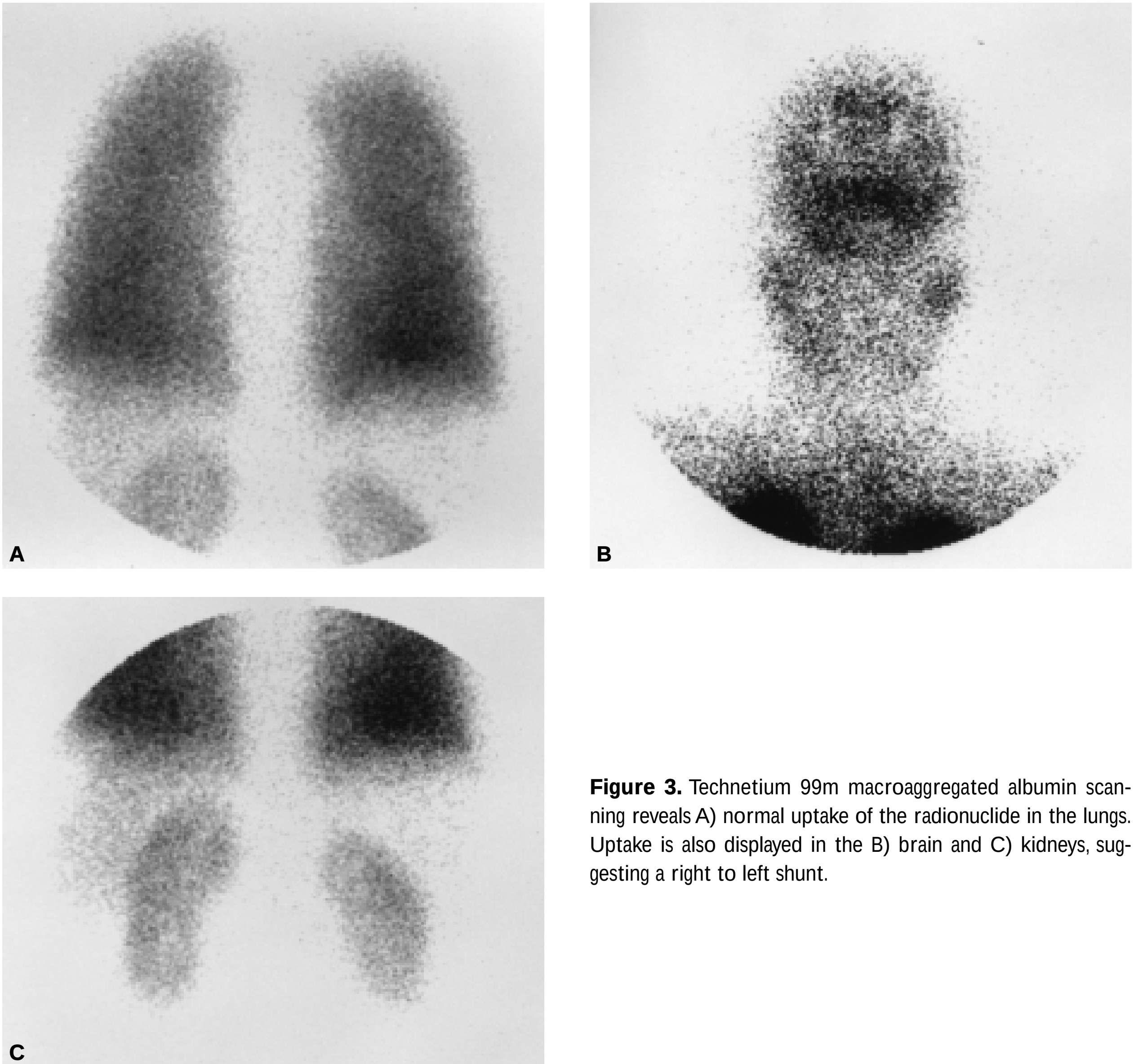

Figure 3. Technetium 99m macroaggregated albumin scanning reveals A) normal uptake of the radionuclide in the lungs. Uptake is also displayed in the B) brain and C) kidneys, suggesting a right to left shunt.

plasma exchange, chemotherapeutic agents, prostaglandin inhibitors, estrogen blockers, and almitrine bismesylate) have either failed or produced minimal improvement.[18]

Supplemental oxygen at a low-flow rate (2 to 4 L/min) by nasal cannula improves the hypoxemia and may provide symptomatic relief in patients with HPS. However, effects are usually transient,[18] and HPS patients eventually lose their response to oxygen supplementation.

Coil-Spring Embolization

Coil-spring vascular embolization is a more invasive option available to some patients (ie, patients with Type II HPS [localized dilatations], patients not qualified for liver transplantation, patients who are poor surgical candidates, patients not responding to supplemental oxygen).[24] Coil-spring embolization involves the percutaneous transcatheter occlusion of the pulmonary vascular dilatations through the placement of an occluding coil-spring device.[31] The best results are seen in patients with type II lesions, although some improvement occurs in patients with type I lesions.

Liver Transplantation

As recently as 1988, HPS was considered a

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contraindication for liver transplantation. However, liver transplantation currently is the most promising therapy for HPS.[22,23,30] Many studies have demonstrated improvement in oxygenation and a reversal of pulmonary shunts in patients who undergo liver transplantation.[8,23,28,32,33] However, these effects are unpredictable and may not occur until many weeks after transplantation. In addition, a transient worsening of the hypoxemia initially may occur; interestingly, recent studies have noted improved postoperative oxygenation with the use of nitric oxide in these patients.[34,35] Furthermore, whereas spirometric parameters may improve early after transplantation, a reduced diffusing capacity may persist up to 15 months after surgery.[36]

SUMMARY

Intrapulmonary vascular dilatations that cause profound hypoxemia may develop in patients with severe liver disease. In a minority of these patients, this hypoxemia may indicate the development of HPS. HPS is temporarily correctable with supplemental oxygen, but the syndrome is only reversible with the elimination of the underlying liver disease. Liver transplantation is being increasingly recognized as the only option available to treat HPS and dramatically improve hypoxemia in select patients. However, research is necessary to identify the optimal methods and criteria for selection of patients for liver transplantation. Further studies are also needed to understand the mechanism of pulmonary vasodilatation, the specific humoral factors involved, and the mechanism and prediction of reversal with liver transplantation. Finally, because HPS is still an under-recognized complication of end-stage liver disease, health care providers must consider its development in every patient with advanced liver disease manifesting symptoms of dyspnea and hypoxemia. **HP**

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