Arterial Hypoxemia in Patients with Cirrhosis of Liver

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Abstract

Introduction: Mild hypoxia has been seen in approximately one third of patients with chronic liver disease. Development of hypoxemia in patients with chronic liver disease, modifies the line of management and worsens the prognosis of the disease. Hence an early detection of hypoxemia in these patients is essential. Hypoxemia results from various causes in patients with chronic liver disease. Hepato pulmonary syndrome is an important cause in a patient with hypoxemia and chronic liver disease. Development of this complication in chronic liver disease indicates a poorer prognosis in these patients. Chronic liver disease is also known to be associated with pulmonary manifestations that affect both the pleural space and lung parenchyma. This study was undertaken to study the prevalence of hypoxemia and assess the prognosis in patients with chronic liver disease.

Materials and Methods: Forty three patients aged 18 years and above with evidence of cirrhosis, admitted under the department of Medicine and Gastroenterology, were included in the study. A detailed history was taken and clinical examination were done in all patients. All patients underwent ultrasonography, LFT, biochemical tests and upper gastrointestinal endoscopy to confirm chronic liver disease, portal hypertension and varices, if any chest X-ray, 2-D transthoracic echocardiogram, viral studies and pulmonary function tests. The patients in whom arterial hypoxemia was detected with a positive contrast echocardiogram were considered to have hepato pulmonary syndrome.

Results: Six out of the 43 patients (13.9%) included in the study had hypoxemia. Among these 6 patients with hypoxemia, 3 were found to have contrast enhanced echocardiographic evidence of intra pulmonary vascular dilatations and diagnosed hepato pulmonary syndrome. The other 3 patients had evidence of both, interstitial lung disease and pleural effusion contributing to hypoxemia. The patients with hepato pulmonary syndrome had a significant P (A-a) O2 gradient, died during the study period, indicating a poorer prognosis.

Conclusions: We conclude that identification of hypoxemia and its aetiology in patients with chronic liver disease is essential. Identification of hepato pulmonary syndrome is important, as it carries a poor prognosis in patients with chronic liver disease.
1. Patients less than 18 years of age,
2. Patients with coexisting primary pulmonary pathology,
3. Coexisting intrinsic heart disease,
4. Patients with hepatic encephalopathy,
5. Bed ridden patients,
6. Patients with active uncontrolled upper gastrointestinal haemorrhage
7. Active smokers were excluded.

Criteria for hepatopulmonary syndrome:

Delayed positive contrast Echocardiography (left atrial microbubble opacification occurring within 3 to 6 beats after right atrial opacification) and abnormal oxygenation defined by PaO$_2$<70 mmHg or P(A-a) O$_2$>20 mmHg in any position (supine, standing), assuming a respiratory quotient of 0.8 in a patient with cirrhosis of liver was used to define hepatopulmonary syndrome.

Detailed history was taken and clinical examination done. Ultrasonography was done for all the patients to find evidence for portal hypertension, the size and echotexture of the liver, presence of ascites and splenomegaly. Liver biopsy was carried out to confirm the presence of cirrhosis and to determine its etiology as and when permitted by coagulation parameters. All the patients underwent upper gastrointestinal endoscopy.

A 2-D transthoracic contrast-enhanced echocardiography was done for all the patients. 10 ml of hand-agitated normal saline solution was administered to all patients in the supine position via a three-way cannula fixed to the antecubital vein of the right forearm. A positive test was defined as any visual opacification of the left heart chambers more than three cardiac cycles after appearance of microbubbles in the right ventricle in any of three injections.

Arterial blood gas analysis was done by a single radial puncture under local anaesthesia, while the patient was in the supine position breathing room air and the sampling was repeated with the patients standing, breathing 100% oxygen. Each of these positions was maintained for a minimum of 10 min. Breathing 100% oxygen was performed by making the patient breathe through a sealed mouth piece with nostrils occluded to ensure adequate inhalation of 100% oxygen. Pure (100%) oxygen was delivered via an E tank at an approximated rate of 25 L/min. Arterial blood gas was analysed using Ecosys II blood gas analyser.

The presence of hypoxemia and orthodeoxia was also detected. Orthodeoxia was defined as fall in PaO$_2$ levels more than 3 mmHg on changing position from supine to standing and hypoxemia if PaO$_2$ was less than 70 mmHg breathing room air in any position at rest (supine, sitting or standing). Alveolar-arterial gradient of partial pressure of oxygen was taken as elevated if it was elevated more than 20 mmHg(calculated as P(A-a) O$_2$=PaO$_2$-150-1.25xPaCO$_2$). PaO$_2$ determinations were done while breathing 100% oxygen.

Pulmonary Function Tests (PFT):

All patients were subjected to PFT using a vitalograph spirometer (vitalograph 2120) in the standing position according to standard procedures. Forced expired volume in one second (FEV1); forced vital capacity (FVC), FEV 1% were measured. Predicated values for each of the parameters were obtained from standardized references.

Chest radiography:

Posteroanterior chest radiographs were obtained and Interpreted by the same radiologist. The radiographs were examined for the presence or absence of reticular, nodular, or reticulonodular interstitial opacities; visible arteriovenous malformations; cardiomegaly, increased or decreased lung volume, pleural effusion or increased pulmonary vascular markings.

All patients underwent the following investigations; complete blood picture, liver function tests, bleeding time, clotting time and prothrombin time, HBsAg, anti-HCV antibodies, Renal function tests, electrolytes, urine routine, ultrasound abdomen, chest- X-ray, upper gastrointestinal endoscopy.

RESULTS

A total of 43 patients with cirrhosis of liver were studied. Cirrhosis was more common in the sixth decade with 15 patients (34.8%) in the age group 51 to 60 years. The mean age was 54.02 years (range 29-88 years) 33 patients (76.8%) were females.

Out of the 43 patients, 25 patients (58.1%) had alcohol associated cirrhosis, 8 patients (18.6%) had cryptogenic cirrhosis, 7 patients (16.3%) had Hepatitis-B associated cirrhosis, 2 patients (4.6%) were found to have post-necrotic cirrhosis and 1 patient (2.3%) had Hepatitis-C associated cirrhosis.

Clinical review revealed ascites as the commonest finding in twenty nine (67.5%) patients. Platypnoea was present in six (13.9%) cases and orthodeoxia in 4 (9.3%) cases. Three of the forty three patients (6.9%) were found to have contrast-enhanced echocardiographic evidence of intra pulmonary vascular dilatations diagnostic of Hepato pulmonary syndrome (Table 1).

Hypoxemia (PaO$_2$<70 mm of Hg) was present in 6 patients (13.9%). Of these patients with hypoxemia only 3 patients (case 6, case 17 and case 22) had positive contrast-enhanced echocardiography. All 3 of these patients fulfilled the stringent criteria for hepato pulmonary syndrome. Two of these three patients had a PaO$_2$<500 mm of Hg on breathing 100% oxygen, while all three of them had hypoxia, orthodeoxia and increased P (A-a) O$_2$ of >20 mm of Hg. Two patients with hepatopulmonary syndrome had a normal PFT and one patient had a restrictive type of abnormality (Tables 2, 3 and 4).

The most common radiographic abnormality was increased interstitial basal markings which was seen in 8 patients (18.6%). All the 4 cases with orthodeoxia showed
increased interstitial basal markings.

9 (20.9%) deaths occurred during the study period. All the 3 patients with hepato pulmonary syndrome expired during study period. Gastro-intestinal bleeding was the major contributing factor for death in four patients (9.3%), respiratory failure and renal failure in 2 patients (4.7%). Three patients (7%) died due to sepsis syndrome and one of the HPS patients died of septicemia with ARDS.

**DISCUSSION**

The important finding of our study was the detection of hypoxemia and its causes in the presence of chronic liver disease. Hypoxemia was seen in 13.9% of patients which was comparable to a study conducted by Lange P A et al.5 The clinical markers of hypoxemia like cyanosis (16.3%), clubbing (9.3%) and orthodeoxia (9.3%) were noted, which were similar to the studies of De BK et al., Anand AC et al., Howrani et al., and Krowka et al.

In our study hepato pulmonary syndrome was found in 3 (6.9%) patients which is consistent with literature reports.6,10-12 However, Anand’s group quoted prevalence of 17.5% in 63 patients.

All the patients with HPS had esophageal varices indicating the presence of portal hypertension. Elevated portal pressure probably is a significant contributor to the development of HPS. Similarly this syndrome has been reported in the setting of non-cirrhotic portal hypertension with preserved hepatic function.7,13 In our study, except for cyanosis, platypnoea and orthodeoxia, no other clinical or biochemical factors seemed to correlate with HPS, also seen in the study of Abram et al.,14 where they found 15 of 25 cases of HPS (60%) had Child’s grade A and only two had grade C.

All the patients with HPS had an alveolar-arterial gradient [P(A-a)O2] >20 mmHg and echocardiographic evidence of intra pulmonary shunting. Two patients with HPS had an abnormal oxygenation (PaO2<500mmHg) while breathing 100% O2 pointing to diffusion/perfusion defect16 as the most important physiological abnormality which is similar to the study of Krowka MJ et al.17 A favourable PaO2 while breathing 100% O2 (PaO2 > 500 mmHg) would virtually exclude the existence of a clinically significant anatomic (or physiologic) right to left shunt. Very little improvement in PaO2 while breathing 100% O2 would be expected in such situations.16,17

One patient with HPS had normal oxygenation while breathing 100% O2 indicating ventilation/perfusion

### Table 1: Clinical and biochemical profiles of patients with positive as well as negative contrast echocardiograms (CE)

<table>
<thead>
<tr>
<th>CE</th>
<th>CE Negative (n=40)</th>
<th>CE Positive (n=3)</th>
<th>Case 6</th>
<th>Case 17</th>
<th>Case 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>54.1</td>
<td>56</td>
<td>53</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>31:9</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Ascites (n)</td>
<td>26</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gastro intestinal bleed (n)</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyspnoea (n)</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clubbing (n)</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spider naevi (n)</td>
<td>8</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyanosis (n)</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Platypnoea (n)</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Orthodeoxia (n)</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Table 2: Mean arterial blood gas and pulmonary function parameters according to CE echocardiographic result

<table>
<thead>
<tr>
<th>Mean Parameter</th>
<th>Negative CE-ECHO (n=40)</th>
<th>Positive CE-ECHO (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PaO2 (mm Hg) (supine)</td>
<td>88.28</td>
<td>61.33</td>
</tr>
<tr>
<td>2. PaCO2 (mm Hg) (supine)</td>
<td>35.26</td>
<td>30.67</td>
</tr>
<tr>
<td>3. PaO2 (mm Hg) (standing)</td>
<td>87.20</td>
<td>52.66</td>
</tr>
<tr>
<td>4. PaO2 breathing 100% O2 (mm Hg)</td>
<td>558.78</td>
<td>389</td>
</tr>
<tr>
<td>5. P(A-a)O2 (mmHg)</td>
<td>17.80</td>
<td>50.33</td>
</tr>
<tr>
<td>6. FVC (%predicted)</td>
<td>87.90</td>
<td>86</td>
</tr>
<tr>
<td>7. FEV1 (%predicted)</td>
<td>88.10</td>
<td>92</td>
</tr>
<tr>
<td>8. FEV1/FVC (%)</td>
<td>81.95</td>
<td>91.33</td>
</tr>
</tbody>
</table>

### Table 3: Results of arterial blood gas and pulmonary function tests in cases with positive contrast echocardiography

<table>
<thead>
<tr>
<th>Pulmonary function abnormality</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restriction</td>
<td>7</td>
<td>16.2</td>
</tr>
<tr>
<td>Obstruction</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased P(A-a)O2 &gt;20mm Hg</td>
<td>7</td>
<td>16.2</td>
</tr>
<tr>
<td>Patients with PaO2 &lt;500 mm Hg</td>
<td>4</td>
<td>9.3</td>
</tr>
</tbody>
</table>
inequality as the physiological abnormality,\textsuperscript{16} which is similar to the study of Rolla G et al.\textsuperscript{18}

It has been reported that the characteristic manifestation of hepato pulmonary syndrome on plain radiographs is basilar medium sized nodular or reticulo-nodular opacities in 5% to 100%.\textsuperscript{7,19} All the three HPS patients had increased interstitial basal markings, which were bilateral, which was also seen by other authors like Adams HP et al.\textsuperscript{20} Yet another finding in our study was the presence of interstitial markings in 18.6% of patients, pleural effusion in 16.2% of the patients.

Right sided pleural effusions are common compared to bilateral pleural effusion, as also seen in the study of Howrani et al.\textsuperscript{6}

A restrictive pattern of respiratory function tests could be expected in 25% of cases and 3.4% of obstructive abnormality.\textsuperscript{4} In this series, 16.2% had restriction and 2.3% of patients had obstruction with no historical support for this abnormality.

Orthodeoxia was the characteristic feature of the three patients who had hepato pulmonary syndrome. Comparable findings were seen in other studies including De BK,\textsuperscript{6} Anand AC et al,\textsuperscript{7} Howrani et al\textsuperscript{6} and Krowka et al.\textsuperscript{9}

**CONCLUSIONS**

The highlighting feature of our study was detection of hypoxemia, in patients with chronic liver disease, the etiology of which needs to be evaluated as this would assist in the prognostication and management of these patients.

**REFERENCES**


