

Filtering the Facts: Management of Portopulmonary Hypertension

Joel Wirth, MD
*Division of Pulmonary and Critical Care
 Medicine
 Maine Medical Center
 Portland, ME*

Summary of PHPN Symposium Session by Joel Wirth, MD, and Traci Stewart, RN, MSN

Traci Stewart, RN, MSN
*Heart and Vascular Center
 University of Iowa
 Iowa City, IA*

Portopulmonary hypertension (PoPH) is included in the World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) classification. PoPH is defined by a mean pulmonary artery pressure (mPAP) of >25 mm Hg, pulmonary artery wedge pressure (PAWP) <15 – 18 mm Hg, pulmonary vascular resistance (PVR) >3 Woods units in a patient with portal hypertension, and no other etiologies of pre- or postcapillary pulmonary hypertension.¹ PoPH is more prevalent in women and those with autoimmune disease.² A small proportion (2% to 8%) of patients with portal hypertension go on to develop PoPH, which accounts for approximately 5% to 10% of the subset of PAH WHO Group 1.³

The underlying cause of PoPH is not clear, but is commonly thought to be related to higher cardiac output associated with liver disease, leading to shear stress and circulating mediators, causing remodeling to the pulmonary vasculature. The pathology of PoPH is similar to the remodeling seen in idiopathic PAH, including pulmonary vessel fibrosis, smooth muscle proliferation, in situ thrombosis, and plexiform lesions.⁴ Patients with PoPH usually present with dyspnea upon exertion and may have signs of right heart failure upon physical examination.

Echocardiography is the diagnostic screening tool of choice in patients with advanced liver disease and those being

evaluated for liver transplantation. A follow-up confirmatory right heart catheterization is necessary when PoPH is suspected. Hemodynamic measures are essential to identify which of several scenarios is contributing to an elevated mPAP in patients with PoPH. An elevated mPAP can be caused from a high cardiac output with a normal PAWP and PVR. Indeed, high output states are common in liver disease. Pulmonary venous hypertension must also be excluded: demonstrated by an elevated mPAP and PAWP with a normal cardiac output, and PVR and transpulmonary gradient <12 mm Hg. Symptoms related to PVH may improve with just diuresis.¹ Distinguishing PAH from either of these situations is necessary to guide appropriate treatment.

PoPH is characterized as mild, moderate, or severe depending on the degree of elevation of the mPAP (mild 25 to <35 , moderate 35 to <45 , and severe >45 mm Hg). However, a more complete assessment of severity also includes exercise capacity and measures of right heart function by catheterization and echocardiogram, similar to other Group 1 conditions. The severity of PoPH is not related to the severity or cause of the liver disease.¹ PoPH is diagnosed in approximately 6% of patients being evaluated for liver transplant.⁵ Patients needing liver transplantation have a poor survival when transplanted when PoPH is present. In patients with true

Group 1.4.3 PoPH, liver transplantation is contraindicated when mPAP exceeds 35 mm Hg. PAH treatments are required in an attempt to lower mPAPs and allow for transplant listing.

Patients with PoPH have typically been excluded from clinical trials assessing safety and endpoints of PAH therapy. Phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, endothelin receptor antagonists, and prostacyclin analogs have all been used in the PoPH patient population. Case series have shown improvement in hemodynamics and functional capacity, but data are limited. It is important to consider the recommended precautions and contraindications in the medication's package insert before initiating therapy. Dose reduction may be necessary to avoid toxicity from increased exposure or reduced clearance depending on the severity of the liver disease, often based on Child-Pugh scores.

Patients with PoPH have additional special care considerations requiring attention of providers. Treating underlying liver disease can be beneficial: for example, abstaining from alcohol and treating hepatitis. Patients are at risk for hypotension; therefore, avoid treatment with beta-blockers and calcium channel blockers to prevent systemic hypotension and decreased right ventricular filling. Patients can

have complications with spontaneous bacterial peritonitis, umbilical hernias, and hepatorenal syndrome. Avoid nonsteroidal anti-inflammatory medications, as PoPH patients are at high risk of gastrointestinal bleeding. Typically, anticoagulation is avoided. Patients can experience confusion from elevated ammonia levels, making adherence and infused therapy challenging.

Fluid retention and ascites should be closely monitored. Implement a low-sodium diet (2-3 grams/day) and restrict fluid when hyponatremia is present. Consulting a dietitian and providing instruction on reading food labels and serving sizes can help patients understand how to reduce

sodium intake. Initiation and then titration of daily loop and potassium-sparing diuretics with close monitoring of potassium and kidney function can improve quality of life and improve symptoms. Paracentesis can be beneficial to palliate symptoms.

In summary, PoPH is uncommon and screening is necessary in liver disease. Right heart catheterization determines PAH from high output or pulmonary venous hypertension states. PAH medications should be implemented with caution and monitored closely. Addressing comorbidities of PoPH patients must be considered as part of the patient's chronic management. Additional research to assess safety and outcomes in PoPH is

necessary to improve the poor survival of this subpopulation.

References

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