

Review article: Update on current and emergent data on hepatopulmonary syndrome

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Abstract

Hepatopulmonary syndrome (HPS) is a frequent pulmonary complication of end-stage liver disease, characterized by impaired arterial oxygenation induced by intrapulmonary vascular dilatation. Its prevalence ranges from 4% to 47% in patients with cirrhosis due to the different diagnostic criteria applied among different studies. Nitric oxide overproduction and angiogenesis seem to be the hallmarks of a complicated pathogenetic mechanism, leading to intrapulmonary shunting and ventilation-perfusion mismatch. A classification of HPS according to the severity of hypoxemia has been suggested. Contrast-enhanced echocardiography represents the gold standard method for the detection of intrapulmonary vascular dilatations which is required, in combination with an elevated alveolar arterial gradient to set the diagnosis. The only effective treatment which can modify the syndrome's natural history is liver transplantation. Although it is usually asymptomatic, HPS imparts a high risk of pretransplantation mortality, independently of the severity of liver disease, while there is variable data concerning survival rates after liver transplantation. The potential of myocardial involvement in the setting of HPS has also gained increasing interest in recent research. The aim of this review is to critically approach the existing literature of HPS and emphasize

unclear points that remain to be unraveled by future research.

Key words: Hepatopulmonary syndrome; Liver cirrhosis; Liver transplantation; Portal hypertension; Contrast echocardiography

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Core tip: Hepatopulmonary syndrome (HPS) constitutes a relatively frequent complication of end-stage liver disease, characterized by impairment of arterial oxygenation. The only effective treatment is liver transplantation, improving hypoxemia. While there are controversial data regarding HPS prognosis before and after liver transplantation, the question remains whether HPS constitutes an independent factor of morbidity, providing HPS patients priority for liver transplantation. Furthermore, possible associations with myocardial function, which could support the utility of echocardiographical parameters as markers of HPS, remain yet to be established.

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INTRODUCTION

Liver cirrhosis is often accompanied by complications from the pulmonary system. These include hepatic hydrothorax, portopulmonary hypertension and hepatopulmonary syndrome (HPS). Hepatic hydrothorax affects approximately 6%-10% of patients with end-stage liver disease and is the result of ascetic fluid passage to the pleural space through diaphragmatic defects^[1]. Portopulmonary hypertension is characterized by pulmonary vasoconstriction and increased vascular resistance, developing in 2%-8.5% of patients with portal hypertension, combined with poor prognosis^[2].

HPS constitutes a pulmonary disorder of chronic liver disease, characterized by poor arterial oxygenation and intrapulmonary vascular dilatations^[3]. Although Fluckiger was the first to describe the syndrome in 1884, treating a woman with liver cirrhosis and cyanosis without any other obvious reason for pulmonary disease, the term "Hepatopulmonary Syndrome" was suggested in 1977 by Kennedy and Knudson^[4]. Former autopsy studies had previously demonstrated the potential role of pulmonary vascular dilatations in the development of the syndrome^[5,6].

The revised diagnostic criteria for HPS comprise the triad of chronic liver disease, pulmonary vascular

dilatation and gas exchange abnormalities in the absence of other causes of impaired pulmonary function^[7]. Except for chronic liver disease, HPS can coexist with acute or chronic hepatitis, portal hypertension without liver disease, alpha 1 antitrypsin deficiency, Wilson's disease and Abernathy malformation^[8,9]. Defining gas exchange abnormalities, an increased alveolar-arterial oxygen gradient (> 15 mmHg or > 20 mmHg for age > 65 years) was suggested as a more sensitive marker of impaired pulmonary function in cirrhotic patients^[3]. The presence of intrapulmonary dilatations can be assessed by several methods, but contrast-enhanced echocardiography with agitated saline is considered the gold standard technique^[7].

The aim of this review is to provide a critical overview on prevalence, pathogenesis, diagnosis, clinical manifestations, treatment options and current data regarding prognosis before and after liver transplantation in patients with HPS. Upcoming data suggest remarkable associations between the presence of HPS and specific serum markers, clinical signs and echocardiographic parameters which are worthy of discussion.

SEARCH STRATEGY

A literature search was conducted using the online databases Medline, Embase and Scopus until January 2017 for original research papers and review articles concerning pathogenesis, clinical manifestations, diagnosis and management of HPS. Studies evaluating myocardial function in the setting of HPS were also included. The combination of the following terms was used to identify relevant publications: "liver cirrhosis" OR "prevalence" OR "diagnosis" OR "vasodilatation" OR "clinical features" OR "orthodeoxia" OR "platypnea" OR "treatment" OR "liver transplantation" OR "cardiac involvement" OR "myocardial function" AND "hepatopulmonary syndrome". The collected literature was examined for cited articles relevant to the subject to ensure that no important research data were missed. Articles that had been published as full journal articles in English were included. The above terms were used in ClinicalTrials.gov to search for recently completed or ongoing trials on HPS. Not accessible abstracts, conference proceedings or articles not translated in English were excluded.

PREVALENCE AND SEVERITY

Previous studies have used different criteria in terms of diagnostic methodology for HPS. More specifically, different thresholds for alveolar-arterial gradient and partial pressure of oxygen (PaO₂) have been used in order to define gas-exchange abnormalities, leading to a wide range of HPS prevalence rates^[10]. Furthermore, different diagnostic methods have been performed to evaluate intrapulmonary dilatations. Based on

Table 1 Hepatopulmonary syndrome-diagnostic criteria

Presence of liver disease and/or portal hypertension AND
Partial pressure of oxygen < 80 mmHg or alveolar-arterial oxygen gradient [P(A-a)O ₂ gradient] ≥ 15 mmHg (or > 20 mmHg for patients > 65-years-old) while breathing ambient air AND
Documented intrapulmonary vascular dilatation by contrast-enhanced echocardiography or lung perfusion scanning with radioactive albumin

Table 2 Hepatopulmonary syndrome-severity classification

Mild	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ 80 mmHg
Moderate	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ 60 mmHg to < 80 mmHg
Severe	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ 50 mmHg to < 60 mmHg
Very severe	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen < 50 mmHg

reports from several liver transplantation centers, the prevalence of HPS ranges from 4% to 47% in patients with liver cirrhosis^[11-14]. The introduction of specific diagnostic criteria (Table 1), including the definition of impaired oxygenation, by the European Respiratory Society Task Force in 2004, provides the opportunity to obtain comparable results from recent studies^[3]. The establishment of alveolar-arterial gradient as a more sensitive marker of pulmonary function as well as the screening of asymptomatic patients has led to higher rates of HPS diagnosis. Nevertheless, further well-designed, prospective, multicenter studies are needed for more accurate estimation of the syndrome's prevalence. Interestingly, intrapulmonary vascular dilatations can be detected in 13%-80% of liver transplantation candidates regardless of the development of arterial oxygenation abnormalities^[15].

The evaluation of PaO₂ in the arterial blood is crucial for classification of the syndrome. According to arterial blood gas analysis, four severity stages of HPS can be distinguished while the patient is breathing ambient air (Table 2): mild (PaO₂ ≥ 80 mmHg), moderate (PaO₂ ≥ 60 and < 80 mmHg), severe (PaO₂ ≥ 50 to < 60 mmHg), and very severe (PaO₂ < 50 mmHg)^[2]. The existing data suggest that the majority of HPS patients are mild or moderate stage, while severe and very severe cases seem to be less common^[16,17]. No associations have been demonstrated between the presence or severity of HPS and the severity of liver disease^[18]. However, there is restricted data concerning HPS severity assessment, highlighting the need for well-designed HPS protocols in future studies.

PATHOGENESIS AND PATHOPHYSIOLOGY

Intrapulmonary capillary vasodilatations constitute the main anatomic disturbance of HPS leading to impaired arterial oxygenation through ventilation-perfusion mismatch^[3,19]. The diameter of the dilated vessels may vary from 15-100 μm and in some cases to 500 μm when HPS is present, whereas normally it ranges between 8 μm and 15 μm^[20,21]. Dilatation of pre-capillary and capillary vessels in combination with

reduced or absent tone of pulmonary vasculature result in increased pulmonary blood flow, which is also boosted by hyperdynamic circulation in liver disease. In this way, there is an overperfusion of the alveolar capillary bed combined with a decrease in transit time of red blood cells, while ventilation remains unchanged. As a result, an excessive amount of blood passes through the pulmonary circulation without completing gas exchange, leading to increased alveolar arterial gradient and arterial hypoxemia^[22], particularly during muscular activity^[23].

Oxygen molecules have to cross a longer distance in less time to reach red blood cells in the center of the pulmonary capillaries due to vascular dilatation^[24], while an increase in pulmonary capillary wall thickness has also been observed^[21,25]. This alteration in oxygen diffusion contributes in the impaired oxygenation of HPS and could be correlated to the abnormal values of carbon monoxide diffusing capacity observed in these patients^[14].

Intrapulmonary arteriovenous shunting constitutes another mechanism causing arterial hypoxia in HPS^[6]. Mixed blood passes through pleural and pulmonary arteriovenous communications directly into the central circulation, without coming in touch with the alveoli. A few portopulmonary vascular communications can also be observed. The presence of more pronounced vascular dilatations and arteriovenous communications in lower lung zones, as it was suggested by thoracic computed tomography scans, may interpret the mechanism of orthodeoxia, *i.e.* reduction of PaO₂ from supine to upright patient position^[26]. Gravitational pulmonary blood flow redistribution leads to overperfusion of these lower lung zones and increased intrapulmonary shunting, perhaps due to a more altered, maladjusted vascular tone^[27].

It seems that the severity of arterial hypoxemia is related to the extent of ventilation-perfusion mismatch, intrapulmonary shunting and diffusion impairment^[28]. Administration of 100% oxygen [≥ 300 mmHg (40.0 kPa)] may improve hypoxia in some cases of HPS, as it provides enough pressure to partly overcome the diffusing limitation arising from the dilated pulmonary

vessels^[29,30]. However, there is no effect in partial pressure of oxygen when hypoxia is the result of excessive arteriovenous blood shunting.

Pulmonary vasodilatation

Intrapulmonary vascular dilatations seem to be the result of an imbalance between several vasodilators and vasoconstrictors. Much of our knowledge arises from studies on rat experimental models, in which a common bile duct ligation has been performed in order to develop secondary biliary cirrhosis. The increased production of nitric oxide (NO) and carbon monoxide (CO), two pulmonary vasodilators, constitutes the key process for the development of pulmonary vasodilatation^[31]. In common bile duct ligation animal models, the proliferation of cholangiocytes is followed by production and secretion of endothelin-1 (ET-1) after the stimulation by transforming growth factor beta-1 (TGFβ-1)^[32,33]. The binding of endothelin-1 to its pulmonary receptor ET-1B triggers the activation of endothelial and inducible nitric oxide synthase (eNOS and iNOS) resulting in elevated NO production and NO-induced pulmonary vasodilatation^[34,35]. The selective up-regulation of pulmonary ET-1B receptor in response to ET-1 biliary production in experimental portal hypertension has also been suggested^[36]. In addition, levels of eNOS and iNOS protein are increased in HPS cirrhotic rats^[37,38], while elevated levels of exhaled NO in HPS patients seem to return to normal after liver transplantation^[39,40]. Furthermore, NO inhibition by methylene blue administration transiently improves oxygenation, whereas NG-nitro-L-arginine methylester, *via* iNOS inhibition, did not prove to affect hypoxemia of HPS^[41-43]. Interestingly, a recent biopsy study comparing explanted livers from 76 patients with cirrhosis found that focal parenchyma extinction as well as vascular lesions, such as intrahepatic portal vein thrombosis, thickening or obstruction of centrilobular veins and sinusoidal proliferation, were more prevalent in those patients with HPS compared to those without, suggesting an association between liver ischemia and the production of proangiogenic and vasodilatation factors^[44].

In patients with liver dysfunction, activation and massive accumulation of intravascular macrophages is observed as a result of intestinal bacterial translocation and endotoxemia^[45-47]. These macrophages in the pulmonary vasculature produce proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), contributing in the NO-mediated vasodilatation through iNOS activation. Furthermore, ET-1 seems to promote the accumulation of pulmonary monocytes^[48]. In support of this theory, TNF-α inhibition by pentoxifylline administration has been shown to improve HPS in rat experimental models^[49,50]. Norfloxacin also improved HPS through a reduction in intestinal bacterial load and bacterial translocation^[51].

CO produced from the degradation of heme by

heme oxygenase, may act as a vasodilator in HPS patients. The latter have elevated levels of arterial carboxyhemoglobin reflecting CO production^[52]. Both bacterial accumulation and NO synthesis stimulate heme oxygenase expression^[47,53]. Finally, administration of protoporphyrin IX, an inhibitor of heme oxygenase, seems to improve HPS hypoxemia^[54].

Angiogenesis

Beside NO-mediated vasodilatation, angiogenesis is considered another crucial mechanism interpreting HPS pathogenesis. Intestinal bacterial translocation and the consequent endotoxemia due to liver dysfunction lead to the recruitment of monocytes and activated macrophages to the lung. These inflammatory cells together with circulating TNF-α stimulate the activation of vascular endothelial growth factor (VEGF) signaling pathways, which are related to angiogenesis^[55,56]. The accumulation of CD68+ macrophages in the lungs of common bile duct ligation rats, expressing iNOS and VEGF, has been correlated to the presence of HPS^[57]. Remarkably, increased endothelial tube formation and pulmonary artery smooth muscle cell proliferation in HPS plasma was observed. The depletion of CD68+ macrophages improved both histological and hemodynamic features of HPS, while iNOS inhibition disclosed exaggerated vasoconstrictor responses.

TNF-α neutralization in cirrhotic rats has been shown to decrease intrapulmonary shunt as well as alveolar-arterial O₂ gradient^[49,58]. The role of specific chemokines, such as the circulating chemokine ligand 1 (CX3CL1), in the activation of VEGF is also under investigation^[59,60]. Anti-VEGF therapy with sorafenib administration, a kinase inhibitor, was found to improve HPS hypoxia and restrict VEGF-mediated angiogenesis and intrapulmonary shunting in rats with biliary cirrhosis^[33,61,62]. Besides, it was recently demonstrated that HPS is independently associated with the presence of hepatocellular carcinoma, an entity also characterized by extensive angiogenesis and VEGF production^[62]. Although it can be postulated that VEGF constitutes a regulator of angiogenesis with a possible role in the development of HPS, further studies with measurements of VEGF are needed to unravel the exact pathogenetic pathways. Figure 1 schematically summarizes the main events in HPS pathogenesis.

CLINICAL FEATURES

Progressive dyspnea is the most frequent symptom among HPS patients^[63]. In a large cohort of patients listed for liver transplantation, it was found that dyspnea was significantly more frequent in patients with HPS than in those without HPS^[64]. However, dyspnea is not specific for HPS, as it is common between patients with liver disease due to complications such as anemia, ascites, hydrothorax and muscular cachexia. Furthermore, HPS can also be asymptomatic, especially

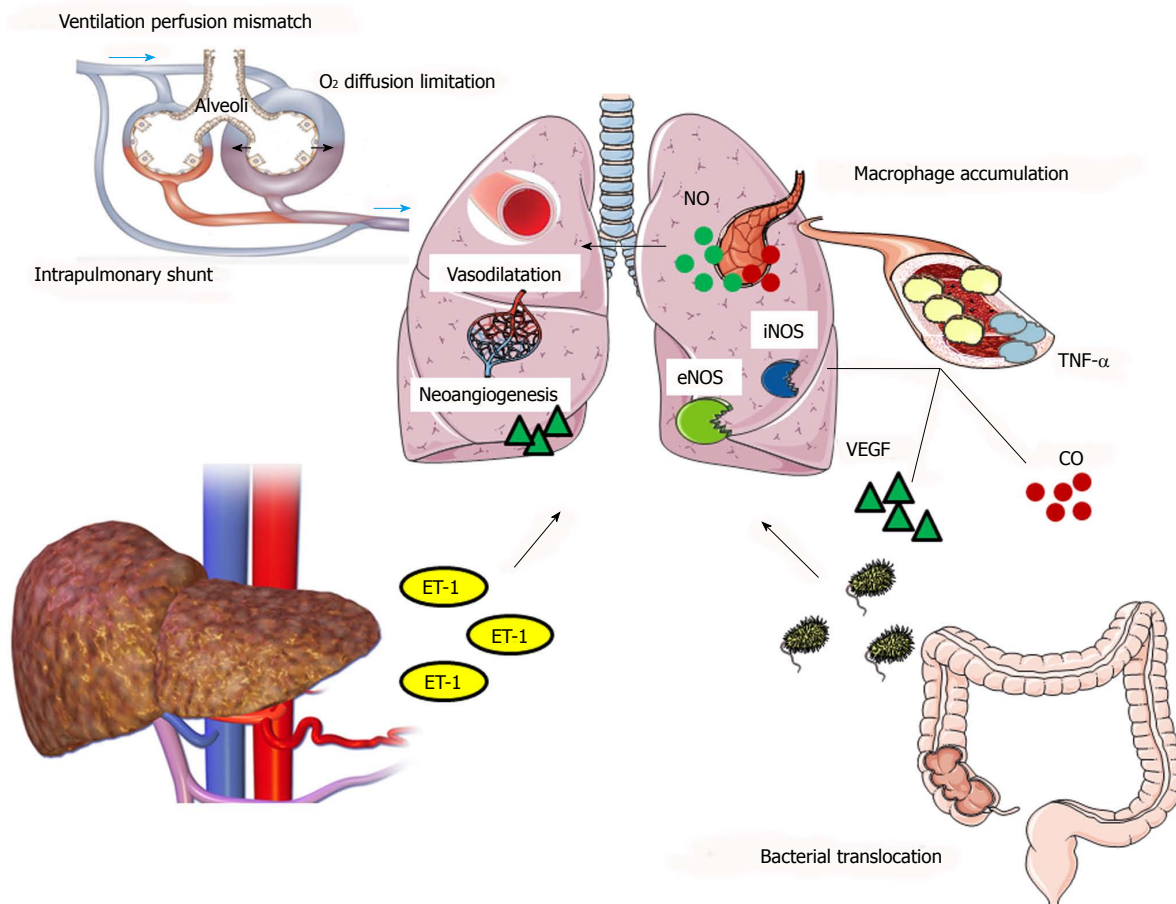


Figure 1 Schematic overview of the main pathways of the pathogenesis of hepatopulmonary syndrome. Liver cirrhosis and portal hypertension lead to endothelin-1 (ET-1) secretion. The binding of ET-1 to its receptor, activates pulmonary endothelial nitric oxide synthase (eNOS), leading to excessive production of nitric oxide (NO), a natural vasodilator. Bacterial translocation and the subsequent pulmonary macrophage accumulation result in the production of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), which contribute in NO-mediated vasodilatation through inducible nitric oxide synthase (iNOS)-enhanced expression. Carbon monoxide constitutes another pulmonary vasodilator produced by macrophage-induced heme oxygenase-1 (HO-1) increased expression. Pulmonary macrophage accumulation and TNF- α -increased circulation trigger vascular endothelial growth factor (VEGF) pathways, concluding in VEGF-mediated pulmonary angiogenesis. Mixed venous blood passes rapidly, due to hyperdynamic circulation observed in liver cirrhosis, through the dilated capillaries without completing gas exchange. An oxygen (O_2) diffusion limitation occurs, as O_2 molecules need to cross a longer distance to reach the center of dilated vasculature. As a result, there is an impairment of arterial oxygenation due to ventilation perfusion mismatch, also boosted by direct right-to-left shunt through arteriovenous communications.

in those with mild hypoxia and alveolar arterial gradient disturbance, with dyspnea observed more frequently in HPS patients with PaO_2 lower than 70 mmHg^[10].

Another form of dyspnea, platypnea, is considered to be pathognomonic for HPS^[65]. Platypnea is the condition of worsening dyspnea when patient moves from a supine to an upright position. It is the result of the decrease in PaO_2 in the arterial blood of $\geq 5\%$ (or ≥ 4 mmHg) from supine to upright position due to increased perfusion of the basis of the lungs and elevated intrapulmonary shunting, a phenomenon called orthodeoxia^[27]. Orthopnea, the worsening of dyspnea in lying position, has also been observed more frequently in patients with HPS^[64].

Cyanosis, fatigue, spider naevi and digital clubbing are other clinical findings of HPS^[63]. Spider angiomas have been suggested as cutaneous markers of HPS, possibly sharing the same pathogenetic mechanism

with HPS, *i.e.* imbalance between vasoconstrictor and vasodilator substances^[66]. In addition, digital clubbing has a positive predictive value of 75% in HPS diagnosis^[67]. In the same study, dyspnea showed a negative predictive value of 75% in HPS diagnosis, whereas no correlation was found between HPS and splenomegaly, ascites, edema, jaundice, oliguria, and collateral veins. Oxygen desaturation during sleep was also correlated to the presence of HPS in another study^[68].

Although none of the aforementioned clinical signs are considered to be specific for HPS and the majority of patients may not present any characteristic symptoms, HPS patients seem to have a worse quality of life and higher New York Heart Association functional class compared to patients without HPS^[64]. Therefore, once again there is need for further larger studies to investigate thoroughly the exact clinical features that

may be related to HPS.

DIAGNOSIS

According to the European Respiratory Society Task Force in 2004, HPS diagnosis consists of the following criteria: (1) the presence of liver disease and/or portal hypertension; (2) elevated room air alveolar arterial oxygen gradient (≥ 15 mmHg or ≥ 20 mmHg in patients > 64 -years-old; and (3) evidence of intrapulmonary vascular dilatations^[3]. Diagnosis should be based on arterial blood gas analysis and alveolar arterial gradient calculation rather than a simple assessment of arterial hypoxemia. Several techniques have been developed for the evaluation of intrapulmonary vasodilatation, but contrast-enhanced echocardiography with agitated saline is considered the gold standard. Modern imaging techniques are also useful for the verification of pulmonary vascular dilatation and right-to-left communications as well as for the exclusion of other pulmonary complications associated with liver disease or lung disease that may coexist with HPS. Furthermore, pulmonary function tests are also valuable to detect abnormalities that may be indicative of HPS or helpful to unmask other underlying lung or cardiac diseases.

The fact that most HPS patients are asymptomatic or manifest nonspecific symptoms in combination with the application of different diagnostic criteria has led to an underestimation of the syndrome in the past. As there is lack of a reliable and simple screening method for diagnosis of HPS, liver transplantation centers should adopt strict diagnostic protocols using unified criteria in order to detect all HPS cases and export comparable results.

Intrapulmonary vascular dilatations

Contrast-enhanced transthoracic echocardiography with agitated saline is considered the cornerstone in the detection of pulmonary vascular dilatations^[69]. Normal saline is shaken to produce microbubbles > 10 μm in diameter and is administered to a peripheral vein in the arm while a four-chamber transthoracic echocardiography is performed. Microbubbles are normally trapped in the pulmonary circulation and absorbed by the alveoli as they cannot pass through normal capillaries. However, in the presence of a dilated vascular bed and/or arteriovenous shunting, microbubbles elude pulmonary capture and reach the left cardiac chambers. Left atrial opacification with microbubbles between the fourth and sixth cardiac cycle after the repletion of the right atrial is indicative of intrapulmonary vasodilatation. Notably, the appearance of microbubbles in the left cardiac chambers within less than three cardiac cycles insinuates intracardial shunting and cannot be diagnostic for intrapulmonary vasodilatation^[70].

Contrast-enhanced echocardiography constitutes

a practical tool for HPS diagnosis. It is a minimally invasive, low-cost technique providing high sensitivity for the qualitative evaluation of intrapulmonary vascular dilatations and shunting. A positive test is not enough for HPS diagnosis, as the two other parameters of the HPS diagnostic triad must be fulfilled. Interestingly, a quantitative classification of intrapulmonary shunting based on the maximum number of microbubbles bypassing to the left ventricle in one still frame has been suggested^[71,72]. According to this classification, severity of intrapulmonary shunting can be graded as stage 1 (< 30 microbubbles), 2 (30-100 microbubbles) or 3 (> 100 microbubbles) (Table 3). A possible correlation between this shunt grading and the proposed classification of HPS based on arterial PaO₂ remains to be verified in future studies.

Contrast transesophageal echocardiography is superior to transthoracic echocardiography concerning the sensitivity of the technique in the diagnosis of intrapulmonary vasodilatation^[73]. However, it is not preferred for the assessment of HPS in cirrhotic patients due to the risk regarding possible trauma to esophageal varices.

Macroaggregated albumin lung perfusion is performed by injecting technetium-99m-labeled macroaggregated albumin followed by a lung and brain perfusion scanning. Brain uptake of the radionuclide higher or equal to 6% implies intrapulmonary or intracardiac shunting, as the large molecules of radiolabeled albumin are normally trapped in the pulmonary capillary bed^[74]. Estimating the pathological retention of the radionuclide in the brain, this technique allows an indirect quantitative assessment of the intrapulmonary shunting. However, it is not as sensitive as contrast echocardiography, especially in early stages of HPS^[75], while it cannot distinguish intrapulmonary from intracardiac shunting.

Chest radiographs are only useful to exclude concomitant pulmonary disease as they rarely show evidence of dilated vasculature^[3]. High resolution computed tomography may also identify large, dilated pulmonary vessels^[76].

Pulmonary angiography provides a double contribution in HPS, diagnostic and therapeutic. Two types of HPS can be distinguished on the basis of angiographic findings^[77]. Type 1 is characterized by minimally dilated vessels, and type 2 delineated by well-defined arteriovenous communications and resistance to 100% oxygen administration. The invasive character of pulmonary angiography makes it a less convenient method for the diagnosis of HPS.

Arterial oxygenation

Arterial blood gas analysis is required to detect all patients with HPS^[78]. The calculation of the alveolar-arterial gradient is proposed as a better diagnostic parameter than the evaluation of the PaO₂ alone to identify those patients with impaired oxygenation. The sensitivity of this marker is attributed to the fact that the

Table 3 Intrapulmonary shunt quantitative classification

Contrast-enhanced echocardiography based on the number of microbubbles passing in the left ventricle	
No shunt	No detection of microbubbles
Stage 1	< 30 microbubbles
Stage 2	30-100 microbubbles
Stage 3	> 100 microbubbles
Macroaggregated albumin lung perfusion	
No shunt	< 6% brain uptake of radiolabeled albumin
Intrapulmonary shunt	≥ 6% brain uptake of radiolabeled albumin

partial pressure of carbon dioxide (PaCO₂) is included to its calculation, so that lower values of PaCO₂ lead to an increased alveolar-arterial gradient, reflecting an elevated respiratory effort to maintain normal blood oxygenation, even before PaO₂ is affected. According to the European Respiratory Task Force, alveolar-arterial gradient greater than or equal to 15 mmHg (or ≥ 20 mmHg in patients > 64-years-old) is indicative of impaired oxygenation, calculated at sea level while the patient is breathing ambient air at rest^[3].

The potential role of pulse oximetry as a screening test for the presence of HPS has also been investigated. Lower values of oxygen saturation were measured in HPS patients compared to cirrhotic patients without HPS (96.8% vs 98.4%, $P = 0.02$)^[79], while pulse oximetry values below 96% presented a sensitivity and specificity of 100% and 88% respectively for detecting patients with PaO₂ < 60 mmHg^[80]. On the other hand, the utility of pulse oximetry in HPS diagnosis was not confirmed in children with cirrhosis^[81]. The difference in oxygen saturation between supine and standing position was suggested as a method to detect HPS^[82]. However, the use of low values of oxygen saturation (< 92%) as well as a decrease of ≥ 4% after change from supine to upright position was unreliable as screening test for diagnosis of HPS. Notably, the majority of HPS patients present oxygen desaturation during sleep, proportional to the syndrome's severity^[68]. Finally, the variation in oxygen saturation between supine and standing position was reported as a marker of possible intrapulmonary vascular dilatations^[83].

A reduced diffusing capacity for carbon monoxide (DLCO) is the single most common defect among pulmonary function tests that has been correlated to the presence of HPS^[14]. However, there is controversial data concerning DLCO as a diagnostic tool for HPS screening^[84,85]. In contrast to ventilation-perfusion imbalance, which seems to resolve after liver transplantation, a restricted number of observational studies have suggested a persistence of low DLCO values after liver transplantation due to permanent liver-induced structural vascular changes in the pulmonary vasculature^[86,87].

As pulse oximetry fails to detect mild and moderate HPS and the value of other screening markers remains undefined, alveolar-arterial gradient represents, as

yet, the most remarkable method for HPS screening

TREATMENT

Liver transplantation constitutes the only established successful treatment that modifies the natural history of HPS, improving arterial hypoxemia within 6-12 mo^[88]. The identification of HPS through established diagnostic protocols among liver transplantation candidates in combination with the model for end-stage liver disease (MELD) exception policy to facilitate liver transplantation may achieve an 88% 5-year posttransplantation survival for HPS patients^[89]. Besides, oxygen therapy is recommended for those cases with severe hypoxemia^[3]. Restricted data report improvement in liver function and oxygenation after 1 year of oxygen supplement^[90].

Many pharmaceutical interventions have been studied both in humans and animal models, targeting the syndrome's pathogenetic pathways, without reaching encouraging outcomes. NO-mediated pulmonary vasodilatation and angiogenesis induced by proinflammatory cytokines, which represent the hallmarks of HPS pathogenesis, have constituted the main targets of medical intervention, in an effort to reverse the syndrome's evolutionary process and confirm the assumptions concerning the pathogenetic mechanisms.

Administration of octreotide, a somatostatin analogue inhibiting angiogenesis, failed to improve hypoxemia in patients with HPS^[91]. Contrariwise, sorafenib improves experimental HPS by reducing VEGF-mediated angiogenesis and down-regulating eNOS activation through tyrosine kinase receptor inhibition^[33,61]. Treatment with antibiotics, such as norfloxacin, in order to reduce endotoxemia and NO production triggered by bacterial translocation, did not improve gas exchange, in contrast to promising results in experimental models^[92,93]. Single case reports suggest improvement of HPS after administration of cyclooxygenase inhibitors, such as indomethacin, and immunosuppressants, such as mycophenolate mofetil, but there are no randomized studies to investigate these findings^[94-96].

Methylene blue is an oxidizing agent that restricts NO-mediated vasodilatation through blockage of soluble guanylate cyclase stimulation by NO^[97]. Intravenous administration of methylene blue reduced intrapulmonary shunting and improved oxygenation

in experimental models and in a restricted number of patients with HPS^[98,99].

There are conflicting results regarding the effect of pentoxifylline on HPS. Pentoxifylline is a TNF- α inhibitor that improves HPS in experimental models by reducing TNF-induced NO production through down-regulation of iNOS^[50,58]. A dosage of 400 mg of pentoxifylline, three times per day for 3 mo significantly improved oxygenation and decreased TNF- α levels in 9 patients with symptomatic HPS^[100]. Nevertheless, another pilot study enrolling 9 patients with advanced HPS reported no significant therapeutic response after pentoxifylline administration, while the drug was poorly tolerated due to gastrointestinal adverse events^[101].

N(G)-nitro-L-arginine methylester, a nebulized inhibitor of NO synthesis, did not improve oxygenation in HPS patients, even if a reduction in exhaled NO was recorded^[43,102]. Almitrine bismesylate, a potential vasoconstrictor, does not affect impaired oxygenation in HPS^[103]. Finally, a few studies have demonstrated that garlic supplementation improves arterial oxygenation and symptoms in HPS^[104]. A total reversal of HPS was observed in 14 of 21 patients after 9 mo of garlic treatment, compared to 1 of 20 HPS patients under placebo treatment^[105].

Transjugular intrahepatic portosystemic shunting (commonly known as TIPS) was performed as a therapeutic maneuver in a limited number of patients with severe HPS, leading to variable results^[106,107]. Although TIPS could be considered as a bridge towards transplantation, there is concern that persistent right-to-left shunting *via* TIPS prevents the reversal of intrapulmonary structural alterations^[108]. Embolotherapy has also been performed to treat persistent hypoxemia of HPS, either before or after liver transplantation, in the presence of large arteriovenous communications^[109,110].

Clearly, their poor outcomes as well as the small number of enrolled patients make the aforementioned studies insufficient to suggest effective therapeutic options for the management of HPS. In addition, these data underline the complexity of pathogenetic interactions in HPS and outline potential areas of interest and future research.

PROGNOSIS

Despite the relative high prevalence of HPS among cirrhotic patients, there is an inadequate number of prospective studies evaluating the syndrome's impact on overall morbidity and mortality. Once again, the use of varying thresholds, concerning arterial oxygenation, for the diagnosis of the syndrome, has led to ambiguous results about HPS prognosis. The main question remains whether the presence of HPS should be considered as an independent factor for morbidity, giving HPS patients priority to liver transplantation, and whether any correlations between the severity of HPS and the posttransplantation survival rates exist.

A retrospective analysis reported 41% mortality

over an approximate 2.5-year period in 22 patients with HPS^[77]. Comparing survival rates between cirrhotic patients with HPS and matched for the severity of liver disease by MELD and Child-Pugh score classification and age patients without HPS, who did not undergo liver transplantation, patients with HPS had a worse 5-year survival (23% vs 63%, $P = 0.0003$)^[111]. Patients with PaO₂ less than 50 mmHg had significantly worse survival rates. Similar results were confirmed by a prospective study that reported lower median survival among HPS subjects compared to nonHPS cirrhotic patients (10.6 mo vs 40.8 mo, $P < 0.05$), while the mortality remained higher even after adjusting for age and liver disease severity^[112]. Furthermore, HPS was associated with worse quality of life, assessed by the New York Heart Association classification, and higher risk of death compared to nonHPS matched for age, sex and MELD score cirrhotic subjects [hazard ratio = 2.41, 95% confidence interval (95%CI): 1.31-4.41, $P = 0.005$]^[64]. On the other hand, no significant difference in overall survival between HPS and nonHPS transplantation candidates was demonstrated in a prospective study including 316 cirrhotic patients^[16]. Notably, even in those studies that reported high HPS-related mortality, the causes of death were mainly attributed to liver dysfunction rather than pulmonary complications.

Liver transplantation is the only therapeutic intervention that reverses HPS between the first 6 to 12 mo, even for cases with severe preoperative hypoxemia^[111]. The general policy is prioritizing patients with HPS and hypoxemia for liver transplantation, regardless of the severity of liver disease^[113]. Beside poor prognosis of HPS, the progressive aggravation of hypoxemia, estimated at 5.2 mmHg per year, probably boosts the decision for a prompt management^[111]. However, there is concern that through this organ allocation policy, HPS patients may be offered a pretransplantation survival advantage over nonHPS cirrhotic transplantation candidates, prompting the need for reassessment of the MELD exception criteria^[114].

There is controversial data concerning posttransplantation mortality in HPS transplanted patients. A prospective study suggests higher 6-mo postoperative mortality rates in HPS patients compared to transplanted patients without HPS (33% vs 9.25%, $P = 0.0012$)^[115]. A PaO₂ of 50 mmHg or less and a macroaggregated albumin shunt fraction > 20% are demonstrated as the most important predictors of mortality following transplantation, suggesting preoperative HPS staging to assess the risk of postoperative mortality^[116]. Conversely, no difference in posttransplantation survival between patients with and without HPS was demonstrated in a large prospective study that enrolled 316 patients^[16]. One-year posttransplantation survival may reach 93% in HPS patients^[117], while the presence of HPS does not seem to affect duration of intensive care unit stay, duration of total hospital stay, rate of pulmonary complications or 3-mo survival after liver

transplantation^[118]. Finally, there is a growing number of reports suggesting no differences in short- and long-term posttransplantation morbidity between patients with and without HPS, and no association between the severity of baseline hypoxia and survival after transplantation^[17,119].

The discrepancies between the aforementioned studies can be attributed to different methodological approaches and HPS assessment protocols. The possibility of transplantation denial to patients with HPS and significant hypoxemia should always be considered as a confusing factor that may influence the comparison between different research outcomes^[120].

HPS AND MYOCARDIAL FUNCTION

Liver cirrhosis is characterized by hyperdynamic circulation as a consequence of systematic vasodilatation^[121] in order to preserve normal blood flow. Diastolic dysfunction and impaired cardiac contractile response to stress define cirrhotic cardiomyopathy, another cardiovascular complication strongly associated with chronic liver disease^[122]. The possible association between specific markers of cardiac dysfunction and HPS remains an issue of debate.

Right ventricular diastolic dysfunction assessed by Doppler echocardiography was found to be more remarkable in the presence of HPS, in a study enrolling 46 cirrhotic patients, 10 of whom had HPS^[123]. Significantly higher right ventricle and right atrial diameters as well as right ventricle wall thickness values were recorded in the HPS group. Moreover, patients with compared to those without HPS had higher estimated mean pulmonary artery pressure (48.9 ± 4.8 mmHg vs 40.6 ± 5.3 mmHg, $P < 0.05$) and higher pulmonary vascular resistance (3.97 ± 1.31 Wood's unit vs 3.25 ± 0.96 Wood's unit, $P < 0.05$).

Intrapulmonary shunting in the context of liver disease may aggravate hemodynamic imbalance, followed by further increase in cardiac output^[124]. Reflecting hyperdynamic circulatory state, left atrial enlargement was associated with the presence of intrapulmonary vasodilatation, both in human and experimental studies^[125]. Remarkably, left atrial volume equal or greater than 50 mL was suggested as a strong echocardiographic predictor of HPS in patients with liver cirrhosis (area under the receiver operating characteristic curve: 0.903, sensitivity 86.3%, specificity 81.2%)^[126]. Left ventricular enlargement was also proposed as an independent, indirect echocardiographic marker of HPS^[127]. In addition, higher systolic myocardial velocity of the mitral valve measured by tissue Doppler imaging technique was independently associated with HPS (odds ratio: 1.428, 95%CI: 1.049-1.943, $P = 0.026$), a finding implying left ventricular systolic dysfunction^[127].

In contrast to the previous reports, Voiosu *et al.*^[128] found no correlations between HPS and echocardiographic markers of systolic or diastolic myocardial dysfunction in 74 patients with liver cirrhosis. Cirrhotic

cardiomyopathy did not differentiate between patients with and without HPS, suggesting an independent pathogenetic nature of these complications. The methods and results of previous studies evaluating cardiac involvement in HPS are presented in Table 4.

While hyperdynamic circulation as a response to systemic vasodilatation in liver cirrhosis is well documented, the subsequent myocardial structural changes are not yet fully understood. Increased cardiac output seems to be the main pathogenetic event triggering systemic multifactorial, cellular, neuronal and humoral signaling mechanisms that induce cardiac contractile dysfunction, electrophysiological abnormalities and chronotropic incompetence in the setting of liver cirrhosis^[129]. The most prevalent feature of this entity known as cirrhotic cardiomyopathy is silent diastolic dysfunction with impaired ventricular relaxation and ventricular filling, which may become overt after rapid increase in venous return after liver transplantation.

Currently, literature data cannot support an intimate association between cirrhotic cardiomyopathy and HPS^[130]. A complicated interaction between different pathogenetic mechanisms is thought to involve myocardial function in the presence of intrapulmonary shunting. The available studies are not only restricted in number but also heterogenous concerning the assessed features of myocardial dysfunction and the evaluated parameters.

The hypothesis is that NO overproduction, which leads to intrapulmonary vasodilatation, is responsible for an intense hyperdynamic circulating state resulting in higher cardiac output and long-term left ventricle myocardial dysfunction. The potential structural myocardial alterations of the right ventricle in the presence of intrapulmonary vasodilatation as well as the effect of HPS hypoxemia on increased myocardial demands also remain to be clarified. Of great importance is to unravel the exact mechanisms affecting cardiac function that differentiate in patients with HPS. In order to extract more accurate results, the assessment tools of myocardial function should be independent of expanded plasma volume and bias correlated to the presence of ascites, diuretic treatment and sodium intake^[131].

In this direction, novel promising echocardiographic techniques offering a more accurate assessment of cardiac structure as well as sensitive biomarkers of cardiac dysfunction need further evaluation in future research in order to elucidate possible interactions between pulmonary vasodilatation, hypoxemia and myocardial dysfunction in the context of chronic liver disease. Last but not least, the effect of possible HPS-related myocardial dysfunction on pre- and posttransplantation total survival is yet to be investigated.

CONCLUSION

HPS is a relatively common complication of chronic liver disease, with many of its aspects remaining still

Table 4 Hepatopulmonary syndrome and cardiac involvement

Study	Cirrhotic patients	Parameters assessed	Assessment tools	Associations
Karabulut <i>et al</i> ^[123]	36 without HPS 10 with HPS	RV diastolic dysfunction PVR Systolic PAP	M-mode ECHO TDI	RV diastolic dysfunction-HPS HPS was associated with higher RV wall thickness (0.61 ± 0.13 cm <i>vs</i> 0.51 ± 0.10 cm) RVEDD (3.81 ± 0.38 cm <i>vs</i> 3.11 ± 0.94 cm) RA (3.96 ± 0.53 cm <i>vs</i> 3.58 ± 0.47 cm), systolic PAP (48.9 ± 4.8 mmHg <i>vs</i> 40.6 ± 5.3 mmHg) PVR (3.97 ± 1.31 Wood's unit <i>vs</i> 3.25 ± 0.96 Wood's unit)
Zamirian <i>et al</i> ^[124]	53 without IPS	LA dimension	M-mode ECHO	IPS was associated with higher LA dimension (4.58 ± 0.54 cm <i>vs</i> 3.87 ± 0.63 cm)
Zamirian <i>et al</i> ^[126]	39 with IPS 108 without HPS 41 with HPS	Cardiac output LA volume	M-mode ECHO	Cardiac output (5.62 ± 0.83 L/min <i>vs</i> 4.75 ± 0.76 L/min) Greater LA volume in HPS (55.1 ± 7.5 mL <i>vs</i> 37.1 ± 9.3 mL) LA volume ≥ 50 mL, AUC: 0.903, sensitivity: 86.3%, specificity: 81.2%
Pouriki <i>et al</i> ^[127]	67 without HPS 12 with HPS	Markers of LV and RV diastolic and/or systolic cardiac function	M-mode ECHO TDI	HPS was associated with higher LVEDD (OR = 1.230, 95%CI: 1.036-1.482; <i>P</i> = 0.019) S wave at left lateral wall of MV (TDI) (OR = 1.428, 95%CI: 1.049-1.943; <i>P</i> = 0.026) S wave lateral ≥ 13.5 cm/s, AUC: 0.736, sensitivity: 83.3%, specificity: 65.7%
Voiosu <i>et al</i> ^[128]	57 without HPS 17 with HPS	Association between HPS and cirrhotic cardiomyopathy	M-mode ECHO TDI	LVEDD ≥ 50.5 mm, AUC: 0.724, sensitivity: 75%, specificity: 68.7% Higher RV wall width in HPS (3.8 ± 1.2 mm <i>vs</i> 3.4 ± 0.6 mm) No association between HPS and cirrhotic cardiomyopathy No echocardiographic measurement predictive of HPS

AUC: Area under the curve; ECHO: Echocardiography; HPS: Hepatopulmonary syndrome; IPS: Intrapulmonary shunt; LA: Left atrial; LV: Left ventricle; LVEDD: Left ventricle end diastolic diameter; MV: Mitral valve; OR: Odds ratio; PVR: Pulmonary vascular resistance; PAP: Pulmonary artery pressure; RV: Right ventricle; RVEDD: Right ventricle end diastolic diameter; TDI: Tissue Doppler imaging.

largely unknown. HPS screening with the establishment of standardized protocols among patients with liver disease is crucial in the direction of achieving higher survival rates. Prospective studies evaluating long-term outcomes before and after liver transplantation in large patient cohorts will demonstrate the specific characteristics of HPS requiring management in priority. The precise events that trigger HPS pathogenesis as well as secondary clinical and subclinical vital organ interactions will constitute the field of future research.

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