

## Respiratory Dysfunction and Pulmonary Disease in Cirrhosis and Other Hepatic Disorders

Julie L Huffmyer MD and Edward C Nemergut MD

### Introduction

### General Effects of Liver Disease on Lung Function

### Hepatopulmonary Syndrome

#### Pathogenesis

#### Clinical Manifestations

#### Diagnosis

#### Treatment

### Portopulmonary Hypertension

#### Clinical Manifestations

#### Pathophysiology

#### Diagnosis

#### Treatment

### Summary

**End-stage liver disease and its complications are a leading cause of death among adults in the United States, and thousands of patients await liver transplantation. The liver plays a central role in health and homeostasis and thus the diseased liver leads to many deleterious effects on multiple organ systems, including the pulmonary system. We review the general effects of cirrhosis on the respiratory system, including mild hypoxemia, atelectasis, and hepatic hydrothorax. Cirrhosis is associated with 2 unique entities that affect the pulmonary vasculature: hepatopulmonary syndrome and portopulmonary hypertension. Hepatopulmonary syndrome, which is found in approximately 20% of patients awaiting liver transplantation, refers to the triad of hepatic dysfunction, hypoxemia, and intrapulmonary vascular dilations, and responds well to liver transplantation. In portopulmonary hypertension, cirrhosis and portal hypertension lead to pulmonary arterial hypertension, and portopulmonary hypertension has been considered a contraindication for transplantation. Currently, patients must have mild to moderate pulmonary hypertension to be considered for transplantation, and may still require long-term therapy with vasodilators to prevent right-ventricular failure and, consequently, failure of the newly transplanted liver allograft. *Key words: liver disease, cirrhosis, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension.* [Respir Care 2007;52(8):1030–1036. © 2007 Daedalus Enterprises]**

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Julie L Huffmyer MD and Edward C Nemergut MD are affiliated with the Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia. Edward C Nemergut MD is also affiliated with the Department of Neurosurgery, University of Virginia Health System, Charlottesville, Virginia.

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Correspondence: Edward C Nemergut MD, Department of Anesthesiology, University of Virginia Health System, PO Box 800710, Charlottesville VA 22908. E-mail: en3x@virginia.edu.

## Introduction

End-stage liver disease and its complications were the 12th leading cause of death among adults in the United States in 2002.<sup>1</sup> Autopsy series have estimated the prevalence of cirrhosis in the United States at 5–10%, but that figure may be an overestimate, owing to selection bias.<sup>2</sup> Nevertheless, more than 17,500 patients await liver transplant in the United States, and most wait at least 2 years before receiving an organ. Given the high prevalence and incidence of liver disease, patients with substantial hepatic disease are frequently encountered, especially in the intensive care unit. Familiarity with the unique effects of the liver on the respiratory system is important to the delivery of optimal care.

In health, the liver plays a central role in organism homeostasis. It plays a major role in metabolism, including glycogen synthesis and storage, gluconeogenesis, and protein and lipid metabolism. The liver is also responsible for the production of bile, plasma protein synthesis (including most clotting factors), and drug detoxification. Indeed, the liver has important interactions with every organ system. In ancient Chinese medicine, the liver—not the heart—was considered “the center” of the body. Given the important role the liver plays in health, the diseased liver has deleterious effects on every other organ system, and ubiquitous systemic manifestations. Cirrhosis leads to a state of increased cardiac output, decreased systemic vascular resistance, and systemic hypotension, which may result in hepatic cardiomyopathy.<sup>3</sup> In the gastrointestinal system, portal hypertension results in ascites and gastroesophageal varices. Hematologically, coagulopathy, and thrombocytopenia are commonly encountered. Hepatorenal syndrome and an overall decrease in renal function frequently complicate cirrhosis. In the central nervous system, cognitive dysfunction and hepatic encephalopathy may range from mild to severe. The pulmonary system is no exception, and the unique effects of liver disease on pulmonary function merits review.

### General Effects of Liver Disease on Lung Function

Regardless of the etiology, chronic liver disease has well-established effects on respiratory function. It is common for cirrhotic patients to suffer from a mild degree of hypoxemia, most likely from cephalad displacement of the diaphragm by increased abdominal pressure and ascites. Pulmonary edema causes difficulty with secretion clearance, while pleural effusions and ascites may result in atelectasis. Hepatic hydrothorax, a pleural effusion that develops in patients with cirrhosis in the absence of substantial cardiac or pulmonary disease, may occur in as many as 10% of patients with chronic liver disease.<sup>4,5</sup> The pathogenesis of hepatic hydrothorax is similar to the other

causes of fluid accumulation in cirrhosis. Increased venous pressure resulting from sodium retention, and consequent extracellular volume expansion, coupled with low plasma oncotic pressure resulting from hypoalbuminemia, undoubtedly contribute to the development of hepatic hydrothorax. Though both of these conditions are present in many patients with cirrhosis, only a minority develop hydrothorax. Thus, other factors are clearly important. There is substantial evidence that fluid develops in the peritoneal space, rather than the pleural space itself. Small openings in the diaphragm may allow the passage of ascitic fluid from the abdomen into the chest. With negative inspiratory pressure, fluid may pass easily through the diaphragmatic openings and accumulate in the chest. Indeed, hepatic hydrothorax essentially only develops in patients with ascites. Patients present with dyspnea, cough, hypoxemia, and chest discomfort.<sup>6</sup> Diagnosis is made by the presence of a pleural effusion on chest radiograph, followed by diagnostic thoracentesis to evaluate for other causes of effusion. Patients may be treated with serial thoracenteses, fluid and sodium restriction, and/or diuretics.

### Hepatopulmonary Syndrome

Hepatopulmonary syndrome is found in approximately 20% of patients who await liver transplantation. It consists of a triad of hepatic dysfunction, hypoxemia ( $P_{aO_2} < 70$  mm Hg at an inspired oxygen fraction of 0.21), and extreme vasodilation in the form of intrapulmonary vascular dilations.<sup>7,8</sup> Hepatopulmonary syndrome may be further characterized by the evidence of an increased alveolar-arterial oxygen difference ( $P_{(A-a)O_2}$ ), evidence of intrapulmonary shunting (measured via echocardiography or technetium-99-labeled lung perfusion scans), and the absence of arterial carbon dioxide retention.

### Pathogenesis

The pathophysiology of hepatopulmonary syndrome includes the distinction between type 1 and type 2 hepatopulmonary syndrome.<sup>8</sup> In type 1 hepatopulmonary syndrome, patients have dilated precapillary or capillary blood vessels, and alveolar transit time is decreased. In simple terms, blood passes through the enlarged dilated capillary bed of the lung too quickly to become completely oxygenated. These patients do not have a true anatomic shunt and usually respond to the administration of oxygen with increased  $P_{aO_2}$ . Increased alveolar oxygen tension allows improved passage of oxygen across the alveolar membrane to the red blood cells. Type 2 hepatopulmonary syndrome results from the formation of pulmonary arteriovenous connections and anatomic shunt. Because blood bypasses the alveoli in type 2 hepatopulmonary syndrome, increasing the alveolar oxygen does not improve oxygen-

ation. In most patients there is evidence of both type 1 and type 2 disease.

All patients with hepatopulmonary syndrome have intrapulmonary vascular dilations,<sup>9</sup> which can form as a result of either failure of the diseased liver to clear circulating pulmonary vasodilating substances, the formation of a vasodilator by the liver, or possibly by inhibition of a vasoconstrictive substance by the liver. Most likely, decreased hepatic clearance of various vasodilatory substances (including vasoactive intestinal peptide and other substances synthesized by intestinal bacteria) results in widespread dilation. Further, portal hypertension may lead to decreases in gut perfusion, allowing bacterial translocation and the presence of endotoxin in the portal blood. Nitric oxide (NO) plays a key role in the abnormal vasodilation and ventilation/perfusion mismatch seen in hepatopulmonary syndrome.<sup>10</sup> In a study of 45 cirrhotic patients, exhaled NO was significantly higher than in normal controls, and in all the patients there was a significant correlation between exhaled NO and alveolar-arterial oxygen difference.<sup>11</sup> In the same study, the 9 patients who met the criteria for the diagnosis of hepatopulmonary syndrome also had the highest values of exhaled NO.<sup>11</sup> Animal models of hepatopulmonary syndrome showed an up-regulation of NO synthase in the pulmonary arteries and NO-mediated impairment of vasoconstriction produced by phenylephrine.<sup>12,13</sup> Inhibition of guanylate cyclase by methylene blue in patients with hepatopulmonary syndrome may enhance oxygenation and decrease  $P_{(A-a)O_2}$ .<sup>14</sup> Curiously, inhibition of tumor necrosis factor alpha by pentoxifylline prevented the hepatopulmonary syndrome in cirrhotic rats.<sup>15</sup>

### Clinical Manifestations

The clinical manifestations of hepatopulmonary syndrome encompass a spectrum of findings. Signs and symptoms include cyanosis, clubbing, nail-bed telangiectasias, orthodeoxia, platypnea, dyspnea, and hypoxemia. Telangiectasias are often a strong indicator that the patient has substantial systemic and pulmonary vasodilation, problems with gas exchange, and a diminished capability of the lung vascular bed to perform hypoxic pulmonary vasoconstriction.<sup>16</sup> Patients with hepatopulmonary syndrome have hyperdynamic circulatory systems, manifested by increased cardiac output, diminished systemic vascular resistance, diminished pulmonary vascular resistance (PVR), and a reduced arterial/mixed-venous oxygen difference.<sup>17</sup> The pulmonary manifestations of hepatopulmonary syndrome include platypnea and orthodeoxia. These conditions refer to the increasing sensation of dyspnea and arterial desaturation in the upright position, respectively. Both of these are improved by reclining into the supine position. It is thought that orthodeoxia is caused by a gravity-induced

increase in perfusion of the intrapulmonary vascular dilations in the upright position.<sup>18</sup> In some patients the hypoxemia may be subclinical, whereas other patients may present with symptoms of liver disease more than pulmonary issues.<sup>7</sup> Patients who have the more typical respiratory symptoms will describe exertional dyspnea and will also exhibit cyanosis, nail clubbing, and spider nevi.<sup>19,20</sup>

### Diagnosis

Diagnosis of hepatopulmonary syndrome focuses on the search for intrapulmonary vascular dilations in patients affected by liver disease. Chest radiograph and pulmonary function tests are often used initially in the evaluation of patients with respiratory difficulties, but are nonspecific for patients with hepatopulmonary syndrome. Thus, more in-depth evaluation for hepatopulmonary syndrome is warranted. Currently, the preferred diagnostic tool is contrast-enhanced echocardiography.<sup>17</sup> Contrast is given intravenously in the form of agitated saline. In the normal patient, the microbubbles would be seen only in the right heart chambers because of filtering by the lung capillary bed. In patients with hepatopulmonary syndrome, the microbubbles are seen in the left heart 3–6 cardiac cycles after the appearance of contrast in the right heart. The presence of contrast in the left heart is indicative of intrapulmonary shunting. Technetium-99 labeled macroaggregated albumin scanning may also be performed to demonstrate intrapulmonary shunting. Macroaggregated albumin is large enough that it should be trapped in the pulmonary vascular bed; however, intrapulmonary vascular dilations allow albumin to pass through the lungs, and it will often appear as abnormal uptake in the kidneys or brain.<sup>21</sup>

### Treatment

The medical options for the treatment of hepatopulmonary syndrome include the mechanical occlusion of intrapulmonary vascular dilations, antagonism of circulating vasodilators, and treatment of the underlying liver disease; however, most clinicians regard liver transplantation as the definitive treatment for hepatopulmonary syndrome, because many other medical/mechanical therapies have proven ineffective or impractical. Indeed, medical therapy is best regarded as a bridge to transplantation. As noted above, methylene blue results in short-term improvement in  $P_{aO_2}$  and decreases the  $P_{(A-a)O_2}$ , probably through the inhibition of NO-stimulated guanylate cyclase.<sup>14</sup> Somatostatin analogues, cyclophosphamide, bismesylate almitrine, indomethacin, plasma exchange, and physical occlusion of the intrapulmonary vascular dilations have also been reported; they provide minimal improvement for patients with hepatopulmonary syndrome.<sup>22,23</sup> Some NO synthase inhibitors have been studied in animals, to oppose

the vasodilating effects of NO, and cases of human use have been reported.<sup>24</sup>

As noted above, liver transplantation remains the definitive treatment for hepatopulmonary syndrome and conveys a significant survival benefit. Without transplantation, hepatopulmonary syndrome is uniformly fatal and has a 5-year mortality of approximately 20%.<sup>25</sup> There is significant variability as to when hepatopulmonary syndrome improves after transplant; some patients may note improvement in oxygenation within days, whereas other patients may require months to achieve improvement in their hypoxemia and shunt fraction.<sup>26</sup> Nevertheless, transplantation uniformly increases  $P_{aO_2}$  and decreases  $P_{(A-a)O_2}$ .

### Portopulmonary Hypertension

Portopulmonary hypertension is characterized by pulmonary arterial hypertension complicating portal hypertension in patients with liver disease. The prevalence of true portopulmonary hypertension ranges from 2–10% (average approximately 5%) in patients who are waiting for liver transplantation.<sup>8</sup> As noted earlier, patients with liver disease have a hyperdynamic circulation that leads to an increased cardiac output in the face of low systemic vascular resistance. Approximately 20% of patients with liver cirrhosis have an increase in pulmonary arterial pressure that is not due to true portopulmonary hypertension.<sup>27</sup> This increase may be due to volume overload, but is most commonly caused by increased right-ventricular output across a normal (or even reduced) PVR. It is absolutely essential to accurately characterize the hemodynamics in suspected portopulmonary hypertension, because increased pulmonary arterial pressure can be caused by multiple entities, and a misdiagnosis can lead to inappropriate treatment.

Although consensus criteria for the diagnosis of portopulmonary hypertension do not exist, most investigators define portopulmonary hypertension as including the following hemodynamic measurements: mean pulmonary artery pressure  $> 25$  mm Hg at rest or  $> 30$  mm Hg during exercise; pulmonary artery occlusion pressure  $< 15$  mm Hg; PVR  $> 240$  dyn  $\cdot$  s  $\cdot$  cm<sup>-5</sup>; evidence of portal hypertension in the form of esophageal varices and other stigmata of portal hypertension; imaging showing portal hypertension, or liver biopsy results confirming cirrhosis.<sup>23,28</sup> Portopulmonary hypertension may be further characterized as mild, moderate, and severe, based on the degree of pulmonary arterial hypertension, and each category carries its own therapeutic implications (Table 1).<sup>8,28</sup> Patients with mild or moderate portopulmonary hypertension may experience reversal of their disease with liver transplantation, but they often must be maintained on long-term vasodilator therapy while pulmonary vascular bed remodeling occurs. Liver transplantation probably will not correct the pulmonary

Table 1. New York Heart Association Classification System for Portopulmonary Hypertension

|   | New York Heart Association Class |                         |                       |
|---|----------------------------------|-------------------------|-----------------------|
|   | Mild<br>(I or II)                | Moderate<br>(II or III) | Severe<br>(III or IV) |
| Mean pulmonary artery pressure (mm Hg)                                  | 25–34                            | 35–44                   | $> 45$                |
| Cardiac index (L/min/m <sup>2</sup> )                                   | $> 2.5$                          | $> 2.5$                 | $< 2.5$               |
| Pulmonary vascular resistance (dyn $\cdot$ s $\cdot$ cm <sup>-5</sup> ) | 240–500                          | 500–800                 | $> 800$               |
| Right atrial pressure (mm Hg)   | 0–5                              | 0–5                     | 5–8                   |

(Data from Reference 28.)

hypertension in patients with severe portopulmonary hypertension.

### Clinical Manifestations

Portopulmonary hypertension has an insidious onset, with nonspecific symptoms. The clinical features may be subtle initially; however, patients with cirrhosis who complain of dyspnea either at rest or with exercise should be formally evaluated for portopulmonary hypertension. Chest pain and syncope are late to develop and are harbingers of a poor prognosis. Physical examination findings include jugular venous distention, increased P2 component of second heart sound, tricuspid regurgitation murmur, and signs of right heart failure.

Portopulmonary hypertension is associated with high mortality, and its development is an ominous prognostic sign. Without treatment, mortality is 50–90% in 5 years. In 1991, median survival was 6 months. By 1998, median survival had improved to 2 years, and it continues to improve today. In 2005, Kawut et al compared 13 patients with portopulmonary hypertension to 33 patients with idiopathic pulmonary hypertension. The patients with portopulmonary hypertension had a higher cardiac index and lower PVR than did the patients with idiopathic pulmonary hypertension, whereas right atrial pressure and pulmonary artery pressure were similar between the groups. Patients with portopulmonary hypertension had a higher risk of death in multivariate analysis. This suggests that patients with portopulmonary hypertension have a higher risk of death than do patients with idiopathic pulmonary hypertension, despite having a higher cardiac index and lower PVR.<sup>29</sup>

### Pathophysiology

The mechanisms by which portal hypertension causes pulmonary hypertension remain poorly understood. Some

investigators believe that a humoral substance with vasoactive properties and that is normally metabolized by a healthy liver is allowed to reach the pulmonary circulation and causes the perturbations seen in portopulmonary hypertension. Potential mediators include serotonin, interleukin-1, endothelin-1, glucagon, secretin, thromboxane B2, and vasoactive intestinal peptide.<sup>30–32</sup> Other investigators have suggested that portopulmonary hypertension results from venous thromboembolism, as blood clots pass through portosystemic shunts and reach the pulmonary circulation, causing pulmonary hypertension.<sup>33</sup> Finally, some investigators have suggested that the high cardiac output associated with cirrhosis exposes the pulmonary vascular bed to increased shear stress. If adequate PVR persists despite increased cardiac output and shear stresses, the patient will not develop any pulmonary syndrome. If the pulmonary vasculature responds with dilation, the patient will develop abnormally decreased vascular resistance and hepatopulmonary syndrome. If the pulmonary vasculature responds to the increased shear stresses with vasoconstriction, hypertrophy, and the proliferation of pulmonary arterial endothelial cells, the patient develops portopulmonary hypertension.<sup>28</sup> Indeed, Mal et al reported a case where a patient with oxygen-dependent hepatopulmonary syndrome noted a marked improvement in dyspnea and gas exchange after the development of portopulmonary hypertension, which suggests that hepatopulmonary syndrome and portopulmonary hypertension are not mutually exclusive.<sup>34</sup>

Since no theory explains why portopulmonary hypertension develops in only a minority of patients with cirrhosis, an underlying genetic propensity among certain patients is thought to exist. A gene has been identified on chromosome 2 which causes dysfunction of bone morphogenetic protein receptor type 2, leading to idiopathic pulmonary arterial hypertension.<sup>35</sup> Mutations in the anaplastic lymphoma kinase (ALK-1) gene, which is another member of the transforming growth factor receptor family, have been linked specifically to pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia.<sup>36</sup> Nevertheless, a specific genetic defect that results in proliferative pulmonary vasculopathy in cirrhotic patients has not been described.

### Diagnosis

The medical evaluation of any patient suspected of having portopulmonary hypertension should include a thorough history and physical examination, electrocardiogram, and chest radiograph. Electrocardiogram typically reveals right-ventricular hypertrophy and right-axis deviation and may reveal a right bundle branch block. Chest radiograph demonstrates large pulmonary arteries and cardiomegaly.<sup>37</sup> Though not specific for portopulmonary hypertension, these

modalities are very sensitive and may help to eliminate other causes. More specific studies, including transthoracic echocardiogram, are necessary to rule out other causes of pulmonary hypertension. If there is concern that venous thromboembolism is the cause of pulmonary hypertension, then ventilation-perfusion scan and/or computed tomography pulmonary angiography can be carried out to evaluate for pulmonary arterial thrombosis. Right heart catheterization is ultimately necessary to obtain the hemodynamic measurements that are diagnostic of portopulmonary hypertension. It is important to calculate PVR, because this is an estimation of right-heart afterload and right-ventricular function, which is essential to the success of potential liver transplantation. If the right heart is in failure, there will be increased central venous pressure, and the increased pressure will be transmitted backward to the hepatic system. If a patient receives a transplant when in right heart failure or overload, the donor organ will probably become congested and fail.<sup>8</sup>

### Treatment

Intravenous vasodilators are the mainstay of treatment for patients with portopulmonary hypertension. Prostacyclin (epoprostenol) is a powerful systemic and pulmonary vasodilator that also reduces platelet aggregation. It is administered via continuous central intravenous infusion and has been shown to reduce PVR, reduce mean pulmonary artery pressure, and increase cardiac output, if the pulmonary vascular disease has not progressed to fibrosis.<sup>38</sup> Common adverse effects of prostacyclin include jaw pain, headache, diarrhea, flushing, leg pain, and nausea and vomiting. For patients with idiopathic pulmonary hypertension, prostacyclin increases exercise tolerance and improves survival. There are open-label data that show improvement in PVR and mean pulmonary artery pressure in patients with portopulmonary hypertension receiving long-term prostacyclin,<sup>38</sup> but a large randomized controlled trial has not been performed. Some preliminary data suggest that intravenous epoprostenol does not improve long-term survival.<sup>28</sup> Sildenafil also reduces mean pulmonary artery pressure and improves cardiac output in patients with portopulmonary hypertension awaiting liver transplantation.<sup>39</sup>

Based on extrapolation of data and experience with idiopathic pulmonary arterial hypertension, patients with portopulmonary hypertension may also be treated with anticoagulants to improve sluggish pulmonary blood flow and prevent in-situ thrombosis. Nevertheless, as most patients with cirrhosis are coagulopathic and have a substantial risk of a catastrophic gastrointestinal bleed, anticoagulation is often contraindicated.

As opposed to hepatopulmonary syndrome, in which liver transplantation improves the condition, transplanta-

## RESPIRATORY DYSFUNCTION AND PULMONARY DISEASE IN HEPATIC DISORDERS

Table 2. Hepatopulmonary Syndrome Versus Portopulmonary Hypertension

|                          | Hepatopulmonary Syndrome   | Portopulmonary Hypertension  |
|--------------------------|--|--|
| Defining characteristics | Liver dysfunction<br>Intrapulmonary vascular dilations<br>Abnormal $P_{(A-a)O_2}$ ( $> 15$ mm Hg on room air)<br>Other cardiopulmonary etiologies excluded | Commonly cited criteria:<br>Portal hypertension<br>Resting mean pulmonary artery pressure $> 25$ mm Hg<br>PAOP $< 15$ mm Hg<br>Other etiologies excluded |
| Common symptoms          | Platypnea<br>Orthodeoxia<br>Arterial desaturation  | Fatigue<br>Dyspnea on exertion<br>Orthopnea<br>Right heart failure   |
| Diagnostics              | Decreased $D_{LCO}$<br>Contrast echocardiogram positive*<br>Technetium-99 labeled macroaggregated albumin scanning   | Right heart catheterization<br>Echocardiogram  |
| Management               | Oxygen supplementation<br>Liver transplant   | Vasodilators (epoprostenol, sildenafil)  |

\*Contrast echocardiogram is "positive" when contrast appears in left heart within 3–6 cardiac cycles of appearance in right heart, and in the absence of other etiology.

$P_{(A-a)O_2}$  = alveolar-arterial oxygen difference

PAOP = pulmonary artery occlusion pressure

$D_{LCO}$  = diffusing capacity of the lung for carbon monoxide

tion may not improve portopulmonary hypertension, especially if the pulmonary hypertension is moderate to severe. At most centers, a patient with portopulmonary hypertension must have a mean pulmonary artery pressure  $< 35$  mm Hg to be considered a candidate for liver transplantation. Moderate to severe pulmonary hypertension puts the liver transplant candidate at higher risk of perioperative morbidity and mortality. With a mean pulmonary artery pressure  $> 35$  mm Hg, the transplanted liver may develop substantial venous congestion after reperfusion.<sup>8</sup> Some data suggest that patients with mean pulmonary artery pressure  $> 45$  mm Hg have perioperative mortality approaching 70%.<sup>40,41</sup> If a patient has a mean pulmonary artery pressure  $> 35$  mm Hg, it may take months of vasodilator therapy to reduce the pulmonary pressure to an acceptable level for transplant. Conditioning of the right ventricle to the extra work load is also important prior to transplant. If the right ventricle fails perioperatively, the increased central venous pressure is transmitted to the donated organ and causes congestion and, ultimately, failure. Diuretics and  $\beta$  blockers may be used in conjunction with vasodilators to reduce intravascular volume, hepatic congestion, and circulating catecholamine levels, which may all help to reduce the pulmonary pressure.<sup>8</sup> Inhaled epoprostenol can also be used to reduce mean pulmonary artery pressure and improve cardiac output during the perioperative care of liver transplant patients and in critically ill patients with acute decompensation.<sup>42</sup>

### Summary

Given the central role of the liver in organ homeostasis, liver disease and cirrhosis affect many organ systems. The increase in extracellular fluid associated with liver disease, ascites, and portal hypertension causes pulmonary edema and increases the work of breathing. Hepatic hydrothorax may occur in some patients. Liver disease is also associated with 2 unique pulmonary diseases: hepatopulmonary syndrome and portopulmonary hypertension. The differences are summarized in Table 2.

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