Pulmonary Dysfunction in Chronic Liver Disease

MICHAEL B. FALLON AND GARY A. ABRAMS

Pulmonary abnormalities and symptoms are common in patients with chronic liver disease. If questioned, up to 70% of cirrhotic patients undergoing evaluation for liver transplantation complain of dyspnea. In screening studies of patients with chronic liver disease, arterial blood gas abnormalities are found in as many as 45% and abnormal pulmonary function tests in as many as 50%. A variety of causes for pulmonary dysfunction in liver disease have been identified and include intrinsic cardiopulmonary disorders not specifically related to liver disease as well as unique problems associated with the presence of liver disease and/or portal hypertension (Table 1). The recognition that a subset of patients with hepatic disease develop significant pulmonary vascular alterations, either microvascular dilation leading to the hepatopulmonary syndrome (HPS) or arteriolar vasoconstriction leading to portopulmonary hypertension, indicates that unique changes in the pulmonary vasculature may occur in liver disease. These pulmonary vascular syndromes significantly impact morbidity and mortality in affected patients and influence candidacy for liver transplantation. This review will focus on the most common abnormality in the pulmonary vasculature in liver disease: HPS. It will address the differential diagnosis, clinical features, diagnostic evaluation, therapy, and pathogenesis of this increasingly well-recognized syndrome.

HEPATOPULMONARY SYNDROME

HPS is caused by intrapulmonary microvascular dilation that occurs in a subgroup of patients with liver disease and/or portal hypertension. It is defined by the presence of hepatic dysfunction or portal hypertension, a widened age-corrected alveolar-arterial oxygen gradient on room air with or without hypoxemia and intrapulmonary vasodilation. Although the association between pulmonary dysfunction and liver disease has been recognized for more than 100 years, the term “hepatopulmonary syndrome” was not used until 1977 as the concept that intrapulmonary vasodilation caused the gas exchange abnormalities in these patients emerged. At present, studies have shown that as many as 40% of cirrhotic patients have detectable intrapulmonary vasodilation that up to 8% to 15% will develop impaired oxygenation, which results in significant functional limitations. Early definitions emphasized that the exclusion of intrinsic cardiopulmonary disease or hepatic hydrothorax were required to make the diagnosis of HPS. However, it is now clear that HPS may occur in the setting of other cardiopulmonary abnormalities and contribute significantly to gas exchange abnormalities in these patients.

CLINICAL SIGNIFICANCE OF HPS

The importance of detecting HPS in patients with liver disease and/or portal hypertension derives from a number of clinical observations in patients who have both hepatic and pulmonary dysfunction. First, what is known about the natural history of HPS suggests that most patients develop progressive intrapulmonary vasodilation and worsening gas exchange over time and that spontaneous improvement is rare. Mortality is significant in this group and may be due in part to causes related to intrapulmonary vasodilation. In addition, many patients with moderate to severe HPS have comparatively well-preserved hepatic synthetic function (Child's-Pugh class A or B). Consequently, it is likely that over time HPS will significantly alter the quality of life and survival in affected patients. Second, liver transplantation has emerged as an effective therapy for HPS and over 80% of patients transplanted to date have had resolution or marked improvement in intrapulmonary vasodilation. However, significant postoperative morbidity and mortality occurs in these patients and may be anticipated and more effectively managed if the diagnosis is made before transplantation. In addition, moderate to severe portopulmonary hypertension, in contrast to HPS, significantly increases liver transplant-related mortality and is considered a contraindication. Thus, distinguishing these two entities is extremely important, especially if liver transplantation is being contemplated. Finally, the recognition that HPS may coexist with intrinsic cardiopulmonary disease emphasizes the need to be able to define the relative contribution of intrapulmonary vasodilation to gas exchange abnormalities in these patients. Specifically, transplant candidacy or the use of experimental therapies for HPS may be influenced by this information.

CLINICAL FEATURES

HPS is usually diagnosed in patients with concomitant cirrhosis and portal hypertension. However, no specific etiology of cirrhosis has been found to increase the risk of developing HPS, and it has been observed in noncirrhotic portal hypertension as well. The majority of noncirrhotic patients have some degree of liver injury that may include nodular regenerative hyperplasia, congenital hepatic fibrosis, or Budd-Chiari syndrome. These findings suggest that both liver injury and portal hypertension contribute to the development of intrapulmonary vasodilation in most cases. A single case of HPS has been noted in a patient with metastatic carcinoid, normal
liver function, and no evidence of portal hypertension.\textsuperscript{16} This observation raises the possibility that vasoactive substances, possibly released from the tumor, may have triggered intrapulmonary vasodilation in the absence of liver disease or portal hypertension.

Most patients with HPS complain of the insidious onset of dyspnea. Classically, an increase in dyspnea when standing (platypnea), caused by the predominance of vasodilation in the lung bases in HPS, has been described. However, no studies have assessed the frequency or usefulness of this observation in the diagnosis of HPS. In addition, poor physical conditioning, smoking, ascites, and/or intrinsic lung disease are often present in cirrhosis and may also cause dyspnea. Therefore, the diagnosis of HPS is often delayed and identified after severe arterial hypoxemia has ensued. In preliminary work, we have found that 72% of 112 cirrhotic patients undergoing evaluation for liver transplantation complained of dyspnea when specifically questioned.\textsuperscript{1} Most of these patients had normal arterial oxygenation and did not have HPS. However, in patients found to have HPS, dyspnea was present in over 95%. These findings suggest that dyspnea is a reasonably sensitive but poorly specific indicator of the presence of HPS. Using an index that quantifies dyspnea may improve the diagnostic usefulness of this common symptom in identifying patients with HPS.\textsuperscript{1}

Spider angiomata, digital clubbing, and cyanosis are clinical features commonly described in patients with HPS. However, these features have not been prospectively investigated as indicators of the presence of HPS. In our unpublished observations, spider angiomata were noted in 11 of 15 patients with HPS compared with 42 of 112 cirrhotic patients without HPS, providing a sensitivity and specificity of 73% and 63%, respectively. Clubbing was observed in 7 of 15 patients with HPS compared with only 2 of 112 cirrhotic patients without HPS, providing a sensitivity and specificity 47% and 98%, respectively. Cyanosis was observed in 5 of 15 HPS patients and in none of 112 cirrhotic patients without HPS, providing a sensitivity of 33% and a specificity of 100%. These findings suggest that the presence of spider angiomata is not a useful clinical marker for HPS, although clubbing and cyanosis, when present in cirrhosis, appear to be specific.

### Diagnostic Evaluation

The diagnosis of HPS rests on documenting the presence of arterial deoxygenation and intrapulmonary vasodilation. In patients in whom symptoms (dyspnea) or clinical findings (clubbing, cyanosis) raise the possibility of HPS, further diagnostic evaluation is warranted to assess gas exchange and intrapulmonary vasodilation.

#### Pulmonary Gas Exchange Abnormalities.

Arterial hypoxemia is arbitrarily defined when an arterial blood gas reveals an arterial pO\textsubscript{2} of less than 70 mm Hg. However, diagnostic criteria for HPS frequently include a widened alveolar-arterial oxygen gradient (>20 mm Hg) alone as sufficient to indicate the presence of gas exchange abnormalities.\textsuperscript{4} Although such a definition maximizes the potential for detecting “early” HPS, it is important to recognize that the alveolar-arterial oxygen gradient normally widens with age. In our cohort of 207 consecutive liver transplant candidates who underwent arterial blood gas screening, 66% had alveolar-arterial oxygen gradients greater than 15 mm Hg (unpublished observations). However, after correcting for age [normal = 10 + 0.43(age - 20)], alveolar-arterial oxygen gradients remained abnormal in only 35%. Therefore, a significant overestimation of HPS may be reported if age is not taken into consideration when evaluating the alveolar-arterial oxygen gradient. In addition, obtaining arterial blood gases in the standing position may enhance the detection of arterial deoxygenation in HPS, because vasodilation is often maximal in the lower lung fields and standing will increase intrapulmonary shunting through these regions. Studies of 100% oxygen shunt are also often used in patients with documented or suspected HPS. In this test, an arterial blood gas is performed with the patient breathing 100% oxygen. Accurate results require the use of a nose clip and a mouth piece to inspire the oxygen. Breathing 100% oxygen helps to distinguish “functional” shunting characterized by microvascular dilation in gas exchange regions and a normal increase in the pO\textsubscript{2} on 100% oxygen from “anatomic” shunting characterized by dilation outside of gas exchange regions and a significantly diminished increase in the pO\textsubscript{2} on 100% oxygen. Both functional and anatomic shunting may be seen in HPS. However, 100% oxygen shunt study results are reported as positive only if anatomical shunting is observed. Therefore, a “normal” 100% oxygen shunt study may be seen in HPS.

Pulse oximetry is a noninvasive modality that indirectly measures oxygen saturation and provides a screening test for hypoxemia. From a practical standpoint, it could provide a rapid and inexpensive screen for HPS in patients with symptoms or clinical findings. However, no prospective studies using pulse oximetry to detect hypoxemia in cirrhosis have been published. In preliminary studies, we have compared pulse oximetry with oxyhemoglobin saturation levels determined by arterial blood gases in 207 liver transplantation candidates.\textsuperscript{17} We found that pulse oximetry significantly overestimated the arterial oxyhemoglobin saturation, an effect not influenced by serum bilirubin levels. Using a pulse oximetry level of ≤97% provided a sensitivity of 96% and a specificity of 76% for detecting mild hypoxemia (pO\textsubscript{2} < 70 mm Hg) and would have limited the need for arterial blood gas testing to 32% of the cohort. It would have missed one hypoxemic patient (pO\textsubscript{2} = 69 mm Hg). Using a pulse oximetry value of ≤94% would have identified all patients with moderate to severe hypoxemia (pO\textsubscript{2} < 60 mm Hg) and would have limited arterial blood gas testing to only 9% of the total cohort. Of note, 8 of 13 patients with mild hypoxemia (pO\textsubscript{2} = 60-69 mm Hg) would have been missed using an oximetry value of 94%.

<table>
<thead>
<tr>
<th>Table 1. Causes of Pulmonary Abnormalities in Chronic Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic cardiopulmonary disease</strong></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td><strong>Specific to liver disease</strong></td>
</tr>
<tr>
<td>Associated with specific liver diseases</td>
</tr>
<tr>
<td>Panacinar emphysema: alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Fibrosing alveolitis, pulmonary granulomas: primary biliary cirrhosis</td>
</tr>
<tr>
<td>Fluid retention complicating portal hypertension</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Hepatic hydrothorax</td>
</tr>
<tr>
<td>Pulmonary Vascular abnormalities</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
</tr>
</tbody>
</table>
These findings indicate that pulse oximetry may be a useful screening test for hypoxemia and HPS in cirrhosis, but reveal that the threshold value for obtaining an arterial blood gas is higher than typically expected.

**Intrapulmonary Vasodilation.** Contrast echocardiography, lung perfusion scanning, and pulmonary angiography are the diagnostic modalities that have been used to detect intrapulmonary vasodilation. Two-dimensional transthoracic contrast echocardiography is the most commonly used technique. Typically, agitated saline, which creates microbubbles visible on echocardiography, is used as a contrast agent. A positive test for intrapulmonary vasodilation occurs when delayed visualization of intravenously administered microbubbles are observed in the left heart (3rd heartbeat after injection). Immediate visualization of injected contrast in the left heart indicates intracardiac shunting. Transthoracic echocardiography is more sensitive than lung perfusion scanning in detecting intrapulmonary vasodilation. Transesophageal contrast echocardiography may increase the sensitivity of detecting intrapulmonary vasodilation compared with transthoracic echocardiography because it improves visualization of the heart and may identify early HPS that is missed by transthoracic echocardiography. However, no study has proven it to be advantageous compared with transthoracic echocardiography in detecting intrapulmonary vasodilation in hypoxemic patients with HPS. Transesophageal echocardiography is also invasive and more expensive than transthoracic echocardiography and is not generally used as the initial screening test for HPS. Contrast echocardiography, using either technique, is positive in up to 40% of cirrhotic patients with normal arterial blood gases, suggesting that mild intrapulmonary vasodilation is insufficient to alter gas exchange and cause HPS is common in cirrhosis. The natural history of pulmonary vasodilation in these patients is unknown. Thus, a positive transthoracic echocardiography or transesophageal echocardiography in a hypoxemic patient with HPS is insufficient to establish the diagnosis of HPS, because either intrapulmonary vasodilation or the underlying pulmonary process could be responsible for gas exchange abnormalities.

Radionuclide lung perfusion scanning, using technetium-labeled macroaggregated albumin particles, is also commonly used to detect intrapulmonary shunting. A significant advantage of the radionuclide lung perfusion scan over contrast echocardiography is that a positive lung scan is specific for the presence of HPS even in the setting of coexistent intrinsic lung disease. Additionally, it can be used to quantify pulmonary abnormalities. However, radionuclide lung perfusion scanning is less sensitive than contrast echocardiography in detecting intrapulmonary vasodilation, and cannot evaluate cardiac function, intracardiac shunting or assess pulmonary artery pressure. Therefore, the radionuclide lung perfusion scan is not an optimal screening test for HPS.

Pulmonary angiography is an invasive and insensitive diagnostic modality for detecting intrapulmonary vasodilation in HPS and is not useful as a screening test. Two types of angiographic findings have been reported: type 1—a diffuse "spongy form" appearance of pulmonary vessels during the arterial phase and type 2—small discrete arteriovenous communications. However, many patients have normal angiograms in the setting of clinically significant HPS. Angiography may have a therapeutic role in the rare HPS patient with a poor response to 100% oxygen (arbitrarily defined as a pO2 <150 mm Hg) and anatomic shunting due to type 2 lesions that may be amenable to embolization.

A recent study has shown that high-resolution chest computerized tomography (CT) may be a less invasive radiologic method to detect dilated pulmonary vessels in the lung in HPS. The degree of dilatation observed on CT correlated with the severity of gas exchange abnormalities in these patients with HPS, suggesting that quantitation of intrapulmonary vasodilation was possible. Further studies are warranted to define if chest CT will be useful in assessing the presence and severity of HPS.

**DIAGNOSTIC ALGORITHM FOR PULMONARY DYSFUNCTION IN CIRRHOSIS**

Figure 1 presents one approach to evaluating pulmonary abnormalities in liver disease. Patients with dyspnea are targeted for screening because virtually all patients in our studies with hypoxemia complain of this symptom. Pulse oximetry, with a cutoff value of 97%, is used to screen for hypoxemia to detect patients with a pO2 less than 70 mm Hg. If the pulse oximetry is greater than 97%, an arterial blood gas is not obtained. A chest radiograph is ordered to exclude pleural effusions or cardiopulmonary disease as a cause for dyspnea. If the chest radiograph is normal, we assess if poor conditioning, smoking, ascites, or obesity may account for the symptoms. Patients are treated where possible and followed to define if changes in pulse oximetry or progressive dyspnea occur. Patients with progressive symptoms undergo contrast echocardiography to assess cardiac function, evaluate for intrapulmonary shunting, and estimate pulmonary artery systolic pressures and consider the possibility of portopulmonary hypertension. Portopulmonary hypertension is found in approximately 2% to 5% of patients with cirrhosis and is defined

![DIAGNOSTIC ALGORITHM FOR PULMONARY DYSFUNCTION IN CIRRHOSIS](image-url)
by the presence of a mean pulmonary artery pressure greater than 25 mm Hg and a normal pulmonary capillary wedge pressure. Estimated pulmonary artery systolic pressures greater than 50 mm Hg on echocardiography warrant right heart catheterization. If contrast echocardiography is positive for delayed intrapulmonary shunting or pulse oximetry declines, an arterial blood gas is obtained to determine if HPS is present.

If the pulse oximetry is ≤97% an arterial blood gas is obtained. If gas exchange abnormalities are detected (widened alveolar-arterial oxygen gradient or hypoxemia), then contrast echocardiography and pulmonary function tests are performed. In HPS, the chest radiograph is typically normal, but increased interstitial markings caused by vascular distention may be found and mistaken for interstitial fibrosis. In patients where contrast echocardiography shows intrapulmonary shunting and chest radiograph and pulmonary function tests are normal, the diagnosis of HPS is confirmed. If contrast echocardiography is positive but the chest radiograph or pulmonary function tests show a significant abnormality, then the diagnosis of HPS is uncertain because intrinsic cardiopulmonary disease rather than HPS could be responsible for hypoxemia. In this situation, we perform a radionuclide lung perfusion scan, which, if abnormal, indicates that HPS is contributing significantly to the decreased pO2. If contrast echocardiography is normal, then other causes for gas exchange abnormalities are evaluated.

### TREATMENT

No clearly effective medical therapy for HPS has been found (Table 2). Somatostatin, amiltrine, indomethacin, L-NNAME, and plasma exchange have all been tried unsuccessfully. Aspirin increased arterial oxygenation in 2 children with HPS and a case report and subsequent open-label trial using garlic also suggested a beneficial effect. In the later trial, garlic powder was administered for a minimum of 6 months, and 6 of 15 HPS patients had improvements greater than 10 mm Hg in the pO2, and 1 subject had resolution of hypoxemia (pO2: 46 mm Hg to 80 mm Hg) over a 1.5-year period. A randomized, placebo-controlled trial will be necessary to confirm these preliminary findings.

Three case reports have suggested that transjugular intrahepatic portosystemic shunt (TIPS) may improve gas exchange in HPS. However, short duration of follow-up in one and the presence of coexistent hepatic hydrothorax, also treated with TIPS in another, limit evaluation of the use of TIPS in these cases. A third report clearly showed an increase in arterial oxygenation of 20 mm Hg 6 months after TIPS placement. However, significant intrapulmonary shunting persisted based on radionuclide lung perfusion scanning and the cardiac output increased after TIPS. These findings suggest that improved oxygenation was not caused by reversal of intrapulmonary vasodilatation but was more likely caused by a redistribution of pulmonary blood flow to normal ventilation to perfusion ratio regions induced by an increase in cardiac output. This observation raises the possibility that TIPS may be detrimental in patients who cannot further increase cardiac output after stent placement. In addition, there is a reported observation that TIPS did not improve oxygenation in one patient with HPS and that HPS developed in two patients with functioning TIPS. Taken together, these findings support that TIPS should be considered an experimental treatment for HPS and its use confined to the setting of clinical trials so that efficacy may be judged.

Liver transplantation is the only proven therapy for HPS based on the total resolution or significant improvement in gas exchange postoperatively in more than 85% of reported patients. However, the length of time for arterial hypoxemia to normalize after transplantation varies and may be more than 1 year. In addition, mortality is increased after transplantation in HPS patients compared with subjects without HPS, and unique postoperative complications including pulmonary hypertension, cerebral embolic hemorrhages, and immediate postoperative deoxygenation requiring prolonged mechanical ventilation have been reported. Innovative approaches such as frequent body positioning or inhaled nitric oxide have been used to improve postoperative gas exchange. Further research focused on the perioperative medical management of HPS patients is needed to optimize survival.

### PATHOGENESIS

The pathogenesis of intrapulmonary vasodilatation in HPS is an area of active investigation. Studies in humans have implicated enhanced pulmonary production of nitric oxide in the development of vasodilation by assessing exhaled nitric oxide production. However, what triggers the increase in pulmonary nitric oxide, how it relates to the presence of portal

---

**Table 2. Medical Therapies for HPS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Medication</th>
<th>Patients</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Phenylephrine/isoproterenol.</td>
<td>2</td>
<td>No improvement</td>
<td>24</td>
</tr>
<tr>
<td>1987</td>
<td>Almitrine</td>
<td>5</td>
<td>1/5 Better</td>
<td>58</td>
</tr>
<tr>
<td>1990</td>
<td>Plasma exchange</td>
<td>6</td>
<td>No improvement</td>
<td>59</td>
</tr>
<tr>
<td>1991</td>
<td>PGF/indomethacin</td>
<td>1</td>
<td>Mild improvement</td>
<td>60</td>
</tr>
<tr>
<td>1992</td>
<td>Garlic</td>
<td>1</td>
<td>Improvement</td>
<td>29</td>
</tr>
<tr>
<td>1992</td>
<td>Cyclophosph./pred.</td>
<td>1</td>
<td>Improved after 1 yr</td>
<td>61</td>
</tr>
<tr>
<td>1992</td>
<td>Somatostatin analogue</td>
<td>3</td>
<td>No improvement</td>
<td>62</td>
</tr>
<tr>
<td>1993</td>
<td>Almitrine</td>
<td>6</td>
<td>Minimal change pO2</td>
<td>63</td>
</tr>
<tr>
<td>1993</td>
<td>Indomethacin</td>
<td>6</td>
<td>No improvement</td>
<td>64</td>
</tr>
<tr>
<td>1993</td>
<td>Somatostatin analogue</td>
<td>7</td>
<td>No improvement</td>
<td>10</td>
</tr>
<tr>
<td>1994</td>
<td>Somatostatin analogue</td>
<td>2</td>
<td>No improvement</td>
<td>65</td>
</tr>
<tr>
<td>1994</td>
<td>Methylene blue</td>
<td>1</td>
<td>Improved</td>
<td>66</td>
</tr>
<tr>
<td>1994</td>
<td>L-NAME</td>
<td>1</td>
<td>No improvement</td>
<td>67</td>
</tr>
<tr>
<td>1996</td>
<td>Aspirin</td>
<td>3</td>
<td>Improved</td>
<td>28</td>
</tr>
<tr>
<td>1998</td>
<td>Garlic</td>
<td>15</td>
<td>6/15 pO2 increase &gt;10 mm Hg</td>
<td>30</td>
</tr>
</tbody>
</table>
hypertension, the hyperdynamic circulation and the degree of liver injury, and why only 8% to 15% of cirrhotic patients are affected remain undefined. Reports of HPS in patients with prehepatic portal hypertension\textsuperscript{14} and in the presence of inferior vena cava obstruction without cirrhosis\textsuperscript{45} suggest that the presence of severe hepatic dysfunction is not a prerequisite for the development of intrapulmonary vasodilation. In addition, although most patients reported with HPS have a picture consistent with portal hypertension and a hyperdynamic circulatory state, reports that HPS has developed after portal decompression\textsuperscript{34} and the recognition that only a subset of all patients with cirrhosis and a hyperdynamic circulation develop HPS, suggest that other factors contribute to the onset of intrapulmonary vasodilation.

The development of an animal model of HPS (common bile duct ligation in the rat\textsuperscript{46}) has provided a system to investigate the mechanisms of intrapulmonary vasodilation. Early studies suggested that altered pulmonary eicosanoid production and an influx of intravascular macrophages triggered pulmonary vascular alterations.\textsuperscript{47,48} However, more recent work has shown that the endothelial form of nitric oxide synthase is increased in the pulmonary microcirculation and contributes to enhanced nitric oxide activity and vasodilation in affected animals.\textsuperscript{49,50} Changes in lung endothelial nitric oxide synthase and intrapulmonary vasodilation were found only in common bile duct ligated animals and not in animals with prehepatic portal hypertension alone, suggesting that a combination of liver injury and portal hypertension contribute to

**Fig 2.** Endothelin-1 effects in the normal and HPS pulmonary microvasculature. In the normal vasculature, endothelin-1 (ET-1), produced locally in endothelial cells, acts as a paracrine vasoconstrictor through activation of the endothelin A (ET\textsubscript{A}) receptor on smooth muscle cells. To a lesser extent, luminal release of ET-1 stimulates nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS) through activation of the endothelin B (ET\textsubscript{B}) receptor on endothelial cells. In HPS, ET-1 reaches the lung through the pulmonary circulation and acts as an endocrine vasodilator by stimulating the ET\textsubscript{B} receptor on the luminal surface of the endothelial cell and preferentially increasing NO production.
the pathogenesis of pulmonary vascular changes in this system. Subsequent studies focused on determining how hepatic injury contributes to intrapulmonary vasodilation, revealed that an unexpected potential mediator of HPS, endothelin-1 (classically known as a vasoconstrictor), is overproduced in the common bile duct ligated liver and found in the systemic circulation. Endothelin-1 production occurred in part in biliary epithelium in these animals, and plasma levels correlated with the increase in pulmonary endothelial nitric oxide levels and intrapulmonary vasodilation. Further work has shown that endothelin-1 can directly stimulate endothelial nitric oxide production in cultured pulmonary vascular endothelial cells and when infused chronically at low levels into animals with isolated portal hypertension can trigger pulmonary endothelial nitric oxide production, intrapulmonary vasodilation, and gas exchange abnormalities indicative of HPS. These studies support the hypothesis that certain forms of hepatic injury may trigger the production and release of hepatic endothelin-1, which contributes to the onset of intrapulmonary vasodilation.

Whether the observations in common bile duct–ligated animals are also found in human HPS and whether other factors, in addition to endothelin-1, contribute to vasodilation in this system are undefined. However, biliary endothelin-1 production and increased plasma endothelin-1 levels have been described in human cirrhosis. Figure 2 provides a working model of the potential effects of endothelin-1 in the pulmonary microcirculation after common bile duct ligation. Under normal conditions, endothelin-1 is a paracrine vasoconstrictor that regulates vascular tone. In this situation, endothelin-1 is released from vascular endothelial cells, predominately in an abluminal direction, where it targets the endothelin A receptor on vascular smooth muscle cells and initiates vasoconstriction. To a lesser degree, endothelin-1 released into the lumen targets the endothelin B receptor on endothelial cells and triggers nitric oxide production, which counterbalances vasoconstrictive effects. After common bile duct ligation, endothelin-1 reaches the pulmonary circulation from the liver and may preferentially interact with the endothelin B receptor on the luminal surface of the pulmonary vascular endothelium. In this setting, endothelin-1 may act as an endocrine vasodilator triggering enhanced endothelial nitric oxide production and intrapulmonary vasodilation.

CONCLUSION

HPS has become a well recognized complication of liver disease and portal hypertension over the last 15 years. Although symptoms and clinical features of HPS are non-specific, a diagnostic algorithm for detecting gas exchange abnormalities and intrapulmonary vasodilation is proposed. Because a widened alveolar-arterial oxygen gradient on arterial blood gas testing, in the setting of intrapulmonary vasodilation, is sufficient to make the diagnosis of HPS, it is important to correct the alveolar-arterial oxygen gradient for age to avoid unwarranted evaluation for HPS. Distinguishing portopulmonary hypertension from HPS and defining the contribution of HPS to gas exchange abnormalities in patients who also have intrinsic lung disease has become critical as liver transplantation has emerged as a successful treatment for the syndrome. Medical therapies for HPS are suboptimal, but may improve as the pathogenetic mechanisms of intrapulmonary vasodilation are elucidated. Use of TIPS for HPS remains experimental. Liver transplantation reverses HPS in more than 80% of patients, but unique postoperative complications may occur and should be anticipated when transplantation is undertaken.

REFERENCES


