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TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Portopulmonary hypertension in liver transplant candidates

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Abstract

Pulmonary vascular disorders including portopulmonary hypertension (PoPHT) are among the common complications of liver disease and are prognostically significant. Survival is very low without medical treatment and liver transplantation. With advances in medical therapy for elevated pulmonary artery pressure (PAP) and liver transplant surgery, survival of patients with PoPHT and advanced liver disease is significantly improved. Because of the prognostic significance of PoPHT and the limited donor pool, a comprehensive preoperative cardio-pulmonary assessment is of great importance in cirrhotic patients prior to transplant surgery. Therefore, a detailed transthoracic Doppler echocardiographic examination must be an essential component of this evaluation. Patients with mild PoPHT can safely undergo liver transplant surgery. In cases of moderate to severe PoPHT, right heart catheterization (RHC) should be performed. In patients with moderate to severe PoPHT on RHC (mean PAP 35-45 mmHg), vasodilator therapy should be attempted. Liver transplantation should be encouraged in cases that demonstrate a positive response. Bridging therapy with specific pulmonary arterial hypertension treatment agents should be considered until the transplant surgery and should be continued during the peri- and post-operative periods as needed.

Key words: Portopulmonary hypertension; Pulmonary arterial hypertension; Liver disease; Liver transplantation; Portal hypertension

Core tip: Portopulmonary hypertension (PoPHT) is one of the most common findings on preoperative assessment of cirrhotic patients prior to liver transplant surgery. Since it has prognostic significance, diagnosis of PoPHT by Doppler echocardiography and further characterization by right heart catheterization is critical in classifying these patients. Therapy with pulmonary arterial hypertension (PAH)-specific agents should be started when PoPHT is moderate to severe. Patients with a positive response should be encouraged to undergo liver transplant surgery. Bridging therapy with

these agents should be considered until the time of transplant surgery and continued during the peri and postoperative periods as needed.

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INTRODUCTION

Patients with advanced liver disease display a variety of pulmonary abnormalities. Pulmonary vascular disorders - including portopulmonary hypertension (PoPHT) - are among the common complications of liver disease. Pulmonary hypertension in these patients is also defined as PoPHT when pulmonary arterial hypertension (PAH) is associated with portal hypertension[1-3]. Although it is commonly seen in cirrhotic patients, it may also occur in the absence of liver disease. The Nice World Pulmonary Hypertension Symposium classified PoPHT as one of the associated forms of PAH[4]. In this paper we review the literature about PoPHT in liver transplant candidates.

DIAGNOSIS

The diagnosis of PoPHT requires the following 2 conditions: (1) Elevated pulmonary arterial pressure (PAP) and other hemodynamic variables obtained by right heart catheterization (RHC). Mean PAP > 25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15 mmHg and pulmonary vascular resistance > 240 dynes/s per cm^{-5}; and (2) presence of portal hypertension (with or without liver disease). Documentation of splenomegali, portosystemic shunts, thrombocytopenia or varices - these are accepted as signs of portal hypertension.

Assessment and staging severity of PoPHT based on transthoracic Doppler echocardiography (TTDE) and RHC are provided in Table 1[1].

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Although evidence varies widely, PoPHT is seen in as many as quarter of patients with advanced liver disease[5]. Krowka *et al*[6] demonstrated that 5% of patients with chronic liver disease have hemodynamic criteria for PoPHT. Data from a French PAH registry showed a prevalence of 9.4%[7]. A report from the multicenter United States-based REVEAL registry involving more than 3500 patients showed that 5% had PoPHT[8]. The exact pathogenesis of PoPHT is not well defined. Arterial hyperdynamic circulation, increased venous blood volume and pressure, pulmonary artery vasoconstriction and neurohumoral activation are responsible for the development of PoPHT in cirrhotic patients[9]. It has similar histopathological features as other types of PAH[10,11]. Obstruction of pulmonary arterial blood flow, proliferation of periarteriolar smooth muscle cells, vasoconstriction, increased endothelin concentrations, platelet aggregation/in situ thrombosis are characteristic findings in PoPHT and other forms of PAH[11-14]. The severity of liver disease did not correlate with the severity of PoPHT[15].

Table 1 Summary on assessment, grading and therapy for portopulmonary hypertension

TTDE in all patients prior to transplant surgery, systolic PAP ⩾ 30 mmHg
RHC in selected cases, confirmation and grading of PoPHT:
Mild PoPHT: mPAP > 25 mmHg, PVR > 240 dynes/s per cm^{-5}, PCWP ⩽ 15 mmHg, allow LT
Moderate PoPHT: mPAP 35-45 mmHg, PVR > 240 dynes/s per cm^{-5}, PCWP ⩽ 15 mmHg if responder to vasodilator therapy, allow LT
Severe PoPHT: mPAP > 45 mmHg, PVR > 240 dynes/s per cm^{-5}, PCWP ⩽ 15 mmHg, medical therapy

PoPHT: Portopulmonary hypertension; TTDE: Transthoracic Doppler echocardiography; PAP: Pulmonary artery pressure; RHC: Right heart catheterization; PVR: Pulmonary vascular resistance; LT: Liver transplantation.

SYMPTOMS AND SIGNS

Symptoms of PoPHT may not be overt and may be attributed to underlying liver disease or associated conditions. Therefore, the recognition of PoPHT requires high clinical suspicion. Symptoms are similar to those in other forms of PAH. Dyspnea is the most common symptom in patients with PoPHT. Weakness, easy fatigue, edema, orthopnea, palpitation and chest pain on exertion are other common symptoms. Syncope may occur in patients with severe PoPHT.

On physical examination, there may be jugular venous distension, a loud S2, left parasternal systolic murmur due to tricuspid regurgitation, peripheral edema, and ascites.

Chest X-ray findings are non-diagnostic and may show cardiomegaly and dilation of main pulmonary arteries. Electrocardiographic findings include right bundle branch block, right axis deviation and precordial T wave inversions. Mild-moderate hypoxemia and hypocapnia are common in arterial blood gases analyses.

ASSESSMENT

TTDE is an accurate, reliable, and reproducible tool to estimate systolic PAP in the absence of pulmonary stenosis or right ventricular outflow tract obstruction[8]. It has high sensitivity as a screening test. Its non-invasive nature makes it a recommended method

to screen for PoPHT in patients with cirrhosis[7]. Pulmonary artery pressure should be carefully evaluated. For this purpose, the maximum tricuspid regurgitant flow velocity (v) should be obtained using continuous wave Doppler examination followed by systolic PAP calculations using the modified Bernoulli equation. [Systolic PAP (mmHg) = $4v^2$ + estimated mean right atrial pressure]. Patients with a systolic PAP value $\geqslant$ 30 mmHg are usually diagnosed with PoPHT[16]. With this cutoff (30 mmHg), positive and negative predictive values of 59% and 100% respectively were reached[17].

TTDE also provides additional valuable information about the indirect signs of PAH such as right ventricular dilatation, right ventricular hypertrophy and abnormal septal motion[18]. TTDE has a pivotal role in the initial evaluation of PoPHT as recommended by both European and the American guidelines[19,20].

Because PoPHT has prognostic significance it is common belief that TTDE is mandatory in the evaluation of cirrhotic patients prior to liver transplant even when the patient is asymptomatic.

However, the exact timing of RHC and systolic PAP cutoff values have yet to be identified. Different centers report varying approaches. A systolic PAP value > 50 mmHg *via* TTDE gave a sensitivity of 97% and a specificity of 77% *via* RHC[21]. This suggests that RHC should be considered when systolic PAP > 50 mmHg and in situations where systolic PAP is 30-50 mmHg with other signs of PoPHT such as right ventricular dilation or dysfunction as well as signs of right ventricular failure.

RHC is the gold standard method for the diagnosis of PoPHT[3,22]. Not only does it confirm PoPHT but it also provides additional data to exclude other causes of PAH in liver transplant candidates. By obtaining pulmonary vascular resistance (PVR), cardiac output, mean PAP and PCWP, the nature and severity of PoPHT can be highlighted (Table 1). For example, in cases of left heart disease, the cardiac output (CO) is reduced and PVR and PCWP are increased. In patients with PoPHT, CO and PCWP are low while PVR is elevated. In the hyperdynamic state the CO increases, PCWP is normal and PVR decreases. Because the treatment and prognosis of these clinical conditions are entirely different, their documentation is very important. Patients with elevated mean PAP but normal PVR (hyperdynamic state) benefit from liver transplantation. These patients should proceed to liver transplant surgery without further characterization and treatment. The trans-pulmonary gradient can be calculated as a mean PAP-PCWP. Values above 12 mmHg have been shown to correlate with increased PVR[23,24].

PROGNOSIS AND OUTCOME

Without liver transplantation and medical therapy, cirrhotic patients with PoPHT have very poor prognosis[13,25,26]. Before the availability of PAH-specific therapies, the survival of patients with PoPHT is very poor[27]. Swanson *et al*[28] from the Mayo Clinic reported a 14% survival at 5 years in PoPHT patients without liver transplantation and PAH-specific therapies. Complications of advanced liver disease and right ventricular failure due to progressive elevation in PAP are responsible for poor survival rates.

A study by Kia *et al*[29] demonstrated that elevated PAP determined by TTDE was associated with increased mortality and morbidity following liver transplant surgery. Data from the Multicenter Liver Transplant Database demonstrated a mortality rate of 36% in patients with PoPHT undergoing liver transplantation[30]. The exact mechanism of how the risk increases in cirrhotic patients with PoPHT following liver transplant surgery is unclear. However, multisystemic involvement, pleural effusion, right-sided heart failure, peri- and post-operative fluid shift, hypoxia and surgical trauma are among the possible mechanisms.

The REVEAL registry provides us with valuable information regarding treatment and outcome of PoPHT[8]. Initiation of PAH-specific therapies were delayed in PoPHT *vs* idiopathic PAH. Baseline hemodynamics were better in PoPHT than those in idiopathic PAH; survival was worse in PoPHT.

TREATMENT

Drug therapy

Calcium channel blockers are not advised in patients with PoPHT. As a consequence of mesenteric vasodilation, they have the potential to worsen portal hypertension. Beta-blockers are not suggested because they may reduce exercise capacity. Warfarin anticoagulation is not recommended because of the risk of hemorrhage in cirrhotic patients. Diuretics are useful agents for symptomatic benefits in patients with volume overload and fluid retention. Both loop and potassium sparing diuretics can be used for this purpose. Oxygen therapy is recommended in hypoxic patients (PaO_2 < 60 mmHg, O_2 saturation < 90%).

Data regarding the use of PAH-specific therapies are limited in patients with PoPHT. This is because most studies excluded patients with PoPHT. Table 2 provides a short summary on the new PAH specific agents in use. However, these agents were used in small studies that enrolled a limited number of patients with PoPHT[31-35]. In general, these agents provided significant hemodynamic improvement.

Liver transplantation

Innovation in surgical techniques, improvements in peri-operative care and developments in immune suppressant drugs have made organ transplantation the preferred therapy for patients with end stage

Table 2 Pulmonary arterial hypertension-specific therapy: A summary of agents used

Entothelin receptor antagonists
Agents used in PoPHT: bosentan, ambrisentan
Mechanism of action: blockade of endothelin receptors
Route of administration: oral
Effects: vasodilation, decrease in PVR and portal pressure
Adverse effects: hepatotoxicity
PDE-5 inhibitors
Agents used in PoPHT: sildenafil, tadalafil, vardenafil
Mechanism of action: inhibition of PDE-5 enzyme
Route of administration: oral
Effects: vasodilation, decrease in portal pressure
Adverse effects: hypotension
Prostacyclins
Agents used in PoPHT: epoprostenol, iloprost
Mechanism of action: prostaglandin analogue, increase in cAMP
Route of administration: epoprostenol IV, iloprost inhalation
Effects: vasodilation, antiaggregation
Adverse effects: flushing, headache, nausea, diarrhea. Problems with IV epoprostenol use: cost, infection, catheter thrombosis, and thrombocytopenia

PAH: Pulmonary arterial hypertension; PoPHT: Portopulmonary hypertension; PDE-5: Phosphodiesterase type 5 enzyme; PVR: Pulmonary vascular resistance; IV: Intravenous.

organ failure. Liver transplantation is the best available therapeutic option for the treatment of patients with end stage liver disease. Advances in medical therapy for elevated PAP and liver transplant surgery, survival of patients with PoPHT and advanced liver disease are thus significantly improved[28]. Treatment strategies for PoPHT in cirrhotic patients are mainly based on recommendations for idiopathic PAH management and the treatment of underlying liver disease. Thus, by definition, a functioning transplanted liver graft emerges as a therapeutic option for PoPHT in such cases. As surgical techniques, hospital care, and PAH-specific therapies have improved, the stabilization and improvement and even cure of PoPHT in cirrhotic patients is achievable with liver transplantation. In a previous study we determined that liver transplantation improves PoPHT[36].

Patients with mild PoPHT can safely undergo liver transplant surgery. In cases of moderate to severe PoPHT, the response to vasodilator therapy should be evaluated. When mean PAP is lowered to < 35 mmHg, patients benefit from liver transplant surgery and liver transplantation should be encouraged.

Swanson *et al*[28] demonstrated that a combination of PAH-specific therapy and liver transplantation provided the best outcome *vs* those who did not receive any therapy and those who only received medical therapy. Survival at 5 years were 76%, 14% and 45%, respectively. These findings are valuable and clinically relevant. Therefore it is of great value to evaluate patients with moderate to severe PoPHT whether they respond or not. Unfortunately, there is no way to predict long-term response to vasodilator therapy. The evaluation of PAP should be repeated at 3-mo intervals because response to vasodilator therapy cannot be obtained with short-term use. Thus, the determination of acute responders during RHC is not recommended[37].

When PoPHT is severe it usually contraindicates liver transplantation[38,39]. Conversely, liver transplantation is a therapeutic option in patients with PoPHT and advanced liver disease. A functioning liver graft decreases pulmonary artery pressure in these patients[28,36].

In a study by Starkel *et al*[5] PoPHT was identified in 38 of 145 patients (26%). It was mild in 82% of cases. The duration of mechanical ventilation and intensive care unit stay was similar between patients with and without PoPHT. One of the 5 patients who had severe PoPHT (mean PAP > 40 mmHg) died, but the remaining 4 patients were alive and in excellent clinical condition during the 3 years of follow up.

In the United States, transplant programs prioritize if the hemodynamics can be improved with PAH-specific therapies and meet standardized MELD exception guidelines[40]. Goals of treatment for this approach are as follows: (1) Documentation of moderate to severe PoPHT by RHC (mean PAP $\geqslant$ 35 mmHg, PCWP $\leqslant$ 15 mmHg, and PVR > 400 dynes/s per cm^{-5}); (2) Improvement in hemodynamics with PAH-specific therapy (mean PAP < 35 mmHg, PVR < 400 dynes/s per cm^{-5} and satisfactory right ventricular function on TTDE, as well as improvement in right ventricular dilation and function); and (3) MELD exception update every 3 mo.

The aim of this policy is to perform liver transplantation before irreversible changes related to PoPHT occur. When liver transplantation is to be performed in patients with severe PoPHT demonstrating a positive response to vasodilator therapy, perioperative use of inhaled nitric oxide and intravenous epoprostenol should be considered. Adequate right ventricular function is very significant with regard to a successful transplant operation in patients with PoPHT. Prolonged PoPHT and progressively increasing PAP may predispose subjects to right ventricular hypertrophy and eventually right ventricular dysfunction. In such cases an acute rise in cardiac output to more than 15 L/min during the reperfusion of the liver graft may precipitate acute right ventricular failure. Liver transplant surgery itself induces marked hemodynamic alterations that can adversely affect the peri-operative course in patients with pulmonary vascular disease. Acute right ventricular failure and right ventricular dysfunction may develop in patients with severe PoPHT that may be fatal. Therefore right ventricular function should also be evaluated during the peri- and post-operative periods. In case of right ventricular failure, milrinone can be used, and PAH specific agents should be continued following transplant surgery as necessary.

Growing evidence suggests that unless severe and associated with right ventricular dysfunction, PoPHT should no longer be considered to be an

absolute contraindication to liver transplantation. The current data indicate that PoPHT improves and even normalizes in some cases following successful liver transplantation[5,36,41]. Therefore, this suggests that liver transplantation should not be denied in all patients with severe PoPHT. When patients are in good clinical condition, young, and without severe right ventricular dysfunction or high pulmonary vascular resistance, improvements in PAP with vasodilator therapy liver transplantation should still be considered even when PoPHT is severe.

Khaderi *et al*[42] reported the long-term follow up results of patients with severe PoPHT who underwent orthotopic liver transplantation. Of the 488 liver transplant patients, 7 had severe PoPHT. All 7 of these patients received vasodilator therapy (6 patients IV epoprostenol, 1 oral sildenafil) and their mean PAP reduced to ⩽ 35 mmHg. They also received IV or inhaled epoprostenol during the peri-operative period. The survival rate was 85.7% after a median follow up of 7.8 years. Furthermore, all the surviving patients were in good functional status (NYHA Ⅰ or Ⅱ). Although the number of patients enrolled is small, the findings of this study are valuable and clinically relevant. This demonstrates that liver transplantation improves PoPHT even when severe. The authors concluded that moderate to severe PoPHT responsive to vasodilator therapy does well with liver transplantation, and such patients should be accepted as good candidates for transplant surgery.

CONCLUSION

Given the prognostic significance of PoPHT and the limited donor pool, a comprehensive preoperative cardio-pulmonary assessment is of paramount importance in cirrhotic patients prior to transplant surgery. A detailed Doppler echocardiographic examination must be the essential component of this evaluation. Pulmonary artery pressure should be calculated and right ventricular function should also be assessed. The RHC should be considered when PoPHT is moderate to severe.

PAH-specific agents - either alone or in combination - are critical when deciding on liver transplant surgery in patients with moderate to severe PoPHT. Liver transplantation should be encouraged in cases displaying a positive response. Bridging therapy with specific PAH treatment agents should be considered until transplant surgery. This should be continued during the perioperative period and following surgery as needed.

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