Portopulmonary Hypertension: Understanding Pulmonary Hypertension in the Setting of Liver Disease

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Introduction

A relationship between the liver and lung was proposed by the Greek physician Galen (AD *c.* 126-216), who believed that venous blood was "concocted in the liver," migrated via a tidal motion to the right ventricle of the heart, and divided into two blood streams, one to the lungs and one through the heart into the left ventricle. According to Galen (so say medical historians) the liver provided "natural spirit" to the body.[1] It wasn't until the 1500s that these pulmonary vascular teachings were questioned, and the first accurate description of the pulmonary circulation evolved from the Spanish theologian and physician Miguel Servetus.[1]

Nearly 500 years later we have witnessed both the remarkable success of orthotopic liver transplantation and a renewed interest in the seemingly mysterious relationship between the liver and the lung. Why do some patients with advanced liver dysfunction develop pulmonary vascular dilatations leading to severe arterial hypoxemia, which may totally resolve after liver transplantation (hepatopulmonary syndrome)? Why do patients with similar liver disorders experience a pulmonary vasoproliferative and vasoconstrictive process leading to pulmonary artery hypertension and right heart failure frequently *not* reversible by liver transplantation (portopulmonary hypertension)? Although these pulmonary vascular consequences of liver disease are relatively uncommon (up to 4% to 15% of transplant candidates), with 5000 transplants being done annually and another 18,000 patients on the Organ Procurement Transplant Network (OPTN) liver transplant wait lists, these clinical problems are no longer trivial.[2]

Definition of Portopulmonary Hypertension

First described in 1951, the coexistence of pulmonary arterial hypertension as a consequence of hepatic dysfunction has been well documented.[3,4] The most important cause of increased mean pulmonary artery pressure (mPAP >25 mm Hg) in the setting of advanced liver disease remains the pulmonary arterial vasculopathy known as portopulmonary hypertension.[4,5] Vasoconstriction, endothelial and smooth muscle proliferation, plexogenic arteriopathy, and in situ thrombosis and/or fibrosis characterize portopulmonary hypertension.[6,7] Since a hyperdynamic circulatory state and the increased blood volume that accompany liver disease may raise mPAP (in addition to the pulmonary vasculopathy), specific hemodynamic criteria have evolved to define portopulmonary hypertension.[5,8,9]

Pathology and Pathogenesis

It is important to recognize that portopulmonary hypertension has pulmonary vascular pathology *indistinguishable* from that seen in primary pulmonary hypertension.[4,10] A spectrum of pathology has been described from autopsy and lung explant specimens (open lung biopsy has been rightfully discouraged because of potential complications). Medial hypertrophy, endothelial and smooth muscle proliferation, in situ thrombosis, fibrosis, and classic plexogenic arteriopathy have been noted (**Figure 1**). Platelet aggregates lodged within the pulmonary vascular lumen have been reported and may contribute to acute right heart deterioration in the post liver transplant period.[11,12] The lack of prostacyclin synthase within the pulmonary endothelium[2,8,9] in portopulmonary hypertension has been documented, suggesting a lack of vasodilator capability.[10] Recently the evolving "signaling" relationship between angiopoietin-1 and the TIE receptors within the pulmonary endothelium has received attention; this relationship in the setting of liver disease needs to be understood.[13] To date there has been no relationship documented between portopulmonary hypertension and mutations in the bone morphogenetic protein receptor BMPR2 gene, as noted in other causes of pulmonary arterial hypertension such as primary pulmonary hypertension.

Epidemiology

Poor correlations with Childs-Turcotte-Pugh severity of liver disease, levels of liver enzymes, serum total bilirubin, and splanchnic hemodynamics such as the azygous blood flow and hepatic venous pressure gradient[6,14,16] have been reported. An increased frequency of alcoholic cirrhosis has been noted.[16,17] Noncirrhotic portal hypertension has been associated with portopulmonary hypertension.[17-20] Two retrospective series have documented that surgical portosystemic shunt procedures preceded the diagnosis of portopulmonary hypertension in 30% to 76% of patients.[16,20]

In the pre-liver transplant era, the NIH pulmonary hypertension registry of 204 patients with primary pulmonary hypertension classified 17 (8%) of the patients as having cirrhosis-associated pulmonary hypertension.[16] In the current era of liver

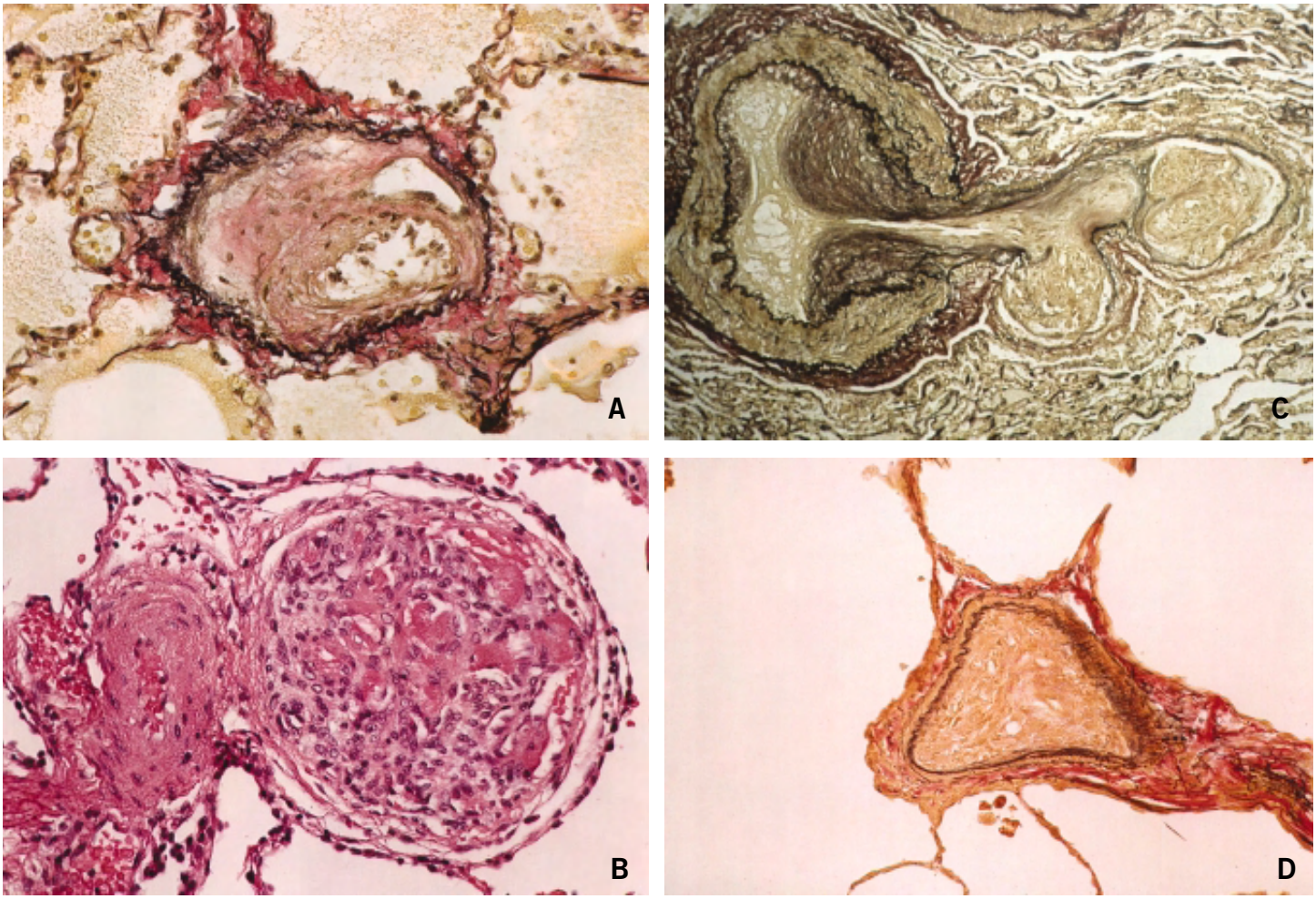

Fig. 1—The spectrum of portopulmonary hypertension. These color microphotographs of pulmonary arterial lesions, which also appear on the cover of this journal, show a) thrombotic type (autopsy), b) plexogenic type with platelet aggregates (autopsy), c) plexogenic type with microaneurysm (lung explant), and d) fibrotic type (autopsy). Reproduced with permission from *Liver Transplantation*. 2000;6:241-242.

transplantation, major transplant centers have reported the frequency of portopulmonary hypertension to be 4% to 15%.[8,20-23] Remarkably, a review of published portopulmonary hypertension cases through 1999 documented that 65% of diagnoses were *first recognized* during the liver transplant procedure.[18]

Clinical Presentation and Significance

The clinical presentation of portopulmonary hypertension is subtle; exertional dyspnea is the most common nonspecific symptom.[4,16] Other symptoms and signs, including fatigue and leg edema, can be easily confused with those of underlying heart and/or liver disease so that making the diagnosis requires a high degree of suspicion. Chest pain and/or pressure and syncope are usually later manifestations of portopulmonary hypertension. The chest examination is quite unremarkable except for the usual cardiac findings of pulmonary hypertension.

In the pre-liver transplant era, survival from a French series reporting portopulmonary hypertension ranged from 72% mortality within 12 months of diagnosis[14] to a US study from the Cleveland Clinic describing a 6 month (median)/[15] month (mean) survival as determined from a literature review of 78 patents.[15] Recent 2-year, single institution survival of portopulmonary hypertension patients (liver transplant patients excluded) ranged from 50% to 72%.[4,17] The importance of pulmonary hypertension in the setting of advanced liver disease reflects the high risk of conducting liver transplantation in such patients.[18,19,21] In 43 portopulmonary hypertension patients who underwent orthotopic liver transplantation, a 35% perioperative mortality was reported.[18] Right heart failure and cardiopulmonary collapse caused most deaths; intraoperative death occurred in 5 patients.[18] In a recent multicenter study, despite excluding 45% of 66 portopulmonary hypertension patients from liver transplantation consideration due to the severity of the condition, transplant outcome remained problematic. Transplant hospitalization mortality was 36%, with all deaths occurring within 18 days of transplant; intraoperative death was reported in 38%.[19]

Screening

Routine posteroanterior and lateral chest radiography and resting electrocardiography are insufficient for portopulmonary hypertension screening purposes. By the time enlarged pul-

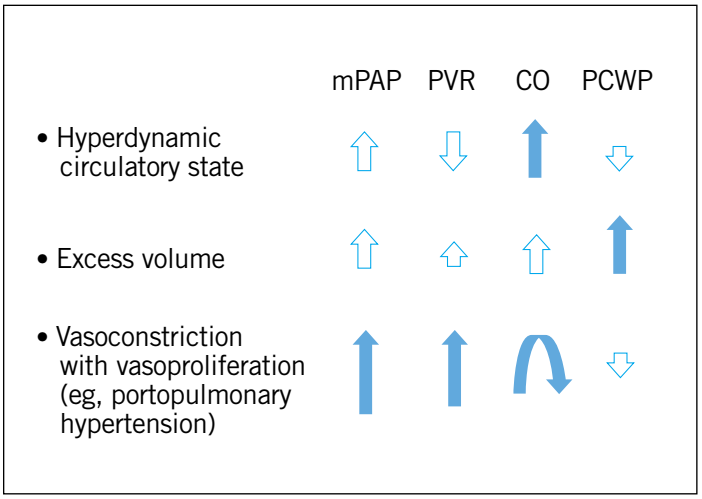

Fig. 2—Via right heart catheterization, several hemodynamic patterns can be documented in the setting of advanced liver disease. The main patterns associated with increased mean pulmonary artery pressure (mPAP) are shown above. High cardiac output (CO) characterizes the hyperdynamic circulatory state that follows the development of decreased systemic vascular resistance. Excess central volume is reflected by increased pulmonary capillary wedge pressure (PCWP). Slight increase in pulmonary vascular resistance (PVR) may be noted. The vasoconstriction and vasoproliferation that characterize portopulmonary hypertension initially result in marked increases in PVR, mPAP, and CO.

monary arteries and/or cardiomegaly are seen, pulmonary hemodynamics are markedly abnormal. Likewise, the electrocardiographic findings of right axis deviation, right bundle branch block, and t-wave inversions in the precordial leads are associated with advanced hemodynamic abnormality (mPAP >35 mm Hg), and thus these findings are not useful for detecting early disease.

Transthoracic Doppler echocardiography (DE) is relatively sensitive in detecting increased right ventricular systolic pressure (RVsys) as an estimate of pulmonary artery systolic pressure, as long as the pulmonary valve is normal. However, DE may not distinguish between causes of increased RVsys such as seen in the hyperdynamic circulatory state, increased central volume, and the true pulmonary vasculopathy of portopulmonary hypertension.[4,5,25] DE is the current screening procedure of choice if portopulmonary hypertension is suspected,[4,5,28] but right heart catheterization is mandatory for the definitive diagnosis.[22-27] However, although many screened patients have increased RVsys (30 to 50 mm Hg by DE), they do not have increased pulmonary vascular resistance as determined via right heart catheterization.[4,8,23,25] Using the more discriminatory screening criteria RVsys >50 mm Hg to determine indication for right heart catheterization, 85% to 97% of patients with clinically significant portopulmonary hypertension (mPAP >35 mm Hg) were identified.[23,25] In an unpublished series from the Mayo Clinic (N = 360 over the time period 2001 to 2003), approximately 10% of all orthotopic liver transplantation candidates had RVsys >50 mm Hg; 20% had RVsys >40 mm Hg. RVsys could not be accurately measured in 20%.

Table 1—Current Diagnostic Criteria for Portopulmonary Hypertension.

- Portal hypertension (ie, ascites, esophagogastric varices, splenomegaly)
- Mean pulmonary artery pressure >25 mm Hg
- Pulmonary capillary wedge pressure <15 mm Hg
- Pulmonary vascular resistance >240 dynes.s.cm^{-5}

Right Heart Catheterization

Right heart catheterization is necessary to explicitly delineate the pulmonary hemodynamic patterns that exist in the setting of hepatic dysfunction. In patients with advanced liver disease, increased pulmonary artery pressures can be found as a result of multiple underlying causes, including the high flow hyperdynamic state, excess volume, and the vasoproliferation and vasoconstriction pulmonary vasculopathy associated with portopulmonary hypertension (**Figure 2**). The current portopulmonary hypertension diagnostic criteria recently endorsed by the European Respiratory Society-European Association for Study of the Liver (ERS-EASL) task force on pulmonary-hepatic vascular disorders are summarized in **Table 1**.[4-6,18,19,28]

Consensus regarding "normal" pulmonary vascular resistance in the setting of advance liver disease varies.[28] It is well documented that a reduced pulmonary vascular resistance exists in association with the hyperdynamic high-flow circulatory state in such patients.[8,10,16,28] It is useful to describe evidence-based, clinically significant hemodynamic cutoffs as well as respect textbook-listed lower limits of normal in such patients. Data from the ERS-EASL task force on at least 200 patients with portopulmonary hypertension suggest that pulmonary vascular resistance >240 dyne.s.cm-5 is distinctly abnormal; it is always associated with mPAP >25 mm Hg, and it poses increased risk of right heart failure in the setting of liver transplantation.[28]

A subgroup of liver disease patients with 120 < pulmonary vascular resistance <240 dynes.s.cm-5 and increased pulmonary capillary wedge pressure are of interest.[8,19] If these patients have increased transpulmonary gradients (mPAP - PCWP >15 mm Hg), they should be considered to have mild portopulmonary hypertension and treated as such. The natural history of this subgroup is unclear and careful follow-up is required. It is also recognized that selected hemodynamic data (cardiac output and pulmonary vascular resistance) should be reported as indices that reflect body surface area in this subgroup. Rapid volume infusion during right heart catheterization (1.0 liter of saline over 10 minutes) has been suggested as a means to identify patients susceptible to ventricular failure during liver allograft reperfusion.[29] The clinical implications and/or benefits of vasoactive testing during right heart catheterization in the setting of portopulmonary hypertension are unclear, since

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Screening and Diagnostic Algorithm for Portopulmonary Hypertension

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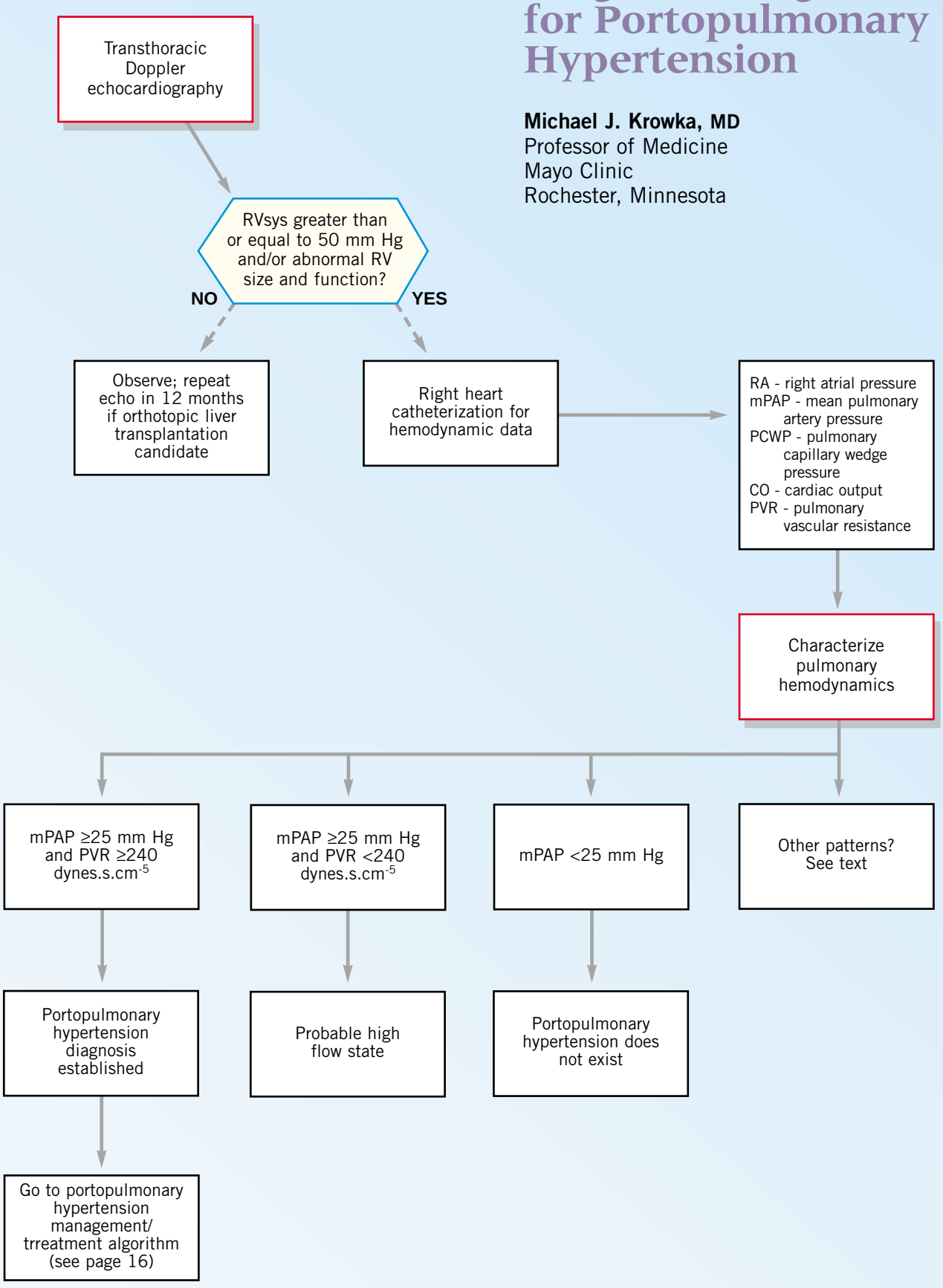

the use of calcium channel blockers in this group of patients could theoretically worsen portal hypertension.

Other Pulmonary Studies

Although pulmonary function abnormalities are not specific for portopulmonary hypertension, arterial hypoxemia (mean PaO2 = 76±9; range, 53 to 97 mm Hg) was reported in 80% of patients with moderate to severe disease.[26] Increased alveolar-arterial oxygen gradient and significant accentuation of respiratory alkalosis compared with cirrhotic patients without portopulmonary hypertension have been reported.[9] Reduced diffusing capacity is frequent[8,16] but nonspecific. In order to consider other possible causes of pulmonary hypertension in the setting of liver disease, recommended diagnostic assessments are summarized in the accompanying portopulmonary hypertension algorithm.

Conclusion

Recognition of the unique clinical associations and characteristics of portopulmonary hypertension has evolved rapidly over the last 15 to 20 years as a result of advances in medical therapies and implications for orthotopic liver transplantation (both cadaveric and living donor). Further understanding of the natural history and pathophysiology of portopulmonary hypertension is essential as our potential therapeutic interventions expand.

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