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Original Research Article

The Occurrence Of Hepato Pulmonary Syndrome In End Stage Liver Disease By Using Bubble Contrast Echocardiography And Its Correlation With Arterial Blood Gas Analysis

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Abstract

Background: Hepatopulmonary syndrome (HPS) is a characterized by abnormalities in blood oxygenation secondary to the presence of intrapulmonary vascular dilations (IPVD) in the setting of end-stage liver disease. Hepatopulmonary syndrome (HPS) affects 10–32 % of patients with cirrhosis and is defined by liver abnormalities, intrapulmonary vascular dilatations (IPVDs), and abnormal oxygenation.

Aim and Objectives: The aim of study to detect the Hepatopulmonary syndrome by using bubble contrast Echocardiography in patients with cirrhosis with reference to arterial hypoxemia.

Material and Methods: This is a prospective study was done from September 2022 to August 2023 in Shyam Shah Medical College and Sanjay Gandhi hospital Rewa M.P. All patients with the end stage liver disease were evaluated for the presence of hepatopulmonary syndrome by arterial blood gas analysis and bubble contrast echocardiography. In addition, all the patients underwent routine blood tests, pulse oximetry, chest X-rays, pulmonary function test, and diffusion capacity of the lungs for carbon monoxide (DLCO).

Results: Out of 100 patients in our study, HPS was identified in 19 patients (19%). All 19 patients had hypoxemia (PaO2 <70 mm Hg) and intra pulmonary shunting as established by contrast echo. The correlation between PaO2 and severity of liver disease was also done. Total of 19 Patients who turned out to be positive for HPS via bubble contrast echocardiography, among them 4 (21.05%) of them were HBsAg positive cases and 15(78.95%) of them were HBsAg negetive. Then 2(10.52%) of them were HCV positive cases and Remaining 17 (89.48%) of them were HCV negative. The bubble contrast echocardiography positive cases were found in alcoholic male 57.89% and 26.31% cases were female. Alcohol is the most common cause for the liver cirrhosis.

Conclusion: The study showed that when the blood gas analysis is performed in the supine position, hepatopulmonary syndrome prevalence is higher than when Performed with the patient seated . The blood gas criteria currently proposed as a standard is the most sensitive.

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Among the Bubble contrast Echocardiography Positive patients Majority of them had alcohol as a etiology as compared with viral and post necrotic etiology.

Keywords: Hepatopulmonary Syndrome, Cirrhosis, Blood Gas Analysis, Bubble Contrast Echocardiography.

1. Introduction

Hepatopulmonary syndrome (HPS) is a characterized by abnormalities in blood oxygenation secondary to the presence of intrapulmonary vascular dilations (IPVD) in the setting of end-stage liver disease[1-2] The complex pathogenic mechanism revolves around overproduction of vasoactive mediators such as tumor necrosis factor-alpha, heme oxygenase-derived carbon monoxide and nitric oxide, and angiogenesis within the pulmonary circulation leading to intrapulmonary shunting and ventilation-perfusion mismatch in the background of liver cirrhosis and portal hypertension.[3] Furthermore, based on the alveolar-arterial oxygen gradient (A-a gradient) and partial pressure oxygen (PaO2), it can be classified into four distinct categories ranging from mild (PaO2 ≥ 80 mm Hg), moderate (PaO2 60 - 79 mm Hg), severe (PaO2 50 - 59 mm Hg) to very severe (PaO2 ≤ 50 mm Hg) disease.[4] The prevalence of HPS is estimated to range from 4% to 47% in patients with cirrhosis . There is no clear effective medical therapy for HPS, but liver transplantation has shown to improve survival even in patients with severe disease. Overall, in patients with liver cirrhosis, HPS significantly impacts quality of life and survival outcomes.

Bubble Contrast echocardiography using agitated saline bubbles of minimum of 15 microns can be used as a diagnostic tool for hepatopulmonary syndrome.[4] normally, microbubbles are trapped in pulmonary vasculature and absorbed. However, in presence of pulmonary arteriovenous shunts like hepatopulmonary syndrome or pulmonary arteriovenous malformations, the bubbles are seen in the left heart after the third heartbeat, [5] usually between the third and sixth heartbeat as demonstrated. Whereas, in presence of intracardiac right to left shunts, these microbubbles are seen in the left heart within the first three cardiac cycles.[6] Perfusion scans using technetium-labeled albumin macro aggregates (Tc-99m MAA) are diagnostic tests for pulmonary arteriovenous malformations and permit precise shunt quantification ,[7] but they need mobilization of the patient outside ICU, which is often associated with potential risks in critically ill patients, whereas bubble contrast echocardiography can be done at bedside without any such concerns.

Aim and Objectives: The aim of study to detect the Hepato pulmonary syndrome by using bubble contrast Echocardiography in patients with cirrhosis with reference to arterial hypoxemia.

2. Material and Methods

This is a prospective study was done from September 2022 to August 2023 in Shyam Shah Medical College and Sanjay Gandhi hospital Rewa M.P. All patients with the end stage liver disease were evaluated for the presence of hepatopulmonary syndrome by arterial blood gas

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analysis and bubble contrast echocardiography. In addition, all the patients underwent routine blood tests, pulse oximetry, chest X-rays, pulmonary function test, and diffusion capacity of the lungs for carbon monoxide (DLCO).

Sample size: 100 cases (satisfying inclusion and exclusion criteria during the study period)

Inclusion Criteria:

- Patients above 18 years of age with Hepatopulmonary syndrome.
- Patients who gave consent.

Exclusion Criteria:

- Patients below 18 years of age.
- Grade 3&4 hepatic encephalopathy
- Patients who reported history of pre-existing cardiopulmonary diseases
- Patients who had abnormal chest X-ray
- Patients with sepsis or septic shock.

Procedure Plan:

All HPS patients will be hospitalised after preliminary clinical & lab assessment. This includes

- fasting plasma glucose (FPG),
- 2 hrs postprandial plasma glucose (PPPG),
- Fasting and postprandial lipid profile,
- Kidney function tests,
- X-ray chest and an electro cardiogram.

Bubble contrast echocardiography- All the patients underwent 2-dimensional and bubble contrast echocardiography to evaluate for right to left intrapulmonary shunting and any evidence of cardiomyopathy. Microbubble detection within the left atrium after 3 cardiac cycles signified a positive result (IPVD or extracardiac shunt). If microbubbles appeared in the left atrium within 3 cardiac cycles, it was taken as intracardiac shunt. Ejection fraction, presence of left ventricular dysfunction, or diastolic dysfunction was noted. Pulmonary artery pressure will be measured in every patient.

Criteria for the diagnosis of Hepatopulmonary syndrome

The diagnosis of Hepatopulmonary syndrome was made based on the following 3 criteria:

1. Presence of chronic liver disease and or portal hypertension
2. Alveolar–arterial oxygen gradient > 15 mmHg (> 20 mmHg in patients 64 years or older) while breathing room air
3. Documented IPVD on contrast echocardiography

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Severity of HPS were determined by the degree of hypoxemia (i.e. PaO2 range), designated as mild (≥ 80 mmHg), moderate (< 80 mmHg but ≥ 60 mmHg), severe (<60 mmHg but ≥ 50 mmHg), and very severe (< 50 mmHg).
Portopulmonary hypertension was defined as the mean pulmonary artery pressure > 25 mmHg (in 2D echo) in the presence of portal hypertension.[8]

Investigations Details:

- Complete hemogram
- Liver function tests
- Renal function tests
- USG abdomen
- Chest X-ray
- ECG
- Echocardiogram
- Viral markers
- Arterial blood gas analysis
- Pulmonary function tests

Data Collection and Methods:
All of the data was collected by the principal investigator. After collecting demographic data (age, gender) and medical record numbers at the time of enrolment, the investigator took a detailed history of and performed relevant clinical examinations on each patient. Relevant laboratory and imaging findings were recorded. All the data pertaining to the study was entered into data collection forms directly and were later entered into an Excel sheet for statistical analysis.

Statistical Analysis: Data was collected and managed on an excel work sheet. All values are expressed as mean. Data were calculated by appropriate statistical test.

3. Results

In our study out of 100 patients, 71 were males and 29 were females. Males to female ratio were 3:1. Majority of cases were age group of 41 to 60 yrs male was 30 (42.25%) cases and female were 16 (55.17%) cases. Second most common age group was 61 to 80 yrs male were 17 (23.94%) cases and then female were 11 (37.93%) cases. Mean age was 55.33±15.72.

Table 1- Distribution of cases according to investigations

Investigations	Total (n=100)		Mean ± SD	t test	P value
	No	%			
Haemoglobin gm/dl					
<12	84	84.0	9.07 ± 1.94	8.66	< 0.0001
>12	16	16.0	13.36 ± 0.83		
Serum bilirubin					

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<1 mg/dl	43	43.0	0.56 ± 0.26	4.89	< 0.0001
>1 mg/dl	57	57.0	2.87 ± 3.08		
Serum albumin					
1.16 to 2.5	45	45.0	1.94 ± 0.37	4.76	< 0.0001
2.51 to 3.5	46	46.0	2.98 ± 0.25		
> 3.5	09	9.0	7.11 ± 6.09		
Blood urea					
<40 mg/dl	70	70.0	24.08 ± 7.80	12.59	< 0.0001
>40 mg/dl	30	30.0	71.82 ± 29.57		
Serum Creatinine					
<1.0 mg/dl	61	61.0	0.72 ± 0.20	7.45	< 0.0001
>1.0 mg/dl	39	39.0	1.71 ± 1.01		

In our study most common presenting complaints was found in abdominal distension 93.0%, followed by Breathlessness 89.0%, Fatigability 80.0%, cough expectoration 53.0%, melena 36.0%, hematemesis 33.0% and swelling of leg 25.0% cases. The past history was found in hypertension 35.0%, blood transfusion and jaundice 56.0% each, diabetes mellitus 17.0% cases. Personal history was alcohol 70.0% cases. Second most common personal history was smoking intake 59.0% cases. Pallor and icterus were most sign of HPS.

Table 2- Distribution of cases according to USG findings

USG findings	No of cases	%
LC	97	97.0
PHTN	91	91.0
Ascites	98	98.0
Viral Marker		
HBsAg	8	8.0
HCV	5	5.0
HIV	-	-
Bubble Contrast Echocardiography		
Based on IPVD positive	19	19.0
Based on IPVD negative	81	81.0

In our study the majority of USG finding was ascites 98.0% cases followed by LC 97.0% cases and PHTN were 91.0% cases. Viral marker was HBsAg 8.0% cases. Second most common was HCV 4.0% cases. The bubble contrast echocardiography was IPVD positive 19 (19.0%) cases and negative cases were 81 (81.0%).

Table 3- Distribution of Cases According To Atrial Blood Gas Analysis

Atrial blood gas Analysis (ABG)	No of cases	%	Unpaired t test	P value
Ph				
Ph <7.35	48	48.0	0.160	0.6892
Ph >7.35	52	52.0		

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PaCo2 mmHg				
PaCo2 <45 mmHg	85	85.0	49.00	<0.0001
PaCo2 >45 mmHg	15	15.0		
PaO2 mmHg				
PaO2 <100 mmHg	86	86.0	51.84	<0.0001
PaO2 >100 mmHg	14	14.0		
HCO_3 mEq/L				
HCO3 <26 mEq/L	95	95.0	81.00	<0.0001
HCO3 > 26 mEq/L	05	5.0		

Table 4- Bubble Contrast Positive V/S ABG (N=19)

Atrial blood gas Analysis (ABG)	No of cases	%
Ph		
<7.35	11	57.89
>7.35	08	42.11
PaCo2 mmHg		
<45 mmHg	13	68.42
>45 mmHg	06	31.58
PaO2 mmHg		
<100 mmHg	19	100.0
>100 mmHg	-	-
HCO_3 mEq/L		
<26 mEq/L	18	94.73
> 26 mEq/L	01	5.27

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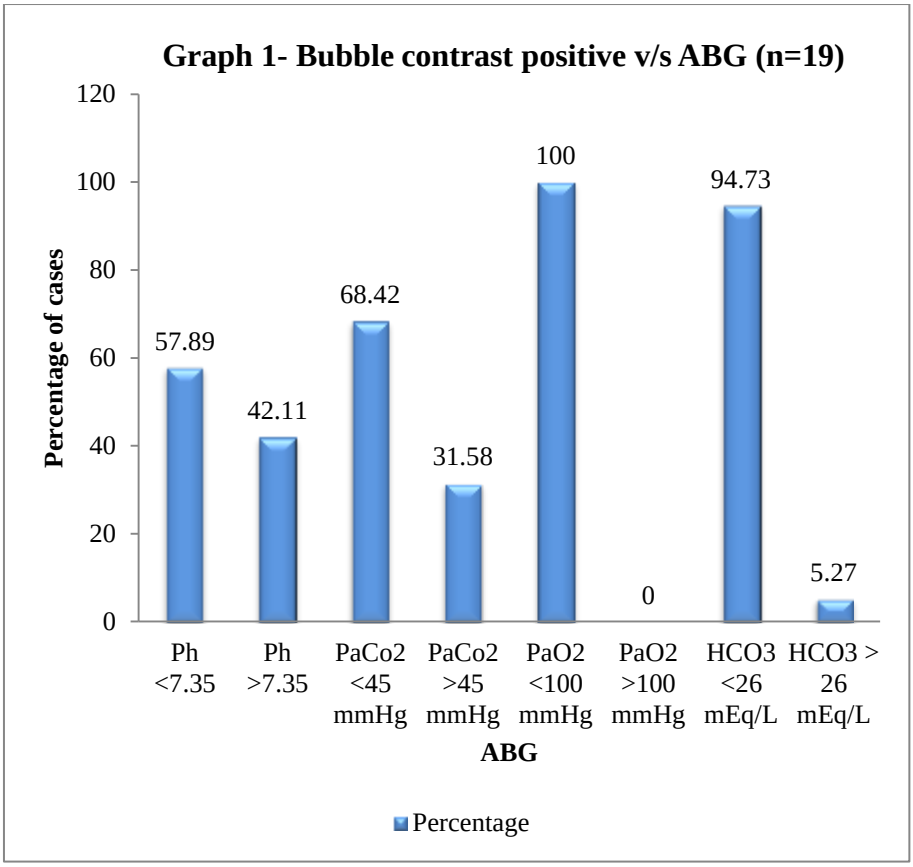

Table 5- Bubble Contrast Positive V/S Viral Marker (N=19)

Viral marker	Bubble Contrast Positive		Bubble Contrast Negative	
	No	%	No	%
HBsAg	4	21.05	15	78.95
HCV	2	10.52	17	89.48
HIV	-	-	19	100.0

In our study the HBsAg positive patients with bubble contrast positive were turned to be 4 (21.05%) cases and negative were 15 (78.95%) cases followed by HCV positive patients with bubble contrast positive were turned to be 2 (10.52%) cases and 17 (89.48%) were bubble contrast negative. and HIV cases were not found in positive bubble contrast cases.

Table 6- Bubble contrast positive v/s Alcoholic (n=19)

Bubble Contrast Positive	Alcoholic Male		Alcoholic Female	
	No	%	No	%
Positive	11	57.89	5	26.31
Negative	8	42.11	14	73.69

It is evident from the above table shows that the bubble contrast cases were found in alcoholic male 57.89% and 26.31% cases female cases. Alcohol is the most common cause for the liver cirrhosis.

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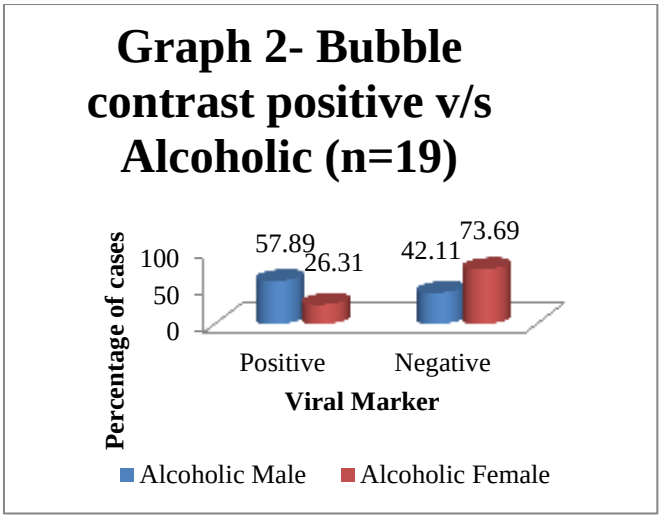

4. Discussion

The hepatopulmonary syndrome (HPS) is characterized by the presence of changes in blood oxygenation levels caused by the presence of intrapulmonary vascular dilations (IPVD) in the setting of a liver disease, usually hepatic cirrhosis [9-10] A decrease in blood oxygenation and the presence of IPVD are diagnostic criteria for this syndrome.

HPS prevalence varies widely in the literature between 4 and 32%. This is likely due to the use of different criteria for the diagnosis of decreased blood oxygenation, the method used for the demonstration of IPVD (transthoracic or transesophageal contrast echocardiography or macro aggregated albumin lung scan) and the characteristics of the study population [11-13].

A decreased blood oxygenation is demonstrated by performing an arterial blood gas analysis, although pulse oximetry is also used, especially in HPS screening [14-16]. Blood gas criteria with different cutoffs and assessment using both the PaO2 and A-a PO2 methods have been used for the diagnosis of HPS. The position of the patient when obtaining blood gas levels has also changed; it is often performed in both the supine and seated/upright position [11-13].

In present study out of 100 patients, majority of cases were age group of 41 to 60 yrs male was 30 (42.25%) cases and female were 16 (55.17%) cases. Second most common age group was 61 to 80 yrs male were 17 (23.94%) cases and then female were 11 (37.93%) cases. This showed that cirrhosis is most commonly seen in middle age adults.

In present study out of 100 patients in this study, 71 patients (71.0%) were male and 29 patients (29.0%) were females. Male to female ratio is 3:1. In the present study among 100 patients, Alcohol was the most common etiology in 70 patients (70%) followed by other causes of cirrhosis in 30 patients (30.0%). This can be compared to studies of De BK et al., [17] Rao MY et al. [18]

In present study among the presenting complaints, abdominal distension was most common symptoms in abdominal distension 93.0%, followed by breathlessness 89.0%, fatigability 80.0%, cough expectoration 53.0%, melena 36.0%, hematemesis 33.0% and swelling of leg 25.0% cases.

In present study Out of 100 patients studied the past history was found in hypertension 35.0%, blood transfusion and jaundice 56.0% each, diabetes mellitus 17.0% cases.

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In present study out of 100 patients studied 35 patients (35%) had Pallor, followed by 23 patients (23%) had icterus. pedal edema was present in 9 patients (9.0%), clubbing in 1 patients (1.0%).

In present study out of 100 patients, majority of USG finding was ascites 98.0% cases followed by LC 97.0% cases and PHTN were 91.0% cases.

Out of 100 patient, 14 patients (14.0%) showed hypoxemia with PaO2 >100 mm Hg which was comparable to a study of Lange P A et al.[19] Clinical signs of hypoxemia like cyanosis was present in 4 patients (10%), orthodeoxia in 4 patients (10%) which were similar to the finding observed by Krowka et al.[20]

The correlation between partial pressure of oxygen (PaO2) and grading of oesophageal varices was done in this study. It was observed that there was a decrease in PaO2 with higher grade of varices. This was statistically significant with p-value of 0.0001. It was similar to the observations in the study of Zhang J et al [21] and Schenk P et al.[22]

The correlation between PaO2 and severity of liver disease was also done. It was observed that there is progressive decrease in PaO2 with increasing severity of liver disease. This was statistically significant in our study.

Out of 100 patients in our study, HPS was identified in 19 patients (19%). All 19 patients had hypoxemia (PaO2 <70 mm Hg) and intra pulmonary shunting as established by contrast echo. They all had varices indicating portal hypertension. Hence increased portal venous pressure is a significant factor for development of HPS. The prevalence of HPS in cirrhotics in this study was comparable to studies conducted by Schenk P et al.,[22] Krowka et al.,[20] De BK et al.,[17] Rao MY et al.,[18] and Hourani et al.[23]

In present study among the viral etiology majority of the patient's positive for HBsAg (8.0%) cases. Second most common was HCV (4.0%) cases. The bubble contrast echocardiography was IPVD positive 19 (19.0%) cases and negative cases were 81 (81.0%).

In present study direct positive correlation between all ABG parameter to bubble contrast echocardiography, hence association with statistically highly significant.

Total of 19 patients who turned to be positive for HPS via bubble contrast echocardiography among them 4(21.05%) of them were HBsAG positive cases and 15(78.95%) of them were HBsAG negative. Then 2(10.52%) of them were HCV positive patients and Remaining17 (89.48%)of them were HCV negative cases and HIV cases were not found in positive bubble contrast echocardiography cases.

In the present study the bubble contrast echocardiography cases were found in alcoholic male 57.89% and 26.31% cases female cases. Alcohol is the most common cause for the bubble contrast positive.

5. Conclusion

We found that the position at which arterial blood gas analysis and blood gas criteria are used for the diagnosis of HPS influences the prevalence and distribution of the severity. The study showed that when the blood gas analysis is performed in the supine position, hepatopulmonary syndrome prevalence is higher than when performed with the patient seated. The blood gas criteria currently proposed as a standard is the most sensitive. Among

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the Bubble contrast Echocardiography Positive patients Majority of them had alcohol as a etiology as compared with viral and post necrotic etiology

Regardless of the criteria used, the presence of HPS is associated with increased mortality of patients on the waiting list for liver transplantation or post- LT. Further studies are required to determine what criteria should be used for the diagnosis of HPS.

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