PORTOPULMONARY HYPERTENSION AND THE LIVER TRANSPLANT CANDIDATE

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Abstract
The management of the liver transplant (OLT) candidate with portopulmonary hypertension (PPHTN) has dramatically changed in the past 3 years. Careful preoperative evaluation with functional characterization of right ventricular function plays a critical role. The pulmonary vascular response to epoprostenol infusion serves as a deciding factor for OLT candidacy. Careful perioperative attention to avoid right ventricular failure from acutely elevated pulmonary artery pressures or sudden increases in right ventricular preload is a key physiologic tenet of management. With increased surgical expertise, anesthetic sophistication, and availability of epoprostenol, PPHTN is no longer considered an absolute contraindication for OLT.

DEFINITION
PPHTN can be loosely characterized as pulmonary hypertension in the setting of portal hypertension. Although PPHTN does not carry a precise, universally accepted definition, most investigators have applied the following criteria of the NIH Patient Registry for the Characterization of Primary Pulmonary Hypertension to patients being considered for OLT: a) mean pulmonary artery pressure (MPAP) > 25 mm Hg, and 2) pulmonary capillary wedge pressure (PCWP) < 15 mm Hg (6). The presence of portal hypertension is generally inferred by a history of variceal bleeding, characteristic physical stigmata such as caput medusae, or imaging studies demonstrating hepatic cirrhosis, varices, or extrahepatic portal venous obstruction. This definition assumes the absence of secondary processes as the cause of pulmonary hypertension, such as cardiac valvular disease, pulmonary emboli, collagen vascular disease, schistosomiasis, or ingestion of certain toxins or appetite suppressants. Based on previous reviews and case reports documenting PPHTN in the presence of extrahepatic portal venous thrombosis without cirrhosis, the presence of portal hypertension is considered the essential antecedent to the development of PPHTN (7).

Less commonly used criteria of pulmonary hypertension include a pulmonary vascular resistance (PVR) > 120 dyne/sec/cm^5, transpulmonary gradient (TPG) > 10 mm Hg, or MPAP > 30 mm Hg during exercise (8). PPHTN has also been subjectively subcategorized as mild, moderate, and severe (1, 2, 9). These definitions have been based on MPAP
or systolic pulmonary artery (PA) pressure and vary from author to author. In general, use of this subcategorization should be avoided because it does not reflect the anatomy or functional capacity of the right heart. In the primary pulmonary hypertension population, the New York Heart Association (NYHA) classification I-IV is also used to convey functional information. However, in patients with PPHTN, fatigue or dyspnea may reflect the severity of liver disease rather than pulmonary dysfunction. Therefore, if a patient carries the diagnosis of PPHTN, the clinical decision algorithm should be based on anatomic, functional, and hemodynamic data rather than stratification alone.

The relationship between PPHTN and another pulmonary syndrome associated with end-stage liver disease, hepatopulmonary syndrome (HPS), remains largely unknown. HPS is defined as the presence of intrapulmonary vasodilatation with hypoxemia (arterial oxygen tension less than 70 mm Hg on an FiO₂=0.21) (10). Although HPS and PPHTN were originally thought to be distinct entities, case reports are now emerging which document the co-existence of both disease states (10). The relevance of HPS in the setting of PPHTN to a patient being considered for OLT is unknown. Given the evolving understanding of this relationship, we concentrate on PPHTN as an isolated entity in this review.

PREVALENCE OF PPHTN

PPHTN was first described in 1951 by Mantz and Craigie in an article entitled, "Portal axis thrombosis with spontaneous portocaval shunt and resultant cor pulmonale." In 1983, McDonnell and colleagues reviewed a single institution's autopsy files of 17,901 patients older than 1 year. They found that the prevalence of primary pulmonary hypertension was 0.13%. In contrast, the prevalence of pulmonary hypertension in those with cirrhosis was almost 6-fold greater at 0.73%. In an accompanying clinical series of 2459 patients with biopsy-proven cirrhosis, the prevalence of concomitant pulmonary hypertension was 0.61% (11). Hadengue and colleagues examined a series of 507 patients with portal hypertension who underwent prospective right heart catheterization and found the prevalence of pulmonary hypertension to be 2% (12). Based on these studies, the prevalence of PPHTN in patients with portal hypertension or cirrhosis is approximately 1-2%. Although these data indicate that PPHTN may be an issue of academic interest only, subsequent clinical studies from liver transplant centers suggest that the prevalence of PPHTN is higher in patients with end-stage liver disease being evaluated for transplantation. Four centers have retrospectively analyzed the incidence of PPHTN in their patients who have undergone OLT (1-3, 9). The earliest study was conducted in 1993 by Plevak and colleagues, who found that 33 of 263 (12.5%) patients who underwent OLT at the Mayo Clinic between 1985 and 1991 had PPHTN, as defined by a PVR > 120 dyne/sec/cm⁵ (9). Subsequent studies by Taura et al. and Castro et al. found that the prevalence of PPHTN, as defined by MPAP > 25 mm Hg, in patients undergoing OLT was 3.5% and 4.0%, respectively (1, 3). Finally, Ramsay and co-workers found the prevalence of PPHTN to be 8.3% in 1205 patients undergoing OLT at Baylor University Medical Center (9). Given that these studies included only patients undergoing OLT, the prevalence of PPHTN in patients presenting for OLT evaluation is undoubtedly higher. Patients with excessive levels of pulmonary hypertension were viewed as having a contraindication for OLT and, as a result, were not included in these retrospective analyses of OLT patients. A reasonable estimate of the prevalence of PPHTN in patients presenting for OLT evaluation is 5-10%.

PATHOLOGY AND PATHOPHYSIOLOGY OF PPHTN

The pulmonary pathology of PPHTN is similar to that of primary pulmonary hypertension (13). The muscular pulmonary arteries exhibit medial hypertrophy and intimal fibrosis in a concentric laminar configuration. The smaller muscular pulmonary arteries frequently demonstrate plexiform lesions typified by a circumscribed dilatation of a pulmonary artery at its origin or bifurcation with thinning of the media, loss of smooth muscle cells, and disappearance of the internal elastic lamina. In addition, a plexus of narrow slit-like channels are present within the lumen of the dilated segment. The distal portion of the plexiform lesion then drains into a dilated, thin-walled vessel terminating in the alveolar capillaries. In their autopsy study of pulmonary hypertension and cirrhosis, McDonnell and colleagues found the pulmonary vascular changes to be identical to those in hypertensive pulmonary vascular disease without evidence for veno-occlusive disease or recurrent thromboembolism (11). These authors graded the pulmonary pathologic changes and found that all PPHTN patients exhibited plexiform lesions with dilation of postglomeroid precapillary vessels and/or vascular necrosis. However, it should be noted that the pathologic changes occur in a patchy fashion within the lung and correlate very poorly with cardiopulmonary hemodynamic function (14). Matsubara and colleagues performed a histometric study comparing pulmonary vasculature with portal venous vasculature in 21 autopsy cases of hepatic cirrhosis (15). When compared with controls, those with cirrhosis exhibited significantly increased mean wall thickness in the small pulmonary arteries. In addition, the authors found an increased ratio of wall thickness to radius in the small pulmonary arteries of patients with cirrhosis, suggesting increased resistance to flow.

The pathophysiology of PPHTN and its associated clinical signs and symptoms have not been extensively studied until recently. In a retrospective study of 26 patients with documented PPHTN, Hadengue and co-workers found that cardiac index varied inversely with the mean pulmonary artery pressure and was significantly lower in five patients who died from pulmonary hypertension (1.52±0.14 L/min-m²) when compared with five who died from liver failure (3.69±1.88 L/min-m²). In addition, those who died from pulmonary hypertension had lower Childs-Pugh scores and hepatic venous pressure gradients and had higher MPAP and PVR (12). To further characterize the hemodynamic profile of PPHTN, we compared 30 PPHTN patients with 30 patients with cirrhosis and 30 patients with primary pulmonary hypertension alone. All patients underwent right heart catheterization, transthoracic echocardiography,
pulmonary function tests, ventilation-perfusion scanning, and arterial blood gas measurements. Patients with PPHTN exhibited hemodynamic features of both primary pulmonary hypertension and cirrhosis. In addition to increased MPAP and PVR, those with PPHTN also had an elevated cardiac index and depressed systemic vascular resistance. The PPHTN patients also had an accentuation of the chronic respiratory alkalosis typically seen in primary pulmonary hypertension and an increased alveolar-arterial gradient in comparison with those patients with liver disease alone (7). These data indicate that PPHTN represents a clinical entity with some features specific to pulmonary hypertension and others specific to cirrhosis.

Other investigators have found patients with PPHTN to exhibit evidence on the electrocardiogram (ECG) of right ventricular hypertrophy (79%), right axis deviation (79%), and right bundle branch block (59%). However, only 4% of PPHTN patients had a normal ECG. On CXR, this group of PPHTN patients had prominent pulmonary arteries (78%) and cardiomegaly (74%) (16). The corresponding signs and symptoms of PPHTN have been tabulated by Robalino and Moodie in their retrospective multicenter study of 78 patients with PPHTN (16). The most common complaints were: dyspnea on exertion (81%), syncope (24%), and chest pain (24%). The parallel physical findings were a loud P2 heart sound (82%), systolic murmur (6%), edema (35%), and right heart failure (34%). Unfortunately, in the setting of portal hypertension and cirrhosis, many signs and symptoms such as dyspnea, edema, or ascites (representative of right heart failure) may be masked or attributed purely to liver dysfunction.

The natural history of PPHTN was examined by Robalino and Moodie in 1991 (16). In the absence of any pharmacologic interventions, the prognosis with this syndrome is poor, with a mean survival period after diagnosis of 15 months and a 6-month mortality of 50%. The causes of death in 66% were right heart failure and infection. Despite this grim picture, the recent introduction of epoprostenol and alternative surgical techniques for OLT have significantly altered the prognosis for selected PPHTN patients.

**PPHTN AND OLT**

The original designation of PPHTN as an absolute contra-indication to OLT was based on clinical "lore" and case reports demonstrating excessive perioperative mortality with PPHTN in OLT. DeWolf and colleagues quoted an 80% perioperative mortality for PPHTN patients undergoing OLT based on their experience with five patients with "severe" PPHTN (17). Subsequent retrospective studies by Castro, Taura, Plevak, and Ramsay have further defined the role of PPHTN in perioperative mortality after OLT (1-3, 8). In 1993, Plevak retroactively reviewed the Mayo Clinic experience with 307 consecutive OLTs. There were 33 (12.5%) who had PPHTN as defined by PVR > 120 dyne·sec·cm⁻⁵ (range 121-277); no perioperative deaths were found, and there were no long term deaths related to PPHTN. These authors conclude that "mild to moderate" PPHTN is not a contraindication to OLT (2). Similarly, Taura found 8 cases of PPHTN from a retrospective study of 226 patients undergoing OLT and found no adverse outcomes associated with "mild to moderate" pulmonary hypertension. These patients had MPAP in the range of 28-38 mm Hg (1). In a retrospective review of 1205 consecutive OLTs, Ramsay and colleagues found that mild (n = 81; systolic PAP 30-44 mm Hg) and moderate (n = 14; systolic PAP 45-59 mm Hg) PPHTN did not influence the outcome after OLT. In contrast, severe PPHTN (n = 7; systolic PAP > 60 mm Hg) was associated with progressive right heart failure after OLT, 42% mortality at 9 months after OLT, and 71% mortality at 36 months after OLT (9). To date, there have been no reports that attempt to stratify OLT outcome in this population based on right atrial and ventricular pressures, right atrial and ventricular anatomy, overall cardiac performance, or functional NYHA status. In total, these studies indicate that mild-to-moderate PPHTN does not alter outcome after OLT, although severe PPHTN remains problematic. However, these studies lack conformity to a specific definition of PPHTN and the mild-moderate-severe subcategories. As a result of their retrospective nature, these studies are biased, because the recipients were preselected and the diagnosis and categorization of PPHTN were determined in the operating room after placement of the pulmonary artery catheter. Ideally, the diagnosis of PPHTN is made preoperatively during evaluation for candidacy and pharmacologic intervention instituted before transplantation.

**PHARMACOLOGIC INTERVENTION FOR PPHTN**

A right heart catheterization and vasodilator trial should be considered before empirical vasodilator therapy is initiated in patients with pulmonary hypertension or PPHTN (18). Baseline hemodynamic assessment will help determine the degree of pulmonary hypertension, reveal characteristic hemodynamic parameters, and exclude left heart filling problems (7, 19). At the time of catheterization, a vasodilator trial using short acting agents such as inhaled nitric oxide or epoprostenol provides a guide to therapy (20). Some 20-30% of patients with primary pulmonary hypertension have a decrease in mean pulmonary artery pressure and an increase in cardiac output in response to a vasodilator trial. This positive response predicts sustained hemodynamic improvement and prolonged survival with chronic vasodilator therapy (21, 22). We have applied this management paradigm to other forms of intrinsic pulmonary vascular disease, such as PPHTN.

Inhaled nitric oxide is a specific pulmonary vasodilator; however, proper use of nitric oxide in the treatment of PPHTN remains unclear (23). Nitric oxide may be useful perioperatively in patients with milder pulmonary hypertension who develop significant hypertension with hepatic allograft reperfusion (24). However, this approach is less likely to be successful in patients with more severe baseline pulmonary hypertension or in patients with a more complicated...
perioperative course. As a result, attention is focused on chronic treatment of the pulmonary hypertension to achieve optimal conditions at the time of transplantation (4).

There have been no trials of oral vasodilators in the chronic treatment of PPHTN. However, in studies of primary pulmonary hypertension, patients with a favorable response to an acute vasodilator trial during right heart catheterization demonstrated improved survival and regression of right ventricular hypertrophy with calcium channel blockers (21, 22). Indiscriminate use of oral vasodilator therapy in pulmonary hypertension without first determining an individual's response during a initial vasodilator trial may result in worsening gas exchange, hypotension, or death (25, 26). However, abrupt discontinuation can lead to fatal rebound pulmonary hypertension (22). Ambiodipine (2.5-20 mg/day), nifedipine (30-240 mg/day) and diltiazem (120-900 mg/day) are the most commonly used agents. Verapamil is generally avoided because of its negative inotropic effects and lack of activity in the pulmonary circulation. Although the role of calcium channel blockers in chronic therapy of PPHTN is unknown, consideration may be given to their use in isolated instances, such as lack of availability of epoprostenol for chronic infusion.

Epoprostenol is a potent vasodilator with a short half-life (3-5 min) that requires delivery through a permanent indwelling catheter by a continuous infusion pump. In a randomized trial in primary pulmonary hypertension, epoprostenol improved hemodynamics and exercise tolerance and prolonged survival in patients with severe primary pulmonary hypertension (NYHA III-IV) who did not have a favorable response during acute vasodilator testing and were therefore not candidates for calcium channel blocker therapy (27-29). Whereas epoprostenol is currently only approved for treatment of primary pulmonary hypertension, it has demonstrated efficacy in patients with other forms of intrinsic pulmonary vascular disease, including PPHTN, scleroderma, and systemic lupus erythematosus (30). However, epoprostenol should be avoided in postcapillary pulmonary hypertension because of the risk of acute pulmonary edema (27). To preempt the recurrence of symptoms, regular dose adjustments of epoprostenol are required during the first year of therapy. It is speculated that the reason for the increased dose requirement may be either enhanced drug degradation or an increase in vasoconstrictive mediators such as thromboxane. Epoprostenol is also effective long-term in patients with severe primary pulmonary hypertension who do not demonstrate an acute vasodilator response at the time of initial catheterization, suggesting chronic non-vasodilator modes of action, such as vascular remodeling and antiproliferative properties (29, 31, 32). Beneficial effects of epoprostenol in PPHTN have also been reported (30). Four patients with PPHTN who received epoprostenol over a period of 6-14 months had a 29-46% decrease in mean pulmonary artery pressure and a 22-71% decrease in PVR (30).

Experience with epoprostenol has directed research toward alternative approaches to reversing the pathologic vascular lesions that were previously considered to be irreversible (32). Agents currently under consideration include specific phosphodiesterase inhibitors, endothelin receptor antagonists, and prostacyclin analogs. Inhaled iloprost, a stable prostacyclin analogue, is undergoing prospective study in Europe. Chronic inhaled nitric oxide or oral nitric oxide donors continue to have potential benefit.

**SUGGESTIONS FOR DETECTION AND MANAGEMENT OF PPHTN**

Preoperative diagnosis of PPHTN is essential because of the increased morbidity and mortality associated with transplantation. The proven efficacy of chronic epoprostenol therapy for pulmonary hypertension, with its capacity to induce right ventricular remodeling and improve function, makes preoperative identification of PPHTN crucial. The ideal diagnostic screening test must be sensitive and specific in detecting altered pulmonary vascular reactivity and right ventricular dysfunction. It must assess pulmonary and cardiac responses to rapid changes in preload and afterload. Finally, it must be cost-effective and entail minimal risk to the patient.

Although right heart catheterization remains the “gold standard,” various noninvasive studies are used as screening tools. Of these, transthoracic echocardiography is most widely used. Findings of a dilated or hypertrophied right ventricle or atrium, pulmonary valvular insufficiency, or shifting of the interventricular septum into the left ventricle raise suspicion of pulmonary hypertension. Pulmonary systolic pressures can be estimated in the presence of a tricuspid regurgitant jet. At our institution, the room air arterial blood gas is used as an adjunctive screening tool. We have shown that patients with PPHTN demonstrate an exaggerated respiratory alkalosis, more profound even than that characteristic of patients with either primary pulmonary hypertension or end-stage liver disease alone (7). The combination of a suspicious blood gas result with an abnormal echocardiogram has been a successful screening regimen to identify patients with PPHTN (Fig. 1). In our recent series of OLT performed from 1994 to 1998, this regimen was associated with a positive predictive value of 96% and a negative predictive value of 100%.
If PPHTN is suspected, right heart catheterization is indicated to confirm and quantify pulmonary hypertension. There is consensus that patients with "mild to moderate" PPHTN may have transplantation risk similar to patients without pulmonary hypertension, although the definition of "mild to moderate" varies among institutions (1, 2). It is also thought that those with "moderate to severe" disease are an unacceptable risk (8, 17). As an alternative to stratification, we designate an MPAP < 40 mm Hg as the level at which OLT can be performed safely. Those patients with a MPAP > 40 mm Hg are treated with chronic intravenous epoprostenol and followed at 3-6 month intervals with right heart catheterization. The goal of treatment is lowering the MPAP to < 40 mm Hg. In combination with initial right heart catheterization, it is also necessary to determine the state of left ventricular function. Dobutamine stress echocardiography has proven itself invaluable in this role. Its sensitivity and specificity in diagnosing coronary artery disease is important because those patients with coexistent coronary artery disease may be ruled out as potential transplant candidates. Finally, pulmonary function testing and ventilation-perfusion scanning are also necessary to rule out alternative etiologies of pulmonary hypertension, such as chronic pulmonary embol or chronic hypoxia.
Once the MPAP is < 40 mm Hg and left ventricular function is deemed adequate, we proceed to assess the right ventricular response to rapid volume infusion. Although right heart catheterization identifies patients with static pulmonary hypertension, the effect of volume-mediated pulmonary hypertension is an additional consideration that could be lethal at the time of allograft reperfusion. In patients with end-stage liver disease, the pulmonary vasculature reacts in an aberrant fashion to rapid volume infusion. We have shown that these patients will develop significantly elevated MPAP and PCWP after rapid infusion of one liter of crystalloid solution compared with normal patients (19). Consequently, we have added a fluid challenge to the standard DSE protocol to evaluate the dynamic function of the right ventricle and pulmonary vasculature. When the maximum dose of dobutamine has been achieved (40-50 µg/kg/min), 1 liter of normal saline is infused over 10 min in the presence of a pulmonary artery catheter. Pulmonary hemodynamic and right ventricular responses are noted and pressure changes measured. If mean pulmonary pressures do not exceed 40 mm Hg, we feel that the right ventricle demonstrates adequate functional reserve, and the patient is allowed to undergo transplantation. However, if the MPAP increases to > 40 mm Hg or the right ventricle develops significant dysfunction, chronic infusion of epoprostenol is continued, and the process repeated in 3-6 months. Even in those patients who exhibit acceptable hemodynamic profiles, epoprostenol should be continued while awaiting OLT. It has been shown that right ventricular remodeling can occur in these patients and, theoretically, further improvement may occur in the interim.

A subcategory of PPHTN patients merits special mention. Patients with elevated right atrial and ventricular pressures may exhibit normal or only mild elevations in pulmonary artery pressure. This occurs as a result of significantly depressed right ventricular function in the face of long-standing elevations in pulmonary artery pressures. Decompensation of right sided pump function in these cases suggests a poor overall outcome. If OLT candidacy remains an issue, we believe volume challenge in these patients should be performed with great caution. In addition, although right ventricular remodeling has been documented after chronic epoprostenol infusion therapy, it is unknown whether this specific subcategory of patients will also respond.

Other pulmonary vasodilating agents, such as inhaled nitric oxide, have not been shown to be of any value during the perioperative management of these patients (6, 33). As a result, it is unknown what role inhaled nitric oxide should have in the initial preoperative evaluation. Certainly, if a specific patient demonstrates a response to inhaled nitric oxide, then it may serve as an additional therapeutic option for use in the operating room or the intensive care unit.

SUGGESTIONS FOR PERIOPERATIVE MANAGEMENT OF PPHTN

Perioperative communication and cooperation between the anesthesia and surgery teams are imperative to a successful outcome. Maintenance of good right ventricular function and low pulmonary arterial pressures are foremost among the management goals. Using the "piggy-back" technique results in a short anhepatic period and decreases the magnitude of hemodynamic changes associated with reperfusion. Alternatively, use of a veno-venous bypass, including use of a portal venous cannula, also minimizes the consequences of vena caval clamping and unclamping.

Intraoperative monitoring should include peripheral and pulmonary arterial catheters and transesophageal echocardiography (TEE), in addition to standard noninvasive monitors. Hemodynamic parameters should be maintained in a fairly narrow range: MAP>=70 mmHg, cardiac index >=3.0 l/min/m², and PCWP 10-14 mmHg. TEE is useful in confirming adequate preload in settings in which central venous pressure and PCWP may be unreliable and in assessing right ventricular function. The patient should be kept warm, especially in light of the detrimental effect of hypothermia on pulmonary vascular resistance. Unfortunately, physiologic changes known to exacerbate pulmonary hypertension are exactly those routinely seen on allograft reperfusion, that is, hypercarbia, hypothermia, and acidosis. Several steps are taken before reperfusion to decrease the physiologic effects of the combination of caval unclamping and washout of the newly perfused allograft. These include hyperventilating with 100% oxygen and correcting metabolic parameters as much as possible, especially acidosis, hypocalcemia, and hyperkalemia. Also, adequate depth of anesthesia is important, and, should hypoxia and hypercarbia occur, they should be treated immediately. The upper caval clamp should be removed slowly and may need to be replaced should the acute volume load prove be in excess of the functional reserve of the right ventricle. Pulmonary vasodilators, including epoprostenol, inhaled nitric oxide, nitroglycerin, and sodium nitroprusside, should be available if pressures become excessive, although hypoxia resulting from pulmonary shunting, systemic hypotension, and general lack of efficacy, limit their usefulness. We preferentially use epoprostenol titrated from 2 to 10 ng/kg/min as a specific pulmonary vasodilator, although systemic hypotension may ensue.
Unlike other settings in which higher filling pressures are desirable, hypervolemia should be avoided both to minimize the detrimental effect on pulmonary pressures and to avoid allograft engorgement seen with impaired inferior vena cava and hepatic venous drainage. Nevertheless, volume therapy is important in maintaining left ventricular filling to prevent shifting of the interventricular septum into the left side. TEE has proved especially useful in attempting to balance these conflicting management goals. Epinephrine is our inotrope of choice to preserve systemic perfusion pressures as well as augment the inotropic state of the heart. Milrinone, a phosphodiesterase III inhibitor, is useful if a second inotrope is required. More extreme strategies have been reported to deal with catastrophic hemodynamic changes occurring on reperfusion, including emergency right heart assist devices and compression of the abdominal aorta (34).

Postoperative management of patients with PPHTN is similar to that discussed for the intraoperative period. Any specific pharmacologic therapy instituted in the operating room should be continued. Mechanical ventilation will be required for a minimum of several hours and up to several days. Extubation may prove problematic in the face of intrinsic pulmonary disease, because hypoxia or hypercarbia, which develops during the weaning process, will exacerbate the pulmonary hypertension. Systemic hypotension and right heart failure may then ensue and evolve into a vicious cycle of more hypercarbia and hypoxia causing more pulmonary hypertension. Also, the increased mobilization of fluids, which occurs mostly on postoperative days 2 or 3 can precipitate right heart failure (35).

After transfer from the intensive care unit and even discharge from the hospital, management differs minimally from that of other liver transplant recipients. However, chronic diuretic therapy is generally avoided to maintain right-sided and left-sided preload. Epoprostenol is continued for 6 months. At that time, the patient is weaned as tolerated, or oral diltiazem is substituted, guided by repeat right heart catheterization and patient symptoms.

PPHTN AFTER OLT

Because the etiology of PPHTN is unknown, it is difficult to determine whether PPHTN will resolve after OLT. Yoshida and co-workers published 2 case reports comparing a lung transplant recipient and a liver transplant recipient, both of whom underwent transplants for PPHTN. In this instance, PPHTN recurred in the lung recipient, but not in the liver recipient (36). Although this suggests that hepatic dysfunction and accompanying portal hypertension are required for development of PPHTN, OLT does not normalize pulmonary pressures in all instances. A review of the literature shows that seven published reports document the outcome of PPHTN after OLT. In combination with our patient, the cumulative data indicate that 7 of 10 PPHTN liver transplant recipients demonstrated improved or normalized pulmonary artery pressures within 6 months after the transplant (17, 36-41). In addition, the retrospective reports of Castro, Taura, Plevak, and Ramsay have further defined the outcome of PPHTN patients after OLT (1-3, 8). Although they do not address the issue of resolution of PPHTN, they document that "mild-to-moderate" PPHTN does not alter long term outcomes after OLT. In contrast, the "severe" subcategory carries a poor outcome. Ramsay describes 5 of 7 patients with "severe" PPHTN (systolic PAP > 60 mmHg) with progressive right heart failure after OLT, suggesting persistent PPHTN or decompensated right ventricular function (8). We hypothesize that PPHTN patients with a fixed level of pulmonary vascular resistance will not exhibit regression of PPHTN after OLT. In this regard, chronic administration of epoprostenol will segregate those OLT candidates with a fixed level of pulmonary vascular resistance (Figure 1). In addition, the remodeling effects of epoprostenol have not been addressed in these previous studies and may dramatically alter the outcomes.

CONCLUSION

The management of the OLT candidate with PPHTN has dramatically changed in the past 3 years. At our institution, careful preoperative evaluation with functional characterization of right ventricular function plays a critical role. The pulmonary vascular response to epoprostenol infusion serves as a discriminating decision point in proceeding with OLT candidacy. Careful perioperative attention to avoid right ventricular failure, from acutely elevated PA pressures or sudden increases in right ventricular preload, is a key physiologic tenet to management. With increased surgical expertise, anesthetic sophistication, and availability of epoprostenol, PPHTN should no longer be considered an absolute contraindication for OLT.

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*Abbreviations used: HPS, hepatopulmonary syndrome; MPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; OLT, orthotopic liver transplant; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PPHTN, portopulmonary hypertension; PVR, pulmonary vascular resistance. [Context Link]