Hepatopulmonary Syndrome and Portopulmonary Hypertension in Children: Recent Advances in Diagnosis and Management

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Pulmonary vascular disease is an important complication of portosystemic shunting in children and adults with chronic liver diseases and cirrhosis, extrahepatic portal vein obstruction/thrombosis or congenital portosystemic shunts (CPSSs).[1] Two major types of pulmonary vascular disease in this context are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH),[1] both of which may indicate the need for liver transplantation.[2] The hallmark of HPS is intrapulmonary vascular dilatation (IPVD) and shunting leading to an increased alveolar-arterial gradient and, generally, hypoxemia (**Table I**). In contrast, POPH is characterized by progressive remodeling of the wall of small pulmonary arteries with vasoconstriction and/or vascular obstruction because of thickening of the arterial wall leading to pulmonary arterial hypertension (PAH) and right heart failure (**Table I**).[2] Both HPS and POPH significantly impair the quality of life in affected children and are risk factors for mortality.[3] Thus, patients with HPS and POPH are given exception model end-stage liver disease/pediatric end-stage liver disease points under United Network for Organ Sharing policy and are prioritized for liver transplantation because of their high pre- and postliver transplantation mortality.[4] Current pharmacotherapies have not been proven to reverse either of these conditions in affected children.[5] Liver transplantation, a life-saving procedure for irreversible chronic liver disease with end-stage liver disease or other serious complications, is indicated in patients with severe HPS.[6] Generally, POPH by itself is not an indication for liver transplantation, but mild-to-moderate POPH may respond to liver transplantation if there is another indication for liver transplantation.[6] In addition, medically treated POPH may safely facilitate an otherwise needed liver transplantation. However, the optimal timing of liver transplantation in these conditions in children has not been clearly defined.

Definitions and Diagnostic Criteria

Definitions

HPS is defined by the presence of the triad of IPVD and abnormal arterial oxygenation in the setting of advanced liver disease, portal hypertension, or CPSS (**Table I**).[5,7] Although most cases of HPS are associated with advanced liver disease, the pathophysiologic features of HPS can also be seen in survivors of the Fontan procedure for single ventricle disease and with no pre-existing liver disease.[8] Chronic venous hypertension after Fontan procedure may lead to liver congestion, fibrosis, and, eventually, pulmonary arteriovenous fistulas and HPS.[8] Clinically, HPS is characterized by the presence of an increased age-corrected alveolar-arterial oxygen gradient on room air, with or without hypoxemia.[3,9] The development of IPVD in HPS (detected by agitated saline contrast-enhanced transthoracic echocardiography) leads to an oxygenation defect in pulmonary capillaries and effective right to left shunting.[3] Although advanced cirrhosis is the most common liver condition associated with HPS, it may also develop in noncirrhotic portal hypertension, CPSS, and ischemic hepatitis.[3]

POPH is defined as PAH associated with portal hypertension either inferred clinically (from the presence of splenomegaly, thrombocytopenia, portosystemic shunts, esophageal varices, or portal vein abnormalities) or confirmed with hemodynamic measurements showing a raised mean pulmonary artery pressure (mPAP >25 mm Hg), increased pulmonary vascular resistance (>3 Wood units), and pulmonary artery wedge pressure <15 mm Hg (**Table I**).[5]

Most of the studies on HPS in children have used the diagnostic criteria described by Donovan et al, with some modifications (**Table II**; available at www.jpeds.com).[9] The European Cardiology Society/European Respiratory Society Joint Task Force on the Diagnosis and Treatment of Pulmonary Hypertension and the International Liver Transplant Society (ILTS) Practice Guidelines recommend uniform diagnostic criteria for both HPS and POPH (**Table I**),[5,13] which will be helpful for future epidemiology studies and therapeutic trials.

Pathogenesis

The pathophysiology of HPS and POPH is shown in **Figures 1** and **2**. The hallmark of HPS is the presence of IPVD[3]

CPSS	Congenital portosystemic shunt
HPS	Hepatopulmonary syndrome
ILTS	International Liver Transplant Society
IPVD	Intrapulmonary vascular dilatation
mPAP	Mean pulmonary arterial pressure
PAH	Pulmonary arterial hypertension
PaO_2	Arterial partial pressure of oxygen
POPH	Portopulmonary hypertension
TDE	Transthoracic Doppler echocardiography

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Table I. Diagnostic criteria for HPS and POPH

Conditions	Diagnostic criteria
HPS	Advanced liver disease (most common), portal hypertension, CPSSs
	IPVD: a positive contrast-enhanced transthoracic echocardiogram: presence of microbubbles in the left heart ≥3 cardiac cycles after right heart microbubbles following 10 mL agitated saline injection in a peripheral vein.
	Abnormal arterial oxygenation: hypoxemia ($PAaO_2$ ≥15 mm Hg)
POPH	Presence of portal hypertension: either a clinical diagnosis, such as gastroesophageal varices, splenomegaly, ascites, or elevated portal pressure confirmed by hemodynamic measurement
	Plus
	Right heart catheterization showing:
	mPAP >25 mm Hg
	PVR >3 wood units
	Normal PAWP <15 mm Hg

$PAaO_2$, alveolar-arterial oxygen gradient; *PAWP*, pulmonary artery wedge pressure; *PVR*, pulmonary vascular resistance.Adapted from Krowka MJ, et al. International Liver Transplant Society Practice Guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation 2016;7:1440-52.

characterized by diffuse or localized dilated abnormal pulmonary capillaries as well as arteriovenous communications.[3] Three mechanisms are thought to play a role in the impaired oxygenation of venous blood as it flows through the pulmonary circulation: ventilation/perfusion (V′/Q′) mismatch, intrapulmonary shunting, and limitation of oxygen diffusion.[14-17] Nitric oxide, a potent vasodilator, has been linked to IPVD.[15] The pathogenesis of HPS is shown in **Figure 2**. Recent animal studies on the inhibition of pulmonary angiogenesis in HPS by placental growth factor may represent a novel strategy in the therapy for HPS.[18]

The pathophysiology of POPH is not fully understood,[3,14] partially because of a lack of a suitable animal model as well as the rarity of the condition.[3] Histologically, there is a similarity between POPH and PAH. Both are characterized by obstruction of pulmonary arterial blood flow caused by intimal proliferation, medial smooth muscle hypertrophy, fibrosis, and in situ thrombosis.[19] This leads to a thickening of the arterial wall and blood vessel occlusion and, eventually, elevated pulmonary vascular resistance.[19] A case-control study showed that POPH was associated with female sex, single nucleotide polymorphisms in genes involved in estrogen metabolism (estrogen receptor-1), and raised circulating estrogen levels,[20] supporting the potential role of sex hormones in the pathogenesis of POPH.[20] Other causes of PAH, which need to be considered include sleep apnea, chronic obstructive airway disease, and interstitial pulmonary fibrosis.[19] A proposed mechanism for POPH suggests that the increased blood flow because of high cardiac output seen in chronic liver disease causes pulmonary vascular wall shear stress, which triggers the dysregulation of vasoactive, proliferative, and angiogenic mediators, eventually leading to changes in the arterial wall characteristic of POPH.[19] Another proposed mechanism includes an imbalance of vasoactive substances and portosystemic shunting leading to the increased vasoactive and proliferative agents reaching the lung vasculature.[21]

Epidemiology

Clinical Features of HPS

Although HPS is most commonly seen in children with portal hypertension and cirrhosis, it may also occur in patients with noncirrhotic portal hypertension (including focal nodular hyperplasia and nodular regenerative hyperplasia), acute and chronic hepatitis, acute liver failure, and vascular abnormalities that limit hepatic venous outflow to the lungs

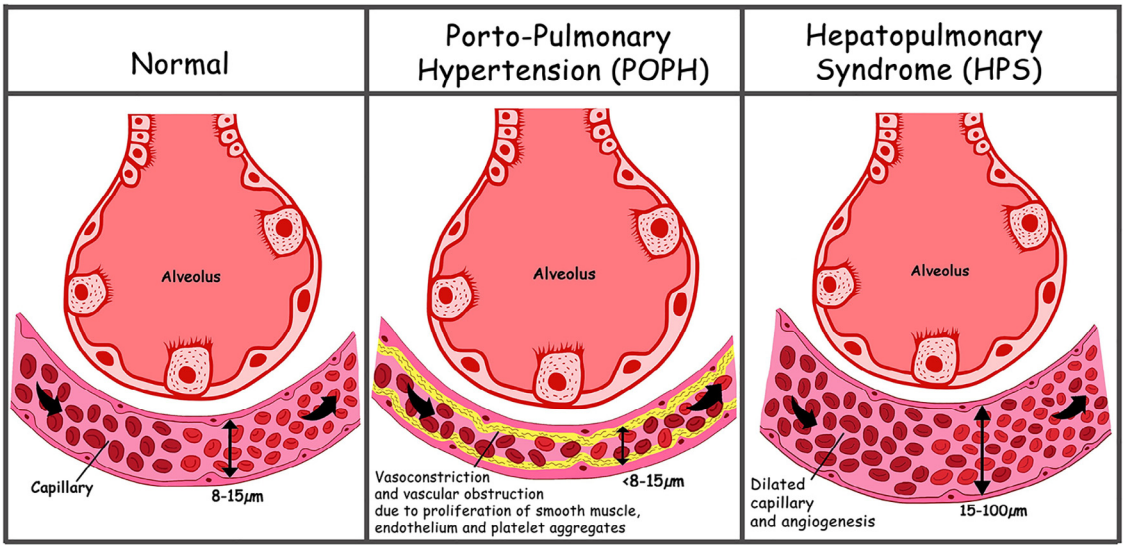

Figure 1. Pathophysiology of POPH and HPS. In POPH, progressive remodeling of the wall of small pulmonary arteries with vasoconstriction and thickening of the arterial wall leading PAH and right heart failure. In HPS, IPVD leads to effective intrapulmonary arterial shunting and hypoxemia.

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