ERS TASK FORCE

Pulmonary–Hepatic vascular Disorders (PHD)

R. Rodríguez-Roisin*, M.J. Krowka#, Ph. Hervé†, M.B. Fallon‡, on behalf of the ERS Task Force Pulmonary–Hepatic Vascular Disorders (PHD) Scientific Committee


CONTENTS

Background ........................................... 862
Hepatopulmonary syndrome ......................... 862
Definition ........................................... 862
Staging of severity .................................. 863
Natural history and outcome ........................ 868
Pathophysiology ...................................... 863
Pathology ............................................ 864
Pathogenesis ......................................... 864
Clinical diagnosis .................................... 864
Symptoms and physical examination ............... 864
Lung function tests .................................. 865
Haemodynamics ...................................... 865
Biochemistry and noninvasive exhaled biomarkers ........................................... 865
Lung imaging ........................................ 866
Contrast-enhanced echocardiography .............. 866
Transoesophageal echocardiography ............. 866
Perfusion lung scanning ............................. 866
Pulmonary angiography .............................. 866
Thoracic computed tomographic scanning ....... 866
Screening ............................................ 867
Management .......................................... 867
Pharmacological treatment ........................ 867
Nonpharmacological treatment .................... 867
Long-term oxygen therapy .......................... 867
Transjugular intrahepatic portosystemic shunt .... 867
CavoPlasty .......................................... 867
Embolisation ........................................ 867
Orthotopic liver transplantation ................... 868
Task Force recommendations ........................ 868
Research prospects .................................. 868
Portopulmonary hypertension ........................ 868
Definition ........................................... 868
Staging of severity .................................. 868
Natural history and outcome ........................ 868
Pathology ............................................ 869
Pathophysiology and pathogenesis ............... 869
Vasoproliferation ..................................... 869
Genetics ............................................. 869
Inflammation ........................................ 869
Neurohormones ...................................... 869
Clinical diagnosis and screening ................... 870
Symptoms and physical examination ............... 870
Transthoracic Doppler echocardiography .......... 870
Haemodynamics ...................................... 870
Acute vasodilator testing ........................... 870
Pulmonary haemodynamic subsets .................. 870
Management .......................................... 871
Pharmacological treatment ........................ 871
Nonspecific therapy .................................. 871
Diuretics ............................................ 871
Cardiac glycosides .................................. 871
Vasodilator therapy .................................. 871
Calcium channel blockers ........................... 871
Nitrates .............................................. 871
Continuous i.v. epoprostenol infusion ............. 871
Other prostacyclin analogues (treprostinil, iloprost and beraprost) ......................... 872
Endothelin receptor antagonists (bosentan) ....... 872
Nonpharmacological treatment .................... 872
Long-term oxygen therapy .......................... 872
Transjugular intrahepatic portosystemic shunt .... 872
Orthotopic liver transplantation ................... 872
Task Force recommendations ........................ 873
Research prospects .................................. 873

*Service of Pneumology, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain. †Mayo Clinic, Rochester, MN, and ‡University of Alabama, Birmingham, AL, USA. ††Surgical Centre Lannelongue, Le Plessis Robinson, France.

Correspondence: R. Rodríguez-Roisin, Servei de Pneumologia, Hospital Clinic, Villarroel 170, 08036-Barcelona, Spain. Fax: 34 932275404. E-mail: rororo@clinic.ub.es
"The tantalizing problem of the connective link in cirrhotic patients between oxygen unsaturation and possible arteriovenous shunting in the lungs remains unsolved, and any relation between arterial unsaturation and pulmonary vasodilation remains obscure."

BERTHELOT et al. [1]

"Portal venous hypertension coexisted with pulmonary arterial hypertension. These observations suggested two questions: What was the origin of the pulmonary vascular changes? Was there a possible relationship between these pulmonary vascular lesions and abnormalities in the portal venous system?"

NAEYE [2]

Background

Owing to the success of orthotopic liver transplantation (OLT), there has been increasing recognition of the importance of pulmonary vascular complications of hepatic disease states. Such vascular complications, namely hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN), are commonly present as dyspnoea and are not always easily distinguished from nonpulmonary symptoms caused by manifestations of advanced liver disease (such as anaemia, ascites and muscle wasting). More importantly, since the late 1980s, experience has taught that such complications influence survival and candidacy for OLT. Currently, OLT is the only effective treatment for improving outcome in patients with HPS, a life-threatening condition whose prevalence can approach 20% in some series of patients awaiting OLT. PPHTN, pulmonary arterial hypertension (PAH) occurring in the setting of liver disorders, another systemic and, less commonly, pleural and pulmonary arteriovenous communications. Although HPS and PPHTN encompass a clinical triad characterised by arterial deoxygenation, IPVD and liver disease. Although HPS is predominantly seen in middle-aged patients without sex difference, it can also occur in children [7, 8].

The most common hepatic disorder leading to HPS is liver cirrhosis, irrespective of aetiology [3–6], although HPS has also been observed in many other chronic, and even acute, hepatic conditions [3–13]. The pulmonary gas exchange abnormality is characterised by arterial deoxygenation that may be mild, moderate or severe [3, 5, 13–16]. There is an increased alveolar–arterial oxygen tension difference (PA–aO2). In contrast, arterial carbon dioxide retention (arterial carbon dioxide tension (PaCO2) >6.0 kPa (45 mmHg)) is never present [3–5, 13, 14]. On the contrary, since patients with advanced liver disease usually hypertentilate, hypocapnia (PaCO2 <4.7 kPa (<35 mmHg)) and respiratory alkalosis are common. Calculation of PA–aCO2 is one of the most sensitive approaches for the detection of early arterial deoxygenation [3, 5], since PA–aO2 can increase before arterial oxygen tension (PaO2) itself becomes abnormally low. At sea level and while breathing room air, a resting PA–aO2 of ≥2.0 kPa (≥15 mmHg) can be considered abnormal [15, 16], but, for patients aged >64 yrs, a PA–aO2 of ≥2.7 kPa (≥20 mmHg) can be recommended [14]. However, an increased PA–aO2 alone is not sufficient to confirm the existence of HPS [13]. IPVD must also be present and is considered to exist when pulmonary capillary diameter ranges 15–60 μm, being the major structural derangement in HPS [1]. Contrast-enhanced echocardiography (CEE) and perfusion lung scanning using technetium-99m-labelled macroaggregated albumin (99mTcMAA) are the two most well-accepted approaches for assessing IPVD [3–6]. Although some imaging techniques, such as pulmonary angiography and conventional or high-resolution computed tomography (HRCT) scanning, may also provide information about the shape, appearance and distribution of pulmonary vessels [17], their diagnostic accuracy has not yet been sufficiently well established. This

Table 1. – Diagnostic criteria for hepatopulmonary syndrome

<table>
<thead>
<tr>
<th>Liver disease</th>
<th>PA–aO2, atm–mmHg ≥15 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive CEE</td>
<td></td>
</tr>
<tr>
<td>PA–aO2: alveolar–arterial oxygen tension difference; CEE: contrast-enhanced echocardiography; **: abbreviated formula: PA–aO2 = F50PaO2~PaTH2O–PaCO2/R–PaO2, where PAO2 is alveolar oxygen tension, PaO2 arterial oxygen tension, F50PaO2 inspiratory oxygen fraction, Pam atmospheric pressure, PH2O water vapour partial pressure and RER exchange respiratory ratio (assumed to be 0.8) [14]. For patients aged &gt;64 yrs, a cut-off value for PA–aO2 of ≥20 mmHg can be recommended [14]. 1 mmHg = 0.133 kPa.</td>
<td></td>
</tr>
</tbody>
</table>
combination of arterial deoxygenation, IPVD and liver disease is so unique that it supports the diagnosis of HPS even in the presence of associated chronic cardiopulmonary diseases, such as chronic obstructive pulmonary disease (COPD), bronchial asthma or idiopathic pulmonary fibrosis, which can also cause (or aggravate) arterial gas exchange abnormalities, including hypoxaemia with or without hypercapnia [18].

**Staging of severity**

Staging of the severity of HPS is important because severity influences survival [19–22], and is useful in determining the timing and risks of OLT [5, 21–23]. A classification of the severity of HPS based on oxygenation abnormalities in four stages is proposed (table 2) [3–6, 13, 14]. More severe HPS causes greater clinical symptoms [13, 14], probably affects quality of life and signals the need to consider specific therapeutic interventions (i.e. long-term oxygen therapy and embolotherapy) to offset the deleterious effects of tissue hypoxia [24]. Assessment of the severity of IPVD is difficult by means of CEE because this technique does not provide a quantitative evaluation. Extrapulmonary uptake of 99mTcMAA can be quantified, but the procedure has not been sufficiently standardised beyond a few centres. The sensitivity of both approaches for the detection of anatomical pulmonary arteriovenous communications or diffuse or localised vascular dilatations alone is similar [25].

**Natural history and outcome**

Definite statements concerning the natural history of HPS have been limited by two factors. First, few HPS patients are followed in any single centre. A multicentric database for OLT candidates described 20% of HPS patients who were denied this surgical procedure due to extrapulmonary comorbid conditions, with follow-up not reported [26]. In the largest single-centre-based series to date, in HPS patients (Pao2 cut-off of <9.3 kPa (<70 mmHg)) who did not undergo OLT until 1988 [27], median survival was 41 months following diagnosis of HPS, and the longest survivor not having undergone transplantation lived >10 yrs. Mortality is usually due to complications of hepatic disease, as opposed to a primary respiratory event. A more recent prospective study demonstrated a shorter median survival (~11 months) with similar causes of death [23].

Secondly, OLT interrupts or modulates the natural course of HPS. Not only has OLT become the treatment of choice for HPS in many centres, but successful OLT has also resulted in complete resolution of HPS in the majority of survivors of the early post-surgical period [6, 27]. Preliminary data suggests, however, slow recovery of arterial hypoxaemia, but long-term survival following OLT in some HPS patients [6, 27]. Sporadic cases of PPHTN after OLT-induced HPS resolution have been reported [6, 28, 29].

In patients with portal hypertension, the natural history of HPS is not sufficiently understood, since its precise pathogenic mechanisms remain unsettled [6]. Moreover, the prevalence of HPS varies widely between pulmonary and liver centres. In patients with cirrhosis, the mean prevalence of subclinical HPS is 15% [3, 30], depending on the cut-off values of Pao2 used to define the entity [14] and/or means of calculation of P-A-aO2 to diagnose HPS (table 1) [3, 5, 13, 14]. In patients with unusual hepatic diseases, the prevalence of HPS is unknown, although it may be anticipated to be extremely low, given the lower incidence of these hepatic conditions compared with that of liver cirrhosis. In chronic viral hepatitis with or without cirrhosis, the prevalence of HPS is ~10% [9]. The prevalence of HPS in OLT candidates (18%) is elevated [13] and has been reported to be as high as 28% in Budd-Chiari syndrome [11]. Rare cases of HPS in combination with PPHTN before OLT have also been documented (Ph. Hervé and R. Rodríguez-Roisin, personal communications) [31]. The behaviour of Pao2 in advanced cirrhotic patients without HPS remains unknown [32], as does the outcome of HPS with coexisting cardiopulmonary comorbid conditions.

**Pathophysiology**

The major primary structural disturbance in HPS is dilatation of the pulmonary pre-capillary and post-capillary vessels that allows mixed venous blood to pass either very quickly or even directly into the pulmonary veins [3–6]. Absent or reduced pulmonary vascular tone with impaired hypoxic vasoconstriction may also occur [33, 34]. There are three well-known intrapulmonary determinants of arterial deoxygenation, namely alveolar ventilation–perfusion (V' A/ Q') imbalance, increased intrapulmonary shunt (i.e. non-ventilated or zero V' A/Q' units) and diffusion impairment to oxygen, essentially reflecting a diffusion-perfusion defect [35], and all may be present in advanced HPS [3–6, 33, 34, 36–40]. By contrast, the role of direct portopulmonary venous communications to arterial deoxygenation is negligible [3]. However, the relative contributions of the former three determinants appear to vary. Although it is agreed that V' A/Q' mismatching is the pivotal mechanism for arterial deoxygenation since it fits well with the presence of lung regions in which alveoli are normally ventilated but over-perfused, the relevance of the other two factors remains somewhat speculative [41]. An added conceptual difficulty is the reconciliation of the presence of elevated levels of increased intrapulmonary shunt (i.e. ≥20% of cardiac output (Q')) despite the active Pao2 response to 100% oxygen (i.e. Pao2 >40 kPa (>300 mmHg)) observed in many patients. Diffusion impairment to oxygen, as shown by a greater predicted (according to the multiple inert gas elimination technique) [42] than measured Pao2 [40, 41] while breathing room air, is also present in advanced HPS, a mechanism also consistent, in part, with the common finding of a low diffusing capacity of the lung for carbon monoxide (DLCO). It is of note that the presence of an elevated Q' facilitates, in part, this favourable Pao2 response to breathing 100% oxygen, other things being equal. Presumably, DLCO is reduced because the distance between the alveoli and the red cells in the central stream of the dilated pulmonary microvessels is too great for complete equilibration of carbon monoxide with haemoglobin. Although capillary blood volume is likely to be increased, diffusion impairment to
oxygen may be aggravated, in part, by a high \( Q' \), resulting in a shorter transit time of the red blood cell and, hence, contributing to the development of a diffusion–perfusion imbalance [35]. Nevertheless, this pulmonary gas exchange status is still consistent with the coexistence of the three mechanisms of hypoxaemia mentioned previously, their individual roles varying according to HPS severity (table 2) [3]. Thus, early HPS stages with normoxaemia \((P_{a,O_2} \geq 10.6 \text{ kPa} \ (\geq 80 \text{ mmHg}))\) and increased \(P_a-A_{a,O_2}\) (\(\geq 2.0 \text{ kPa} \ (\geq 15 \text{ mmHg}))\) alone or with moderate levels of hypoxaemia \((P_{a,O_2} \geq 8.0-10.6 \text{ kPa} \ (\geq 60-80 \text{ mmHg}))\) may be associated with mild \(V'/A'Q'\) inequality and modest intrapulmonary shunt (<10% of \( Q' \)), but rarely with diffusion impairment, whereas, in severe HPS \((P_{a,O_2} \geq 6.7-8.0 \text{ kPa} \ (\geq 50-60 \text{ mmHg}))\), and also in the most severe hypoxaemic stages \((P_{a,O_2} < 6.7 \text{ kPa} \ (<50 \text{ mmHg}))\), all three determinants of arterial deoxygenation can coexist. Hyperventilation, by increasing alveolar oxygen tension, and high \( Q' \), by raising mixed venous oxygen tension, may diminish the reduction in \(P_{a,O_2}\) [43]. The influence of coexisting chronic lung disorders, such as COPD or idiopathic pulmonary fibrosis, of relatively common occurrence in HPS patients, on arterial desaturation remains unsettled [18].

Pathology

Several pathological abnormalities have been documented in the pulmonary vasculature of cirrhotic patients with HPS [44]. These abnormalities include diffuse or localised dilatation of alveolar pre-capillary and post-capillary vessels, pleural (surface) and pulmonary anatomical artery-to-vein communications and portopulmonary venous anastomoses [1]. However, the few detailed pathological studies were carried out before the standardisation of a universal definition of HPS and prior to the availability of imaging modalities used to detect IPVD. Nonetheless, dilatation of capillary vessels in alveolar regions [1, 45] is a central prerequisite and the principal pathophysiological hallmark of arterial deoxygenation in both human and experimental HPS [46, 47]. In addition, in animal models, intravascular accumulation of macrophages in the pulmonary microcirculation and increased numbers of pulmonary capillaries have been shown, suggesting a vasogenic response [47, 48]. Whether similar changes occur in humans and are important pathogenically has not been resolved.

Pathogenesis

Most clinical cases have been reported in the setting of liver cirrhosis and portal hypertension, although controversy exists over whether the frequency and severity of HPS correlate with the dynamic of hepatic synthetic dysfunction and portal hyperdynamic circulation [6, 19, 25, 49]. The evidence that HPS occurs in both extrahepatic portal venous obstruction [50] and hepatic venous outflow obstruction without cirrhosis (extrinsic liver disease) [51] shows that severe hepatic dysfunction and cirrhosis are not absolutely required for HPS to develop. In addition, the finding that HPS can occur in the setting of acute [52] and chronic noncirrhotic hepatitis [7, 9] demonstrates that portal hypertension may not be present in all cases. Finally, a clinical syndrome similar to HPS is observed in congenital disorders without liver injury in which either hepatic venous blood flow does not reach the lung [53] or portal venous blood reaches the inferior vena cava without passing through the liver [54], supporting the theory that factors either produced or metabolised in the liver can modulate the pulmonary vasculature.

Enhanced pulmonary production of nitric oxide (NO) has been implicated in the development of IPVD in cirrhotic patients with HPS [55–59]. Exhaled NO levels are increased in HPS patients and normalise after OLT [56–58], as HPS resolves or is minimised. However, the mechanism of increased endogenous NO production and its relationship to the presence of portal hypertension, the hyperdynamic circulation and the degree of liver injury, remains uncertain. In addition, whether other mediators might contribute to IPVD has not yet been studied.

Experimentally, chronic common bile duct ligation (CBDL) is the only identified rat model of HPS [60, 61], whereas partial portal vein ligation has been used as a control intervention in which both portal hypertension and a hyperdynamic circulation develop without hepatic injury and subsequent HPS [61]. Early studies focused on the vasoconstrictor role of eicosanoids and the increased numbers of intravascular macrophage-like cells [48, 60, 62]. Subsequent work identified increased pulmonary vascular endothelial (eNOS) and inducible (iNOS) in macrophages NO synthase expression and activity as the origin of the increase in pulmonary NO production [63–68]. Intravenous N-ω-nitro-l-arginine methyl ester (L-NAME) improved hypoxaemia in CBDL rats, thereby supporting the pathogenic role of excessive pulmonary NO release in HPS [69]. Further studies have demonstrated that increased hepatic production and release of low levels of endothelin (ET)-1 is one mechanism for triggering an increase in pulmonary eNOS levels and vasodilatation after CBDL [64, 65]. This is associated with a selective increase in pulmonary vascular ET₁ receptor expression in cirrhosis and portal hypertension, an event that appears to enhance ET₁ receptor-mediated ET-1-induced NO production [66]. The roles of other enzymes and mediators investigated have recently refocused interest on the accumulation of intravascular macrophages. An increase in pulmonary iNOS expression [63] has been observed in CBDL [67], predominantly in intravascular macrophage-like cells, and was felt to be an important source of NO. Furthermore, treatment of CBDL with norfloxacin decreased macrophage accumulation and normalised iNOS but not eNOS levels [68], hence, supporting a role for bacterial translocation in pulmonary macrophage accumulation and its contribution to IPVD. Pentoxifylline, an inhibitor of tumour necrosis factor (TNF)-α production in macrophages [70], also prevented HPS in the rat model [71], thereby supporting its pathogenic role. Recent work suggests that ET-1 and TNF-α can both interact in the development of experimental HPS [72]. More recently, the findings of increased haem oxygenase-1 expression and carbon monoxide production in CBDL support their role in the progression of IPVD [73, 74]. Figure 1 highlights some of these mechanisms.

Clinical diagnosis

Symptoms and physical examination. Shortness of breath is a common symptom when arterial hypoxaemia associated with HPS develops in the setting of chronic liver disease. The development of HPS does not appear to correlate uniformly with the severity of underlying liver disease, as characterised by the Child-Pugh score [19, 49]. Characteristic but not pathognomic of HPS, however, is the typical complaint of platypnoea (increased dyspnoea from the supine to upright position) [5] and the associated finding of orthodeoxia (decrease in \(P_{a,O_2} \geq 5\%\) or 3.0 mmHg from the supine to upright position) [36, 75], whose mechanism has been recently
clarified [75]. Early exertional dyspnoea may evolve into dyspnoea at rest as hypoxaemia progresses. Fatigue resulting from anaemia and hepatic dysfunction may be difficult to distinguish from HPS-induced hypoxaemia. Spider naevi, digital clubbing, and cyanosis of the lips and nail beds are consistent findings in advanced HPS, although they are not entirely specific [5, 33, 76]. Clinicians should also be aware that common chronic comorbid conditions, in particular COPD, bronchial asthma and idiopathic pulmonary fibrosis, coexist in approximately a third of HPS patients [18, 23, 77]. Extrapulmonary complications of right-to-left pulmonary communications, such as the development of a brain abscess [78, 79] or intracranial haemorrhage [80], and hypoxaemia-induced polycythaemia [81], have been reported. Information on health status is not available.

Lung function tests. Both forced spirometric results and static lung volumes (by plethysmography or helium-dilution) are characteristically within normal limits in HPS in the absence of pulmonary comorbid conditions [12, 22, 82]. Although mild-to-moderate ventilatory abnormalities may be present in some patients [22, 82], a moderately to severely reduced DLCO after adequate correction for anaemia [83] appears to be a common functional marker of HPS [3, 13]. Compared to the full reversibility of all functional and clinical outcomes, a sustained low DLCO in HPS patients 1 yr after successful OLT is an intriguing finding [84, 85], which could be related to collagen tissue deposition in pulmonary capillary and venule walls, as shown in a single post mortem study [86]. Since the mechanism of low DLCO remains unsettled, this gas exchange descriptor is not recommended for the screening evaluation of HPS (see below).

Arterial blood gas tensions, assessed at rest while breathing room air and in the sitting position by arterial puncture or through an indwelling arterial catheter, are mandatory for both the diagnosis and staging of severity of HPS, and encompass a wide spectrum of abnormalities from a simple increase in PA-aO₂ alone to very severe, life-threatening levels of hypoxaemia, usually associated with hypocapnia. During exercise, patients with HPS achieve lower peak oxygen uptakes than cirrhotics without HPS, with more hypoxaemia and an elevated dead space, hence, suggesting that abnormal pulmonary circulations contributes to further exercise limitation in HPS [87]. Pulse oximetry for the assessment of arterial oxygen saturation (SaO₂) is useful in the follow-up of patients with moderate-to-severe HPS, particularly children, before OLT, but is not sufficiently accurate to replace the detailed information provided by routine arterial blood gas tension determination (because of the shape of the oxyhaemoglobin dissociation curve).

Haemodynamics. A hyperkinetic circulatory state, with high Q' and low systemic vascular resistance and pulmonary vascular resistance (PVR), is present in 30–50% of cirrhotic patients and generally correlates with the Child-Pugh score [88–92], especially in patients with moderate-to-severe HPS. Patients with portal hypertension show a low median PVR with a wide range [88] Systemic and pulmonary vasodilatation in cirrhosis and portal hypertension appears to be the consequence of a widespread decrease in vascular tone [92, 93] that results in impaired responsiveness to vasoconstrictors [94, 95]. Hypoxic pulmonary vasoconstriction is absent or mitigated in ~30% of patients with advanced cirrhosis, with or without associated HPS, and appears to become less evident as liver disease worsens [33, 34, 96–98]. Whether or not a progressive loss of pulmonary vascular tone as liver disease deteriorates contributes to IPVD and the development of HPS remains controversial [22, 98, 99].

Biochemistry and noninvasive exhaled biomarkers. No serum test of hepatic function has been shown to be of value in the diagnosis of HPS [3–6]. However, serum progesterone and oestradiol levels are generally elevated in HPS [99] and both hormones have been correlated with the appearance of spider
naevi, a finding also related to haemodynamic and gas exchange abnormalities in cirrhotic patients [33]. Sex hormone levels and IPVD return to normal after OLT, suggesting a pathogenic role in HPS [99]. Serum nitrite/nitrate levels are increased in liver cirrhosis and this is related to endotoxaemia [100]. Increased exhaled NO levels, derived from the alveolar region [101,102], are observed in patients with advanced cirrhosis with and without HPS [55, 58, 103], and correlate with the abnormally increased PA-aO 2 [57] and high Q' [103]. Partial or complete resolution of clinical and functional markers of HPS after using different inhibitors and/or interventions that block the effects of NO, such as methylene blue [59, 104] and L-NAME [105], or following smoking [106] and OLT [56], sporadically or anecdotally reported, support the idea that increased endogenous pulmonary NO could play a pivotal role in the development of arterial deoxygenation. Further clinical studies are needed to establish the precise utility of exhaled NO in the clinical work-up of HPS. To date, no data are available regarding exhaled gas condensates [107].

Contrast-enhanced echocardiography. Transoesophageal echocardiography with contrast enhancement (CE-TTE) provides a sensitive, non-invasive and qualitative screening approach for the detection of IPVD, the central defining structural characteristic of HPS [108], and is considered the gold standard for the diagnosis of HPS. It is commonly accomplished by hand agitation of 10 mL normal saline, resulting in microbubbles (≤90 μm in diameter), which are injected into an upper extremity vein. Detection of microbubbles within the left atrium is considered positive CEE. Microbubbles are physiologically trapped and absorbed by normal alveoli during the first pass and should not appear in the left atrium. Following microbubble appearance in the right atrium, immediate appearance in the left atrium (within less than three cardiac cycles) suggests an intra-atrial right-to-left communication, whereas delayed appearance in the left heart cavities (within greater than three cardiac cycles) implies definite IPVD [5, 108]. Although positive CE-TTE results are found in 11–47% of patients with liver disease (with or without associated HPS), only 32–59% of these patients have arterial hypoxaemia [49, 109–113]. Patients with positive CE-TTE results and normal arterial oxygenation may have forme fruste (or clinically silent) HPS, but their outcome remains unknown [114]. Indocyanine green solution (microbubble size ≤90 μm) [109] or a modified gelatin solution (which creates microbubbles of 10±2 μm) [115] are the alternative contrast agents used and possibly contribute to the different prevalence findings [14].

Transoesophageal echocardiography. Alternatively, transoesophageal echocardiography with contrast enhancement (CE-TTE) may be superior to CE-TTE for the diagnosis of IPVD in cirrhotic patients with HPS, being more sensitive and showing better correlation with Pao2, CO2 and DLCO than in patients without HPS [116]. Further, it can definitively discern the passage of microbubbles through an interatrial pathway versus microbubble entrance into the left atrium from the pulmonary veins. However, CE-TTE is more expensive, requires sedation and poses a theoretical risk in patients with oesophageal varices, which may be present in patients with liver disease. Since CE-TTE has been shown to be more sensitive than lung perfusion scanning for the detection of IPVD [19], with the additional advantage that it can be conducted as part of routine echocardiographic screening for pulmonary hypertension by Doppler assessment of tricuspid systolic peak regurgitant jet velocity (see Portopulmonary hypertension section), it can be recommended as the best choice for screening for both HPS and PPHTN.

Perfusion lung scanning. Whole-body 99mTcMAA scanning allows for the detection of IPVD, along with their quantification, detecting areas with both low and zero V'A/ Q' units [49, 117]. Since macroaggregates are ≥20 μm in diameter, they are normally trapped in the pulmonary vascular bed and are transported to and retained by extrapulmonary regions, such as the brain, kidneys, spleen and liver. The major disadvantage of perfusion lung scanning relative to CE-TTE is its inability to differentiate between intracardiac communications and IPVD. In addition, the sensitivity of lung perfusion scanning is lower than that of CE-TTE in detecting HPS [49]. However, the radionuclide approach allows the quantification of IPVD by assessment of systemic and pulmonary uptake, and various indices have been proposed [19, 118]. In addition, increased systemic distribution of radiolabelled particles does not occur in chronic associated respiratory comorbid conditions, whereas CEE results remain positive, such that the 99mTcMAA approach may be of help in evaluating the contribution of HPS to arterial hypoxaemia in these patients. One validated perfusion (or shunting) index not, however, used routinely takes into account the 99mTcMAA activity of the liver and the brain [19, 20, 49], with a cut-off value of ≥6% of Q' when intracardiac communications or IPVD are present. The assessment of IPVD using the isotopic method provides shunt estimates that often exceed the functional estimates of shunt provided by the conventional 100% oxygen method [25]. This is because IPVD may continue to participate in alveolar gas exchange, especially when the driving oxygen pressure is increased by the administration of high oxygen concentrations. Finally, the combination of quantifying the severity of arterial deoxygenation and the degree of intrapulmonary shunting indices by 99mTcMAA may offer complementary information for the stratification of HPS patients at greater risk of OLT mortality [19–21].

Pulmonary angiography. One pulmonary angiographic study in a small subset of HPS patients demonstrated two angiographic patterns: type I, or diffuse, and type II, or focal [17]. The type I pattern was subdivided into a "minimal" pattern, characterised by normal vessels or fine diffuse spidery arterial vascular abnormalities, and an "advanced" pattern, with a diffuse spongiform or blotchy appearance. The type II pattern, more infrequent, consisted of focal arteriovenous communications similar to those seen in hereditary haemorrhagic telangiectasia. Patients with "advanced" type I and type II patterns may exhibit a poor response to oxygen breathing (Pao2 <40 kPa (<300 mmHg)). Under these circumstances, the latter subset of patients may be considered for vascular embolisation, as type II lesions are not reversible and the patients may be at risk of cerebral embolism and/or abscess [17, 78, 79]. Type I lesions can also be successfully embolised with subsequent marked increases in Pao2, as shown in a case report [24].

Thoracic computed tomographic scanning. There is little information regarding the use of conventional thoracic computed tomography (CT) scans for the diagnosis of
HPS. In one small study, CT demonstrated that the peripheral pulmonary arteries were significantly dilated compared with controls and normoxaemic cirrhotic patients [119]. However, a retrospective study did not confirm these results [120]. A thoracic HRCT scan may be useful for excluding coexistent chronic respiratory conditions when HPS is suspected [18].

**Screening**

The major screening steps for HPS are summarised in figure 2, and are particularly recommended for all OLT candidates and for hepatic patients who have shortness of breath. Arterial blood gas levels, including calculation of \( PA-aO_2 \) using the abbreviated formula (table 1), are measured, and, if an abnormally increased \( PA-aO_2 \) is confirmed, with or without coexisting hypoxaemia, both CEE and a complete set of lung function tests (forced spirometry with bronchodilator response, static lung volumes and DLCO) are carried out. A negative CEE result excludes the diagnosis of HPS, whereas a positive CEE result establishes the diagnosis of HPS, irrespective of the presence or absence of intrinsic cardiopulmonary disease. In the event of normoxaemic HPS (increased \( PA-aO_2 \) alone with positive CEE results), arterial blood gas levels should be measured, at least once a year, to detect any abnormal \( PaO_2 \) change, and/or if symptoms (essentially dyspnoea) appear. In addition, thoracic HRCT may be carried out, irrespective of the detection of any abnormal lung function tests, in order to rule out underlying subclinical chronic pulmonary disorders. Complementarily, the perfusion index calculated from a whole-body \( ^{99m} \text{Tc} \text{MAA} \) scan [49] can be helpful in estimating the outcome after OLT (see below).

If hypoxaemia is mild to moderate (\( PA-aO_2 \geq 2.0 \text{kPa} (\geq 15 \text{mmHg}) \) and/or \( PaO_2 \geq 8.0-<10.6 \text{kPa} (\geq 60-<80 \text{mmHg}) \)), periodic follow-up is recommended, at least once a year, with assessment of lung function, including pulse oximetry and/or arterial blood gas levels if necessary (\( SaO_2 <89\% \)). If hypoxaemia progressively deteriorates in a symptomatic (breathless) patient, then OLT can be considered. Likewise, if hypoxaemia is severe (\( PaO_2 \geq 6.7-<8.0 \text{kPa} (\geq 50-<60 \text{mmHg}) \)), consideration of OLT is vital. If the hypoxaemia is very severe or extreme (\( PaO_2 <6.7 \text{kPa} (<50 \text{mmHg}) \)) [21] and/or cardiopulmonary comorbid conditions exist [18], OLT needs to be considered on an individual basis after full assessment of the severity and prognosis of the associated extrahepatic disorders. Lung biopsy specimens are not required for diagnosis of HPS as IPVD are not reliably detected in tissue specimens. However, if coexisting idiopathic lung fibrosis is suspected in the face of potential OLT indication on the basis of severe HPS, then lung biopsy can be required to determine suitability for OLT.

**Management**

**Pharmacological treatment.** A number of small uncontrolled trials using various classes of drug, such as somatostatin analogues [17], \( \beta \)-blockers [121, 122], cyclooxygenase inhibitors [123, 124], glucocorticoids and immunosuppressors (cyclophosphamide) [125], pulmonary vasoconstrictors (almitrine) [126, 127], NO inhibitors [59, 104–106, 128], inhaled NO [129, 130] and antimicrobials [68, 131] and garlic preparation [132], for the treatment of HPS have been reported. None of the studies, however, demonstrated consistent improvement in oxygenation and/or IPVD, as all were of inadequate size to test efficacy. In addition, rare spontaneous recovery has been observed in HPS [7, 133], although the mechanism remains uncertain. Future randomised placebo-controlled multicentric trials are needed in order to further investigate these and new therapeutic interventions.

**Nonpharmacological treatment.** Long-term oxygen therapy. HPS patients with severe hypoxaemia (\( PaO_2 <8.0 \text{kPa} (<60 \text{mmHg}) \)) at rest are commonly seen and should receive continuous long-term low-flow oxygen therapy. No data are available, however, regarding the efficacy, compliance, tolerance and cost-effectiveness of such a therapeutic approach.

Transjugular intrahepatic portosystemic shunt (TIPS). Portal hypertension appears to play a central role in the pathogenesis of HPS. Accordingly, a reduction in portal pressure might be beneficial in HPS [134–137]. To date, only a few case reports using transjugular intrahepatic portosystemic shunt (TIPS) for HPS have been published, and have shown variable short-term effects on pulmonary gas exchange [134, 137]. Therefore, insufficient data are available to support TIPS as a compassionate therapeutic approach in HPS [138].


Emboliolisation. Coil embolisation (embolotherapy) in type II angiographic pattern HPS [17] has been reported to improve arterial oxygenation (as a temporary measure) in a single case report [24].
Orthotopic liver transplantation. Complete resolution of HPS following OLT has been observed in >80% of reported cases, and many centres currently view HPS as an indication for OLT [139–145], particularly in the paediatric population [146–149]. Morbidity may be higher after OLT in severe HPS, based on pre-OLT severity of hypoxaemia and abnormal extrapolunary \(^{99m}\)TcMAA uptake [21, 22]. Such patients, depending on local surgical and post-OLT expertise facilities, might benefit from referral to highly specialised transplantation centres with significant HPS experience. Spontaneous recurrence of HPS [150, 151] and development of PPHTN before [31] or following OLT for HPS [6, 29] have been reported, but appear to be rare events. Liver transplantation from living donors for HPS has been shown to be successful in children [152], but no data are available in adults.

**Task Force recommendations**

The major Task Force recommendations concerning the diagnosis and treatment of HPS are summarised in table 3.

**Research prospects**

1) Natural history, incidence and prevalence, particularly in the most advanced hepatic patients, remain controversial. All these aspects should be investigated prospectively through large multicentric studies, including the influence of long-term oxygen therapy.

2) The relevance and implications of positive CEE results suggestive of underlying IPVD, in the context of normal gas exchange, are completely ignored. There is a need for studies investigating the importance of this positive hallmark and its impact on the natural history of HPS.

3) The potential of experimental HPS models and their interplay with clinical studies need to be explored. This would facilitate greater insight into the pathogenic mechanisms of HPS. OLT is the only reliable treatment for full or partial resolution of HPS. Multicentric prospective studies of the natural history of OLT outcomes of HPS need to be developed.

4) Given the pathogenic role of some mediators, such as NO and ET, clinical trials of long-term inhaled NOS and ETB receptor antagonists, TNF-α inhibitors and antibiotics are necessary research topics that could result in new therapeutic approaches.

**Table 3. – Summary of major Task Force recommendations for hepatopulmonary syndrome (HPS)**

| Screen for HPS using arterial blood gas levels in hepatic patients who: 1) complain of dyspnoea, or 2) are OLT candidates Proceed to CEE if: 1) \(P_aO_2 <80\) mmHg, and/or 2) \(P_A-aO_2 \geq 15\) mmHg. \n| Diagnosis of HPS must be completed with: 1) PFTs, 2) thoracic HRCT scan, and 3) \(^{99m}\)TcMAA shunting index (if available). No medical treatment for HPS is available except for symptomatic measures (i.e. long-term oxygen therapy). Conserves notable indication for OLT if \(P_aO_2 \geq 50–60\) mmHg: OLT should be considered on an individual basis if \(P_aO_2 <50\) mmHg.

**Portopulmonary hypertension**

**Definition**

PPHTN can be defined as a PAH associated with portal hypertension, with or without hepatic disease [153–156]. Diagnosis of PPHTN is based on pulmonary haemodynamic criteria obtained via right heart catheterisation [6, 153]. Diagnostic criteria for PAH include a mean pulmonary arterial pressure \((P_{PA})\) of >25 (at rest) or >30 mmHg (during exercise), with a mean pulmonary artery occlusion pressure \((mPAOP)\) of <15 mmHg [153, 154, 157]. A moderate increase in \(P_{PA}\) (25–35 mmHg) is seen in up to 20% of patients with cirrhosis and portal hypertension [158]. This increase in \(P_{PA}\) is most commonly caused by increases in \(Q^*\) (despite reduced PVR) and/or in blood volume (increased mPAOP) [158, 159], without pulmonary vascular remodelling. Less commonly, moderate-to-severe PAH with extensive pulmonary vascular remodelling (increased PVR) develops [6, 153, 158, 160, 161]. In order to distinguish between these two forms of PAH, criteria have evolved for the diagnosis of PPHTN (table 4) [162–165]. These haemodynamic criteria are consistent with the definitions and classification proposed by the 3rd World Symposium on Pulmonary Arterial Hypertension [166]. Unlike HPS, arterial deoxygenation is not a major functional feature of PPHTN.

**Staging of severity**

A classification of severity of PPHTN is proposed (table 5), based on \(P_{PA}\) [167]. Such severity staging correlates with the increased mortality following OLT in moderate-to-severe PPHTN (pre-OLT \(P_{PA}\) of >35 mmHg) [164, 168].

**Natural history and outcome**

Initially described in 1951, the existence of portal hypertension and development of PAH are not coincidental [169]. Pulmonary hypertension has been reported in 0.13% of unselected patients versus 0.73% of patients with cirrhosis.

**Table 4. – Diagnostic criteria for portopulmonary hypertension**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung disease (causing clinical portal hypertension)</strong></td>
</tr>
<tr>
<td>(P_{PA}) &gt;25 mmHg</td>
</tr>
<tr>
<td>(mPAOP) &lt;15 mmHg</td>
</tr>
<tr>
<td>PVR (&gt;240) dyn-s-cm(^{-5}) (3.0 mmHg L(^{-1})-min(^{-1}); cut-off may vary*)</td>
</tr>
</tbody>
</table>

**Table 5. – Staging of severity of portopulmonary hypertension**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (early)</td>
<td>(P_{PA}) &gt;25–&lt;35 mmHg</td>
</tr>
<tr>
<td>Moderate</td>
<td>(P_{PA}) &gt;35–&lt;45 mmHg</td>
</tr>
<tr>
<td>Severe</td>
<td>(P_{PA}) &gt;45 mmHg</td>
</tr>
</tbody>
</table>

\(P_{PA}\): mean pulmonary arterial pressure; mPAOP: mean pulmonary arterial occlusion pressure; PVR: pulmonary vascular resistance. \(^*\): classical textbook criteria for normal PVR vary up to 240 dyn·s·cm\(^{-5}\); several liver transplantation centres have previously used a cut-off of >120 dyn·s·cm\(^{-5}\) as abnormal, but some patients in the 120–240 dyn·s·cm\(^{-5}\) range exhibit normal \(P_{PA}\) or increased mPAOP. Evidence-based data favour >240 dyn·s·cm\(^{-5}\) as the definitive clinically significant cut-off for abnormal PVR in the setting of advanced liver disease (see Portopulmonary hypertension: Haemodynamics section). 1 mmHg L\(^{-1}\)-min\(^{-1}\)=80 dyn·s·cm\(^{-5}\).
The concept of a vasoproliferative process. Pathophysiology and pathogenesis

Pathology

In the pre-OLT era, mean and median survivals of 15 and 6 months, respectively, were reported in a literature review of PPHTN patients (Ppa 48 mmHg) [178]. A single-centre study reported that 58% died within 1 yr of the PPHTN diagnosis. Causes of death were equally distributed between liver- and lung-related problems [88]. A 5-yr survival of 30% was reported in a study of PPHTN patients, not treated with i.v. epoprostenol, referred to the Mayo Clinic [179]. Causes of death were equally distributed between complications of liver disease and right heart failure.

Pathophysicsiology and pathogenesis

Vasoproliferation. The concept of a vasoproliferative process in PAH, including PPHTN, that causes increased resistance to arterial flow has been hypothesised [181]. Monoclonal proliferation of the endothelium has been documented in PPH, but not in PPHTN to date [181]. A decrease in prostacyclin (prostaglandin I₂) expression in the pulmonary arteries of PPHTN patients has been noted [180]. Proposed factors responsible for such findings are discussed as follows. Portal hypertension induces systemic inflammatory changes and increased vascular wall shear stress, which may trigger a cascade of intracellular signals [6]. Activation or repression of various genes in the endothelial and/or smooth muscle cells may follow and this could lead to pulmonary vascular remodelling and/or vasculogenesis in genetically susceptible patients [184, 185]. Abnormal plasma levels of vasoconstrictors (i.e. noradrenalin, rennin-angiotensin-aldoosterone and arginine vasopressin) and vasodilators (i.e. NO, glucagon, vasoactive peptide and substance P) have been measured in the setting of portal hypertension [186–188]. In short, investigators have hypothesised that an imbalance of vasoactive substances could reach the pulmonary circulation in abnormally high concentrations due to portosystemic shunts or defective hepatic metabolism, causing the pathological pulmonary vascular lesions seen in PPHTN [6, 153].

Genetics. Heterozygous mutations in the bone morphogenetic protein receptor type II and activin receptor-like kinase 1 genes (encoding different types of receptor member of the transforming growth factor-β signalling superfamily) were recently reported in familial, as well as sporadic, PPH and PAH associated with hereditary haemorrhagic telangiectasia, respectively [185, 189–191]. Such receptors presumably control diverse cellular processes, including cell differentiation, endothelial/smooth muscle cell proliferation and apoptosis [190]. These abnormalities have not been found in patients with PPHTN (M. Humbert, Hôpital A Béclère, Clamart, France; personal communication, 2002).

Inflammation. The development of portosystemic shunts and dramatic decrease in the phagocytic capacity of the liver allows circulating bacteria or bacterial endotoxins from the gastrointestinal tract to enter the pulmonary circulation [192–197]. An increase in pulmonary phagocytic activity is ascribable to extensive accumulation of pulmonary intravascular macrophages that adhere to the pulmonary endothelium [6, 67, 196]. Following phagocytosis, activated macrophages release numerous cytokines, including TNF-β, growth factors and NO into the extracellular milieu [67, 196–198]. This pulmonary phagocytosis has been demonstrated in cirrhotic patients, suggesting that induction of pulmonary intravascular macrophages might contribute to the development of the pulmonary vascular disease, such as HPS and PPHTN, seen in these patients [196].

Neurohormones. Both serotonin and ET-1 are dual-action neurohormones that may cause vasoconstriction and mitogenesis in pulmonary arteries [199–202]. Their abnormal regulation of portal hypertension makes them potentially important candidates in the pathogenesis of PPHTN. Circulating levels of serotonin, a potent pulmonary vasoconstrictor, correlate with PVR in patients with PPH [199]. Serotonin predominantly originates from the enterochromaffin cells within the gastrointestinal tract wall. The lung is normally protected from high levels of free plasma serotonin by normal hepatic metabolism and the storage of serotonin in platelets [203]. Portal hypertension is associated with decreased platelet levels, reduced platelet uptake and increased levels of serotonin [203–205]. Compared with controls, patients with PPH more frequently carry the LL genetic variant of the serotonin transporter [206]. This functional insertion/deletion polymorphism results in increased serotonin transporter expression and enhanced uptake of serotonin by pulmonary artery smooth muscle cells [206]. This polymorphism has not been found in PPHTN (S. Adnot, Hôpital H Mondor, Créteil, France; personal communication, 2003).

ET-1 is produced by the pulmonary endothelium and liver [207, 208]. Binding to ET₄ receptors on smooth muscle cells results in vasoconstriction and mitogenesis. Circulating ET-1 also binds to ET₄ receptors, resulting in
endothelium-dependent vasodilatation, mediated by NO and prostaglandin I2 production [208–211]. Increased circulating levels of ET-1 have been documented in PPH and portal hypertension without pulmonary hypertension [67, 212, 213]. Without knowing the concentration gradients across the hepatic and pulmonary circulations, it is unclear what the net effect is on the pulmonary vascular bed in the setting of advanced liver disease [208, 213].

**Clinical diagnosis and screening**

*Symptoms and physical examination.* Patients with portal hypertension who report dyspnoea, at rest or during exercise, should be assessed for the presence of PPHTN. Chest discomfort and syncope are features of advanced PPHTN. Physical examination results include elevated jugular venous pressure, an accentuated P2 component, a tricuspid regurgitation murmur, right ventricular heave or increasing lower extremity oedema (with other evidence of right-sided heart failure) [214, 215]. In the setting of advanced PPHTN, chest radiography may show increased main pulmonary artery size or cardiomegaly in the absence of other pulmonary parenchymal abnormalities [216–218]. Pulmonary function tests may show a reduced DLCO. Arterial blood gas levels may show mild-to-moderate hypoxaemia, an increased PA—aO2 and a decreased PaCO2 [156, 179]. Electrocardiography suggests right atrial enlargement, right ventricular hypertrophy or right axis deviation [215, 216]. Conventional lung perfusion scanning may show "mosaic" perfusion, but other segmental perfusion abnormalities should prompt evaluation for pulmonary emboli [216, 217]. Specific thoracic CT scan findings for PPHTN have not been documented. B-type natriuretic peptide may be a useful serum marker of right ventricular stress [218]. To date, no data are available regarding exhaled markers [107].

**Transthoracic Doppler echocardiography.** Transthoracic echocardiographic findings (increased tricuspid peak regurgitant jet velocity, pulmonary valve insufficiency, paradoxical septal motion, right ventricular hypertrophy–dilatation and an increased right ventricular systolic pressure estimate (RV55s) by the Bernoulli equation) in the setting of portal hypertension suggest, but do not prove, PPHTN [175, 219–221]. Accordingly, pulmonary haemodynamic measurements by right heart catheterisation must be performed in order to confirm the diagnosis [153, 156, 219]. Lung biopsy is not advised due to increased risk of bleeding.

Screening for PPHTN is extremely important when OLT is considered [77, 164]. A retrospective analysis showed that screening Doppler echocardiography (RV55s of >50 mmHg) identifies essentially all patients who should proceed to right heart catheterisation [219]. A prospective study of OLT candidates who underwent Doppler echocardiography (RV55s of >30 mmHg) and catheterisation measurements revealed sensitivity, specificity, and positive and negative predictive values for a diagnosis of PPHTN of 100, 96, 59, and 100%, respectively [221]. These studies support the value of echocardiography for screening OLT candidates for PPHTN. Therefore, transthoracic Doppler echocardiography should be the screening test of choice for OLT candidates, as recommended by the 3rd World Symposium on Pulmonary Arterial Hypertension [166]. Patients who are listed for OLT without evidence of PPHTN on initial evaluation should undergo echocardiography annually; those with PPHTN may need to be followed more frequently, at least twice or three times every year.

**Haemodynamics.** Right heart catheterisation is the gold standard for the diagnosis of PAH, including PPHTN [6, 153, 219]. The procedure measures pressures and flow and provides assessment of disease severity, right heart function and potential acute vasoreactivity. Haemodynamic measurements must include the following parameters: Ppa, mPAP, mean right atrial pressure and Q′, by either thermodilution or the Fick method, such that PVR can be calculated [6, 153].

Acute vasodilator testing. In PPH, acute vasodilator testing is usually performed with either i.v. epoprostenol or inhaled NO. Although both agents exert similar effects on Ppa, i.v. epoprostenol produces greater increases in Q′ than does NO [222, 223]. It is possible that patients with PPHTN could be less reactive to NO because liver cirrhosis is a condition of persistent endogenous NO overproduction [223–226]. Indeed, significant acute pulmonary vasodilatation has been shown in PPHTN when using higher concentrations of NO (40 ppm) [225, 226]. Accordingly, changes in selected haemodynamic parameters, such as PVR, should take into account the vasodilating agent that has been employed. Most investigators agree that acute decreases in both Ppa and PVR (>20% from baseline), with no change or increase in Q′, can be considered a significant vasodilatory response [214, 215]. The goal of such vasodilator testing is to determine staging severity and therapeutic expectations; there is no clinical relevance for calcium channel blockers use since they are contraindicated in portal hypertension (see below).

The acute vasodilatory effect of i.v. epoprostenol in PPHTN seems to be greater than that of NO. A significant decrease in pulmonary arterial pressure (>20%) in almost half of a small subset of patients with severe PPHTN during acute infusion of i.v. epoprostenol was reported [227, 228]. In patients with PPHTN tested with both agents, the proportion of haemodynamic responders was greater when using i.v. epoprostenol than with inhaled NO (J.A. Barbera, Hospital Clinic, Barcelona, Spain; personal communication, 2003).

Pulmonary haemodynamic subsets. Unlike PPH, most patients with advanced liver disease experience a hyperdynamic circulatory state, namely increased Q′ and decreased systemic vascular resistance [6, 158, 167]. In addition, some patients exhibit increased pulmonary venous volume due to systemic volume or left ventricular abnormalities. It is clinically useful, therefore, to characterise the pulmonary haemodynamics that complicate liver disease into the three following subsets on the basis of measured haemodynamic outcomes, such as Ppa, Q′ and mPAP, and calculated PVR, via right heart catheterisation in the stable resting state (table 6) [6, 167, 216, 229].

1. **Hyperdynamic circulatory state.** In this condition, the pulmonary vascular bed shows a marked increase in pulmonary arterial pressure with increased Q′, due to passive distension of compliant arterial vessels and recruitment of upper lung blood vessels [6, 167]; Ppa can increase, usually by <35 mmHg, in response to high Q′. This subgroup is the most frequent finding in liver disease, including HPS [158].

2. **Increased pulmonary venous volume.** Volume increase reflects probable excess of volume and/or pressure increase due to limitation in pulmonary blood flow to the left atrium because of left ventricular dysfunction (systolic or diastolic). This results in increased mPAP. This subset occurs in alcoholic cirrhosis, familial amyloidosis and combined liver–renal insufficiency [6, 167]. Long-standing changes may increase PVR, but not to the degree
Table 6. – Pulmonary haemodynamic subsets most frequently associated with advanced chronic liver disease

<table>
<thead>
<tr>
<th></th>
<th>(P_{pa})</th>
<th>PVR</th>
<th>(Q')</th>
<th>mPAOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdynamic circulatory state</td>
<td>Moderate increase</td>
<td>Mild decrease</td>
<td>Moderate increase</td>
<td>Mild decrease</td>
</tr>
<tr>
<td>Excess volume*</td>
<td>Moderate increase</td>
<td>No change</td>
<td>Moderate increase</td>
<td>Severe increase</td>
</tr>
<tr>
<td>Vascular obstruction with vasoproliferation*</td>
<td>Severe increase</td>
<td>Severe increase</td>
<td>Severe increase followed by severe decrease</td>
<td>Mild decrease</td>
</tr>
</tbody>
</table>

All groups can be associated with increased pulmonary arterial pressures. Only the last group (i.e. vascular obstruction) is associated with vascular remodelling and characterises the entity of portopulmonary hypertension (PPHTN). \(P_{pa}\): mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; \(Q'\): cardiac output; mPAOP: mean pulmonary artery occlusion pressure. *: e.g. hepatopulmonary syndrome; #: e.g. PPHTN.

documented in PPHTN. The transpulmonary pressure gradient (*TPG* = \(P_{pa} – mPAOP\)) can discern between excess of volume (*TPG* <10 mmHg) and additional pulmonary vascular abnormalities (*TPG* >10 mmHg) [230].

3) Vascular obstruction (i.e. PPHTN). Here, the pathological features of PPHTN include vasoconstriction and obstruction/obliteration due to endothelial proliferation, smooth muscle proliferation, fibrosis and in situ thrombosis [6, 160, 161]. The pulmonary haemodynamics in early PPHTN are unique, with markedly increased \(P_{pa}\), PVR and \(Q'\) [156, 163, 228]. As PVR increases, right ventricular failure ensues, characterised by falling \(Q'\).

Prognostic implications for OLT using staging of severity and pulmonary haemodynamic subsets can exist. The combination of a \(P_{pa}\) of <35 mmHg and a PVR of <250 dyn·s·cm⁻² has been associated with an excellent post-OLT outcome [164]. By contrast, a \(P_{pa}\) of >35 mmHg has been associated with increased mortality [164, 168]. Intuitively, the measurement of right atrial pressure, right ventricular function and effects of volume loading should not be ignored [231, 232]. Figure 3 demonstrates the importance of right heart catheterisation relationships between \(Q'\), \(P_{pa}\) and PVR in the setting of advanced liver disease states. Most patients with significant increases in \(P_{pa}\) show reduced \(Q'\) and a PVR of >240 dyn·s·cm⁻². Patients showing PVR ranging 120–240 dyn·s·cm⁻² were more likely to exhibit both increased TPG and increased mPAOP.

Management

Pharmacological treatment. In patients with PPHTN, thrombocytopenia and/or an increase in prothrombin time are common events [233]. Under these conditions of a high risk of gastrointestinal bleeding, oral anticoagulant therapy should not be recommended in PPHTN patients.

Nonspecific therapy. Diuretics. The goal of diuretics is to reduce both the intravascular volume and hepatic congestion that occur in patients with right-sided heart failure. Alternatively, hypovolaemia induced by an excessive amount of diuretics can reduce the \(Q'\) needed by decreasing right ventricle pre-load [233]. Furosemide and/or spironolactone (up to 400 mg·day⁻¹) should be prescribed carefully [233].

Cardiac glycosides. Digoxin has been shown to improve \(Q'\) acutely in PPH [234]. Digoxin toxicity may be enhanced if hypoaemia and diuretic-induced hypokalaemia are also present. The efficacy of cardiac glycosides in PPHTN patients is unknown. It is of note that \(\beta\)-blockers could contribute to deterioration of PPHTN.

Vasodilator therapy. Pulmonary artery vasoconstriction contributes to the pathogenesis of PAH [235–237], and has been demonstrated in PPHTN [228]. Although pure vasodilators reverse this component of the disease, they have little or no effect on the fibrotic and proliferative remodelling changes that predominate in PPHTN. Several agents are available (listed as follows).

Calcium channel blockers. Calcium channel blockers are not recommended in patients with portal hypertension as they may increase the hepatic venous pressure gradient [228, 238, 239].

Nitrites. A single case report described a patient who showed acute and chronic improvement in haemodynamics with isosorbide-5'-mononitrate [240].

Continuous i.v. epoprostenol infusion. Prostacyclin (prostaglandin I₂ or epoprostenol) is a potent systemic and pulmonary vasodilator, powerful inhibitor of platelet aggregation, and possible inotrope [214, 215]. Epoprostenol can only be administered by continuous i.v. infusion (central venous access via portable infusion pump), since its half-life in the circulation is brief (3–5 min) [214, 215]. Common adverse effects attributable to epoprostenol include jaw pain, headache, diarrhea, flush, leg pain, nausea and vomiting [239]. More serious complications

![Fig. 3. – Plot demonstrating the relationship between cardiac output (\(Q'\)) and transpulmonary pressure gradient (\(TPG\); mean pulmonary artery occlusion pressure) in the various ranges of calculated pulmonary vascular resistance (—: 240 dyn·s·cm⁻², corresponding to the haemodynamic limit for diagnosis of portopulmonary hypertension (PPHTN); - - - - -: 120 dyn·s·cm⁻²) for patients with advanced liver disease (●: PPHTN patients; □: liver cirrhosis patients without PPHTN). Unpublished data from the combined French (463 patients; O. Sitbon, Hôpital A Béclère, Clamart, France, and Ph. Hervé), North American (64 patients; M.J. Krowka) and Spanish (54 patients; J.A. Barberá) experience.](image-url)
may occur due to the delivery system (catheter-related infections or thrombosis). The interruption of infusion may be life-threatening because of the sudden loss of vasodilatation. Ascites may be related to severe right heart failure, but also to increased permeability of the peritoneal membrane promoted by epoprostenol.

Randomised clinical trials using i.v. epoprostenol have not been performed in PPHTN, but several case series have shown substantial acute short-term and long-term improvement in pulmonary haemodynamics in New York Heart Association Functional Class III and IV patients [228, 241–244]. Long-term continuous infusion of epoprostenol (up to 30 months) has resulted in significant and favourable changes in Ppa, PVR, Q' and the 6-min walking distance (6MWD) [228, 244]. Regarding long-term survival and the use of epoprostenol in PPHTN, preliminary data from the Mayo Clinic (Rochester, MN, USA) suggest that i.v. epoprostenol may not result in long-term survival benefit (at 5 yrs) compared to controls with portal hypertension, unless OLT can be accomplished [179]. As a cautionary note, continuous i.v. epoprostenol therapy has been followed by the development of progressive splenomegaly and worsening thrombocytopenia and leukopenia [245].

Other prostacyclin analogues (treprostinil, iloprost and beraprost). Patients with PPHTN have been treated with long-term subcutaneous infusion of treprostinil, resulting in an improved 6MWD [246]. A single patient with PPHTN was tested acutely with inhaled aerosolised iloprost, resulting in a 26% decrease in Ppa and 42% fall in PVR [247]. Although oral beraprost was given to patients with moderate PAH (Ppa >35 mmHg) is made on the operating table, a careful assessment of the haemodynamic data must be undertaken. The diagnosis of PPHTN must be considered due to the major risks related to cardiac failure, particularly right ventricular failure and immediate graft failure as the result of venous congestion [163, 168]. In this scenario, cardiac function is best determined by transoesophageal echocardiography [232]. Indicators that would promote further therapy and cancellation of OLT surgery are poor left ventricular function, a dilated right ventricle and right atrium, and severe volume overload.

A factor to take into consideration during OLT is the 5–10% increase in Q' that may occur on reperfusion of the liver graft [232]. This increase in Q' is, however, unpredictable and may reach >300% in a small number (up to 3.8%) of patients, precipitating right heart failure in a ventricle that is already under strain [232]. The increased Q' is probably the result of the removal of the obstruction to portal blood flow by the extraction of the diseased liver, together with the systemic vasodilatation caused by washout of acid metabolites.

Orthotopic liver transplantation. Unlike HPS, PPHTN is not considered an indication for OLT [6, 154, 164, 256]. For those with PPHTN who have undergone OLT, the survival and change in pulmonary haemodynamics has been variable, namely worsening, unchanged, improved and normalised [152, 257–277]. Moderate-to-severe pulmonary hypertension (Ppa >35 mmHg) places the OLT patient at increased risk of perioperative morbidity and mortality [164, 168]. Current data indicate a perioperative mortality of >50% if OLT is carried out when Ppa is 35–45 mmHg and PVR >250 dyn·s·cm⁻⁵ [168]. By contrast, there is no increase in mortality if Ppa is <35 mmHg (158, 168). Nonetheless, there are reports of successful OLT and long-term survival in a few patients with a Ppa of >50 mmHg and elevated PVR [265].

In a recent literature review, >60% of patients with PPHTN were detected for the first time on the operating table, on induction of anaesthesia for OLT [168]. When a diagnosis of moderate PAH (Ppa >35 mmHg) is made on the operating table, a careful assessment of the haemodynamic data must be undertaken. The diagnosis of PPHTN must be considered due to the major risks related to cardiac failure, particularly right ventricular failure and immediate graft failure as the result of venous congestion [163, 168]. In this scenario, cardiac function is best determined by transoesophageal echocardiography [232]. Indicators that would promote further therapy and cancellation of OLT surgery are poor left ventricular function, a dilated right ventricle and right atrium, and severe volume overload.

Endothelin receptor antagonists (bosentan). Bosentan is an orally available dual ET (ET₁ and ET₂) receptor antagonist that may cause a transient increase in hepatic enzyme levels (observed in 14% of patients in two randomised trials) [249–251]. Severe cases of acute hepatitis (one fatality) have been described with sitaxsentan, an ET₁-receptor-selective antagonist [250]. Since there are hepatic concerns, these agents should not be administered routinely to patients with PPHTN, but further studies in patients with minimal hepatic dysfunction are advised [249]. ET₁ and ET₂ receptor antagonists could be considered in extrahepatic portal hypertension.

Nonpharmacological treatment. Long-term oxygen therapy. Mild-to-moderate degrees of arterial hypoxaemia at rest are a common finding in PPHTN [252]. Theoretically, hypoxaemia may aggravate pulmonary hypertension by increasing pulmonary vasoconstriction, and supplemental oxygen therapy should be considered in patients with severe hypoxaemia at rest (Pao₂ <60 mmHg). Severe hypoxaemia is, however, uncommon and should lead to investigation of the possibility of an intracardiac right-to-left shunt due to reopening of a patent foramen ovale [253], a possibility that can be suspected if the Pao₂ response to 100% oxygen breathing is modest (<300 mmHg), or, alternatively, raise the coexistence of HPS.

Transjugular intrahepatic portosystemic shunt. There is no role for TIPS in PPHTN. In fact, the result of TIPS may acutely enhance pre-load and thus increase pulmonary arterial pressure and PVR [254, 255].

Fig. 4. – Algorithm for screening and therapeutic decisions, including orthotopic liver transplantation (OLT) consideration/management, in portopulmonary hypertension (PPHTN). RVsys right ventricular systolic pressure; RV: right ventricle; RHC: right heart catheterisation; Ppa: mean pulmonary arterial pressure.
Table 7.—Summary of major Task Force recommendations for portopulmonary hypertension (PPHTN)

| Screen for PPHTN by transthoracic Doppler echocardiography. Proceed to RHC if: 1) RV_{sys} is \(>40–50\) mmHg (cut-off may vary), or 2) RV is qualitatively abnormal and/or high suspicion for PPHTN. The diagnosis of PPHTN must be confirmed by RHC. Suggested criteria are: 1) \(P_{pa}\) of \(>25\) mmHg, 2) mPAOP of \(<15\) mmHg, and 3) PVR of \(>240\) dyn·s·cm\(^{-2}\) (cut-off may vary). Medical treatment of PPHTN should include case controls and multicentric clinical trials with i.v. and inhaled prostacyclin preparations. Experience should be gained in the use of phosphodiesterase inhibitors and endothelin antagonists. Severe PPHTN cannot be considered an indication for OLT at this time. Pulmonary vasodilators/vascular mediators should be used before OLT to improve and optimise pulmonary haemodynamics.

Task Force recommendations

Both PPHTN screening and haemodynamic treatment recommendations are summarised in figure 4 [163, 164, 274]. Despite clinical intervention, right heart failure may develop in the immediate post-OLT period [163, 164, 276]. The new graft is immediately compromised and the survival of the patient may be in jeopardy. It should be noted that living-donor liver transplantation [152] and heart–double lung transplantation have been accomplished in highly selected patients [278]. If conventional measures fail, atrial sepsostomy [279] and/or the insertion of a right ventricular assist device may be life-saving [280].

The major Task Force recommendations concerning the diagnosis and treatment of PPHTN are summarised in table 7. The principal differential traits between PPHTN and HPS are set out in table 8. HPS is primarily a pulmonary gas exchange abnormality, whereas PPHTN is a major haemodynamic problem. Both entities can be clinically debilitating, and their diagnostic and therapeutic strategies are quite distinct [153, 281].

Research prospects

1) The genetic predisposition and mutations associated with portopulmonary hypertension and hepatopulmonary syndrome should be characterised. Similarities and distinctions as compared to the disorders of hereditary haemorrhagic telangiectasia and primary pulmonary hypertension, respectively, need to be investigated.
2) Efforts should be undertaken to identify circulating vascular mediators and their respective concentration gradients over the portal–hepatic venous and pulmonary arterial–venous circulations.
3) From a treatment perspective, further multicentric randomised trials of both the efficacy and safety of new molecules, such as oral endothelin receptor antagonists, phosphodiesterase inhibitors, serotonin transport inhibitors and inhaled prostanoids, should be considered in portopulmonary hypertension.
4) Identification of subsets of portopulmonary hypertension patients amenable to early orthotopic liver transplantation should be considered, and long-term follow-up reported.

Table 8.—Distinction between hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN)

<table>
<thead>
<tr>
<th>HPS</th>
<th>PPHTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatology</td>
<td>Progressive dyspnoea</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>Cyanosis</td>
</tr>
<tr>
<td></td>
<td>Finger clubbing</td>
</tr>
<tr>
<td></td>
<td>Spider angiomas (?)</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>ECG findings</td>
<td>None</td>
</tr>
<tr>
<td>Arterial blood gas levels</td>
<td>Moderate-to-severe hypoxaemia</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>Always positive; left atrial opacification for &gt;3–6 cardiac cycles after right atrial opacification</td>
</tr>
<tr>
<td>(^{99m})TcMAA shunting index</td>
<td>(\geq 6%)</td>
</tr>
<tr>
<td>Pulmonary haemodynamics</td>
<td>Normal/low PVR</td>
</tr>
<tr>
<td></td>
<td>Normal mPAOP</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
<td>Normal&quot;spongy&quot; appearance (type I)</td>
</tr>
<tr>
<td></td>
<td>Discrete arteriovenous communications (type II)</td>
</tr>
<tr>
<td>OLT</td>
<td>Always indicated in severe stages</td>
</tr>
</tbody>
</table>

RV: right ventricle; ECG: electrocardiography; RBBB: right bundle-branch block; CEE: contrast-enhanced echocardiography; \(^{99m}\)TcMAA: technetium-99m-labelled macroaggregated albumin; PVR: pulmonary vascular resistance; mPAOP: mean pulmonary artery occlusion pressure; OLT: orthotopic liver transplantation.
Acknowledgements. The authors would like to express their gratitude to J. Bruix (Hospital Clinic, Barcelona, Spain) for facilitating the support of the European Association for the Study of the Liver (EASL) during the 2002 Madrid (Spain) workshop. They also thank L. Morte (Hospital Clinic, Barcelona, Spain) for administrative and expert secretarial assistance.

References

intrapulmonary vasodilatation and hepatopulmonary syndrome. 


81. García-Casasola G, Nacher J, Fernandez C, Guijarro C, Bilbao J, Zapatero A. Severe polycythemia as the first


166.


Lane KB, Machado RD, Paucliffe MW. Heterozygous germline mutations in BMPR2 encoding a TGF-β receptor causes familial primary pulmonary hypertension. Nat Genet 2000; 26: 81–84.


Möller S, Hendriksen JH. Circulatory abnormalities in cirrhosis with focus on neurohumoral aspects. Semin Nephrol 1997; 17: 505–519.


