Respiratory Complication in Liver Disease

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KEYWORDS

- Chronic liver disease • Hepatopulmonary syndrome • Hepatic hydrothorax
- Spontaneous bacterial pleuritis • Portopulmonary hypertension
- Liver transplantation

KEY POINTS

- Chronic liver disease is associated with multiple pulmonary complications.
- Hepatopulmonary syndrome, hepatic hydrothorax and portopulmonary hypertension are the most important complications with significant morbidity and mortality.
- Liver transplantation is a treatment option for eligible patients.

HEPATOPULMONARY SYNDROME

Kennedy and Knudson coined the term hepatopulmonary syndrome (HPS) in 1977. It is characterized by an oxygenation defect caused by intrapulmonary vascular dilatation (IPVD) in the setting of liver disease (**Table 1**).[1–4]

Pathophysiology

The unique pathologic feature of HPS is gross dilatation and increase in the number of pulmonary precapillary and capillary vessels to 15 to 100 μm in diameter at rest (normal range of the capillary diameter, <8–15 μm) and less commonly, pleural and pulmonary arteriovenous malformations and portopulmonary venous anastomoses.[4,5] This leads to ventilation-perfusion mismatch characterized by impaired oxygenation of venous blood caused by rapid or direct passage of mixed venous blood through the shunt into the pulmonary veins. Another mechanism is that oxygen molecules from adjacent alveoli fail to diffuse to the center of the dilated vessel to oxygenate

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Table 1
Triad of HPS

Feature	Definition
Liver disease	Portal hypertension with or without cirrhosis
Abnormal oxygenation	Pa_{O_2} <80 mm Hg or A-a gradient ≥15 mm Hg on room air
Abnormal pulmonary vascular dilatation	Positive findings on contrast-enhanced transthoracic echocardiography or abnormal uptake in the brain (>6%) with lung perfusion scan

hemoglobin in the red blood cells in the center of venous bloodstream. This diffusion impairment is worsened by the increased cardiac output associated with liver disease because the transit time of red blood cells through the pulmonary vasculature is reduced and hence the time available for diffusion is also reduced.[1,4,6]

Multiple mechanisms have been proposed to explain IPVD. Increased pulmonary production of nitric oxide has been implicated to play a key role.[7] Studies in rats showed that there is increased activity of endothelial nitric oxide synthase and inducible nitric oxide synthase in the pulmonary microcirculation.[8,9] Enhanced hepatic production of endothelin (ET)-1 and increased expression of pulmonary vascular ET-B receptors results in nitric oxide overproduction through ET-1 mediated activation of endothelial nitric oxide synthase.[10,11] ET-1 also leads to pulmonary accumulation of monocytes, which express inducible nitric oxide synthase.[11,12] Bacterial translocation and endotoxemia also result in accumulation of macrophages in the pulmonary microcirculation.[13,14]

Nitric oxide independent mechanisms of IPVD have also been proposed: enzymatic carbon monoxide production by increased expression of heme oxygenase-1[15,16] and stimulation of calcium-activated potassium channels by endothelial-derived hyperpolarizing factor.[17] Monocytes bind to the pulmonary vasculature and produce vascular endothelial growth factor A contributing to angiogenesis, which is also identified as a major contributor to HPS.[18]

Clinical Manifestations

The estimated prevalence of HPS ranges from 5% to 32%.[4] No prospective multicenter prevalence studies have been reported to date. HPS is more common in whites than in Hispanics and African Americans, and less common in smokers.[19] It affects patients of all ages. Dyspnea on exertion, at rest, or both is the predominant presenting symptom. Platypnea and orthodeoxia (defined as dyspnea on standing and the fall in partial pressure of oxygenation in arterial blood [Pa_{O_2}] by 5% or more or by 4 mm Hg or more on standing, respectively) are present in almost 25% of patients with HPS. These are attributed to the predominance of IPVD in the lung bases, and the increase in blood flow through these regions when upright. There are no hallmark signs or symptoms of HPS. The presence of spider nevi, cyanosis, digital clubbing, and severe hypoxemia (Pa_{O_2} <60 mm Hg) strongly suggests HPS.[20] Patients with HPS may have marked hypoxemia during sleep despite the presence of only mild to moderate daytime hypoxemia.[21] Chest radiographs may be normal or may show bibasilar nodular or reticulonodular opacities to reflect IPVD.[22] Pulmonary function tests demonstrate a consistently reduced diffusion capacity for carbon monoxide and this may not normalize after liver transplantation (LT).[23–25]

HPS can be classified as mild, moderate, severe, and very severe (**Table 2**).[4,6,20]