

The Art and Science of Diagnosing and Treating Lung and Heart Disease Secondary to Liver Disease



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Patients with chronic liver disease are at risk of extrahepatic complications related to cirrhosis and portal hypertension, as well as organ-specific complications of certain liver diseases. These complications can compromise quality of life, while also increasing morbidity and mortality before and after liver transplantation. Patients with chronic liver disease are at risk for pulmonary complications of hepatopulmonary syndrome and portopulmonary syndrome; the cardiac complications fall under the general concept of cirrhotic cardiomyopathy, which can affect systolic and diastolic function, as well as cardiac conduction. In addition, patients with certain diseases are at risk of lung and/or cardiac complications that are specific to the primary disease (ie, emphysema in α -1-antitrypsin deficiency) or occur with increased incidence in certain conditions (ie, ischemic heart disease associated with nonalcoholic steatohepatitis). This article focuses on the epidemiology, clinical presentation, pathogenesis, treatment options, and role of transplantation for lung and heart diseases secondary to liver disease, while also highlighting select liver diseases that directly affect the lungs and heart.

Keywords: Hepatopulmonary Syndrome; Portopulmonary Hypertension.

Patients with chronic liver disease are at risk of extrahepatic complications related to cirrhosis and portal hypertension, as well as organ-specific complications of certain liver diseases. These complications can compromise quality of life, while also increasing morbidity and mortality before and after liver transplantation. This article focuses on lung and heart disease secondary to liver disease, focusing on the pulmonary and cardiac complications related to cirrhosis and portal hypertension, while highlighting select liver diseases that directly affect the lungs and heart.

Pulmonary Manifestations of Liver Disease

Hepatopulmonary Syndrome

Epidemiology. Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilatations

(IPVDs), leading to altered gas exchange and right-to-left shunting of blood within the pulmonary vasculature. Although HPS occurs more commonly in patients with cirrhosis and portal hypertension, it can occur with any degree of hepatic dysfunction.^{1–5} True HPS is estimated to occur in at least 10% of all patients with cirrhosis and portal hypertension; the disease is more prevalent in patients with more advanced liver disease, occurring in approximately one third of patients evaluated for liver transplantation.^{4,6–8}

Pathogenesis. Animal models of advanced liver disease have been used to identify the potential mechanisms underlying the formation of IPVDs, which develop in response to endothelial injury within the pulmonary vasculature. The inciting factors for endothelial injury include the following: (1) increased bile acids, (2) bacterial translocation and release of endotoxin, and (3) increased cytokines such as tumor necrosis factor α and endothelin-1. The damaged endothelium then releases mediators that direct the pathogenesis of HPS: vasodilation owing to carbon monoxide and nitric oxide, and angiogenesis resulting from activation of p-AKT and p-ERK.^{9,10} The intrapulmonary shunting results from precapillary and postcapillary dilatation of the pulmonary microvasculature, which is exacerbated by the formation of new blood vessels within the pulmonary microvasculature.^{11,12}

Diagnostic criteria and evaluation for hepatopulmonary syndrome. The diagnostic criteria for HPS are based on consensus opinion of expert pulmonologists and hepatologists focused on this disease. In part, the diagnosis of HPS is one of exclusion, as there is no test that is specific to the diagnosis of HPS. However, hypoxemia is

Abbreviations used in this paper: AAT, α 1-antitrypsin; HCV, hepatitis C virus; HPS, hepatopulmonary syndrome; IPVD, intrapulmonary vascular dilatation; MELD, Model for End-Stage Liver Disease; mPAP, mean pulmonary artery pressure; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function test; POPH, portopulmonary hypertension; SpO₂, pulse oximetry; SVR, systemic vascular resistance; TTE, transthoracic echocardiogram.

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required for the diagnosis of HPS, as isolated IPVDs can be seen in up to 60% of patients with cirrhosis, and based on current evidence, isolated IPVDs in the absence of hypoxemia are not associated with adverse outcomes, and thus are not sufficient to diagnose HPS.⁶ Hypoxemia is caused by the intrapulmonary shunting of blood through the IPVDs, with increasing hypoxemia occurring with more pronounced vasodilation, in addition to a greater size and number of vascular dilatations.

The diagnostic criteria for HPS include clinical and laboratory testing, in the setting of chronic liver disease (with exceptions), and an absence of cardiopulmonary disease (ie, chronic obstructive pulmonary disease) that could lead to hypoxemia (Table 1, Figure 1).^{7,13} Pulse oximetry is insufficient to diagnose HPS, although it can be a useful screening tool. An oxygen saturation on pulse oximetry (SpO₂) of 97% or less has a 96% sensitivity and positive likelihood ratio of 3.9 for detecting arterial hypoxemia at or near sea level, with a cut-off value of 94% or less identifying all subjects with a PaO₂ less than 60 mm Hg.¹⁴ Arterial blood gas sampling is required for the diagnosis of HPS to calculate the alveolar-arterial gradient. Patients with cirrhosis commonly have central hyperventilation, which leads to exhalation of increased CO₂, and a corresponding increase in PaO₂; this can lead to a normal SpO₂ in the setting of marked intrapulmonary shunting. The HPS alveolar-arterial gradient criteria are as follows: 15 mm Hg or greater for patients younger than 65 years of age, and 20 mm Hg or greater for patients 65 years of age and older owing to increased baseline shunting with aging.

A transthoracic echocardiogram (TTE) with agitated saline (bubble echo) is the standard imaging test to identify IPVDs. In the absence of IPVDs (and intra-atrial shunting), the microbubbles created by agitating saline get trapped within the pulmonary microvasculature capillaries. By contrast, in patients with HPS and IPVDs, these bubbles are visualized in the left atrium on a 4-chamber TTE as they are shunted through the IPVDs.¹⁵ The timing of visualization of the microbubbles is

important because intra-atrial shunts can lead to right-to-left shunting of these microbubbles within the first 3 cardiac cycles after injection of the agitated saline.¹⁵ In HPS, however, there is a delay in the shunting of the microbubbles because they first must pass through the right ventricle; thus, they are not seen until 4 to 6 cardiac cycles after injection of agitated saline. For patients whose body habitus precludes high-quality, 4-chamber views needed to visualize IPVDs, an alternative imaging techniques is transesophageal echocardiography. Although a radiolabeled macroaggregated albumin scan historically was used as an alternative to echocardiographic testing, its major limitation is its inability to distinguish between intracardiac vs intrapulmonary shunting.¹⁶

There are no specific guidelines dictating the testing needed to exclude other cardiopulmonary conditions such as intrinsic lung disease (ie, chronic obstructive pulmonary disease). It is recommended that minimal testing include pulmonary function tests (PFTs), especially in patients with a history of cigarette smoking. Other testing should be dictated by a patient's symptoms and/or risk factors for cardiopulmonary diseases, and can include high-resolution computed tomography scanning, exercise stress testing, and PFTs after thoracentesis in patients with a substantial hepatic hydrothorax.⁶

Clinical manifestations. Patients with HPS may be asymptomatic, but commonly have some degree of dyspnea, impairments in quality of life, and lower functional capacity as measured by the New York Heart Association functional class.⁶ The symptoms of dyspnea may be more pronounced in the upright position (platypnea) because the intrapulmonary vascular dilations are more prominent in the lung bases, leading to preferential shunting of blood to the bases in the upright position. This shunting causes pronounced V/Q mismatch and subsequent hypoxemia.¹² This change in gas exchange in the upright position manifests with a decrease in the SpO₂ (orthodeoxia), the objective correlate of platypnea.

Table 1. Diagnostic Criteria for Hepatopulmonary Syndrome

Physiologic abnormality	Diagnostic criteria
Impaired gas exchange	Arterial blood gas sampling while breathing ambient air with: <ol style="list-style-type: none"> 1. PaO₂ <80 mm Hg or 2. Alveolar-arterial oxygen gradient ≥15 mm Hg if age <65 years, or ≥20 mm Hg if age ≥ 65 years^a
Intrapulmonary shunting	<ol style="list-style-type: none"> 1. Transthoracic echocardiogram with agitated saline showing late passage (after >3 cardiac cycles) of bubbles into the left atrium 2. Radiolabeled macro-aggregated albumin scan with a brain shunt fraction of >6%
Liver disease	Cirrhosis and/or portal hypertension ^b
Liver disease	No specific defined testing required, but other causes of hypoxemia must be ruled out ^c

^aAaPO₂ = (FiO₂ [P_{atm} - PH₂O] - [PCO₂/0.8]) - PaO₂; where FiO₂ represents the fraction of inspired oxygen, P_{atm} represents the atmospheric pressure, PH₂O represents the partial pressure of water vapor at body temperature, and PaCO₂ represents the partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest).

^bPatients may have acute and/or chronic hepatitis in the absence of cirrhosis and/or portal hypertension, although nearly all patients with HPS have cirrhosis.

^cTesting may include high-resolution pulmonary computed tomography scanning to assess for parenchymal abnormalities, or pulmonary function testing to evaluate for obstructive or restrictive defects.

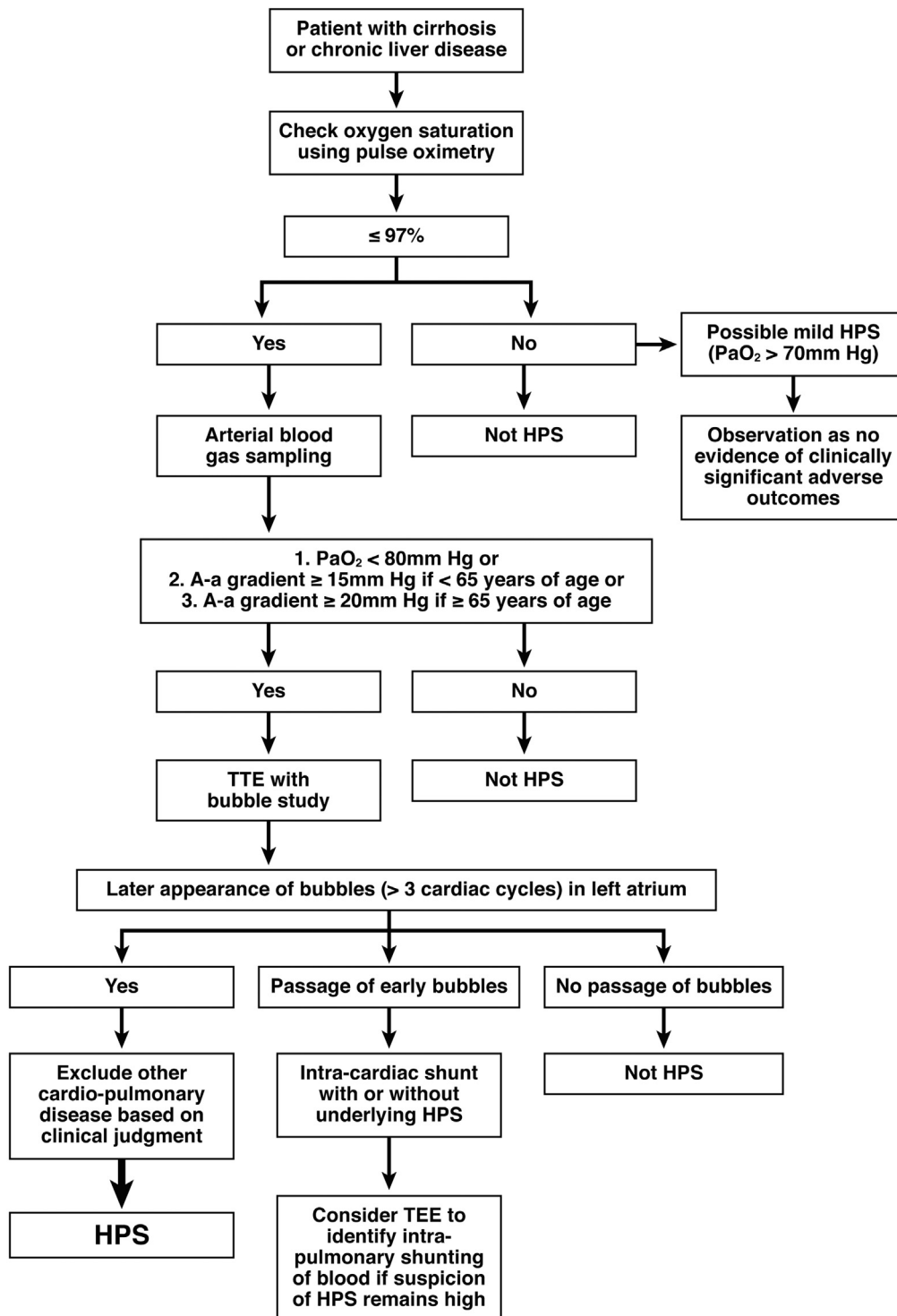


Figure 1. Diagnostic algorithm for suspected hepatopulmonary syndrome: balancing clinical science and expert opinion. A-a, Alveolar-arterial; COPD, chronic obstructive pulmonary disease; PaO₂, partial-pressure of oxygen; TEE, trans-esophageal echocardiogram; TTE, trans-thoracic echocardiogram.

Notable physical examination findings include distal cyanosis, clubbing, and/or spider angiomas. Spider angiomas, defined as dilated blood vessels on the surface of the skin, can be seen in patients with cirrhosis of any etiology, but are more common in patients with HPS.⁶ All of these findings, however, are of low sensitivity in patients with HPS.⁶

Prognosis. Cirrhotic patients with HPS have a significantly increased mortality rate in comparison with cirrhotic patients without HPS. In a multicenter cohort of

cirrhotic patients being evaluated for liver transplantation at 7 US liver transplant centers, patients with HPS had a 2- to 2.4-times increased risk of mortality compared with all other patients being evaluated for transplantation.⁶ These findings were replicated in an Austrian cohort of cirrhotic patients evaluated for liver transplantation, with a median survival of 10.6 months from evaluation for liver transplantation for patients with HPS, compared with 40.6 months in patients without HPS.⁸

Treatment. There are no Food and Drug Administration–approved medical treatments for HPS, and the only proven treatment is liver transplantation. Although animal studies and small case series initially suggested potential benefits of pentoxifylline^{17,18} and garlic,^{19,20} neither has provided durable improvement in PFTs in human clinical trials. Management of symptoms has been the mainstay of therapy, including supplemental oxygen as needed, and vaccination for pneumococcus and influenza.¹⁵ There have been several reports of placement of a transjugular intrahepatic portosystemic shunt as a treatment for HPS, but these data are limited.^{21–23} Based on animal data, sorafenib, a multikinase inhibitor that is Federal Drug Administration–approved for the treatment of hepatocellular carcinoma, is a potential treatment for HPS. This is being explored in an ongoing National Institutes of Health–sponsored multicenter phase II clinical trial of sorafenib for hepatopulmonary syndrome (ClinicalTrials.gov identifier: NCT02021929).

Transplantation for hepatopulmonary syndrome. Liver transplantation is the only curative option for HPS. There has been well-documented normalization of pulmonary function and resolution of hypoxemia within a short time period after transplantation.^{5,6,24–26} Because of the significantly increased risk of mortality among patients with HPS,^{6,8} in the United States, patients with HPS meeting specific criteria are eligible to receive Model for End-Stage Liver Disease (MELD) exception points to increase their prioritization on the waitlist. This policy has allowed for expedited transplantation of these patients, without compromising overall long-term post-transplant outcomes. In fact, the long-term post-transplant survival of transplant recipients with HPS is excellent, and is as good, if not better, than many patients with other indications for liver transplantation.^{27,28} The challenge is identifying those patients in need of a liver transplant for HPS, and, among those, whether there is a subset that can be considered too high risk. Early data on transplantation for HPS suggested that the risk of post-transplant mortality was higher in patients with a Pao₂ less than 50 mm Hg on room air.^{8,24} More recent data have challenged this and have shown very good post-

transplant survival in patients with HPS, irrespective of the pretransplant impairment in gas exchange, with complete resolution of pretransplant lung abnormalities within 1 year of transplantation.^{25,26} These data stand in contrast to 10-year analyses of national transplants in the United States that included more than 700 transplant recipients with HPS. In this analysis, there was a significant association between pretransplant gas-exchange abnormalities, and post-transplant survival, with patients with a Pao₂ of 44.0 mm Hg or less at the time of waitlisting having a 3-year post-transplant survival rate of 68%, compared with 84% and 86% in transplant recipients with Pao₂ levels of 44.1 to 54.0 and 54.1 to 61.0 mm Hg, respectively.²⁸ Although further data are needed to reconcile the findings from these different cohorts, it remains clear that transplantation for HPS can be curative and lifesaving for many patients.

Portopulmonary Hypertension

Epidemiology. The epidemiology, evaluation, and clinical parameters of portopulmonary hypertension (POPH) and HPS differ substantially (Table 2). Pulmonary hypertension is a disorder characterized by increased pressures within the pulmonary arteries or veins. Pulmonary arterial hypertension (PAH) represents a subset of pulmonary hypertension that essentially is limited to the arterial component of the pulmonary vasculature. PAH that occurs in the setting of portal hypertension without other identifiable causes is deemed POPH.¹⁵ It is estimated that approximately 5% of all patients with cirrhosis and portal hypertension have POPH, with an even higher prevalence among patients evaluated for liver transplantation.²⁹

Diagnostic criteria and evaluation for portopulmonary hypertension. The diagnostic criteria for POPH are the presence of portal hypertension (almost always in the setting of cirrhosis), exclusion of other etiologies of PAH, and corresponding hemodynamic criteria that define all forms of PAH, which are defined by evidence-based criteria. Although a TTE can be used to screen for POPH, the diagnosis rests on hemodynamic parameters that can

Table 2. Comparison of Hepatopulmonary Syndrome and Portopulmonary Hypertension

	Hepatopulmonary syndrome	Portopulmonary hypertension
Prevalence in cirrhotic patients	10%–33%	5%–10%
Portal hypertension	Usually present	Always present
Pulmonary vasculature changes	Vasodilation and angiogenesis in alveolar regions	Arterial thickening and remodeling in resistance vessels
Hypoxemia	Always present	Sometimes present
Echocardiographic findings	Left atrial bubbles present 4–6 cardiac cycles after injection of agitated saline	Increased pulmonary artery systolic pressure
Indication for transplantation	Indication; increased prioritization for patients meeting specific criteria	Increased prioritization for patients with mild disease controlled by POPH therapy; contraindication if severe,
Improves with transplantation	Always	Variable

be obtained only via right-heart catheterization. The TTE can serve as a screening tool to identify which patients should undergo right-heart catheterization, with the estimated systolic pulmonary artery pressure serving as a marker of true PAH. Traditionally, transplant centers use cut-off values ranging from 30 to 40 mm Hg on TTE to triage patients for right-heart catheterization. However, recent data on 152 patients undergoing pretransplant echocardiography showed that a cut-off value of 30 mm Hg is associated with a specificity of 54%, resulting in unnecessary right-heart catheterizations, whereas a cut-off value of 38 mm Hg yields a specificity of 82% and a sensitivity of 100%.³⁰

The hemodynamic parameters for PAH (and POPH) include the following: (1) mean pulmonary artery pressure (mPAP) greater than 25 mm Hg; (2) pulmonary vascular resistance greater than 3 Wood units (or 240 dynes·s/cm⁵); and (3) normal left-sided filling pressure (pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of 15 mm Hg or less.¹⁵ However, because patients with cirrhosis may have marked volume overload, POPH still can be diagnosed in the setting of an increased PCWP (>15 mm Hg) if the difference between the mPAP and the PCWP is 12 mm Hg or higher (deemed the transpulmonary gradient).^{15,29,31} These parameters can be measured only by right-heart catheterization, and are needed to differentiate POPH from volume overload and left-sided heart failure, both commonly seen in patients with cirrhosis (Table 3). In addition to hemodynamics consistent with PAH, POPH cannot be diagnosed without ruling out other potential etiologies of pulmonary hypertension, including chronic obstructive pulmonary disease,³² sleep-disordered breathing, and left-ventricular systolic or diastolic dysfunction.

Clinical manifestations. Patients with POPH may range from being asymptomatic, to having signs and symptoms of right heart failure, which include dyspnea on exertion, lower-extremity edema, and difficult-to-control ascites. Because POPH may be asymptomatic in the early stages of disease, TTE should be used to screen for increased pulmonary arterial pressures, especially in patients with cirrhosis being evaluated, or currently waitlisted for liver transplantation.

Prognosis and treatment. POPH is associated with significant morbidity and mortality. Among cirrhotic

patients diagnosed with POPH, the estimated 1-year survival without treatment is 60%.^{15,29,33} The medical treatments that can be used for patients with POPH are similar to those offered to patients with PAH, and include the following: endothelin-receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin analogues. Although the medical management of PAH is evidence-based, resulting from many multi-center randomized controlled trials of different treatment regimens, treatment algorithms for POPH derive mainly from clinical experience with small cohorts of patients. The medical management of POPH patients is based on the art of medicine, rather than science, owing to the small number of patients with this disease who meet current criteria for treatment, based on expert opinion. As a result, there are limited data evaluating the long-term survival of patients with POPH managed with medical therapy alone because POPH occurs in the setting of cirrhosis and portal hypertension, which influences long-term patient survival. As a result, liver transplantation is seen as a potential option for patients with POPH, although it does come with risks of increased perioperative and postoperative mortality. Among patients evaluated for liver transplantation, the optimal medical therapy remains unknown. Most commonly, these patients are treated aggressively with intravenous prostacyclin therapy. However, case series of patients have suggested that oral therapy alone, even in patients with severe POPH pretransplantation, may serve as a sufficient bridge to liver transplantation.³⁴

Transplantation for portopulmonary hypertension. A large series of transplant recipients was published in 2002, with aggregated center-level data, in combination with published case reports and case series. Among 43 transplant recipients with POPH, 15 (35%) died after transplantation, with 14 of the deaths related to cardiopulmonary dysfunction.³⁵ The post-transplant deaths occurred exclusively in patients with a mPAP of 35 mm Hg or greater,³⁵ which led to widespread adoption of this cut-off value for determining transplant eligibility. However, because of concerns about the inclusion criteria for patients included in this cohort, notably the large proportion diagnosed with POPH in the operating room at the time of transplantation, individual transplant centers adopted individualized policies for transplantation.³⁵ Between 2006 and 2012,

Table 3. Examples of Hemodynamic Parameters Seen in Cirrhotic Patients With POPH, Left-Sided Heart Failure, and Volume Overload

Diagnosis	Mean pulmonary arterial pressure ^a	Pulmonary capillary wedge pressure ^a	Cardiac output ^a	Pulmonary vascular resistance ^b
Portopulmonary hypertension	45 mm Hg	10 mm Hg	7 L/min	5 Wood units
Left-sided heart failure	40 mm Hg	30 mm Hg	4 L/min	2.5 Wood units
Volume overload	40 mm Hg	15 mm Hg	10 L/min	2.5 Wood units

^aValues obtained at the time of right heart catheterization.

^bCalculation: [(mean pulmonary artery pressure) - (pulmonary capillary wedge pressure)] / (cardiac output).

3 US centers published small case series of successful transplantation in patients with POPH, however, there were small sample sizes at each of these centers with short-term follow-up evaluation.³⁶⁻³⁸ One of these case series recently was updated, and with long-term follow-up evaluation (median, 7.8 y) has shown 85.7% patient and graft survival of their 7 transplant recipients with POPH. These results are tempered, however, by the fact that 4 of 6 of the surviving patients still require oral vasodilator therapy for persistent PAH.³⁹

In contrast to these small case series, a recent analysis of United Network for Organ Sharing data from 2006 to 2013 identified 100 transplant recipients with POPH MELD exception points who had hemodynamic criteria consistent with POPH. The unadjusted 3-year post-transplant patient survival rate in this cohort was 64.3%, which was dramatically lower than the overall transplant population, with 9 of 12 deaths occurring within the first 35 days of transplantation, independent of pretransplant mPAP.⁴⁰ Although these data require further validation, they suggest that even with pretransplant medical treatment of POPH, transplant outcomes may not be acceptable in these patients. However, despite these discouraging data, there have been several case reports and case series showing successful living donor liver transplants for patients with POPH.⁴¹⁻⁴³ Most of these patients had normalization of their pulmonary arterial pressures after transplantation despite requiring intravenous therapy pretransplantation. Despite these successes, however, transplant physicians still must exercise caution in evaluating patients with POPH for transplantation given the increased risk of post-transplant morbidity and mortality. Future multicenter collaborative studies are needed to better define selection criteria for transplantation that integrate both pulmonary hemodynamics as well as residual cardiac function.

α 1-Antitrypsin and Lung Disease

α 1-antitrypsin (AAT) deficiency involving the liver can manifest as abnormal liver enzyme levels, and, in a subset of patients, advanced fibrosis and cirrhosis, whereas in others it can lead to features of chronic obstructive pulmonary disease.⁴⁴ Deficiency in AAT leads to alveolar septal destruction and airspace enlargement, which on gross pathology shows basilar panacinar emphysema.⁴⁴ However, not all patients with AAT deficiency will develop emphysema. The risk of developing pulmonary complications is dependent partly on the molecular genotype of an individual patient, and may exist in the absence of overt liver disease. The presence of secondary factors risk factors for chronic obstructive pulmonary disease also augments the risk of developing emphysema in patients with AAT deficiency, most notably a history of cigarette smoking.⁴⁴ Unlike hepatic complications of AAT deficiency, which are related solely to the deposition of the abnormal AAT protein,

pulmonary disease derives from a lack of the enzymatic action of AAT. As a result, pulmonary AAT deficiency can be managed with intravenous augmentation therapy that contains high concentrations of AAT.⁴⁵

Liver transplantation is curative for hepatic complications of AAT deficiency. Recent data have suggested that liver transplantation also can help the pulmonary complications of AAT deficiency. An initial analysis of 7 liver transplant recipients with pretransplant and post-transplant pulmonary function tests available showed essentially no change in lung function after liver transplantation, despite an expected decrease over time without liver transplantation.⁴⁶ A more recent analysis of 17 liver transplant recipients with AAT showed that despite a statistically significant decrease in the forced expiratory volume in 1 second/forced vital capacity ratio before vs after liver transplantation, this value was numerically similar, whereas all other PFT parameters were not significantly different after liver transplantation.⁴⁷ More importantly, post-transplant survival in these patients was excellent. Together, these recent data highlight that liver transplantation likely slows the progression of lung disease in these patients.

Cardiac Manifestations of Liver Disease

Vascular Response to Cirrhosis and Portal Hypertension

Cardiac manifestations of liver disease involve aspects of both the cardiac and vascular systems. Portal hypertension leads to a state of marked peripheral arterial vasodilation as a result of the release of vasodilatory mediators such as nitric oxide,⁴⁸ carbon monoxide,⁴⁹ and prostacyclin.⁵⁰ This peripheral arterial vasodilation leads to a decrease in the systemic vascular resistance (SVR), activation of the renin-angiotensin-aldosterone system, and, consequently, sodium retention and volume overload.

Left Ventricular Systolic Function

Peripheral arterial vasodilation leads to a progressive decrease in the SVR, thus reducing the cardiac afterload. In response, the cardiac output must increase to maintain adequate blood pressure to sustain end-organ tissue perfusion (blood pressure = cardiac output * SVR). This increase in cardiac output manifests as a hyperdynamic left ventricle, with estimated ejection fractions that are greater than normal relative to patients without cirrhosis, and an increased cardiac index on right heart catheterization. This state may persist indefinitely until death or liver transplantation, but in a subset of patients will progress to impaired systolic function.⁵¹ This decrement in systolic function frequently occurs in the setting of decreased renal perfusion, impaired renal function, and, ultimately, the hepatorenal syndrome. This

cardiorenal failure is associated with increased mortality, and reflects the end stage of cirrhosis and portal hypertension.⁵¹

Diastolic Dysfunction

It is estimated that more than 50% of patients with cirrhosis may have abnormal diastolic function measured by TTE.⁵² This abnormal stiffening of the ventricular wall leads to inadequate ventricular filling, and, when severe, leads to overt heart failure. The diastolic dysfunction usually is mild (grade 1), but in approximately 25% of patients with diastolic dysfunction, can be more severe (grade 2).⁵² Patients who progress to having diastolic dysfunction are those with more advanced liver disease, evidenced by higher MELD and Child–Pugh scores, lower values of serum albumin, and a greater prevalence of ascites.⁵² The exact pathophysiological mechanisms underlying the cardiac remodeling and increased stiffness are unknown.

QT Prolongation

The QT interval on an electrocardiogram reflects myocardial depolarization and repolarization, and its prolongation is associated with cardiac arrhythmias that potentially can be life-threatening.^{53,54}

Several case series clearly have shown an increased prevalence of QT interval prolongation in patients with chronic liver disease, independent of other known risk factors for this condition.^{53,54} The mechanism underlying this conduction abnormality remains unknown, although one hypothesis focused on increased autonomic dysfunction.⁵⁵

Cardiac Manifestations of Specific Liver Diseases

Hemochromatosis. Hereditary hemochromatosis is a multisystemic disease and can affect organs such as the heart and pancreas. Iron deposition within the heart can lead to congestive heart failure, conduction abnormalities, and, rarely, a restrictive cardiomyopathy.^{56,57} The prevalence of heart failure symptoms in patients with hereditary hemochromatosis is variable, with estimates ranging from 0% to 35%.^{58–62} Despite these risks of congestive heart failure, cardiac function in patients with hereditary hemochromatosis can improve in response to therapeutic phlebotomy.⁵⁷ However, cardiac complications after liver transplantation are higher in patients undergoing a transplant for hereditary hemochromatosis compared with other transplant recipients, thus these patients require close evaluation before and after transplantation, with imaging that can include a TTE, magnetic resonance imaging, and/or positron emission tomography scan.⁶³

Nonalcoholic steatohepatitis. Although there are several theories as to the exact pathophysiologic mechanism leading to the development of fatty liver disease in patients with NASH, insulin resistance and altered fatty acid metabolism are supported by the most robust data. As a result, nonalcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of the metabolic syndrome,⁶⁴ with NAFLD being considered an independent risk factor for coronary artery disease.⁶⁴ This risk is amplified in patients with NASH, as compared with those with NAFLD and bland steatosis. To date, there are limited medical therapies to decrease the inflammation and fibrosis related to NASH. However, there are data to suggest that in patients with abnormal liver enzyme levels attributable to NAFLD, statin therapy can reduce cardiovascular morbidity.⁶⁵

Hepatitis C. Early data were unclear about the relationship between chronic hepatitis C virus (HCV) and coronary heart disease, however, new data have emerged from a cohort of nearly 15,000 HCV-negative controls, 8000 isolated HCV antibody-positive patients, and 1400 patients with active viremia. Those with isolated HCV antibody positivity had a 32% increased risk of coronary artery disease when compared with controls, whereas patients with detectable HCV RNA levels had a nearly 60% increased risk, independent of factors such as hypertension and diabetes.⁶⁶

Screening for Cardiac Complications in Patients With Liver Disease

The cardiac evaluation of patients with chronic liver disease should focus on detecting complications that can impact their mortality before and after liver transplantation, in addition to specific screening for patients with liver disease associated with cardiac complications. TTE should be performed routinely in patients being evaluated for, and awaiting, a liver transplant. The optimal timing of such TTE screening has not been defined, although most centers perform yearly TTEs to identify patients with echocardiographic parameters suggestive of PAH.³⁰ Furthermore, the performance of routine TTEs can identify patients with cirrhotic cardiomyopathy complicated by decreased left- and/or right-ventricular systolic function. Despite the sensitivity of TTE, however, to identify depressed cardiac function, which places patients at risk of overt heart failure post-transplantation, there still is a risk for postoperative heart failure despite a normal pretransplant TTE.⁶⁷

Patients being evaluated for liver transplantation are evaluated routinely for coronary artery disease because of the risk of perioperative and postoperative cardiac events that may impact mortality. There are no clear data on the optimal testing strategy for asymptomatic patients who are at low risk for coronary artery disease. In patients with nonhepatic cardiac risk factors for coronary disease (ie, diabetes), pretransplant assessment for

coronary artery disease is recommended, although there are no clear data identifying the ideal mechanism to screen patients (stress echocardiography, nuclear imaging, and/or routine left heart catheterization).⁶⁸ Patients with NASH should be evaluated for coronary artery disease because this is considered a risk factor for coronary artery disease.⁶⁸ In patients with coronary artery disease or significant risk factors (ie, hyperlipidemia), statin therapy is safe, indicated, and can decrease morbidity and mortality.^{65,69}

Conclusions

In summary, chronic liver disease is associated with the development of potentially severe pulmonary and cardiac complications. HPS and POPH are common in patients with advanced liver disease, and adversely may influence quality of life and survival. Although HPS is an indication for liver transplantation, severe POPH generally is considered a contraindication. Patients with POPH who respond to medical therapy can tolerate transplantation, but consistent reversal has not been found. Cirrhotic cardiomyopathy manifests with systolic, diastolic, and conduction abnormalities, and is a manifestation of end-stage cirrhosis and portal hypertension. The role of liver transplantation in this setting has not been defined fully. Individuals with AAT deficiency are at increased risk for emphysema, although patients with chronic HCV and NASH are at risk for coronary disease, each of these complications has the potential to influence transplant candidacy. Understanding the pathogenesis of these unique consequences of liver disease and defining the precise role of liver transplantation in therapy is needed to optimize outcomes in these individuals.

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Conflicts of interest

The authors disclose no conflicts.

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