Portopulmonary Hypertension and Liver Transplant:
Recent Review of the Literature

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Abstract

Portopulmonary hypertension is one of the main pulmonary conditions affecting patients with liver disease and/or portal hypertension. Other conditions include hepatopulmonary syndrome and hepatic hydrothorax. Portopulmonary hypertension is caused by pulmonary vasoconstriction and increased pulmonary vascular resistance. It develops as a result of portal hypertension with or without liver disease and is associated with a higher morbidity and mortality. However, portopulmonary hypertension is usually asymptomatic; the most common symptoms are dyspnea, fatigue, and peripheral edema. All liver transplant candidates should be screened for potential portopulmonary hypertension because its coexistence can affect survival rates after transplant. All patients with cirrhosis who present with dyspnea should also be screened. Transthoracic echocardiography is a noninvasive, useful method for screening, but right heart-sided catheterization remains the criterion standard for diagnosis. Portopulmonary hypertension carries a poor prognosis without liver transplant, and its severe form is considered to be a contraindication for liver transplant. Treating patients with pulmonary arterial hypertension-specific therapies before liver transplant for moderate and severe portopulmonary hypertension appears to be beneficial.

Key words: Pulmonary complications of cirrhosis

Introduction

Portopulmonary hypertension is a severe, uncommon pulmonary vascular complication of liver disease. It is a pulmonary hypertension that develops as a result of portal hypertension with or without liver disease.1 The combination of pulmonary arterial hypertension (PAH) and portal hypertension was first described by Mantz and Craigie in 1951. They reported a 53-year-old female patient with portal vein thrombosis with spontaneous portocaval shunt who exhibited an enlarged pulmonary artery; the patient’s postmortem examination revealed intimal thickening in the medium and large pulmonary arteries and endothelial proliferation of terminal pulmonary arterioles.2,3 Portopulmonary hypertension is characterized by vascular obstruction and increased resistance to pulmonary arterial flow due to varying degrees of pulmonary endothelial and smooth muscle proliferation, vasoconstriction, and in situ thrombosis.4 The European Cardiologic Society and the European Respiratory Society Task Force have defined the diagnostic criteria for portopulmonary hypertension as follows: mean pulmonary artery pressure > 25 mm Hg, pulmonary vascular resistance > 240 dyne·s·cm⁻⁵, and a pulmonary capillary wedge pressure < 15 mm Hg, measured during right heart catheterization (RHC) and clinical portal hypertension with or without significant chronic liver disease.5 According to the World Health Organization classification (Dana Point 2008), portopulmonary hypertension is located within PAH group 1 (Table 1).6

In this study, we provide an overview of portopulmonary hypertension, its epidemiology, pathophysiology and pathogenesis, clinical presentation, prognosis, and especially updated treatment options and indications for liver transplant.
Epidemiology
In different studies, the prevalence of portopulmonary hypertension has varied from 1% to 2% among portal hypertension patients. In liver transplant candidates, the prevalence of portopulmonary hypertension increases to 5% to 8% in the United States. However, in China, portopulmonary hypertension is estimated to be present in 4% of liver transplant candidates. Furthermore, in a recent study in Saudi Arabia, of 524 liver candidate patients with end-stage liver disease, 4 patients (1%) showed diagnostic criteria consistent with portopulmonary hypertension. Differences in causes could play a role in the differences in prevalence between the United States and other countries. In the US studies, the primary causes of liver cirrhosis have been alcohol abuse and hepatitis C virus infection. However, in other studies, the primary reason for liver disease was viral hepatitis. Those results agree with a previous study in which a negative correlation between hepatitis C virus infection and portopulmonary hypertension was shown to exist.

Portopulmonary hypertension is usually diagnosed in the fourth or fifth decades of life. Female sex and autoimmune hepatitis are independently associated with portopulmonary hypertension. In addition, the prevalence and severity of portopulmonary hypertension are not correlated with the severity of liver disease. The severity of portopulmonary hypertension measured by RHC has also not been found to correlate with the severity of portal hypertension. Portopulmonary hypertension occurs 4 to 7 years after patients are diagnosed with portal hypertension.

Pathophysiology and Pathogenesis
Although the exact mechanism is unknown, there are different theories behind the cause of portopulmonary hypertension. Some of them are related to genetic predisposition, pulmonary vascular wall shear stress, and dysregulation of vasoactive, proliferative, angiogenic, and inflammatory mediators, suggesting that portopulmonary hypertension may have a multifactorial pathogenesis. Histologically, it is characterized by obstruction of pulmonary arterial blood flow similar to idiopathic PAH. Intimal proliferation, media hypertrophy, fibrosis, and in situ thrombosis lead to thickened arterial walls and blood vessel occlusion and finally an increased pulmonary vascular resistance. In terms of pathophysiology, hyperdynamic circulation contributes first to the development of portal hypertension. Accompanying splanchnic arteriolar vasodilation, increased blood flow through the portal venous system at the microcirculation level causes characteristic hyperdynamic circulation. This leads to vascular stress and remodeling of the pulmonary arteriolar endothelium. However, this mechanism is not the only model explaining the development of portopulmonary hypertension because not all patients with portal hypertensive also develop portopulmonary hypertension. The second mechanism involves vasoconstrictors and vasodilators promoting pulmonary vascular tonus. The proliferative and vasoconstrictive substances produced by the diseased liver or substances normally metabolized by the liver can reach the pulmonary circulation through portosystemic shunts and disturb pulmonary circulation. Some of these substances are endothelin 1, thromboxane A2, interleukin 1, interleukin 6, angiotensin I, glucagon, serotonin, calcitonin gene-related peptide, and vasoactive intestinal peptide. Of these, endothelin 1A is the most studied substance. There are different studies that showed endothelin 1A levels are higher in cirrhosis with portopulmonary hypertension than in cirrhosis without portopulmonary hypertension.

Endothelin 1 causes vasoconstriction in pulmonary arteries and has mitogenic effects that stimulate the production of cytokines and growth factors. Whereas vasoconstrictive substances are increased, one study showed that the vasodilator substance prostacyclin (prostaglandin F2) is decreased in the small and medium pulmonary arteries of patients with portopulmonary hypertension. Some studies have shown that there is a strong relation among large portosystemic shunts, hepatofugal

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<th>Table 1. Updated Classification of Pulmonary Hypertension</th>
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<td><strong>Group 1. Pulmonary Arterial Hypertension</strong></td>
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<tr>
<td>- Idiopathic pulmonary arterial hypertension</td>
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<td>- Heritable pulmonary arterial hypertension</td>
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<td>- Drug and toxin induced</td>
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<td>- Associated with (associated pulmonary arterial hyperten</td>
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<td>- Connective tissue disease</td>
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<td>- Congenital heart disease</td>
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<td>- Schistosomiasis</td>
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<td>- Chronic hemolytic anemia</td>
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<td>Persistent pulmonary hypertension of the newborn</td>
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<td><strong>Group 2. Pulmonary Hypertension Due To Left-sided Heart Diseases</strong></td>
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<td><strong>Group 3. Pulmonary Hypertension Due To Lung Diseases and/or Hypoxemia</strong></td>
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blood flow, and portopulmonary hypertension. Furthermore, these shunts allow bacteria and bacterial endotoxins to pass from the gut to the pulmonary circulation, thus leading to an increase in inflammatory factors in pulmonary circulation. The fact that portopulmonary hypertension does not develop in all patients with portal hypertension (as mentioned above) suggests that there might be different causes such as genetic predisposition. One study found no association between mutations and consequent dysfunction of the bone morphogenetic protein receptor type 2 and portopulmonary hypertension, although an association between estrogen receptor 1, aromatase, phosphodiesterase 5, angiopoietin 1, calcium binding protein A4, cell growth regulator gene, and portopulmonary hypertension was observed. In a recent study, researchers found that CD16-positive/CD56-positive numbers representing the function of the natural killer cell were decreased in 5 of 9 patients (55.6%) with portopulmonary hypertension. The investigators suggested that portopulmonary hypertension might be a disease of acquired natural killer cell-mediated immune deficiency and that virus infection may be an important cause of portopulmonary hypertension. Further investigations regarding these mechanisms are still needed.

**Clinical Presentation**

Portopulmonary hypertension is usually asymptomatic. The first presenting symptom is dyspnea. However, dyspnea is not specific for portopulmonary hypertension as it can be seen with most cirrhosis complications like ascites. As the disease progresses, dyspnea begins to appear during rest, along with syncope and chest pain. Orthopnea, fatigue, and peripheral edema are other symptoms of portopulmonary hypertension. In a patient’s first physical examination, there may only be signs of liver disease and portal hypertension such as spider nevus, jaundice, palmar erythema, and ascites. As the disease progresses, a loud pulmonic component of the second heart sound, a holosystolic murmur in the left sternal border resulting from tricuspid regurgitation, a diastolic murmur of pulmonary regurgitation, and a right-sided third sound and then elevated jugular venous pressure, peripheral edema, pulsatile liver, ascites, and cool extremities can appear.

**Screening and Diagnosis**

Doppler transthoracic echocardiography (TTE) is a noninvasive and useful method for screening, but RHC is the criterion standard for diagnosis of portopulmonary hypertension. Electrocardiography may show findings of right ventricular hypertrophy and right atrial dilation, but these are not specific to portopulmonary hypertension. A chest radiograph would show a prominent main pulmonary artery, cardiomegaly due to enlarged right cardiac chambers, and increased vascularity in the upper lobes. Pulmonary function tests would show decreased lung diffusion capacity and reduced lung volume. In arterial blood gas analyses, hypoxemia and hypocapnia associated with an elevated alveolar-arterial oxygen gradient would be shown. Furthermore, the right heart chambers would appear dilated when viewed with computed tomography and magnetic imaging scans.

Patients who are not on the wait list for liver transplant should be screened if they have signs and symptoms of portopulmonary hypertension, whereas patients on a wait list should be screened even if they do not have signs and symptoms because this situation can affect their transplant candidacy.

The American Association for the Study of Liver Diseases and the European Society for Cardiology/European Respiratory Society task force recommends that all patients should be screened for portopulmonary hypertension during liver transplant evaluation. As mentioned above, TTE is the most useful method for screening; it can calculate right ventricular systolic pressure or pulmonary arterial systolic pressure by measuring tricuspid regurgitation. The consensus is that screening for portopulmonary hypertension with TTE is mandatory before liver transplant; however, the optimal cut-off for estimated right ventricular systolic pressure has not been universally decided. Colle and associates evaluated 165 patients waiting for liver transplant with TTE and RHC together. When they used 30 mm Hg as the cutoff value for diagnosis of transthoracic echocardiography, they found that 17 of 165 patients met the criteria, with RHC confirming 10 of them. Positive and negative predictive values were 59% and 100%. In a different study, when the group used a 50 mm Hg cutoff value, sensitivity and specificity of 97% and 77% were reported. These studies show that a right
ventricular systolic pressure < 30 mm Hg can be used to exclude portopulmonary hypertension, whereas a right ventricular systolic pressure > 50 mm Hg is predictive for portopulmonary hypertension; therefore, these patients should be evaluated later with RHC. Patients on a liver transplant wait list with no evidence of portopulmonary hypertension should be screened by TTE annually. After portopulmonary hypertension diagnosis, these patients require closer follow-up. Transthoracic echocardiography should be repeated every 3 months in patients on a liver transplant wait list because it can develop in as short as 2 to 3 months.

Although TTE is a good screening method, a definitive diagnosis of portopulmonary hypertension requires a hemodynamic assessment by RHC. The European Cardiologic Society and the European Respiratory Society Task Force have determined the hemodynamic criteria as follows: mean pulmonary artery pressure > 25 mm Hg, pulmonary vascular resistance > 240 dyne·s·cm⁻², and a pulmonary capillary wedge pressure < 15 mm Hg, as measured during RHC. Right heart catheterization is also important for disease staging. With the use of mean pulmonary artery pressure, the disease can be classified into 3 stages (Table 2). Staging is important for determination of risk of surgery and treatment decisions. As a summary, all patients on a liver transplant wait list should be screened for portopulmonary hypertension with TTE, and patients with high right ventricular systolic pressure should be evaluated with RHC.

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<th>Table 2. Staging of Severity of Portopulmonary Hypertension (the European Respiratory Society Task Force 2004)</th>
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<td>Stage</td>
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**Prognosis**

Prognosis of portopulmonary hypertension is not easily predictable, but it is generally poor. Severity of liver disease and stage of portopulmonary hypertension are not correlated. Without medical intervention, the 1-year survival rate is approximately 35% to 46%. In the Registry to Evaluate Early and Long-term PAH Disease Management Report, despite the better initial hemodynamics shown in patients with portopulmonary hypertension, 2- and 5-year survival rates were worse in patients with portopulmonary hypertension than in patients with PAH. At 5 years, survival rates for patients with PAH were determined to be 64% ± 2% and 40% ± 6% for patients with portopulmonary hypertension. Swanson and associates divided patients with portopulmonary hypertension into 4 groups according to treatment. Five-year survival rates according to treatment were as follows: 14.2% without medical intervention, 45.3% with medical treatment only, 25.4% with liver transplant only, and 67% with medical treatment and liver transplant. There were no associations between mortality, type of liver disease, and severity of liver disease.

**Treatment**

**General rules**

Treatment strategies for portopulmonary hypertension are derived from studies of idiopathic PAH. The effectiveness of these treatment strategies in patients with portopulmonary hypertension is still under investigation. First, evaluation of the severity of portopulmonary hypertension is important because therapy response is assessed according to change from baseline. The aim of therapy is to provide symptomatic relief and to improve the quality of life and exercise capacity and to facilitate liver transplant.

Because of venous stasis, slowed pulmonary blood flow, and right heart enlargement, patients with portopulmonary hypertension are at risk for thrombosis. There are some studies showing that anticoagulation can improve survival in idiopathic PAH patients. The goal international normalized ratio is 1.5 during anticoagulant therapy. However, patients with portopulmonary hypertension usually have an increased bleeding risk associated with gastroesophageal varices and thrombocytopenia; therefore, the decision for anticoagulation should be considered very cautiously.

The second problem in patients with portopulmonary hypertension is volume overload, as occurs with ascites. Diuretics can be used for fluid removal. Oxygen supplementation rules are the same as that used for PAH therapy. Calcium channel blockers can be used because of acute vasoreactive properties in PAH but can be dangerous in patients with portopulmonary hypertension because of their mesenteric dilatation properties, which may result in worsening of portal hypertension. Beta blockers...
and transjugular intrahepatic portosystemic shunts are indicated for portal hypertension but can be harmful to patients with portopulmonary hypertension.\textsuperscript{5,48} Because of these adverse effects, these therapies should be given careful consideration before implementation.

**Pulmonary arterial hypertension-specific therapies**

The aim of therapy for patients with group 1 PAH is based on 3 pathways of pulmonary vasoconstriction and vascular remodeling: the prostacyclin, nitric oxide, and endothelin pathways.\textsuperscript{45} Prostacyclin analogs (prostanoids), phosphodiesterase 5 inhibitors, endothelin receptor antagonists, and soluble guanylate cyclase stimulators target these main pathways.

**Prostanoids**

Prostacyclin derivatives are potent pulmonary and systemic vasodilators, and they have antiplatelet-aggregating and antiproliferative effects. In idiopathic PAH, these properties can improve hemodynamics and increase exercise tolerance.\textsuperscript{49} In 1993, Yoshida and associates showed the benefits of intravenous prostacyclin in patients with portopulmonary hypertension during and after the surgical procedure.\textsuperscript{50} The most commonly used prostacyclin is epoprostenol,\textsuperscript{49} and it has been reported that it can improve pulmonary hemodynamics through pulmonary vasodilatation.\textsuperscript{31} It is often used before liver transplant. For idiopathic PAH, it is the only treatment that can improve survival.\textsuperscript{49} In a recent study comparing time of treatment initiation, 5-year survival from the time of diagnosis in patients with portopulmonary hypertension who received early treatment was almost twice as high as that observed in the Registry to Evaluate Early and Long-term PAH Disease Management Report.\textsuperscript{52} These agents are effective, but they have adverse effects like jaw pain, diarrhea, erythema, arthralgia, and hypersplenism. Because they are administered intravenously, they are also associated with increased risk of catheter thrombosis, infection, and sepsis.\textsuperscript{53,54}

There are newer prostanoids for treatment. One of these newer prostanoids is treprostinil, which can be given as an intravenous or subcutaneous infusion. It can be used alone or in combination with other agents.\textsuperscript{55,56} A comparison between results with oral treprostinil in combination with other background PAH therapy in the FREEDOM-C and FREEDOM-C2 studies did not demonstrate a significant improvement in exercise capacity.\textsuperscript{57,58} Iloprost is a prostacyclin analogue that is beneficial to patients with idiopathic PAH when administered via inhalation. A recent study showed that inhaled iloprost has acute beneficial effects on pulmonary hemodynamics and resulted in both acute and sustained symptomatic improvement in patients with portopulmonary hypertension.\textsuperscript{39} In another recent report, the use of the oral synthetic prostanoid beraprost reduced pulmonary arterial pressure and resulted in sustained improved symptoms in 1 cirrhotic patient with portopulmonary hypertension.\textsuperscript{60}

**Endothelin receptor antagonists**

The potent vasoconstrictor molecule endothelin 1 is up-regulated in cirrhotic patients with portopulmonary hypertension.\textsuperscript{18} For blocking the endothelin receptors, there are different oral therapeutic options.\textsuperscript{61} Bosentan is an oral dual effective, nonselective receptor antagonist that blocks both endothelin A and B receptors. Bosentan can be used for different forms of PAH.\textsuperscript{39} Ambrisentan is a more selective endothelin A-receptor antagonist. Bosentan and ambrisentan can be given orally, and both can be used in patients with idiopathic PAH and in patients with portopulmonary hypertension.\textsuperscript{62} Liver function of patients with portopulmonary hypertension should be monitored closely during endothelin receptor antagonist therapy because these agents have been associated with hepatotoxicity in unselected patients with idiopathic PAH.\textsuperscript{63}

**Phosphodiesterase 5 inhibitors**

Phosphodiesterase 5 inhibitors inhibit the growth of pulmonary vascular smooth muscle cells and lower mean pulmonary artery pressure and pulmonary vascular resistance, mediating vasodilation through guanosine monophosphate.\textsuperscript{29,54} Sildenafil can cause splanchnic vasodilation and increase portal hypertension by preventing the breakdown of cyclic guanosine monophosphate, thus leading to nitric oxide-induced vasodilation of the vascular pulmonary bed; therefore, it should be used carefully.\textsuperscript{61} Sildenafil, vardenafil, and tadalafil are phosphodiesterase 5 inhibitors that can be used for pulmonary hypertension. In addition, sildenafil also improved hemodynamics in portopulmonary hypertension, and it can be used as a first step before liver transplant.\textsuperscript{64,65}
**Nitric oxide**

Nitric oxide is a selective vasodilator. It can use via inhalation. In mild cases of portopulmonary hypertension, it can be useful perioperatively.66,67

**Riociguat**

Riociguat stimulates soluble guanylate cyclase and increases cyclic guanosine monophosphate production that leads to vasodilatation.62,68 In the PATENT-1 study, riociguat improved exercise capacity and pulmonary hemodynamics in patients with PAH.68 Headache, dyspepsia, edema, nausea, dizziness, diarrhea, and hypotension are the most common adverse effects of riociguat.62,68

**Liver transplant**

Recently, because of high perioperative morbidity and mortality related to right heart failure, untreated moderate-to-severe portopulmonary hypertension is considered a contraindication to liver transplant.69-71 Krowka and associates divided 36 patients with portopulmonary hypertension who had undergone liver transplant into 3 groups according to mean pulmonary artery pressure: > 50 mm Hg, 35 to 50 mm Hg, and < 35 mm Hg. Mortality rates of the 3 groups were 100%, 50%, and 0%.33 To lower perioperative risk of liver transplant in portopulmonary hypertension, we should improve pulmonary hemodynamic measurements by means of vasodilation therapy before transplant. At the same time, there are some studies showing that portopulmonary hypertension can be resolved with liver transplant.72,73

Swanson and associates showed that the best treatment option is medical treatment plus liver transplant.39 According to the European Respiratory Society Task Force, patients with mean pulmonary artery pressure < 35 mm Hg can undergo a liver transplant, patients with mean pulmonary artery pressure of 35 to 45 mm Hg should receive vasodilator therapy before transplant, and patients with mean pulmonary artery pressure > 45 mm Hg should receive vasodilator therapy only.5 Patients with portopulmonary hypertension are eligible for Model for End-Stage Liver Disease standard exceptions. In a recent study, Goldberg and associates compared mortality rates of Model for End-Stage Liver Disease-approved patients with portopulmonary hypertension and nonexception wait list liver transplant candidates from 2006 to 2012. They found that patients with portopulmonary hypertension have a higher wait list position and higher posttransplant mortality rates.74

**Conclusions**

Portopulmonary hypertension is caused by pulmonary vasoconstriction and increased pulmonary vascular resistance. Portopulmonary hypertension is a pulmonary hypertension that develops due to portal hypertension with or without liver disease. It is associated with high morbidity and mortality. All liver transplant candidates should be screened for portopulmonary hypertension because it can affect survival rates after transplant. Portopulmonary hypertension cases should be discussed in an multidisciplinary fashion in conjunction with transplant hepatology, transplant cardiology, liver transplant anesthesia, and liver transplant surgery to make the ultimate decision regarding their liver transplant candidacy. All patients with cirrhosis who present with dyspnea also should be screened. Portopulmonary hypertension has a poor prognosis without liver transplant, but its severe form is considered to be a contraindication for transplant. In patients with moderate and severe portopulmonary hypertension, treatment with pulmonary arterial hypertension-specific therapies are recommended before liver transplant.

**References**


