Hepatopulmonary Syndrome

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Opinion statement

The hepatopulmonary syndrome (HPS) is an important and often under-recognized vascular complication of cirrhosis and portal hypertension characterized by pulmonary vascular dilatation, which results in hypoxemia. This syndrome is identified in as many as 20% of patients who are evaluated for orthotopic liver transplantation (OLT), and it has recently been found to increase mortality in affected patients, particularly when hypoxemia is severe. Currently, OLT is the only therapy established to reverse intrapulmonary vasodilatation, although postoperative mortality is increased in patients with severe hypoxemia. No randomized controlled trials of pharmacologic therapies have been undertaken, but supplemental oxygen improves oxygenation. Data derived from case reports, small studies, and experimental models suggest that pharmacologic therapies may be effective. In cirrhotic patients with HPS, particularly those with moderate hypoxemia (PaO2 < 60 mmHg), OLT should be considered prior to the development of severe deoxygenation. Supplemental oxygen should be given to patients with a PaO2 < 60 mmHg or those with exercise oxygen desaturation. For those patients with mild hypoxemia or those who are not OLT candidates, a trial of pharmacologic treatment may be considered.

Introduction

The hepatopulmonary syndrome (HPS) is defined by the presence of a widened age-corrected alveolar-arterial oxygen gradient on room air with or without hypoxemia and intrapulmonary vasodilatation in the setting of hepatic dysfunction and/or portal hypertension [1,2]. The association between pulmonary dysfunction and liver disease was first described by Fluckiger in 1884 [3], but it was not until 1977 that the term "hepatopulmonary syndrome" was first used [4]. The prevalence of HPS in patients with cirrhosis is 8% to 20%, although as many as 40% to 60% of patients have detectable intrapulmonary vasodilatation [1,5]. There appears to be no association between a specific etiology of chronic liver disease and the presence of HPS, and there is conflicting data on whether the presence or severity of HPS correlates with the degree of hepatic synthetic dysfunction and portal hypertension [5,6,7•,8–10]. Even though HPS develops most commonly in patients with cirrhosis and portal hypertension, HPS may also develop in patients with isolated portal hypertension (prehepatic portal hypertension, nodular regenerative hyperplasia, congenital hepatic fibrosis, and hepatic venous outflow obstruction [11–14]) and in patients with hepatic dysfunction without portal hypertension (acute and chronic hepatitis [15,16]). Therapeutic options may be different in HPS patients without cirrhosis.

The underlying structural alteration in HPS is dilatation of the precapillary and postcapillary pulmonary vasculature [17], which leads to impaired oxygenation of pulmonary venous blood [18,19]. The pathogenesis of these vascular changes remains an area of active investigation. Data from animal and human studies suggest increased intrapulmonary production of nitric oxide (NO) through increased expression and activity of endothelial nitric oxide synthase derived from a combination of enhanced hepatic production and release of endothelin-1 and a shear stress-mediated increase in pulmonary endothelial endothelin B receptor expression [20–22]. Additionally, in experimental HPS, macrophages accumulate in the lungs, in part related to tumor necrosis factor alfa (TNF-α) overproduction,

which is due to bacterial translocation across the gut [23]. These cells produce inducible nitric oxide synthase (iNOS, [24–26]) and heme oxygenase 1 (HO-1) [25,27] that contribute to vasodilatation through production of iNOS-derived NO and HO-1-derived carbon monoxide.

The natural history of HPS is incompletely characterized, but it appears that most patients develop progressive intrapulmonary vasodilatation and worsening gas exchange over time [28,29]. A recent prospective study demonstrated that the median survival among patients with HPS was significantly less compared with patients without HPS (10.6 months vs 40.8 months). This occurred even after adjusting for the severity of underlying liver disease and excluding patients who underwent orthotopic liver transplantation [OLT]. The causes of death in patients with HPS were mainly due to complications of hepatocellular dysfunction and portal hypertension and correlated with the severity of hypoxemia [7•]. Mortality after OLT also appears to be higher in patients with HPS compared with those without HPS, particularly in advanced disease (preoperative PaO2 of ≤50 mmHg) [30•]. These results support the idea that the presence of HPS may adversely affect survival in patients with cirrhosis and that the outcome of transplantation for HPS worsens as HPS progresses. These findings have been confirmed in a recent study showing that 5-year survival was significantly decreased in patients with HPS compared with controls matched for age and severity of liver disease and that mortality correlated with the degree of hypoxemia [29]. In addition, posttransplant mortality was highest among patients with severe hypoxemia (PaO2 of ≤50 mmHg).

A key to considering any therapeutic intervention in HPS is recognition of its presence. In patients with decompensated cirrhosis, a number of factors such as physical deconditioning and muscle wasting, ascites, hepatic hydrothorax, and intrinsic cardiopulmonary disease may cause dyspnea. Therefore, in patients with cirrhosis, particularly those being evaluated for OLT, screening or targeted testing for the presence of HPS should be undertaken. Simple and effective screening procedures including pulse oximetry to detect hypoxemia and contrast echocardiography to detect intrapulmonary vasodilatation are available [31•,32]. A similar approach for evaluation is also reasonable in patients established to have portal hypertension in the absence of cirrhosis, particularly if dyspnea is present.

Treatment

Diet and lifestyle

- There are no trials of dietary or lifestyle modifications in HPS. However, improvement in liver function may result in improvement in HPS. Therefore, avoidance or discontinuation of ethanol consumption and hepatotoxic medications, as well as treatment of underlying liver disease, should be considered.
- All cirrhotic patients, particularly those with HPS, should follow a sodium-restricted diet (2 g) in order to minimize fluid retention and volume overload.
- Although a single case report has speculated that smoking might limit intrapulmonary vasodilatation in HPS and transiently improve oxygenation, the established long-term adverse effects of cigarette use on cardiopulmonary function outweigh any theoretical benefits.
- Maintenance of aerobic/exercise capacity may be a challenge in HPS, particularly when severe. In patients with HPS receiving continuous long-term low-flow oxygen therapy, a low-level aerobic exercise regimen is reasonable as long as oxygen saturation can be maintained at over 90% during exertion.

Pharmacologic treatment

- The aims of pharmacologic therapy in HPS are to decrease intrapulmonary vasodilatation, improve arterial oxygenation, and relieve symptoms.
- No controlled studies with sufficient statistical power to fully assess efficacy for any pharmacologic treatment have been reported. Nonetheless, oxygen is in use and a number of drugs have been reported in small studies and case reports in humans or have been tested in experimental models.
- Therefore, the use of pharmacologic therapy is empiric and should be considered within the context of candidacy for OLT and potential adverse effects. Multicenter trials are needed to assess efficacy of drug therapy.

Oxygen

The rationale for oxygen therapy in HPS is the observation that the presence of HPS increases mortality in cirrhotic patients in proportion to the severity of hypoxemia [7•,29]. In addition, oxygen therapy appears to improve symptoms and increase exertional capabilities.

Standard dosage Two to 5 liters/min delivered by nasal cannula, titrated to maintain oxygen saturation of more than 90% at rest and exertion.

Contraindications None.

Complications Dryness and bleeding of nasal mucosa.

Special points Oxygen should be delivered with a humidified system to decrease nasal dryness. Air travel and travel to high altitudes significantly decreases ambient oxygen levels and may worsen hypoxemia and symptoms in patients with HPS. Special arrangements should be made to ensure that oxygen is available if such travel is necessary.

Cost effectiveness Unknown.

Empiric pharmacologic agents

- Noncardioselective beta adrenergic blockers (propranolol and nadolol) are frequently used in primary and secondary prophylaxis of gastroesophageal variceal bleeding in cirrhosis [33]. Data from animal studies suggest that the decrease in shear stress results from beta adrenergic blocker administration could improve experimental HPS [21,22,34]. The use of beta adrenergic blockers in patients who also have HPS who also have established indications for prophylaxis of gastroesophageal varices is a reasonable consideration.
- Antimicrobials are also frequently used as prophylaxis for spontaneous bacterial peritonitis in patients with cirrhosis [33]. One such agent, norfloxacin, has also been reported to improve human HPS in a single case and to decrease the severity of experimental HPS [23,35]. Antimicrobials result in selective intestinal decontamination and may improve HPS by inhibiting bacterial translocation across the gut. As above, the use of these agents in HPS patients with established indications for spontaneous bacterial peritonitis prophylaxis is a reasonable consideration.
- Allium sativum L. (garlic) powder has been studied as a treatment of HPS in the largest human pilot treatment trial undertaken to date. Fifteen patients were treated for a minimum of 6 months in an open-label uncontrolled fashion [36]. There was 40% of the patients who had objective improvement in arterial blood gases. No adverse effects were seen. The potential mechanisms for the beneficial effects of garlic powder in HPS are unknown.

Surgery

- The aim of surgical therapy for HPS is reversal of the underlying abnormalities associated with the development of this syndrome (cirrhosis and portal hypertension).
- Liver transplantation is the only established therapy for HPS, based on the observation that complete resolution or marked improvement in gas exchange occurs in more than 85% of patients [37].

Liver transplantation

Standard procedure Currently, patients with HPS and a PaO2 < 60 mmHg who are otherwise candidates for OLT, are eligible for 24 model for end-stage liver disease exception points in order to increase priority for transplantation. This exception is based on the observations that the presence of HPS increases mortality in cirrhosis [7•], that hypoxemia is generally progressive in [29] and that peri-operative mortality increases significantly in patients with a PaO2 < 50 mmHg [30•].

Contraindications Commonly accepted contraindications include significant comorbidities and active illicit substance or alcohol abuse.

Complications In patients with HPS, unusual postoperative complications such as pulmonary hypertension [38], cerebral embolism [39], and adult respiratory distress syndrome [40] have been described. Whether or not these events are consistently more common in patients without HPS remains to be established.

Special points In HPS patients with mild or moderate hypoxemia, postsurgical survival is similar to post-OLT patients without HPS [30•]. In patients with severe hypoxemia, mortality is increased and the length of time for normalization of gas exchange abnormalities may be prolonged [41].

Cost effectiveness Expensive, but no cost-effectiveness and/or economical impact of liver transplantation in patients with HPS has been performed.

Other treatments

TIPS

A series of case reports have described the use of portal decompression by placement of a transjugular intrahepatic portosystemic shunt (TIPS) in patients with HPS [42–47]. Although several reports have shown clinical improvement, others have not. In several cases, short duration of follow-up and co-existent ascites or hepatic hydrothorax limit the ability to draw useful conclusions. In addition, TIPS may have adverse effects on hepatic function and encephalopathy. Therefore, TIPS should be considered an experimental treatment and its use confined to the setting of clinical trials.

Inferior vena cava decompression

In patients with Budd-Chiari syndrome or suprahepatic inferior vena cava obstruction associated with portal hypertension and the development of HPS, several studies have shown that venous decompression can reverse HPS [13,14].

Coil embolization of vascular dilatation

A small subset of patients with HPS may have focal pulmonary arteriovenous connections visible by a chest computed tomography scan or pulmonary angiography, and many more have diffuse vasodilatation most prominent in the lower lung fields. A single report has suggested that coil embolization may have improved PaO2 in a post-OLT patient with a focal arteriovenous connection and prolonged hypoxemia [48]. Another report suggests that embolization of diffuse lower lobe dilatation may have been useful as a palliative therapy in a patient awaiting OLT [49]. The utility of this expensive and invasive modality is not established.

Emerging and experimental therapies

- Other agents including pentoxifylline (TNF-α inhibitor [50]), bosentan (mixed endothelin receptor antagonist [22]), and inhaled N(w)-nitro-L-arginine methyl ester (nitric oxide synthase inhibitor [51]) have been effective in experimental HPS or in human cases. These agents are promising as potential therapies in humans, but each has potential adverse effects and should be evaluated in clinical trials.

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