Therapy Insight: hepatopulmonary syndrome and orthotopic liver transplantation

Pastor, Catherine; Schiffer, Eduardo

How to cite

PASTOR, Catherine, SCHIFFER, Eduardo. Therapy Insight: hepatopulmonary syndrome and orthotopic liver transplantation. In: Nature clinical practice gastroenterology & hepatology, 2007, vol. 4, n° 11, p. 614–621. doi: 10.1038/ncpgasthep0965

This publication URL: https://archive-ouverte.unige.ch/unige:42514
Publication DOI: 10.1038/ncpgasthep0965

www.nature.com/clinicalpractice/gasthep

Therapy Insight: hepatopulmonary syndrome and orthotopic liver transplantation

Catherine M Pastor* and Eduardo Schiffer

SUMMARY

Hepatopulmonary syndrome (HPS)—a pulmonary complication observed in patients who have chronic liver disease and/or portal hypertension—is attributed to intrapulmonary vascular dilatation and induces severe hypoxemia. HPS is mainly detected when patients are included on the waiting list for orthotopic liver transplantation (OLT) and can be diagnosed by blood gas analysis, transthoracic contrast-enhanced echocardiography or body scan with ^{99m}Tc-labeled macroaggregated albumin perfusion. When the partial pressure of arterial oxygen (PaO_2) is ≥80 mmHg, it is unlikely that the patient has HPS. When the PaO_2 is <80 mmHg, imaging techniques should be used to confirm or exclude pulmonary vascular dilatation. When a diagnosis of HPS is confirmed, knowing the degree of hypoxemia is crucial for optimum patient management. Patients who have a PaO_2 ≥50 mmHg but <60 mmHg should be prioritized for OLT. This procedure is not indicated for patients with a PaO_2 between 60 mmHg and 80 mmHg, although follow-up every 3 months is recommended to detect any deterioration of the PaO_2. A PaO_2 of <50 mmHg might preclude OLT, because mortality and morbidity after OLT are greatly increased in these patients.

KEYWORDS hepatopulmonary syndrome, hypoxemia, liver transplantation

REVIEW CRITERIA

PubMed was searched in January 2007 and again in June 2007 for full papers published in English-language journals, using the following keywords alone and in combination: "orthotopic liver transplantation", "hypoxemia", and "hepatopulmonary syndrome".

CM Pastor is the Chief and E Schiffer is a Principal Investigator in the Laboratoire de Physiopathologie Hépatique et Imagerie Moléculaire, Hôpitaux Universitaires de Genève, 1205 Geneva, Switzerland.

Correspondence
*Laboratoire de Physiopathologie Hépatique et Imagerie Moléculaire, Hôpitaux Universitaires de Genève, Rue Micheli-du-Crest, 24, 1205 Geneva, Switzerland
catherine.pastor@hcuge.ch

Received 9 February 2007 **Accepted** 23 August 2007
www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep0965

INTRODUCTION

Twenty years ago, hepatopulmonary syndrome (HPS)—an impaired oxygenation attributable to a pulmonary vascular complication of liver disease—was an absolute contraindication to orthotopic liver transplantation (OLT), because of the high mortality associated with OLT in patients with hypoxemia. Subsequent reports of improvements in survival rates after OLT in some patients with HPS, the discovery that HPS can resolve after liver transplantation, and the lack of effective medical treatments for HPS (Box 1) have led to the inclusion of patients with HPS on the waiting list for OLT. Such improved access to OLT means that an increasing number of candidates with HPS are included on the waiting list. This Review provides information that is pertinent to the diagnosis of HPS and its management in OLT candidates.

DIAGNOSIS OF HEPATOPULMONARY SYNDROME

HPS is characterized by the combined presence of hypoxemia, intrapulmonary vascular dilatation and liver disease (Box 2).[1]

Hypoxemia

Hypoxemia (when breathing room air) is defined as a partial pressure of arterial oxygen (PaO_2) of either ≤70 mmHg or ≤80 mmHg.[2,3] Such impaired oxygenation can be classified as very severe (PaO_2 <50 mmHg), severe (PaO_2 ≥50 mmHg to <60 mmHg), or moderate (PaO_2 ≥60 mmHg to <80 mmHg).[1–4] The definition of hypoxemia in HPS can also include an alveolar–arterial pressure gradient for oxygen ($AaPO_2$) of ≥15 mmHg,[4] ≥20 mmHg,[5] or greater than or equal to the age-adjusted value ($[0.26 \times age] - 0.43$;[6] Box 2 and Box 3). The threshold values for impaired oxygenation defined by the European Respiratory Society are a PaO_2 ≤80 mmHg and an $AaPO_2$ ≥15 mmHg.[1,4]

Shortness of breath that might worsen on standing (platypnea) is a characteristic symptom of HPS and probably reflects the decreased

Box 1 Treatments for hepatopulmonary syndrome.

Various therapies for hepatopulmonary syndrome (HPS) have been tested in small and uncontrolled trials, but no therapy has consistently decreased the pulmonary vascular dilatation and improved the partial pressure of arterial oxygen (PaO_2).

Oxygen therapy
Oxygen therapy (0.5 l/min at rest and 2 l/min during exercise) prevents the deleterious consequences of hypoxemia, but few data exist on its efficacy and on patient compliance. Fukushima *et al*.[31] have shown that treatment for 1 year had a beneficial effect on liver function in two patients (their Child–Pugh score markedly improved).

Transjugular intrahepatic portosystemic shunt
The placement of a transjugular intrahepatic portosystemic shunt to relieve portal hypertension that might participate in the pathophysiology of HPS has failed to improve patient outcome.[32,33]

Cavoplasty and coil emboli
In some patients with Budd–Chiari syndrome, cavoplasty reversed HPS.[13] The injection of coil emboli that preferentially distribute to dilated vessels might also decrease hypoxemia by obstructing flow to these areas.[3]

Pentoxifylline
Pentoxifylline inhibits tumor necrosis factor-α overproduction and is effective in attenuating HPS in rats with ligated common bile ducts. The drug has not been tested in patients with HPS.

Nitric oxide inhibition
As excess production of nitric oxide (NO) is central to pulmonary vascular dilatation, therapies that reduce pulmonary NO levels or control its effects have been tested. By blocking the NO-induced activation of guanylate cyclase in smooth muscle cells, methylene blue has been shown to improve pulmonary vascular dilatation and hypoxemia.[34,35] Inhalation of the NO synthase inhibitor N^G-nitro-arginine methyl ester, by reducing intrapulmonary vascular dilatation, also improved the PaO_2 and decreased the associated dyspnea in some patients,[36] although such findings have not been replicated in other patients.[37] Almeida *et al*.[38] have disputed whether there is any benefit from inhibiting the NO–cyclic guanosine monophosphate pathway.

Box 2 Diagnostic criteria for hepatopulmonary syndrome.

There are three diagnostic criteria for hepatopulmonary syndrome:

- Chronic liver disease and/or portal hypertension;
- An $AaPO_2$ of ≥15 mmHg,[4] ≥20 mmHg,[5] or greater than or equal to the age-adjusted value[6 a] and/or PaO_2 ≤80 mmHg[4] or ≤70 mmHg[5];
- Pulmonary vascular dilatation at contrast-enhanced echocardiography[4] or ^{99m}Tc-MAA[4].

[a]Age-adjusted value: (0.26 × age) − 0.43. Abbreviations: $AaPO_2$, alveolar–arterial pressure gradient for oxygen; PaO_2, partial pressure of arterial oxygen; ^{99m}Tc-MAA, perfusion body scan with ^{99m}Technetium-labeled macroaggregated albumin.

Box 3 Calculating the alveolar arterial pressure gradient for oxygen.

The alveolar (A) arterial (a) pressure gradient for oxygen ($AaPO_2$) is calculated from the partial pressure of arterial oxygen (PaO_2), atmospheric pressure (AP) at sea level, water vapor pressure at 37 °C (47 mmHg), and the fraction of inspired oxygen (FIO_2) at room air (0.21) and assumes a ventilation/perfusion ratio = 0.8.

$$AaPO_2\ (mmHg) = P_AO_2 - PaO_2$$
$$P_AO_2 = [0.21 \times (AP - 47)] - (PaCO_2/0.8)$$

Abbreviations: P_AO_2, partial pressure of alveolar oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.

oxygenation of patients when they move from a supine to an upright position (orthodeoxia). Standing redistributes the pulmonary blood flow to the lower lung regions, increasing pulmonary shunt and ventilation/perfusion mismatch.[1] Orthodeoxia is diagnosed when the PaO_2 decreases by ≥5% or by ≥4 mmHg.[7] A less-invasive method than arterial puncture for the measurement of oxygenation might be to measure the decrease in oxygen saturation by pulse oximetry (SpO_2) when a patient moves from a supine to an upright position. The SpO_2, however, overestimates the arterial oxygen saturation (SaO_2) by 2% in most OLT candidates.[8] This overestimation is unrelated to the presence of liver disease or an increased serum concentration of total bilirubin.

In addition to pulmonary shunt and ventilation/perfusion mismatch,[7] impaired oxygen diffusion is also thought to contribute to hypoxemia, the diffusing capacity of carbon monoxide through the alveolocapillary membrane (DL_{CO}) being frequently decreased.[7,9,10] Low partial pressure of arterial carbon dioxide ($PaCO_2$) measurements are commonly found in patients with HPS

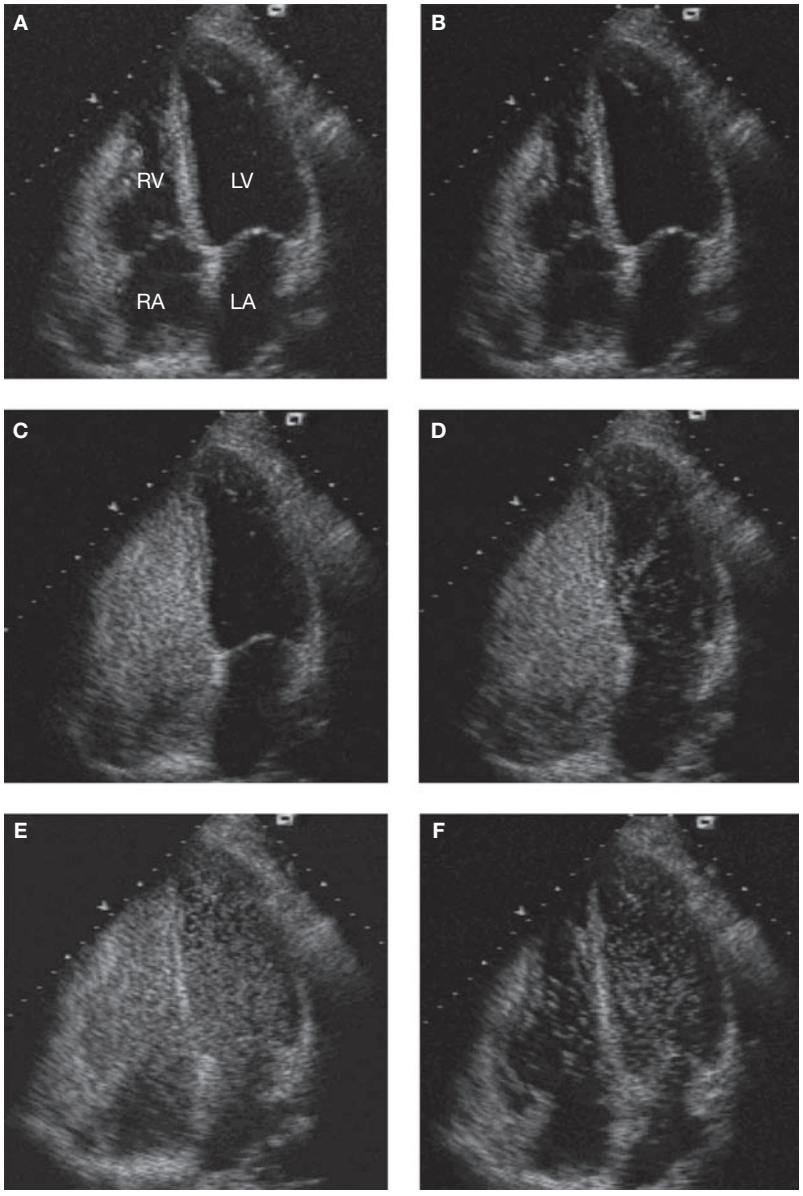

Figure 1 An illustration of a positive test result for hepatopulmonary syndrome by contrast-enhanced echocardiography. (**A**) A normal view of the four chambers of the heart in the absence of microbubbles. (**B**) One heartbeat after the injection of microbubbles, no microbubbles are present in the left cardiac chambers. (**C**) Four heartbeats after the injection of microbubbles, microbubbles are present in the right atrium and right ventricle. (**D**) Five heartbeats after the injection of microbubbles, microbubbles appear in the left cardiac chambers (left atrium and left ventricle). (**E**) Ten heartbeats after the injection of microbubbles, the left cardiac chambers are filled with microbubbles. (**F**) Twenty-two heartbeats after the injection of microbubbles, microbubbles progressively disappear. The timing of the appearance of microbubbles in the left side of the heart distinguishes between an intrapulmonary shunt and an intracardiac shunt (with intracardiac shunts, microbubbles appear in the left side of the heart within three heartbeats of their initial appearance in the right side of the heart). Permission obtained from Blackwell Munksgaard © Schiffer E *et al.* (2006) Hepatopulmonary syndrome increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. *Am J Transpl* **6:** 1430–1437. Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

as a result of increased alveolar ventilation. In the absence of pulmonary comorbidities, the results of other pulmonary function tests are within normal limits.[10]

Pulmonary vascular dilatation

In patients with HPS, vascular abnormalities include diffuse or localized dilated pulmonary capillaries and, less frequently, pleural and pulmonary arteriovenous vascular communications.[3] Two techniques are generally used to confirm intrapulmonary vascular dilatation: transthoracic contrast-enhanced echocardiography, and perfusion body scan with ^{99m}Technetium-labeled macroaggregated albumin (^{99m}Tc-MAA).

During transthoracic contrast-enhanced echocardiography, intravenous injection of microbubbles (diameter <90 μm) is used to visualize intrapulmonary shunts—defined by the appearance of microbubbles in the left side of the heart four to six beats after they first appear in the right side of the heart (Figure 1). The timing of the appearance of the microbubbles in the left side of the heart makes the distinction between intrapulmonary and intracardiac shunts; with intracardiac shunts, the microbubbles appear in the left side of the heart within three beats after they first appear in the right side of the heart. The echogenicity of the left atrium versus the right atrium has been quantified during contrast-enhanced echocardiography as follows[11]: grade 0, no microbubble; grade 1, few bubbles without change in echogenicity; grade 2, a moderate number of microbubbles without complete filling of the left atrium; grade 3, complete filling of the left atrium; grade 4, the same number of bubbles in both atria. Significant interobserver differences in echogenicity grade have been observed and no correlation has been shown between these echogenicity grades and arterial hypoxemia.

In normal individuals, a perfusion body scan with ^{99m}Tc-MAA visualizes macroaggregates that are almost completely trapped in the pulmonary circulation. In the presence of cardiac right-to-left shunts or intrapulmonary vascular dilatation, the uptake of ^{99m}Tc-MAA in other organs, such as the brain or the spleen, can be visualized.

Pulmonary shunts can be quantified by several techniques. In addition to the oxymetric shunt ratio that is estimated when patients are made to breath 100% O_2, the pulmonary shunt fraction can be estimated by calculating the

extra-pulmonary radioactivity to total body radioactivity ratio during the ^{99m}Tc-MAA body scan.[12] The pulmonary shunt fraction is increased when the radioactive pulmonary shunt fraction is >6%. Interestingly, the higher the pulmonary shunt fraction, the more severe the arterial hypoxemia.[12]

Liver disease

Regardless of its etiology, hepatic cirrhosis is the liver disease that most commonly leads to the development of HPS. HPS is also observed in patients who have acute or chronic liver diseases with or without portal hypertension. HPS has also been documented in patients with Budd–Chiari syndrome,[13] hypoxic hepatitis,[14] nodular regenerative hyperplasia, and portal vein thrombosis.[15] Pregnancy might also reveal the presence of HPS in asymptomatic cirrhotic patients.[16]

Careful evaluation

For some experts, the combined presence of liver disease, impaired arterial oxygenation while breathing room air and pulmonary vascular dilatation is so unique that it supports the diagnosis of HPS, even in the presence of other chronic cardiopulmonary diseases.[3] For other experts, however, a patient might be considered to have all three criteria incidentally and would not be diagnosed with HPS.[15,17] Hypoxemia can be unrelated to pulmonary vascular dilatation and originate instead from an alteration in lung mechanics caused by ascites, hydrothorax and increased intrathoracic blood volume.[17] Cirrhotic patients might have comorbid lung diseases such as chronic obstructive pulmonary disease or interstitial pulmonary disease, while other diseases such as α_1-antitrypsin deficiency affect both the lungs and liver. Diseases unrelated to HPS should be carefully eliminated whilst ensuring that HPS in the presence of these pulmonary diseases is not missed.

When oxygenation impairment is related to pulmonary vascular dilatation there is no consensus on the threshold criteria for hypoxemia.[18] More cases of HPS are diagnosed when the $AaPO_2$ criteria, rather than the PaO_2 criteria, are used to define hypoxemia. In addition, the prevalence of HPS is 15% when the threshold value is a PaO_2 <70 mmHg and 19% when the threshold value is PaO_2 <80 mmHg.[1,4,18] The various definitions of hypoxemia are confusing when it comes to identifying clearly the incidence of HPS, the appropriate timing for liver transplantation, and the outcome of patients who have HPS after OLT.[17] Moreover, to be able to compare results from different studies, it is important that all oxygenation parameters are measured while the patient is breathing room air and in the sitting position.

The use of imaging techniques to attribute pulmonary vascular dilatation to HPS can also be troublesome because the images generated can be difficult to interpret. Transthoracic contrast-enhanced echocardiography is a very sensitive method, but it is not very specific: 30% of cirrhotic patients have positive echocardiograms when their PaO_2 is in the normal range.[19,20] More-recent studies have shown that 80% of cirrhotic patients whose PaO_2 was ≥70 mmHg had positive transthoracic contrast-enhanced echocardiograms.[11,17] The very good quality of images obtained with transesophageal contrast-enhanced echocardiography means that positive tests for HPS are obtained even more frequently.[21]

Although the ^{99m}Tc-MAA body scan has a lower sensitivity than transthoracic contrast-enhanced echocardiography, its specificity is higher. In one study of 25 cirrhotic patients with HPS, the perfusion body scan was positive for 21 patients who had a PaO_2 <60 mmHg, whereas 4 other patients who had a PaO_2 in the range 68–90 mmHg had a normal scan.[12] This finding indicates that a perfusion body scan with ^{99m}Tc-MAA might be more specific than transthoracic contrast-enhanced echocardiography for the diagnosis of HPS. The technique of ^{99m}Tc-MAA body scanning, however, is not standardized between transplantation centers and, according to experts and most guidelines, the technique is not recommended for the initial screening of patients with suspected HPS.[1,22] In addition, a ^{99m}Tc-MAA body scan cannot differentiate between pulmonary and intracardiac shunts.[1,12]

PREVALENCE OF HEPATOPULMONARY SYNDROME

HPS is mainly detected when patients are included on the waiting list for OLT. In addition, a few patients with mild liver disease might develop HPS over time, in which case OLT is performed to treat the pulmonary disease.[1] No information is available on the number of patients with mild hepatic disease who undergo OLT because of the pulmonary complication, or on these patients' outcomes.

The prevalence of HPS among patients with chronic liver disease before they are considered

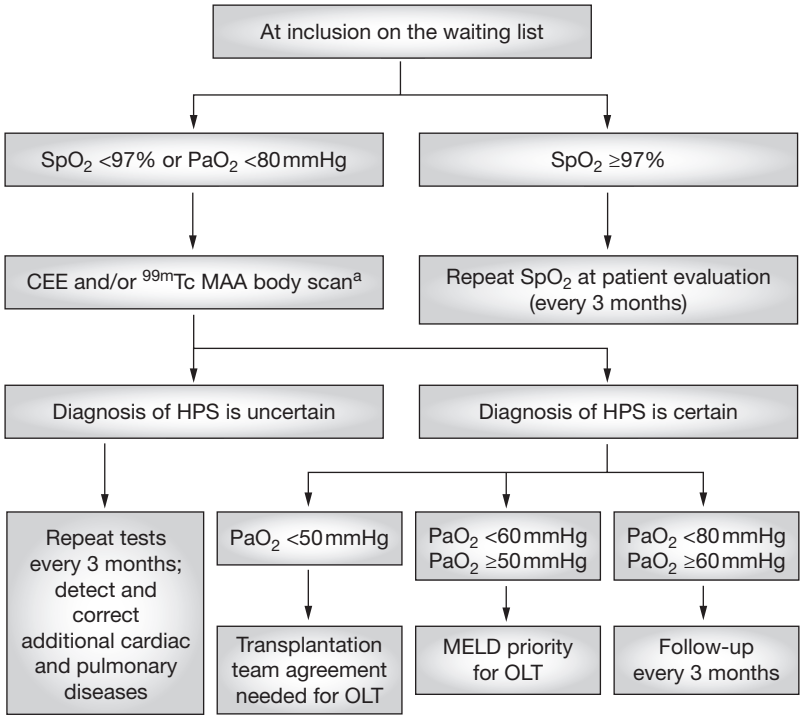

Figure 2 The algorithm used for the screening of patients on the waiting list for orthotopic liver transplantation and the therapeutic decisions made thereafter. [a]The choice between transthoracic contrast-enhanced echocardiography and perfusion body scan with ^{99m}Tc-MAA is an issue of debate. Abbreviations: CEE, contrast-enhanced echocardiography; HPS, hepatopulmonary syndrome; MELD, Model for End-Stage Liver Diseases; OLT, orthotopic liver transplantation; PaO_2, partial pressure of arterial oxygen; SpO_2, oxygen saturation measured by pulse oximetry; ^{99m}Tc-MAA, ^{99m}Technetium-labeled macroaggregated albumin.

for OLT is in the range 4–24%, depending on the criteria used to define hypoxemia.[18] In a study that included 111 cirrhotic patients, 24% had HPS.[23] Assessing the prevalence of HPS in OLT candidates is also difficult. In most studies, patients with severe hypoxemia were not included on the waiting list for OLT or patients with minimal pulmonary vascular dilatation were not diagnosed as having HPS. In a prospective study performed from 2001 to 2004, 10% of all candidates had HPS at the time of inclusion on the waiting list,[9] which is a similar result to that obtained in a retrospective study by Mohamed and colleagues.[24]

ORTHOTOPIC LIVER TRANSPLANTATION

Indications and liver allocation

All patients evaluated for OLT must be screened for hypoxemia. When a patient listed for OLT has a PaO_2 >80 mmHg or an SpO_2 ≥97%, it is unlikely that they have HPS (Figure 2). All patients who have an SpO_2 ≥97% will have a PaO_2 ≥65 mmHg, a threshold that does not prioritize these candidates for OLT.[8] An SpO_2 ≤94% can detect all patients who have a PaO_2 <60 mmHg, limiting the number of blood gas analyses that need to be performed, but would miss several patients who have mild hypoxemia.[8] Consequently, the information provided by the SpO_2 does not replace that provided by the analysis of arterial blood gases[3]: when the SpO_2 is ≤97%[2] or ≤96%[22] the PaO_2 should be measured. Moreover, limiting the threshold value for hypoxemia to 80 mmHg (rather than 70 mmHg) and conducting tests to detect whether the patient has pulmonary vascular dilatation, as indicated in Figure 2, might increase the number of HPS diagnoses made, but this has no consequence for OLT indication as long as the preoperative PaO_2 of these patients is ≥60 mmHg (as explained below). While on the waiting list, the SpO_2 is measured every 3 months, at the same time that the severity of the hepatic disease is evaluated, or when patients are hospitalized because of complications of the hepatic disease.

If a patient's PaO_2 is ≤80 mmHg while they are breathing room air and in a sitting position, a transthoracic contrast-enhanced echocardiography or a ^{99m}Tc-MAA body scan should be performed to confirm whether or not there is pulmonary vascular dilatation.[1,25] When the diagnosis of HPS is uncertain from the results of one imaging technique (contrast echocardiography or ^{99m}Tc-MAA body scan), the other technique should be performed (this can also be done while the patient is on the waiting list).

When the diagnosis of HPS is certain, knowing the degree of hypoxemia is crucial for optimum patient management. According to expert guidelines,[1,3] when the PaO_2 is ≥60 mmHg but <80 mmHg, HPS is considered moderate and there is no indication for OLT at this stage. As HPS deteriorates over time, the severity of oxygenation impairment should be assessed every 3 months; a 5 mmHg decrease in the PaO_2 per year has been documented in a small number of candidates.[5]

When the patient's PaO_2 is <50 mmHg (very severe HPS), mortality and morbidity after OLT is very high, and such a low PaO_2 might preclude surgical intervention. Most transplantation teams carefully evaluate each candidate and make decisions on a case-by-case basis. For

Table 1 One-year outcomes of patients with hepatopulmonary syndrome as reported in major studies.

Investigators	Study period	Study type	Number of HPS patients	Number of non-HPS patients	Main findings
Schiffer *et al*.[9]	2001–2004	Single center, prospective	9	72	No peroperative mortality Postoperative mortality within 6 months: 33% in HPS patients vs 9% in non-HPS patients All HPS patients had a PaO_2 ≥52 mmHg but ≤70 mmHg The postoperative PaO_2 improved in all patients who survived up to 6 months
Swanson *et al*.[5]	1985–2002	Single center, retrospective	61 (OLT performed in 24)	77 (OLT performed in 30)	OLT increased the 5-year survival in HPS patients The mean decline in PaO_2 on the OLT waiting list was 5.2 ± 2.3 mmHg/year No peroperative mortality Long-term survival after OLT was similar in HPS and non-HPS patients Long-term survival of HPS patients after OLT tended to be higher when the preoperative PaO_2 was >60 mmHg Resolution of HPS in all patients within 12 months
Krowka *et al*.[28]	1996–2001	Multicenter, retrospective	40	0	20% of HPS patients denied OLT (patients with a low PaO_2) Early postoperative mortality in HPS patients: 16% (all patients who died had a low preoperative PaO_2)
Arguedas *et al*.[29]	1996–2001	Dual center, prospective	24	0	27% of HPS patients died within 12 months HPS was more severe in patients who died HPS resolved in all patients who survived
Collisson *et al*.[30]	1993–1997	Single center, retrospective	6	0	No postoperative mortality Resolution of HPS in all patients
Taillé *et al*.[27]	1991–2000	Multicenter, retrospective	23	0	HPS patients had 9% postoperative mortality within 3 months and 26% within 12 months No correlation between preoperative PaO_2 and death Resolution of HPS in most patients after OLT The lower the preoperative PaO_2, the longer the time for recovery of a normal PaO_2

Abbreviations: HPS: hepatopulmonary syndrome; OLT, orthotopic liver transplantation; PaO_2, partial pressure of arterial oxygen.

those patients with such a low PaO_2, long-term O_2 therapy is necessary.

When the patient has a PaO_2 of ≥50 mmHg but <60 mmHg, the United Network for Organ Sharing, the organization that controls organ allocation in the US, applies a specific policy and these candidates are given high priority on the waiting list.[22,26] The priority for liver allocation is made on the basis of the Model for End-Stage Liver Disease (MELD) score—a severity score derived from total bilirubin and creatinine concentrations in serum as well as from the international normalized ratio for prothrombin time. Once the diagnosis of HPS is certain, patients with a PaO_2 in the range 56–59 mmHg receive 22 additional MELD points and those with a PaO_2 in the range 51–55 mmHg receive 24 additional MELD points.[22] When patients have a PaO_2 <50 mmHg, and the transplantation team agrees to the OLT, these patients receive 26 additional MELD points and then another 2 additional MELD points every 3 months.[22] While waiting for OLT, all patients with a PaO_2 <60 mmHg should be treated with long-term O_2 therapy.

Perioperative management

Although no peroperative deaths have been directly attributed to HPS in published studies (Table 1), the impaired oxygenation further deteriorates immediately following OLT because of volume overload and infections commonly observed after major surgery. Mechanical ventilation is often prolonged and the length of stay in the intensive care unit is extended.[15]

Outcomes

Mortality

The 5-year survival rate for patients who have liver disease and HPS before they are considered for OLT is lower than it is for cirrhotic patients who have no pulmonary complication.[5,23]

Moreover, the survival rate is more severely impaired when the PaO_2 is between 50 mmHg and 60 mmHg than it is when the PaO_2 is higher than 60 mmHg. By contrast, after OLT, the long-term survival is similar for patients who do and do not have HPS.[5] OLT is, therefore, indicated for patients with HPS, because HPS patients die sooner than non-HPS patients in the absence of OLT, and HPS does not markedly impair the long-term survival rate after OLT.

To determine the optimal time for OLT in patients with HPS, survival after OLT has been compared for HPS patients with a preoperative PaO_2 ≤60 mmHg versus a preoperative PaO_2 >60 mmHg.[5] The long-term survival rate tends to be higher when patients have a preoperative PaO_2 >60 mmHg than when they have a preoperative PaO_2 ≤60 mmHg. In patients with a preoperative PaO_2 ≤50 mmHg, the survival rate after OLT is either close to that for patients with a preoperative PaO_2 between 50 mmHg and 60 mmHg,[5] or is so bad that such hypoxemia might preclude surgery. Such rare cases are carefully discussed by all members of the transplantation team before a decision is made about whether or not to undertake OLT.

On the other hand, several studies have found that patients with HPS have a high postoperative mortality up to 12 months after OLT: 9% within 3 months and 26% within 12 months;[27] 16%[28] and 33%[9] within 6 months; and 27% within 12 months.[29] In the postoperative period, causes of death in patients with HPS are septic shock with multiple organ failure,[9] opportunistic pulmonary infection or abdominal sepsis,[5] biliary duct leakage or hepatic vessel thrombosis,[28] and multiple organ failure, ventilation-acquired pneumonia, cerebral hemorrhage or liver abscess.[27] It is not clear whether a low preoperative PaO_2 is associated with early postoperative mortality, because the results of the studies are conflicting.[5,9,27,29] The hepatic functions of the donor organ might also influence the postoperative mortality.

Reversibility of hepatopulmonary syndrome

In addition to providing patients with HPS with a favorable long-term survival rate, another reason to perform OLT in patients with HPS is the reversal of impaired oxygenation after OLT.[27] Hypoxemia can be corrected as early as 6–12 months after OLT,[9,30] although the time taken for hypoxemia to reverse can be longer in patients who have severe HPS. An increased recovery time is observed when the patient has a preoperative PaO_2 ≤52 mmHg, a preoperative $AaPO_2$ ≥66 mmHg, is >48 years of age, or if the liver disease is a result of alcohol abuse.[27] No study has investigated whether delayed recovery might parallel graft dysfunction. Finally, delayed resolution of HPS might explain the increases in mortality observed within 6 months following OLT.

CONCLUSIONS

The small number of patients with HPS in each transplantation center means that there are several issues that are difficult to investigate. As discussed, it is important to be able to diagnose HPS more accurately. In particular, there is still no consensus on what the preferred definition of impaired oxygenation should be, or on which imaging technique is best placed to provide evidence of pulmonary vascular dilatation leading to hypoxemia. Overestimation of the number of patients with HPS on the OLT waiting list has no consequence for OLT indication as long as their PaO_2 is ≥60 mmHg. More importantly, the preferential allocation of grafts to patients who have a PaO_2 ≥50 mmHg but <60 mmHg should be applied by all transplantation centers, and future studies need to confirm that this MELD score prioritization system is adequate. Having access to such information will help to make sure that those patients who have a MELD score prioritization for OLT owing to HPS do not receive an unfair advantage over other patients on the waiting list who do not have HPS.

KEY POINTS

- Hepatopulmonary syndrome is defined by hypoxemia, intrapulmonary vascular dilatation, and liver disease
- Careful evaluation of these three criteria is important
- When the diagnosis of hepatopulmonary syndrome is certain, the severity of the syndrome should be regularly assessed
- The priority for liver allocation in patients with hepatopulmonary syndrome and a partial pressure of arterial oxygen (PaO_2) in the range 50–60 mmHg should be confirmed
- The decision to perform liver transplantation in patients with hepatopulmonary syndrome and a PaO_2 below 50 mmHg is made on a case-by-case basis

References

1 Rodriguez-Roisin R *et al.* (2005) Highlights of the ERS Task Force on pulmonary-hepatic vascular disorders (PHD). *J Hepatol* **42:** 924–927
2 Palma DT and Fallon MB (2006) The hepatopulmonary syndrome. *J Hepatol* **45:** 617–625
3 Herve P *et al.* (2007) Pulmonary vascular abnormalities in cirrhosis. *Best Pract Res Clin Gastroenterol* **21:** 141–159
4 Rodriguez-Roisin R *et al.* (2004) Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J* **24:** 861–880
5 Swanson KL *et al.* (2005) Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology* **41:** 1122–1129
6 Gaines DI and Fallon MB (2004) Hepatopulmonary syndrome. *Liver Int* **24:** 397–401
7 Gomez FP *et al.* (2004) Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. *Hepatology* **40:** 660–666
8 Abrams GA *et al.* (2002) Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates. *Liver Transpl* **8:** 391–396
9 Schiffer E *et al.* (2006) Hepatopulmonary syndrome increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. *Am J Transpl* **6:** 1430–1437
10 Lima BL *et al.* (2004) Frequency, clinical characteristics, and respiratory parameters of hepatopulmonary syndrome. *Mayo Clin Proc* **79:** 42–48
11 Kim BJ *et al.* (2004) Characteristics and prevalence of intrapulmonary shunt detected by contrast echocardiography with harmonic imaging in liver transplant candidates. *Am J Cardiol* **94:** 525–528
12 Abrams GA *et al.* (1998) Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. *Gastroenterology* **114:** 305–310
13 De BK *et al.* (2002) Occurrence of hepatopulmonary syndrome in Budd-Chiari syndrome and the role of venous decompression. *Gastroenterology* **122:** 897–903
14 Fuhrmann V *et al.* (2006) Hepatopulmonary syndrome in patients with hypoxic hepatitis. *Gastroenterology* **131:** 69–75
15 Arguedas MR and Fallon MB (2005) Hepatopulmonary syndrome. *Clin Liver Dis* **9:** 733–746
16 Sammour RN *et al.* (2006) Pregnancy exacerbating hepatopulmonary syndrome. *Obstet Gynecol* **107:** 455–457
17 Mandell MS (2006) The diagnosis and treatment of hepatopulmonary syndrome. *Clin Liver Dis* **10:** 387–405
18 Schenk P *et al.* (2002) Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. *Gut* **51:** 853–859
19 Mimidis KP *et al.* (1998) Prevalence of intrapulmonary vascular dilatations in normoxaemic patients with early liver cirrhosis. *Scand J Gastroenterol* **33:** 988–992
20 Lange PA and Stoller JK (1995) The hepatopulmonary syndrome. *Ann Intern Med* **122:** 521–529
21 Aller R *et al.* (1999) Diagnosis and grading of intrapulmonary vascular dilatation in cirrhotic patients with contrast transesophageal echocardiography. *J Hepatol* **31:** 1044–1052
22 Fallon MB *et al.* (2006) Model for end-stage liver disease (MELD) exception for hepatopulmonary syndrome. *Liver Transpl* **12:** S105–S107
23 Schenk P *et al.* (2003) Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* **125:** 1042–1052
24 Mohamed R *et al.* (2002) Pulmonary gas exchange abnormalities in liver transplant candidates. *Liver Transpl* **8:** 802–808
25 Swanson KL (2007) Should we screen for hepatopulmonary syndrome in liver transplant candidates? *Liver Transpl* **13:** 183–184
26 United Network for Organ Sharing. Organ distribution: allocation of livers [http://www.unos.org/policiesandbylaws/policies.asp?ressources=true] (accessed 5 September 2007)
27 Taillé C *et al.* (2003) Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation* **75:** 1482–1489
28 Krowka MJ *et al.* (2004) Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl* **10:** 174–182
29 Arguedas MR *et al.* (2003) Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* **37:** 192–197
30 Collisson EA *et al.* (2002) Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl* **8:** 925–931
31 Fukushima KY *et al.* (2007) Two cases of hepatopulmonary syndrome with improved liver function following long-term oxygen therapy. *J Gastroenterol* **42:** 176–180
32 Martínez-Pallí G *et al.* (2005) Effect of transjugular intrahepatic portosystemic shunt on pulmonary gas exchange in patients with portal hypertension and hepatopulmonary syndrome. *World J Gastroenterol* **11:** 6858–6862
33 Lasch HM *et al.* (2001) Use of transjugular intrahepatic portosystemic shunt as a bridge to liver transplantation in a patient with severe hepatopulmonary syndrome. *Liver Transpl* **7:** 147–149
34 Rolla G *et al.* (1994) Methylene blue in the hepatopulmonary syndrome. *N Engl J Med* **331:** 1098
35 Schenk P *et al.* (2000) Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* **133:** 701–706
36 Brussino L *et al.* (2003) Effect on dyspnoea and hypoxaemia of inhaled N^G-nitro-L-arginine methyl ester in hepatopulmonary syndrome. *Lancet* **362:** 43–44
37 Gomez FP *et al.* (2006) Effects of nebulized N(G)-nitro-L-arginine methyl ester in patients with hepatopulmonary syndrome. *Hepatology* **43:** 1084–1091
38 Almeida JA *et al.* (2007) Deleterious effect of nitric oxide inhibition in chronic hepatopulmonary syndrome. *Eur J Gastroenterol Hepatol* **19:** 341–346

Competing interests
The authors declared no competing interests.