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REVIEW ARTICLE

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Pulmonary hypertension: considerations in the liver transplant candidate

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Abstract Pulmonary hypertension is a potentially lethal complication of end-stage liver disease with a prevalence of 2 %. In the setting of liver transplantation, the prevalence may be as high as 12 %. Given the potential importance of this syndrome to the transplantation community, the purpose of this review is to summarize the current state of understanding of portopulmonary hypertension and to suggest potential management strategies for (1) liver transplant candidates with suspected pulmonary hypertension and (2) intraoperative pulmonary hypertension following liver allograft reperfusion.

Key words Liver transplantation, pulmonary hypertension · Pulmonary hypertension, liver transplantation

Introduction

With the acceptance of orthotopic liver transplantation (OLT) as therapy for end-stage liver disease, indications for transplantation have broadened and potential recipients with extrahepatic complications are undergoing evaluation and transplantation. Within this context, pulmonary hypertension is a complication of liver disease that will be seen with increased frequency. Its rapidity of onset during OLT, the nonspecific nature of associated signs and symptoms, the lack of specific noninvasive preoperative testing, and the increasingly complicated profile of the OLT recipient make pulmonary hypertension a difficult management problem. Although discussions of pulmonary hypertension in the liver transplant setting have been largely academic, recent insights in pulmonary endothelial biology and the therapeutic use of inhaled nitric oxide have elevated the subject to that of clinical relevance. As a result, the diagnosis, pathophysiology, and management of pulmonary hypertension have become important issues for the liver transplant physician. Therefore, the purpose of this overview is to summarize: (1) the clinical and pathophysiologic features of pulmonary hypertension, (2) preoperative screening modalities, and (3) management strategies for the liver transplant candidate with pulmonary hypertension.

Clinical and pathophysiologic features

Mantz and Craige first described the coexistence of chronic liver disease and pulmonary hypertension in 1951 [30]. Variably defined as a mean pulmonary artery pressure greater than 18–20 mm Hg or a pulmonary artery systolic pressure greater than 30 mm Hg, pulmonary hypertension is characterized by three distinct histologic patterns: plexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy, and pulmonary veno-occlusive disease [12, 17, 41]. In the setting of concomitant portal and pulmonary hypertension (or portopulmonary hypertension), the histological features are identical to those of plexogenic pulmonary arteriopathy with medial hypertrophy, concentric intimal fibrosis, and plexiform lesions of the small pulmonary arteries [31]. Organized thrombi found in association with plexiform lesions are considered to be secondary to local injury and stasis [31].

The etiology of pulmonary hypertension in this setting is unknown; however, multiple reports document

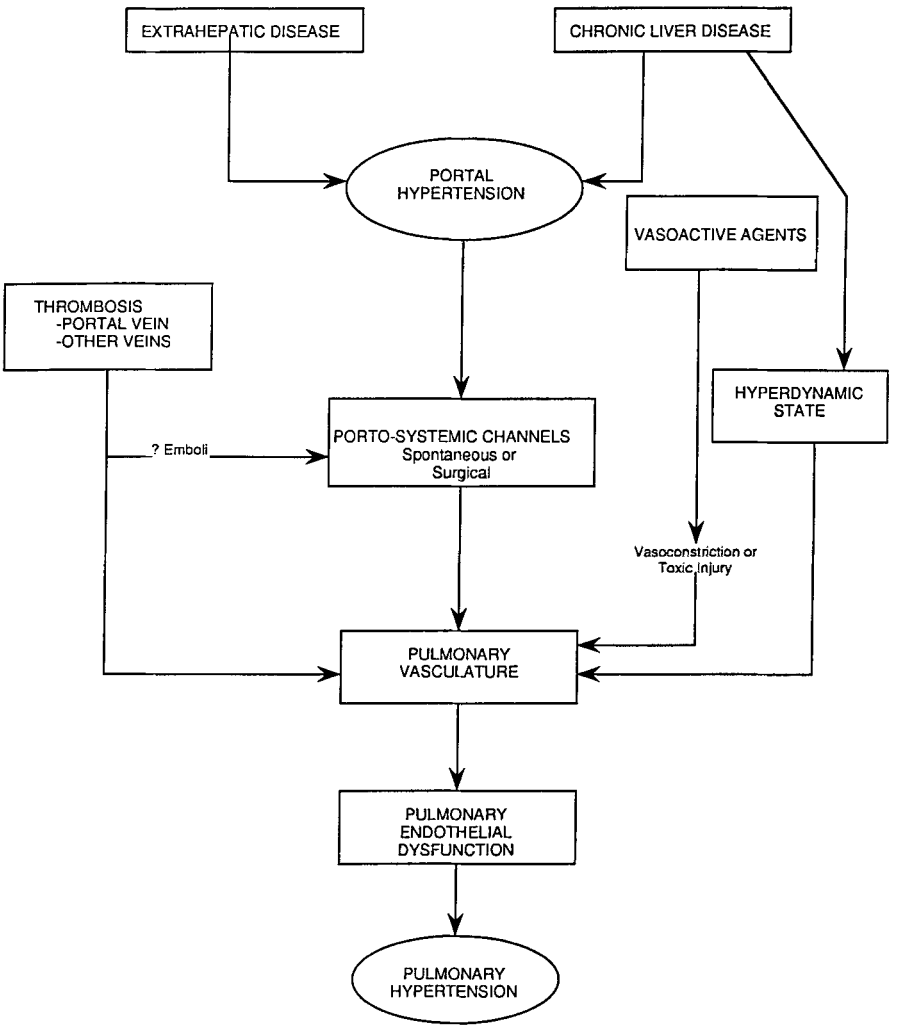

Fig. 1 Hypothetical scheme for the development of portopulmonary hypertension

the association between pulmonary hypertension and portal hypertension, rather than intrinsic hepatocellular dysfunction [2, 10, 13, 18, 26, 35, 41, 49, 53]. In a study by Hadengue and coworkers, the degree of liver failure as estimated by the Pugh score did not correlate with pulmonary vascular resistance [18]. In addition, a specific etiology of the concomitant portal hypertension has not been associated with an increased incidence of pulmonary hypertension. Two hypotheses have been suggested to explain the syndrome of portopulmonary hypertension, one involving thromboembolism and the other vasoactive substances (Fig. 1). Thromboembolism as a potential etiologic factor has been suggested by observations of plexogenic pulmonary arteriopathy with coexistent thromboembolic lesions [10]. Injection studies have demonstrated grossly visible anastomoses of the portal venous bed with the superior vena cava through periesophageal, mediastinal, and azygos veins, which may allow the passage of pulmonary emboli [45]. In spite of these findings, most have deemed thromboembolism to be an unlikely cause for portopulmonary hypertension [41]. On histologic grounds alone, it is difficult to distinguish recurrent pulmonary emboli from in situ thrombosis in small pulmonary arteries [10, 31]. In addition, the incidence of portopulmonary hypertension is not higher in patients with portal vein thrombosis than in those without thrombosis [26].

A widely accepted explanation for the syndrome is the portosystemic shunting of vasoactive substances, normally metabolized by the liver, into the pulmonary circulation with resultant vasoconstriction and chronic arterial changes in 40- to 100-μm vessels [41, 46]. Indeed, portal hypertension is invariably diagnosed before or concurrently with pulmonary hypertension. Potential vasoconstrictive substances include serotonin, bradykinin, neuropeptide Y, and thromboxanes [10, 37, 41]. Animal models of pulmonary hypertension induced by hepatically derived toxins support this hypothesis with evidence of pyrolizidine alkaloid-associated hepatic centrilobular necrosis with subsequent pulmonary artery con-

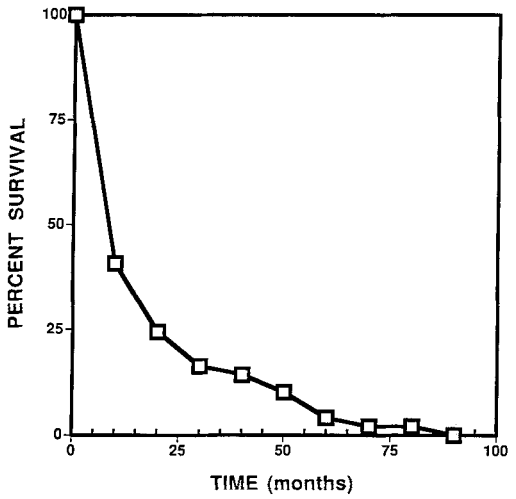

Fig. 2 Survival curve in 49 patients with portopulmonary hypertension. Adapted from [41]

striction and medial hypertrophy [3, 50]. In humans, administration of aminorex is associated with a similar picture [22].

While the shunting of vasoactive substances is an attractive explanation, a growing body of data regarding endothelial-derived vasoactive substances suggests pulmonary endothelial dysfunction as an alternative. In 1989, Wanless suggested that portopulmonary hypertension may occur as the result of differential inability to regulate vascular tone or to develop compensatory shunts in the hyperdynamic state of liver failure [48]. Capillary pressure would then be controlled only by arteriolar spasm with consequent intimal injury, secondary thrombosis, medial necrosis, and the appearance of plexiform lesions in the pulmonary arterioles. He postulated that portopulmonary hypertension was, therefore, the result of aberrant pulmonary endothelial activity [48].

Under normal circumstances, the endothelial cell elaborates a variety of substances that promote vasodilation, inhibit platelet adhesion and activation, and prevent thrombin generation. Hypoxia, acidosis, reactive oxygen intermediates, inflammatory mediators, increased shear forces, and fibrin formation promote endothelial injury [28]. Therefore, endothelial dysfunction can exacerbate the pulmonary hypertensive process. Decreased elaboration of prostacyclin and nitric oxide (NO) with increased production of endothelin promote pulmonary vasoconstriction. Decreased synthesis or release of thrombomodulin, heparan sulfate, and tissue-type plasminogen activator in conjunction with increased release of plasminogen activator inhibitor type 1 and tissue factor promote fibrin formation [7, 15, 28, 55]. Certainly, recent reports suggest altered endothelial function in pulmonary hypertension; in patients with pulmonary hypertension, fibrinopeptide A levels are increased, reflecting thrombin activity, while prostacyclin metabolites are decreased [5].

Of potential import is the presumed role of NO in pulmonary hypertension. Pulmonary artery endothelial cells release NO, which mediates both endothelium-dependent and -independent arterial relaxation. NO induces relaxation of pulmonary arterial smooth muscle in response to a variety of agonists such as acetylcholine and bradykinin, modulates contractile responses to catecholamines and prostaglandin F_{2a}, reverses hypoxic pulmonary vasoconstriction, and mediates flow-enhanced decreases in vascular resistance. In human subjects, evidence implicates NO synthetic activity in the regulation of normoxic pulmonary vascular tone and blood flow. Inflammatory, metabolic, and hemodynamic disorders in pulmonary vascular homeostasis appear to be modulated in part by NO or a lack thereof. Certainly, aberrant NO metabolism, with its associated effects on pulmonary vascular activity, is a potential etiologic candidate in portopulmonary hypertension. Consequently, delivery of NO or NO donors is receiving increased attention for treatment of pulmonary hypertension associated with diseases such as adult respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD) [7, 15, 54, 55].

While multiple case reports exist, few large series definitively document the syndrome of portopulmonary hypertension. In a group of 507 patients with portal hypertension who underwent prospective cardiac catheterization, 10 (2 %) were found to have accompanying pulmonary hypertension [18]. In an unselected autopsy series of 17,901 patients, the incidence of primary pulmonary hypertension was 0.13 %. In contrast, among patients with cirrhosis, the prevalence of pulmonary hypertension was 0.73 %, over five times greater than that of controls [31]. In a clinical series of 2,459 patients with biopsy-proven cirrhosis, the same investigators noted the prevalence of pulmonary hypertension to be 0.61 % [31]. In the setting of liver disease, it is generally thought that the prevalence of coexisting primary pulmonary hypertension is 1 %–2 % [31]. In particular, among patients undergoing OLT, Plevak and colleagues found the prevalence of pulmonary hypertension to be as high as 12.5 % (33/263) [34].

The ultimate outcome in patients with portopulmonary hypertension is largely unknown. In their retrospective review of the literature, Robalino and Moodie report that the mean survival after diagnosis was 15 months with a 6-month mortality rate of 50 % (Fig. 2) [41]. Patients with primary pulmonary hypertension alone had a mean survival of 2–3 years and an estimated 2-year survival of 57 %. In contrast, in the group of 26 patients reported by Hadengue, although five patients died within 1 month of diagnosis and ten died within 12 months, another ten patients actually survived

Table 1 Hemodynamic characteristics of patients with portopulmonary hypertension[a]

Pulmonary artery pressures (mm Hg)	
Mean	59 ± 19
Systolic	89 ± 24
Diastolic	40 ± 13
Wedge	9 ± 4
Pulmonary vascular resistance (dyne/sec-cm^5)	661 ± 400
Cardiac output (l/min)	6.6 ± 1.7
Systemic oxygen saturation – room air	93 ± 5

[a] Acapted from [18, 41]

longer than 2 years and two survived longer than 10 years [18]. Among the ten deaths that occurred within 1 year, five were the result of liver disease while the remainder were related to the underlying pulmonary hypertension. The patients who died from a pulmonary hypertensive cause had significantly lower Pugh scores, hepatic venous pressure gradients, and cardiac indices and higher pulmonary artery pressure and pulmonary vascular resistance. Among those who died, the average survival time from diagnosis was 19 months [18].

In the setting of OLT, coexisting pulmonary hypertension is thought to be associated with increased perioperative mortality and morbidity. An informal survey of transplant programs by Prager concluded that patients with severe pulmonary hypertension are unlikely to survive OLT [36]. DeWolf et al. reported that five patients with moderate-to-severe pulmonary hypertension (pulmonary systolic pressures 55–79 mm Hg) underwent OLT at the University of Pittsburgh; all underwent preoperative challenge with pulmonary vasodilators (nitroglycerin, prostaglandin E_1, and nifedipine) without a significant response. Of these five patients, four (80 %) died intraoperatively or in the immediate postoperative setting [9]. Hamdani found a mortality rate of 70 % following OLT in patients with pulmonary hypertension. Half of these deaths were the result of cardiogenic shock, typical of pulmonary hypertension-related deaths [19]. The sequence of events leading to death was onset or exacerbation of pulmonary hypertension, progressive right ventricular failure, and systemic hypotension, followed by death. In contrast, in a series from the Mayo Clinic, 33 of 263 patients undergoing OLT were noted to have mild-to-moderate pulmonary hypertension with pulmonary vascular resistances of 120.5–267.7 dyne/sec-cm^5; there was no mortality in this group [34]. These reports suggest that portopulmonary hypertension per se is not necessarily an absolute contraindication to OLT. Certainly, the degree of pulmonary hypertension should be a consideration. Of greater significance may be the degree of plasticity of the pulmonary circulation. In studies on patients with primary pulmonary hypertension alone, a favorable response to therapeutic challenge with vasodilators was predictive of improved 5-year survival [40, ,41]. Interestingly, the degree of hypertension was less important than the reversibility of the hypertension, suggesting a potential algorithm for evaluation of OLT candidates with pulmonary hypertension. Those who respond favorably to therapeutic vasodilator challenge may be suitable, albeit high-risk, candidates, while those who demonstrate a fixed level of pulmonary hypertension by lack of vasodilator response, such as the group reported by De Wolf, should not undergo OLT [9].

The reversibility of portopulmonary hypertension in this setting remains controversial. Case reports detail both the resolution and persistence of pulmonary hypertension following transplantation [24, 37, 45]. Potential factors or criteria associated with reversibility of pulmonary hypertension after OLT remain unknown. Given the paucity of controlled longitudinal studies in this patient population and the reluctance of transplant centers to accept candidates with pulmonary hypertension, the relevance of degree of pulmonary hypertension, degree of plasticity, or severity of underlying portal hypertension has not been analyzed. However, in the population of patients with primary pulmonary hypertension alone, the absence of hemodynamic improvement in the context of vasodilator therapy was associated with dramatically decreased survival [39]. This suggests that liver failure patients with fixed degrees of pulmonary hypertension may be unacceptable risks for OLT. Again, the extent of pulmonary hypertension and the degree of plasticity that pose acceptable risks for OLT are unknown. Interestingly, Yoshida and colleagues reported the outcomes of two patients with portopulmonary hypertension [52]. One underwent OLT while the other received a single-lung transplant. Following lung transplantation, pulmonary hypertension recurred following a short period of normality. In contrast, following OLT, a sustained improvement in pulmonary hypertension was seen (from 43 to 22 mm Hg). This example, although isolated, suggests that portal hypertension rather than intrinsic pulmonary disease is the major underlying cause of portopulmonary hypertension [52].

Hemodynamic characteristics and biochemical mediators

Hemodynamic findings in portopulmonary hypertension reflect the hyperdynamic state of cirrhosis with defined pulmonary hypertension (Table 1). Although cardiac output is increased after portocaval shunts and in cirrhosis with portal hypertension, this alone is of insufficient magnitude to be the primary etiology for this syndrome [41]. This consideration notwithstanding, increased pulmonary venous pressure, increased pulmonary blood flow, increased pulmonary vascular resistance secondary to hypoxic pulmonary vasoconstriction, and right ventricular dysfunction may contribute to the

hemodynamic findings in portopulmonary hypertension [4, 33]. De Wolf and colleagues studied right ventricular function in a series of 20 patients undergoing OLT with venoveno bypass. They found that graft reperfusion was associated with a significant increase in mean pulmonary artery pressure and pulmonary capillary wedge pressure and a concomitant decrease in mean systemic artery pressure. None of these patients had pre-existing, or developed intraoperative, pulmonary hypertension. These results indicate that the OLT procedure was not associated with significant right ventricular dysfunction [8]. Nevertheless, in combination with the report by Koneru and colleagues, these data suggest that hepatic allograft reperfusion is associated with increased pulmonary and decreased systemic pressures and, as a result, is the phase of OLT during which pulmonary hypertension may be most apt to develop or worsen [4, 8, 24, 33, 45, 52].

While a variety of etiologic factors may be responsible, an altered response of the pulmonary circulation in the setting of portal hypertension is a consideration. In a study by Kuo and coworkers, 22 OLT candidates underwent prospective right heart catheterization, and the pulmonary hemodynamic response to rapid infusion of one liter of crystalloid was measured [25]. Forty one percent (9/22) of the patients developed pulmonary hypertension after volume infusion in contrast to 0 of 11 controls. Only one study patient had pre-existing pulmonary hypertension. The development of volume-mediated pulmonary hypertension was associated with significant increases in both mean pulmonary artery pressure and pulmonary capillary wedge pressure, suggesting intravascular volume overload and/or left ventricular dysfunction as an etiologic factor [25]. In another study, Agusti and coworkers studied the pulmonary hemodynamic response to exercise in cirrhosis. In comparison to normals, patients with cirrhosis exhibited a significantly increased elevation in pulmonary driving pressure (mean pulmonary pressure-capillary wedge pressure) with similar exercise-induced work loads. In addition, selected patients developed pulmonary hypertension in association with supranormal pulmonary capillary wedge pressures and slightly depressed pulmonary vascular resistance. These results again suggest an aberrant left ventricular response to stress in the setting of cirrhosis [1].

Considered in the aggregate, these studies indicate that portopulmonary hypertension is associated with the hyperdynamic circulation of cirrhosis and the defined parameters of pulmonary hypertension. In addition, evidence supports an element of left ventricular dysfunction in the pulmonary hemodynamic response to rapid volume administration and/or a state of increased contractility [1, 25]. These states may exist at any point during the surgical procedure, but are most notably present during allograft reperfusion. These conditions may lead to irremediable pulmonary hypertension of fulminant onset during the course of OLT.

An additional consideration is that of released biochemical mediators following graft reperfusion. Previous studies have reported associations between portopulmonary hypertension and levels of vasoactive substances such as endotoxin, serotonin, estrogen, prostaglandins, kinins, and neuropeptide Y [24], but evidence is lacking that implicates a specific biochemically mediated mechanism. In this regard, two lines of investigation may prove to be useful. Stansby and Nakamura have demonstrated the systemic release of endothelin-1, a potent vasoconstrictor peptide with mitogenic properties, following liver allograft reperfusion [32, 47]. Endothelin-1 acts as a constrictor of pulmonary vasculature and is thought to be the effector molecule in hypoxic pulmonary vasoconstriction [16]. In addition, patients with primary pulmonary hypertension have increased endothelin-1 mRNA and immunoreactivity in pulmonary endothelial cells [16]. These data suggest that endothelin-1 may play a role in the development of pulmonary hypertension following graft reperfusion. Tumor necrosis factor (TNF) is also released upon liver allograft reperfusion [6, 21]. Colletti and colleagues have found that TNF-alpha release following allograft reperfusion is associated with increased pulmonary injury [6]. Histologically characterized by pulmonary edema and intra-alveolar hemorrhage, reperfusion-mediated lung injury is ablated by the administration of anti-TNF antibody. While pulmonary hypertension was not specifically addressed in these studies, the hypoxic pulmonary vasoconstriction accompanying TNF-mediated lung injury is another potential etiology for pulmonary hypertension following reperfusion. These and other research endeavors concerning the release of biochemical mediators following graft reperfusion have resulted in the use of blood from the portal circulation as the initial washout during OLT with the discard of the initial cytokine- and endothelin-rich blood perfusate [11].

The precise biochemical mediators of portopulmonary hypertension and reperfusion-mediated pulmonary hypertension remain obscure. While endothelin and TNF are potential candidates, a number of other cytokines have yet to be addressed. Therefore, the clinical practice of liver allograft washout with blood and subsequent discard of the initial effluent is a potentially efficacious technique to avoid delivery of vasoactive substances to the pulmonary circulation.

Diagnostic approaches

The diagnosis of pulmonary hypertension depends on a variety of clinical signs and symptoms and noninvasive testing, such as pulse oximetry, electrocardiography

Table 2 Clinical characteristics of patients with portopulmonary hypertension ($n = 76$)[a]

Age (years)	38.7
Sex (M/F)	43/33
Etiology of portal hypertension	
Alcoholic cirrosis	43 %
Posthepatic cirrhosis	20 %
Cryptogenic cirrhosis	16 %
Portal vein thrombosis	11 %
Portacaval shunt	43 %
Interval between:	
Diagnosis of portal and pulmonary hypertension (months)	75.5
First symptom and diagnosis of pulmonary hypertension (months)	19.2

[a] Adapeted from [18, 41]

(ECG), chest roentgenography, and echocardiography. The gold standard remains right heart catheterization, which allows definitive measurement of pressure and flow with titration of hemodynamic responses to therapy [38]. The advantages and disadvantages of these modalities have been well outlined and will be only briefly reviewed here.

The clinical symptomatology of patients with portopulmonary hypertension has been summarized by Robalino and Moodie [41]. In their retrospective analysis of 78 cases, exertional dyspnea was the most frequent presenting symptom (81 %), followed by syncope (26 %), chest pain (24 %), and fatigue (15 %). In contrast, in the report by Hadengue and coworkers in which 507 cirrhotics were prospectively catheterized, 10 patients had pulmonary hypertension. Only 4 found complained of exertional dyspnea while 6 were asymptomatic [18]. The authors note that the mean pulmonary vascular resistance was lower in these 10 patients than in a group of 26 patients with suspected portopulmonary hypertension before catheterization (258 vs 661 dyne/sec-cm^5). In these 26 patients, again analyzed retrospectively, exertional dyspnea (96 %), exertional syncope (29 %), and chest pain (15 %) were the most common symptoms. Physical findings included an accentuated P_2 heart sound (82 %), systolic murmur (69 %), edema (35 %), and ascites (21 %) [18]. Given the overlap in signs and symptoms between the pulmonary and hepatic components of this syndrome, these presenting complaints and physical findings are, at best, suggestive but are insufficiently sensitive. Additional characteristics of patients with portopulmonary hypertension are presented in Table 2. While one might argue that asymptomatic patients fall into the mild-to-moderate pulmonary hypertension category without associated OLT mortality, the data suggest that the pulmonary component of portopulmonary hypertension is progressive, with a two- to threefold increase in mean pulmonary pressure occurring over 1–2 years [12, 18]. This time interval is in keeping with waiting times for UNOS status 3 patients awaiting OLT.

ECG, echocardiography, and chest x-ray (CXR) studies provide added supportive evidence for the diagnosis of portopulmonary hypertension. Robalino found ECG evidence for right ventricular hypertrophy and right axis deviation (79 %) and right bundle branch block (59 %) [41]. Cardiomegaly and pulmonary artery prominence were noted on CXR in 78 % and 74 % of patients, respectively [41]. Echocardiography with color-flow Doppler allows accurate estimation of mean pulmonary artery pressure in the presence of tricuspid regurgitation (present in 80 % of patients with pulmonary hypertension) while simultaneously evaluating ventricular performance [38, 51]. Echocardiography is an excellent screening tool for preoperative assessment of the OLT candidate and, together with history, physical exam, ECG, and CXR, provides evidence for pulmonary hypertension.

Magnetic resonance imaging (MRI) is potentially useful for noninvasive diagnosis of portopulmonary hypertension. Abdominal MRI is presently used to screen OLT candidates for hepatic parenchymal masses, splanchnic venous thrombosis or anomalies, and localization of prominent varices [27]. MRI offers additional information, such as determination of portal venous or hepatic arterial flow. Similarly, MRI can aid in the diagnosis of pulmonary hypertension by demonstration of right ventricular enlargement with hypertrophy, right atrial enlargement, and abnormal septal motion [14]. MRI-specific patterns of flow in the pulmonary artery can be used to noninvasively determine pulmonary artery pressure and pulmonary vascular resistance [23]. The development of these techniques could allow preoperative OLT assessment with a single diagnostic screening method.

Following the diagnosis of pulmonary hypertension in the patient with liver disease, consideration should be given to causes other than portopulmonary hypertension, especially in the transplant candidate (Table 3). Major items of concern include COPD, pulmonary fibrosis, thoracic cage deformities, neuromuscular disease, sleep-disordered breathing, thromboembolic diseases, and congenital heart disease with cor pulmonale. As a result, ventilation-perfusion scans, pulmonary function tests including arterial blood gas determinations, pulmonary angiography, sleep studies, and full cardiac catheterization may be required [38].

Once pulmonary hypertension is diagnosed in the absence of shunts, valvular disease, and pulmonary emboli, the patient should undergo cardiac catheterization with therapeutic trials of pulmonary vasodilators, including calcium channel blockers, nitroglycerin, prostacyclin, prostaglandin E_1, sodium nitroprusside, and inhaled nitric oxide [20, 39, 41, 44]. In some OLT centers,

Table 3 Chronic disorders associated with pulmonary hypertension[a]

Obstructive airways disease
Emphysema
Chronic bronchitis
Bronchiectasis
Cystic fibrosis
Thoracic cage deformities
Kyphoscoliosis
Thoracoplasty
Hyperventilation syndromes
Neuromuscular diseases
Obesity-hypoventilation syndrome
Obstructive sleep apnea syndrome
Interstitial fibrosis
Pneumoconioses
Sarcoidosis and other granulomatous diseases
Collagen vascular diseases
Idiopathic pulmonary fibrosis
Drug reactions
Radiation pneumonitis
Thromboembolism/embolic disease
Pulmonary thromboembolism (chronic major vessel)
Sickle hemoglobinopathies
Foreign body emboli
Metastatic carcinoma (tumor embolism)
Cardiac defects
Congenital disorders with left-to-right shunts
Chronic mitral stenosis
Idiopathic disorders
Primary pulmonary hypertension
Pulmonary veno-occlusive disease
Diffuse smooth muscle proliferation
Fibrosing mediastinitis

[a] Adapted from [38]

a favorable response to pharmacologic intervention determines OLT candidacy, albeit one with high risk [29]. In addition, the presence of a reversible component of pulmonary hypertension predicts improved survival with calcium channel blocker therapy [40]. In the specific instance of the OLT candidate, prolonged survival in the pretransplant period increases the potential for ultimate transplantation.

Management considerations

Management of the pulmonary component of the patient with portopulmonary hypertension is based upon the experience with isolated primary pulmonary hypertension. Among available therapeutic options, vasodilator therapy and anticoagulation have proven to be the most effective in prolonging survival. In 64 patients with primary pulmonary hypertension, Rich and colleagues instituted therapy with high-dose calcium channel blockers [40]. Patients who exhibited a 20 % decrease in pulmonary artery pressure and vascular resistance were designated responders and were maintained on long-term therapy. Nonresponders were placed on warfarin anticoagulation therapy alone. While only 26 % of the patients were responders, the associated 5-year survival was 94 % in comparison to 55 % in nonresponders. These results are surprising in light of the 2.8-year median survival of untreated patients. These investigators concluded that calcium channel blockade therapy and anticoagulation prolonged survival in primary pulmonary hypertension. Alternative strategies using indwelling infusion pumps for continuous delivery of prostacyclin have been associated with similar reductions in pulmonary pressures and resistance [44].

In general, patients undergo right heart catheterization with a therapeutic trial of short-acting vasodilator agents, such as nitroglycerin, nitroprusside, inhaled nitric oxide, or prostacyclin to assess the individual hemodynamic response. In one-third of patients, pulmonary artery pressures decrease and cardiac output increases while symptomatic systemic hypotension is absent. By definition, these patients have reversible components to their disease and are candidates for long-term therapy (and, by inference, OLT). In another one-third, cardiac output will increase without affecting pulmonary pressures. While right ventricular function and exercise tolerance may improve in this group, long-term effects on survival are unknown. In the remaining patients, vasodilator therapy reduces systemic blood pressure without alteration in cardiac output or pulmonary pressures. These patients have a fixed component to their disease and should not receive vasodilator therapy. Experience from the National Institutes of Health Registry suggests that patients with right heart failure are at greatest risk for adverse outcomes associated with long-term vasodilator therapy. To date, there are no hemodynamic or demographic variables that predict vasoreactivity; therefore, catheterization with monitored therapeutic trials remains essential for directing the care of patients with pulmonary hypertension [43]. In the specific case of patients with portopulmonary hypertension, warfarin anticoagulation to an international normalized ratio (INR) of 1.5–2.5 may not be necessary. However, patients who show themselves to be responders during cardiac catheterization should be placed on vasodilator therapy with oral calcium channel blockers or intravenous prostacyclin. Since the absence of vasodilator reactivity of the pulmonary circulation is judged to be a contraindication to OLT in some centers, one approach might be the institution of calcium channel blockade therapy for OLT candidates and consideration of anticoagulation in nonresponders.

Acute management of the OLT patient with portopulmonary hypertension who develops refractory hypotension and shock can be challenging and often frustrating. Pulmonary hypertension may occur rather rap-

idly following graft reperfusion or pre-existing pulmonary hypertension may rapidly worsen, resulting in decreased systemic blood pressure followed by cardiopulmonary arrest and death. While a discussion of specific management techniques is beyond the scope of this review, guiding principles include systematic evaluation for reversible causes of hemodynamic compromise including correcting oxygenation and acid-base status, titrating circulating volume to optimize right and left ventricular preload, enhancing right ventricular myocardial contractility, reducing right ventricular afterload, maintaining adequate blood pressure to maintain right ventricular perfusion, and correcting intercurrent left ventricular dysfunction [38]. Intraoperative maneuvers that may address the issue of optimization of right ventricular preload and contractility include minimizing venous return by decreasing flow through the venoveno bypass circuit, reapplying the vena caval cross-clamps and, potentially, venting of the right ventricle. The institution of vasodilators may be useful, but major drawbacks include systemic hypotension, worsening of pulmonary gas exchange, and lack of pulmonary vascular specificity. Also, in spite of the availability of these vasodilator agents, patients with portopulmonary hypertension undergoing OLT and those who develop intraoperative pulmonary hypertension continue to have a high rate of mortality and morbidity. These unfavorable outcomes may, in part, be the result of patient selection, but lack of specific, effective therapy is an additional consideration.

Recently, the introduction of inhaled nitric oxide (NO) has engendered a great deal of excitement as a potential therapeutic agent. As discussed previously, NO is a product of pulmonary endothelial cells with many roles in the regulation of pulmonary vascular tone. When inhaled, its lipophilic characteristic allows diffusion across the alveolar membrane, causing vascular smooth muscle relaxation. Intravascular contact with hemoglobin results in NO inactivation by virtue of its avidity for hemoglobin, over 1000 times greater than that of carbon monoxide. As a result, there is no systemic activity. NO is renally excreted as nitrate. While the ideal dose is as yet unknown, pulmonary vasodilator responses can occur at 5 ppm, and doses as high as 80 ppm have been administered without untoward effects [42]. Ideally, for the individual OLT patient, a dose-response relationship will have been determined during right heart catheterization. In addition to absence of systemic hypotension, inhaled NO also reduces intrapulmonary shunting of blood and, as a result, preserves oxygenation. Onset of effect is rapid, on the order of minutes. In the setting of ARDS, inhaled NO has been administered to patients for periods up to 53 days. Inhaled NO has proven to be efficacious in the reversal of pulmonary hypertension in ARDS, hypoxic pulmonary vasoconstriction, COPD, and primary pulmonary hypertension [15, 42, 54]. In these settings, inhaled NO was associated with decreases in mean pulmonary pressures, and improved oxygenation, improved right ventricular ejection fraction without inducing systemic hypotension. In contrast, to achieve equivalent decreases in pulmonary artery pressure, the required doses of prostacyclin and nitroprusside were associated with systemic hypotension and deterioration in oxygenation. Recently, Mandell and Duke reported their experience with the intraoperative use of inhaled NO in OLT [29]. Inhalation of doses up to 40 ppm was effective in reducing pulmonary artery pressure. The authors suggest that the NO-mediated reduction in pulmonary pressure may have prevented right ventricular deterioration, especially during allograft reperfusion. While certainly not a panacea for the care of the patient with portopulmonary hypertension, inhaled NO offers effective, specific therapy of rapid onset and without associated systemic hypotension. This therapy could be applicable to patients with pre-existing pulmonary hypertension and to those who develop acute pulmonary hypertension with hemodynamic compromise during the perioperative course of OLT.

Summary and conclusion

The association between pulmonary hypertension and portal hypertension is well described with a prevalence of 2 % [18]. In the setting of OLT, the prevalence may be as high as 12 % [34]. The precise etiology of this syndrome is unknown but may involve thrombosis, vasoactive substances that bypass hepatic metabolism and, ultimately, pulmonary endothelial dysfunction. This state may be exacerbated by the hyperdynamic state associated with coexisting liver disease. In addition, a subgroup of patients with liver dysfunction manifest a form of pulmonary hypertension that develops in the setting of rapid volume shifts and increased ventricular contractile states, as during the reperfusion period of OLT. This occurs in the absence of pre-existing pulmonary hypertension and may be representative of those episodes of pulmonary hypertension that occur with rapid onset during the course of OLT.

The mortality of this syndrome is significant, with a mean survival after diagnosis of 15 months and a 6-month mortality of 50 %, even greater than that of patients with primary pulmonary hypertension [41]. Perioperative OLT mortality can be prohibitive, depending upon the severity of the pulmonary hypertension and the algorithm for patient selection. While diagnosis is hampered by nonspecific signs and symptoms, Doppler echocardiography is useful for noninvasive screening. MR imaging may offer additional benefits in this regard. In the absence of secondary causes, the patient with portopulmonary hypertension should undergo right

heart catheterization for quantification of disease severity and assessment of response to short-acting vasodilator agents, including inhaled NO. Patients who demonstrate a reversible component of pulmonary hypertension by response to vasodilator therapy may be considered high-risk OLT candidates. With its proven survival advantage in primary pulmonary hypertension, calcium channel blocker therapy may be instituted.

As transplant centers continue to expand the indications for OLT, the syndrome of portopulmonary hypertension will be seen with increased frequency. It is our belief that pulmonary hypertension per se is not an absolute contraindication to transplantation. With appropriate preoperative management, patient selection, and attention to intraoperative and postoperative care, certain patients can successfully undergo OLT. In this regard, inhaled NO may represent a major addition to the clinical armamentarium for the care of these patients.

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