REVIEW

Clinical aspects of portopulmonary hypertension

Boris I. Medarov, Amit Chopra, Marc A. Judson*

Division of Pulmonary and Critical Care Medicine, Albany Medical College, MC-91, 47 New Scotland Avenue, Albany, NY 12208, USA

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Summary
Portopulmonary hypertension (PoPH) is an often neglected form of pulmonary hypertension where pulmonary hypertension occurs in the presence of portal hypertension. PoPH is important to diagnose and treat as it may improve the patient’s quality of life and improve the outcome after liver transplantation. In this review, we discuss the clinical aspects of PoPH including its pathophysiology, diagnosis, treatment, and prognosis.

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* Corresponding author.
E-mail address: judsonm@mail.amc.edu (M.A. Judson).

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Introduction

Portopulmonary hypertension (PoPH) is a well-recognized complication of portal hypertension (PH). PoPH has a great impact on quality of life, survival, and suitability for liver transplantation. The aim of this article is to provide a detailed discussion concerning the epidemiology, diagnosis, treatment and clinical significance of PoPH.

Historical background

In 1951, Mantz and Craige reported a peculiar case of a 53-year-old woman who expired while undergoing a thoracotomy for hematemesis [1]. The authors noted that the patient’s pulmonary artery was enlarged and exhibited forceful pulsations more characteristic of the aorta than of the typically low-pressure pulmonary trunk. The intra-operative findings and subsequent autopsy revealed a stenotic portal vein, a portocaval shunt, and esophageal varices. The pulmonary arteries demonstrated intimal thickening, endothelial proliferation and thrombotic changes. In retrospect, this patient suffered from what subsequently became known as portopulmonary hypertension—a syndrome characterized by pulmonary hypertension in the setting of portal hypertension.

On the basis of this initial description, it was unclear if the association of portal hypertension and pulmonary hypertension was coincidental. However, subsequent reports of similar cases suggested that there was an undeniable relationship between the two conditions. Initially, the observation that PoPH was a distinct clinical entity did not have major practical implications because treatment for pulmonary hypertension and advanced liver disease was not yet available. However, today, in the era of pulmonary vasodilators and orthotopic liver transplantation, the diagnosis of PoPH is imperative as current treatment may improve symptoms, function, and survival.

Definition

The World Health Organization (WHO) classifies PoPH as a form of Group 1 (pulmonary arterial hypertension): mean pulmonary arterial pressure (mPAP) > 25 mmHg and pulmonary artery occlusive pressure (PaOP) < 15 mmHg at rest.

PoPH is defined as pulmonary arterial hypertension associated with portal hypertension. The traditional WHO definition of pulmonary arterial hypertension does not require that the pulmonary vascular resistance (PVR) exceed any particular value. This is because in the setting of a normal or decreased cardiac output, an increased mPAP implies an increased PVR. However, patients with liver disease often develop an abnormally high cardiac output that can result in an elevated pulmonary artery pressure without a concomitant increase in the PVR because of the phenomena of pulmonary vascular recruitment and distention.

Some authors have questioned if the diagnosis of PoPH can be made in the absence of an increased PVR and have labeled this phenomenon as a "hyperdynamic state" [2]. In 2004, the European Respiratory Society (ERS) guidelines required that the PVR exceed 240 dyn s cm⁻⁵ for the diagnosis of PoPH [3]. The guidelines acknowledged that this PVR cut-off value was arbitrary. PoPH patients who have a PVR > 240 dyn s cm⁻⁵ clearly exhibit intimal thickening, smooth muscle hypertrophy and plexiform lesions in the pulmonary vasculature similar to other forms of PAH. Plexiform changes have not been documented in patients...
Pathogenesis

Although the pathological changes in the pulmonary vasculature observed with PoPH are similar to other types of WHO Group 1 pulmonary arterial hypertension, the mechanisms involved in the development of PoPH remain poorly understood [4]. PoPH is an uncommon complication of liver disease; furthermore, there is a weak association between pulmonary hypertension and the severity of liver disease [5,6]. A “multi-hit hypothesis” proposed to explain the mechanism of other types of pulmonary hypertension may also apply to PoPH [7]. According to this hypothesis, genetically predisposed individuals (first “hit”) develop a pulmonary vasculopathy resulting in intimal proliferation, medial thickening and plexogenic changes when subjected to additional environmental or genetic factors (second “hits”). In the case of PoPH, the necessary second “hit” may result from additional genetic factors, vasoactive metabolites that are inadequately metabolized by the liver, and pulmonary vascular stress induced by an increased cardiac output associated with liver disease. These potential mechanisms will be discussed subsequently.

Genetic factors

Several gene polymorphisms including bone morphogenetic protein receptor 2 (BMPR2) and other ligands belonging to the transforming growth factor-β (TGF-β) family are responsible for a significant proportion of hereditary PAH cases. However, these mutations do not appear to be associated with PoPH [3]. Data on gene polymorphisms associated with PoPH are very limited [8,9]. Only one study substantiated associations between PoPH and specific gene polymorphisms in 31 PoPH cases and 104 controls (advanced liver disease without evidence of PoPH) (Table 1) [8].

Vasoactive metabolites

Portal hypertension results in collateral circulation and shunts that drain the splanchnic bed directly into the systemic venous circulation and subsequently to the pulmonary circulation, bypassing metabolism in the liver. Failure of the liver to metabolize vasoactive substances has been considered a rational, although unproven mechanism to cause PoPH [10]. Increased serum concentrations of many vasoactive substances have been found in portal hypertension, though the specific offending metabolites remain unproven. A potential role for several of these substances in the development of PoPH is summarized in Table 2.

Vascular stress

A low systemic vascular resistance (SVR) commonly occurs with liver disease. The low SVR causes a compensatory increase in the cardiac output, occasionally up to 2-3-fold. The mechanism of low SVR involves vasodilatation that is either diffuse or limited to the splanchnic circulation [29]. The increased cardiac output augments pulmonary blood flow and may potentially cause stress of the vascular endothelial layer.

The mechanisms of pulmonary vasculature compensation for the high flow/hyperdynamic state remain controversial [30]. It is known that as the cardiac output rises, the resistance of the pulmonary vasculature decreases rapidly so that pulmonary pressures return to normal or near-normal levels. This response occurs within 60 min with moderate exercise. [31] Most situations that demand a high cardiac output are temporary (exercise, fever, distributive shock). Although this compensatory response of the pulmonary vascular bed is usually maintained for a prolonged period of time, persistent circulatory overload could potentially exhaust the compensatory mechanisms resulting in irreversible vascular changes of pulmonary hypertension. Studies demonstrating a wide variation in the pulmonary vascular response to increases in cardiac output

<table>
<thead>
<tr>
<th>Table 1 Genetic factors associated with PoPH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected pathways</td>
</tr>
<tr>
<td>Nitric oxide metabolism</td>
</tr>
<tr>
<td>Estrogen metabolism</td>
</tr>
<tr>
<td>Angiogenesis, Intracellular signaling, Others</td>
</tr>
</tbody>
</table>

PoPH-portopulmonary hypertension; NADPH-nicotinamide adenine dinucleotide phosphate.
among normal individuals [32] suggest that only a percentage of individuals are susceptible to pulmonary vascular damage from high cardiac output states. This theory of vascular stress may be relevant in other types of PAH associated with high cardiac output (hyperthyroidism, chronic hemolytic anemia, left-to-right atrial shunt, AV fistula) [33,34].

**Epidemiology**

PoPH accounts for approximately 5%—10% of all WHO Group 1 (pulmonary arterial hypertension) cases [35,36]. The prevalence of PoPH in liver transplant candidates with advanced cirrhosis may be as high as 8.5%, though most cases are mild [37]. Prevalence rates as high as 16% have been reported in decompensated patients with refractory ascites [13]. Although liver cirrhosis is overwhelmingly the most common cause of PoPH, it may occur in patients with non-cirrhotic liver disease [10]. Female sex and autoimmune liver disease are associated with a higher risk of PoPH (odds ratios 4 and 9.8 respectively) whereas hepatitis C liver disease may be relatively protective of PoPH (odds ratio 0.2) [6].

**Clinical presentation**

The symptoms and signs of PoPH are similar to those in other types of pulmonary arterial hypertension. Exertional dyspnea is the most frequent symptom, which is the presenting complaint in more than 80% of cases. Syncope, chest pain and fatigue are symptoms at presentation in less than one third of the cases of PoPH. An accentuated pulmonary component of the second heart sound (82%) and a systolic murmur (69%) are the most common physical findings [38]. Stigmata of portal hypertension may be present including ascites, splenomegaly, esophageal varices, “caput medusae”. In addition, signs of liver disease may be present such as “spider” angioma and palmar erythema.

**Screening**

Establishing the diagnosis of PoPH can be challenging because the disease is uncommon, screening tests are

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Table 2: Roles of mediators in PoPH.

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Serum level of mediator elevated in cirrhosis</th>
<th>Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-1</td>
<td>Yes, especially with portal hypertension and ascites</td>
<td>Higher levels of ET-1 are a risk factor for PoPH independent of the severity of portal hypertension.</td>
<td>[11–13]</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Yes</td>
<td>Glucagon increases portal blood flow and attenuates mediators of vasoconstriction causing a hyperdynamic state/pulmonary vascular stress.</td>
<td>[14,15]</td>
</tr>
<tr>
<td>VIP</td>
<td>Yes</td>
<td>VIP is 100-times more potent than acetylcholine as a splanchnic and peripheral vasodilator and may induce vascular stress.</td>
<td>[16–19]</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Yes. Also elevated in idiopathic pulmonary hypertension.</td>
<td>Serotonin has been implicated in PAH related to anorexigenic drug use.</td>
<td>[20–25]</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Yes with altered downstream metabolism.</td>
<td>Genetic variations in both the estrogen receptors and estrogen synthesis are associated with PoPH.</td>
<td>[26–28]</td>
</tr>
</tbody>
</table>

PoPH-portopulmonary hypertension; ET-1-endothelin-1; VIP-vasoactive intestinal peptide; PAH-pulmonary arterial hypertension; S100A4-S100 calcium binding protein A4.

Table 3: Causes of dyspnea in patients with liver disease.

<table>
<thead>
<tr>
<th>Pulmonary Parenchymal</th>
<th>Pulmonary edema (volume overload, renal failure)</th>
<th>Pneumonia</th>
<th>Pulmonary hemorrhage</th>
<th>Pleural effusion</th>
<th>Hepatic hydrothorax</th>
<th>Ascites causing lung restriction</th>
<th>PoPH</th>
<th>Hepatopulmonary syndrome</th>
<th>Cirrhotic cardiomyopathy</th>
<th>Anemia</th>
<th>Cirrhotic myopathy</th>
<th>Other common causes of dyspnea not related to liver disease (obesity, heart failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraparenchymal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pulmonary vascular disease</td>
<td></td>
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<td></td>
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<tr>
<td>Extrapulmonary</td>
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</tr>
</tbody>
</table>

PoPH-portopulmonary hypertension.
inexact and the diagnostic test is expensive and invasive. Nevertheless, it is imperative to diagnose PoPH early in its course as undetected disease may progress to a life-threatening state and/or preclude liver transplantation. All patients with portal hypertension reporting dyspnea should be screened for PoPH. The presence of PoPH is associated with an increased risk of perioperative morbidity and mortality from liver transplantation [37]. Therefore, it is imperative to screen for POPH in all liver transplantation candidates.

Although PoPH is a potential cause of dyspnea in patients with portal hypertension, advanced liver disease may result in dyspnea via many alternative mechanisms. A detailed diagnostic evaluation should be performed to exclude other potential causes of dyspnea (Table 3). Chest imaging is useful in identifying hepatic hydrothorax, cirrhosis-related cardiomyopathy or lung conditions unrelated to liver disease. Hepatopulmonary syndrome (HPS) is another pulmonary vascular disease associated with advanced liver disease. HPS is characterized by the presence of hypoxemia with an increased alveolar—arterial gradient (A–a gradient) and evidence of pulmonary vascular dilation. The diagnosis of HPS is usually confirmed by identifying the presence of an intrapulmonary shunt via echocardiography: intravenous instillation of agitated saline results in saline bubbles being visualized in the left atrium three or more cardiac cycles after they appear in the right atrium [3]. HPS and PoPH can coexist in the same patient.

The following routine clinical test results may suggest the possibility of PoPH: a) a chest radiograph showing decreased retrosternal space (enlarged right ventricle) and pruning of the pulmonary vasculature (large proximal arteries and disproportionately small peripheral vessels); b) an arterial blood gas revealing mild respiratory alkalosis with an increased alveolar-arterial oxygen gradient; c) an electrocardiogram demonstrating a right ventricular strain pattern; d) pulmonary function tests demonstrating a reduced diffusing capacity. None of these tests are sensitive enough to be used as a screening tool for PoPH.

2-dimensional surface Doppler echocardiography (2D Echo) is a universally accepted screening test for PoPH in patients with portal hypertension [39]. 2D Echo not only provides an estimate of right ventricular systolic pressure (RVSP), but also indicates structural changes associated with advanced pulmonary hypertension such as right-sided cardiac chamber enlargement and right ventricular pressure or volume overload. In a prospective study of patients undergoing liver transplant evaluation, a RVSP estimate of ≤30 mmHg on 2D Echo had a 100% sensitivity and negative predictive value for right-heart catheterization confirmed pulmonary hypertension [40]. The positive predictive value, however, proved to be poor at 59%. Based on the available data, the ERS recommends that PAH should be considered unlikely if the 2D Echo estimate of RVSP is < 36 mmHg and likely if the estimated RVSP is > 50 mmHg (Fig. 1) [41].

Unfortunately, an estimate of RVSP cannot always be obtained from echocardiography because of an inadequate tricuspid regurgitation jet. This scenario occurred in 22% of PoPH patients in one echocardiographic study [5]. Transesophageal echocardiography may be helpful in those cases, especially in obese patients. If the echocardiogram estimate of RVSP is < 50 mmHg or cannot be determined, right heart catheterization may be appropriate to evaluate patients for pulmonary hypertension if other morphologic features of the echocardiogram suggest pulmonary hypertension (pulmonic valve insufficiency, paradoxical septal motion, right ventricular hypertrophy/dilatation, poor tricuspid annular systolic excursion) or the clinical suspicion remains high (e.g., disproportionately severe dyspnea and/or reduced DLCO compared to spirometry, physical findings consistent with pulmonary hypertension, oxygen
desaturation with ambulation, diminished 6-min walk distance without an alternative clinical explanation).

### Diagnosis

The diagnosis of PoPH is established by right heart catheterization. The following criteria are required: mean pulmonary arterial pressure $>25$ mmHg; PaOP $<15$ mmHg; PVR $>240$ dyn s cm$^{-5}$; evidence of portal hypertension (Fig. 1). Patients meeting these criteria but demonstrating an elevated PaOP deserve a special mention. This scenario cannot be ascribed to pulmonary venous hypertension alone considering the elevation of PVR and often indicates a mixed etiology of pulmonary arterial hypertension and pulmonary venous hypertension. Although an elevated transpulmonary gradient (TPG, which equals mPAP-PaOP) of $>12$ mmHg has been used to identify pulmonary arterial hypertension in the presence of pulmonary venous hypertension in other forms of pulmonary hypertension, this finding is of limited value in identifying PoPH. This is because the requirement that the PVR exceed 240 dyn s cm$^{-5}$ in PoPH implies that the TPG will be elevated unless the cardiac output is lower than 4 L/min, which is uncommon in advanced liver disease. Patients showing this mixed form of pulmonary hypertension require clinical judgment in terms of whether the arterial and/or venous pulmonary hypertension should be treated; repeat right heart catheterization after a successful diuresis may be required for adequate management of these patients.

### Therapy

Therapy for PoPH is based on limited evidence and is often extrapolated from trial of other forms of pulmonary hypertension. Given these caveats, in this section we report the limited evidence and our recommendations for treatment of PoPH.

## Conventional PAH therapies

### Long-term oxygen therapy

Mild hypoxemia is common in PoPH. In a study of 20 patients with PoPH, 80% had an increased A-a gradient [42]. Hypoxemia can worsen pulmonary hypertension; therefore, supplemental oxygen therapy is recommended when the serum partial oxygen pressure (PaO$_2$) is $<60$ mmHg at rest [3].

### Diuretics

Diuretics are often used for the treatment of PH associated volume overload or ascites. However, the RV is preload-dependent and excessive diuresis may decrease preload causing hypotension and systemic hypoperfusion. In addition, excessive diuresis in the setting of diminished effective arterial blood volume, which is common in advanced cirrhosis, can result in kidney injury [43]. Therefore, diuretics should be cautiously used in PoPH.

## Pulmonary vasodilator therapy

Vasodilator treatment of PoPH is still not standardized because PoPH patients are typically excluded from PH trials; therefore, clinical data are meager concerning this condition (Table 4). As previously mentioned, the histopathological findings of PH and PoPH are very similar [44]. For these reasons, the ERS has recommended that PoPH be treated similarly to other forms of PAH [41]. In this section, we discuss the limited clinical data and recommendations concerning pulmonary vasodilator therapy for PoPH.

### Prostanoids

Prostanoids have been used for the treatment for PH for more than two decades [30]. Prostacyclin synthase is
Clinical aspects of portopulmonary hypertension

**Epoprostenol (EPO).** EPO is an intravenous synthetic form of prostacyclin. Because of its short half-life (∼6 min), EPO requires continuous infusion though a central access via an infusion pump. In idiopathic pulmonary arterial hypertension (IPAH), epoprostenol has shown to improve exercise tolerance, hemodynamics, quality of life and survival [46,47]. However, there are minimal data concerning EPO therapy for PoPH and they are less promising. Although two long-term retrospective studies of EPO treatment of PoPH demonstrated that hemodynamic improvement was sustained, there was no difference in survival [48,49]. Even though no survival advantage has been demonstrated, EPO may be used in patients with moderate to severe PoPH in an effort to improve symptoms or improve the outcome of liver transplantation (vide infra). EPO has been used as a bridge to liver transplantation with satisfactory results [49–51].

Common side effects of EPO include flushing, headache, nausea/vomiting, hypotension, bradycardia, chest pain, jaw pain, diarrhea and musculoskeletal pain [52]. EPO infusion requires maintenance of aseptic techniques to avoid blood stream infections. EPO pump failure or loss of vascular access may lead to rebound pulmonary vasoconstriction that can be life-threatening and requires immediate attention. A few reports suggested that EPO may cause ascites even without liver disease [53]. Worsening splenomegaly and hypersplenism has also been observed in PoPH patients treated with EPO [54].

**Treprostinil.** Treprostinil is a prostanoid that is available in an intravenous, subcutaneous and inhalational form. In a small case series of 3 patients with end stage liver disease and PAH, long-term administration of intravenous treprostinil was shown to improve hemodynamics [55]. Similar to EPO, treprostinil could be considered for the treatment of moderate to severe PoPH.

**Inhaled iloprost.** Because inhaled iloprost has a short therapeutic half-life of 20–30 min, it requires frequent administration 6–9 times per day. A study of 21 PoPH patients who received iloprost demonstrated a rapid reduction in PAP and PVR without any significant change in cardiac output, or hepatic venous pressure gradient [56]. These authors also found that the use of inhaled iloprost for PoPH improved WHO functional class and the 6-min walk distance (6MWD) at 12 months. Inhaled iloprost can be considered for the treatment of PoPH in patients capable of using this medication at its demanding dosing schedule.

**Endothelin receptor antagonists (ERAs).** ERAs block the production of endothelin-1 (ET-1), a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH. Elevated ET-1 concentrations have been reported in patients with advanced liver cirrhosis, and there is accumulating evidence that ET-1 may originate from the hepatosplanchnic circulation [11,57]. Several studies have shown that plasma levels of ET-1 are increased in PAH and correlate with severity and prognosis of PAH [58,59].

**Bosentan.** Bosentan is an oral, dual ET-1A and ET-1B receptor antagonist. There is a paucity of information concerning bosentan for the treatment of PoPH due to the risk of hepatotoxicity from this drug. In a small prospective case series (n = 11) and single case reports, bosentan was shown to improve exercise capacity, hemodynamics with good tolerance and without drug related toxicities [60–62].

**Ambrisentan.** Ambrisentan is a highly selective ET-1A receptor antagonist. Advantages of ambrisentan over bosentan include once daily dosing and a lower risk of hepatotoxicity. In a small observational study of 13 PoPH patients, monotherapy with ambrisentan was associated with significant improvement in mPAP and PVR without adverse effects on hepatic function [63]. Presently, although there are inadequate data to routinely recommend ERA’s for the treatment of POPH, those agents can be considered, and ambrisentan is preferred over bosentan.

**Phosphodiesterase-5 (PDE-5) inhibitors**

PDE-5 inhibitors prolong the vasodilatory effects of cyclic guanosine monophosphate (cGMP) by preventing its hydrolysis. PDE-5 inhibitors are commonly used for the treatment of PAH.

**Sildenafil.** Sildenafil has been used extensively in the treatment of PAH. Sildenafil alone or in combination with inhaled prostanooids significantly increased mean 6MWD and cardiac index as well as reduced mPAP, PVR and mean pro-brain-natriuretic-peptide levels in PoPH patients [64]. However, the hemodynamic improvements were not sustained at 12 months. In very small observational studies, sildenafil monotherapy has shown to improve pulmonary hemodynamics in liver transplant candidates, and may thereby facilitate liver transplantation [65,66]. Although these data are not conclusive, in our opinion, sildenafil can be used as monotherapy in mild cases of PoPH and in combination with prostanooids in moderate to severe PoPH.

**Tadalafil.** Tadalafil is an oral PDE-5 inhibitor with longer half-life than sildenafil so that it requires once daily administration. To date, only one case describing treatment of PoPH has been reported that showed a small improvement in portal venous and pulmonary artery pressures [67]. We believe that the role for tadalafil in the treatment of PoPH is similar to that of sildenafil.

**Drugs not routinely recommended for PoPH**

**Calcium channel blockers (CCB).**

Vasodilator testing during right heart catheterization is often performed in patients with PAH to determine the vasoreactive subgroup that may benefit from long-term CCB. However, the only data on CCB in PoPH consist of a retrospective study of 153 patients where just 2 (1.3%)
patients were vasoreactive and 1 of the 2 had a long-term sustained response with CCB [68]. In addition, CCB can cause splanchnic vasodilation that could, theoretically, increase the risk of variceal bleeding by raising the hepatic venous pressure gradient and portal vein bloodflow [69]. Given the lack of clinical data and the aforementioned theoretical concern, the use of calcium channel blockers in PoPH is not recommended.

**Beta-blockers**
Nonselective beta-blockers are often used in portal hypertension to reduce the risk of variceal bleeding. However, beta-blockers may impair exercise capacity and cardiovascular hemodynamics because of their negative chronotropic effects [70]. In a small study, beta-blocker withdrawal in PoPH was associated with improved exercise capacity and increased cardiac output [70]. We suggest cautious use of beta-blockers in PoPH; the clinician should weigh the potential risk of worsening hemodynamics against the benefits of improving portal hypertension.

**Anticoagulants**
Unlike other forms of PAH, anticoagulation is contraindicated in PoPH because of increased risk of GI bleeding [3].

Table 5 lists our recommendations concerning the use of pulmonary vasodilators to treat PoPH.

### Table 5  Therapy in PoPH.

<table>
<thead>
<tr>
<th>Agent class</th>
<th>Specific medications</th>
<th>Utility in PoPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostanoids</td>
<td>Epoprostenol ++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Treprostinil (inhaled, ++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>parenteral)</td>
<td></td>
</tr>
<tr>
<td>ERA’s</td>
<td>Iloprost ++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ambrisentan ++</td>
<td>++</td>
</tr>
<tr>
<td>PDE-5 Inhibitors</td>
<td>Sildenafil ++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tadalafil ++</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ channel blockers</td>
<td>All</td>
<td>-</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>All</td>
<td>-</td>
</tr>
<tr>
<td>Diuretics</td>
<td>All</td>
<td>+</td>
</tr>
<tr>
<td>Oxygen</td>
<td>N/A</td>
<td>++</td>
</tr>
</tbody>
</table>

PoPH-portopulmonary hypertension; ++ recommended to use; + use with caution; -use is discouraged; N/A not applicable.

Liver transplantation in PoPH
The presence of moderate to severe pulmonary hypertension in liver disease patients increases the risk of graft dysfunction and cardiopulmonary-related mortality after orthotopic liver transplant (OLT) [71]. For these reasons, the criteria for liver transplantation and management of liver transplantation of PoPH patients are highly relevant issues.

During liver transplantation, there is an acute three-fold increase in cardiac output from a) relief of portal vein obstruction by removing the diseased liver; and b) systemic vasodilation related to anesthesia, ischemia and reperfusion-induced cytokine release [72]. Given that the pulmonary vasculature in PoPH is a relatively low compliance and high resistance circuit, this increase in cardiac output can acutely raise the pulmonary arterial pressure significantly to precipitate acute RV dysfunction leading to graft congestion and failure [73–75]. Intraoperative transesophageal echocardiography during OLT may be useful to monitor RV function to detect and treat this complication.

The importance of adequately treating PoPH in patients undergoing OLT was demonstrated in a retrospective study of 43 OLT recipients with untreated PoPH who had a cardiopulmonary mortality proportional to the degree of PH (Table 6) [75].

The data in Table 6 and additional small studies suggest that PoPH patients with moderate to severe PH (≥35 mmHg) should be treated with vasodilator therapy before consideration for OLT [51]. In a study of PoPH patients with moderate to severe PH who were otherwise OLT candidates, 12 out of 16 (75%) had reduction of mPAP to <35 mmHg and 11 successfully underwent OLT. One-year survival was excellent at 91% [50]. The ERS Task Force Pulmonary-Hepatic Vascular Disorders Scientific Committee Guidelines state that OLT may be considered in mild pulmonary hypertension (mPAP <35 mmHg) with good cardiac function [3]. In OLT candidates with moderate PH (mPAP 35–45 mmHg), vasodilator therapy should be initiated and OLT could be considered if the mPAP can be successfully lowered to or below 35 mmHg. OLT is contraindicated in PoPH patients with a mPAP ≥45 mmHg (Fig. 2).

EPO has been effective in reducing the mPAP below 35 mmHg in PoPH patients, thus making these patients viable candidates for OLT [49–51]. Such patients have been successfully transplanted with a satisfactory post-transplant survival.

The response of PoPH to OLT is inconsistent. Some patients show an improvement in hemodynamics and, occasionally, are able to discontinue vasodilator therapy [50,76]. However, PoPH often fails to resolve after OLT, and it is prudent to continue vasodilator therapy immediately after transplantation. Periodic assessments with echocardiography and right heart catheterization should be performed to assess for the presence and severity of PoPH as well as the need for vasodilator therapy. There are inadequate data to determine if the outcome from combined liver-lung transplantation is superior to OLT for PoPH.

### Table 6  Cardiopulmonary mortality associated with Pre-OLT hemodynamic parameters in untreated PoPH patients (from Krowka, MJ et al., reference [75]).

<table>
<thead>
<tr>
<th>Pre-OLT hemodynamic parameter</th>
<th>Cardiopulmonary mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP &gt;50 mmHg</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>mPAP &gt; 35 mmHg</td>
<td>14/29 (48%)</td>
</tr>
<tr>
<td>mPAP &lt; 35 mmHg</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>PVR ≥ 250 dyn s cm⁻⁵</td>
<td>11/20 (55%)</td>
</tr>
<tr>
<td>PVR &lt;250 dyn s cm⁻⁵</td>
<td>1/18 (6%)</td>
</tr>
</tbody>
</table>

OLT-orthotopic liver transplantation; mPAP-mean pulmonary artery pressure; PVR-pulmonary vascular resistance.
In highly selected cases with liver and lung disease, combined liver-lung transplant has been successful [77].

Special considerations in PoPH

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS is frequently performed in advanced liver disease patients for gastrointestinal bleeding who have failed sclerotherapy or have refractory ascites. However, in small studies, TIPS has been shown to worsen pulmonary hypertension. As with liver transplantation, TIPS reduces the resistance in the portal circuit and thereby increases right ventricular pre-load resulting in an increase in pulmonary artery pressure [78]. Clinicians need to individualize the decision to perform TIPS in patients with PoPH, weighing the benefits of lessening the chance of life-threatening gastrointestinal bleeding with the risk of worsening pulmonary hypertension. Therapy for PoPH may need to be initiated or intensified when TIPS is performed in such patients.

Prognosis

Individuals with PoPH have a worse outcome compared to other forms of PAH even when matched for hemodynamic parameters (Fig. 3) [79]. A dismal median survival of 6 months for PoPH was reported in the era prior to the advent of specific vasodilator therapy [38]. These prognostic data are not surprising because PoPH patients have generally advanced liver disease in addition to pulmonary hypertension. PoPH patients are less likely to be on a PAH-specific therapy compared to other PH patients, perhaps due to lack of studies specifically studying pharmacological therapy in the PoPH population [80]. The disparity in the treatment of PoPH and other forms of PH may contribute to the difference in survival. In support of the need to treat PoPH, Swanson and colleagues compared survival of PoPH in relation to the use of medical therapy and/or OLT [81]. Overall, the survival was better in patients treated with either medical therapy or OLT as compared to those who were untreated. The combination of both interventions was superior to either used alone. The most common causes of death in PoPH are caused by either the underlying liver disease and pulmonary hypertension with a fairly even distribution [82].

The mortality rates for PoPH in the most recent studies in the past decade are less dire than previously; the improved survival may be attributable to the wider use of pulmonary vasodilator therapy and liver transplantation but

![Figure 2](https://example.com/ERS_Task_Force_Pulmonary_Hepatic_Vascular_Disorders_Scientific_Committee_Guidelines_for_PoPH_candidates_for_OLT.png)

**Figure 2** ERS Task Force Pulmonary-Hepatic Vascular Disorders Scientific Committee Guidelines for PoPH candidates for OLT [3]. OLT-orthotopic liver transplantation; PoPH-portopulmonary hypertension; mPAP-mean pulmonary artery pressure.

![Figure 3](https://example.com/Survival_in_PoPH.png)

**Figure 3** Survival in PoPH. PoPH-portopulmonary hypertension; IPAH-idiopathic pulmonary arterial hypertension (includes familial pulmonary arterial hypertension).
also to increased awareness and early diagnosis ("lead time bias") [83]. Because pulmonary vasodilator therapy and liver transplantation have concomitantly become more frequent options for PoPH, it is problematic to quantify the benefit that is specifically attributable to each modality [81].

Summary

PoPH is an important complication of advanced liver disease. It has a major impact on quality of life and suitability for liver transplantation. Timely diagnosis is essential to improve survival, alleviate symptoms and assess the perioperative risk of orthotopic liver transplantation. The etiology of PoPH remains unclear and may be related to poor hepatic clearance of certain metabolites and/or vascular stress in genetically susceptible individuals. With some specific nuances, treatment of PoPH is similar to the treatment of other types of PAH. Medical therapy and OLT improve survival in PoPH; however, PoPH patients are less likely to be on medical therapy compared to other forms of PAH. Raising awareness and specifically targeting the PoPH population in future studies could improve these patients’ management and further improve our understanding of this deadly condition.

Conflicts of interest

Boris Medarov-member of advisory board, Gilead; participant of a clinical trial by Lung LLC studying beraprost in PAH.

References

Clinical aspects of portopulmonary hypertension


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