

Hepatopulmonary syndrome: A recent review of the literature

Ahmed M. EL-Eraky, Amany Hasson, Mona Arafa



Summary

Hepatopulmonary syndrome (HPS) is a serious vascular complication of liver disease reported to be present in 4-32% of cirrhotic adults and 9-20% of children. HPS diagnosis depends on the presence of a triad of liver disease with intra-pulmonary vascular dilation that causes abnormal arterial oxygenation. Pulmonary microvascular dilation and angiogenesis are two central mechanisms in pathogenesis of HPS. No effective medical therapies are currently available and liver transplantation is the only established treatment option.

Keywords: *Hepatopulmonary syndrome, liver disease and pulmonary microvascular.*

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(Ahmed M. EL-Eraky, Amany Hasson, Mona Arafa) Tropical Medicine dept, Faculty of Medicine, Mansoura Univ., Egypt

* CA: Ahmed EL-Eraky
omtyomty2@yahoo.com

Epidemiology

Hepatopulmonary syndrome is defined as a clinical triad of advanced liver disease, intrapulmonary vascular dilatation and abnormal arterial oxygenation¹. HPS is reported to be present in 4-32% of cirrhotic adults and 9-20% of children². It was found that there exists no correlation between the development of HPS and the severity of cirrhosis³. Since most studies had been performed in patients who were expected to undergo transplantation, the exact prevalence of HPS and its clinical significance in the overall cirrhotic population have not been identified⁴. Hepatopulmonary syndrome most commonly occurs in portal hypertension and cirrhosis. However, it may also occur in patients with acute and chronic hepatitis, acute liver failure and vascular abnormalities that limit hepatic venous out flow to the lungs (cavo-pulmonary shunts, Abernethy malformation)⁵.

Pathogenesis

The key event in the pathogenesis of HPS is believed to involve a number of factors. Together, these factors lead to IPVD and oxygenation abnormalities in patients with liver disease⁶. Increased production of endothelin-1 (ET-1), a potent vasoconstrictor derived from the cholangiocyte, and tumor necrosis factor (TNF) activate the nitric oxide synthases (NOS), which include endothelial NOS (eNOS) and inducible NOS (iNOS). This in turn leads to an increased production

of nitric oxide (NO), a potent vasodilator. Activated eNOS also results in over expression of endothelin B receptor in the pulmonary vascular endothelium. Both bacterial translocation, which is more commonly seen in cirrhosis, as well as endotoxemia, attract macrophages to the pulmonary vasculature. Monocytes express inducible NO synthase (and produce NO) and produce hemeoxygenase-1, leading to carbon monoxide generation, both of which further exacerbate pulmonary vasodilatation. lastly, pulmonary angiogenesis, promoted by vascular endothelial growth factor (VEGF) signaling and production of chemokine fractalkine soluble (CX3CL1), is also an important contributor of pulmonary vascular changes seen in HPS⁷. Three mechanisms explain impaired oxygenation that occurs after this abnormal IPVD. Firstly, vasodilatation results in an increased blood flow while ventilation remains unchanged (ventilation perfusion mismatch). Secondly, oxygen diffusion limitation, by dilation of the pulmonary vessels, the distance that oxygen molecules have to travel to the center of the capillary increases. This diffusional barrier is exacerbated by hyper dynamic circulation in patients with liver disease. Finally, direct arteriovenous communications exist, causing blood by passing the alveoli, which results in mixed venous blood passing into the central circulation⁸.

Clinical features

Some patients may be asymptomatic throughout the early stage of the disease. Classic symptoms contain dyspnea on exertion or at rest. Dyspnea upon standing (platypnea) and hypoxemia exacerbated in the upright position (orthodeoxia) may be seen in about 25% of patients⁵. Fatigue, digital clubbing, cyanosis and diffuse telangiectasia are described in advanced stages¹. Very interesting finding is that, capillary vasodilatation is most evident at the lung bases; thus, explaining orthodeoxia and platypnea associated with HPS.

Screening

Even although the clinical symptoms used to identify HPS seem clear, there is no consensus on strong definitions for each diagnostic criterion⁹. In adult patients, pulse oximetry with O₂ saturation <96% is sensitive and cost-effective in identifying patients with hypoxemia (arterial partial pressure of oxygen [Pa O₂] <70 mm Hg) at sea level¹⁰. In children with cirrhosis, yet, hyperemic arterialized capillary blood gas examination may be a better screening tool for HPS¹¹. To identify all patients with HPS, ABG analysis is mandatory. Patients with hepatopulmonary syndrome have increased levels of exhaled

nitric oxide (NO) (alveolar fraction), however measuring such levels have not been validated for HPS screening¹².

Noninvasive diagnostic tests

The standard method for detection of intrapulmonary shunting is contrast-enhanced Transthoracic echocardiogram (CE-TTE). The normal diameter of the lung vascular capillary vessels is less than 8 µm. Agitated saline creates micro-bubbles greater than 10 µm in diameter that normally do not pass through the pulmonary capillary bed. Therefore, delayed appearance of intravenously injected micro-bubbles in the left heart 3 or more cardiac cycles after visualization in the right heart indicate abnormal intra-pulmonary capillary beddilatation as shown in figure (1). Intracardiac shunting (i e, due to persistent foramen ovale or atrial septal defect) demonstrates early appearance of micro bubbles in the left heart within 1 to 2 cardiac cycles after appearance in the right heart. Transesophageal echocardiography (TEE) can differentiate intracardiac shunts from intrapulmonary shunts by imaging the source of microbubbles arriving into the left atrium (across the atrial septum versus pulmonary veins)¹³.

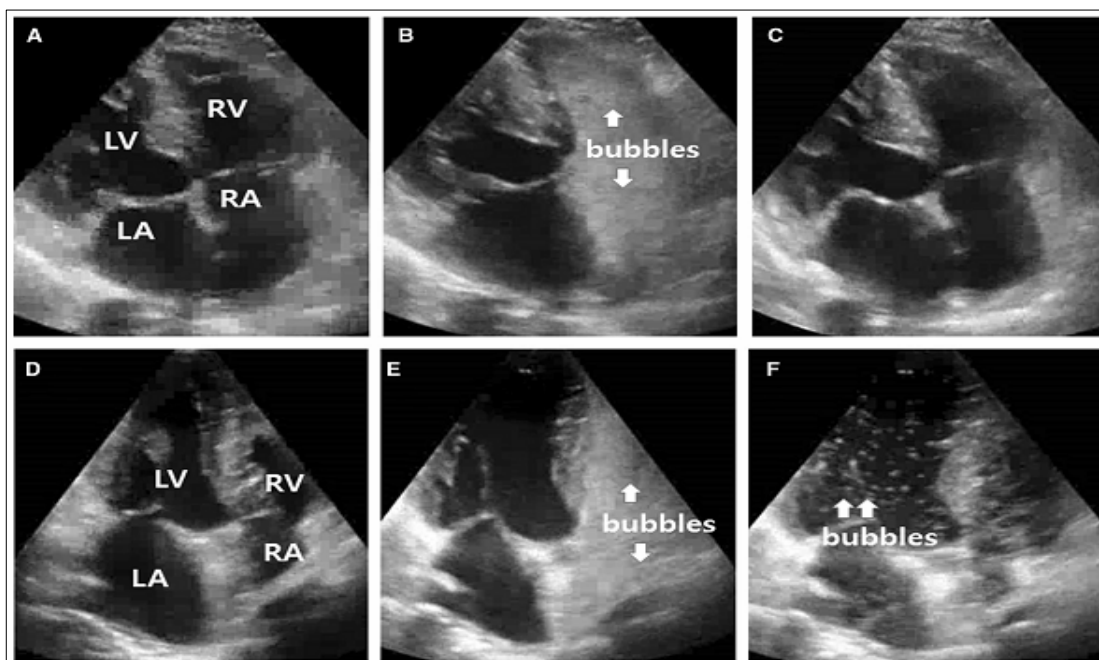


Figure (1) showing representative saline-agitated contrast-enhanced echocardiography of negative finding (**a-c**) and positive finding (**d-f**) for hepatopulmonary syndrome. The bubbles are visualized in the rightatrium (**b**) they become trapped in the pulmonary vascular bed and therefore cannot be visualized in the left heart (**c**). In patient with HPS, saline contrast bubbles appear in the left heart (**f**) three to six cycles after right atrial passage (**e**). RA right atrium, RV right ventricle, LA left atrium, LV left ventricle².

Nuclear/Invasive diagnostic tests

Peripheral vein injection of 20 μm labeled $^{99\text{m}}\text{Tc}$ macroaggregated albumin [MAA] with brain uptake imaging is another method for detecting and quantifying IPVD as shown in figure (2). The MAA lung-brain perfusion scan is normal in non-HPS causes of hypoxemia. However, the lung perfusion

scan does not differentiate intra-cardiac and intra-pulmonary shunting and has inferior sensitivity compared to CEE for recognition of mild or moderate HPS in adults. In children, MAA lung perfusion scans may have satisfactory sensitivity for detecting mild degrees of IPVD relative to CE-TTE.

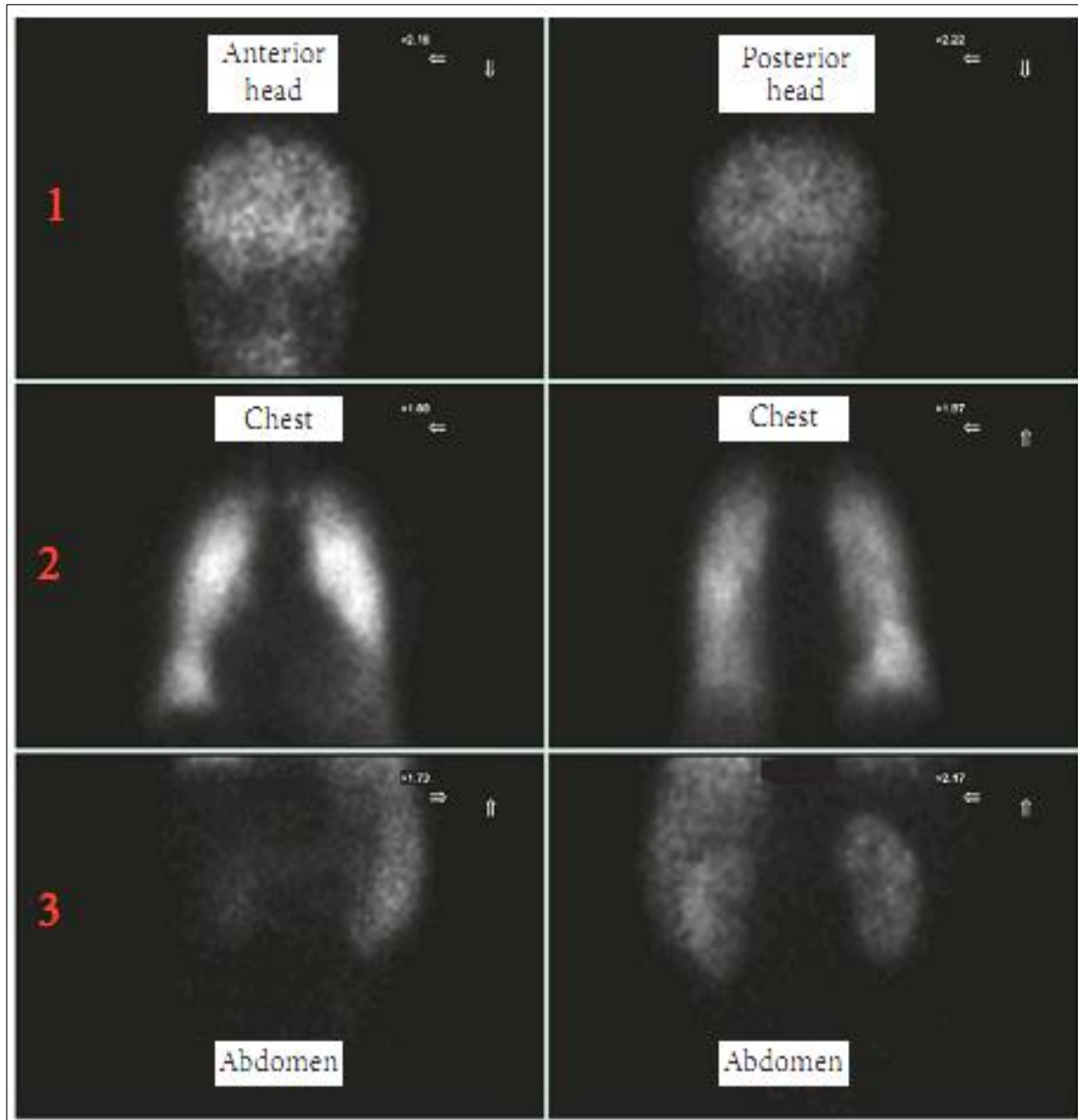


Figure (2) showing macro aggregated albumin lung perfusion scan (MAA scan) showing radioactivity in the lungs (panel 2) as well as in the cerebrum (panel 1) and in the kidneys (panel 3), suggesting right to left shunt¹⁴.

Other investigations

Additional examinations are frequently performed to exclude other etiologies of pulmonary disease. Chest radiographs may be normal or, like high resolution computed tomography, may show evidence of intrapulmonary vascular dilations^{15,16}. Pulmonary angiography is indicated when large arterio-

venous shunts are suspected, amenable for embolization¹⁵. Lung function tests, and especially the diffusing capacity for carbon monoxide may be abnormal in patients with HPS, ranging from mild to more severe forms¹⁷.

Diagnostic criteria

Before the final diagnosis of HPS, exclusion of other contributing cardiopulmonary causes such as pulmonary atelectasis, ascites, chronic obstructive pulmonary disease, and hepatic hydrothorax is mandatory when evaluate Table (1) Diagnostic criteria of HPS¹.

hypoxemic cirrhotic patient. A careful history and physical examination aids in the consideration of alternative diagnoses of Dyspnea, as listed in table (1).

Diagnostic criteria	Transcriptions
Liver disease (usually cirrhosis with portal hypertension)	
Positive CE-TTE	Microbubbles in the left heart ≥ 3 cardiac cycles after right heart micro bubbles following 10 mL agitated saline injection in a peripheral arm vein
Abnormal arterial oxygenation:	$AaO_2 \text{ mm Hg} = P \text{ Alveolar}O_2 - P \text{ arterial}O_2$
Alveolar-arterial oxygen gradient (AaO₂) ≥ 15 mm Hg (> 20 mm Hg if age > 64)	$= [FIO_2 (P_{atm} - PH_2O) - PaCO_2 / .8] - PaO_2$ Where: FIO ₂ , inspiratory oxygen fraction; P _{atm} , atmosphere pressure; PH _{2O} , water vapor partial pressure; Pa CO ₂ , arterial carbon dioxide pressure; and Pa O ₂ , partial pressure of oxygen.

Severity & angiographic Classifications

Pulmonary angiography is an invasive procedure that can delineate the appearance of the pulmonary vasculature. It is reserved for those patients who have a poor response to 100% oxygen, demonstrated by an increase Table (2) HPS classifications.

in the PaO₂ to less than 300 mm Hg Pulmonary angiographic study in HPS patients demonstrated two angiographic patterns: type I, or diffuse, and type II, or focal, as listed in table (2).

Classification ERS Task Force ¹⁸	
Very severe	< 50 mmHg
Severe	≥ 50 PaO ₂ < 60 mmHg
Moderate	≥ 60 PaO ₂ < 80 mmHg
Mild	≥ 80 mm Hg
Angiographic pattern ¹⁹	
Type I	Diffuse, normal vessels or fine diffuse spiderly vascular abnormalities
Type II	Focal, more infrequent, similar focal arteriovenous communications

ERS = European respiratory society

Treatment

The single known effective therapy for HPS is LT²⁰⁻²², with an improvement in oxygenation at 1 year^{23, 24}, fig. (3). After LT in HPS patients, the 5-year survival rate was shown to be around 76%, which is similar to patients with non-HPS²⁵. Some studies showed worse survival in patients who have PaO₂ < 50 mmHg alone or with MAA shunt fraction $> 20\%$ ^{21, 26}. Iyer et al. reported that there was no association between PaO₂ levels at diagnosis

and survival rates after transplantation²³. Moreover, some other studies presented that, there were no significant differences in survival between any HPS and non-HPS patients²². Patients with advanced HPS (PaO₂ < 60 mmHg) are eligible for MELD exception points to increase priority for transplantation which may give them a survival advantage^{27,28}. To increase survival after LT, patients who are on the waiting list should

be screened properly, and adequate oxygen should be given²². It should be recalled that HPS patients who are not candidates for LT may be candidates for localized resection or coil embolization of the dilated pulmonary vessels as a palliative treatment¹⁶. This is particularly true for patients with type 2 lesions who would not respond to LT²⁹. Transjugular intrahepatic portosystemic shunt (TIPS) placement is a medical intervention that has been linked with improvement of HPS in several case reports^{30,31}, but there is also a risk that TIPS may worsen HPS by increasing the hyperkinetic state, leading to more pulmonary vasodilatation, shunting, and hypoxemia. The American Association for the Study of Liver Disease guidelines do not recommend TIPS placement for the treatment of HPS³².

Medical/Nonsurgical management

Though no clearly real medical therapy for HPS is available, somatostatin, almitrine, indomethacin, norfloxacin, inhaled (nebulized) L-NAME, aspirin, and plasma exchange have all been tried in small studies without clear benefit³⁰⁻³⁵. The norfloxacin randomized, cross-

over, pilot study in 9 HPS patients was negative for an improvement in alveolararterial oxygen gradient³⁰. Garlic extracts have shown some benefit in HPS³⁶⁻³⁹. Newly, pentoxifylline, a phosphodiesterase inhibitor with known mild inhibitory effects on TNF- α and NO, has been connected to improved oxygenation in experimental HPS⁴⁰⁻⁴². Yet, results of small uncontrolled studies in human HPS with pentoxifylline are conflicting⁴¹. Extra interventions have included inhaled prostacyclin derivatives to improve ventilation-perfusion matching⁴³ and withdrawal of chronic methadone⁴⁴. The administration of supplemental oxygen to maintain O₂ saturations above 88% is advised based on experience in treating non specific pulmonary vascular and parenchymal disorders³³. However, increased mortality in HPS is not confined to those with severe hypoxemia, thus potential medical treatments may be appropriate in all stages of disease⁴⁵. Liver transplantation should be considered before the development of severe or very severe disease¹. Ravens et al suggested an algorithm for screening and treatment of HPS as shown in figure (3).

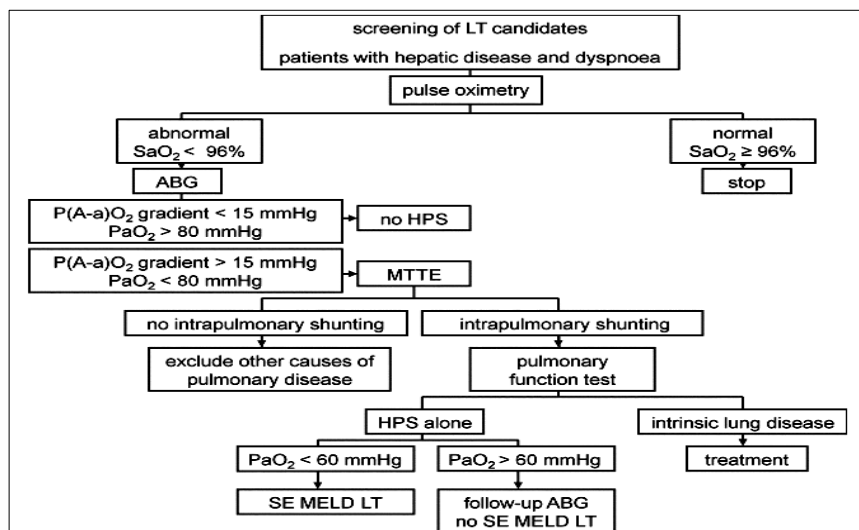


Figure (3) showing Algorithm for screening and treatment of HPS. In symptomatic patients and LT candidates. Abbreviations: LT, liver transplantation, ABG, arterial blood gas; P(A-a) O₂ gradient, alveolar-arterial oxygen gradient; PaO₂, arterial oxygen tension; MTTE: microbubble transthoracic echocardiography; HPS, hepatopulmonary syndrome; SE, standard exception⁴⁶.

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