Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Portopulmonary hypertension

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Abstract:

Portopulmonary hypertension (POPH) is defined as pulmonary arterial hypertension (PAH) complicated by portal hypertension, with or without advanced hepatic disease. Significant percentage of patients with cirrhotic liver disease has high cardiac output and subsequently elevated pulmonary arterial pressures (PAP). However, patients with POPH develop a progressive increase in pulmonary vascular resistance (PVR), which is generally lower than that observed in other forms of PAH.

The prognosis of untreated patients with POPH is very poor and the outcome of liver transplant (LT) in those patients is determined by the degree of severity of the associated pulmonary hemodynamics.

In this narrative review, we describe the clinical presentation of POPH, the pathobiology, and the clinical implication of pulmonary hemodynamics. We also provide evidence-based recommendations for the diagnosic and management approaches of POPH.

Key words:

Liver transplant, portal hypertension, portopulmonary hypertension, pulmonary arterial hypertension, vasodilator therapy, Saudi Association for Pulmonary Hypertension Guidelines

Portopulmonary hypertension (POPH) is defined as pulmonary arterial hypertension (PAH) complicated by portal hypertension, with or without advanced hepatic disease. It is classified as Group 1 in the current classification of pulmonary hypertension (PH). Although, it affects only 2-5% of the population suffering from portal hypertension, its clinical implications are enormous.[1-3] The prevalence of POPH in patients undergoing liver transplant (LT) is considered to be higher,[4] with one study showing prevalence of 8.5%.[5] Recent evidence from France shows that POPH was the third-most common type of PH seen in the consortium of 17 French hospitals.[6]

The outcome of LT in the presence of POPH is poor, with a 35% reported mortality rate in LT recipients having a mean pulmonary artery pressure (mPAP) >35 mmHg. A patient with high mPAP may be denied the opportunity for transplant unless the mPAP is brought below 35 mmHg with medical treatment. In patients who do undergo successful LT, there can be the resolution of PH with time.

The diagnostic criteria for POPH are shown in Table 1.

Approximately 30-50% of patients with cirrhotic liver disease have low systemic vascular resistance and high cardiac output (CO). In these patients, pulmonary arterial pressures (PAP) may be elevated due to increased CO. These patients have lower values of pulmonary vascular resistance (PVR). Some investigators propose that a cut-off of PVR >2 Wood unit be used in order to define POPH in the presence of hyperdynamic circulatory state.[7]

Certain risk fact is found to be associated with the development of POPH. Female sex and autoimmune hepatitis were associated with an increased risk of POPH, while patients with hepatitis C infection had a lower risk.[8] In addition, genetic variation in estrogen signaling and cell growth regulators have also been associated with the risk of POPH.[9]

The survival of untreated patients with POPH is very poor. In a recent retrospective study from the Mayo Clinic LT Group, they identified 74 POPH patients from 1994 to 2007, and categorized them in to three groups:

1. No therapy for POPH or LT,
2. Therapy for POPH alone and
3. Therapy for POPH followed by LT.

The 5-year survival in patients who received no therapy for POPH and no LT represents the natural history of POPH and was 14%, with 54% dying within 1 year of diagnosis. The median survival in patients who received medical therapy for POPH, but did not undergo LT was 46 months,

and 5-year survival was 45%, being significantly better than the former group (P = 0.03). Twelve patients underwent LT, and 5-year survival for the 9 patients receiving therapy for POPH was 67% as compared to 25% in 3 patients who were not pretreated with prostacyclin therapy.[10]

Pathogenesis

It has been found that the development of POPH is independent of the cause of the portal hypertension.[4,11,12] The severity of the underlying liver disease does not appear to correlate with the severity of POPH.[5] Hyperdynamic circulatory state and high CO are the hallmarks in most patients with POPH leading to increased shear stress on the pulmonary circulation. The PVR then rises owing to vasoconstriction, progressive pulmonary vascular remodeling, and *in situ* thrombosis.[13] The histological abnormalities in POPH are identical to those found in idiopathic pulmonary arterial hypertension (IPAH). The main pathological abnormalities include proliferate arteriopathy, obliteration of the vascular lumen by endothelial and smooth-muscle cells, formation of plexiform lesions, necrotizing arteritis, fibrinoid necrosis and *in situ* thrombi.[14-16]

The presence of portosystemic shunts may allow the shunting of the vasoactive substances from the splanchnic circulation to the pulmonary circulation, allowing these vasoactive mediators to bypass the liver metabolism and causing substantial effects on the pulmonary vasculature.[17,18]

Clinical Features

Dyspnea on exertion is the most common symptom. Other symptoms include fatigue, generalized weakness, light-headedness, and orthopnea. Physical examination may show abnormalities include accentuated and split second heart sound, systolic murmur, right ventricular (RV) heave, right sided S3 gallop, jugular vein extension, edema and the signs of either decompensated cirrhosis or overt right-heart failure, such as ascites and lower leg edema. Lower leg edema out of proportion to ascites due to portal hypertension may suggest associated POPH.[19,20] Arterial blood gases may show hypoxemia and increased alveolar-arterial oxygen gradient. The decrease in arterial oxygenation was found to be significantly worse in patients with POPH when compared with a cohort of patients that underwent screening for LT and normal RV systolic pressures (RVSP).[21] Hypoxemia may worsen POPH through pulmonary vasoconstriction, and therefore supplemental oxygen should be considered for all patients with hypoxemia to maintain oxygen saturation higher than 90% at all times. Electrocardiogram may show evidence of RV hypertrophy, right atrial enlargement, and right axis deviation. Chest X-ray is usually normal, but may show enlarged pulmonary arteries. Pulmonary function tests may be normal or may show mild restrictive defect and decreased diffusion capacity.

Table 1: Diagnostic criteria for portopulmonary hypertension

Diagnostic criteria
Clinical portal hypertension with or without significant chronic liver disease
mPAP >25 mmHg
PAWP <15 mmHg
PVR >2-3 wood units

mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure, PVR = Pulmonary vascular resistance

Diagnosis

According to the guidelines by American Association for the Study of Liver Disease, all patients being screened for LT should be evaluated for POPH by transthoracic echocardiography (TTE).[22] In a large prospective POPH screening study (N = 1235), RVSP of >50 mmHg was noted in 10.9% of patients. Right-heart catheterization (RHC) was conducted in this group of patients. The diagnosis of POPH based upon the current diagnostic criteria was made in 65% of patients having RVSP >50 mm on TTE. Therefore, 35% of these had "false positives" based solely upon Doppler echocardiography results.[23]

After initial screening with TTE, definitive diagnosis should be made by RHC that includes measurements of mPAP, pulmonary artery wedge pressure, CO, and calculated PVR.[17] Acute vasoreactivity test with either nitric oxide or prostacyclin may be done for prognostic significance and not to determine patient selection for calcium channel blocker therapy.

The diagnosis of POPH by RHC before LT is crucial as mentioned above because of the increased risk of death following LT in patients with mPAP >35 mmHg. Figure 1 illustrate the recommended for POPH if pre-LT mPAP is >35 mmHg. Patients with mPAP of <35 mmHg can be transplanted without undergoing specific PAH therapy for POPH.[24-27]

Right-heart catheterization is also important to help classify the severity of POPH[20] and therapeutic options based on the severity of disease [Table 2].

Management of Portopulmonary Hypertension

General measures

In addition to the general psychosocial factors, vaccination, and rehabilitation, keeping optimum oxygen saturation is

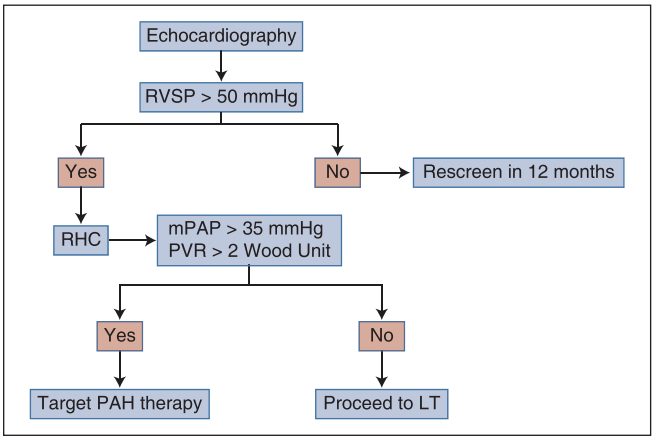

Figure 1: Screening for portopulmonary hypertension. RVSP = Right ventricular systolic pressure, mPAP = Mean pulmonary arterial pressure, PVR = Pulmonary vascular resistance, PAH = Pulmonary arterial hypertension, LT = Liver transplant

Table 2: Staging of severity of portopulmonary hypertension

Variable	Normal	Mild	Moderate	Severe
NYHA class	—	I-II	II-III	II-IV
mPAP (mmHg)	15-24	25-34	35-44	>45
CI (L/min/m^2)	2.5-4	>2.5	>2.5	<2.0
PVR (dynes/s/cm^5)	<80	240-500	500-800	>800
RAP (mmHg)	0-5	0-5	5-10	>10
Prognosis	—	Favorable	Questionable	Poor
Specific therapy	—	No	Questionable	Yes
Reversibility after LT	—	Yes	Questionable	No

NYHA = New York heart association, mPAP = Mean pulmonary arterial pressure, CI = Cardiac index, PVR = Pulmonary vascular resistance, RAP = Right atrial pressure, LT = Liver transplantation

crucial, as ongoing or episodic hypoxemia can make POPH worse.

Diuretics

Diuretics are useful in reducing the increased intrapulmonary vascular volume commonly present in chronic liver disease and thus having modest effect on PAP and improvement of RV function. Diuretics have to be used with caution in patients with POPH as they can reduce the CO by decreasing the RV preload.[18]

Digoxin

Although digoxin has been shown to improve CO acutely in IPAH, its efficacy is unknown when administered chronically in patients with POPH.[28]

Anticoagulation

There is a favorable response with anticoagulation in other forms of PAH, especially in IPAH and chronic thromboembolic pulmonary hypertension (CTEPH) for its ability to slow disease progression. Anticoagulation is traditionally not recommended in patients with POPH because of the inherent risk of hemorrhagic complications in patients with underlying liver disease and portal hypertension, especially in patients with a prior history of gastrointestinal bleeding.[17]

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt may worsen POPH because of acute hemodynamic change causing RV strain and dysfunction. It is not recommended in patients with POPH.

Specific therapy

Very limited data exist in term of specific medical therapy in POPH. Most of the studies are case series or case reports.

Calcium channel blockers

Calcium channel blockers, which are often considered the first-line treatment in patients who have a positive response to the acute vasodilator challenging test during RHC, are not recommend in POPH, as they could potentially increase the hepatic venous pressure gradient.[29,30]

Prostanoids

Prostanoids have been shown to be effective in the treatment of POPH. Epoprostenol is the best-studied prostanoid in POPH. In moderate to severe POPH, intravenous epoprostenol results in significant improvement (both acute and long-term) in PVR, mPAP, and CO. Pulmonary hemodynamics may be improved and brain natriuretic peptide and human atrial natriuretic peptide decrease to normal levels during epoprostenol therapy. Epoprostenol has been shown to significantly improve pulmonary hemodynamics, and so facilitate acceptance of patients who may otherwise be denied LT as a result of POPH.[31,32] As use of epoprostenol may potentially worsen hepatic function and cause clinical deterioration of liver disease, careful clinical follow-up is advisable. Another important reported concern with epoprostenol is the development of progressive splenomegaly with worsening thrombocytopenia.[33] However, recent data from Mayo Clinic does not demonstrate a statistically significant decrease in platelet count in a large cohort of patients with POPH treated with epoprostenol.[34] Iloprost, a stable prostacyclin analogue, is a valuable alternative to epoprostenol.[35]

Endothelin receptor antagonists

Combination therapy with intravenous Iloprost and oral bosentan, a dual endothelin-1 receptor antagonist, might extend the survival of selected patients suffering from POPH and recurrent right-heart failure.[36] Bosentan has been shown to be effective in the treatment of POPH, showing clinical, functional, and hemodynamic benefits without significant elevation of hepatic aminotransferases.[37-42] Bosentan is an attractive therapy in POPH as it may improve both pulmonary and portal hypertension. Macitentan, a new dual endothelin-receptor antagonist may show a useful addition in the management of POPH in future studies.

Phosphodiesterase inhibitors

Sildenafil has been reported to be effective in decreasing PVR.[43,44] Sildenafil was used in 14 patients with moderate to severe POPH from diverse etiologies. Eight patients were newly started on sildenafil, while 6 patients were already on therapy with inhaled prostanoids (iloprost in five and treprostinil in one). Sildenafil appeared to provide therapeutic benefit in term of decreasing the mPAP and PVR when evaluated at 3 months, but the hemodynamic benefit was not sustained after 12 months in 7 patients. The 6-min walk test continued to improve at 3 and 12 months.[45]

Soluble guanylate cyclase stimulator

Riociguat, a soluble guanylate cyclase stimulator, has been approved for treatment PAH and CTEPH after showing positive results in a double blind randomized controlled trial.[46] Riociguat has a potential role for future research in POPH.

Combination therapy

Combination therapy has been shown to be effective in patients with IPAH,[47] but its role in POPH has not been established.

Lung transplant

Patients with end-stage liver disease and severe PH may be considered for combined liver — lung, which is offered in a few highly specialized centers in the world. The largest series of combined liver — lung transplantation so far has reported a 3-year survival of 62%.[48] However, patients with mild to moderate POPH do not routinely require lung transplantation, as the disease might stabilize, or even improve, after LT.

Table 3: Recommendations for PAH associated with POPH

Statement	Class of recommendation	Level of evidence
Echocardiographic screening for the detection of POPH is recommended in symptomatic or hypoxic patients with liver diseases and/or in candidates for liver transplantation	I	B
RHC should be performed in all patients with RVSP >50 mmHg by echocardiography and in those who are candidate for liver transplant	I	B
In patients with POPH the same treatment algorithm as in patients with IPAH should be considered, taking into consideration comorbidities	IIa	C
The use of anticoagulation in POPH patients with increased risk of bleeding	III	C
The use of calcium channel blocker in POPH patients (as they could potentially increase the hepatic venous pressure gradient)	IIb	C
POPH patient with severe PAH (PAP is >45 mmHg and/or PVR is >800 dynes.s/cm^5) should not be cleared for liver transplant because of very high mortality	I	C
POPH patient with moderate PAH (PAP is >35-45 mmHg and/or PVR is 500-800 dynes.s/cm^5) should be treated to improve hemodynamics before LT can be considered	IIa	C
POPH patient with mild PAH (PAP is <35 mmHg and/or PVR is <400 dynes.s/cm) should be cleared for liver transplant without medical therapy	IIa	C

POPH = Portopulmonary hypertension, RHC = Right-heart catheterization, RVSP = Right ventricular systolic pressure, IPAH = Idiopathic pulmonary arterial hypertension, PAH = Pulmonary arterial hypertension, PVR = Pulmonary vascular resistance, PAP = Pulmonary artery pressure, LT = Liver transplantation

Conclusion

Portopulmonary hypertension is a type of PAH associated with portal hypertension. The proposed pathophysiology includes hyperdynamic pulmonary circulation leading to shear stress of pulmonary vasculature causing obstructive vasculopathy and increased pulmonary resistance. The diagnosis of POPH is suggested by TTE and is confirmed by RHC. Mortality in advance liver disease in the presence of PH is high. Every effort should be made to treat these patients with specific vasodilator therapy to reduce mPAP and PVR, and ultimately improve RV function. Treatment with a combined approach of specific PAH therapy and LT may improve long-term survival in patients with POPH. Randomized controlled trials are needed to determine the future direction in the management of POPH. Table 3 shows the class of recommendation and the level of evidence for POPH management.

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