Prevalence of clinically significant Hepatopulmonary Syndrome among Patients with Chronic Liver Disease and Portal Hypertension

*Dr. Sadiq Almohana

Abstract

Background: The hepatopulmonary syndrome (HPS) is defined as the triad of liver disease, arterial deoxygenation, and pulmonary vascular dilatation. The reported prevalence of HPS in cirrhotic patients varies between 5% - 17.5%.

Objective: To estimate the prevalence of hepatopulmonary syndrome among patients with chronic liver disease and portal hypertension and to study the correlation between HPS and the severity of liver disease.

Patients and methods: Thirty patients were studied for the presence of HPS using transthoracic contrast echocardiography for detection of pulmonary vasodilatation. Arterial oxygen saturation (SaO2) was determined in erect and supine position using a pulse oximeter, (SaO2 ≤ 92 % in supine position and/or a decrease of ≥ 4% after change from supine to upright position) to detect hypoxia and orthodeoxia.

Result: Eleven of thirty patients (36.6%) with chronic liver disease and portal hypertension were found to have contrast echocardiographic evidence of intrapulmonary right-to-left shunting. Arterial oxygen desaturation was present in 3 patients (27.3%) of those with intra-pulmonary right-to-left shunting, they were considered as clinically significant HPS, the remaining 8 patients were considered as subclinical HPS. Dyspnoea was more often present in patients with clinically significant HPS (100%) compared with subclinical HPS (25%), and patients without HPS (9%). HPS correlated significantly with severity of liver disease according to the Child-Pugh score.

Conclusion: Hepatopulmonary syndrome is not uncommon, the prevalence of clinically significant hepatopulmonary syndrome (in this study) was 10% of patients with chronic liver disease and it correlated with disease severity according to the Child-Pugh score.

Key wards: cirrhosis, hepatopulmonary syndrome, orthodeoxia, hypoxia.

Introduction

Definition: HPS is a disorder of pulmonary oxygenation caused by intrapulmonary vasodilatation, occurring in the clinical setting of liver disease or portal hypertension. In early studies, HPS was thought to be found only in patients with cirrhosis and portal hypertension and it is still most commonly diagnosed in this situation. However, HPS is now recognized to occur in both acute and chronic hepatitis without portal hypertension and in prehepatic portal hypertension and hepatic venous obstruction without cirrhosis (1). Sever hepatic synthetic dysfunction is not required and HPS frequently present in patients with relatively mild liver disease (2). HPS may occur as an isolated disorder in patients with liver disease, or it may compound other cardiac or pulmonary diseases. There is no evidence that a specific etiology of chronic liver disease is more likely to cause HPS (1).

Pathophysiology: The hallmark of HPS is microvascular dilatation occurring within the pulmonary arterial circulation. The cause of this abnormality appears to be multifactorial (Fig. 1). Pulmonary nitric oxide (NO) levels are increased in patients with HPS (3, 4) and in experimental models; increased levels of both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) are found in the pulmonary microcirculation (5, 6).

NO is a potent vasodilator, particularly in the pulmonary circulation and overproduction may lead to widespread intrapulmonary vasodilatation. In addition, NO may induce hemeoxygenase-1 and result in production of carbon monoxide that may also contribute to vasodilatation (7, 8). Microvascular dilatation impairs V/Q matching and may result in anatomic and functional shunt physiology, leading to hypoxemia.
Clinical manifestations and prognosis:
The clinical manifestations of HPS primarily involve respiratory complaints and findings associated with chronic liver disease. Dyspnea, insidious in onset and occurring especially on exertion, is the most common complaint but is nonspecific. Platypnea (shortness of breath exacerbated by sitting up and improved by lying supine) is a less sensitive but more specific finding. Hypoxemia with exertion or at rest is common; this may be exacerbated in the upright position (orthodeoxia) due to increased shunting and V/Q mismatch. Cough is not a common finding in HPS. Spider angiomata, one of the stigmata of chronic liver disease, are common but not specific; clubbing and distal cyanosis, while relatively insensitive findings, are more specific for HPS when they occur in the setting of liver disease or portal hypertension. In addition to causing dyspnea and decreased activity tolerance, HPS also appears to have significant effects on mortality in cirrhosis. Cirrhotic patients with HPS have significantly higher mortality than patients without HPS, regardless of Childs-Pugh score, age, or blood urea nitrogen. Mortality may be as high as 41% at 2.5 years after onset of dyspnea. In addition, severe HPS increases postorthotopic liver transplant mortality; one study found one-year survival was 71% in patients with HPS, compared with overall 90% and 92% one-year post transplant survival at the two institutions involved. In that study, the strongest predictor of mortality was a room air PaO2 less than or equal to 50mmHg plus a macro aggregated albumin (MAA) shunt fraction of at least 20%; sensitivity was 86%, specificity was 88% and positive and negative predictive values were 75% and 94%, respectively. These findings underscore the importance of detecting the presence of HPS in patients with liver disease.

Methods:
Thirty patients with chronic liver disease were included in this study from Al-Sader teaching hospital in Al-Najaf during the period from February 2007 through January 2009, twenty patients (66.6%) were male and ten patients (33.3%) were female. Their ages were ranging from 9 to 60 years, with mean age of 39.2 years. According to the data that available in patients records, the diagnosis of chronic liver disorders was based on clinical, biochemical, histopathological and ultrasound criteria, nine patients had liver cirrhosis (30%), twenty patients had chronic hepatitis (66.6%), one patient had non-cirrhotic portal hypertension (3.3%) The patients with liver cirrhosis and chronic hepatitis were classified according to the Child-Pugh classification (Table -1).

Table 1: Child-Pugh classification of prognosis in chronic liver disease
<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Mild</td>
<td>Marked</td>
</tr>
<tr>
<td><strong>Bilirubin (μmol/l)</strong></td>
<td>&lt; 34</td>
<td>34-50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td><strong>Bilirubin in primary biliary cirrhosis and sclerosing cholangitis</strong></td>
<td>&lt; 68</td>
<td>68-170</td>
<td>&gt; 170</td>
</tr>
<tr>
<td><strong>Albumin (g/l)</strong></td>
<td>&gt; 35</td>
<td>28-35</td>
<td>&lt; 28</td>
</tr>
<tr>
<td><strong>Prothrombin time (seconds prolonged)</strong></td>
<td>&lt; 4</td>
<td>4-6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Add the individual scores:
- < 7 = Child's A
- 7-9 = Child's B
- > 9 = Child's C

Measurement of SaO₂ was performed with a portable pulse oximeter. In all patients, the measurements were performed at ambient O₂ partial pressure in supine position. A second reading was taken after 10 minutes in upright position. A pathological test result was defined as: (i) SaO₂ ≤92% in supine position, (ii) a decrease in SaO₂ of ≥4% after change from supine to the upright position (ΔSaO₂)(15).

Contrast echocardiography was done. For all patient agitated saline was used as a contrast medium which creates a stream of micro bubbles after intravenous injection.(16) In healthy individuals, these microbubbles, greater than 15 μm 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(17, 18).

**Statistical study:** The Statistical analyses were based on Chi Square with a P-value of 0.05 or less was considered as statistically significant.

**Results:**

The clinical characteristics of the patients participating in the study were summarized in (Table2). The etiology of chronic liver disease was alcohol use in 16.6%, chronic hepatitis B in 13.3%, non alcoholic steotohepatites in 10%, hemochromatosis in 6.6%, Wilson's disease in 3.3%, primary biliary cirrhosis (PBC) in 3.3%, cardiac cirrhosis in 3.3%, malignancy in 3.3% and unknown in 36.6%, one patients had non-cirrhotic portal hypertension of unknown origin.

**Table 2: The clinical characteristics of the presented patients with liver disease.**

<table>
<thead>
<tr>
<th>Characteristics of the thirty Studied Patients</th>
<th>39.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>20 male (66.6%)</td>
</tr>
<tr>
<td><strong>Etiology of liver disease</strong></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>5</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>4</td>
</tr>
<tr>
<td>NASH</td>
<td>3</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>2</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>1</td>
</tr>
<tr>
<td>PBC</td>
<td>1</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
</tr>
<tr>
<td><strong>Manifestation of liver disease</strong></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic portal hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

Eleven of the thirty patients (36.6%) had intrapulmonary vasodilatation as revealed by contrast echocardiography. For clinical purposes, we subdivided the patient's group with intra-pulmonary vasodilatation (assessed by a positive contrast echocardiography) into two groups: "clinically..."
significant” HPS, that characterized by a pathological 
SaO2 according to the criteria described above, and 
“subclinical” HPS, that characterized by none 
pathological SaO2. Among the thirty patients, there 
were three patients (10%) had clinically significant 
HPS and eight patients had subclinical HPS. The 
patients with liver cirrhosis and chronic hepatitis were 
classified according to the Child-Pugh classification 
(14) as follows: A: 26.6%, B: 53.3% and C: 
20%. (Table 3). Demographic data of the patients with 
and without a positive contrast echocardiography 
were shown in (Table 4).
All patients with “clinically significant” HPS (100%) 
had dyspnoea at rest compared with two “subclinical” 
HPS patients (25%) and two patients from group 
without HPS (9%; p<0.05). Spider naeves were found 
more often in the “clinically significant” HPS group 
(66.6%) compared with the “subclinical” HPS group 
(62.5%) and the group without HPS (3%; p<0.05). The 
frequency of palmer erythema was not 
significantly different between the three groups. 
The Child-Pugh score was highest in “clinically 
significant” HPS patients (11.6), followed by the 
“subclinical” HPS patients (10.5); and lowest in the 
patient’s group without HPS, patients with clinically 
significant and subclinical HPS had Child-Score C 
significantly higher than patient’s group without HPS.

### Table 3: Classification of patients with liver cirrhosis and chronic hepatitis according to the Child-Pugh classification

<table>
<thead>
<tr>
<th>Classification according to Child-Pugh score</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

### Table 4: Clinical features of patients with “clinically significant” hepatopulmonary syndrome (HPS), “subclinical” HPS, and no HPS

<table>
<thead>
<tr>
<th></th>
<th>“Clinically significant” HPS* (n=3) and positive contrast echo</th>
<th>“Subclinical” HPS† (n=8) and positive contrast echo</th>
<th>No HPS (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>3 (100%)</td>
<td>2 (25%)</td>
<td>2 (9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Spider naevi</td>
<td>2 (66.6%)</td>
<td>5 (62.5%)</td>
<td>3 (16.6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Palmer erythema</td>
<td>1 (33.3%)</td>
<td>3 (37.5%)</td>
<td>9 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>Child-Score (mean)</td>
<td>11.6</td>
<td>10.5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Child-Score C</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Defined as: (i) SaO2 ≤92% in supine position, (ii) a decrease in SaO2 of ≥4% after change from supine to the upright position (ΔSaO2).
†Defined as: (i) SaO2>92% in supine position, (ii) a decrease in SaO2 of <4% after change from supine to the upright position (ΔSaO2).

### Discussion:

The hepatopulmonary syndrome (HPS) is a triad of liver disease, arterial deoxygenation, and pulmonary vascular dilatation. The reported prevalence of HPS in cirrhotic patients varies between 5%-17.5% (19,20,21,22). The prevalence of HPS in our study was (10%) which was within the reported range. Available data from the previous publications about the frequency of positive contrast echocardiograms and the prevalence of HPS was different according to their preferred cut off value defining arterial hypoxaemia. Estimations of prevalence vary as different definitions for HPS are used. P Schenk and his colleagues used reduced partial pressure of arterial oxygen (PaO2) as a threshold (<80 mm Hg, 19%; <70 mm Hg, 15%; and age related threshold, 15%) (22); their prevalence was higher compared with our study. This can be explained by the higher rate of hypoxemic patients compared with our study (43% of all patients had PaO2 values <80 mm Hg) because arterial blood gas analysis were more sensitive than pulse oximetry. We used the pulse oximetry as a non-invasive screening for HPS in patients with chronic liver disease (15). A patient with SaO2 >92% and no significant decrease in this value in the upright position is unlikely to have a PaO2 <70 mm Hg and pulmonary shunts (23), however because of pulse oximetry underestimates arterial oxygenation (24), there may be a subgroup of patients with a positive contrast echocardiograms and slightly changed oxygenation were missed and considered as subclinical HPS, so we cannot determine how many
In the study of Deibert et al., oximetry seems to be reliable. Defining pathological criteria for hypoxia using pulse mm Hg, it was 8% (less hypoxaemic patients), so our pathological SaO2, (1.3%) had HPS used to identify patients with HPS, (5.4%) had a class, another study by Vachiéry et al., showed significantly lower PaO2 values and greater contradiction. Some patients we missed to detect due to a lack of a position change in SaO2, the incidence and clinical significance of these forms of HPS is not clear. However, patients with clinically apparent HPS have a significant mortality and have to be identified, because HPS is an indication and not a contraindication for liver transplantation. Our intention was not to determine the true prevalence of HPS including minor forms but to detect a clinically relevant cases by a simple screening algorithm, and if we compared our study to Vedrinne et al.,(23) who studied the prevalence of HPS using PaO2 values <80 mm Hg, it was 8% (less hypoxaemic patients), so our defining pathological criteria for hypoxia using pulse oximetry seems to be reliable.

In the study of Deibert et al., the pulse oximetry was used to identify patients with HPS, (5.4%) had a pathological SaO2, (1.3%) had HPS.(27)

In the study of Vedrine and colleagues(23) the frequency of positive contrast echocardiography and the prevalence for HPS in patients with chronic liver disease was increased by 5% and 19%, respectively, when the transesophageal approach was used compared with the transthoracic procedure. In concordance, using the transesophageal technique, Aller et al., reported an increase of 14% and 6% for detection of intrapulmonary vasodilatation and prevalence of HPS respectively(28), therefore, it seems reasonable that some of our patients with normoxaemia and a negative transthoracic contrast echocardiography would have a positive transesophageal contrast echocardiography. However, most studies investigating HPS have used transthoracic contrast echocardiography for the detection of intra-pulmonary vasodilatations(24,29,30,31), and all literatures about HPS described transthoracic contrast echocardiography as the method of assessment of intrapulmonary vasodilatation, however transesophageal contrast echocardiography had been shown to be superior to the transthoracic approach in the detection of intrapulmonary vasodilatation in patients with chronic liver disease, but the usefulness of transesophageal technique was limited due to the imposed risk as an invasive procedure especially in patients who had a history of variceal bleeding(29). Patients with no pathological SaO2 may also show a positive contrast echocardiography (8/30; 26% in our study); this is higher as compared with previous studies (24,29,31), and may be because some patients were hypoxic but under estimated by pulse oximetry. Conflicting data existed in the literatures regarding the correlation between HPS and the severity of liver disease, whereas a study by Abrams and colleagues(25) showed significantly lower PaO2 values and greater shunt fractions in Child-Pugh A compared with B and C classes, another study by Vachiéry and colleagues(24) showed that hypoxaemic patients had a significantly higher Child-Pugh score. Our study clearly showed a significant correlation between the severity of HPS and Child-Pugh score.

**Conclusion:**

The prevalence of clinically significant hepatopulmonary syndrome was 10% of patients with chronic liver disease and correlated with disease severity according to the Child-Pugh score. To increase the detection of this abnormality we recommended to use transesophageal echocardiography and arterial blood gases to estimate pulmonary shunts and hypoxia, respectively.

**References:**


* Kufa medical college, department of medicine (Kufa Najaf, Iraq P.O Box 18)
**Kufa medical college, department of medicine
***Al-Sadder teaching hospital, Najaf