Perioperative Evaluation and Management of Patients With Portopulmonary Hypertension Aiming for Orthotopic Liver Transplantation

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Background: Portopulmonary hypertension (POPH) is defined as pulmonary arterial hypertension (PAH) in the context of portal hypertension. Severe POPH has been considered an absolute contraindication of orthotopic liver transplantation (OLT).
Objective: Since there are no definitive guidelines for the immediate preoperative, intraoperative, and postoperative evaluation and treatment of POPH patients, we have used published literature along with our experience to review current knowledge in this area.
Summary: Moderate-to-severe POPH has important consequences in the perioperative management of candidates for OLT. Adequate right ventricular function is critical to survive the hemodynamic burden of OLT. Immediate preoperative assessment of hemodynamics; careful intraoperative monitoring and management of volume status, pressure changes, and ventricular function; and postoperative transitions of PAH-specific therapy are key components to successful OLT. We emphasize the advantages of the echocardiogram during all of these phases and stress the importance of a team approach to plan care and respond to the multiple challenges of OLT in POPH.

Initially described in 1951, the coexistence of pulmonary arterial hypertension (PAH) and hepatic dysfunction has been well documented.[1] During the 4th World Symposium held at Dana Point in 2008, the previous clinical classification of portopulmonary hypertension (POPH) as a well-recognized cause of PAH was upheld.[2] Patients with liver disease can present with a continuum of pulmonary vascular resistance profiles, from the characteristic vasodilatation of hepatopulmonary syndrome to increased resistance to pulmonary blood flow in the setting of POPH. The focus of this review is the immediate perioperative assessment and management of patients with POPH undergoing orthotopic liver transplant (OLT).

PREOPERATIVE PERIOD

A methodical diagnostic approach is of the utmost importance in patients with portal hypertension undergoing standard pretransplant evaluation. Transthoracic echocardiography (TTE) plays an integral role in the evaluation of end-stage liver disease (ESLD) patients. Noninvasive screening of elevated right ventricular systolic pressures (RVSP) is the main role of Doppler TTE in the preoperative evaluation of patients with POPH undergoing OLT. However, TTE alone cannot characterize the severity of POPH.[3] In fact, echocardiographically estimated RVSP and measurements by right heart catheterization (RHC) may disagree, particularly at higher estimated RVSP.[4] It is assumed that RVSP equates with systolic pulmonary artery pressure (SPAP). In our practice, we also use echocardiographically measured mean pulmonary artery pressure (MPAP), which appears to correlate well with MPAP measured by RHC.[5,6]

Two recent studies described the cutoff value of RVSP by TTE as an indication for RHC. Krowka et al used a

Key Words—portopulmonary hypertension, pulmonary hypertension, liver transplantation
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Disclosures: The authors have no conflicts related to this manuscript.

cutoff of 50 mm Hg to proceed with RHC (see accompanying manuscript by Cartin-Ceba and Krowka in this issue). A lower threshold was used by Raevens et al, who demonstrated that increasing the cutoff from 30 mm Hg to 38 mm Hg safely reduces the number of patients who need RHC (specificity 82%; negative predictive value of 100%).[7]

An elevated RVSP by TTE does not equate to a diagnosis of POPH, as up to 20% of ESLD patients have a hyperdynamic circulatory state with a direct correlation between pulmonary artery pressure (PAP) and cardiac output (CO). The high-flow hemodynamic profile is as follows: MPAP >25 mm Hg, high CO, and low pulmonary vascular resistance (PVR).[8,9] Even if discovered in the immediate preoperative assessment, this group of patients with pulmonary hypertension (PH) from high-flow state may safely proceed with OLT.

In contrast, "true" POPH documented by RHC in the immediate preoperative period (ie, not previously diagnosed) requires careful assessment and may preclude proceeding with OLT. Our preoperative approach of patients with POPH is shown in Figure 1.

Often volume overload is present in patients with ESLD, complicating the interpretation of an elevated RVSP by TTE. Carefully monitored diuresis to achieve "dry weight" is recommended. At this point, the echocardiographic evaluation should be repeated. If TTE again reveals PH, an RHC should be performed. In those patients with elevated serum creatinine, it may be necessary to evaluate and treat as inpatients. Our practice is to admit for pulmonary artery catheterization with intravenous administration of loop-inhibiting diuretics to achieve "normal" left-heart pressures, ie, pulmonary artery occlusion pressure (PAOP) ≤15 mm Hg. Rarely in those patients with more severe renal disease, renal replacement therapy is used to achieve normal intravascular volume status. Reassessment of the hemodynamic profile is diagnostic of POPH if the MPAP >25 mm Hg, PAOP ≤15 mm Hg, and PVR >240 dyne s cm^{-5} (3 Wood units) as outlined in Figure 1.[10] With hemodynamic confirmation of the POPH, the most appropriate PAH-specific therapy is determined.

The mortality of patients with moderate POPH with MPAP 35-45 mm Hg and PVR >250 dyne s cm^{-5} has been reported to be about 50%-80%,[11,12] while the mortality when MPAP >50 mm Hg has been found to be near 100%.[11,13] Long-term prognosis of patients with POPH remains poor, but intraoperative and immediate perioperative mortality is certainly the major concern in patients with MPAP >50 mm Hg. Indeed, the Registry to Evaluate Early and Long-term pulmonary arterial hypertension disease management (REVEAL) demonstrated that POPH had significantly poorer survival and all-cause hospitalization rates compared with idiopathic PAH, despite having better hemodynamics at diagnosis.[14]

Prognostication and the decision to proceed with OLT are commonly complicated by 1 of 2 scenarios. In the first scenario, the severity of POPH does not necessarily correlate with the severity of liver disease. In that case, United Network for Organ Sharing has approved Model for End-Stage Liver Disease (MELD) exception points for patients with POPH, thereby enhancing the likelihood of earlier OLT (see accompanying manuscript by Cartin-Ceba and Krowka in this issue).[12] In the second scenario, the patient may experience clinical deterioration due to the failing liver but has hemodynamics that are considered borderline eligible for OLT.[10] It is unknown whether the increased risk of OLT should be considered acceptable in this circumstance. We advocate a multidisciplinary discussion, including the hepatologist, transplant surgeon, anesthesiologist, critical care physician, and PH specialist, to discuss the individualized circumstances influencing the decision to proceed with OLT. A team approach marshals the relevant expertise in all subspecialties to provide the most appropriate decision.

PAH-specific therapies are designed to improve or normalize right ventricular (RV) function while reducing the MPAP and PVR to a range considered safe for transplantation.[10] A detailed discussion of these therapies for the outpatient pre-OLT period is detailed in the companion article. This review will address the use of appropriate PAH therapy in the immediate pre-OLT time frame, as well as intraoperative and postoperative time courses. Important clinical considerations include the patient's outpatient medical regimen, hemodynamic profile at the time of OLT, conversion to dose delivery systems permissible under anesthesia and during the perioperative period. A list of applicable PAH medications is shown in Table 1.

While case series of improved hemodynamics and outcome in POPH have been published with outpatient use, limited evidence is available to define their role on patient outcome in the perioperative period.

In the immediate pre-OLT period, reassessment with RHC and transesophageal echocardiography (TEE) is strongly advised. Generally, any current PAH-specific therapy (Table 1) is continued whenever feasible in order to maintain hemodynamic stability and avoid rebound PH. Certainly for those patients who are already receiving continuous intravenous infusion or inhaled treatments, the therapy should be continued and titrated based on the hemodynamic goals as previously discussed.

Oral PAH-specific medications can and should be administered until the patient is no longer taking oral medications in preparation for surgery. Sildenafil has an intravenous formulation that can be substituted for the oral if needed. The 10 mg intravenous dose is roughly equivalent to the 20 mg oral dose; nonetheless, when administering vasodilators by the intravenous route, careful monitoring of the systemic blood pressure is warranted.

Practical considerations for both inhaled and infusion therapy include experience with the various PAH-specific therapies and ease/cost of delivery systems. For example, among the inhaled delivery options, the delivery system and dosing for nitric oxide (NO) offers simplicity and convenience but is expensive compared to inhaled epoprostenol, which is more difficult to

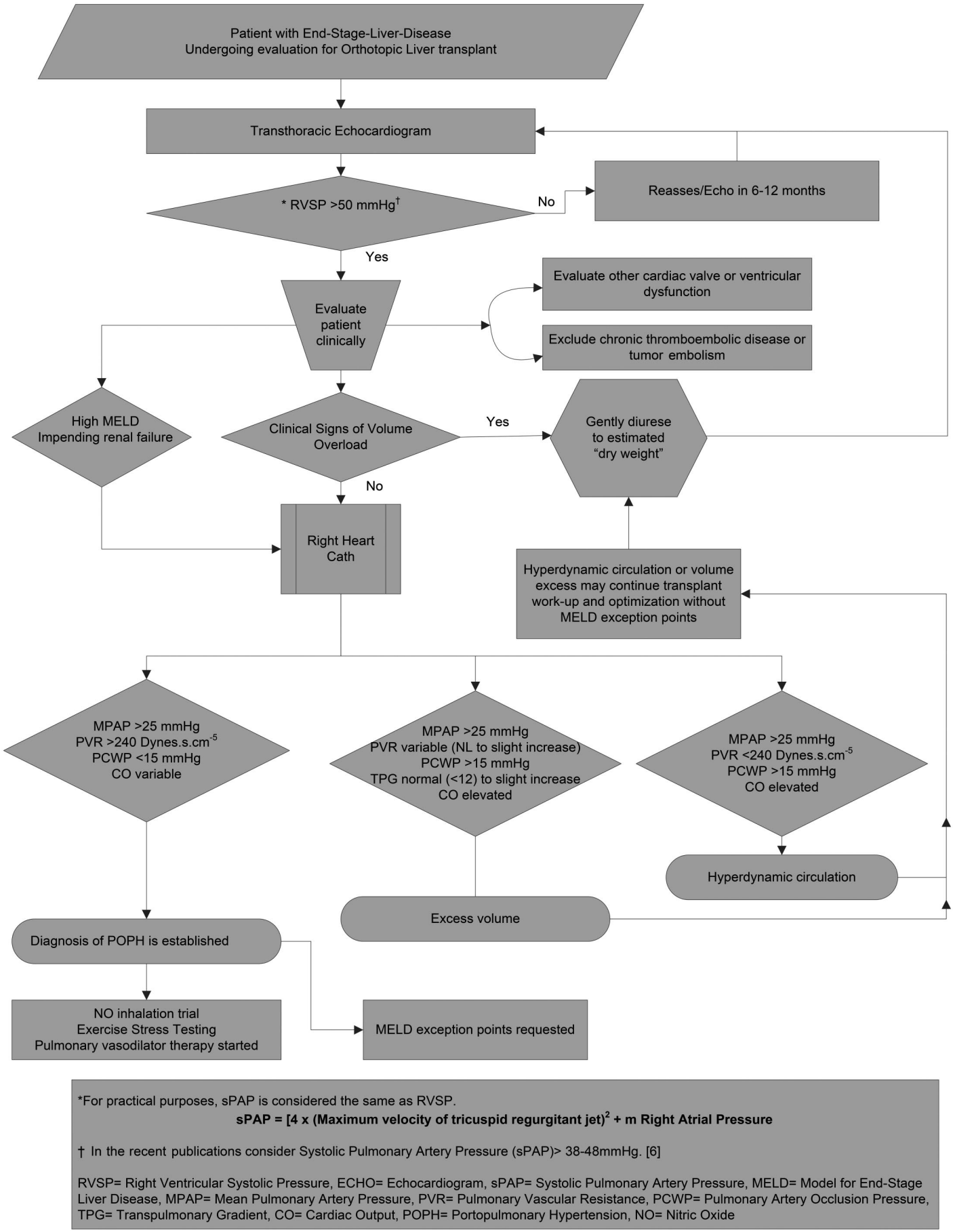

Figure 1. Evaluation of POPH in Patients With ESLD.

Table 1. PAH Medications Used for POPH in the Perioperative Period for OLT

CLASS	MEDICATION	PERIOPERATIVE	USE in POPH
PDE-5 Inhibitor	Sildenafil	IV form 10 mg tid	Case series with improved hemodynamics
	Tadalafil	No IV formulation	Reduce dose to 20 mg daily in Child-Pugh class A or B; avoid for class C
Endothelin Blocker	Ambrisentan	Oral only Should not be crushed	Case series published with improved hemodynamics and no hepatoxicity; multicenter open label trial ongoing
	Bosentan	Oral only	Hepatotoxicity a concern but has been used in case series
Prostacyclin	Iloprost	Inhaled every 2 hours	Case series with improved hemodynamics; interval between dose may be increased to 3 to 4 hours in liver disease
	Treprostinil	Continuous infusion either IV or subcutaneous; inhaled every 4 to 6 hours	Limited data; initial dosing reduced by half to 0.625 ng/kg/min; no data for inhaled formulation
	Epoprostenol	Continuous IV	Case series with improved hemodynamics
		Inhaled continuously	Case reports only
Nitric Oxide	Nitric Oxide	Inhaled 5 to 80 ppm	Case reports only

A comparison of the medications used to manage POPH in patients undergoing OLT. Key: PDE-5 = phosphodiesterase-5, IV = intravenous.

administer. The availability of proprietary inhaled agents (iloprost and treprostinil) often depends on insurance and formulary coverage.

The protocols for initiation and titration of inhaled and intravenous therapy vary among OLT centers. Inhaled NO can be delivered via a facemask or into the inspiratory limb of a ventilator circuit. Generally, the dose is started at 5 ppm with subsequent doubling to desired effect (eg, 10, 20, 40, 80 ppm). Methemoglobinemia is a side effect that requires daily monitoring. Inhaled epoprostenol requires the use of the brand FLOLAN® (epoprostenol sodium). Various dose strengths can be created using different concentrations of the 0.5 mg vial and proprietary FLOLAN diluent. Dose concentrations are generally 2500 to 20,000 ng/mL. The resulting solution is nebulized at 8 mL/hour into the ventilatory circuit. The solution must be protected from light and degrades after 8 hours at room temperature. The glycine buffer may cause the FLOLAN to precipitate and accumulate in the circuit, requiring close monitoring and filter changes as indicated.

Intravenous epoprostenol therapy is commonly initiated in the hospital (2 ng/kg/min) and titrated up by 1-2 ng/kg/min (recommendation on frequency of increase varies from every 30 minutes to every 1-2 hours) to achieve the required hemodynamic effect or until limited by common side effects (headache, nausea, flushing, myalgia, diarrhea, jaw pain, or systemic hypotension). The initial "plateau" dose rarely exceeds 12 ng/kg/min, but thereafter can be increased more slowly if needed. Pharmacologic treatment of side effects may be required to promote tolerance. Treprostinil, a prostacyclin analogue, is an alternative to epoprostenol. The logistics of initiating therapy are similar to epoprostenol. In contrast to epoprostenol, it can be administered subcutaneously with reported 100% bioavailability. Nonetheless, the cachexia associated with ESLD and abdominal distension from ascites raise concerns about the tolerability and absorption in this setting. Initial dosing of treprostinil in patients with mild to moderate hepatic dysfunction is half that of patients without liver disease, with a starting dose of 0.625 ng/kg/min. Limited data are available for use in patients with severe liver dysfunction.

Of specific note, long-term complications of intravenous prostacyclins include thrombocytopenia, systemic hypotension, central line infection, post-insertion bleeding, and progressive splenomegaly (which may worsen thrombocytopenia and produce leukopenia). Since the goal is to continue the PAH-specific therapy until the postoperative period following OLT, clinicians must appreciate the nuances of medication administration, hemodynamic goals, and unusual side effect profile of these medications.[15,16]

Some authors have published case reports describing the successful use of combined therapies to maximize the benefit from pulmonary vasodilation.[17] In many centers, combination treatment is often utilized to obtain the goal of MPAP ≤35 mm Hg for OLT candidacy. Although this may be a plausible option, there are limited data regarding the best combination or sequence of therapy.

INTRAOPERATIVE PERIOD

Utilization of Intraoperative Transesophageal Echocardiography During OLT

In addition to routine monitoring for OLT, TEE may be of added value in managing patients with POPH.[18] In recent years, preexisting esophageal varices are no longer considered an absolute contraindication for TEE during OLT. Often, esophageal bleeding is self-limited and mild to moderate in severity. The TEE examination can be performed using limited views and avoiding excessive manipulations of the probe. However, intraoperative examination should be performed with immediate availability of a gastroenter-

ology specialist to address any severe bleeding. The main intraoperative goal of managing hemodynamics for patients with POPH is to maintain optimal mechanical matching between the RV function and pulmonary circulation.

There are several intraoperative phases in which the patient is at risk for severe systemic arterial hypotension: during the dissection phase, the manipulation of the liver, drainage of large ascites, and clamping of the inferior vena cava (IVC) (if the "piggy-back" technique is not used) and/or portal vein. It is advised to have immediate availability of continuous infusions of vasopressor and inotropic agents for the treatment of shock. Continuous assessment of volume status is critical intraoperatively. Left ventricular end diastolic area (<5.5 cm/m^2 surface area) in the transgastric short axis view by TEE is suggestive of hypovolemia.[19] Other applications of TEE include placement of venovenous bypass cannula (again not an issue with the "piggy-back" technique), identification of hemodynamically significant thrombosis of the IVC, intracardiac thrombus, complications of transjugular intrahepatic portosystemic shunts, and management of patients with underlying valvular heart disease, coronary artery disease, or cardiomyopathy (eg, alcohol-induced, hemochromatosis, or amyloidosis).[20-23]

During the anhepatic phase, there are predictable hemodynamic changes including decreased systemic vascular resistance and increased CO, MPAP, and PVR. The TEE assessment should be focused on determining ventricular dysfunction and volume status.

The reperfusion phase is perhaps the most important period of TEE evaluation during OLT. Post-reperfusion syndrome is the hallmark of this hemodynamic disturbance.[24] It is manifest as a vasodilatory state with worsening POPH and RV function. Thus, the most important signs to confirm RV failure are dilation and dysfunction of the RV, as well as septal dyskinesia. Air embolism is an under-recognized condition that can aggravate or precipitate RV failure. The RV is compromised due to the anterior anatomic position of the right coronary artery. Finally, it is important to note that hypovolemia, tachycardia, and overutilization of inotropic support can all lead to a systolic anterior motion of the mitral valve with subsequent dynamic obstruction of the left ventricular outflow tract.

Therapeutic strategies. Preoperative use of intravenous epoprostenol is usually continued intraoperatively. Inhaled NO may be used as an adjunct inhalation agent to optimize RV function and mitigate elevated MPAP. Intraoperative fluid management should be adequate to achieve euvolemic state and ensure adequate RV preload. Inhaled NO is generally quite easy to transition from the intraoperative to the postoperative setting, a distinct advantage for the peri-OLT management of POPH. Phosphodiesterase-3 inhibition with intravenous milrinone reduces PVR and assists in managing MPAP; however, care must be taken not to compromise systemic pressures when this agent is used. Several vasodilator therapies by inhalation route as previously discussed may be administered intraoperatively to manage patients with POPH who present for OLT. These agents offer unique advantages since they can be delivered directly to the alveoli. Consequently, the ventilated areas may give rise to a decrease in the pulmonary shunt and improved oxygenation whenever these agents are administered.[25]

Rarely, a patient may develop or be recognized as having POHP in the operating room (OR) suite. Intravenous epoprostenol can be initiated in the OR, but hemodynamic changes and responsiveness can be variable and challenging. Inhaled agents like iloprost and treprostinil cannot be administered in the OR. Inhaled epoprostenol or NO are alternatives for treatment of POPH. Milrinone has also been used and can be continued both intra- and postoperatively. Occasionally, anesthesiologists have used it before the anhepatic/reperfusion phase in anticipation of known hemodynamic alterations that occur during reperfusion. Furthermore, the duration of cold ischemic time may play a role in PAH therapy selection; therefore, an agent that is reliable with rapid onset and is easily and accurately titratable needs to be used (eg, intravenous epoprostenol). Initiation of intravenous epoprostenol intraoperatively is essentially no different than in the pretransplant environment for a POPH patient who requires treatment but is still appropriate to proceed with OLT. For the most part, the hemodynamic contraindication for OLD, and hence the need to cancel surgery, is the finding of MPAP $\geq$50 mm Hg from RHC. Treatment may be attempted in the OR to reduce the MPAP to a range of 40-49 mm Hg if time allows, whereas MPAP 36-39 mm Hg may warrant consideration for treatment after careful interpretation of hemodynamic profile to differentiate "volume-induced," "hyperdynamic-induced," or true POHP. Hyperdynamic-induced PH is usually well tolerated at this range (MPAP 36-39 mm Hg). However, both of these hemodynamic interpretations are best done in conjunction with TEE evaluations to assess RV size and function in order to make the decision regarding proceeding with OLT.

POSTOPERATIVE PERIOD

The resolution of POPH after OLT is unpredictable. Most of the studies report that up to 76% of the patients improve or resolve POPH following OLT.[26] However, this improvement varies (up to 27 months).[27]

It is a common practice in our institution to continue the PAH-specific therapy that was used in the pre- and intraoperative periods. All patients with known POPH, or de novo POPH, are admitted to the intensive care unit (ICU) after OLT. We attempt early postoperative extubation in all patients with postsurgical optimization. If inhaled NO was used intraoperatively, it is discontinued if possible during the weaning from mechanical ventilation; however, some patients may need longer support with gradual weaning postextubation. Routine post-OLT care is provided with special considerations and attention given to avoiding/minimizing rapid volume infusions, need for vasopressors, use of appropriate PAH-specific therapy, and evidence of postoperative RV failure. Infrequently, the use of milrinone infusions has been either continued from the operating room or started in the ICU

due to its vasodilatory action and inotropic effects, provided that adequate and stable systemic blood pressure is present. In the case that multiple agents are used simultaneously, careful titration is mandatory. Agents not used preoperatively will usually be discontinued first (eg, milrinone and inhaled NO). Postoperative use and transition of PAH-specific therapy depends on whether the patient was on such therapy preoperatively and the clinical status of the patient. Infusions of intravenous epoprostenol that were initiated perioperatively often can be transitioned to oral PAH-specific therapy within 2-4 days. We maintain the RHC in place while titrating care or transitioning medications. Once there is documented stability in pressures on oral and/or inhaled agents, the RHC can be discontinued. If the patient has been on long-standing PAH-specific therapy, that therapy will be continued postoperatively and slowly tapered over weeks to months as an outpatient.

Careful clinical observation for sudden or progressive changes in pulmonary status or central venous pressure measurements are important clues to possible RV failure. Postoperative deterioration of POPH is anticipated in the immediate postoperative period due to multiple factors (eg, post-reperfusion syndrome, blood product transfusions, hypothermia, pain, etc).[13] Thus, we continue infusion of intravenous epoprostenol, and administer the oral agents via a nasogastric tube if possible. We taper intravenous epoprostenol infusion in decrements of 1-2 ng/kg/min if started perioperatively, and its subsequent dose depends on the invasive hemodynamic monitoring and/or pulmonary pressure estimates on TTE examination. Patients requiring continuous epoprostenol presurgery are maintained on that dose (or higher if needed). The decision to titrate off the infusion is made as an outpatient after careful follow-up evaluation. Likewise, chronic oral or inhaled PAH-specific therapy is continued into the discharge follow-up period. The duration of PAH-specific therapy after OLT is variable and depends on regular follow-up and TTE and/or RHC evaluations. The weaning process after OLT can often be achieved over several weeks. Some patients can be weaned off all vasodilators, revealing that the procedure itself can rapidly improve and resolve POPH.

Postoperative Follow-Up of Patients With POPH and OLT

Right ventricular dysfunction is one of the most important conditions the clinician will face in the postoperative period. There are 4 hemodynamic principles that frame the understanding of this devastating complication. First, PVR is the main factor that affects the RV afterload. Second, it is the RV afterload and not the MPAP that precipitates RV failure. Third, the appearance of RV dilatation, RV dysfunction, and septal dyskinesia are the most valuably evaluated echocardiography signs. Fourth, the RV outflow tract (RVOT) is a key physiological element in the interaction between the RV and the pulmonary artery.[28] Perioperative Doppler TTE is crucial in the assessment of this interaction. Patients with evidence of RV dysfunction and "notching" in Doppler imaging envelope in the RVOT are considered dependent on RV afterload.[29] In order to obtain an adequate imaging of the RVOT, parasternal short-axis view at heart base level (TTE) or transgastric long axis view at 135 degrees are recommended.[28]

Once the patient is transferred to the recovery ward, there is usually no titration of medications. A pre-discharge TTE and b-type natriuretic peptide (BNP) are recommended for documentation, as well as close follow-up at the outpatient clinic at 1 week with the OLT team. Specific instructions are provided to call or come to the emergency department with any symptoms of deterioration. Otherwise, our practice has been a 1-month follow-up with a TTE with the intention to formulate a sensible plan for weaning medications. A multidisciplinary discussion between specialists in transplant and PH is warranted. It is possible to safely withdraw medications in a matter of months, depending on the severity of persistent elevated MPAP or the presence of RV dilation on TTE. Subsequent follow-up visits at our center are anywhere from 2 to 6 months post-OLT and include functional class, BNP, 6-minute walk test, and TTE to assess the clinical status. There are some accounts of medication titrations taking more than a year to complete. Some patients may need medication for an indefinite amount of time (or lifelong), perhaps pointing to possible undetected primary causes besides portal hypertension or to irreversible vascular remodeling. Reevaluation with RHC may be necessary if TTE reveals absence or incomplete tricuspid regurgitant (TR) jet, which precludes assessment of right heart pressures. For patients on continuous infusion prostacyclin therapy, RHC may be needed for safe transition to oral therapy. Lastly, repeat RHC may be indicated if the clinical information is disparate or there is consideration of escalation of PAH-specific therapy.

CONCLUSION

The management of POPH in patients undergoing OLT involves an immediate pretransplant assessment with RHC and often TTE. With that information in hand, a multidisciplinary approach to determine the best PAH-specific treatment plan is recommended.

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