Review

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Hepatopulmonary syndrome

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Summary

Hepatopulmonary syndrome (HPS) is a pulmonary vascular complication of liver disease, which adversely affects prognosis. The disease is characterised by intrapulmonary vascular dilatations and shunts, resulting in impaired gas exchange. A complex interaction between the liver, the gut and the lungs, predominately impacting pulmonary endothelial cells, immune cells and respiratory epithelial cells, is responsible for the development of typical pulmonary alterations seen in HPS. Liver transplantation is the only therapeutic option and generally reverses HPS. Since the implementation of the model for end-stage liver disease (MELD) standard exception policy, outcomes in patients with HPS have been significantly better than they were in the pre-MELD era. This review summarises current knowledge and highlights what's new regarding the diagnosis and management of HPS, and our understanding of pathogenesis based on experimental models and translational studies.

Keywords: cirrhosis; portal hypertension; MELD exceptions

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Introduction

Circulatory changes, with increased blood flow and a disrupted balance between vasodilation/vasoconstriction, are an inherent consequence of cirrhosis and portal hypertension and may affect the pulmonary circulation. These changes may affect the lung and are responsible for the development of pulmonary vascular disorders, of which hepatopulmonary syndrome (HPS) is the most common.

HPS affects 10–30% of patients evaluated for a liver transplantation (LT).[1] The syndrome is characterised by intrapulmonary vascular dilatations (IPVDs), which result in ventilation-perfusion mismatch, diffusion restriction and arteriovenous (AV) shunts, causing impaired gas exchange. Patients with HPS are frequently asymptomatic, resulting in under-recognition of the disease and a delay in diagnosis. However, HPS is associated with increased mortality.[1]

Currently, LT is the only effective treatment for HPS, yet medical options are needed. Continued progress in translational studies exploring the pathogenesis of HPS hold promise for the development of medical treatments.

In this review, we provide an update and highlight what is new regarding diagnostic modalities and general management, including the role of LT, as well as reviewing pathogenesis and potential therapeutic targets.

Definition and clinical presentation

HPS is characterised by impaired gas exchange due to IPVDs and right-to-left shunts. Diagnostic criteria are represented in Fig. 1.[2]

HPS most commonly occurs in patients with cirrhosis and portal hypertension, but can also occur in patients with acute or chronic inflammatory liver disease, Budd-Chiari syndrome, and a number of vascular abnormalities characterised by altered blood flow between the liver and lung, *e.g.* cavopulmonary shunts and Abernethy malformation.[2]

The presence or severity of HPS does not closely parallel the severity of the underlying liver disease.[1,3] More recent studies have found a modestly higher model for end-stage liver disease (MELD) score in patients with HPS compared to controls.[4,5]

HPS is frequently asymptomatic, indicating the need for active screening in patients on the waitlist for LT. Clinical signs may include digital clubbing, cyanosis and diffuse telangiectasias. More classically described in HPS, but less frequently observed is platypnoea (dyspnea worsening when moving from supine to upright position) and orthodeoxia (>5% or >4 mmHg decrease in partial pressure of arterial oxygen [PaO_2] after changing from supine to upright position), which occurs in 18–20% of patients.[6]

Co-existence of pulmonary diseases, including chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, etc., should be investigated, as they may exacerbate clinical symptoms and gas exchange abnormalities.

Case reports have described the potential co-existence of HPS and portopulmonary hypertension, meaning the presence of disturbed gas exchange in combination with increased pulmonary arterial pressure, which confers a risk of right heart failure. Case studies have also reported on the

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transition to, or unmasking of, co-existent portopulmonary hypertension following the resolution of HPS after LT.

Key points

- HPS affects 10-30% of patients evaluated for liver transplantation and significantly affects prognosis.
- Patients with HPS are frequently asymptomatic, resulting in under-recognition of the disease and a delay in diagnosis.
- Work-up consists of arterial blood gas and contrast echocardiography. The use of biomarkers is a field of active research.
- The bile duct ligation model of experimental HPS has significantly contributed to our understanding of the disease.
- Effective pharmacological therapies are still not available.
- Liver transplantation is an effective therapeutic option and results in complete resolution of the syndrome.
- Long-term survival in HPS has drastically changed since the implementation of the MELD standard exception policy.

Screening and diagnosis

HPS is frequently under or inaccurately diagnosed. A recent study evaluated how often and how accurately HPS was diagnosed using ICD codes in 42,749 patients with cirrhosis in a large integrated health care system from 2014–2019.[7] The authors found that less than 0.5% of patients with cirrhosis were diagnosed with HPS, which is markedly lower than observations in targeted studies.[1,7,8] Also, less than 25% of those patients who were diagnosed with HPS fulfilled diagnostic criteria at the time the diagnosis was made.[7] These findings highlight the problem of incomplete diagnostic assessment, likely due to a lack of familiarity with diagnostic criteria and the investigations required.

The diagnosis of HPS relies on documenting IPVDs and/or shunts and impaired gas exchange in the absence of another explanation for gas exchange abnormalities. IPVDs are detected using contrast-enhanced transthoracic echography. During this examination, saline is agitated, creating microbubbles (>10 μm diameter), which are injected into a peripheral vein. Under normal circumstances these do not pass through the pulmonary capillary bed (<8–15 μm diameter) and are therefore only visualised in the right heart. The 'delayed' presence of microbubbles in the left heart after peripheral injection (3 or more cardiac cycles after being observed in the right heart) indicates the presence of IPVDs or shunts.[2,9] Echocardiography can distinguish intrapulmonary from intracardiac right-to-left shunts, in which microbubbles appear in the left atrium within 3 cardiac cycles. An alternative, yet less well standardised, method to document IPVDs is a ^{99m}Technetium-labeled macroaggregated albumin (Tc-MAA) lung perfusion scan. In normal circumstances, the injected particles (>20 μm diameter) are trapped in the pulmonary capillaries. In case of intracardiac or intrapulmonary shunts, the aggregates are retained in the brain and kidneys. A Tc-MAA scan allows for quantification of pulmonary and systemic radionuclide uptake. In contrast to echocardiography, a Tc-MAA scan cannot differentiate between intracardiac and intrapulmonary shunting.[2,9,10]

Impaired gas exchange is documented by arterial blood gas (ABG) analysis with measurement of the alveolar-arterial oxygenation gradient ($P(A\text{-}a)O_2$) as a measure of ventilation-perfusion (V/Q) mismatch. ABG should be obtained while the patient is sitting in an upright position, breathing ambient air. The $P(A\text{-}a)\ O_2$ gradient is calculated as: $([Patm - PH_2O] \times 0.21 - PaCO_2/0.8) - PaO_2$. The severity of HPS is classified based on PaO_2 levels (Table 1).[2]

Chest radiographs are most often normal, though like high-resolution CT, may demonstrate increased lower lobe interstitial or vascular markings as signs of IPVDs. Pulmonary angiography may be indicated in cases of severe hypoxemia (PaO_2 <60 mmHg), when large AV malformations, amenable to embolisation, are detected on high-resolution CT. Two types of HPS patterns have been reported in the uncommon situation where

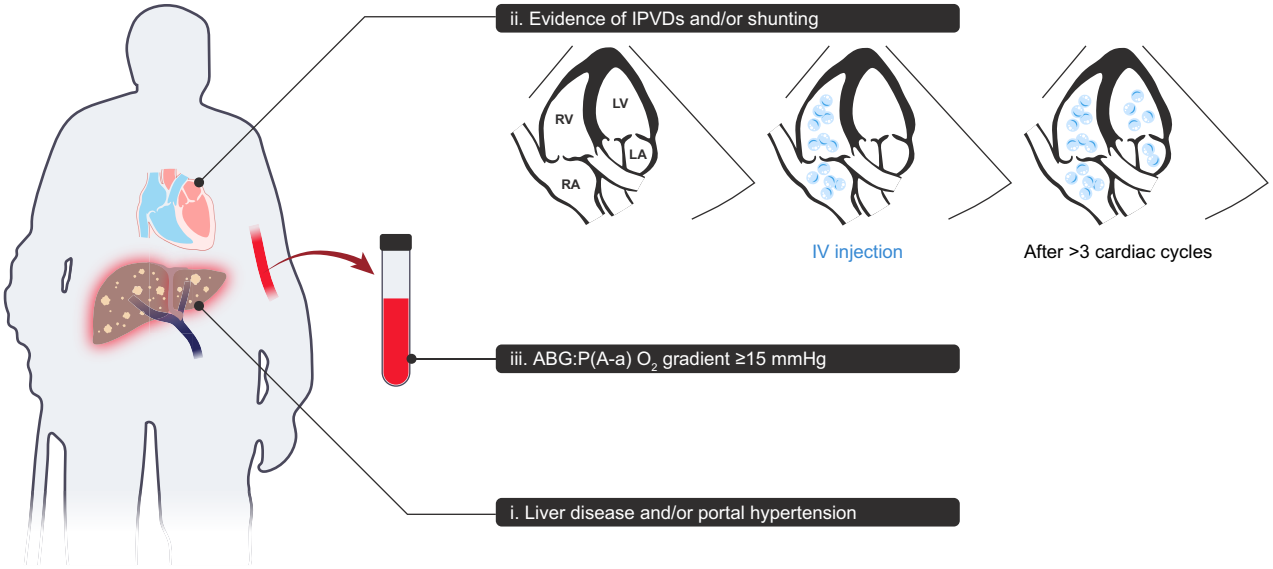


Fig. 1. Diagnostic criteria for HPS. i) Liver disease and/or portal hypertension. ii) Evidence of IPVDs and/or shunting. Gold standard is contrast-enhanced echocardiography. 'Delayed' presence of microbubbles in the left heart after intravenous injection (3 or more cardiac cycles after being seen in the right heart) indicates IPVDs or shunts. iii) $P(A\text{-}a)O_2$ gradient ≥15 mmHg (or >20 in case of ≥65 years of age), as determined by ABG analysis. ABG, arterial blood gas; HPS, hepatopulmonary syndrome; IPVDs, intrapulmonary vascular dilatations; $P(A\text{-}a)O_2$, alveolar-arterial oxygenation gradient.

Table 1. Severity of HPS.

Stage	PaO_2
Mild	≥80 mmHg
Moderate	60–79 mmHg
Severe	50–59 mmHg
Very severe	<50 mmHg

HPS, hepatopulmonary syndrome.

pulmonary angiography is performed. Type I is characterised by normal angiography or diffuse vascular dilations, while type II, which appears to be quite rare, is characterised by focal AV malformations. Type II communications have been reported to persist after LT, and could be a risk factor for paradoxical embolism and cerebral abscesses, so coil embolisation may be considered.

Pulmonary function tests typically show decreased diffusing capacity for carbon monoxide; however, this is frequently seen in patients with cirrhosis and is thus non-specific for HPS.[11] In addition, subtle abnormalities, lower forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), with preserved FEV1/FVC ratio, have been demonstrated in patients with liver disease and HPS.[11]

Contrast-enhanced echocardiography (or Tc-MAA scan as an alternative) in combination with ABG analysis represent the gold standard for diagnosis of HPS, although these studies are invasive, time consuming and costly, and not well suited for screening or serial assessments. Oxygen saturation (SaO_2) measurements by pulse oximetry have been employed as a simple and non-invasive screening strategy to detect hypoxemia in HPS, using a cut-off of 94-96% for further diagnostic testing. However, small changes in SaO_2 may be associated with large changes in PaO_2 due to the shape of the oxyhaemoglobin dissociation curve, limiting the sensitivity and specificity of this technique to detect any form of HPS.[12] Forde *et al.* recently reported that pulse oximetry represents a poor screening test for HPS in LT candidates, and showed that a SaO_2 of 94% provides poor sensitivity (22.1%) and specificity (89.8%) to detect severe HPS.[13] In line with these findings, a recent large prospective study (n = 231, n = 85 with HPS, n = 146 without HPS) showed a mean SaO_2 of 96% in patients with HPS while sitting, which was on average only 2% lower than the SaO_2 of liver patients without HPS.[5] As such, ABG analysis is mandatory to detect increased P(A-a)O_2.

The limitations of current screening techniques have stimulated research on alternative ways to detect HPS. In experimental models, bacterial translocation, increased circulation of endotoxins and subsequent recruitment of immune cells to the lung drive a cascade of events leading to pulmonary endothelial dysfunction and angiogenesis (see below). Based on these observations, the ability of markers of endothelial dysfunction and angiogenesis to differentiate between patients with cirrhosis, with and without HPS, is being assessed. Levels of both vascular cellular adhesion molecule 1 (VCAM1) and von Willebrand factor (vWF) appear to correlate with the presence of HPS and may be more sensitive and accurate than pulse oximetry for detection.[14,15] Recently, these findings have been confirmed in a large prospective study that compared 85 patients with HPS to 146 without HPS in the US.[5] Patients with HPS were characterised by a profile of dysregulated angiogenic proteins, marked by elevated serum levels of VCAM1, vWF, and angiopoietin 1, even after accounting for differences in the severity of liver disease.[5] Although further validation in larger cohorts is needed, these data suggest that these biomarkers could facilitate the identification of HPS in patient with cirrhosis (Fig. 2).

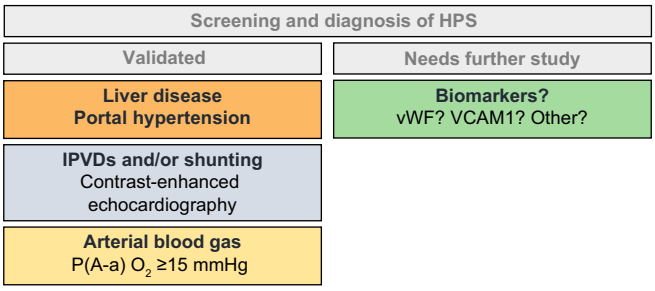


Fig. 2. Screening and diagnosis of HPS. Proper screening and diagnosis of HPS relies on performing contrast-enhanced echocardiography and arterial blood gas analysis. Biomarkers could facilitate the identification of HPS in patients with cirrhosis, but additional studies and validation in larger cohorts is needed. HPS, hepatopulmonary syndrome; IPVDs, intrapulmonary vascular dilatations; P(A-a)O_2, alveolar-arterial oxygenation gradient.

Pathogenesis and potential targets for therapy

The development of impaired gas exchange in HPS has been attributed to 3 mechanisms resulting from alterations in the alveolar microcirculation: V/Q mismatch, diffusion limitation and the presence of direct AV communications.[16] V/Q mismatch results from increased pulmonary blood flow due to microvascular alterations, while ventilation remains unchanged. Diffusion limitation occurs because oxygen must travel a greater distance to bind haemoglobin due to vascular dilation. Direct AV communications bypass the alveolar microcirculation, resulting in direct mixing of venous and arterial blood.

The pathogenesis of alterations in the microcirculation in HPS has been the focus of study over the last 20 years. This work has been facilitated by the recognition that experimental common bile duct ligation (CBDL) recapitulates many features of human HPS.[17,18] Other experimental models including partial portal vein ligation (PVL) which triggers portal hypertension and a hyperdynamic state without liver injury, and non-biliary models of liver injury induced by thio-acetamide (TAA) and carbon tetrachloride-induced, do not result in pulmonary alterations of HPS and have been used as controls.[19–21] CBDL is a surgical technique in which the common bile duct is isolated and ligated, leading to obstructive cholestasis, hepatic inflammation and periportal fibrosis, evolving to cirrhosis after 4 weeks in rats and 6 weeks in mice.[17,18] Within 1 week after the procedure, portal pressure is elevated and a hyperdynamic circulation develops[22,23] followed by IPVDs and a widened P(A-a)O_2 gradient. Hypoxemia worsens with time. Work in the CBDL model has identified underlying pathophysiologic triggers for 3 mechanisms that contribute to the development of hypoxemia in the disease: relaxation of blood vessels leading to vasodilation, angiogenesis leading to shunt formation, and alveolar dysfunction.[19] The underlying processes responsible for these 3 mechanisms are described in more detail below and are summarised in Fig. 3.

Endothelin-1-induced pulmonary vascular relaxation

Circulating endothelin-1 (ET-1) levels and hepatic production are increased in both human and experimental cirrhosis.[21,22,24] ET-1

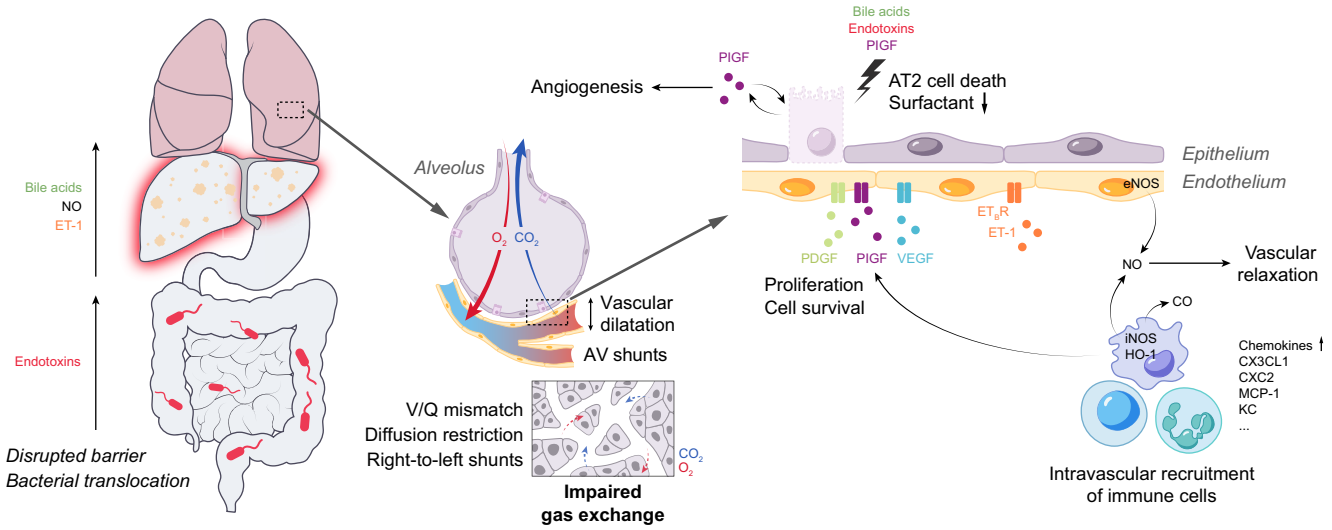


Fig. 3. Pathophysiology and pathogenesis of HPS. A complex interaction between the liver, the gut and the lungs, predominately impacting pulmonary endothelial cells, immune cells and respiratory epithelial cells, is responsible for the development of IPVDs and intrapulmonary shunting in HPS. These phenomena result in V/Q mismatch, diffusion restriction and right-to-left shunting, responsible for impaired gas exchange and hypoxemia. Bacterial translocation with pulmonary intravascular recruitment of immune cells, pulmonary endothelial dysfunction, angiogenesis, and AT2 cell dysfunction represent the most important underlying mechanisms and are considered potential therapeutic targets. AT2, alveolar type II; AV, arteriovenous; CO, carbon monoxide; HPS, hepatopulmonary syndrome; NO, nitric oxide; V/Q, ventilation-perfusion.

classically acts as a potent vasoconstrictor, including in the portal circulation where it increases sinusoidal and pre-sinusoidal resistance. The differential function of ET-1 in the pulmonary vasculature results from binding with its receptors: the vascular smooth muscle expressed endothelin A or B (ET_B) receptors mediate vasoconstriction, while the endothelial expressed ET_B receptor activates endothelial nitric oxide synthase and increases nitric oxide (NO).[25] NO diffuses across the vascular smooth muscle cell membrane and activates the guanylate cyclase/cyclic guanosine monophosphate signalling pathway, leading to vascular relaxation. After CBDL, selective upregulation of the endothelial ET_B receptor (in the setting of hyperdynamic circulation and increased pulmonary shear stress) in association with increased circulating ET-1 levels results in vasodilation and HPS.[26,27] Upregulation of the pulmonary endothelial ET_B receptor also occurs as a hyperdynamic state and increased pulmonary shear stress develop after PVL, although HPS does not develop as circulating ET-1 levels are normal.[21] Circulating ET-1 levels are also normal in experimental cirrhosis models where HPS does not develop (TAA), while ET-1 infusion in PVL animals triggers HPS, supporting an important role for ET-1 activation through the endothelial ET_B receptor in experimental HPS. Finally, increased levels of exhaled NO are also found in experimental and human HPS,[28–32] and nitric oxide synthase inhibition with N-nitroarginine methyl ester improves experimental HPS, consistent with the concept that NO is an important downstream regulator in the pulmonary microcirculation.[32,33]

Bacterial translocation, endotoxemia and pulmonary inflammation

Bacterial translocation or dissemination of gut bacteria into the systemic circulation is common in advanced liver disease. Four mechanisms contribute to this process: intestinal bacterial overgrowth, mucosal barrier disruption, decreased hepatic clearance capacity, and portosystemic shunting.[34–37] Bacterial products and endotoxins then reach the pulmonary circulation where they induce local release of chemotactic factors, resulting in recruitment of immune cells.

Animals with experimental HPS manifest bacterial translocation, which is characterised by an increased number of culture-positive mesenteric lymph nodes and higher serum concentrations of tumour necrosis factor alpha (TNFα) and lipopolysaccharide; parameters that correlate with pulmonary inflammation and the incidence and severity of HPS.[36–38] Plasma endotoxin levels are normal in experimental models where HPS does not develop and prophylactic treatment with antibiotics or TNFα antagonists ameliorates the development of HPS.[34,38–41]

A key finding in experimental HPS is the influx of immune cells into the pulmonary vasculature, an event that may be due in part to bacterial translocation. Neutrophil and monocyte/macrophage depletion studies demonstrated improved gas exchange in rats with CBDL-induced HPS and supported intrapulmonary influx of immune cells as a central event in HPS development.[35,42] The homing of circulating immune cells to specific vascular regions is guided by chemoattractant proteins. In experimental HPS, increased pulmonary expression of multiple chemotactic factors, including fractalkine (also known as CX3CL1), CXCL2 (C-X-C motif chemokine ligand 2), monocyte chemoattractant protein 1, keratinocyte chemoattractant and their respective receptors, has been observed.[18,43–45] Although many aspects of the origin and behaviour of infiltrating monocytes are not fully defined, a subset of these cells may be derived from splenic reservoir monocytes[46] and pulmonary vascular monocytes in experimental HPS have been found to produce inducible nitric oxide synthase, leading to NO-mediated vasodilation, and heme oxygenase 1, leading to increased production of the vasodilator carbon monoxide.[22,47] Moreover, blocking chemotaxis through CX3CR1 (C-X3-C motif chemokine receptor 1) or CXCR2 (C-X-C motif chemokine receptor 2) improves experimental HPS.[43,44]

Angiogenesis and intrapulmonary shunt formation

Pulmonary angiogenesis or formation of new blood vessels from pre-existing vessels is another crucial mechanism in HPS pathogenesis. Single-nucleotide polymorphisms in genes regulating angiogenesis, *e.g.* endoglin and vWF, have been shown to be associated with the risk of developing HPS in humans.[48] In experimental HPS, increased pulmonary expression of pro-angiogenic factors (including vWF, endoglin, vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF], placental growth factors [PlGF] and others), particularly in infiltrating monocytes, has been found.[19] Targeting this vascular inflammation has been shown to downregulate pulmonary angiogenesis and improve HPS in CBDL rats.[39]

Studies in experimental HPS directly targeting classic pro-angiogenic pathways including VEGF, PDGF and Raf kinases, using the receptor tyrosine kinase inhibitor sorafenib have shown beneficial effects in the pulmonary microvasculature and improvement in gas exchange.[49]

More recently, increased levels of PlGF, a pro-angiogenic and pro-inflammatory member of the VEGF family, exclusively upregulated in pathological conditions, have been found in the lung in a mouse CBDL HPS model.[50] Inhibition of PlGF decreased intrapulmonary shunting, reduced inflammation and improved oxygenation.[18]

Alveolar dysfunction

Recent studies suggest that restrictive ventilation defects occur in experimental and human HPS.[51,52] In CBDL animals, impaired alveolar integrity, normally maintained by surfactant protein (SP) production by alveolar type II (AT2) cells, appears to contribute. Apoptosis of AT2 cells with decreased SP levels has been observed in association with decreased alveolar chord length after CBDL.[53] Altered bile acid levels and composition and endotoxemia are hypothesised to contribute, as chenodeoxycholic acid, the bile acid nuclear receptor agonist GW4064, or TNFα increase apoptosis and reduce SP levels in cultured AT2 cells.[51] In addition, AT2 cell integrity and SP production are maintained in PVL rats where HPS does not develop and where circulating bile acid and TNFα levels are not elevated.

To summarise, the CBDL experimental model of HPS has provided valuable insight into the pathogenesis of HPS. The interplay between the diseased liver, the gut-liver axis and the lungs, including a complex interaction between pulmonary endothelial cells, inflammatory cells and respiratory epithelial cells underlies the development of the typical pulmonary alterations responsible for impaired oxygenation in this disease.

Natural history and prognosis

HPS significantly increases mortality and worsens quality of life.[1,5] Two single-centre studies and one prospective multicentre study have evaluated the natural history and prognosis of patients with HPS. The first single-centre study reported a median survival of 4.8 months for patients with HPS (n = 27), compared to 35.2 months for patients without HPS (n = 84).[54] In the second study, patients with HPS (n = 37) had a median survival of 24 months and a 5-year survival rate of 23%, compared to a median survival of 87 months and a 5-year survival rate of 63% in patients without HPS (n = 47).[8] The prospective multicentre study Pulmonary Vascular Complications of Liver Disease (PVCLD) demonstrated that in patients with cirrhosis being evaluated for LT, mortality was doubled in patients with HPS (n = 72) compared to those without HPS (n = 146), even after adjustment for LT, age, sex, race and MELD score.[1] Mortality is the highest in patients with severe HPS, and largely results from complications of liver disease or portal hypertension.[8,55,56] A cohort study of patients with HPS showed that PaO_2 decreases in 85% of patients over time, with an average decline of approximately 5 mmHg per year.[8] Long-term survival in HPS drastically changed with the recognition of LT as a cure for the disease, and after MELD exception implementation (more details below).[57] The natural history of HPS is illustrated in Fig. 4.

Management and treatment options

An overview of treatment options for HPS is provided in Box 1.

Medical treatment

Despite significant progress in HPS research, effective pharmacological therapies are not available. Novel treatments that either resolve and cure HPS or slow down its progression are needed to facilitate successful LT.

Case reports and small observational studies in which methylene blue, nebulized NG-nitro-L-arginine methyl ester, pentoxifylline, norfloxacin, aspirin, somatostatin, indomethacin, garlic or mycophenolate mofetil were administered either failed to show clear benefit or reported contradictory results. We refer to[19] for an overview of the studies performed.

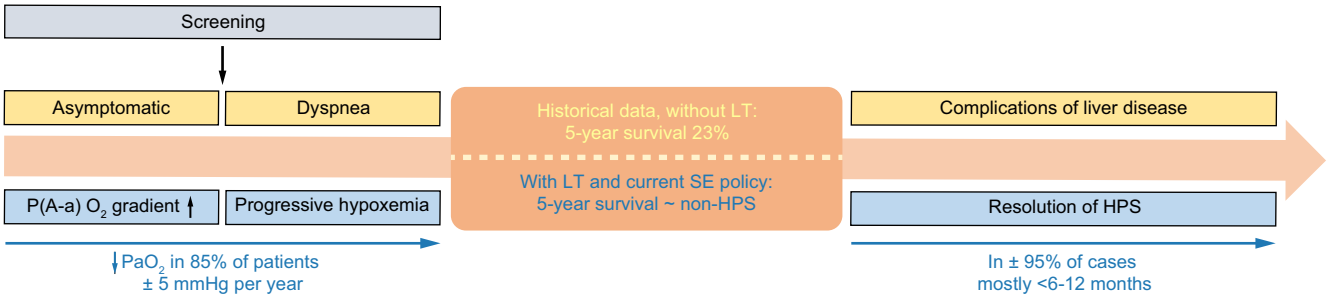
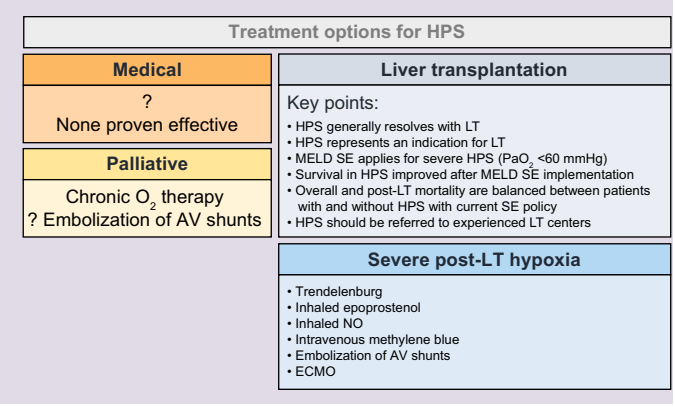


Fig. 4. Natural history of HPS. HPS is frequently detected by screening; most patients are asymptomatic or only experience dyspnea on exertion. ABG reveals a widened P(A-a) O_2 gradient. Hypoxemia is usually progressive over years. Untreated HPS carries poor prognosis. LT represents the only curable treatment option, and has led to significant survival improvements for affected patients over recent years. ABG, arterial blood gas; HPS, hepatopulmonary syndrome; LT, liver transplantation; P(A-a)O_2, alveolar-arterial oxygenation gradient; SE, standard exception.

Box 1. Treatment options for HPS.



AV, arteriovenous; ECMO, extracorporeal membrane oxygenation; HPS, hepatopulmonary syndrome; LT, liver transplantation; MELD, model for end-stage liver disease; NO, nitric oxide.

The identification of angiogenesis as an essential driver of HPS development stimulated interest in the use of angiogenesis inhibitors. In a first randomised-controlled pilot trial in HPS, 28 patients with Child-Pugh A/B cirrhosis were treated with low-dose sorafenib (400 mg per day) or placebo for 12 weeks based on findings in experimental HPS.[49] Sorafenib did not improve gas exchange or functional status at the dose used and was associated with recognised side effects.[58] Future trials will need to enhance targeting to critical pathways in humans and limit side effects.

Supportive and palliative therapy

Continuous long-term low-flow oxygen is the only effective supportive therapy for HPS, and should be started in case of severe hypoxemia at rest, based on the concept that the effect of chronic hypoxemia itself may contribute to mortality in HPS.[1] For patients with HPS who are not candidates for LT, coil embolisation of AV malformations is a potential palliative treatment.[59]

Liver transplantation

The role of LT in HPS has significantly evolved over the years. Initially, HPS was considered an absolute contraindication to LT, due to the perceived risk of poor post-LT outcome. Subsequently, several case series and small studies reported on the improvement of arterial oxygenation and IPVDs and the resolution of HPS after LT, with HPS becoming an indication for LT.

A 5-year post-LT survival of 76% has been observed in patients with HPS, which is comparable to that in patients with cirrhosis without HPS.[8] MELD standard exception (SE) points can be awarded to those with severe HPS (PaO_2 <60 mmHg), as hypoxemia in HPS is generally progressive, post-LT mortality is highest as severity worsens, and HPS severity does not correlate with the severity of the underlying liver disease.[60] LT has been shown to successfully improve HPS in the vast majority of patients (complete resolution in ±95% of cases, mostly within 6 to 12 months) with good overall survival.[55,57]

Data from large studies in the US and Europe, as well as a recent systematic review, indicate that, since the implementation of the MELD SE policy, outcomes in patients with HPS have been significantly better than they were in the pre-MELD era.[56,57,61–63] There have been discussions to determine the degree of hypoxemia at which patients with HPS will benefit from LT and still be able to achieve satisfactory post-LT outcomes. Earlier studies associated very severe HPS with an increased risk of complications and mortality after LT.[64] Analyses from the United Network for Organ Sharing (UNOS) database (from 2002-2012) indicated that post-LT outcome is similar in patients with HPS and without HPS, except in those with very severe HPS (PaO_2 ≤44 mmHg).[56] A recent study, collecting data from the UNOS database study through to 2019, found that overall survival was not different between patients with PaO_2 <45 mmHg, 45 to <60 mmHg and ≥60 mmHg.[63] Although post-LT survival was lower in patients with PaO_2 <45 mmHg, the outcomes were still good, given the median survival of 11.5 years, compared to 14.1 years in patients with PaO_2 ≥45 to <50 mmHg.[63] In any case, patients with severe HPS should be referred to specialised high-volume LT centres, with experience of treating severe post-LT hypoxemia.

Management of severe post-transplant hypoxemia

Severe post-transplant hypoxemia, defined as a need for 100% FiO_2 to maintain a saturation of ≥85%, occurs in 6-21% of patients with HPS and is associated with a peri-transplant mortality rate of 45%.[65] Due to impaired vasoconstriction in the dilated pulmonary blood vessels in HPS, normal pulmonary vessels may constrict disproportionately, resulting in increased flow through the dilated vessels, thereby worsening the V/Q mismatch. Trendelenburg position, inhaled epoprostenol, inhaled NO and/or intravenous methylene blue are potential medical interventions that aim to restore the V/Q equilibrium. Experts recommend maintaining all initially effective therapies, with sequential addition of others if needed in case of recurrent hypoxemia. If these options fail, large AV malformations can be embolised, and extracorporeal membrane oxygenation can be used as a "last resort".[65] A recent systematic review reported good outcomes with extracorporeal membrane oxygenation in patients with HPS either as a bridge to LT or to aid recovery after LT.[66]

Conclusion

Liver-lung interactions in liver disease, especially HPS, have gained increasing attention over the last decade. The CBDL model of experimental HPS has provided a pathogenic framework to further investigate underlying mechanisms and has significantly contributed to our current understanding of the disease. However, despite significant progress in HPS research, effective pharmacological therapies are still not available. Fortunately, LT is effective and complete resolution of the syndrome can be expected, with special attention being warranted in those with very severe disease. Future priorities include identifying links between experimental and human HPS, and organising studies trialling (probably a combination of) drugs directed at pathophysiological targets identified in preclinical studies.

Abbreviations

ABG, arterial blood gas; AT2, alveolar type II; AV, arteriovenous; CBDL, common bile duct ligation; ET-1, endothelin-1; ET_B, endothelin receptor B; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HPS, hepatopulmonary syndrome; IPVDs, intrapulmonary vascular dilatations; LT, liver transplantation; NO, nitric oxide; $P(A\text{-}a)O_2$, alveolar-arterial oxygenation gradient; PaO_2, partial pressure of arterial oxygen; PDGF, platelet-derived growth factor; PIGF, placental growth factor; PVL, portal vein ligation; SaO_2, oxygen saturation; SE, standard exception; SP, surfactant protein; TAA, thio-acetamide; Tc-MAA, ^{99m}Technetium-labeled macroaggregated albumin; TNFα, tumour necrosis factor alpha; UNOS, United Network for Organ Sharing; VCAM1, vascular cellular adhesion molecule 1; VEGF, vascular endothelial growth factor; V/Q, ventilation-perfusion; vWF, von Willebrand factor.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SR, MB and MBF: concept and design, writing of article, approval of final manuscript.

Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Fallon MB, Krowka MJ, Brown RS, Trotter JF, Zacks S, Roberts KE, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. Gastroenterology 2008;135:1168–1175. https://doi.org/10.1053/j.gastro.2008.06.038.

[2] Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, et al. International Liver Transplant Society Practice Guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation 2016;100:1440–1452. https://doi.org/10.1097/TP.0000000000001229.

[3] Krowka MJ, Wiseman GA, Burnett OL, Spivey JR, Therneau T, Porayko MK, et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO(2) response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. Chest 2000;118:615–624.

[4] Younis I, Sarwar S, Butt Z, Tanveer S, Qaadir A, Jadoon NA. Clinical characteristics, predictors, and survival among patients with hepatopulmonary syndrome. Ann Hepatol 2015;14:354–360.

[5] Kawut SM, Krowka MJ, Forde KA, Al-Naamani N, Krok KL, Patel M, et al. Impact of hepatopulmonary syndrome in liver transplantation candidates and the role of angiogenesis. Eur Respir J 2021:2102304. https://doi.org/10.1183/13993003.02304-2021.

[6] Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. Hepatology 2014;59:1627–1637. https://doi.org/10.1002/hep.26745.

[7] Bommena S, Gerkin RD, Agarwal S, Raevens S, Glassberg MK, Fallon MB. Diagnosis of hepatopulmonary syndrome in a large integrated health system. Clin Gastroenterol Hepatol 2021;19:2370–2378. https://doi.org/10.1016/j.cgh.2020.09.050.

[8] Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: impact of liver transplantation. Hepatology 2005;41:1122–1129. https://doi.org/10.1002/hep.20658.

[9] Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology 1995;109:1283–1288.

[10] Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallon MB. Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. Gastroenterology 1998;114:305–310.

[11] Martinez GP, Barbera JA, Visa J, Rimola A, Pare JC, Roca J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 2001;34:651–657.

[12] Raevens S, Colle I, Geerts A, Van Vlierberghe H. Why pulse oximetry is inaccurate in liver cirrhosis: ancient knowledge. Hepatology 2019;69:462–463. https://doi.org/10.1002/hep.30260.

[13] Forde KA, Fallon MB, Krowka MJ, Sprys M, Goldberg DS, Krok KL, et al. Pulse oximetry is insensitive for detection of hepatopulmonary syndrome in patients evaluated for liver transplantation. Hepatology 2019;69:270–281. https://doi.org/10.1002/hep.30139.

[14] Raevens S, Coulon S, Van Steenkiste C, Colman R, Verhelst X, Van Vlierberghe H, et al. Role of angiogenic factors/cell adhesion markers in serum of cirrhotic patients with hepatopulmonary syndrome. Liver Int 2014. https://doi.org/10.1111/liv.12579.

[15] Horvatits T, Drolz A, Roedl K, Herkner H, Ferlitsch A, Perkmann T, et al. Von Willebrand factor antigen for detection of hepatopulmonary syndrome in patients with cirrhosis. J Hepatol 2014;61:544–549. https://doi.org/10.1016/j.jhep.2014.04.025.

[16] Rodriguez-Roisin R, Roca J, Agusti AG, Mastai R, Wagner PD, Bosch J. Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. Am Rev Respir Dis 1987;135:1085–1092. https://doi.org/10.1164/arrd.1987.135.5.1085.

[17] Fallon MB, Abrams GA, McGrath JW, Hou Z, Luo B. Common bile duct ligation in the rat: a model of intrapulmonary vasodilatation and hepatopulmonary syndrome. Am J Physiol 1997;272:G779–G784.

[18] Raevens S, Geerts A, Paridaens A, Lefere S, Verhelst X, Hoorens A, et al. Placental growth factor inhibition targets pulmonary angiogenesis and represents a novel therapy for hepatopulmonary syndrome in mice. Hepatology 2017. https://doi.org/10.1002/hep.29579.

[19] Raevens S, Fallon MB. Potential clinical targets in hepatopulmonary syndrome: lessons from experimental models. Hepatology 2018. https://doi.org/10.1002/hep.30079.

[20] Königshofer P, Brusilovskaya K, Schwabl P, Reiberger T. Animal models of portal hypertension. Biochim Biophys Acta (BBA) - Mol Basis Dis 2019;1865:1019–1030. https://doi.org/10.1016/j.bbadis.2018.07.018.

[21] Luo B, Liu L, Tang L, Zhang J, Ling Y, Fallon MB. ET-1 and TNF-α in HPS: analysis in prehepatic portal hypertension and biliary and nonbiliary cirrhosis in rats. Am J Physiol-Gastrointestinal Liver Physiol 2004;286:G294–G303. https://doi.org/10.1152/ajpgi.00298.2003.

[22] Ling Y, Zhang J, Luo B, Song D, Liu L, Tang L, et al. The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. Hepatology 2004;39:1593–1602. https://doi.org/10.1002/hep.20244.

[23] **Geerts AM**, **Vanheule E**, Praet M, Van Vlierberghe H, De Vos M, Colle I. Comparison of three research models of portal hypertension in mice: macroscopic, histological and portal pressure evaluation. Int J Exp Pathol 2008;89:251–263. https://doi.org/10.1111/j.1365-2613.2008.00597.x.

[24] Fallon MB, Abrams GA, Luo B, Hou Z, Dai J, Ku DD. The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. Gastroenterology 1997;113:606–614.

[25] Zhang M, Luo B, Chen SJ, Abrams GA, Fallon MB. Endothelin-1 stimulation of endothelial nitric oxide synthase in the pathogenesis of hepatopulmonary syndrome. Am J Physiol 1999;277:G944–G952.

[26] Luo B, Liu L, Tang L, Zhang J, Stockard CR, Grizzle WE, et al. Increased pulmonary vascular endothelin B receptor expression and responsiveness to endothelin-1 in cirrhotic and portal hypertensive rats: a potential mechanism in experimental hepatopulmonary syndrome. J Hepatol 2003;38:556–563.

[27] Tang L, Luo B, Patel RP, Ling Y, Zhang J, Fallon MB. Modulation of pulmonary endothelial endothelin B receptor expression and signaling: implications for experimental hepatopulmonary syndrome. Am J Physiol Lung Cell Mol Physiol 2007;292:L1467–L1472. https://doi.org/10.1152/ajplung.00446.2006.

[28] Rolla G, Brussino L, Colagrande P, Dutto L, Polizzi S, Scappaticci E, et al. Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. Hepatology 1997;26:842–847. https://doi.org/10.1053/jhep.1997.v26.pm0009328302.

[29] Rolla G, Brussino L, Colagrande P, Scappaticci E, Morello M, Bergerone S, et al. Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation. Ann Intern Med 1998;129:375–378.

[30] Luo B, Tang L, Wang Z, Zhang J, Ling Y, Feng W, et al. Cholangiocyte endothelin 1 and transforming growth factor beta1 production in rat experimental hepatopulmonary syndrome. Gastroenterology 2005;129:682–695. https://doi.org/10.1016/j.gastro.2005.05.050.

[31] Cremona G, Higenbottam TW, Mayoral V, Alexander G, Demoncheaux E, Borland C, et al. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. Eur Respir J 1995;8:1883–1885.

[32] Nunes H, Lebrec D, Mazmanian M, Capron F, Heller J, Tazi KA, et al. Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. Am J Respir Crit Care Med 2001;164:879–885. https://doi.org/10.1164/ajrccm.164.5.2009008.

[33] Zhang XJ, Katsuta Y, Akimoto T, Ohsuga M, Aramaki T, Takano T. Intrapulmonary vascular dilatation and nitric oxide in hypoxemic rats with chronic bile duct ligation. J Hepatol 2003;39:724–730.

[34] Sztrymf B, Rabiller A, Nunes H, Savale L, Lebrec D, Le Pavec A, et al. Prevention of hepatopulmonary syndrome and hyperdynamic state by pentoxifylline in cirrhotic rats. Eur Respir J 2004;23:752–758.

[35] **Thenappan T**, **Goel A**, Marsboom G, Fang YH, Toth PT, Zhang HJ, et al. A central role for CD68(+) macrophages in hepatopulmonary syndrome. Reversal by macrophage depletion. Am J Respir Crit Care Med 2011;183:1080–1091. https://doi.org/10.1164/rccm.201008-1303OC.

[36] Sztrymf B, Libert JM, Mougeot C, Lebrec D, Mazmanian M, Humbert M, et al. Cirrhotic rats with bacterial translocation have higher incidence and severity of hepatopulmonary syndrome. J Gastroenterol Hepatol 2005;20:1538–1544. https://doi.org/10.1111/j.1440-1746.2005.03914.x.

[37] Fouts DE, Torralba M, Nelson KE, Brenner DA, Schnabl B. Bacterial translocation and changes in the intestinal microbiome in mouse models of liver disease. J Hepatol 2012;56:1283–1292. https://doi.org/10.1016/j.jhep.2012.01.019.

[38] Rabiller A, Nunes H, Lebrec D, Tazi KA, Wartski M, Dulmet E, et al. Prevention of gram-negative translocation reduces the severity of hepatopulmonary syndrome. Am J Respir Crit Care Med 2002;166:514–517. https://doi.org/10.1164/rccm.200201-027OC.

[39] Zhang J, Ling Y, Tang L, Luo B, Chacko BK, Patel RP, et al. Pentoxifylline attenuation of experimental hepatopulmonary syndrome. J Appl Physiol (1985) 2007;102:949–955. https://doi.org/10.1152/japplphysiol.01048.2006.

[40] Liu L, Liu N, Zhao Z, Liu J, Feng Y, Jiang H, et al. TNF-alpha neutralization improves experimental hepatopulmonary syndrome in rats. Liver Int 2012;32:1018–1026. https://doi.org/10.1111/j.1478-3231.2012.02821.x.

[41] Zhang HY, Han DW, Su AR, Zhang LT, Zhao ZF, Ji JQ, et al. Intestinal endotoxemia plays a central role in development of hepatopulmonary syndrome in a cirrhotic rat model induced by multiple pathogenic factors. World J Gastroenterol 2007;13:6385–6395.

[42] Chen B, Yang Y, Yang C, Duan J, Chen L, Lu K, et al. M2 macrophage accumulation contributes to pulmonary fibrosis, vascular dilatation, and hypoxemia in rat hepatopulmonary syndrome. J Cell Physiol 2021;236:7682–7697. https://doi.org/10.1002/jcp.30420.

[43] Zhang J, Yang W, Luo B, Hu B, Maheshwari A, Fallon MB. The role of CX(3)CL1/CX(3)CR1 in pulmonary angiogenesis and intravascular monocyte accumulation in rat experimental hepatopulmonary syndrome. J Hepatol 2012;57:752–758. https://doi.org/10.1016/j.jhep.2012.05.014.

[44] Li X, Chen Y, Chang Y, Li S, Zhao Z, Zhang H. CXCR2 is involved in pulmonary intravascular macrophage accumulation and angiogenesis in a rat model of hepatopulmonary syndrome. Clin Sci (Lond) 2017;131:159–168. https://doi.org/10.1042/CS20160593.

[45] Zhang J, Yang W, Hu B, Wu W, Fallon MB. Endothelin-1 activation of the endothelin B receptor modulates pulmonary endothelial CX3CL1 and contributes to pulmonary angiogenesis in experimental hepatopulmonary syndrome. Am J Pathol 2014;184:1706–1714. https://doi.org/10.1016/j.ajpath.2014.02.027.

[46] Wu W, Zhang J, Yang W, Hu B, Fallon MB. Role of splenic reservoir monocytes in pulmonary vascular monocyte accumulation in experimental hepatopulmonary syndrome. J Gastroenterol Hepatol 2016;31:1888–1894. https://doi.org/10.1111/jgh.13388.

[47] Zhang J, Ling Y, Luo B, Tang L, Ryter SW, Stockard CR, et al. Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. Gastroenterology 2003;125:1441–1451.

[48] Roberts KE, Kawut SM, Krowka MJ, Brown Jr RS, Trotter JF, Shah V, et al. Genetic risk factors for hepatopulmonary syndrome in patients with advanced liver disease. Gastroenterology 2010;139:130–139. https://doi.org/10.1053/j.gastro.2010.03.044.

[49] Chang CC, Chuang CL, Lee FY, Wang SS, Lin HC, Huang HC, et al. Sorafenib treatment improves hepatopulmonary syndrome in rats with biliary cirrhosis. Clin Sci (Lond) 2013;124:457–466. https://doi.org/10.1042/CS20120052.

[50] Fischer C, Jonckx B, Mazzone M, Zacchigna S, Loges S, Pattarini L, et al. Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. Cell 2007;131:463–475. https://doi.org/10.1016/j.cell.2007.08.038.

[51] Yang W, Hu B, Wu W, Batra S, Blackburn MR, Alcorn JL, et al. Alveolar type II epithelial cell dysfunction in rat experimental hepatopulmonary syndrome (HPS). PLoS One 2014;9:e113451. https://doi.org/10.1371/journal.pone.0113451.

[52] Melo-Silva CA, Gaio E, Trevizoli JE, Souza CS, Goncalves AS, Sousa GC, et al. Respiratory mechanics and lung tissue remodeling in a hepatopulmonary syndrome rat model. Respir Physiol Neurobiol 2011;179:326–333. https://doi.org/10.1016/j.resp.2011.10.001.

[53] Chen B, Ning JL, Gu JT, Cui J, Yang Y, Wang Z, et al. Caspase-3 inhibition prevents the development of hepatopulmonary syndrome in common bile duct ligation rats by alleviating pulmonary injury. Liver Int 2014. https://doi.org/10.1111/liv.12655.

[54] Schenk P, Schoniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Muller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology 2003;125:1042–1052.

[55] Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology 2003;37:192–197. https://doi.org/10.1053/jhep.2003.50023.

[56] Goldberg DS, Krok K, Batra S, Trotter JF, Kawut SM, Fallon MB. Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: an analysis of the UNOS database. Gastroenterology 2014;146:1256–1265. https://doi.org/10.1053/j.gastro.2014.01.005.

[57] Aragon Pinto C, Iyer VN, Albitar HAH, Anderson A, Cajigas H, Simonetto DA, et al. Outcomes of liver transplantation in patients with hepatopulmonary syndrome in the pre and post-MELD eras: a systematic review. Respir Med Res 2021;80:100852. https://doi.org/10.1016/j.resmer.2021.100852.

[58] Kawut SM, Ellenberg SS, Krowka MJ, Goldberg D, Vargas H, Koch D, et al. Sorafenib in hepatopulmonary syndrome: a randomized, double-blind, placebo-controlled trial. Liver Transpl 2019;25:1155–1164. https://doi.org/10.1002/lt.25438.

[59] Grady K, Gowda S, Kingah P, Soubani AO. Coil embolization of pulmonary arteries as a palliative treatment of diffuse Type I hepatopulmonary syndrome. Respir Care 2014. https://doi.org/10.4187/respcare.03198.

[60] Fallon MB, Mulligan DC, Gish RG, Krowka MJ. Model for end-stage liver disease (MELD) exception for hepatopulmonary syndrome. Liver Transpl 2006;12:S105–S107. https://doi.org/10.1002/lt.20971.

[61] Iyer VN, Swanson KL, Cartin-Ceba R, Dierkhising RA, Rosen CB, Heimbach JK, et al. Hepatopulmonary syndrome: favorable outcomes in the MELD exception era. Hepatology 2013;57:2427–2435. https://doi.org/10.1002/hep.26070.

[62] Raevens S, Rogiers X, Geerts A, Verhelst X, Samuel U, van Rosmalen M, et al. Outcome of liver transplantation for hepatopulmonary syndrome: a Eurotransplant experience. Eur Respir J 2019;53. https://doi.org/10.1183/13993003.01096-2018.

[63] Kadry Z, Schaefer E, Krok K, Faust A, Stine JG, Schreibman IR, et al. Excellent outcomes with liver transplantation in hepatopulmonary syndrome across pre-transplant PaO2 spectrum. JHEP Rep 2021;3:100351. https://doi.org/10.1016/j.jhepr.2021.100351.

[64] Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Liver Transpl 2004;10:174–182. https://doi.org/10.1002/lt.20016.

[65] Nayyar D, Man HS, Granton J, Gupta S. Defining and characterizing severe hypoxemia after liver transplantation in hepatopulmonary syndrome. Liver Transpl 2014;20:182–190. https://doi.org/10.1002/lt.23776.

[66] Wu WK, Grogan WM, Ziogas IA, Patel YJ, Bacchetta M, Alexopoulos SP. Extracorporeal membrane oxygenation in patients with hepatopulmonary syndrome undergoing liver transplantation: a systematic review of the literature. Transplant Rev 2022;36:100693. https://doi.org/10.1016/j.trre.2022.100693.