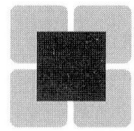

DAVID L. LONGWORTH, MD, AND JAMES K. STOLLER, MD, EDITORS

A 37-year-old woman with end-stage cirrhosis, progressive dyspnea, platypnea, and hypoxemia

A 37-YEAR-OLD WOMAN with cirrhosis due to chronic active hepatitis presents with progressive dyspnea that began 6 months previously. She notes shortness of breath with exertion and standing, which is relieved by lying flat. She has otherwise been in good health. She does not smoke, and denies any history of cough, fever, chills, hemoptysis, or wheezing. She has no history of chest pain, palpitations, or deep venous thrombosis. She has noted a mild increase in abdominal girth over the last 2 months, and a hepatologist has started spironolactone therapy. She is currently being considered for liver transplantation.

On physical examination her blood pressure is 110/72 mm Hg, respiratory rate 28 per minute, and heart rate 102 beats per minute with a regular rhythm. She has numerous cutaneous spider nevi. There is no jugular venous distension. The lungs are clear to auscultation and percussion. No cardiac murmurs or extra sounds are detected. Abdominal examination shows mild distension with shifting dullness, a small nodular liver, and a palpable spleen tip. There is +1 peripheral edema, and all peripheral pulses are normal.

The chest roentgenogram shows reduced lung volumes and a small right pleural effusion. Pulmonary function test results are entirely normal except for a moderate reduction in diffusing capacity (a diffusing capacity for carbon monoxide [DLCO] of 62% of predicted). Arterial blood-gas analysis performed while the patient is breathing room air reveals the pH to be 7.46, $PaCO_2$ 32 mm Hg, and PaO_2 60 mm Hg. The oxygen saturation (determined by pulse oximetry) is 92% while lying flat, 86% standing.

1 What is the most likely diagnosis?

- ❑ Pulmonary embolism
- ❑ Primary pulmonary hypertension
- ❑ Interstitial lung disease
- ❑ Hepatopulmonary syndrome
- ❑ Restrictive lung impairment due to ascites

Moderate-to-severe hypoxemia and cirrhosis should lead one to strongly suspect the hepatopulmonary syndrome, defined as the triad of liver disease, increased alveolar-arterial gradient while breathing room air, and intrapulmonary vascular dilatation. The true prevalence of the hepatopulmonary syndrome among people with chronic liver disease is unknown, but estimates range from 4% to 47% in available series, depending upon the diagnostic criteria and methods used.

Clinical features of the hepatopulmonary syndrome include signs and symptoms of both hepatic dysfunction and pulmonary disease. Most patients present with signs and symptoms of chronic liver disease, including esophageal varices, ascites, and splenomegaly. Pulmonary features include tachypnea, digital clubbing, and dyspnea. In some patients dyspnea may be accompanied by platypnea (an increase in shortness of breath induced by the upright position and relieved by recumbency) and orthode-

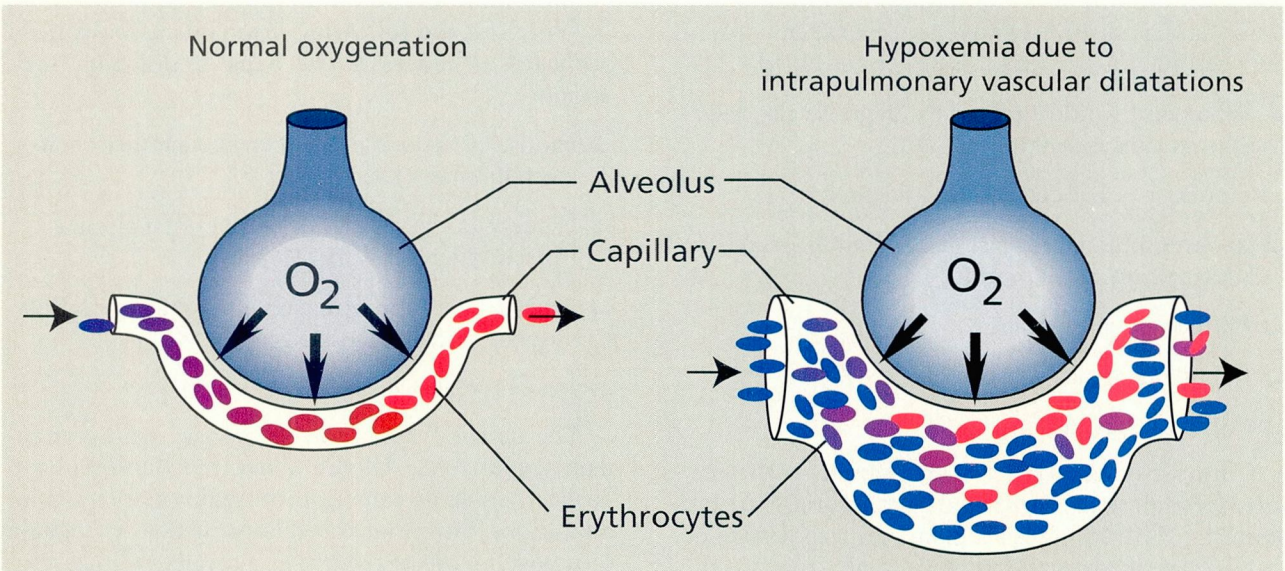

FIGURE. *Left*; In a normal pulmonary capillary, nearly all the hemoglobin in erythrocytes can become oxygenated. *Right*; Intrapulmonary vascular dilatations, which sometimes accompany liver disorders, allow erythrocytes to traverse the capillary bed without becoming fully oxygenated. Hypoxemia may be severe (PaO_2 < 60 mm Hg).

oxia (arterial desaturation—often defined as a decline in PaO_2 of ≥ 10 mm Hg or 10%—upon assuming an upright posture and improved by recumbency). In a patient with liver disease, orthodeoxia strongly suggests the hepatopulmonary syndrome.

Impaired arterial oxygenation is the hallmark of the hepatopulmonary syndrome. Even among cirrhotic patients without the hepatopulmonary syndrome, mild hypoxemia is common, occurring in 45% to 60% of such people. In contrast, severe hypoxemia (PaO_2 < 60 mm Hg) is less common in cirrhosis and, in the absence of associated cardiopulmonary disease, should strongly suggest the hepatopulmonary syndrome.

A FUNCTIONAL SHUNT

In general, hypoxemia can result from a number of causes, such as a decrease in the partial pressure of inspired oxygen, hypoventilation, regional ventilation-perfusion mismatch, or shunting. There are two types of shunts, either anatomical or functional. An anatomical shunt, such as a ventricular septal defect or a direct connection between a pulmonary artery and a pulmonary vein, allows unoxygenated blood to bypass the lungs.

However, in a functional (or physiologic) shunt, the connections are normal, but an abnormality allows unoxygenated blood to pass through the pulmonary vasculature without being properly oxygenated. Intrapulmonary vascular dilatations, the major cause of hypoxemia in patients with cirrhosis, can cause such a functional right-to-left shunt. The dilated capillaries range in diameter from 15 to 500 µm, as opposed to normal pulmonary capillaries, which are from 8 to 15 µm in diameter.

The expanded size of the dilated capillaries allows hemoglobin in erythrocytes to pass through without coming in contact with alveolar air (*Figure*). Giving supplemental oxygen enhances oxygenation more than would be expected with a true anatomical shunt because the driving pressure across the dilated pulmonary capillary can increase.

Patients with the hepatopulmonary syndrome generally have normal lung volumes (total lung capacity) and normal expiratory flow rates (FEV_1 [forced expiratory volume in 1 second] and FVC [forced vital capacity]) if they do not have any coexistent obstructive or restrictive lung disease. The DLCO may be mildly to severely reduced.

Like most patients with cirrhosis, patients with the hepatopulmonary syndrome typically exhibit a hyperdynamic circulation with increased cardiac output, normal-to-low pulmonary artery pressure, decreased systemic and pulmonary vascular resis-

tance, and a narrowed difference in oxygen content between the arterial and mixed venous blood.

2 What test would be best to diagnose the hepatopulmonary syndrome?

- ❑ Contrast-enhanced echocardiography
- ❑ Technetium macroaggregated albumin scanning (perfusion scanning)
- ❑ Pulmonary angiography
- ❑ Chest radiography
- ❑ All of the above

Contrast-enhanced echocardiography is the preferred diagnostic test for detecting right-to-left shunting. This test uses a stream of microbubbles 60 to 150 µm in diameter that normally opacify the right heart chambers, but which are then filtered by the pulmonary capillary bed and do not appear in the left side of the heart. However, in the presence of a right-to-left shunt, these microbubbles opacify the left heart chambers as well. In intrapulmonary shunts, such as intrapulmonary vascular dilatations, these microbubbles appear in the left heart chambers three to six heart beats after they appear in the right heart chambers. On the other hand, in intracardiac shunts (such as in an atrial septal defect or ventricular septal defect), the microbubbles appear in the left heart chambers within three beats of appearing in the right heart.

Technetium 99m-labeled macroaggregated albumin scanning can also detect intrapulmonary vascular dilatations. Albumin macroaggregates exceed 20 µm in diameter and should be trapped in the normal pulmonary capillary bed. A scan demonstrating uptake of radionuclide in the kidneys and brain suggests transit through either an intrapulmonary or intracardiac shunt.

Pulmonary arteriography, the most invasive of the imaging techniques listed here, should be reserved for selected situations: severe hypoxemia and poor response to 100% oxygen (PaO_2 < 150 mm Hg), or to exclude significant pulmonary hypertension as the cause of hypoxemia.

The plain chest radiograph may show fine linear markings corresponding to dilated capillaries, but the appearance is not diagnostic for the hepatopulmonary syndrome and may be confused with pulmonary edema or interstitial fibrosis.

3 Which of the following mechanisms have been proposed as causes of the hepatopulmonary syndrome?

- ❑ Failure of the damaged liver to clear a circulating pulmonary vasodilator
- ❑ Production by the damaged liver of a circulating vasodilator
- ❑ Inhibition by the damaged liver of a circulating vasoconstrictive substance
- ❑ All of the above

The cause of the hepatopulmonary syndrome remains unknown. All the above mechanisms have been proposed as causes of intrapulmonary vascular dilatations. Potential vasodilator mediators include prostacyclin, prostaglandin E_1, prostaglandin E_2, glucagon, and nitric oxide. Proposed circulating vasoconstrictive substances include tyrosine, serotonin, and endothelin.

4 What would be the approach to managing and treating this patient's condition?

- ❑ Supplemental oxygen to maintain a saturation of greater than 92%
- ❑ A somatostatin analog (octreotide)
- ❑ Spring-coil embolization of the intrapulmonary vascular dilatations
- ❑ Orthotopic liver transplantation

If a patient has severe hypoxemia (PaO_2 < 55 mm Hg while breathing room air) or desaturation (< 92% with activity), oxygen therapy is warranted. Medical therapy for the hepatopulmonary syndrome has been generally disappointing, which is not surprising considering the uncertainty regarding its pathogenesis. Various therapeutic strategies have been used in an attempt to target a circulating humoral mediator, but all have produced only minimal or no improvements in oxygenation and shunting. Several small observational studies have examined drugs of different classes, including octreotide, nitric oxide synthase inhibitors, prostaglandin inhibitors, almitrine bismesylate, and even garlic. Similarly, attempts to remove a circulating vasodilator via plasma exchange or to physically occlude intrapulmonary vascular dilatations with spring coils have had only modest efficacy at best.

Reports of the hepatopulmonary syndrome reversing after spontaneous improvement in liver function or after the underlying liver disease was corrected have led investigators to consider liver transplantation. The role of liver transplantation as treatment for the hepatopulmonary syndrome has had an evolving and controversial history. As recently as 1988, severe hypoxemia was considered a strong contraindication to liver transplantation because hypoxemia persists afterwards. Reports that hypoxemia can worsen in clinically stable liver disease and that the hepatopulmonary syndrome may reverse after liver transplantation challenge this older view. In fact, liver transplantation may be indicated for patients with incapacitating hypoxemia due to the hepatopulmonary syndrome. It is important to point out, however, that successful resolution of hypoxemia has not been universal, and that a clear understanding of the cause of reversal and of what factors predict improvement after liver transplantation remains to be determined.

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