Pulmonary Vascular Complications of Liver Disease

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Hepatopulmonary syndrome and portopulmonary hypertension are two pulmonary vascular complications of liver disease. The pathophysiology underlying each disorder is distinct, but patients with either condition may be limited by dyspnea. A careful evaluation of concomitant symptoms, the physical examination, pulmonary function testing and arterial blood gas analysis, and echocardiographic, imaging, and hemodynamic studies is crucial to establishing (and distinguishing) these diagnoses. Our understanding of the pathobiology, natural history, and treatment of these disorders has advanced considerably over the past decade; however, the presence of either still increases the risk of morbidity and mortality in patients with underlying liver disease. There is no effective medical treatment for hepatopulmonary syndrome. Although liver transplantation can resolve hepatopulmonary syndrome, there appears to be worse survival even with transplantation. Liver transplantation poses a very high risk of death in those with significant portopulmonary hypertension, where targeted medical therapies may improve functional status and allow successful transplantation in a small number of select patients.

Keywords: hepatopulmonary syndrome; hypertension; pulmonary; liver cirrhosis; pulmonary circulation

The pulmonary circulation may be affected by pathogenic processes arising within the liver and portal venous system. Reports of abnormalities of the pulmonary vasculature found in association with coexisting chronic liver disease were first published in the 1950s (1, 2). Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH) are both associated with portal hypertension and/or liver disease and in simplest terms are related to excessive pulmonary microvascular dilation (in HPS) or vasoconstriction/vascular obstruction in pulmonary resistance vessels (in PoPH). The fact that these seemingly disparate conditions can occur within the same patient population (and even simultaneously or sequentially in the same patient) suggests the role of disease modifiers that determine the particular pulmonary vascular phenotype. These important pulmonary complications both commonly present with dyspnea, yet have unique pathophysiologies, diagnostic modalities, approaches to treatment, and distinct implications regarding liver transplantation (LT). A thorough understanding of the approach to evaluation and treatment of patients with cirrhosis and possible pulmonary vascular disease is imperative to minimize sequelae and to ensure appropriate management of the underlying liver disease.

HEPATOPULMONARY SYNDROME

Definition

HPS is a disorder of altered gas exchange due to abnormal capillary dilatation and/or arteriovenous fistulae within the pulmonary vascular bed (3). The European Respiratory Society Task Force on Pulmonary-Hepatic Vascular Disorders has defined HPS by the presence of (*1*) liver disease (usually chronic); (*2*) abnormal arterial oxygenation (variably defined as alveolar-arterial [A-a] oxygen gradient $\geq$ 15 mm Hg [or $\geq$ 20 mm Hg in those $\geq$ 65 yr of age] or an arterial partial pressure of oxygen [Pa_{O_2}] $<$ 80 mm Hg while breathing room air) in the absence of an alternate cause; and (*3*) evidence of intrapulmonary vascular dilatations (IPVDs), most commonly diagnosed using contrast transthoracic echocardiography (4).

Use of the A-a gradient criterion for abnormal gas exchange captures cases of HPS that would not otherwise meet the Pa_{O_2} criterion (e.g., due to cirrhosis-induced hyperventilation, lowered alveolar Pa_{CO_2}, and elevated alveolar oxygen tension) and leads to higher prevalence estimates of the disease (5). In a prospective study of patients referred for LT evaluation, a pulse oximetry saturation threshold of less than or equal to 97% was 64% sensitive and 68% specific for the diagnosis of HPS; a cutoff of less than or equal to 93% improved specificity to 98% at the cost of greatly reduced sensitivity (21%) (6). Thus, pulse oximetry is not sufficiently sensitive and specific to identify patients with HPS. Therefore, arterial blood gas sampling is necessary to make this diagnosis, especially in patients with normal resting room air oxygen saturations.

Pathophysiology, Histopathology, and Mechanisms

Chronic liver disease has long been associated with abnormal systemic vasomotor tone since the original description of elevated cardiac output and reduced peripheral resistance by Kowalski and Abelmann in 1953, who posited that an imbalance between vasodilators and vasoconstrictors may be responsible (7). In 1956, two case reports described abnormal pulmonary vasculature with arteriovenous communications in patients with cirrhosis (2, 8). In an autopsy series of 14 patients using Micropaque pulmonary arteriography, dilated vessels were visualized along the pleural surface, particularly within the lower lobes, with a "spider nevi"-like appearance (9). One subject displayed evidence of precapillary arteriovenous communications. Microscopic analysis suggested an increase in the number of perfused intraacinar blood vessels.

(*Received in original form September 2, 2012; accepted in final form October 29, 2012*)

Supported by the National Institutes of Health grants K24 HL103844 and R01 HL113988 (S.M.K.).

Author Contributions: All authors contributed equally to the conception, design, and drafting of the manuscript in regard to intellectual content.

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Am J Respir Crit Care Med Vol 187, Iss. 2, pp 133–143, Jan 15, 2013

Originally Published in Press as DOI: 10.1164/rccm.201209-1583CI on November 15, 2012
Internet address: www.atsjournals.org

Three mechanisms account for abnormal gas exchange in HPS to varying degrees (10, 11). Increased alveolar capillary diameter lengthens the distance oxygen molecules must traverse to bind to red blood cell hemoglobin. This increased distance, combined with the decreased transit time commonly seen in patients with cirrhosis and elevated cardiac output (CO), results in a diffusion–perfusion limitation, such that red blood cells exit the pulmonary capillaries before full oxygen equilibration has occurred (12). Second, vascular dilatations lead to increased perfusion relative to local alveolar ventilation (V/Q mismatch) (13–15), which may be exacerbated by impaired hypoxic pulmonary vasoconstriction (16, 17). Supplemental oxygen therapy can at least partially ameliorate the hypoxemia resulting from these mechanisms in most patients with HPS (18). Finally, true shunt may occur when precapillary arteriovenous fistulae allow admixture of pulmonary arterial and venous blood (19, 20). The hypoxemia related to true shunt is refractory to supplemental oxygen.

The pathobiology of HPS has not been fully elucidated. Increased nitric oxide (NO) production with resultant vasodilation has been suggested to explain the hyperdynamic systemic circulation observed in patients with cirrhosis (21–23). In HPS, investigators have documented increased NO production in the lungs (24, 25), possibility mediated by endothelin receptor B signaling (26, 27). Additionally, animal studies suggest that gut translocation of enteric flora may alter macrophage accumulation and activation within the lung (28, 29) and respond to treatment with antibiotics (29, 30). However, a recent randomized, placebo-controlled crossover study of norfloxacin for patients with HPS did not show beneficial effects (31). Intrapulmonary macrophage activation modulates the local expression of NO, vascular endothelial growth factor, and platelet-derived growth factor and influences the histologic as well as hemodynamic profile of HPS in rats (32).

Single nucleotide polymorphisms in genes related to angiogenesis (including endoglin, endostatin, angiopoietin-1, and TIE1) were associated with the presence of HPS in patients with portal hypertension evaluated for LT (33). Increased lung angiogenesis is also seen in the rat model of HPS, and both the angiogenesis and gas exchange abnormalities were inhibited with transfection of endostatin (34). Lung expression of the chemokine fractalkine and its receptor may lead to intrapulmonary monocyte accumulation and angiogenesis in this HPS model (35).

Diagnosis and Clinical Approach

The evaluation for HPS in a patient with liver disease depends on the documentation of the necessary criteria for diagnosis, namely IPVDs and impairment of oxygenation. Demonstration of the transpulmonary passage of a venous-injected indicator that should be trapped in normally sized lung capillaries ($\sim$8 μm) implies that IPVDs are present. Transthoracic contrast echocardiography (usually with agitated saline injected through a peripheral vein) remains the preferred and most commonly used modality. In principle, performing the test with the patient in an upright position may maximize the delivery of bubbles to the lower lung zones where the vascular lesions of HPS tend to predominate (9, 36). The visualization of bubbles entering the left atrium three or more cardiac cycles after opacification of the right atrium is consistent with the presence of IPVDs (37). Opacification of the left atrium in less than three cardiac cycles is consistent with an intracardiac shunt. An intracardiac shunt may make it more difficult (but not impossible) to visualize late opacification. Nuclear scanning with radiolabeled macroaggregated albumin with assessment of abnormal accumulation within the brain is an alternative, but may be less sensitive than contrast echocardiography (38). Transesophageal contrast echocardiography may be more sensitive than transthoracic imaging (39, 40); however, the presence of esophageal varices limits its use in the evaluation of HPS.

Many patients with liver disease may have comorbid lung disease that can impair gas exchange and confound the clinical picture of HPS (4, 41, 42). Thus, the finding of an abnormal A-a gradient or frank hypoxemia should prompt a methodical search for other contributing diagnoses, using chest imaging to identify parenchymal lung disease, pleural effusions, and/or atelectasis (from massive ascites) and pulmonary function testing to rule out obstructive or restrictive ventilatory defects. It is difficult to definitively diagnose HPS in patients with significant coexistent lung disease, as there is no specific test to differentiate oxygenation abnormalities due to HPS from those due to other pulmonary disorders in the presence of IPVDs. Diffusing capacity for carbon monoxide is lower in patients with cirrhosis with HPS compared with those without HPS, but it is not discriminating enough to be used diagnostically (43).

Epidemiology

The published prevalence estimates of HPS have varied according to the diagnostic criteria used. Using contemporary criteria, 8 to 33% of patients with liver disease being evaluated for LT have HPS (43–45). Although HPS typically develops in the presence of cirrhosis or portal hypertension, HPS may also occur in the setting of acute and chronic hepatitis without established portal hypertension (46–48) and in those with vascular abnormalities that limit hepatic venous outflow to the lung (Abernathy malformation, cavopulmonary shunts) (49, 50). Studies have not shown a reliable association between the severity of hepatic impairment and presence or severity of HPS (18, 43, 51–53); thus, patients may present with HPS at any point in the course of their liver disease. Similarly, age and sex do not appear to predispose patients with liver disease to HPS. One study has shown that HPS was more common in lifelong nonsmokers (43).

Clinical Presentation

Dyspnea is commonly reported in hepatic failure as a consequence of the disease itself, ascites with increased abdominal girth, pleural effusions, medication effects, anemia, and/or deconditioning. Forty-eight percent of LT candidates with HPS reported dyspnea, compared with 29% of LT candidates without HPS or other lung disease ($P = 0.007$) (43). Platypnea (dyspnea specifically in the upright position that is alleviated when supine) is classically described in HPS; however, orthopnea is the more common clinical complaint (43).

Patients with HPS may display cyanosis or digital clubbing (17, 54). Such findings are significantly more common with HPS compared with advanced liver disease alone (10 vs. 1%, $P = 0.007$ and 17 vs. 7%, $P = 0.03$, respectively); however, these signs are not discriminating enough to confirm or rule out the diagnosis (43). Orthodeoxia (decreased Pa_{O_2} from supine to upright position) may be seen and is caused by increased shunting and V/Q mismatch in the upright position (14). Spider angiomata are found in approximately one-third of patients with or without HPS. Neurological complications, including hemorrhage, stroke, and cerebral abscess formation, have been described in HPS, presumably related to passage of embolic material from the venous to systemic arterial circulations via IPVDs (30, 45, 51, 55, 56).

Prognosis

Patients with HPS have significantly worse functional class and more impaired quality of life compared with patients with

advanced liver disease without HPS (43). Specifically, patients with HPS had lower General Health, Role Emotional, Mental Health, and Mental Component scales of the Short Form-36 Health Survey compared with patients with cirrhosis without HPS even after adjustment for age, sex, and severity of liver disease.

Patients with HPS also have a significantly lower 5-year survival rate (0–23%) compared with that of patients with advanced liver disease without HPS (30–60%) in the absence of LT (51, 57). A prospective, multicenter cohort study found that the presence of HPS in LT candidates doubled the risk of death compared with those without HPS, even after adjustment for potential confounders (43) (Figure 1). Patients with HPS awaiting LT experience an average decline of approximately 5 mm Hg/yr in Pa_{O_2} (51). Some studies have suggested that more severe hypoxemia in HPS confers a worse prognosis with or without LT (51, 57–60); however, this finding has not been replicated in all series (43, 61). Patients with HPS frequently die of hepatic failure, gastrointestinal hemorrhage, sepsis/infection, and hepatorenal syndrome, all complications of liver disease (51, 57, 58), suggesting that HPS reflects a systemic disorder with implications that extend beyond pulmonary or hypoxemia-related events.

Treatment

There is no accepted medical therapy for HPS. Vaccination for influenza and pneumococcus is indicated for patients with advanced liver disease (62). The use of supplemental oxygen to correct hypoxemia at rest, with exercise, or during sleep seems intuitive; however, no data are available to confirm clinical benefit. Various interventions targeting purported pathways related to NO signaling or pulmonary or splanchnic vasoregulation have been largely unsuccessful in HPS. By virtue of its ability to block tumor necrosis factor-α and macrophage-derived NO synthesis, pentoxifylline has garnered attention, as rodent studies suggested potential benefit in experimental HPS (63, 64). However, two small studies in patients with HPS reached conflicting conclusions (65, 66). Occasionally, patients may present with large pulmonary arteriovenous malformations that are amenable to angiographic embolization, which can at least transiently improve oxygenation (67); however, this is the rare exception. Transjugular intrahepatic portosystemic shunt (TIPS) placement is not recommended for the treatment of HPS in recent guidelines from the American Association for the Study of Liver Disease (68, 69).

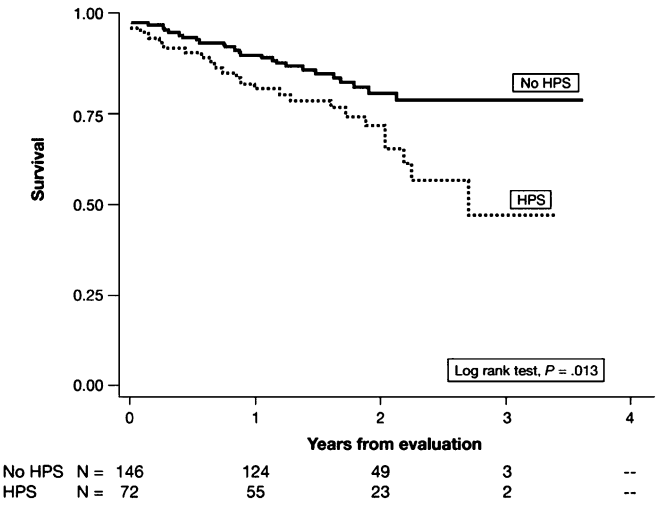

Figure 1. Kaplan-Meier survival estimates of lung transplant candidates with and without hepatopulmonary syndrome (HPS). Reprinted by permission from Reference 43.

LT remains the only known treatment for HPS. Several studies suggest that LT is associated with improved survival in HPS (51, 53). Swanson and colleagues showed that patients with HPS who underwent LT (with mean Pa_{O_2} 57 ± 17 mm Hg) had better 5-year survival compared with those who did not (~75 vs. 23%, respectively) (51). This same group recently published longer-term follow-up in an expanded cohort of patients, which appears to confirm a survival benefit of LT in HPS, although this did not reach statistical significance (hazard ratio for death in LT group versus non-LT group = 0.52; 95% CI, 0.26–1.05; $P = 0.067$) (61). As a nonrandomized study without multivariate analysis, it is possible that confounding factors could play a role. A series of 21 patients with HPS transplanted after 2004 (~50% with $Pa_{O_2} < 50$ mm Hg) showed an overall survival rate of 95%, with a median follow-up of 20.2 months (range, 1.8–70.1) (53). Advances in general transplant care or patient selection may have contributed to the higher survival seen in this cohort.

Improvement in or resolution of abnormalities in gas exchange after LT occurs in the majority of individuals with HPS who survive LT (42, 51, 53, 58, 59, 70). Although hypoxemia may persist or worsen transiently after LT (42, 53), most will demonstrate normal gas exchange within 6 to 12 months post-transplant (51, 53, 58, 70), although delayed resolution beyond 12 months has been reported (42). More severe preoperative derangements in gas exchange ($Pa_{O_2} < 52$ mm Hg or A-a gradient > 65 mm Hg) or shunt fraction have been associated with a prolonged time to resolution after LT (42, 53).

Even though hypoxemia usually resolves after LT, HPS may increase the risk of post-transplant death. In a prospective cohort of 218 patients evaluated for LT (43), HPS was associated with a doubling of the risk of death after consideration of the severity of liver disease and performance and timing of LT. This suggests that even if LT is performed, HPS still has an adverse impact on outcomes. In a prospective study, a combination of preoperative room air Pa_{O_2} less than 50 mm Hg and shunt fraction (from quantitative perfusion scan) greater than or equal to 20% conferred a 75% risk of death within 10 weeks after LT (58).

Although HPS was once considered a contraindication to LT, it is now considered an indication, given the acceptable outcomes and the usual resolution of HPS post-transplant. Patients with HPS and Pa_{O_2} less than 60 mm Hg receive additional Model for End-Stage Liver Disease (MELD) points and increased priority for LT (Organ Procurement and Transplantation Network policy 3.6.4.5.1 [71, 72]). Continued assessment of the impact of this policy on outcomes and organ use may be warranted so as to optimize equitable organ allocation (73).

PORTOPULMONARY HYPERTENSION

Definition

PoPH is pulmonary arterial hypertension (PAH) associated with portal hypertension (74). PAH (or Group 1 of the Dana Point classification of pulmonary hypertension) includes other forms of precapillary pulmonary arteriopathy, such as idiopathic (formerly "primary") and heritable PAH as well as forms associated with drug/toxin use, congenital heart disease, connective tissue disease, chronic hemolytic anemias, and schistosomiasis or HIV infection.

Pathophysiology, Histopathology, and Mechanisms

Pathologic changes common to all forms of PAH include muscularization of small pulmonary arteries, intimal thickening, smooth

muscle hypertrophy, *in situ* thrombosis, and plexiform lesions (75). There is no histopathologic profile that distinguishes PoPH from other forms of PAH.

It is unclear whether the mechanisms of other types of PAH cause PoPH. Expression of prostacyclin synthase appears reduced within pulmonary arteries of patients with PAH as well as PoPH (76). Alterations in endothelin biology have been identified in idiopathic PAH (IPAH) as well as cirrhosis and portal hypertension (77). Patients with refractory ascites and PoPH have higher levels of pulmonary arterial endothelin-1 levels compared with patients without PoPH (78). Genetic variants of aromatase and estrogen receptor α were associated with the risk of PoPH, and the "high-risk" aromatase genotype increased plasma estradiol levels (79). Single nucleotide polymorphisms in the genes encoding phosphodiesterase-5 (PDE5) and NADPH oxidase 4 were also associated with an increased risk of PoPH. Estrogen signaling, cGMP metabolism, and oxidative stress have important roles in other forms of PAH (80–86).

Diagnosis and Clinical Approach

A clinical diagnosis of PoPH can be established in the setting of compatible hemodynamics in a patient with portal hypertension in the absence of coexisting conditions that could cause pulmonary hypertension. It should be emphasized that the development of PoPH requires the presence of portal hypertension (of either intra- or extrahepatic origin) and not simply chronic liver disease or cirrhosis *per se.* Current guidelines require a resting mean pulmonary artery pressure (mPAP) greater than 25 mm Hg with a pulmonary capillary wedge pressure less than or equal to 15 mm Hg and pulmonary vascular resistance (PVR) greater than 240 dyn·s/cm^5 from right heart catheterization (RHC) (87, 88). The hemodynamic criteria are key to establishing this diagnosis, which ultimately is a clinical one. Portal hypertension is itself associated with a hyperdynamic circulatory state, sodium avidity, and volume overload, which can cause pulmonary hypertension with a normal transpulmonary gradient (TPG) and PVR, which is not PoPH and does not appear to carry the same dire implications regarding outcome.

Two-dimensional Doppler echocardiography plays an important role in the evaluation of symptomatic patients with cirrhosis with suspected PoPH and in the screening of candidates for LT. In a prospective study of LT candidates, a cutoff for pulmonary artery systolic pressure (PASP) greater than 30 mm Hg had a negative predictive value of 100%, but the positive predictive value was only 59%. This means that no patient with PoPH had a PASP below the cutoff, but 40% of individuals above the cutoff did not actually have PoPH (89). The high negative predictive value of two-dimensional Doppler echocardiography justifies its use as a screening modality as recommended by the American Association for the Study of Liver Disease and the American Heart Association (Class IIa; Level of Evidence B) for all patients being considered for LT (90, 91). Although there is no consensus surrounding the indications for further evaluation, LT candidates with a PASP greater than 50 mm Hg and/or with significant right ventricular hypertrophy or dysfunction likely require RHC to either confirm hemodynamics consistent with PoPH or (as importantly) rule out PoPH and avoid inappropriate management based on an erroneous diagnosis.

Epidemiology

As with HPS, the prevalence estimates of PoPH are influenced by the specific criteria used to define the disease as well as the population studied. An autopsy study of more than 17,000 subjects identified changes suggestive of a pulmonary arteriopathy in 0.13% and in 0.73% of those with cirrhosis (92). A prospective study of 1,235 patients evaluated for liver transplantation (all with Child-Turcotte-Pugh score $\geq$ 7) showed that 5% met current hemodynamic criteria for PoPH (93). Previous retrospective analyses have generally yielded similar estimates (89, 94–96). Neither the severity of liver disease (89, 97–100) nor the degree of portal hypertension (as measured by the hepatic venous pressure gradient) (89, 97) predict the presence or severity of PoPH.

In a multicenter case-control study, female sex and a diagnosis of autoimmune hepatitis were independent risk factors for PoPH in patients evaluated for LT (100). Those with hepatitis C infection were less likely to have PoPH. The sex predilection mirrors that observed for idiopathic PAH. A recent case-control study identified a higher prevalence of large spontaneous portosystemic shunts and hepatofugal portal blood flow among patients with moderate to severe PoPH compared with milder or no PoPH (101).

PoPH accounts for approximately 5 to 10% of patients with PAH in the United States and France (102–104). A contemporary U.S.-based PAH registry has suggested that, despite similar functional class, patients with PoPH display less severely impaired hemodynamics (lower mPAP and PVR, higher CO) at presentation compared with patients with IPAH (105).

Clinical Presentation

Dyspnea is a common feature of PoPH but is nonspecific. Findings on physical examination include elevated jugular venous pressure, a prominent P_2, a holosystolic murmur indicative of tricuspid regurgitation, a right ventricular heave, and edema. However, the common presence of volume overload and pulmonary hypertension of other types in advanced liver disease makes it difficult to use the physical examination to alter the clinical suspicion of PoPH. ECG often shows right axis deviation, right ventricular hypertrophy, or right bundle branch block. A majority of patients with PoPH will demonstrate enlarged pulmonary arteries or cardiomegaly on chest radiography (100, 106).

Elevations in A-a gradient may be seen in up to 80% of patients with PoPH (107, 108). IPAH is associated with a mild reduction in arterial oxygen tension (109, 110), believed to be related to V/Q mismatch and reduced mixed venous oxygen saturation (111, 112). In the context of liver disease, however, moderate to severe hypoxemia ($Pa_{O_2} \leq$ 70 mm Hg) is more consistent with HPS, as only 15% of patients with PoPH in one small series exhibited a Pa_{O_2} below this threshold (108). PoPH with a patent foramen ovale (or atrial septal defect) with intracardiac right-to-left shunting is an exception (113).

Prognosis and Implications for Liver Transplant

PoPH is associated with reduced survival. Available reports suggest a 1-year survival of approximately 35 to 46% without treatment (106, 114, 115). A retrospective study (115) as well as a large, multicenter prospective U.S. registry (105) in the modern treatment era both suggested higher mortality for patients with PoPH relative to patients with IPAH despite higher CO and lower PVR in PoPH (Figures 2 and 3). A retrospective cohort study of patients with PoPH from France reported an increased risk of death with more severe cirrhosis and lower cardiac index (116) (Figure 4). Patients often die of right ventricular failure or from complications from hepatic disease, although the relative frequencies with which each occurs vary by study and potentially by therapy (99, 105, 106, 114, 116).

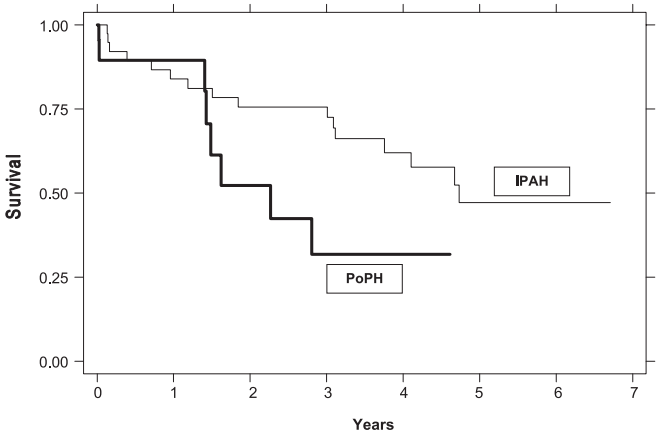

Figure 2. Survival functions for portopulmonary hypertension (PoPH) versus idiopathic pulmonary arterial hypertension (IPAH), adjusted for age and race/ethnicity. Reprinted by permission from Reference 115.

The risk of perioperative mortality after LT is increased in patients with PoPH (60, 114, 117). LT is associated with acute hemodynamic changes with contributions from mechanical ventilation, anesthesia, volume shifts, and replacement of a diseased and restricted hepatic portal circulation with a postischemic graft. Abrupt intraoperative swings in cardiac filling pressures and production of vasoactive substances may precipitate right ventricular failure in susceptible patients with PoPH (60, 114, 118). In one of the earliest studies in untreated patients with PoPH diagnosed at the time of transplantation, all patients with mPAP greater than 50 mm Hg died, whereas all patients with mPAP less than 35 mm Hg and TPG less than 15 mm Hg survived (117). Patients with mPAP between 35 and50 mm Hg or PVR greater than 250 dyn·s/cm^5 demonstrated a 50% mortality rate. In a prospective, multicenter study of patients with PoPH undergoing LT (mean mPAP ~45 mm Hg), a 36% mortality rate was observed, with all deaths occurring within 18 days of LT and right heart failure accounting for a large fraction. More than one-third of the deaths occurred intraoperatively (60).

With the advent of routine screening for PoPH in LT candidates, clinicians have used PAH-specific therapy in an attempt to mitigate the morbidity and mortality associated with LT (*see* section on Treatment below). However, even with treatment, only a very small number of patients are deemed eligible for transplantation and, even then, with a continued high risk of mortality. In a series from the University of California, San Francisco, 36 PoPH cases were identified over a 7-year period. Nineteen of these were treated with intravenous epoprostenol, but only five improved sufficiently to be deemed candidates for LT, of whom only two (~6%) underwent LT; both patients had persistent PoPH post-transplant (98). At the Mayo Clinic over 13 years, only 9 out of 74 PoPH cases (12%) received LT, of whom three died, all within 1 month of LT (114). Sussman and colleagues reported on eight PoPH cases, four of whom underwent successful LT (119).

There have been reports of the resolution of PoPH after LT, although available data suggest this is the exception rather than the rule in the setting of significant PoPH (98, 114, 116, 117, 120). Predictors of hemodynamic improvement after LT have not been identified. Recurrence of PoPH after a period of resolution occurring in conjunction with failure of the hepatic allograft has been described (121). PoPH may develop after LT in patients with preexisting HPS (122). It is not known whether this represents an "unmasking" of concomitant PoPH or the development of *de novo* obliterative pulmonary vascular disease.

Despite the unpredictability in outcomes after LT, a MELD exception is available for PoPH (Organ Procurement and Transplantation Network policy 3.6.4.5.6 [71, 123]). To qualify, LT candidates with PoPH must demonstrate a positive hemodynamic response to therapy, defined as an mPAP less than 35 mm Hg and PVR to less than 400 dyn·s/cm^5.

When otherwise indicated for the treatment of variceal bleeding or refractory ascites, TIPS placement should be considered cautiously in the patient with pulmonary hypertension. The typical post-procedure hemodynamic changes of increased right ventricular filling pressures and increased cardiac output may be poorly tolerated in the patient with significant elevations in PVR and right ventricular volume or pressure overload (124, 125). Recent guidelines have proposed that severe pulmonary hypertension (defined as mPAP $>$ 45 mm Hg) and severe tricuspid regurgitation are absolute contraindications to TIPS, whereas moderate pulmonary hypertension is a relative contraindication (69). The ability to tolerate TIPS in the setting of pulmonary hypertension is likely based on the type (PoPH vs. high-output or volume expanded states), cardiac filling pressures, and right ventricular function.

Treatment

The histopathologic and clinical similarities between PoPH and other forms of PAH have provided a rationale for the use of PAH therapies in PoPH, although this patient subset has been excluded from virtually all clinical trials of these therapies. The role of "conventional" therapies (anticoagulation and calcium channel blockers [CCB]) in PoPH remains undefined. Patients with PoPH were excluded from the observational studies that suggested a long-term survival benefit with oral

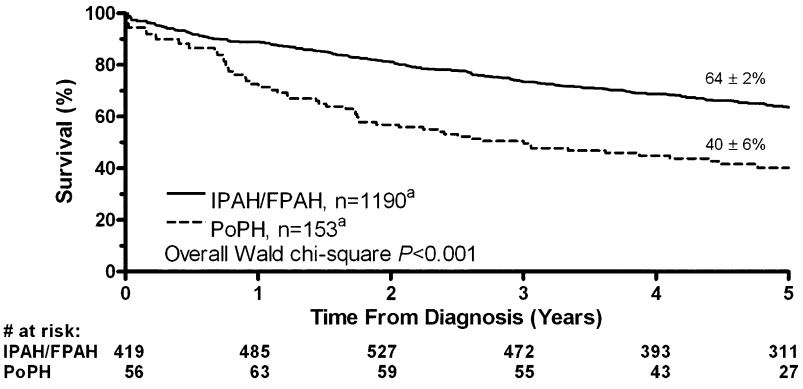

Figure 3. Kaplan-Meier survival estimates for portopulmonary hypertension (PoPH) versus idiopathic pulmonary arterial hypertension (IPAH) or familial pulmonary arterial hypertension (FPAH). Reprinted by permission from Reference 105.

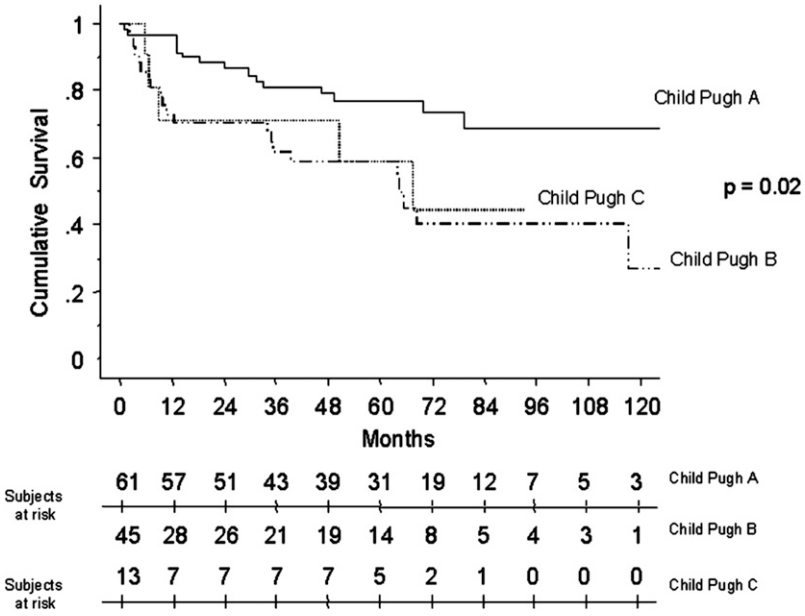

Figure 4. Kaplan-Meier survival estimates of patients with portopulmonary hypertension stratified by grade of cirrhosis. Reprinted by permission from Reference 116.

anticoagulation (126–129), and cirrhosis-related bleeding diatheses and varices likely present strong contraindications to anticoagulation in most patients with PoPH.

Current guidelines recommend using CCB therapy chronically only in those patients with PAH who demonstrate acute vasoreactivity to vasodilator and CCB challenge during RHC (87, 130). A recent study from Clamart, France showed that only 2 of 153 patients with PoPH (1.3%) demonstrated an acute vasodilator response (using older criteria), of whom only one exhibited a favorable long-term response with CCB therapy (131). Acute vasodilator testing therefore appears unlikely to be helpful or necessary in patients with PoPH; however, there is lack of consensus (87, 132).

Patients with cirrhosis and esophageal varices are often treated with β-blockers. In patients with more advanced PoPH (mean PAP $>$ 35–40 mm Hg), withdrawal of β-blocker therapy may increase cardiac output (via release of chronotropic response) as well as exercise capacity (133). Therefore, the risk:benefit ratio of β-blocker therapy should be considered along with alternative means of controlling variceal bleeding risk (e.g., band ligation) in patients with PoPH. As with other forms of PAH, oxygen supplementation to correct hypoxemia and diuretics to maintain euvolemia are commonly used.

Prostacyclin Analogs

Prostacyclin analogs possess vasodilatory, antithrombotic, and antiproliferative properties and are effective in other forms of PAH. Numerous case reports/series have reported improvements in hemodynamics with the use of intravenous epoprostenol in PoPH (98, 119, 120, 134–136); however, definitive improvements in survival have not been found (116, 119). Progressive splenomegaly and thrombocytopenia have been documented (137, 138); slower titration and target doses lower than those used in other forms of PAH may prevent the former issue. Favorable hemodynamic effects have been reported with intravenous treprostinil (139) and inhaled iloprost as well (99, 140).

PDE5 Inhibitors

PDE5 inhibitors prevent the metabolism of cGMP, which mediates the vascular effects of NO. Sildenafil is an oral PDE5 inhibitor approved for treatment of PAH (141). Small retrospective series suggest that sildenafil improves functional capacity and decreases PVR and mPAP in PoPH (142–144), in some cases allowing LT (143, 144). The dosing in these studies was variable and included regimens beyond the currently U.S. Food and Drug Administration (FDA)-approved dose of 20 mg three times daily.

Endothelin Receptor Antagonists

The endothelin pathway in cirrhosis and portal and pulmonary hypertension presents a potential therapeutic target for PoPH. Bosentan is an orally available dual endothelin receptor antagonist approved for use in PAH (145); the FDA label recommends avoiding bosentan in patients with moderate to severe liver dysfunction or elevated transaminases. Several observational studies have shown that bosentan leads to improvements in exercise capacity and hemodynamics in PoPH associated with Child-Pugh class A-B (146–150) as well as Child-Pugh class C cirrhosis (151). Hoeper and colleagues reported a 3-year survival rate of 89% in a retrospective study of 18 patients with PoPH treated with bosentan (99). One patient exhibited a rise in liver transaminases greater than three times the upper limit of normal, which resolved with dose reduction. A recent retrospective study included 34 patients with PoPH treated with bosentan (6 with portal vein thrombosis, 19 with Child-Pugh class A cirrhosis, and 9 with Child-Pugh class B cirrhosis) (152). After 5 months, there was a 31% reduction in PVR and 39% increase in cardiac index. Seven patients (5.5%) developed elevations in liver transaminases greater than three times the upper limit of normal, which resolved with dose reduction or discontinuation. Ambrisentan is a selective endothelin-A receptor antagonist approved for treatment of PAH (153). The FDA label does not recommend ambrisentan in patients with moderate to severe hepatic impairment. Cartin-Ceba and colleagues reported a cohort of 13 patients with PoPH (62% Child-Pugh class A) treated with ambrisentan (median exposure 390 d) (154). Patients demonstrated improved functional class, increased cardiac output, and a mean reduction in PVR of 61%. No significant changes in liver function parameters were observed.

CONCLUSIONS

There is better understanding of the epidemiology, natural history, and management of patients with HPS and PoPH. With

appropriate identification of these disorders, we can more accurately determine the risk of untoward outcomes both within and outside the context of LT. The identification of HPS with significant hypoxemia can prioritize a patient for LT, which can normalize gas exchange. Among etiologies of PAH, the prognosis of PoPH is particularly poor despite a more favorable hemodynamic profile. Screening of all LT candidates with echocardiography is recommended to identify patients who require RHC to diagnose PoPH and stratify risk. For the patient with PoPH in need of LT due to advanced liver disease, treatment with PAH therapies should be considered in an attempt to reduce mPAP, PVR, and TPG and increase cardiac output. Most experience has come from intravenous epoprostenol, but currently available oral agents may be of benefit in patients with milder disease or in those who are not candidates for parenteral therapy. LT in the patient with significant PoPH remains a high-risk proposition, but may be appropriate in carefully selected candidates.

The identification of predisposing genetic abnormalities in some afflicted patients has the potential to better identify at-risk groups as well as provide opportunities for therapeutic interventions. In HPS, future therapies aimed at decreasing intrapulmonary shunting and improving gas exchange abnormalities might be expected to improve outcomes. Patients with PoPH have been excluded from therapeutic trials in PAH. Inclusion of subjects with PoPH in future studies and research focused on outcomes pre- and post-LT may help to inform treatment decisions and further define the role of medical therapy and LT. With both disorders, close collaboration between cardiologists, pulmonologists, hepatologists, and surgical transplant teams is necessary to not only optimize outcomes but also promote multidisciplinary research efforts to identify effective therapeutic approaches.

Author disclosures are available with the text of this article at www.atsjournals.org.

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