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ORIGINAL ARTICLE

A STUDY OF HYPOXEMIA IN LIVER CIRRHOSIS

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ABSTRACT: INTRODUCTION: Pulmonary abnormalities and symptoms are common in patients with chronic liver disease. Hepatopulmonary syndrome is an important cause in a patient with hypoxemia and chronic liver disease. Hepatopulmonary syndrome consists of a triad of hepatic dysfunction and/or portal hypertension, intrapulmonary vascular dilatations and hypoxemia/ widened alveolar-arterial gradient. The present study evaluated the arterial blood gas levels and correlated these with 2D contrast echocardiographic findings in patients of liver cirrhosis. **METHODS**: 40 patients of liver cirrhosis were included in the study. All patients underwent ultrasonography, LFTs, biochemical tests and upper gastrointestinal endoscopy, chest X-ray, 2-D contrast enhanced transthoracic echocardiogram, viral markers and arterial blood gas analysis. The patients in whom arterial hypoxemia/ widened alveolar-arterial gradient was detected with a positive contrast echocardiogram were considered to have hepatopulmonary syndrome. Patients with intrinsic heart disease like patent foramen ovale, atrial septal defect, ventricular septal defect, haemoglobin less than 7gm% and history of COPD were excluded from the study. **RESULTS**: 4 patients of liver cirrhosis with hypoxemia had intrapulmonary vascular dilatations were labelled as hepatopulmonary syndrome. 2 additional patients with IPVDs had widened alveolar arterial gradient without hypoxemia and were also labelled as HPS. Dyspnoea ($p=0.001$), platypnea ($p<0.001$), clubbing ($p=0.002$) and cyanosis ($p=0.001$) were significantly commoner in the six patients of hepatopulmonary syndrome. Patients with cyanosis had poor prognosis. **CONCLUSION**: Hepatopulmonary syndrome is an important cause of hypoxemia in patients of liver cirrhosis. It is not uncommon in patients of liver cirrhosis. Platypnea is both sensitive as well as specific marker of the disease. Transthoracic contrast enhanced echocardiogram is a safe and accurate bedside tool for the detection of IPVDs.

KEYWORDS: Cirrhosis, hepatopulmonary syndrome, platypnea, hypoxemia, intrapulmonary vascular dilatations.

INTRODUCTION: Pulmonary abnormalities and symptoms are common in patients with chronic liver disease.[1] Up to 70% of cirrhotic patients undergoing evaluation for liver transplantation complain of dyspnoea.[2] Development of hypoxemia in patients with chronic liver disease, modifies the line of management and worsens the prognosis of the disease.[3] Hepatopulmonary syndrome forms one of the differential diagnosis for hypoxemia in patients with chronic liver disease and carries a grave prognosis.[4,5]

Hepatopulmonary syndrome consists of a triad of hepatic dysfunction and/or portal hypertension, intrapulmonary vascular dilatations and hypoxemia/ widened alveolar-arterial gradient.[6]

Human models have demonstrated increased pulmonary production of nitric oxide (NO) in patients of hepatopulmonary syndrome.[7] NO is a potent vasodilator, particularly in the pulmonary circulation and overproduction may lead to widespread intrapulmonary vasodilatation.

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In addition, NO may induce hemeoxygenase-1 and results in production of carbon monoxide that may also contribute to vasodilatation.[8,9]

Liver transplantation is the only proved therapy for HPS based on total resolution or significant improvement in gas exchange postoperatively in more than 85% of reported patients.[10] Treatments target the putative mediators of HPS such as nitric oxide and TNF-α although quite often pharmacological agents are tried with no substantive physiological basis.[11]

OBJECTIVES: The study was undertaken to analyze arterial blood gas changes in liver cirrhosis and to determine the presence of Intrapulmonary Vascular Dilatations by 2D contrast echocardiography in patients with liver cirrhosis. The results of arterial blood gas changes were correlated with echocardiographic findings.

MATERIALS AND METHODS:

INCLUSION CRITERION: 40 patients of liver cirrhosis admitted in medicine and emergency wards were included in the study. An informed consent was taken for the study.

EXCLUSION CRITERION:

1. Patients less than 18 years.
2. History of smoking or COPD.
3. Intrinsic heart disease like patent foramen ovale, atrial septal defect or ventricular septal defects.
4. Haemoglobin less than 7 gm %.

Arterial blood gas analysis was done by drawing blood from radial puncture as it was easily accessible, could be compressed and had low risk of occlusion. Once the sample was obtained, care was taken to eliminate visible gas bubbles as these bubbles could dissolve into the sample and cause inaccurate results. The sample was obtained in heparinised glass syringe and analysed within 30 minutes by automatic analyser (Roche cobas b 121 Automatic Analyser). Presence of hypoxemia was detected if partial pressure of oxygen (PaO_2) was less than 80 mm of Hg. Alveolar arterial pressure gradient [$P(A\text{-}a)O_2$] was taken as elevated if more than 20 mm of Hg. The alveolar-arterial pressure gradient was also determined by [$150\text{-}5/4(PCO_2)$]-PaO_2.

All the patients were subjected to echocardiography. Echocardiography was done by using Philips HD 11 XE echocardiogram machine. 2D / M-Mode / Color Doppler was used to rule out any intrinsic heart disease like patent foramen ovale, atrial septal defects and ventricular septal defects. Four chamber apical image was obtained through transthoracic approach. Effective right heart contrast was obtained by injecting a forcefully agitated solution of saline between 10 ml syringes, one of which contains 9.5 ml normal saline and 0.5 ml room air. The second and third injections followed if required. By analysing the timing and location of appearance of contrast the nature of the shunt was determined as being a patent foramen ovale, atrial septal defect or pulmonary arteriovenous malformation. A positive result was defined as any visual opacification of left heart chamber between five to fifteen cardiac cycles after the appearance of micro bubbles in the right ventricle in any of three injections.

All the necessary haematological and biochemical tests including haemoglobin, white blood cell counts, differential counts, platelets, prothrombin time, liver function tests, total serum protein and differential serum protein were done. All the patients were tested for Hepatitis B and Hepatitis C. Chest X-Ray was done. Liver disease was staged according to Child Pugh grading.

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The results of the arterial blood gas levels and 2D contrast echocardiography in patients of liver cirrhosis were correlated and statistically analyzed.

RESULTS: A total of 40 patients with cirrhosis of liver were studied. Cirrhosis was more common in the fifth decade with 15 patients (32.5%) in the age group between 41-50 years. The mean age was 49.18 years. 36 patients (90%) were males and 4 patients (10%) were females.

24 patients (60%) in the study were diagnosed as having alcoholic cirrhosis whereas 5 patients (12.5%) each were having HCV induced cirrhosis and combined HCV plus alcohol induced cirrhosis and 1 patient (2.5%) each of cryptogenic cirrhosis, NASH, Wilson and autoimmune etiology. In our study, dyspnoea was present in 14 patients (65%), clubbing was present in 8 patients (20%), spider naevi was present in 13 patients (32.5%), cyanosis was present in 2 patients (5%) and platypnea in 6 patients (15%). The chest x-ray showed increased interstitial markings (IIM) in 2 subjects (5%) and right pleural effusion (RPE) in 7 patients (17.5%). For statistical analysis of various parameters patients were divided into two groups depending on the presence (n=7) or the absence (n=33) of Intrapulmonary vascular dilatations (IPVDs) on contrast echocardiography The mean partial pressure of oxygen (PaO_2)in the positive group was 79.77±14.88 mmHg and in the negative group was 87.55±16.28 mmHg. The mean alveolar arterial gradient [$P(A\text{-}a)O_2$]in the positive group was 35.87±16.21mmHg and in the negative group was 29.42±18.11mmHg. The mean partial pressure of carbon dioxide ($PCO_{2)}$ in the positive group was 27.55±3.78 mmHg and in the negative group was 26.81±6.98mmHg. Dyspnoea ($p<0.001$), platypnea ($p<0.001$), clubbing ($p<0.001$), cyanosis ($p=0.002$), spider naevi ($p=0.015$) and pedal edema ($p=0.037$) were significantly associated with patients having positive contrast echardiocardiogram.

Clinical and biochemical features of patients of two groups

Parameter	Positive group(N=7)	Negative group(N=33)	p value
Age	42.57±12.177	50.58±12.617	NS
Dyspnoea	7(100%)	7(21.2%)	< 0.001
Platypnea	6(85.7%)	0	<0.001
Clubbing	5(71.4%)	3(9.1%)	<0.001
Cyanosis	2((28.6%)	0	0.002
Spider naevi	5(71.4%)	8(24.2%)	0.015
Ascites	7(100%)	24(73%)	NS
Splenomegaly	6(85.7%)	26(78.8%)	NS
Pedal Edema	6(85.7%)	14(42.4%)	0.037
Esophageal varices	7(100%)	29(87.9%)	NS
PaO_2	79±14.88mmHg	87.55±16.28mmHg	NS
PCO_2	27.55±3.78mmHg	26.81±6.98mmHg	NS
$P(A\text{-}a)O_2$	35.87±16.21mmHg	29.42±18.11mmHg	NS
Child Pugh Score			
A	0	3(9.1%)	NS
B	3(42.5%)	14(42.4%)	NS
C	4(57.1%)	16(48.5%)	NS
Chest X-Ray			
Normal	4(57.1%)	27(81.8%)	NS
IIM*	1(14.3%)	1(3%)	NS
RPE#	2(28.6%)	5(15.2%)	NS

*Increased Interstitial Markings in the lower lung fields.

Right Pleural Effusion.

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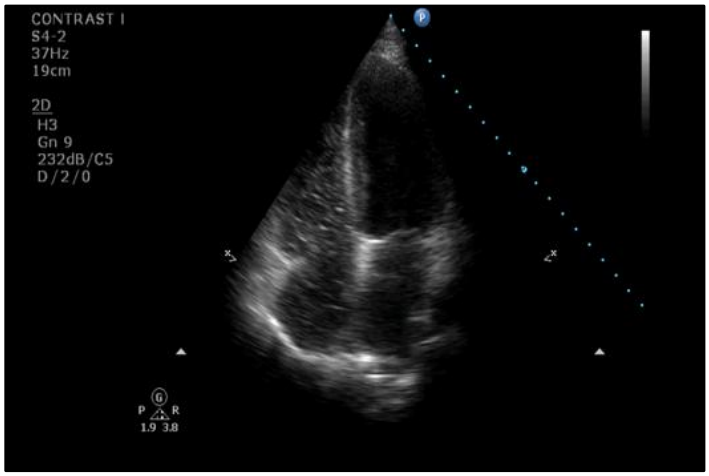

Fig. 1: Air bubbles in the right heart (Negative contrast echocardiogram)

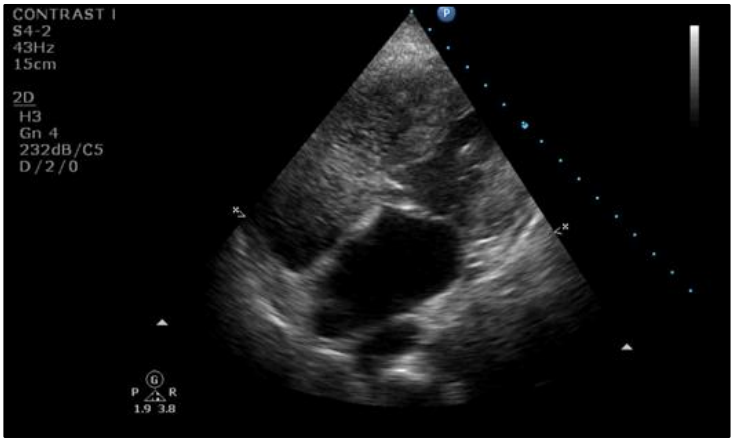

Figure 2: Air bubbles in the left heart (Positive contrast echocardiogram)

Comparison of signs and symptoms between the patients of HPS

Symptoms	Sensitivity	Specificity	p value
Dyspnoea	100%	76.47%	0.001
Clubbing	66.67%	88.24%	0.002
Platypnea	100%	100%	<0.001
Cyanosis	33.33%	100%	0.001
Spider naevi	66.67%	73.53%	0.053

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DISCUSSION: In our study out of 40 patients, 14 patients had hypoxemia (PaO_2<80mmHg). Out of these four patients had intrapulmonary vascular dilatations as detected by contrast echocardiogram and were labelled as hepatopulmonary syndrome. 2 additional patients with IPVDs had widened alveolar arterial gradient without hypoxemia and were also labelled as HPS. Thus HPS was present in 15% of our patients. Hepatopulmonary syndrome (HPS) had been shown to occur in 4 to 19% of patients with liver cirrhosis.[12-15] Incidence of positive contrast echocardiogram varies from 13 to 47%.[1]

In our study, all the patients of HPS had widened alveolar arterial gradient. Anand et al[16] considered only alveolar arterial gradient for diagnosis of HPS and not partial pressure of oxygen. The studies by Hira et al[17] and Rao et al[3] also reported widened alveolar arterial gradient in all their patients of HPS (100%).

All the patients with HPS had esophageal varices indicating the presence of portal hypertension. In our study there was no association between the grades of esophageal varices and HPS. Rao et al[3] reported the presence of esophageal varices in all their patients of HPS (100%).

In our study, dyspnoea was present in all the 6 patients of HPS (100%). Anand et al[16] reported dyspnoea in 92.86% of HPS patients. Hira et al[17] and Rao et al[3] reported dyspnea in all their HPS patients (100%). Thus dyspnoea was sensitive marker (100%) of HPS in our study. But it had poor specificity (76.47%) for the disease as it was also reported in number of patients without HPS. In the present study clubbing was present in 4 out of the 6 patients (66.66%) with hepatopulmonary syndrome. Anand et al[16] reported clubbing in 71.42% of their HPS group. Hira et al[17] reported clubbing in all their patients of HPS (100%). Clubbing had poor sensitivity (66.67%) for HPS in our study.

The cyanosis was present in 2 patients (33.33%) of HPS. Anand et al[16] did not report cyanosis in any of their HPS patients. Hira et al[17] reported cyanosis in all HPS patients (100%). Both these patients expired during the study making cyanosis an indicator of poor prognosis. Platypnea was present in all patients (100%) of HPS in our study. It was present in 57% of HPS in the study by Anand et al[16]. Thus platypnea was a sensitive (100%) as well as specific marker (100%) of the disease in our study. Spider naevi was present in 4 patients (66.66%) of HPS. Anand et al[16] reported the presence of spider naevi in 78.5% of HPS patients. However, spider naevi had a relatively low sensitivity (66.67%) and specificity (73.53%) for HPS in our patients.

Conflicting data existed in the literatures regarding the correlation between HPS and the severity of liver disease. A study by Abrams and colleagues[18] showed significantly lower PaO2 values and greater shunt fractions in Child-Pugh A compared with B and C classes. Another study by Vachiery and colleagues[19]showed that hypoxaemic patients had a significantly higher child pugh score. In our study four patients (66.66%) of HPS belonged to Child Pugh score C and 2 patients (33.33%) to Child Pugh score B. In our study patients with HPS had higher Child Pugh score.

CONCLUSION: Thus we conclude that IPVDs and HPS as detected by contrast echocardiography are not uncommon in patients of liver cirrhosis. They could rarely be present even in the absence of hypoxemia. In the settings of cirrhosis of liver, platypnea strongly points to the presence of hypoxemia. Patients of liver cirrhosis with hypoxemia or widened alveolar arterial gradient should be evaluated for the presence of IPVDs/HPS as a routine. Transthoracic contrast enhanced echocardiogram is a safe and accurate bedside tool for the detection of IPVDs.

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BIBLIOGRAPHY:

1. Fallon MB, Abrams GA. Pulmonary Dysfunction in Chronic Liver Disease. Hepatology. 2000; 32: 859-65.
2. Sood G, Fallon MB, Niwas S, Tutton T, Van Leeuwen DJ, Bloomer JR, McGuire BM. Utility of a dyspnea-fatigue index for screening liver transplant candidates for hepatopulmonary syndrome [Abstract]. Hepatology. 1998; 28 (Suppl): 742.
3. Rao MY, Raghu J, Deshmukh S, Amaravathi KS, Sudhir U. Arterial hypoxemia in patients with cirrhosis of liver.J Assoc Physicians India. 2008 Sep; 56: 681-4.
4. Schiff ER, Sorrel MF, Mardrey WC. Schiff's Diseases of the Liver, 8th edn. Philadelphia, Lippincott-Raven Publishers, 1999:490-491.
5. Mark feldman, Lawarence S, Friedman, Lawrence J, Brandt. Sleisenger and Fordtran's Gastrointestinal and liver disease, 8th edn. Philadelphia, Saunders elsevier publishers, 2006:1972-7.
6. McCormick. Hepatic Cirrhosis. In: Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ. Sherlock's Diseases of the Liver and Biliary System.12th ed. West Sussex: Wiley-Blackwell 2011: p.116.
7. Rolla G, Brussino L, Colagrande P, Dutto L, Polizzi S, Scappaticci E, . Bergerone S. Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. Hepatology. 1997; 26: 842–7.
8. Carter E P, Hartsfield C L, Miyazono M, et al., Regulation of heme oxygenase-1 by nitric oxideduring hepatopulmonary syndrome. Am J Physiol [Lung Cell Mol Physiol] 2002; 283: L346–53.
9. Zhang J, Ling Y, Luo B, et al., Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. Gastroenterology, 2003; 125: 1441–51.
10. Lange PA, Stoller JK. Hepatopulmonary syndrome: effects of liver transplantation. Clin Chest Med.1996; 17: 115–23.
11. Ho V. Current concepts in the management of hepatopulmonary syndrome. Vasc Health Risk Manag. 2008 Oct; 4 (5):1035–41.
12. Vedrinne JM, Duperret S, Bizollon T, et al. Comparison of transesophageal and transthoracic contrast echocardiography for detection of an intrapulmonary shunt in liver disease. Chest1997; 111: 1236–40.
13. Jensen DM, Pothamsetty S, Ganger D, et al. Clinical manifestations of cirrhotic patients with intrapulmonary shunts. Gastroenterology1994; 106: A912.
14. Martinez-Palli G, Barberà J, Visa J, et al. Hepatopulmonary syndrome: Prevalence and clinical markers. Eur Respir J 1996; 9:179.
15. Stoller JK, Lange PA, Westveer MK, Carey WD, Vogt D, Henderson JM. Prevalence and reversibility of the hepatopulmonary syndrome after liver transplantation. The Cleveland Clinic experience. West J Med 1995; 163: 133–8.
16. Anand AC, Mukherjee D, Rao KS, Seth AK. Hepatopulmonary syndrome: prevalence and clinical profile. Indian J Gastroenterol. 2001 Jan-Feb; 20 (1): 24-7.
17. Hira HS, Kumar J, Tyagi SK, Jain SK. A study of hepatopulmonary syndrome among patients of cirrhosis of liver and portal hypertension. Indian J Chest Dis Allied Sci. 2003 Jul-Sep; 45 (3): 165-71.

DOI: 10.14260/jemds/2014/4073

18. Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallon MB. Use of macro aggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. Gastroenterology 1998; 114: 305–10.
19. Vachiéry F, Moreau R, Hadengue A, Gadano A, Soupison T, Valla D, Lebrec D. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. J Hepatol 1997; 27: 492–5.

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