Pulmonary vascular complications of cirrhosis: hepatopulmonary syndrome and portopulmonary hypertension

Verstraeten Maïté[a,b], Lefere Sander[a,b] and Raevens Sarah[a,b]*

[a]*Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium.*

[b]*Hepatology Research Unit, Department of Internal Medicine and Pediatrics, Liver Research Center, Ghent University, Belgium.*

*Corresponding author. Address: Department of Gastroenterology and Hepatology, Ghent University Hospital, 1K12IE, Corneel Heymanslaan 10, 9000 Ghent, Belgium. E-mail address: sarah.raevens@ugent.be.

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Abstract: Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) are two distinct pulmonary vascular complications seen in patients with liver disease and/or portal hypertension. HPS is characterized by disturbed gas exchange and hypoxemia because of intrapulmonary vascular dilatations. POPH is defined by pulmonary arterial hypertension, which might lead to right heart failure. HPS affects up to 30% of patients with end-stage liver disease requiring liver transplantation. POPH is rarer and affects 1-5% of this patient population. If not recognized and left untreated, these disorders result in significant mortality. This review provides an update on HPS and POPH and discusses their clinical characteristics, screening and diagnostic modalities, and management, including the place of liver transplantation.

Keywords: hepatopulmonary syndrome; portopulmonary hypertension; portal hypertension; liver disease; cirrhosis; liver transplantation.

Hepatopulmonary syndrome

Definition and prevalence

Hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder characterized by intrapulmonary vascular dilatations (IPVDs) and arteriovenous (AV) shunts, leading to impaired gas exchange and hypoxemia. HPS affects 10-30% of patients with end-stage liver disease (ESLD) evaluated for liver transplantation (LT) [1]. HPS mostly occurs in patients with portal hypertension and cirrhosis, but it is also seen in patients with acute or chronic inflammatory liver disease, extrahepatic obstruction such as extrahepatic portal vein obstruction (pre-hepatic), inferior vena cava obstruction (post-hepatic) and Budd-Chiari syndrome (post-hepatic), and various vascular abnormalities that disrupt the normal liver-lung blood flow, such as Abernethy malformation. Notably, the severity of HPS does not seem to correlate with the severity of the underlying liver disease.

Clinical characteristics

In the early stages, HPS is frequently asymptomatic. As the hypoxemia progresses, patients increasingly report dyspnea. As disruption of the microvasculature mainly affects the basal parts of the lungs, patients may experience platypnea and orthodeoxia, which are dyspnea and hypoxemia that worsen in an upright position [2]. This specific phenomenon occurs in about 20% of the HPS patients.

Screening and diagnosis

The lack of familiarity with the disorder HPS often results in underdiagnosis. Diagnosis of HPS relies on a triad of criteria: (i) the presence of liver disease and/or portal hypertension, (ii) an elevated room air alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$ gradient] $\geq$ 15 mmHg (or > 20 mmHg when age $\geq$ 65 years) and (iii) evidence of IPVDs

(Figure 1) [3]. Impaired gas exchange is assessed with arterial blood gas (ABG) analysis performed in upright position. The severity of HPS is based on PaO_2 levels (Table 1). Pulse oximetry has been suggested in previous studies as a simple test for detecting oxygenation deficits, however early forms of HPS remain undetected [4]. Therefore, ABG analysis is recommended to capture all stages of HPS, including mild to moderate disease.

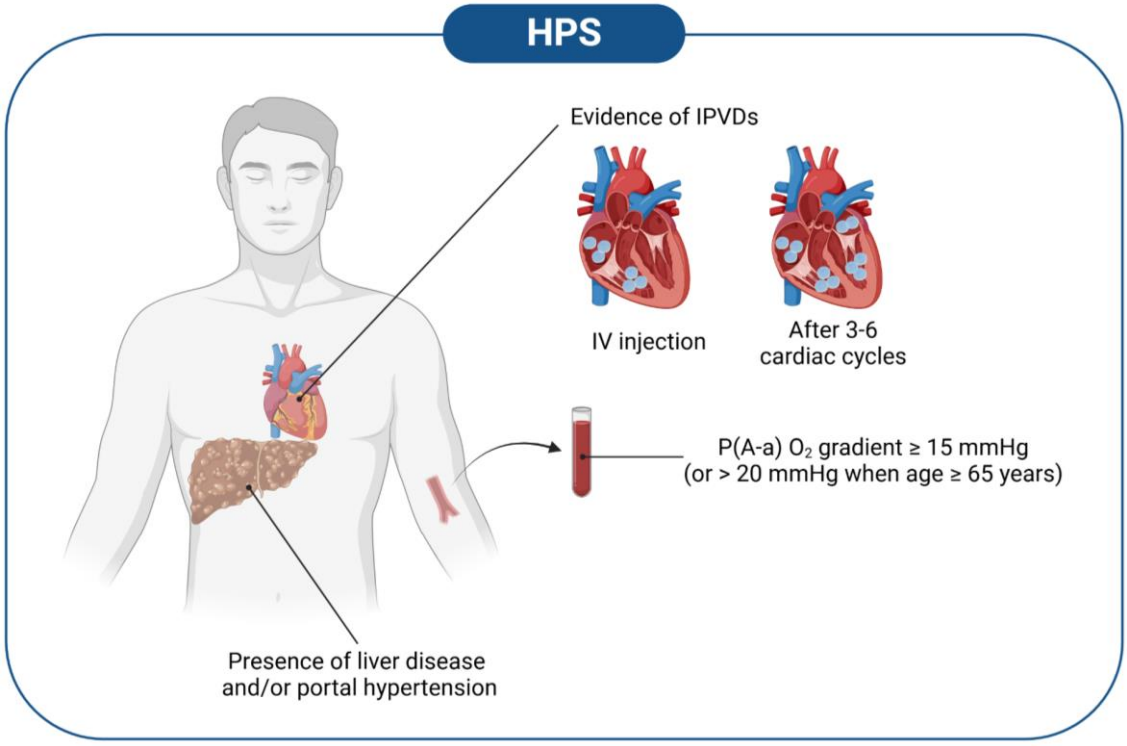


Figure 1. Diagnostic criteria for HPS. The diagnostic criteria for HPS consist of following triad: (i) the presence of liver disease and/or portal hypertension, (ii) $P(A\text{-}a)O_2$ gradient ≥ 15 mmHg (or > 20 mmHg when age ≥ 65 years) documented with arterial blood gas analysis and (iii) evidence of IPVDs. Microbubble transthoracic echocardiography is used to detect the delayed (3-6 cardiac cycles after being observed in the right heart) presence of microbubbles in the left heart after IV injection. Abbreviations: HPS, hepatopulmonary syndrome; IPVDs, intrapulmonary vascular

dilatations; IV, intravenous; P(A-a)O_2 gradient, room air alveolar-arterial oxygen gradient. Figure created in BioRender.

Table 1. Staging of severity of HPS. The severity of HPS is based on documented PaO_2 levels. Staging determined by the European Respiratory Task Force [5]. Abbreviations: HPS, hepatopulmonary syndrome; PaO_2, arterial oxygen pressure. Table created in BioRender.

		HPS
Stage	Mild	$PaO_2 \geq 80$ mmHg
	Moderate	60 mmHg $\leq PaO_2 <$ 80 mmHg
	Severe	50 mmHg $\leq PaO_2 <$ 60 mmHg
	Very severe	$PaO_2 <$ 50 mmHg

IPVDs are best detected using microbubble transthoracic echocardiography (MTTE) [6]. During MTTE, saline is shaken to generate microbubbles (> 10 µm) that, in healthy individuals, do not pass through the pulmonary capillary bed (< 8-15 µm) and are only detectable in the right heart. In patients with HPS, delayed (3-6 cardiac cycles after being observed in the right heart) appearance of microbubbles in the left heart after injection indicates the presence of IPVDs (Figure 1) [3]. An alternative, yet less well standardized method to document IPVDs, is the ^{99m}Technetium-labelled macroaggregated albumin (Tc-MAA) lung perfusion scan, during which Tc-MAA is

injected into a peripheral vein. Uptake of the radionuclide is studied in the brain and kidneys. Under normal circumstances, these injected macroaggregates (> 20 µm) become trapped in the pulmonary capillaries (< 8-15 µm). However, in patients with shunts, these aggregates pass through the capillary bed and are retained in the brain and kidneys. Lastly, biomarkers of endothelial dysfunction and angiogenesis, such as vascular cellular adhesion molecule 1 (VCAM1) and von Willebrand factor (vWF) seem to correlate with HPS, although further validation in larger patient cohorts is necessary [7,8].

Pathogenesis and pathophysiology

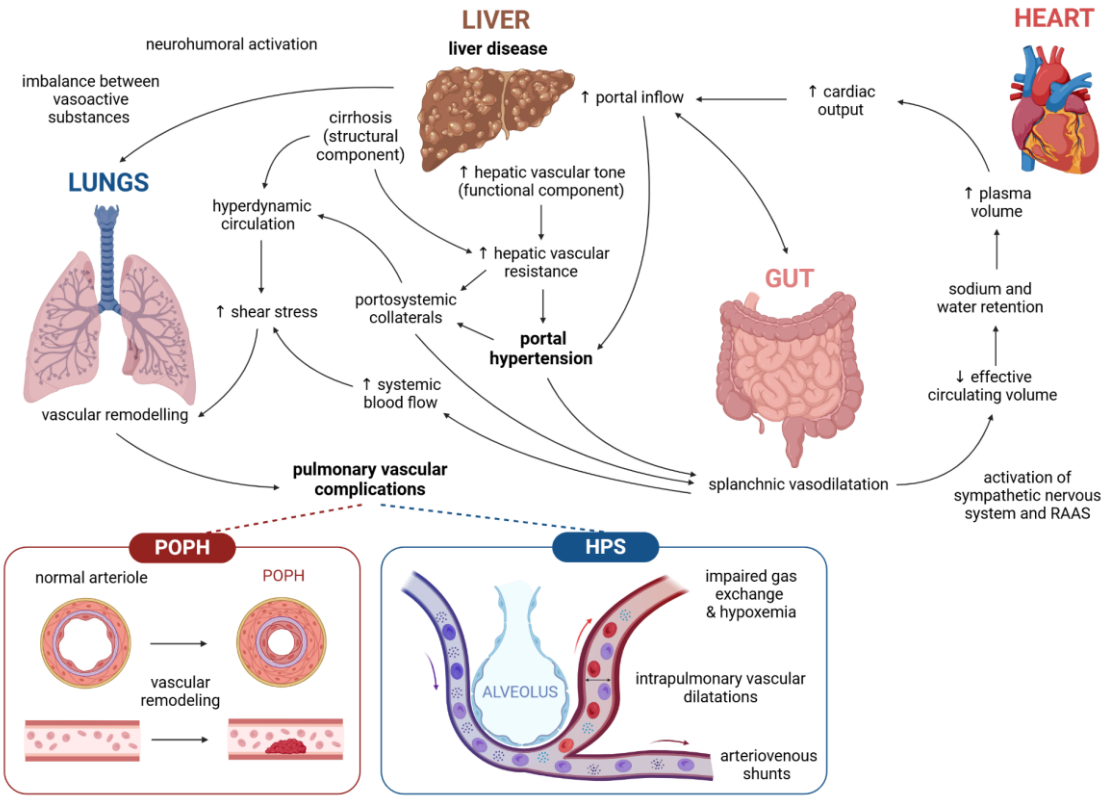


Figure 2. Pathophysiology of pulmonary vascular complications in liver disease and portal hypertension. POPH and HPS arise due to complex processes involving interactions between the lungs, the liver, the gut and the heart. Abbreviations: HPS, hepatopulmonary syndrome; POPH, portopulmonary hypertension; RAAS, renin-angiotensin-aldosterone system. Figure created in BioRender.

HPS arises due to complex interactions between the lungs, the liver, the gut and the heart (Figure 2). Three mechanisms contribute to gas exchange impairment and hypoxemia in HPS [1]. First, vasodilatation results in increased pulmonary blood flow while ventilation remains unchanged, creating a ventilation/perfusion (V/Q) mismatch. Second, oxygen diffusion limitation occurs as the distance that oxygen must travel to bind with hemoglobin in the centre of the capillary increases due to vasodilatation and alveolar dysfunction. Lastly, direct AV shunts allow blood to bypass the pulmonary capillaries, leading to the mixing of arterial and venous blood.

The common bile duct ligation (CBDL) model is a validated rat and mouse model for experimental HPS, in which the common bile duct is isolated and ligated, leading to features compatible with HPS and cirrhosis after 4 weeks in rats and 6 weeks in mice [9,10]. This model has provided valuable insights into the underlying pathophysiological mechanisms contributing to hypoxemia, which include: (i) vasodilatation, (ii) angiogenesis and (iii) alveolar dysfunction (Figure 2) [11]. Research utilizing this CBDL model has demonstrated that a complex interplay exists between the diseased liver, the gut-liver axis and the lungs [1]. This interaction involves pulmonary endothelial cells, monocytes, inflammatory cells and respiratory epithelial cells, leading to the production of chemokines, cytokines and angiogenic growth factors, which drive the typical pulmonary microvascular alterations responsible for impaired oxygenation and hypoxemia.

Vasodilatation

A major contributor to gas exchange abnormalities in HPS is the development of IPVDs, which is attributable to elevated levels of nitric oxide (NO). This NO production is primarily driven by increased levels of endothelial nitric oxide synthase (eNOS) and

inducible nitric oxide synthase (iNOS) [1,12]. Selective upregulation of the endothelin B (ETB) receptors in the pulmonary endothelium occurs as a hyperdynamic circulation with portal hypertension and increased pulmonary shear stress develop after CBDL. Combined with elevated levels of circulating endothelin-1 (ET-1) due to cholangiocyte production, this leads to activation of pulmonary eNOS, resulting in NO-mediated vascular relaxation [13–16].

Bacterial translocation, endotoxemia and pulmonary inflammation

The combination of intestinal bacterial overgrowth, mucosal barrier disruption, decreased hepatic clearance capacity and portosystemic shunting results in translocation of gut bacteria into the systemic circulation, which is commonly observed in cases of advanced liver disease [17,18]. Bacterial products and endotoxins subsequently enter the pulmonary circulation, triggering the local release of chemotactic factors that results in the homing of circulating immune cells into the pulmonary vasculature. These infiltrating pulmonary vascular monocytes have been found to express iNOS and haem oxygenase 1 (HO-1), leading to the production of NO and CO.

Angiogenesis leading to intrapulmonary arteriovenous shunt formation

The process of angiogenesis is defined as the formation of new blood vessels from pre-existing vessels and is mediated by angiogenic growth factors. Single-nucleotide polymorphisms (SNPs) in genes regulating angiogenesis, including endoglin (ENG) and vWF, have been linked to an increased risk of developing human HPS [19]. In experimental HPS, multiple pro-angiogenic factors, including vWF, vascular endothelial (VE)-cadherin, ENG, vascular endothelial growth factor (VEGF), platelet-derived growth

factor (PDGF) and placental growth factor (PlGF), have shown an increased pulmonary expression, especially in infiltrating monocytes [11,20–22].

Alveolar dysfunction

Research indicates that restrictive ventilation defects are present in both experimental and human HPS [23]. Impaired alveolar integrity, resulting from functional and structural alterations in the alveoli, is linked to increased apoptosis of alveolar type II (AT2) epithelial cells. This results in a decrease in the production of surfactant protein (SP), normally maintaining alveolar integrity, preventing collapse and regulating lung injury and inflammation [23]. This phenomenon is believed to further impair gas exchange and contribute to hypoxemia in HPS.

Natural history

HPS significantly increases morbidity and mortality and worsens the patients' quality of life drastically [24]. Historical data indicated that without LT, HPS patients have 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 [25]. 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 [25].

Treatment options

Medical treatment

Despite significant advancements in our understanding of the pathophysiology of HPS, substantial challenges remain in translating this knowledge into effective clinical interventions, which are unfortunately still lacking. Previous clinical studies exploring

pharmacological therapies (e.g., methylene blue, L-N^G-Nitro arginine methyl ester (L-NAME), pentoxifylline and norfloxacin) failed to show clear benefit [11]. There is an urgent need for (pre)clinical trials with novel treatment options focusing on known critical pathways, that can either resolve or significantly slow down the disease progression.

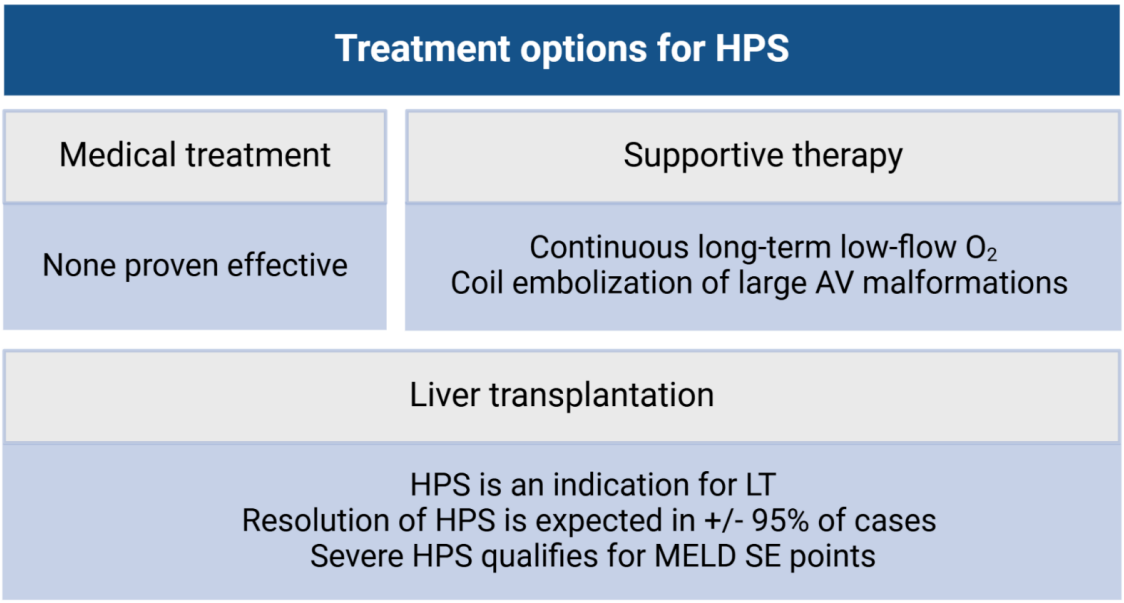
Supportive therapy

Supportive therapy for HPS consists of continuous long-term low-flow oxygen. For patients who are not suitable candidates for LT, coil embolization of large AV malformations may serve as a palliative treatment option [24].

Liver transplantation

Since the recognition that HPS resolves following LT, HPS has become an indication for LT [1]. Indeed, HPS completely resolves in +/- 95% of cases [26,27]. Patients with severe HPS are eligible for standard exception (SE) points, prioritizing them for LT. Since the implementation of this MELD SE policy, there is now no longer a difference in post-LT survival between patients with and without HPS [28–30]. A report from Eurotransplant has shown that with the current SE policy waitlist and post-transplant survival are well-balanced between patients with and without HPS, without disadvantaging the general transplant population (Box 1).

Box 1. Treatment options for HPS. Abbreviations: AV, arteriovenous; HPS, hepatopulmonary syndrome; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; O_2, dioxygen; SE, standard exception. Box created in BioRender.



Portopulmonary hypertension

Definition and prevalence

Portopulmonary hypertension (POPH), a subset of group 1 pulmonary arterial hypertension (PAH), is defined as the presence of PAH that evolves as a severe complication of portal hypertension, with or without liver disease [31]. Diagnosis of POPH relies on demonstrating portal hypertension alongside specific hemodynamic criteria obtained through right heart catheterization (RHC) (Figure 3). Approximately 1-5% of patients with ESLD requiring LT are affected with POPH [32]. Importantly, there is no association between the severity of liver disease nor the degree of portal hypertension and the development of POPH.

Clinical characteristics

Patients with POPH typically present with dyspnea on exertion and fatigue. Very early stages of POPH can be asymptomatic. Cardiomegaly or enlarged pulmonary arteries on chest radiography, right atrial enlargement, right ventricular hypertrophy, right axis deviation and right bundle branch block on electrocardiography can be additional clinical signs.

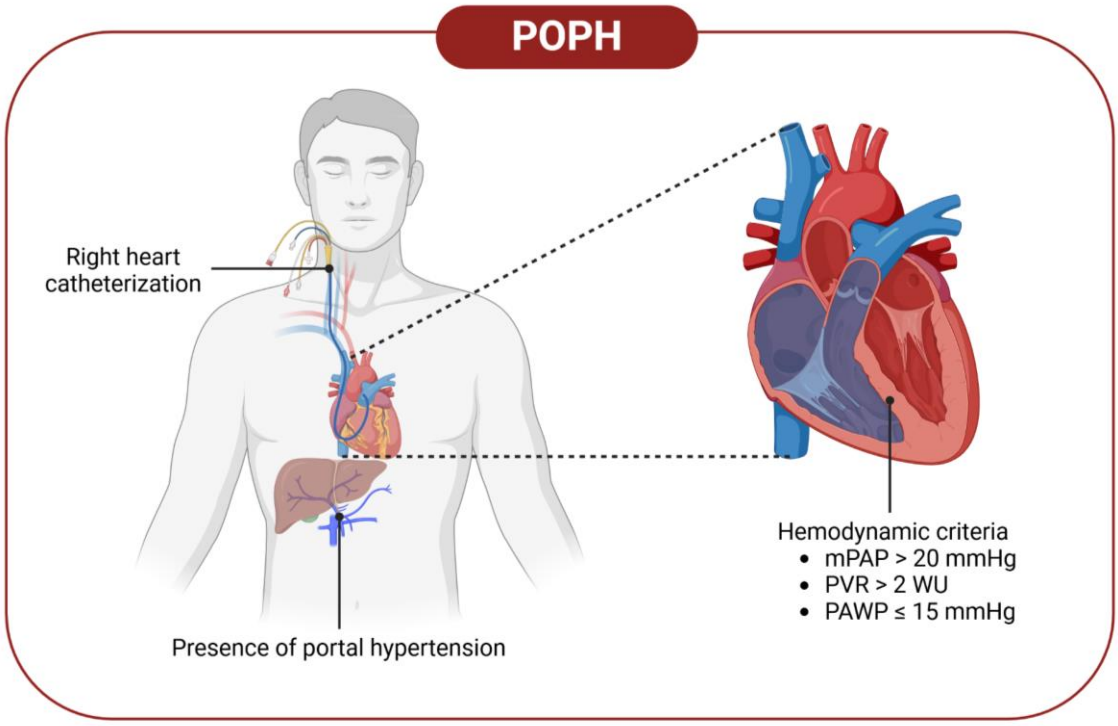


Figure 3. Diagnostic criteria for POPH. The diagnostic criteria for POPH consist of the following triad: (i) the presence of portal hypertension, (ii) a mean pulmonary artery pressure (mPAP) > 20 mmHg, measured with RHC, (iii) a pulmonary vascular resistance (PVR) > 2 WU and (iv) a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, measured with RHC. Abbreviations: POPH, portopulmonary hypertension; WU, Wood units. Figure created in BioRender.

Screening and diagnosis

Transthoracic echocardiography (TTE) is used as a screening method to estimate pulmonary pressure and to look for additional signs suggestive of pulmonary hypertension [31,32]. RHC remains the gold standard for confirming the diagnosis of POPH when pulmonary hypertension is suspected on TTE [33,34]. According to the latest guidelines for the diagnosis and treatment of pulmonary hypertension, the diagnosis of POPH is based on the presence of otherwise unexplained precapillary pulmonary hypertension in patients with portal hypertension or a portosystemic shunt [31]. The diagnostic criteria include (i) the presence of portal hypertension, (ii) a mean pulmonary artery pressure (mPAP) > 20 mmHg, (iii) a pulmonary vascular resistance (PVR) > 2 WU (Wood units) and (iv) a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg (Figure 3) [31]. Classification of POPH severity is based on mPAP levels (Table 2).

Table 2. Staging of severity of POPH. The severity of POPH is based on documented mPAP levels. Staging determined by the European Respiratory Task Force [5]. Abbreviations: mPAP, mean pulmonary artery pressure; POPH, portopulmonary hypertension. Table created in BioRender.

		POPH
Stage	Mild	20 mmHg < mPAP < 35 mmHg
	Moderate	35 mmHg ≤ mPAP < 45 mmHg
	Severe	mPAP ≥ 45 mmHg

Pathogenesis and pathophysiology

As no validated animal models are available to induce POPH, most knowledge about the pathogenesis of POPH comes from observations in humans and experience in PAH. The hyperdynamic circulation in patients with cirrhosis and/or portal hypertension is believed to induce shear stress in the pulmonary vascular bed and induce vascular remodelling. Vascular remodelling includes media hypertrophy with smooth muscle cell proliferation, intima proliferation, platelet aggregation, *in situ* thrombosis and plexogenic arteriopathy, leading to thickening of the arterial walls and occlusion of the blood vessels, both responsible for the increased PVR [35]. Furthermore, the increased intrahepatic resistance in cirrhosis leads to the formation of portosystemic collaterals. Vasoactive substances (ET-1A, TXA2 (tromboxane A2), IL-1 (interleukin-1), IL-6 (interleukin-6), AT1 (angiotensin-1), glucagon and 5-HT (serotonin)) produced by the diseased liver or normally metabolized by a healthy liver reach and disturb the pulmonary circulation through these portosystemic shunts (Figure 2) [32].

Natural history and prognosis

Uncontrolled POPH is associated with a poor prognosis. Severe pulmonary hypertension may lead to right heart failure and ultimately result in death. Without any intervention, patients can expect a mean survival of approximately 15 months, a 6-month survival rate of 50% and a 5-year survival rate ranging from 4 to 14% [35,36].

Treatment options

Medical treatment

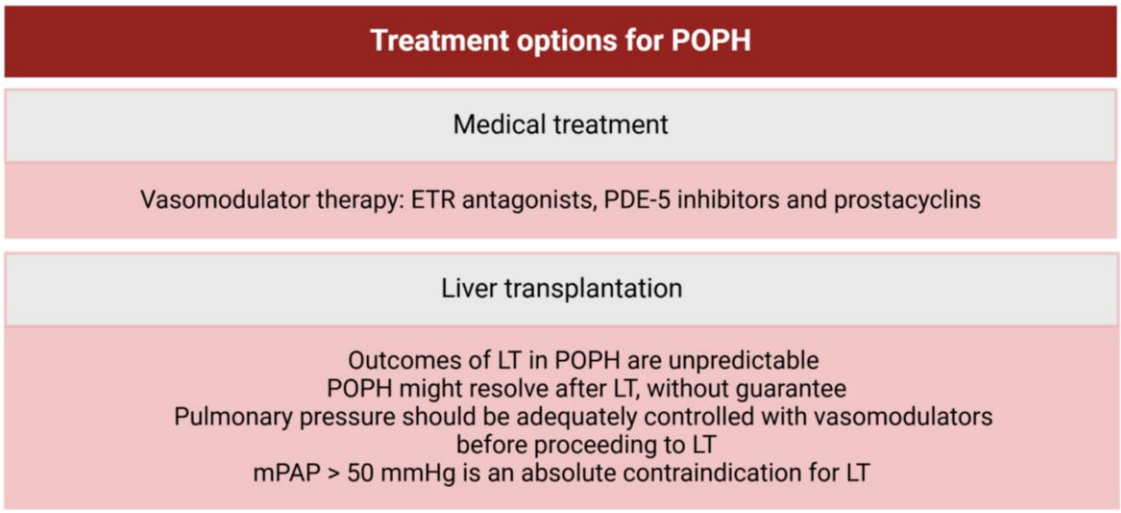
Treatment for POPH largely revolves around vasomodulator therapies, which have demonstrated efficacy in managing PAH. Current PAH drugs target three critical

pathways: the ET pathway, the NO pathway and the prostacyclin pathway [37]. All drugs approved for PAH, including ET receptor antagonists such as bosentan, ambrisentan and macitentan, can principally also be used to treat POPH patients, keeping in mind that patients with POPH were always excluded from PAH studies. Evidence supporting the use of bosentan and ambrisentan in patients with POPH comes primarily from small case series and own observational experience. The PORTICO trial stands out as the only randomized controlled trial (RCT) performed in POPH patients. This 12-week study randomized 85 patients to macitentan (n=43) or placebo (n=42). PORTICO successfully met its primary endpoint, demonstrating an improvement in PVR in POPH patients treated with macitentan, with no hepatic safety concerns [38]. The phosphodiesterase type 5 (PDE-5) inhibitors sildenafil, vardenafil and tadalafil mediate vasodilatation by interfering with cyclic guanosine monophosphate (cGMP) metabolism. They should be used cautiously as they may increase portal hypertension by splanchnic vasodilatation. Riociguat therapy, a guanylate cyclase (GC) inhibitor, has beneficial effects specifically in POPH patients, but with the disadvantage of inducing hypotension in 10% of the patients [32]. Therapy with prostacyclin analogues, including IV epoprostenol, inhaled iloprost and subcutaneous treprostinil results in vasodilatation and has antiplatelet-aggregating and antiproliferative effects. However, adverse effects in terms of safety and tolerability (jaw pain, headache, erythema, arthralgias, gastrointestinal problems, pump malfunction, high cardiac output state and hypersplenism), besides concerns about the administration route (catheter thrombosis, infection and sepsis in case of IV administration) can occur. Moreover, prostacyclins can cause rebound PAH, worsening hepatic function and portal hypertension [32].

Liver transplantation

In contrast to HPS, outcomes of LT in patients with POPH are rather unpredictable. While LT can potentially cure POPH, severely elevated pulmonary pressures in POPH may contraindicate LT due to high perioperative and postoperative risks. Patients with mPAP below 35 mmHg can undergo LT, potentially resolving POPH, whereas patients with an mPAP between 35 and 45 mmHg should first effectively be treated with vasomodulator therapy before proceeding to LT [39]. Patients with mPAP over 45 mmHg should primarily be treated with vasomodulators, and only if pulmonary pressures adequately drop, LT may be considered. mPAP > 50 mmHg is an absolute contraindication for LT [40]. This highlights the importance of careful management and intervention in patients with POPH who are waitlisted for LT. Given the poor outcomes associated with POPH and the effectiveness of vasomodulator therapy in bridging to LT, patients diagnosed with POPH who achieve mPAP < 35 mmHg can qualify for MELD SE points (Box 2) [32].

Box 2. Treatment options for POPH. Abbreviations: ETR, endothelin receptor; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; mPAP, mean pulmonary artery pressure; PDE-5, phosphodiesterase type 5; POPH, portopulmonary hypertension; SE, standard exception. Box created in BioRender.



References

[1] Raevens S, Boret M, Fallon MB. Hepatopulmonary syndrome. JHEP Reports. 2022;4(9). doi:10.1016/j.jhepr.2022.100527

[2] Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. Hepatology. 2014;59(4):1627-1637. doi:10.1002/hep.26745

[3] Krowka MJ, Fallon MB, Kawut SM, et al. International Liver Transplant Society Practice Guidelines. Transplantation. 2016;100(7):1440-1452. doi:10.1097/TP.0000000000001229

[4] Forde KA, Fallon MB, Krowka MJ, et al. Pulse Oximetry Is Insensitive for Detection of Hepatopulmonary Syndrome in Patients Evaluated for Liver Transplantation. Hepatology. 2019;69(1):270-281. doi:10.1002/hep.30139

[5] Rodríguez-Roisin R, Krowka MJ, Hervé Ph, et al. Pulmonary–Hepatic vascular Disorders (PHD). European Respiratory Journal. 2004;24(5):861-880. doi:10.1183/09031936.04.00010904

[6] Abrams GA, Jaffe CC, Hoffer PB, et al. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology. 1995;109(4):1283-1288. doi:10.1016/0016-5085(95)90589-8

[7] Raevens S, Coulon S, Van Steenkiste C, et al. Role of angiogenic factors/cell adhesion markers in serum of cirrhotic patients with hepatopulmonary syndrome. Liver International. 2015;35(5):1499-1507. doi:10.1111/liv.12579

[8] Horvatits T, Drolz A, Roedl K, et al. von Willebrand factor antigen for detection of hepatopulmonary syndrome in patients with cirrhosis. J Hepatol. 2014;61(3):544-549. doi:10.1016/j.jhep.2014.04.025

[9] Fallon MB, Abrams GA, McGrath JW, et al. Common bile duct ligation in the rat: a model of intrapulmonary vasodilatation and hepatopulmonary syndrome. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1997;272(4):G779-G784. doi:10.1152/ajpgi.1997.272.4.G779

[10] Geerts AM, Vanheule E, Praet M, et al. Comparison of three research models of portal hypertension in mice: macroscopic, histological and portal pressure evaluation. Int J Exp Pathol. 2008;89(4):251-263. doi:10.1111/j.1365-2613.2008.00597.x

[11] Raevens S, Fallon MB. Potential Clinical Targets in Hepatopulmonary Syndrome: Lessons From Experimental Models. Hepatology. 2018;68(5):2016-2028. doi:10.1002/hep.30079

[12] Qasim A, Jyala A, Shrivastava S, et al. Hepatopulmonary Syndrome: A Comprehensive Review. Cureus. Published online July 23, 2024. doi:10.7759/cureus.65204

[13] Yang W, Zhang J, Hu B, et al. The role of receptor tyrosine kinase activation in cholangiocytes and pulmonary vascular endothelium in experimental hepatopulmonary syndrome. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2014;306(1):G72-G80. doi:10.1152/ajpgi.00178.2013

[14] Tang L, Luo B, Patel RP, et al. Modulation of pulmonary endothelial endothelin B receptor expression and signaling: implications for experimental hepatopulmonary syndrome. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2007;292(6):L1467-L1472. doi:10.1152/ajplung.00446.2006

[15] Ling Y, Zhang J, Luo B, et al. The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. Hepatology. 2004;39(6):1593-1602. doi:10.1002/hep.20244

[16] Luo B, Liu L, Tang L, 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(5):556-563. doi:10.1016/S0168-8278(03)00012-6

[17] Fouts DE, Torralba M, Nelson KE, et al. Bacterial translocation and changes in the intestinal microbiome in mouse models of liver disease. J Hepatol. 2012;56(6):1283-1292. doi:10.1016/j.jhep.2012.01.019

[18] Zhang HY. 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(47):6385. doi:10.3748/wjg.v13.i47.6385

[19] Roberts KE, Kawut SM, Krowka MJ, et al. Genetic Risk Factors for Hepatopulmonary Syndrome in Patients With Advanced Liver Disease. Gastroenterology. 2010;139(1):130-139.e24. doi:10.1053/j.gastro.2010.03.044

[20] Raevens S, Geerts A, Paridaens A, et al. Placental growth factor inhibition targets pulmonary angiogenesis and represents a therapy for hepatopulmonary syndrome in mice†. Hepatology. 2018;68(2):634-651. doi:10.1002/hep.29579

[21] Zhang J, Luo B, Tang L, et al. Pulmonary Angiogenesis in a Rat Model of Hepatopulmonary Syndrome. Gastroenterology. 2009;136(3):1070-1080. doi:10.1053/j.gastro.2008.12.001

[22] Thenappan T, Goel A, Marsboom G, et al. A Central Role for CD68(+) Macrophages in Hepatopulmonary Syndrome. Am J Respir Crit Care Med. 2011;183(8):1080-1091. doi:10.1164/rccm.201008-1303OC

[23] Yang W, Hu B, Wu W, et al. Alveolar Type II Epithelial Cell Dysfunction in Rat Experimental Hepatopulmonary Syndrome (HPS). PLoS One. 2014;9(11):e113451. doi:10.1371/journal.pone.0113451

[24] Fallon MB, Krowka MJ, Brown RS, et al. Impact of Hepatopulmonary Syndrome on Quality of Life and Survival in Liver Transplant Candidates. Gastroenterology. 2008;135(4):1168-1175. doi:10.1053/j.gastro.2008.06.038

[25] Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome. Hepatology. 2005;41(5):1122-1129. doi:10.1002/hep.20658

[26] Aragon Pinto C, Iyer VN, Albitar HAH, 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. doi:10.1016/j.resmer.2021.100852

[27] Arguedas MR, Abrams GA, Krowka MJ, et al. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology. 2003;37(1):192-197. doi:10.1053/jhep.2003.50023

[28] Goldberg DS, Krok K, Batra S, et al. Impact of the Hepatopulmonary Syndrome MELD Exception Policy on Outcomes of Patients After Liver Transplantation: An Analysis of the UNOS Database. Gastroenterology. 2014;146(5):1256-1265.e1. doi:10.1053/j.gastro.2014.01.005

[29] Raevens S, Rogiers X, Geerts A, et al. Outcome of liver transplantation for hepatopulmonary syndrome: A Eurotransplant experience. European Respiratory Journal. 2019;53(2). doi:10.1183/13993003.01096-2018

[30] Kadry Z, Schaefer E, Krok K, et al. Excellent outcomes with liver transplantation in hepatopulmonary syndrome across pre-transplant PaO2 spectrum. JHEP Reports. 2021;3(5). doi:10.1016/j.jhepr.2021.100351

[31] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 2023;61(1):2200879. doi:10.1183/13993003.00879-2022

[32] Raevens S, Geerts A, Van Steenkiste C, et al. Hepatopulmonary syndrome and portopulmonary hypertension: recent knowledge in pathogenesis and overview of clinical assessment. Liver International. 2015;35(6):1646-1660. doi:10.1111/liv.12791

[33] Bart NK, Liu K, Kotlyar E, et al. Portopulmonary Hypertension: The Interplay Between the Liver and Pulmonary Arteries. Heart Lung Circ. 2022;31(9):1185-1187. doi:10.1016/j.hlc.2022.07.010

[34] Pilatis ND, Jacobs LE, Rerkpattanapipat P, et al. Clinical predictors of pulmonary hypertension in patients undergoing liver transplant evaluation. Liver Transplantation. 2000;6(1):85-91. doi:10.1002/lt.500060116

[35] Jasso-Baltazar EA, Peña-Arellano GA, Aguirre-Valadez J, et al. Portopulmonary Hypertension: An Updated Review. Transplant Direct. 2023;9(8):e1517. doi:10.1097/TXD.0000000000001517

[36] Swanson KL, Wiesner RH, Nyberg SL, et al. Survival in Portopulmonary Hypertension: Mayo Clinic Experience Categorized by Treatment Subgroups.

American Journal of Transplantation. 2008;8(11):2445-2453. doi:10.1111/j.1600-6143.2008.02384.x

[37] DuBrock HM. Portopulmonary Hypertension. Chest. 2023;164(1):206-214. doi:10.1016/j.chest.2023.01.009

[38] Sitbon O, Bosch J, Cottreel E, et al. Macitentan for the treatment of portopulmonary hypertension (PORTICO): a multicentre, randomised, double-blind, placebo-controlled, phase 4 trial. Lancet Respir Med. 2019;7(7):594-604. doi:10.1016/S2213-2600(19)30091-8

[39] Deroo R, Trépo E, Holvoet T, et al. Vasomodulators and Liver Transplantation for Portopulmonary Hypertension: Evidence From a Systematic Review and Meta-Analysis. Hepatology. 2020;72(5):1701-1716. doi:10.1002/hep.31164

[40] Verma S, Hand F, Armstrong MJ, et al. Portopulmonary hypertension: Still an appropriate consideration for liver transplantation? Liver Transplantation. 2016;22(12):1637-1642. doi:10.1002/lt.24625