Hepatopulmonary Syndrome

David G. Koch, MD, MSCR[a,*], Michael B. Fallon, MD[b]

KEYWORDS

• Hepatopulmonary syndrome • Intrapulmonary vasodilatation • Hypoxemia
• Portal hypertension • Contrast echocardiography • Liver transplantation

KEY POINTS

- The hepatopulmonary syndrome (HPS) is a pulmonary complication of cirrhosis and/or portal hypertension that occurs in up to 30% of patients and results in arterial hypoxemia.
- The degree of hypoxemia does not correlate with the severity of liver disease, but patients with cirrhosis with HPS have a higher mortality than do patients with cirrhosis without HPS.
- There are no therapeutic options for HPS aside from liver transplantation.

HISTORICAL PERSPECTIVE

The coexistence between chronic liver disease and alterations in lung function has long been recognized by physicians, with the first report of cyanosis and finger clubbing in patients with cirrhosis appearing in the medical literature in 1884.[1] This clinical association was followed by confirmation that some patients with cirrhosis develop arterial hypoxemia.[2–6] However, the vascular changes that can occur in the lung with liver cirrhosis was not recognized until 1966 when physicians from the Royal Free and Brompton Hospitals in London performed a postmortem examination of the lungs from 13 patients with cirrhosis and described widespread vasodilatation of the precapillary pulmonary arterioles, even commenting on the appearance of "lung spider nevi" along the pleural surface.[7] A few relevant findings from the arteriography and histologic analyses were that (1) there was an increase in the number of vessels along the alveolar wall compared with patients without cirrhosis, especially in vessels measuring less than 35 μm, caused by widespread precapillary arteriole vasodilation; and (2) the primary lung structures (alveoli and connective tissues) were normal. However, a direct correlation with the degree of vasodilatation and severity

Financial Disclosures: None.
[a] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of South Carolina, 25 Courtenay Drive ART 7100A, MSC 290, Charleston, SC 29425, USA; [b] Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, The University of Texas Medical School at Houston, 6431 Fannin Street, MSB 4234, Houston, TX 77030, USA
* Corresponding author.
E-mail address: kochd@musc.edu

Clin Liver Dis 18 (2014) 407–420
http://dx.doi.org/10.1016/j.cld.2014.01.003 **liver.theclinics.com**
1089-3261/14/$ – see front matter

of hypoxemia could not be established. The recognition of the hepatopulmonary syndrome (HPS) as a pathologic entity in cirrhosis came 12 years later when the concept that intrapulmonary vasodilatation (IPVD) could cause hypoxemia was accepted.[8]

PATHOPHYSIOLOGY

Animal Model of HPS

Understanding of the pathogenesis of HPS is limited, and derives almost entirely from a rat common bile duct ligation (CBDL) model that uniquely recreates the features of human HPS.[9–16] In this model, proliferating cholangiocytes in the liver produce and secrete endothelin-1 (ET-1),[9–13] whereas other animal models of portal hypertension that do not result in bile duct proliferation and subsequent biliary cirrhosis do not develop HPS (**Fig. 1**).[14] Sheer stress results in upregulation of the endothelin B receptor (ET_BR) in the pulmonary vasculature that subsequently binds the increased circulating ET-1 and augments pulmonary nitrous oxide (NO) production via endothelial nitrous oxide synthase (eNOS).[9,12,16–21] In addition, CBDL rats with HPS also have increased pulmonary intravascular monocytes caused by increased pulmonary NO levels and bacterial translocation resulting in increased blood levels of tumor necrosis factor alpha (TNF-α).[22–28] These pulmonary monocytes then contribute to IPVD by increasing levels of NO (via inducible nitric oxide synthase [iNOS])[11,29,30] and carbon monoxide (via heme oxygenase-1 [HO-1]).[11,31] Blood levels of vascular endothelial growth factor (VEGF)[30,32–34] are also increased. The complimentary effects of ET-1, pulmonary monocytes, and VEGF on the pulmonary vasculature not only contribute to IPVD but also to pulmonary angiogenesis, which in turn contributes to the underlying oxygen impairment.[11,30,32–34] The role of angiogenesis in HPS is supported by the presence of neovascularization in the lungs of CBDL rats with HPS[30,34] and the improvement in oxygenation with the antiangiogenesis therapy, sorafenib.[32,33] The CBDL model has provided a possible mechanism for IPVD and HPS (**Fig. 2**), but these pulmonary vascular abnormalities in humans are not exclusive to cholestatic liver disease and biliary cirrhosis because IPVD and HPS occur in cirrhosis of any cause.

Human Disease

Understanding of the pathophysiology of HPS in humans is limited. Nitric oxide has been implicated as a mediator of IPVD in cirrhotic patients with HPS because they have higher exhaled levels of NO compared with patients without HPS, and exhaled NO levels normalize after liver transplantation (LT).[35–37] However, attempts to inhibit NO production pharmacologically have given discrepant results.[38–44] Pulmonary angiogenesis has also been implicated in humans because single nucleotide polymorphisms that regulate angiogenesis are associated with the presence of HPS in patients with cirrhosis.[45] Adding to the angiogenesis hypothesis is the observation that resolution of hypoxemia from HPS after LT is not immediate and may take up to 1 year,

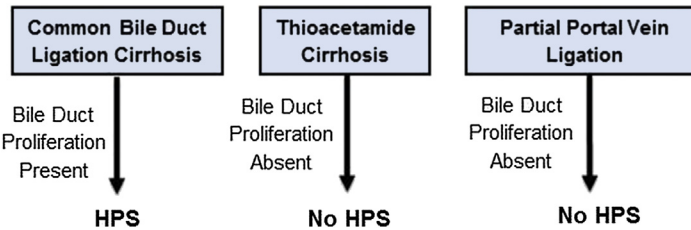

Fig. 1. Outcomes in 3 animal models of portal hypertension. Only the rat CBDL model with accompanying bile duct proliferation and portal hypertension develops hypoxemia.