Portopulmonary Hypertension

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KEYWORDS

• Portopulmonary hypertension • Cirrhosis • Liver transplant • Portal hypertension
• Pulmonary hypertension

KEY POINTS

- Pulmonary arterial hypertension (PAH) is a serious pulmonary vascular disease. When PAH occurs in the setting of portal hypertension, it is known as portopulmonary hypertension (POPH).
- Pulmonary hypertension in patients with liver disease or portal hypertension can be caused by multiple mechanisms, including hyperdynamic (high-flow) state, increased pulmonary venous congestion (pulmonary venous hypertension), and vascular constriction or obstruction of the pulmonary arterial bed (POPH).
- POPH is an uncommon and serious yet treatable pulmonary vascular consequence of cirrhotic and noncirrhotic portal hypertension; its pathophysiology remains unclear with no clear relationship to the cause of the liver disease or the severity of the portal hypertension. Its main presenting symptom is exertional dyspnea, and POPH may lead to right heart failure and death if untreated.
- Because of the spectrum of pulmonary hemodynamic changes associated with hepatic dysfunction, screening by transthoracic echocardiography and confirmation by right heart catheterization is necessary for accurate diagnosis and therapeutic considerations.
- Despite the lack of controlled studies, PAH-specific therapy in POPH can significantly improve pulmonary hemodynamics and right ventricular function. The potential to cure POPH, at least hemodynamically, with a combination of PAH-specific therapy and liver transplant seems to be an attainable goal in a cohort of patients with POPH yet to be optimally characterized.

INTRODUCTION

Portopulmonary hypertension (POPH) is a well-known serious complication of portal hypertension from cirrhotic and noncirrhotic causes. POPH is defined as the presence of pulmonary artery hypertension (PAH) that evolves as a consequence of portal hypertension[1] and is included in group I of the 2008 Dana Point classification of PAH.[1]

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In epidemiologic studies, POPH has been documented in approximately 4.5% to 8.5% of liver transplant (LT) candidates.[2,3] Historically, the first description of POPH was provided by Mantz and Craige[4] in 1951 after describing the necropsy results of a 53-year-old woman with spontaneous portacaval shunt (caused by a probable congenital portal vein narrowing) that originated at the confluence of the portal, splenic, and mesenteric veins and coursed through to the mediastinum. The shunt was lined by varying amounts of thrombus thought to have embolized via the innominate vein into the right heart and pulmonary arteries. In addition to embolized small pulmonary arteries, an extreme endothelial proliferation and recanalization process was documented.[4] For POPH, specific screening recommendations and diagnostic criteria are now clearly defined, including the management of POPH in the setting of LT candidacy. Despite the lack of POPH-specific randomized controlled trials for PAH-specific therapy, extrapolation of the therapeutic advances in treating PAH with beneficial effects in POPH has stimulated ongoing interest and importance in this syndrome. This review article recapitulates the evolving knowledge in the diagnosis, management, and treatment of POPH.

POPH DEFINITION AND GENERAL CHARACTERISTICS

POPH should be clearly defined and recognized based on an accurate interpretation of hemodynamics obtained by right heart catheterization (RHC). All the following criteria should be met for the diagnosis of POPH:

- Portal hypertension: clinical diagnosis (ascites, varices, splenomegaly)
- Mean pulmonary artery pressure (MPAP): 25 mm Hg or greater
- Pulmonary vascular resistance (PVR): greater than 240 dyne/s/cm^{-5}
- Pulmonary capillary wedge pressure (PCWP): 15 mm Hg or less
- Transpulmonary gradient (TPG): greater than 12 mm Hg

In addition, the severity of POPH is defined based on the MPAP as follows: mild ($\geq$25 MPAP, <35 mm Hg), moderate ($\geq$35 MPAP, <45 mm Hg), and severe (>45 mm Hg MPAP). There are different pulmonary hemodynamic patterns that complicate advanced liver disease and are important to recognize during RHC (**Table 1**).[5,6] Distinguishing these 3 patterns is extremely important in the management of portal hypertension because therapies and outcomes clearly differ:

1. Hyperdynamic circulatory state induced by liver dysfunction
2. Excess pulmonary venous volume caused by diastolic dysfunction and/or renal insufficiency (pulmonary venous hypertension)
3. PAH caused by vascular obstruction (POPH)[7]

Furthermore, POPH should be distinguished from hepatopulmonary syndrome (HPS),[5,8] which is another major pulmonary vascular consequence of liver disease. In HPS, arterial hypoxemia is caused by intrapulmonary vascular dilatations (exactly opposite to the vascular obstructions documented in POPH) that form as a remodeling process caused by factors yet to be identified. In addition, the pulmonary hemodynamics associated with HPS reflect a normal PVR and usually a high-flow state characterized by an increased cardiac output (CO). The distinction between these two syndromes is very important, especially if LT is to be considered, because of the differences in risk, treatment options, and outcomes between these two syndromes.[8]

Mainly affecting adults, POPH has also been reported in the pediatric age group.[9] Autoimmune liver disorders (primary biliary cirrhosis and cirrhosis from autoimmune hepatitis) and female sex are more frequently associated with POPH according to