Preoperative Assessment and Management of Liver Transplant Candidates With Portopulmonary Hypertension

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Michael J. Krowka, MD Professor of Medicine Division of Pulmonary and Critical Care Medicine Mayo Clinic Rochester, MN Pulmonary artery hypertension (PAH) that occurs as a consequence of portal hypertension is termed portopulmonary hypertension (POPH) and is associated with significant morbidity and mortality. Among liver transplant (LT) candidates, reported incidence rates of POPH range from 4.5% to 8.5%. The severity of POPH is unrelated to the severity of portal hypertension or the liver disease. In LT patients, intraoperative death and immediate post-LT mortality are feared clinical events when transplantation is attempted in the setting of untreated, moderate to severe POPH. Specific pulmonary artery vasodilator medications (PAH-specific therapy) appear effective in reducing pulmonary artery pressures, improving right ventricular (RV) function and survival. Thus, screening for and accurately diagnosing POPH prior to LT has become a standard of care. The post-LT course of patients with moderate POPH is unpredictable, but most patients can be weaned from PAH-specific therapy over time. In this article, we present an overview of the preoperative assessment of POPH with an emphasis on risk assessment for transplant and the most recent medical treatment options.

Portopulmonary hypertension (POPH) is documented in 4.5% to 8.5% of liver transplant (LT) candidates,¹ and it is a well-recognized relationship of pulmonary artery hypertension (PAH) that evolves as a consequence of portal hypertension.² According to the 2008 Dana Point classification of PAH, POPH is included within the Group 1 of the classification.² The first description of what we now know as POPH was provided by Mantz and Craige in 1951.³ These authors described necropsy results of a 53-year-old female with spontaneous portocaval shunt (due to a probable congenital portal vein narrowing) that originated at the confluence of the portal, splenic, and mesenteric veins and coursed through to mediastinum. The shunt was lined by varying amounts of thrombus thought to have embolized via the innominate vein into the right heart and pulmonary arteries. In addition to embolized small pulmonary arteries, an extreme endothelial proliferation and recanalization process was documented.3 Over the last 30 years, enhanced recognition and renewed importance of POPH has evolved with the evolution of LT and potential outcomes associated with POPH. Specific screening recommendations and diagnostic criteria are now clearly defined for this entity. Despite the lack of randomized controlled trials for pulmonary artery vasodilator medications (PAH-specific therapy), extrapolation of the therapeutic advances in treating PAH with beneficial effects in POPH has stimulated ongoing interest and importance in this syndrome. This article summarizes the most recent advances in the comprehensive preoperative management of POPH patients undergoing LT.

HOW IS POPH DEFINED?

Given the various pulmonary hemodynamic patterns that complicate advanced liver disease,^{4,5} POPH should be clearly defined and recognized; therefore, the importance of accurate interpretation of hemodynamics obtained by right heart catheterization (RHC) cannot be underestimated. The vascular pathology that characterizes POPH includes obstruction to arterial flow due to vasoconstriction, endothelial and smooth muscle proliferation, in-situ thrombosis, and plexogenic

It is important to mention that POPH should be distinguished from the other major pulmonary vascular consequence of liver disease, namely hepatopulmonary syndrome (HPS).^{4,8} In HPS, arterial hypoxemia is caused by intrapulmonary vascular dilatations (exactly opposite to the vascular obstructions documented in POPH) that form

arteriopathy.^{6,7} These changes increase the resistance to pulmonary arterial blood flow, which is the main mechanism of the disease. In the presence of portal hypertension, POPH is therefore defined as a mean pulmonary artery pressure (MPAP) ≥25 mm Hg associated with pulmonary vascular resistance $(PVR) \ge 240 \text{ dynes/sec/cm}^{-5} \text{ and pul-}$ monary capillary wedge pressure $(PCWP) \le 15 \text{ mm Hg based on RHC}$ (Table 1). It is also very important to recognize the 3 main abnormal hemodynamic patterns that can be present during RHC in patients with portal hypertension (Figure 1); distinguishing these patterns is of paramount important for the adequate management and treatment: a) hyperdynamic circulatory state induced by liver dysfunction; b) excess pulmonary venous volume due to diastolic dysfunction and/or renal insufficiency (pulmonary venous hypertension); and c) PAH due to vascular obstruction (POPH).⁶

Key Words—portopulmonary hypertension, cirrhosis, liver transplant, portal hypertension, pulmonary hypertension

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Variable	Criterion
Portal hypertension	Clinical diagnosis (ascites, varices, splenomegaly)
Mean pulmonary artery pressure (MPAP)	\geq 25 mm Hg; and
Pulmonary vascular resistance (PVR) ^a	> 240 dynes/s/cm ⁻⁵
Pulmonary capillary wedge pressure (PCWP)	≤15 mm Hg
Transpulmonary gradient (TPG) ^b	>12 mm Hg
Degree of severity	
Mild	\geq 25 MPAP <35 mm Hg
Moderate	\geq 35 MPAP <45 mm Hg
Severe	≥45 mm Hg MPAP

^aPVR = (MPAP-PCWP) x 80/cardiac output.

^bIn the case where PCWP is >15 mm Hg (abnormal), an abnormal TPG (MPAP-PCWP) may distinguish between simple volume excess causing increased MPAP and the pulmonary artery vasculopathy that characterizes POPH.

as a remodeling process due to factors yet to be identified. In addition, the pulmonary hemodynamics associated with HPS reflect a normal PVR and usually a high flow state characterized by an increased cardiac output (CO). The distinction between these 2 syndromes is very important, especially if LT is to be considered because of the differences in risk, treatment options, and outcomes between these syndromes.⁸

HOW IS THE SCREENING PROCESS FOR POPH PERFORMED?

Transthoracic echocardiography (TTE) has been the most practical screening method to detect POPH.9-11 Bv assessing the tricuspid regurgitant peak velocity (TR), estimating the right atrial pressure by inferior vena cava changes with inspiration, and using the modified Bernoulli equation, an estimate of right ventricle systolic pressure (RVSP) can be determined in \sim 80% of patients with portal hypertension.⁹ This quantitative approach allows one to decide which patients should proceed to RHC for the definitive characterization of pulmonary hemodynamics. In our current practice at Mayo Clinic, the presence of RVSP >50 mm Hg has been the cutoff criteria to proceed to RHC in a clinical algorithm followed since 1996.⁵ Rarely, immeasurable TR with abnormal qualitative RV size or function results in RHC. TTE has been noted to have a 97% sensitivity and 77% specificity to

detect moderate to severe PAH prior to LT.⁹

Current policy adopted by the American Association for the Study of Liver Diseases calls for screening TTE to detect pulmonary hypertension (PH) in every patient considered for LT in the United States.¹² This policy originated, in part, from documentation that POPH was first diagnosed in the operating room in 65% of patients (28/43 patients in 18 peer-reviewed studies) reported in a literature review with a 35% mortality in patients subsequently transplanted. Of particular note, pre-LT MPAP \geq 35 mm Hg (untreated) was associated with higher mortality.¹³ Studies by Castro et al,¹⁴ Starkel et al,¹⁵ and Saner et al¹⁶ reported first diagnosing POPH in the operating room after anesthesia induction (in the era prior to current PAH-specific therapy), noting that mild to moderate POPH patients (MPAP <35 mm Hg) do quite well without pre-LT PAH-specific therapy. The goal of screening is to identify and treat those who have the highest risk of cardiopulmonary adversity during and after LT. Pulmonary hemodynamics in LT candidates may change over time, so repetitive screening (every 12 months) is recommended.17

WHAT IS KNOWN ABOUT THE EPIDEMIOLOGY AND NATURAL HISTORY OF POPH?

Yoshida et al appear to be the first authors to use the term POPH in 1993,

as they described the first successful case of POPH to undergo successful LT (39year-old male with long-standing chronic active hepatitis).¹⁸ In the same paper, the authors also described long-term failure of single lung transplant to stabilize POPH in the setting of continued portal hypertension. Subsequently, several small series and case reports with autopsy results have described pulmonary arterial obstruction and pulmonary plexogenic arteriopathy with and without thromboemboli.^{7,19-22} Two distinct pulmonary vascular obstructive patterns causing PAH in association with portal hypertension are well described: 1) chronic pulmonary emboli from spontaneous or surgical portocaval shunts, in-situ thrombus, and/or platelet aggregates; and 2) a vasoconstrictive, proliferative endothelial/smooth muscle process due to circulating mediators that bypassed normal hepatic metabolism due to flow patterns of portal hypertension.

Large series have confirmed the coexistence of these portal and pulmonary vascular abnormalities and have shown that the association is not coincidental. An unselected series of 17,901 autopsies revealed that PAH was 5 times more likely in cirrhotic patients than those without liver disease.²³ Within the 1981-1987 National Institutes of Health (NIH) registry of "primary" PH from 32 centers reported by Rich et al,²⁴ additional analyses by Groves et al concluded that 8.3% likely had POPH (17/204; 187 had primary PH).²⁵ Hadengue reported the largest prospective study of patients with portal hypertension (n=507) in which portopulmonary hemodynamic measurements concluded that 2% had POPH.²⁶

More recently, prospective studies have focused on the frequency of POPH in clinic settings, including national registries and individual transplant center experiences. In the French PH registry experience over a 12-month period (2002-2003), Humbert reported a 10.4% frequency of POPH (70/674) from 17 university hospitals.²⁷ In the United States, the REVEAL (Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management) registry documented a 5.3% POPH frequency (174/3525) in

Α	MPAP	PVR	СО	PCWP
Hyperdynamic circulatory state (High flow)	t	ŧ	1	₽
Excess volume	1	1	1	1
Vasoconstriction with vasoproliferation (POPH)			Λ	₽
В	А	В		С
RVSP (mm Hg)	69	66		99
MPAP (mm Hg)	33	36		63
CO (L/min)	11.9	9.3		6.1
PCWP (mm Hg)	7	25)	14
PVR (dynes.s.cm⁻⁵)	175	95	\langle	643
Diagnosis:		Excess	5	DODU

Figure 1. A: Pulmonary hemodynamic patterns documented by right heart catheterization in advanced liver disease. B: Three LT candidates with abnormal screening TTE (RVSP >50 mm Hg); all 3 patients had elevated MPAP. However, only patient C had POPH.

TTE: transthoracic echocardiography; RVSP: right ventricular systolic pressure; LT: liver transplantation; MPAP: mean pulmonary artery pressure (normal <25 mm Hg); PVR: pulmonary vascular resistance (normal <240 dyne/s/cm-5 [or 3 Wood units]); PCWP, pulmonary capillary wedge pressure; CO, cardiac output; POPH: portopulmonary hypertension.

which there were 68% prevalent and 32% incident cases, satisfying the criteria that MPAP >25 mm Hg and PVR >240 dynes/s/cm⁻⁵ with PCWP \leq 15 mm Hg.²⁸ Following slightly different PVR diagnostic criteria as part of outpatient RHC diagnostic assessments, the largest POPH-LT center experiences reported to date are as follows: 8.5% (Baylor 102/1205; PVR >120 dynes/s/ cm⁻⁵), 6.1% (Clichy, France 10/165; PVR >120 dynes/s/cm⁻⁵), and 5.3% (Mayo Clinic 66/1235; PVR >240 dynes/s/cm⁻⁵).^{5,17,29}

The natural history of POPH has

been difficult to characterize and has been confounded by small series prior to the availability of current PAH-specific therapy. Robalino and Moodie reported a dismal 5-year survival of 4% (n=78) prior to the availability of continuous intravenous prostacyclin infusion.³⁰ Swanson et al reported a 14% 5-year survival in POPH patients (n=19) denied LT and not treated with any of the current PAH-specific therapies.³¹ From the French National Center for PAH (n=154 over a 20-year span until 2004), Le Pavec described 1-, 3-, and 5-year survivals of 88%, 75%, and 68% respectively for POPH patients (majority Childs A and alcoholic cirrhotics).¹ Only one-third had been treated with PAHspecific therapies with severity of cirrhosis and reduced CO identified as poor prognostic factors. Causes of death in all series mentioned herein were equally distributed between right heart failure due to POPH and direct complications of liver disease (bleeding, sepsis, hepatocellular carcinoma).

From the REVEAL registry, 2 important POPH observations were reported.²⁸ First, POPH treatment patterns reported in the REVEAL registry demonstrated that the use of any PAHspecific therapy for POPH was delayed compared to patients diagnosed with idiopathic PAH (IPAH). Specifically, at the time of entry into the registry only 25% were on PAH-specific therapy and at 12 months follow-up 74% were on treatment. Second, although baseline hemodynamics in POPH (MPAP and PVR) were significantly better than those with IPAH, the 1- and 3-year survivals were worse. The 5-year survival for all POPH patients was 40% compared to 64% for IPAH. Liver disease etiologies and causes of death were not determined in the registry and survival was not analyzed by the type of PAHspecific therapy.

Two caveats are important in characterizing the natural history of POPH. First, with the advent of PAH-specific therapies, every controlled randomized study has excluded POPH patients. This universal exclusion in the United States further complicated the understanding of POPH outcomes compared to other PAH disorders. Second, beginning in 2002 a higher priority for LT was an option for highly selected patients with POPH in the United States.³² Formalization of higher priority pulmonary hemodynamic criteria were put forth in 2006, and standardized in 2010. Only patients with moderate to severe POPH (MPAP > 35 mm Hg) who attained significant hemodynamic improvement with PAH-specific therapy (MPAP <35 mm Hg and PVR $<400 \text{ dynes/s/cm}^{-5}$) were granted higher priority for LT. From 2002 through 2010, 155 POPH patients were granted such priority and transplanted by regional review boards.33



Figure 2. Current POPH screening evaluation and treatment algorithm used at the Mayo Clinic. RVSP: right ventricular systolic pressure; MPAP: mean pulmonary artery pressure (normal <25 mm Hg); PVR: pulmonary vascular resistance (normal <240 dyne/s/cm⁻⁵ [or 3 Wood units]); LT: liver transplantation \rightarrow Yes: risk to proceed with LT is minimal; RX: PAH-specific therapy advised prior to LT; NR: never reported; contraindicated: high risk of intraoperative event at graft reperfusion.

HOW TO TREAT AND MANAGE POPH IN LT CANDIDATES

In Figure 2, we summarize the clinical algorithm followed at our institution based on RHC results: deciding which patients indeed have POPH, deciding who needs PAH-specific therapy based on severity, and determining the risks and timing for potential LT are the most important clinical questions. POPH patients with MPAP >35 mm Hg are particularly vulnerable to poor outcomes with attempted LT, especially if there is no attempt to treat the POPH with current PAH-specific medications. With current treatments, POPH outcomes are variable, yet in highly selected POPH patients with aggressive treatment and successful LT, pulmonary hemodynamics may completely normalize. RV size and function normalizes and liberation from PAH-specific medications may be allowed.

The immediate goal in the management and treatment of POPH is to improve pulmonary hemodynamics by reducing the obstruction to pulmonary arterial flow. This can be accomplished by medications that result in vasodilation, antiplatelet aggregation, and antiproliferative effects.³⁴ This goal may be attained by augmenting the lack of pulmonary endothelial prostacyclin synthase deficiency (prostacyclin infusion), blocking circulating endothelin-1 effects (endothelin receptor antagonists), and enhancing local nitric oxide vasodilatation effects (phosphodiesterase inhibitors).³⁴ The ultimate goal, in addition to favorably affecting pulmonary hemodynamics (decreased MPAP, decreased PVR, and increased CO), is to stabilize, improve, and/or normalize RV function.

Uncontrolled small series and recent case reports have demonstrated that PAH-specific therapies used for other types of PAH could be beneficial for patients with POPH (Table 2).³⁵⁻⁵² It is important to stress that improvements in both MPAP and PVR are the ideal goals in treating POPH. However, MPAP may not decrease as much as desired, as increases in CO associated with reduced obstruction to flow (measured by decreased PVR) will result in higher flow (and increased pressure).

Role of Prostacyclins in POPH

The most dramatic PAH-specific therapy effects in POPH have been with the use of continuous prostacyclin infusion via a central catheter and oral endothelin receptor antagonists. In a summary of 48 patients treated with intravenous epoprostenol from 5 studies, MPAP decreased by 25% (48 \rightarrow 36 mm Hg), PVR decreased by 52% (550 \rightarrow 262 dynes/s/cm⁻⁵), and CO increased by 38% (6.3 \rightarrow 8.7 L/min, all *P*<0.01).^{13,46-50} Other prostacyclins (intravenous treprostinil and inhaled iloprost) have resulted in significant pulmonary hemodynamic improvement in POPH.^{44,48,50}

Role of Endothelin Receptor Antagonists in POPH

Regarding the use of endothelin receptor antagonists, Hoeper et al documented 1and 3-year survival of 94% and 89% in 18 patients with POPH and Childs A severity liver disease using the nonselective endothelin antagonist bosentan.43 No liver toxicity was noted. However, Eriksson et al have correctly warned about potential liver toxicity with the use of bosentan, occurring in up to 10% of patients without documented POPH.37 Although Kahler et al have reported success in POPH with the use of a selective endothelin receptor antagonist sitaxsentan, this medication has not been approved in the United States and has been associated with fatal hepatic failure.45 Cartin-Ceba et al reported 13 POPH patients using the endothelin receptor antagonist ambrisentan (10 mg daily) and documented at 1-year improvement in each of 8 POPH patients (MPAP 58→41 mm Hg and PVR 445 \rightarrow 174 dynes/s/cm⁻⁵; *P*=0.004). Of note, 5 of the 8 patients normalized their PVR.³⁶ In further support of ambrisentan in POPH, Halank et al described significant improvement in both exercise capacity and symptoms in 14 POPH patients.⁴⁰ Importantly, neither of the uncontrolled ambrisentan studies was associated with hepatic toxicity. This may be due to the differences in chemical structure (ambrisentanpropionic acid; bosentan and sitaxsentansulfa base) and distinct hepatic metabolic pathways.⁴² More recently, Savale et al described 34 patients with POPH (Childs A or B severity of liver disease) treated with bosentan documenting significant hemodynamic improvement (more so in the Childs B subgroup), and event-free survival estimates were 82%, 63%, and 47% at 1, 2, and 3 years respectively.53

Role of Phosphodiesterase-5 (PDE-5) Inhibitors in POPH

PDE-5 inhibitors prevent the breakdown of cyclic guanosine monophosphate, the mediator of nitric oxide-induced vasodilation. The use of phosphodiesterase

Study first author (medication)	Number of patients	Comments
ENDOTHELIN RECEPTOR ANTAGONISTS		
Hoeper ⁴³ (bosentan)	18	1- and 3-year survivals 94% and 89%, respectively
Cartin-Ceba ³⁶ (ambrisentan)	13	At 1 year, MPAP and PVR improved in 8/8; PVR normalized in 5
Savale ⁵³ (bosentan)	34	Event-free survival estimates were 82%, 63%, and 47% at 1, 2, and 3 years, respectively
PHOSPHODIESTERASE INHIBITORS		
Reichenberger ⁴⁹ (sildenafil)	12	Improvement at 3 months; not sustained at 1 year
Gough ³⁹ (sildenafil)	11	PVR decreased in all at first RHC follow-up
Hemnes ⁴¹ (sildenafil)	10	At 1-year MPAP and PVR decreased in 3/5 patients
PROSTACYCLINS		
Kuo ⁴⁷ (IV epoprostenol)	4	MPAP and PVR improved
Krowka ⁴⁶ (IV epoprostenol)	15	15 MPAP and PVR improved
Ashfaq ³⁵ (IV epoprostenol)	16	Successful LT in 11 patients; 5-year survival 67%
Fix ³⁸ (IV epoprostenol)	19	PVR improved in 14/14; MPAP improved in 11/14
Sussman ⁵¹ (IV epoprostenol)	8	MPAP and PVR improved in 7/8
Sakai ⁵⁰ (IV treprostinil)	3	Successful LT in 2 patients (moderate POPH)
Hoeper ⁴³ (inhaled iloprost)	13	1- and 3-year survivals 77% and 46%, respectively
Melgosa48 (inhaled iloprost)	21	Acute, but no long-term hemodynamic improvement
COMBINATION THERAPY		
Hollatz ⁴⁴ (sildenafil alone or combined with prostacyclins in 9 patients)	11	MPAP and PVR improved in all patients, all underwent LT and 7/11 are off PAH-specific therapy
Raevens ⁵² (6 patients combined therapy with sildenafil and bosentan; 1 patient only on prostacyclins)	7	MPAP and PVR improved in the 5/6 patients treated with combination of sildenafil and bosentan; 2 underwent LT

MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; LT: liver transplantation; IV: intravenous; POPH: portopulmonary hypertension.

inhibition (sildenafil) to enhance nitric oxide vasodilating effect, either alone or in combination with other PAH-specific therapies, has successfully improved POPH pulmonary hemodynamics and facilitated successful LT. Most of the published experiences have been in patients with less severe POPH.^{39,41,49}

Role of Other Therapies and Interventions in POPH

In a single case report, a dramatic hemodynamic improvement was observed with the 6-week addition of imatinib 400 mg daily (a tyrosine kinase inhibitor) to pre-LT intravenous epoprostenol and post-LT bosentan therapy, resulting in liberation of all PAH-specific medications and normalization of RV function 1 year post-LT. This observation suggests a possible fourth pathway of PAH-specific therapy effectiveness (blocking platelet-derived growth factor receptors) in treating POPH.⁵⁴

The use of beta blockers or transjugular intrahepatic portosystemic shunting (TIPS) in the setting of POPH may be problematic. The former, used to prevent gastrointestinal bleeding by reducing the degree of portal hypertension, may impair needed RV function. In moderate to severe POPH (n=10; mean MPAP = 52 mm Hg), withdrawal of beta blockade increased CO by 28%, decreased PVR by 19% with no change in MPAP, and increased 6-minute walk by 79 meters.⁵⁵ TIPS, as a treatment for uncontrollable gastrointestinal bleeding or refractory ascites, can temporarily increase MPAP, CO, and PVR. In a study of 16 cirrhotic patients without PH, the increase in MPAP was greater than that noted in CO, suggesting an increase in the PVR after TIPS.⁵⁶ Such changes remained for at least 30 days post-TIPS and reflected neurohumoral effects as opposed to increased preload. A significant increase in RV work was

documented and the potential effect on RV function could be deleterious in patients with preexisting POPH.⁵⁷

WHAT IS THE ROLE OF LT IN POPH PATIENTS?

The majority of patients with POPH have cirrhosis and LT is a potentially curative intervention, at least from a hemodynamic perspective. In the United States, a total of 5805 liver transplants were accomplished in 2011. As of mid-2013, there were approximately 16,482 patients on the wait list in over 120 United States LT centers.⁵⁸ Assuming up to 8.5% of LT candidates have POPH, at any point in time there may be approximately 1300 POPH-LT candidates.¹ The outcome of POPH following LT remains unpredictable despite screening, careful patient selection, higher priority for LT, and advances in single and combination PAH-specific therapies (Table 3).^{14-16,59-65} Effective PAH-specific therapy has resulted in

Outcome	References
POPH Wait-list mortality	17,38,39,51
POPH MELD exception pre-LT	33,51
Case canceled in operating room	13,29,47,61
Intraoperative death	1,13,29,31,33,63
Transplant hospitalization death	13,15,16,29,33,35,52,62,63,65
POPH Post-LT	
Resolved; PAH-specific therapy discontinued	33,35,36,38,39,44,50,51,54,60 ^a
Resolved/stable without PAH-specific therapy	14,15,17,18,35
Improved/stabilized/PAH-specific therapy continued	33,38,41,44,49-52,59 ^b
Progressive despite PAH-specific therapy	29
Late death not due to POPH	29,31,35
Late death due to POPH	1,29
Multiorgan (H-Lu-Lv; Lu-Lv transplant)°	64
De novo PAH post-LT ^d	68

^aLiving donor liver transplant (3 patients)

^bCombined PAH-specific therapy use

^cH-Lu-Lv: heart, double lung, liver; Lu-Lv- double lung, liver transplants. It is noted that multiorgan transplants have been reported in the literature for cystic fibrosis, alpha-1 antitrypsin deficiency, and sarcoidosis, but these entities also affect lung parenchyma and many cases were accomplished in the era prior to current PAH-specific medications, therefore were not included herein.

^dPAH – pulmonary artery hypertension; a literature review of 13 such cases.

successful LT and subsequent liberation from pre-LT PAH-specific therapy (Table 3). Importantly, reperfusion during the LT procedure represents a critical time when preload can increase, cytokines may be released, thrombi may migrate into the pulmonary circulation, and intraoperative death follows from acute right heart failure.⁶⁶

Although supporting data are limited, LT programs in the United States now allow higher priority to conduct LT if pulmonary hemodynamics can be significantly improved and meet standardized Model of End-Stage Liver Disease (MELD) exception guidelines. Current treatment targets for POPH MELD exception in the United States are shown in Table 4. The goal and results of such recent policy in US LT programs has been to interrupt the natural history of POPH (reduce waitlist death) and also improve post-LT survival with liberation from PAH-specific therapy after successful LT once pulmonary hemodynamics have normalized (Table 3). However, failure to reduce MPAP below 50 mm Hg is considered by most centers to be a contraindication to LT or, if discovered at the time of the operation, grounds to cancel the LT procedure prior to the abdominal

incision. Despite limited experience, at this time it seems logical that similar pulmonary hemodynamic guidelines should be followed when living-donor POPH transplants are considered.^{60,67}

Although the role of LT in the setting of POPH is evolving with experience, the recognition that severe POPH (measured hemodynamically and qualitatively by echocardiography) can resolve post-LT with aggressive pre-LT PAH therapy is quite remarkable. Although preliminary observations are encouraging, the normalization of pulmonary hemodynamics post-LT does not necessarily equate to pulmonary vascular pathology resolution or long-term stability. Finally, it should be noted that clinically significant PAH could develop de novo following LT (ie, normal pulmonary hemodynamics are noted at the time of LT) for reasons that are clearly not understood.68

FUTURE CONSIDERATIONS AND FINAL REMARKS

From the current evidence available from observational studies, moderate to severe POPH is curable in some cases with a combination of LT and PAH-specific medications. There are 2 important, pressing issues regarding the MELD exception rules that are important to discuss. The first issue has to do with the MELD exception not being granted under current US policy if the MPAP remains >35 mm Hg despite normalization of PVR and RV function with pre-LT therapy. In such patients, the elevation in MPAP reflects a change in physiology and is the result of pulmonary vasoactive therapy increasing the existing high flow state, and decreasing the PVR to flow. We consider that in those patients where there is normalization of RV function and PVR, MELD exception should be granted despite the "abnormal MPAP." Based on observational data, it is hypothesized that for those individuals, cure of POPH after LT can be obtained. Admittedly, it is unknown whether pulmonary hemodynamic normalization post-LT reflects a pathologic pulmonary vascular cure. In addition, in most post-LT patients that have clinical improvement and echocardiographic normalization of RV function, size, and RVSP; RHC is not routinely performed to corroborate the normalization of the hemodynamics. The second pressing issue deals with the adoption of the standard MELD exception for POPH. Even though those

Table 4. MELD Exception Criteria for POPH

1. Moderate to severe POPH diagnosis confirmed by right heart catheterization
a. MPAP ≥35 mm Hg
b. PVR \geq 240 dynes/sec/cm ⁻⁵
c. PCWP ≤15 mm Hg
2. PAH-specific therapy initiated;
improvement documented
a. MPAP <35 mm Hg
b. PVR <400 dynes/sec/cm ^{-5a}
 Satisfactory right ventricular function by transthoracic echocardiography
3. MELD exception updated (additional
10% MELD points) every 3 months
 a. Give additional MELD exception if RHC data satisfies criteria # 2

^aIf PVR is normal, higher MPAP may be allowed and reconsidered due to physiology that is now high flow rather than obstruction to flow due to the therapy. POPH: portopulmonary hypertension; MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; RHC: right heart catheterization; MELD: Model End-Stage Liver Disease. individuals can be tracked in terms of general survival, no data are available regarding PAH-specific therapy management after LT. Unfortunately, there is lack of understanding about the most appropriate post-LT management in order to optimize outcomes. A multicenter survival registry collecting comprehensive information should be performed in POPH patients that undergo LT.

In conclusion, POPH is an uncommon and serious yet treatable pulmonary vascular consequence of portal hypertension that can lead to right heart failure and death if untreated. Due to the different spectrum of pulmonary hemodynamic changes associated with hepatic dysfunction, screening by TTE and confirmation by RHC is necessary for accurate diagnosis and therapeutic considerations. Despite the lack of controlled studies, PAH-specific therapies in POPH can significantly improve pulmonary hemodynamics and RV function. The potential to "cure" POPH, at least hemodynamically, with a combination of PAH-specific therapy and LT appears to be an attainable goal in a cohort of POPH patients yet to be optimally characterized. Controlled, multicenter studies and long-term follow-up post-LT are needed.

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