Research Article

A clinical study of the hepatopulmonary syndrome in Iraqi patients with chronic liver disease

Ziad M. Jureidini, *CABM* [1]**, *Abdulwahhab S. Abdulla,*** *M.B.Ch.B.*[2]
[1]*Department of internal Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq.*
[2]*Department of Medicine, Baghdad Teaching Hospital, Baghdad, Iraq.*

Date Submitted:2.5.2010

Date Accepted:5.8.2010

Address for Correspondence:
Dr. Ziad M Jureidini CABM.
Department of internal Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq.

Abstract

Objective: To evaluate the frequency, clinical, and laboratory features of HPS and to determine their usefulness in its diagnosis in Iraqi patients with liver disease.

Patients and Methods: Fifty-two patients with chronic liver disease were evaluated for the presence of HPS using pulse oximetry, arterial blood gas analysis (ABG), and transthoracic contrast-enhanced echocardiography (CEE). Patients with SaO_2 of ≤92% and/or a decrease in SaO_2 of ≥4% after change from supine to upright position; were further tested with ABG and CEE. Patients who had a PaO_2 of ≤70 mmHg together with positive CEE were considered to have HPS.

Results: Of 52 patients studied, 13 (26.9%) were in Child-Pugh class A, 16 (30.7%) in class B, and 23 (42.3%) in class C. Four patients (7.6%) proved to have HPS; one was in Child-Pugh class B and the other three were in class C (p=0.3574). Among the clinical features assessed as predictors of HPS, dyspnea (p = 0.0027), cyanosis (p < 0.0001), and finger clubbing (p = 0.0514) reached statistical significance. Neither upper GI endoscopy nor biochemical liver tests were statistically different between patients with and without HPS.

Conclusions: HPS is not rare. Dyspnea is a useful marker for its presence in the appropriate clinical setting. Platypnea, cyanosis, and finger clubbing are much less sensitive but more specific features of the syndrome. No particular pattern of biochemical liver tests is useful in predicting the presence or absence of HPS. There was a trend for HPS to occur in patients with more advanced liver disease.

Key Words: liver function, pulmonary function

Introduction

Hepatopulmonary syndrome (HPS) is defined by the triad of (1) Liver disease and/or portal hypertension; (2) Hypoxemia (PaO_2 < 70mmHg or alveolar to arterial oxygen gradient $P(A\text{-}a)O_2$>20 mmHg); and (3) Intrapulmonary vascular dilatations (IPVDs) as detected by contrast-enhanced echocardiography, lung perfusion scanning, or pulmonary angiography.[1,2]

The most common hepatic disorder leading to HPS is liver cirrhosis, irrespective of etiology.[1,2] Nevertheless, HPS has been observed in many other chronic, and even acute, hepatic conditions and also in patients with portal fibrosis and portal vein thrombosis in the presence of normal liver function.[3-5] Therefore, it appears that both portal hypertension & hepatic dysfunction may cause HPS.[6,7]

Interactions between the lung and the liver have been studied since 1884 when Fluckinger first described a woman with cirrhosis,cyanosis, and digital clubbing and used the term "hypoxemia of cirrhosis".[8] The term

"hepatopulmonary syndrome" was first suggested in 1977 by Kennedy andKnudson to describe the association of severe hypoxemiawith IPVDs in the setting of hepatic dysfunction.[9]

Owing to the increasing success of orthotopic liver transplantation (OLT), there has been a renewed interest in the pulmonary vascular complications of hepatic disease states. Such vascular complications, namely HPS and porto-pulmonary hypertension, commonly present nonspecifically as dyspnoea and are not always easily distinguished from non-pulmonary symptoms caused by manifestations of advanced liver disease (such as anemia, ascites and muscle wasting) or other comorbid cardiopulmonary disorders such as heart failure or chronic obstructive pulmonary disease.[10] More importantly, experience has revealed that such complications influence survival and candidacy for OLT.[11] Currently, OLT is the only effective treatment for improving outcome in patients with HPS.[1,2,6,12]

Arterial hypoxemia of various degrees is seen in 30%-70% of patients with chronic liver disease, depending on the severity of liver disorder and the presence or absence of comorbid cardiopulmonary disease while severe hypoxemia of clinical HPS is seen less frequently with the highest rate around 20% in most large studies.[13,14]

It is believed that hypoxemia of HPS occurs as a result of one (or the combination of several) of the following mechanisms: (1) ventilation-perfusion mismatching (reflecting excess perfusion for a given ventilation); (2) true intrapulmonary anatomical shunts; and (3) diffusion-perfusion impairment (due to increased oxygen diffusion distance from alveoli to hemoglobin across the dilated vessels).[1,2,14-16]

The natural history of HPS is not well described because of the lack of adequate prospective data but in general HPS has a progressive course and is associated with high morbidity and mortality.[17-20] A prospective study demonstrated that the survival of patients with HPS is significantly shorter (median survival 11 months), compared to patients without HPS (median survival 41 months).[19]

PATIENTS AND METHODS

From January 2005 to October 2006, 60 patients (in- and outpatients) with chronic liver disease attending Baghdad Teaching Hospital and the Hepatology and Gastroenterology Center were evaluated for the presence of HPS. Eight patients were excluded from the study because of clinically significant cardiorespiratory disease (4 had large pleural effusions, 2 had clinically significant heart failure, and 2 had established chronic obstructive pulmonary disease).

According to generally accepted criteria used to define HPS, patients were divided into two groups, one with evidence of HPS and one without such evidence, and the two groups were compared in terms of age, sex, smoking habits, cause and duration of liver disease, Child-Pugh class and score, and presence of dyspnea, platypnea, cyanosis, finger clubbing, spider nevi, palmar erythema, and ascites. Laboratory values compared between the two groups included hematocrit, serum levels of albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), prothrombine time (PT), and presence of esophagogastric varices on endoscopy.

All patients were initially screened for abnormal SaO_2 using a portable pulse oximeter with the probe applied to the right index finger. Those patients who showed an SaO_2 of $\leq$92% and/or a decrease in SaO_2 of $\geq$4% after change from supine to upright position were further evaluated by ABG and CEE.[21-24]

Arterial blood gas samples were obtained by percutaneous radial artery puncture with the patient in a seated position breathing room air, and were analysed with a ABG analyzer. CEE was performed using hand-agitated saline as a contrast medium which creates a stream of microbubbles after intravenous injection.[25,26] In healthy individuals, these microbubbles, greater than 15µm in diameter, opacify the right heart chambers only because they are filtered in the pulmonary capillary bed and do not appear at the left side of the heart. The distinction between intrapulmonary or intracardiac shunt is made by the time of appearance of the microbubbles in the left heart chambers; in intracardiac shunt the microbubbles appear generally within three heartbeats after appearance in the right heart chambers and in intrapulmonary shunt they appear 4–6 heartbeats after their initial appearance in the right side of the heart.[25,26]

HPS was diagnosed if both of the following echocardiographic and oxygenation criteria were met in a patient with chronic liver disease: (1) positive CEE (left atrial microbubbleopacification>3 beats after right atrial opacification); and (2) abnormal oxygenation defined by PaO_2< 70 mm Hg.[1,2]

Each patient had chronic liver disease with clinical evidence of portal hypertension. Portal hypertension was inferred if the patient had the following: (1) esophagogastric varices documented by esophagogastroduodenoscopy; (2) ascites by physical examination or ultrasonography; or (3) splenomegaly by physical examination, or ultrasonography of the abdomen

in the appropriate clinical setting. Chronic liver disease was confirmed by clinical and routine laboratory markers and by liver biopsy when available. Severity of liver disease was measured by the Child-Pugh classification system (Table 1): A 5 to 6 (least severe); B 7 to 9; and C 10 to 15 (most severe). One to 3 points were assigned according to the increasing degree of abnormality in each of five variables (serum total bilirubin, serum albumin, prothrombin time, hepatic encephalopathy, and ascites).

Table 1. Child-Pugh Classification System.

Factor	Score		
	1	2	3
Serum Bilirubin mg/dl	< 2	2-3	> 3
Serum Albumin g/dl	>3.5	3-3.5	< 3
Prothrombin time (seconds)	0-4	4-6	> 6
Ascites	non	Easily controlled	Poorly controlled
Hepatic encephalopathy	Non	Minimal	Advanced

Echocardiographic Criteria

Patients were determined to have IPVDs if results of transthoracic CEE were positive after the administration of 10 mL of hand-agitated normal saline solution in the supine position via an upper extremity peripheral vein. Positive was qualitatively defined as any visual opacification of the left heart chambers more than three cardiac cycles after appearance of microbubbles in the right ventricle.[25,26] No patient was found to have evidence of an intra-atrial right-to-left shunt (immediate opacification observed in the left atrium), that is, less than three cardiac cycles from the time of right atrial opacification.

Abnormal Oxygenation Criteria

Arterial blood gas samples were obtained from a single radial artery puncture while the patient was in a clinically stable situation. PaO_2 was reported. The diagnosis of HPS was considered in patients with a PaO_2<70 mm Hg breathing room air in any position at rest (supine or sitting).[1,2]

RESULTS

Results obtained are summarized in Table 2 below. Twenty three patients (44.2%) had chronic viral hepatitis (9 had chronic hepatitis B; 11 chronic hepatitis C; and 3 both hepatitis B and C); 9 (17.3%) had chronic alcoholic liver disease; 4(7.6%) had viral hepatitis together with excessive alcohol use (1 with hepatitis C and 3 with hepatitis B); 3(5.7%) had hemochromatosis (1 with excessive alcohol use); 2 (3.8%) had Wilson disease; 2 (3.8%) had primary biliary cirrhosis; 2 (3.8%) had autoimmune hepatitis; and 1 (1.9%) had non-alcoholic fatty liver disease. Five patients (9.6 %) had unknown cause for their liver disease.

Table 2. Demographic and clinical characteristics of patients.

Characteristics	HPS	No HPS	P Value
Age (yr)	49.5 (11.4)	44.8 (14.9)	NS
Duration of liver disease (yr)	5.75 (0.96)	4.09 (3.71)	NS
Male : Female	3/1	36/12	NS
Smoking Statutes			
Past	1 (25)	25 (52.1)	NS
Yes	1 (25)	6 (12.5)	NS
No	2 (50)	17 (35.4)	NS
Child-Pugh class			
A	0 (0)	13 (27.1)	NS
B	1 (25)	15 (31.3)	NS
C	3 (75)	20 (41.7)	NS
Child-Pugh Score	11.3 (1.7)	9.1 (2.9)	NS
Cause of liver disease			
Alcohol	1 (25)	8 (16.6)	NS
HCV	0 (0)	11 (22.9)	NS
HBV	1 (25)	8 (16.6)	NS
HCV+HBV	1 (25)	2 (4.1)	NS
Alcohol + HCV	0 (0)	1 (2.1)	NS
Alcohol + HBV	0 (0)	3 (6.2)	NS
PBC	1 (25)	2 (4.1)	NS
Unknown	0 (0)	5 (10.4)	NS
Others	0 (0)	8 (16.6)	NS
Laboratory Values			
Hemoglobin (g/dl)	13.9 (2.2)	11.5 (2.2)	NS
Hematocrit (%)	40.5 (6.6)	34.4 (12)	NS
S. Albumin (g/dl)	2.4 (0.38)	2.5 (0.58)	NS
S. Bilirubin (mg/dl)	4.05 (1.55)	2.7 (1.79)	NS
S. AST (U/I)	101.8 (12)	143 (61)	NS
S. ALT (U/I)	99.8 (37.2)	132 (64)	NS
S. ALP (U/I)	241 (63.1)	195 (92)	NS
PT (Sec)	25.3 (7.2)	21.1 (6.4)	NS
SaO_2% (Supine)	90.8 (3.8)	96.6 (2.7)	< 0.0001
SaO_2% (Standing)	81 (7.3)	96.8 (2.7)	< 0.0001
PaO_2 (mmHg)	69 (5.7)	86.5 (3.9)	< 0.0001
Endoscopic varices	4 (100)	22 (45.8)	NS
Clinical features			
Dyspnea	4 (100)	9 (18.7)	0.0027
Platypnea	1 (25)	0 (0)	NS
Cyanosis	3 (75)	1 (2.1)	< 0.0001
Finger clubbing	3 (75)	9 (18.7)	0.0514
Spider nevi	2 (50)	15 (31.2)	NS
Palmar erythema	2 (50)	11 (22.9)	NS
Ascites	3 (75)	30 (62.5)	NS

Abbreviations: HBV hepatitis B virus; HCV hepatitis C virus; PBC primary biliary cirrhosis; NS statistically non-significant. Bilirubin total serum bilirubin, PT prothrombin time, AST serum aspartate aminotransferase, ALT serum alanine aminotransserase, ALP serum alkaline phosphatase, SaO_2 percent oxygen saturation, PaO_2 partial pressure of oxygen in arterial blood.

*Values are mean (SD) or number (%).

In patients with HPS, 3 (75%) were in Child-Pugh class C, and 1(25%) in class B, while in patients without HPS 13 (27%) were in class A, 15 (31.2%) were in class B and 20 (41.6%) had class C; so there was a non-

significant trend for HPS to occur in patients with more advanced liver disease as measured by Child-Pugh class (P=0.3574).

Child-Pugh score for patients with HPS was 11.3 (SD 1.7) and for patients without HPS was 9.1 (SD 2.9).The mean duration of liver disease was 5.75 (SD 0.96) and 4.09 (SD 3.71) years in patients with and without HPS respectively.

Causes of liver disease in patients with HPS included alcoholic liver disease, chronic hepatitis B, combined chronic hepatitis B and C, and primary biliary cirrhosis.

Twelve patients (23%) had a pathological SaO_2 according to the criteria described above. All 4 patients with HPS had a significant postural drop in SaO_2 (orthodeoxia); i.e. ≥4%. In the 48 non-HPS patients 7 had a $SaO_2 \leq 92\%$ but with no remarkable change in upright position and 1 had a supine $SaO_2 > 92\%$ combined with a drop of 4 in upright position. CEE demonstrated in all four HPS patients the appearance of microbubbles in the left heart 4–6 heart cycles after the appearance in the right heart. The patient with a $SaO_2 > 92\%$ and position change of 4 had an inconclusive CEE result and the other 7 with supine $SaO_2 \leq 92$ and no position change had a negative CEE result.

The mean SaO_2 levels in patients with HPS as compared to patients without HPS were significantly lower in supine (90.8%, SD 3.8% vs. 96.9%, SD 2.7%, p <0.0001) and upright position (79.5%, SD 5.2% vs. 96.8%, SD 2.7%, <0.0001). Most importantly, not all four HPS patients had a pathological SaO_2 in the supine position but all showed a significant SaO_2 decrease after changing from supine to upright position. The mean ΔSaO_2 in the HPS patients was 11.3 (SD 5.85) compared to non-HPS patients who showed no significant change ($p < 0.0001$). A fall of SaO_2 of 4% on standing with a normal value in the supine position was seen in a single patient with large volume ascites without HPS.

HPS patients showed pronounced hypoxemia (mean PaO_2 = 69.0 mm Hg, SD 5.7) in arterial blood gas analyses under ambient O_2 partial pressure compared to the patients without HPS while SaO_2 levels were only mildly reduced in the supine position (mean 90.8%, SD 3.8%) but more markedly reduced in the standing position (mean 79.5%, SD 5.2%).

All 4 (100%) patients with HPS had dyspnea while it was present in only 9 (18.7) patients without HPS (P=0.0027). Platypnea was present in 1 (25%) patient with HPS and in none of patients without HPS (P=0.1089). Cyanosis was present in 3 (75%) patients with HPS and in 1 (2%) patient without HPS (P<0.0001). Finger clubbing was present in 3 (75%) patients with HPS and in 9 (18.75%) patients without HPS (P= 0.0514). Spider nevi was present in 2 (50%) patients with HPS and in 15 (31.25%) patients without HPS (P=0.8311). Palmar erythema was present in 2 (50%) patients with HPS and in 11 (22.91%) patients without HPS (P=0.5479). Ascites was found in 3 (75%) patients with HPS while it was found in 30 (62.5%) patients without HPS (P=0.9668). All 4 (100%) patients with HPS had endoscopic evidence of esophago-gastric varices while this was found in 22 (45.83%) patients without HPS (P=0.1185). Table 3 shows various clinical features and their usefulness as predictors for the presence or absence of HPS.

Hematological tests showed a non-significant trend towards higher hemoglobin (13.9 g/dl, SD 2.2 vs. 11.5 g/dl, SD 2.2) and hematocrit values (40.5%, SD 6.6 vs. 34.4%, SD 12.1) in patients with HPS compared to patients without HPS. Biochemical liver tests (total bilirubin, albumin, prothrombin time, alanine and aspartate aminotransfrases, and alkaline phosphatase) showed a non-significant trend to be worse in patients with HPS compared to patients without HPS. Chest radiographs showed no obvious abnormalities, such as increased interstitial markings, in either group of patients.

In HPS patients there was a non-significant trend towards higher mean respiratory and pulse rate as well as a lower mean systolic and diastolic blood pressure. No significant correlation between occurrence of HPS and age, sex, smoking status, cause of liver disease, or duration of liver disease, were found.

Table 3. Values of Various Clinical Features in the Diagnosis of HPS.

Clinical Feature	Frequency No. (%)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P* Value
	HPS	No HPS					
Dyspnea	4 (100)	9 (18.7)	100.0	81.3	48.5	100.0	0.0027*
Platypnea	2 (50)	0 (0.0)	50.0	100.0	100.0	88.3	0.1089
Cyanosis	3 (75)	1 (2.0)	75.0	97.9	86.4	95.7	<0.0001*
Finger Clubbing	3 (75)	9 (18.7)	75.0	81.3	41.4	94.8	0.0514
Spider nevi	2 (50)	15 (31.2)	50.0	68.8	22.0	88.6	0.8311
Palmar erythema	2 (50)	11 (22.9)	50.0	77.1	27.8	89.7	0.5479
Ascites	3 (75)	30 (62.5)	75.0	37.5	17.5	89.5	0.9668

Abbreviations: PPV positive predictive value, NPV negative predictive value.

DISCUSSION

Hypoxemia is common in patients with chronic liver disease. A rare cause is the HPS that may cause dyspnea, platypnea, and orthodeoxia and generally entails a poor prognosis.[18,19]Since other abnormalities such as pleural effusion and ascites may coexist in patients with HPS and contribute to respiratory insufficiency, a reduced paO_2 or SaO_2 alone is not sufficient to make a diagnosis of HPS. The diagnostic criteria of HPS include liver disease, hypoxemia (paO_2 <70 mmHg), and evidence of IPVDs. This study used pulse oximetry as a non-invasive screening tool for hypoxemia of HPS in patients with chronic liver disease. Therefore, ABG was only obtained from patients with a SaO_2 below the threshold value of 92% or those with a decrease in SaO_2 of ≥4% after change from supine to upright position (ΔSaO_2). In liver transplant candidates a threshold SaO_2 of ≤94% detected all subjects with an arterial PaO_2<60 mm Hg.[22] A patient with SaO_2>92% with no significant drop in the upright position is unlikely to have a PaO_2<70 mm Hg or IPVDs.[23] There may be a small subgroup of patients with positive CEE and essentially normal or slightly reduced oxygenation due to "subclinical" HPS. We cannot determine how many patients we missed to detect due to a lack of a position change in SaO_2. The incidence and clinical significance of these forms of HPS is not clear. However, patients with clinically apparent HPS have a significantly increased mortality and have to be identified.[17-19] Our intention was to determine the prevalence of "clinical" HPS and not minor forms by a simple screening algorithm.

This study included 52 patients most of them had liver cirrhosis and the others had chronic hepatitis. The majority of patients had decompensated liver disease as assessed by Child-Pugh classification system. Only 12 patients (23%) had a low SaO_2 or a ΔSaO_2 of ≥4%. This is a relatively small percentage compared to other study populations, such as liver transplant candidates.[27] Four patients (7.6%) in our study met the diagnostic criteria for HPS. Eight patients had abnormal oxygenation but negative CEE (7 patients with SaO_2≤92 without a drop in the upright position and one had a ΔSaO_2 of ≥4%).

The reported incidence of HPS in patients with chronic liver disease is variable (1.3–32%) and depends on the study population, the diagnostic criteria, and the tests used to detect IPVDs.[1,2,6,24-26] Higher prevalence reported in patients with advanced liver disease such as liver transplant candidates compared to a mixed sample of patients with chronic liver disease;[23] in studies applying less stringent oxygenation criteria, i.e. PaO_2<80 mmHg or $P(A\text{-}a)O_2$>20 mmHg compared to PaO_2<70 mmHg;[24] and in studies using transesophageal compared to transthoracic contrast echocardiography to detect IPVDs because the former is more sensitive in the detection of IPVDs.[25,26] The prevalence of HPS in our study (7.6%) appears realistic in our mixed sample of patients with chronic liver disease which included both in- and out-patients with various etiologies and stages of liver disease.

Patients with HPS in our study were older than patients without HPS while other studies reported HPS in younger and older patients similarly.[21,23] Rydell and Hoffbauer in 1956 described a 17-year old patient with liver cirrhosis and dilated pulmonary vessels with arteriovenous fistulas found at autopsy.[27] At the same time, Hales described some very young patients with similar pulmonary findings and liver disease.[28] HPS has even been reported to occur in childhood.[29]

Three of the 4 patients with HPS were in Child-Pugh class C and one was in class B. We found no statistically significant correlation between the severity of liver disease as assessed by Child-Pugh class and the presence of HPS, nevertheless, HPS tended to occur more in patients with class C and B compared to class A. This finding is consistent with most other studies.[1,2,21-24] though a small recent study in Iran found a statistically significant correlation between HPS and Child-Pugh class C.[30]

Two of our 4 patients with HPS had liver cirrhosis due to chronic viral hepatitis and the other 2 patients had alcoholic liver disease and primary biliary cirrhosis (PBC), respectively. Both acute and chronic liver diseases have been associated with HPS,[3-5] but most commonly, HPS is seen in patients with chronic liver diseases progressing to liver cirrhosis.[1,2] However, the documented occurrence of HPS in patients with noncirrhotic portal hypertension suggests that cirrhosis is not a prerequisite for the development of HPS.[3]

In our patients there was no correlation between the occurrence of HPS and liver function tests (total bilirubin, albumin and prothrombin time), similar to findings in other studies.[1,2,21-24] In contrast to other studies,[21-24,30,31] we found no association between spider naevi or other skin manifestations of liver disease e.g. palmar erythema, and HPS. The most impressive physical findings in our patients with HPS were cyanosis and digital clubbing which were significantly more frequent in these patients than in non-HPS patients.

Since hypoxemia and orthodeoxia are not pathognomonic for HPS, CEE is necessary to discriminate between intrapulmonary and intracardiac right-to-left shunt. All

patients with low SaO_2 or significant ΔSaO_2 together with PaO_2 <70 mmHg underwent CEE. In 4 patients microbubbles appeared in the left heart after 4–6 heart beats. No patient in our study had an intracardiac shunt (i.e. microbubbles opacifying the left heart within 3 heart beats).

Patients with end-stage liver disease may have various pulmonary abnormalities, including restrictive and obstructive lung disease. Patients with HPS tend to have a decreased CO diffusion capacity with normal lung capacity and expiratory flow rates.[21] These tests were not performed in our study.

Conclusion: HPS is a not an uncommon pulmonary vascular complication of liver disease complicated by portal hypertension. Both cyanosis and platypnea were found to be highly specific clinical markers for the presence of HPS, and ,though not specific, dyspnea was found to be the most sensitive clinical indicator for the presence of HPS in the appropriate clinical setting (chronic liver disease with portal hypertension and no obvious cardiorespiratory disorder). In the setting of liver disease, orthodexoia strongly suggested hepatopulmonary syndrome. Neither routine biochemical liver tests nor upper GI endoscopic findings are useful in predicting the presence or absence of HPS

REFERENCES

1. Krowka MJ. Hepatopulmonary syndrome: recent literature (1997 to 1999) and implications for liver transplantation. Liver Transpl 2000;6: Suppl. 1,S31–S35.
2. Krowka MJ, Cortese DA. Hepatopulmonary syndrome: current concepts in diagnostic and therapeutic considerations. Chest 1994;105:1528–37.
3. Teuber G, Teupe C, Dietrich CF, Caspary WF, Buhl R, Zeuzem S. Pulmonary dysfunction in non-cirrhotic patients with chronic viral hepatitis. Eur J Intern Med 2002;13:311–18.
4. Fuhrmann V, Madl C, Mueller C, et al. Hepatopulmonary syndrome in patients with hypoxic hepatitis. Gastroenterology 2006;131:69-75.
5. Regev A, Yeshurun M, Rodriguez M, et al. Transient hepatopulmonary syndrome in a patient with acute hepatitis A. J Viral Hepat 2001;8:83–6.
6. Martinez GP, Barbera` JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 2001;34:651–7.
7. Roberto R, Krowka MJ. Hepatopulmonary syndrome - A liver-induced lung vascular disorder. N Engl J Med 2008;358:2378-87.
8. Fluckinger M, Vorkommen von trommelschagel-formigenFingerendphalangenohnechronischeverande rungenan den Lungenoder am Herzen. Wien Med Wchnschr 1884;34:1457.
9. Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. Chest 1977; 72:305-9.
10. Rodrı´guez-Roisin R, Krowka MJ, Herve´ Ph, Fallon MB, on behalf of the ERS Task Force Pulmonary–Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary–Hepatic vascular Disorders (PHD). EurRespir J 2004;24:861–80.
11. Gennaro S. Patient selection in liver transplant: when is it the right time to list?. Mayo Clin Proc 2008;83(2):140-2
12. Krowka MJ. Clinical management of hepatopulmonary syndrome. Semin Liver Dis 1993;13:414-22.
13. Møller S, Hillingso J, Christensen E, Henriksen JH. Arterial hypoxaemia in cirrhosis: fact or fiction? *Gut* 1998;42:868-74.
14. Krowka MJ, Cortese DA. Pulmonary aspects of chronic liver disease and liver transplantation. Mayo Clin Proc 1985;60:407-18.
15. Altman M, Robin ED. Platypnea (diffuse zone I phenomenon?). N Engl J Med 1969;281:347-8.
16. Dinh-Xuan A.T, Naeije R. Editorial. The hepatopulmonary syndrome: NO way out?. EurRespir J 2004;23:661–2.
17. Krowka MJ, Porayko MK, Plevak DJ, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. Mayo Clin Proc 1997;72:44-53.
18. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology 2003;125(4):1042–52.
19. 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):192–7.

20. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. Hepatology2005;41:1122-9.
21. Beatriz LG, Lima MD, et al. Frequency, Clinical Characteristics, and Respiratory Parameters of Hepatopulmonary Syndrome: Original article. Mayo Clin Proc 2004;79:42-8.
22. Abrams GA, Sanders MK, Fallon MB. Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates. Liver Transpl 2002;8:391-6.
23. Peter D, Hans-Peter A, Stefanie L, Claudsia M, Manfred O, Hinrich H Klaus-Peter M. Hepatopulmonary syndrome in patients with chronic liver disease: role of pulse oximetry BMC Gastroenterology 2006;6:15-21.
24. Schenk P, Fuhrmann V, Madl C, et al. Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. Gut 2002;51:853–9.
25. Vedrinne JM, Duperret S, Bizollon T, et al. Comparison of transesophageal and transthoracic contrast echocardiography for the detection of an intrapulmonary shunt in liver disease. Chest 1997;111:1236–40.
26. Aller R, Moya JL, Moreira V, et al. Diagnosis of hepatopulmonary syndrome with contrast transesophageal echocardiography. Advantages over contrast transthoracic echocardiography. Dig Dis Sci 1999;44:1243–8.
27. Rydell R, Hoffbauer FW. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. Am J Med 1956;21:450-60.
28. Hales MR. Multiple arteriovenous fistulas of the lungs. Am J Pathol 1956; 32:927-37.
29. Kinane TB, Westra SJ. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31- 2004. A four-year-old boy with hypoxemia. N Engl J Med 2004;351:1667-75.
30. Mohammad A, et al. Rapid Communication: Clinical features of hepatopulmonary syndrome in cirrhotic patients. World J Gastroenterol 2006 28;12(12): 1954-6.
31. Hira H, Jaya K, Tyagi S.K. A study of hepatopulmonary syndrome among patients of cirrhosis of liver and portal hypertension. Indian J Chest Dis Allied Sci 2003;45:165-7.