Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Research Paper

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Mohamed Galal Morsi
Department of
Pulmonary Medicine,
Saudi German Hospital-Riyadh,
King Fahd Street,
Sahafa District,
P.O. Box 84348,
Riyadh 11671, Riyadh,
Saudi Arabia

Tel: 00966 502811012
-00966 14873000/5197
Fax: 00966 1 4871429

J. Med. Sci., 8 (4): 332-341
15th June, 2008

Combined Pulse Oximetry and Carboxyhemoglobin for Detection of Hepatopulmonary Syndrome

[1]Khalid Zaghloul Darwish, [2]Mohamed Galal Morsi and [3]Islam Mahrous

The aim of the study is to evaluate pulse oximetry and carboxyhemoglobin as a combined index for detection of Hepatopulmonary syndrome. HPS is a triad of liver disease, increased $P(A\text{-}a)O_2$ and intrapulmonary vasodilatation. Eighty nine consecutive adult cirrhotic patients underwent history, general examination, pulse oximetry, COHb%, ABG measurement, contrast enhanced echocardiography, ECG, chest radiology and PFTs to exclude cardiopulmonary diseases. HPS was diagnosed in 18 patients (20.2%), while 71 patients (79.8%) non-HPS group. All HPS patients had pulse oximetry ≤94% and PaO_2 ≤80 mmHg. Pulse oximetry and PaO_2 showed significant inverse correlation with $P(A\text{-}a)O_2$. COHb% showed significant inverse correlations with SpO_2% and PaO_2 and significant direct correlation with $P(A\text{-}a)O_2$. ROC derived thresholds for pulse oximetry and COHb% were done for HPS detection. Using both SpO_2 ≤94% and COHb% ≥2.2 as an index for screening HPS revealed 87% diagnostic accuracy, 50% sensitivity and 97% specificity, 0.81 Ppv, 0.88 Npv and +LR of 17.7. Pulse oximetry is a simple and reliable screening tool for detection of HPS. Using combined pulse oximetry and COHb level as an index for screening HPS in cirrhotic patients has a higher diagnostic accuracy and increase the specificity of diagnostic detection.

Key words: ABG, COHb, hepatic cirrhosis, HPS, pulse oximetry

ANSInet
Asian Network for Scientific Information

[1]Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt
[2]Department of Pulmonary Medicine, Faculty of Medicine, Cairo University, Egypt
[3]Department of Cardiology, Faculty of Medicine, Tanta University, Egypt

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a complication of chronic liver disease characterized by the triad of presence of hepatic disease, increased alveolar-arterial O_2 difference and evidence of intrapulmonary vascular dilatation (Krowka and Cortese, 1994; Fuhrmann *et al*., 2006). The intrapulmonary vasodilatations are pre-capillary and post-capillary dilatations that result in arterio-venous communications, that allows mixed venous blood to pass either very quickly or even directly into the pulmonary veins, bypassing the gas exchange unit and can lead to hypoxemia and hepato-pulmonary syndrome (Hopkins *et al*., 1992; Martinez *et al*., 2001). Previous studies have found that transthoracic contrast echocardiography with agitated saline is useful to detect such intrapulmonary vascular dilatation (Meltzer *et al*., 1983; Krowka *et al*., 1990; Barzilai *et al*., 1991).

The etiology of this syndrome remains unknown. The most commonly accepted hypothesis supposed that there is inadequate synthesis or metabolism of pulmonary vasoactive substances such as nitric oxide, prostaglandins, vasoactive intestinal peptide, calcitonin, glucagon, substance P and atrial natriuretic factor, by the impaired liver leading to a functional vasodilatation of the pulmonary vasculature producing hypoxemia. HPS is found in both less and advanced forms of cirrhosis (Krowka *et al*., 2000, 2004). When cirrhotic patients have no sign of any cardiopulmonary diseases, severe hypoxemia (PO_2 < 60 mmHg) strongly recommends hepatopulmonary syndrome (Schenk *et al*., 2002; Hira *et al*., 2003; Lima *et al*., 2004).

The prevalence of HPS in the setting of cirrhosis ranges between 4-30% (Dollinger, 2006). Mortality in patients with this syndrome is considered to be high. In a retrospective analysis, mortality was 41% over an approximate 2.5 year period in 22 patients with HPS (Krowka *et al*., 1993).

HPS is usually diagnosed by Contrast Enhanced Echocardiography (CEE) and increased alveolar-arterial oxygen difference. In terms of cost- effective strategy and practical issues, these could not be applied for all cirrhotic patients. So, screening for HPS has high important value. Pulse oximetry is a useful tool for screening, we tried in this work to use combined pulse oximetry and carboxyhemoglobin for detection of HPS.

In prior study by Abrams *et al*. (2002), digital pulse oximetry [SpO_2%] performed with a standardized protocol in a pulmonary function laboratory at the time of ABG analysis was a useful tool for detecting hypoxemia in cirrhosis. Use of a SpO_2 threshold of 96% or less correctly identified all patients with a PaO_2 < 60 mmHg.

A marked increase in expression of heme oxygenase-1 (HO-1) has been found in intravascular macrophages in experimental HPS (Carter *et al*., 2002). HO-1 is an inducible enzyme that catalyzes the metabolism of hemoglobin into bilirubin, iron and Carbon Monoxide (CO) (Morse and Choi, 2002). CO may function as a vasodilator and circulates bound tightly to hemoglobin, resulting in the formation of carboxyhemoglobin (COHb) (Stevenson and Vreman, 1997). The measurement of COHb levels in blood is used as a reflection of CO production and venous COHb levels have been evaluated in a cohort of patients with cirrhosis (De Las Heras *et al*., 2003). In experimental HPS, arterial COHb levels are increased significantly relative to normal and inhibition of pulmonary HO normalizes arterial COHb levels and improves vasodilatation, supporting the theory that HO-1-mediated CO production is involved (Zhang *et al*., 2003).

The aim of this study is to evaluate pulse oximetery and carboxyhemoglobin level as a combined index for detection of hepatopulmonary syndrome.

MATERIALS AND METHODS

Study population: This prospective study was performed on 89 consecutive adult cirrhotic patients referred to gastroenterology clinic in Saudi German Hospital from January 2005 to June 2007. All patients were asked to provide informed written consent on the approved study protocol. In these patients, cirrhosis was defined histological or by combination of characteristic clinical, laboratory and radiologic findings. The patients with ascities underwent large volume paracentesis.

Inclusion criteria: For inclusion into the study, patients had the following: (1) a negative history of smoking or had achieved and maintained cessation for at least 12 months before enrollment, (2) absence of primary cardiac or pulmonary disease, according to history, electrocardiogram, echocardiography including Doppler measurements, chest radiography (normal results, or increased basilar interstitial markings that are typical for HPS or small pleural effusion) (McAdams *et al*., 1996; Muller and Schenk, 1999) and lung function tests (forced expiratory volume at first second (FEV1) or total lung capacity > 66% predicted and normal spirometry and lung volumes on pulmonary function testing) (Abrams *et al*., 1995; Abrams *et al*., 1998).

Exclusion criteria: Patients for any of the following reasons were excluded from the study: (1) refusal or inability to provide informed consent, (2) atrial fibrillation,

(3) intracardiac shunt, (4) congenital heart defects, (5) mitral stenosis or regurgitation, (6) aortic stenosis or regurgitation, (7) systolic dysfunction (ejection fraction<50%), (8) diastolic dysfunction, (9) abnormal chest radiogram results, (10) abnormal pulmonary function test result (FEV1 < 66% predicted).

Definition of hepatopulmonary syndrome: Diagnosis of HPS was established when the following points were fulfilled: (a) the presence of chronic liver disease, (b) an increased alveolar-arterial difference for the P(A-a) O_2 above the age-related threshold, (c) intrapulmonary vascular dilatation, detected by transthoracic 2-dimensional contrast echocardiography, (d) absence of primary cardiac or pulmonary disease, according to history, electrocardiogram, echocardiography including Doppler measurements, chest radiography and pulmonary function test (Schenk *et al*., 2003).

Study protocol: All patients were tested for hepatitis B, hepatitis C, biliary, autoimmune, metabolic, cardiac, alcoholic and idiopathic etiologies. Complete Blood Count (CBC), Liver Function Test (LFT), creatinine, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), albumin and other routine tests were measured in all patients. Ascitic fluid was tested for protein, albumin and white blood cells.

Pulse oximetry, arterial blood gases and COHb levels: SpO_2 measurements were performed by digital pulse oximeter (NPB-295, Nellcor Puritan Bennett Inc., USA) applied to index finger, with the patient in the sitting position and breathing room air. ABG and echocardiography were performed within 3 days of SpO_2 measurements. ABG analysis was obtained by radial artery puncture at room air in the sitting position immediately before pulmonary function test measurements.

To define the presence of HPS, we used an elevated age-corrected P(A-a)O_2 value in the setting of a positive contrast echocardiogram. The P(A-a)O_2 was calculated using the alveolar gas equation to obtain the alveolar oxygen pressure (PAO_2) (West, 1990) and PaO_2 from the ABG result which is subtracted from the PAO_2 to calculate the P(A-a)O_2.

(PAO_2) = {FiO_2× (airway pressure-water vapor pressure at 37°C)-$PaCO_2$/R}.

As, FiO_2 = fraction of inspired oxygen = 0.21 at room air; airway pressure = 760 mmHg; water vapor pressure at 37°C = 47 mm Hg; $PaCO_2$ = value of ABG; R = respiratory exchange ratio, standardized at 0.84. So, PAO_2 = 0.21×713-$PaCO_2$/0.84.

The expected upper limit of normal for P(A-a) O_2 at a given age in room-air (>95% CI) can be calculated using the following equation: P (A-a) O_2 = [0.26 age-0.43] + 10 (Harris *et al*., 1974). As the P(A-a)O_2 normally increases with age and varies significantly even in healthy individuals, it is therefore recommended to use values above the 95% confidence interval for the age- corrected P(A-a) O_2 to avoid over diagnosis of HPS.

COHb was measured by CO oximetry by using the ABL 700 Series Analyzer (Radiometer, Copenhagen, Denmark) and corrected for hemoglobin levels. The coefficient of variation in COHb levels derived from repeated testing on individual specimens is 0.1%. Demographic, clinical, room-air arterial blood gas results and corrected COHb values were collected and recorded into a computerized database.

Contrast Enhanced Echocardiography (CEE): Participating patients underwent transthoracic CEE by the use of a peripheral intravenous line and two 10 mL syringes connected by a 3-way for injection of intravenous agitated saline. Intrapulmonary right-to-left shunt (IPS) was defined as the delayed appearance of micro-bubbles in the left atrium (three or more beats after the initial appearance of contrast in the right atrium). Appearance of micro-bubbles in the left atrium during the first or second beat or only after provocative maneuvers (cough or valsalva) is indicative of intracardiac shunt (Hopkins *et al*., 1992).

Statistical analysis: Student's t-test was used for comparison between two independent means for quantitative data and Z test for comparison between two proportions to estimate p-value of the results. Data are expressed as mean±SD. A p-value <0.05 was considered to be significant.

The correlation between COHb% and the SpO_2, PaO_2, P(A-a)O_2 and $PaCO_2$ was done by Pearson correlation test using SPSS 10 software (SPSS Inc., Chicago, IL, USA), with measurement of r-statistic and p<0.01 was considered to be significant.

ROC curves were done using SPSS 10 software and Med Calc software version 9, with calculation of sensitivity, specificity, positive predictive value (Ppv), negative predictive value (Npv), likelihood ratio (LR) and AUC for the SpO_2% and COHb% curves.

RESULTS

Eighty nine adult cirrhotic patients were included in the study. The mean age was 55±7.5 (ranged from 42-71 years), 48 patients (53.9%) were male. HPS was

Table 1: The demographic and clinical data of the cirrhotic patients

Variable	HPS (n: 18)	Non-HPS (n: 71)	p-value
Age (Years, mean±SD)	56.0±11.3	54±6.7	0.09
Gender (male, %)	61.1	52.1	0.486
Child-Pugh class (A/B/C)	(2/10/6)	(7/38/26)	
A%	11.11	9.86	0.878
B%	55.56	53.52	0.876
C%	33.33	36.62	0.792
Abnormal chest x-ray	4/18 (22.2%)	12/71 (16.9%)	0.622
Abnormal PFTs	3/18 (16.6%)	11/71 (15.4%)	0.902

Table 2: Comparison between HPS and Non-HPS patients for pulse oximetry, ABG results and COHb%

Variable	HPS (n: 18)	Non-HPS (n: 71)	p-value
SpO_2 (%)	87.66±5.31	94.69±3.47	p<0.01
	(85.02-90.30)	(93.87-95.51)	
PaO_2 (mmHg)	60.88±9.61	84.54±7.46	p<0.01
	(56.11-65.67)	(82.78-86.32)	
$PaCO_2$ (mmHg)	32.44±4.14	37.67±4.11	0.008
	(30.38-34.51)	(36.70-38.65)	
$P(A-a)O_2$ (mmHg)	43.77±15.93	15.23±6.47	p<0.01
	(35.85-51.70)	(13.71-16.77)	
COHb (%)	2.29±0.74	1.22±0.4	p<0.01
	(1.92-2.66)	(1.13-1.32)	

Mean±SD, (lower-upper 95% Confidence interval of the difference)

diagnosed in 18 patients (20.2%), while Non-HPS group included 71 patients (79.8%). All the patients studied were cirrhotic due to chronic hepatitis-C. The patients were distributed according to the severity of liver disease into Child-Pugh class A (10.1%), Child-Pugh class B (53.9%) and Child-Pugh class C (36%).

The demographic and clinical data of the cirrhotic patients are shown in Table 1. The results of arterial blood gases and pulse oximetry and COHb % values for both HPS and Non-HPS patients are shown in Table 2.

Abnormal changes in chest x-ray were found in 4 patients with HPS (22.2%) and 12 patients in the Non-HPS group (16.9%). The radiological findings included: mild pleural effusions (13 patients) and increased basal reticular opacities (4 patients).

Pulmonary functions tests revealed obstructive pulmonary disease in 14 patients (FEV1/FVC<70%), 8 patients with mild disease and 6 patients with moderate obstructive airway disease according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Pauwels *et al.*, 2001).

There was no statistical significant difference between HPS and Non-HPS patients regarding the age, gender, severity of the liver disease by Child-Pugh class, abnormal chest radiology and abnormal PFTs in comparison between both groups, (p>0.05) (Table 1).

The present study revealed that all patients with HPS were found to have pulse oximetry ≤ 94% and PaO_2 ≤ 80 mmHg. The mean SpO_2% was 87.66% (95% CI of difference 85.02, 90.30%), while the mean PaO_2 was 60.88 mmHg (95% CI of difference 56.11, 65.67 mmHg) (Table 2). Also present study revealed that 55.6% of

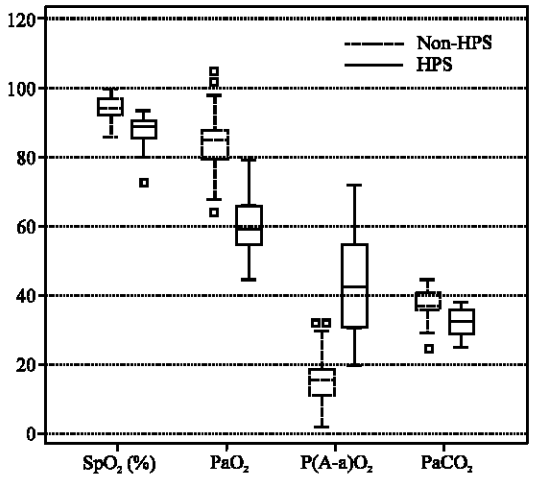

Fig. 1: Box and Whisker plot for SpO_2%, PaO_2, $P(A-a)O_2$ and $PaCO_2$ measurements in HPS and Non-HPS patients, the box represents the interquartile range which contains the 50% of values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. A line across the box indicates the median. The figure showed significant decrease in the values of SpO_2, PaO_2, $PaCO_2$ and significant increase in $P(A-a)O_2$ in HPS than Non-HPS group (p<0.01)

cirrhotic patients with HPS had PaO_2≤60 mmHg which correspond to SpO_2 saturation 89 and 83.3% of the HPS patients had PaO_2≤70 mmHg corresponding to SpO_2 saturation 91%.

There was highly statistically significant decrease in SpO_2%, PaO_2 and $PaCO_2$ in the HPS group compared to the Non-HPS group, mean values were {(87.66Vs 94.69%), (60.88 Vs 84.54%) and (32.44 Vs 37.67%)} for both groups respectively (p<0.01) (Table 2, Fig. 1).

A highly statistically significant increase was found in $P(A-a)O_2$ and COHb % in the HPS group when compared to the Non-HPS group, as the mean values were (43.77 Vs 15.23%) and (2.29 Vs 1.22%) for both groups, respectively (p<0.01) (Table 2, Fig. 1, 2).

There were significant inverse correlations comparing COHb% with SpO_2% (r = -0 .674, p<0.01), arterial PaO_2 (r = -0.747, p<0.01) and $PaCO_2$ levels (r = - 0.598, p<0.01). Also, significant direct correlation between COHb% and $P(A-a)O_2$ values were found (r = 0.825, p<0.01) (Fig. 3).

$P(A-a)O_2$ showed significant inverse correlations with arterial PaO_2 (r = -0.891, p<0.01) and SpO_2% (r = -0.828, p<0.01) (Fig. 4).

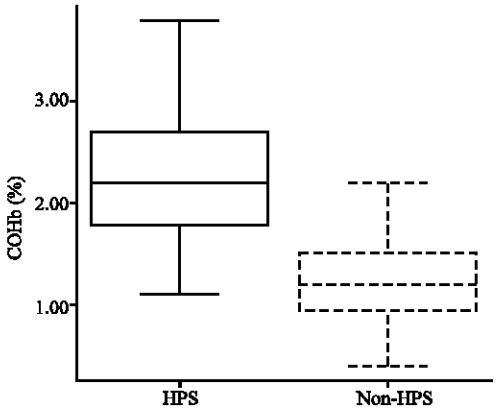

Fig. 2: Box and Whisker plot for COHb% in HPS and non-HPS groups, showed significant increase in the mean value in HPS than Non-HPS group (2.29 vs 1.22), ($p<0.01$)

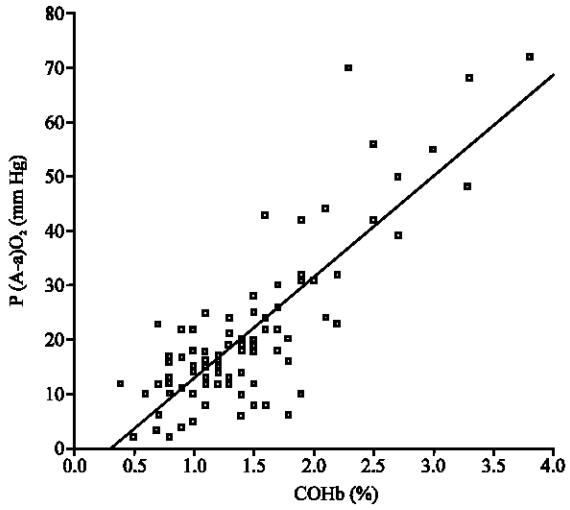

Fig. 3: Correlation between arterial COHb% and $P(A-a)O_2$, showed significant direct correlation ($r = 0.825$, $p<0.01$)

Pulse oximetry for detection of HPS: ROC curves and analysis were done for assessment of different SpO_2 levels and determination of the optimum cutoff level for detection of hypoxemia and HPS with calculation of the sensitivity and specificity (Fig 5-A). Forty seven patients had SpO_2 ≤94% included 18 HPS patients and 29 Non-HPS patients. We found that at SpO_2 ≤94% as a cutoff, had 100% sensitivity (95% confidence interval (CI), 81-100%) and 59% specificity (95% CI, 46-70%). Positive predictive value (Ppv) was 0.38, (95% CI, 0.24-0.52%), negative predictive value (Npv) of 1 (95% CI, 0.96-1%) and Likelihood Ratio (LR) was 2.44 (95% CI, 1.85-3.23%) for positive test.

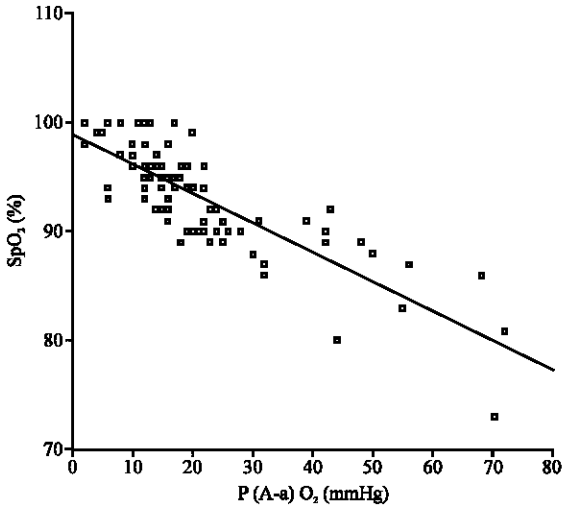

Fig. 4: Correlation between SpO_2% and $P(A-a)O_2$, showed significant inverse correlation ($r = -0.828$, $p<0.01$)

From the ROC curves, the pulse oximetry ≤94% as cutoff threshold detected all patients with HPS (sensitivity 100%, specificity 59%), with an AUC of 0.889 (95% CI, 0.805-0.946%). To detect patients with HPS and a PaO_2 ≤70 mmHg (Fig. 5B), the cutoff value ≤92% was associated with sensitivity of 100% and specificity 33% with an AUC of 0.800 (95% CI, 0.548-0.946%) and (Ppv) was 0.88, (Npv) of 1 and (LR) was 1.5 for positive test. From all the HPS patients, 83.3% were found to have PO_2 ≤70 mmHg. The SpO_2 ≤91% threshold derived from the ROC curve can detect patients with HPS and a PaO_2 ≤60 mmHg (Fig. 5C) with sensitivity of 100% and specificity 37%, with an AUC of 0.894 (95% CI, 0.659-0.984%) and (Ppv) was 0.66, (Npv) of 1 and (LR) was 1.6 for positive test. From all the HPS patients, 55.6% were found to have PO_2 ≤60 mmHg. The test performance characteristics are shown in Table 3.

COHb for detection of HPS: ROC curves and analysis were done for assessment of different COHb levels and determination of the optimum cutoff level as a screening tool for HPS with calculation of the sensitivity and specificity (Fig. 5D). At COHb level ≥1.5, which is used by some laboratories as an upper limit of normal for COHb, we found that the sensitivity and specificity were 83% (95% CI, 58-96%) and 80% (95% CI, 69-88%), respectively, diagnostic accuracy 75% (95% CI, 66-84%), Ppv was 0.51, Npv of 0.95 and LR was 4.2 for positive test.

COHb% ≥1 had 100% sensitivity (95% CI, 81-100%) and lower specificity 35% (95% CI, 24-47%), diagnostic accuracy 40% (95% CI, 30-50%), Ppv was 0.28 (95% CI, 0.2-0.38%), Npv of 1 (95% CI, 0.96-1.0%) and LR was 1.5 for positive test.

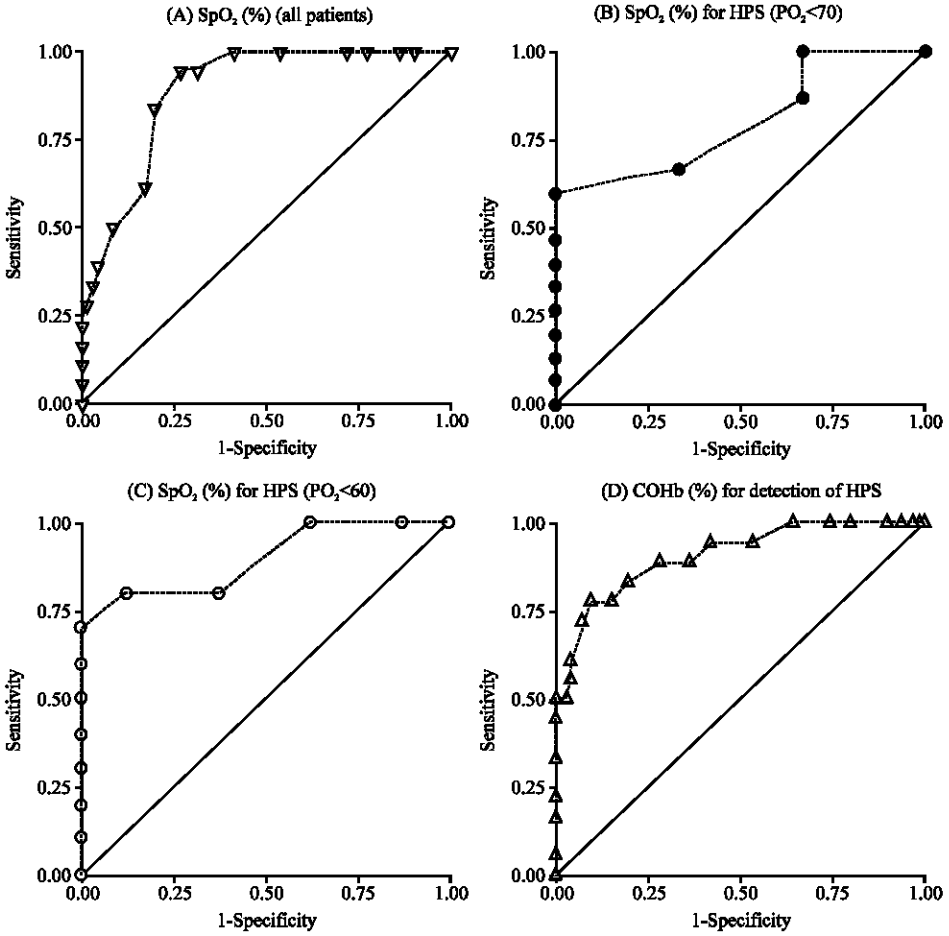

Fig. 5: ROC curves of SpO_2% measurements in (A) all patients for detection of HPS, (B) in HPS patients with PO_2 ≤70 mmHg, (C) in HPS patients with PO_2 ≤60 mmHg and (D) ROC curve for COHb% in all cirrhotic patients for detection of HPS

Table 3: Test performance characteristics of SpO_2 measurements as a screening tool for HPS

SpO_2 (%) positive if ≤	All patients	PaO_2 ≤70	PaO_2 ≤60
80	11/100	13/100	20/100
81	16/100	20/100	30/100
83	22/100	26/100	40/100
86	27/98	33/100	50/100
87	33/97	40/100	60/100
88	38/95	46/100	70/100
89	50/91	60/100	80/87
90	61/83	66/66	80/62
91	83/80	86/33	100/37
92	94/73	100/33	100/12
93	94/69	100/0	100/0
94	100/59	100/0	100/0
95	100/46	100/0	100/0
96	100/28	100/0	100/0
97	100/22	100/0	100/0
98	100/14	100/0	100/0
99	100/9	100/0	100/0
100	100/0	100/0	100/0

(Sensitivity %/Specificity%)

Table 4: Test performance characteristics of COHb measurements for detection of HPS

COHb (%)				
Positive if ≥	Sens %/Spec%	Ppv	Npv	+ LR
0.9	100/25	25.4	100.0	1.34
1.0	100/35	28.1	100.0	1.54
1.1	94/46	30.9	97.1	1.76
1.2	94/57	36.2	97.6	2.24
1.3	88/63	38.1	95.7	2.43
1.4	88/71	44.4	96.2	3.16
1.5	83/80	51.7	95.0	4.23
1.6	77/84	56.0	93.8	5.02
1.7	77/90	66.7	94.1	7.89
1.8	72/92	72.2	93.0	10.26
1.9	61/95	78.6	90.7	14.46
2.0	55/95	76.9	89.5	13.15
2.1	50/97	81.8	88.5	17.75
2.2	50/100	100.0	88.8	17.75
2.3	44/100	100.0	87.7	17.75
2.5	33/100	100.0	85.5	17.75
2.7	22/100	100.0	83.5	
3	16/100	100.0	82.6	

(Sensitivity %/Specificity %)

The COHb% at ≥1.7 as a cutoff was found to have sensitivity of 77% (95% CI, 52-93%) and specificity of 90% (95% CI, 80-95%), respectively with diagnostic accuracy 83% (95% CI, 75-90%), Ppv was 0.66 and Npv of 0.94 and positive Likelihood Ratio (+LR) was 7.89.

At COHb level ≥2.2, the sensitivity and specificity for detection of HPS patients were 50% (95% CI, 26-73%) and 100% (95% CI, 94-100%) respectively, diagnostic accuracy 87% (95% CI, 80-94%) and Ppv was 1 and Npv of 0.88 (Table 4).

So, the higher COHb levels as a cutoff for detection of HPS, the better specificity, Ppv and LR for positive test that can be found, provided with exclusion of any other possible causes of increased level of COHb as smoking. From the ROC curve, the COHb% ≥2.2 as cutoff threshold for detection of HPS had sensitivity 50% and specificity 100%, with an AUC of 0.907 (95% CI, 0.827- 0.986%).

Combined index of SpO_2 and COHb thresholds: Further statistical analysis was done using a combined index of both SpO_2 ≤94% and COHb% ≥ROC derived threshold as a screening tool for HPS detection on all cirrhotic patients. Different cutoff COHb levels were studied depending on the previous ROC curve for COHb% in HPS and cirrhotic patients.

At COHb% ≥1.5 as a cutoff for cirrhotic patients with SpO_2 ≤94%, the sensitivity was 88% (95% CI, 74-100%) and specificity of 80% (95% CI, 71-89%), diagnostic accuracy 82% (95% CI, 74-90%), Ppv was 0.53 (95% CI, 0.35-0.71), Npv of 0.96 (95% CI, 0.91-1.0%) and +LR of 4.5 (95% CI, 2.74-7.4%) for positive test and negative LR (–LR) of 0.13 (95% CI, 0.03-0.51%) for negative test. At COHb% ≥1.7 as a cutoff (with SpO_2 ≤94%), the sensitivity was 77% (95% CI, 58-96%) and specificity of 85% (95% CI, 77-94%), diagnostic accuracy 84% (95% CI, 76-91%), Ppv was 0.58 (95% CI, 0.38-0.78), Npv of 0.93 (95% CI, 0.88 -0.99%) and +LR of 5.5 (95% CI, 2.95-10.32%) and -LR of 0.25 (95% CI, 0.1-0.61%).

Using COHb% ≥2.2 as a cutoff for cirrhotic patients with SpO_2 ≤94% was found to have diagnostic accuracy of 87% (95% CI, 80-94%), sensitivity of 50% (95% CI, 26-73%) and specificity of 97% (95% CI, 93-100%), Ppv was 0.81 (95% CI, 0.59-1.04%), Npv of 0.88 (95% CI, 0.81-0.95%) and +LR of 17.7 (95% CI, 4.19-75.08%) and -LR 0.51 (95% CI, 0.32-0.81%). So, using a combined SpO_2 ≤94% and COHb% ≥2.2 as an index for screening HPS in cirrhotic patients had a higher diagnostic accuracy and increase the specificity of diagnostic detection of HPS with higher positive predictive value and higher likelihood ratio for positive test.

DISCUSSION

Hepatopulmonary syndrome is an important complication of cirrhosis. It is associated with adverse outcome with increased mortality even after liver transplantation compared with those without HPS especially when hypoxemia is severe (Arguedas *et al.*, 2003; Schenk *et al.*, 2003; Swanson *et al.*, 2005). Screening for HPS could enhance detection of patients with sufficient hypoxemia to merit higher priority for transplant.

In this study, all the patients had chronic hepatitis C as the etiology of cirrhosis. The incidence of HPS was not related to Child-Pugh score or the degree of hepatic deterioration. This finding was corresponding with (Arguedas *et al.*, 2003), in which HPS was not more common in advanced liver disease but different form other studies for unclear cause (Vachiery *et al.*, 1997; Schenk *et al.*, 2003).

The clinical presentation of the patients with HPS including dyspnea, cyanosis, spider nevi and ascities were similar to non-HPS patients with no significant difference, which was in agreement with previous studies (Martinez *et al.*, 2001; Schenk *et al.*, 2002; Swanson *et al.*, 2005).

HPS is usually diagnosed by CEE and ABG. In this prospective study we evaluated pulse oximetry and carboxyhemoglobin percentage in arterial blood as simple measures to predict HPS in cirrhosis caused by chronic hepatitis-C patients. The CEE, ABG and A-a gradient in our study was for defining and confirming which cirrhotic patients (according to the gold standard) are truly HPS patients and to define the HPS group from the non-HPS group. Accordingly, the screening will depends on the pulse oximetry and COHb in determined groups. Pulse oximetry is a well-established method for noninvasive evaluation of arterial oxygenation (Jensen *et al.*, 1998). It is accurate and reliable for assessing arterial oxygenation in patients without liver disease and similar results in cirrhotic patients. In both situations, SpO_2 might overestimate oxygen saturation measured directly on ABG analysis by between 1.5-3.5% and in cirrhotic patients resulted in a higher SpO_2 than might be expected to trigger evaluation with ABG to detect hypoxemia. In cirrhotic patients, the overestimation of oxygen saturation by SpO_2 was similar to that in patients without liver disease and was not influenced by severity of liver disease or bilirubin levels, supporting that SpO_2 is of similar utility in patients with and without liver disease (Abrams *et al.*, 2002).

In previous studies, the prevalence of HPS was found to be variable according to the criteria used to

define the arterial oxygen abnormalities (Schenk *et al.*, 2002). In HPS, increased alveolar-arterial O_2 gradient in room air was classically defined as >15 mm Hg or >20 mmHg in patients >64 years of age (Varghese *et al.*, 2007), but as the $P(A\text{-}a)O_2$ normally increases with age and varies significantly even in healthy individuals, it is therefore recommended to use values above the 95% confidence interval for the age- corrected $P(A\text{-}a)$ O_2 to avoid over diagnosis of HPS (Harris *et al.*, 1974). In the present study we used the elevated age-corrected $P(A\text{-}a)O_2$ as abnormal on the basis of prior studies of Schenk *et al.* (2002) and Arguedas *et al.* (2003). We found that all patients with HPS had pulse oximetry ≤94% and PaO_2 ≤80 mmHg, suggesting that HPS could be detected in all patients with SpO_2 value <95%. Pulse oximetry and PaO_2 showed significant inverse correlations with $P(A\text{-}a)O_2$. Study results are in agreement with Arguedas *el al.* (2007) who performed study to define the utility of pulse oximetry, in the setting of a positive CE, in detecting hypoxemic patients with HPS. A cutoff SpO_2 value <96% detects all patients with HPS and hypoxemia (PaO_2 <70 mmHg) with a specificity of 88%. ROC analysis demonstrates that using a SpO_2 <94% also detects all patients with HPS and a PaO_2 <60 mmHg who would be candidates for MELD (HPS Model for End-Stage Liver Disease) exception related to HPS with a high specificity (93%). In addition, they found that different SpO_2% cutoff values reliably identified varying degrees of severity in patients with HPS.

Roberts *et al.* (2007) studied the cost effectiveness of screening for HPS in liver transplant candidates. They searched the cost and outcome in three different strategies: no screening, screening patients with validated dyspnea questionnaire and screening all patients with pulse oximetry. ABG analysis and contrast echocardiography were performed in patients with dyspnea or pulse oximetry ≤97% to define the presence of HPS. They concluded that pulse oximetry screening is a cost effective strategy that improves survival in transplant candidates.

In prior work, digital pulse oximetry performed in a pulmonary function laboratory at the time of ABG analysis was a useful tool for detecting hypoxemia in cirrhosis. They found that a SpO_2 threshold of 96% or less correctly identified all patients with a PaO_2 <60 mmHg (Abrams *et al.*, 2002). The ERS Task Force had proposed a classification system that uses the partial pressure of arterial oxygen (PaO_2) to stage the severity of HPS. According to this system, a PaO_2 <50 mmHg indicates very severe HPS, a PaO_2 in between 50 to 60 mmHg suggests severe HPS, a PaO_2 in between 60 and 80 mmHg corresponds with moderate HPS and PaO_2 ≥80 mmHg correspond to mild HPS (Rodriguez-Roisin *et al.*, 2004).

In the present study, arterial COHb levels showed statistically significant increase in HPS patients compared with non-HPS patients. This increase coincides with the decrease of SpO_2% and PaO_2 in these patients, as COHb% showed significant inverse correlation with SpO_2%, arterial PaO_2 and $PaCO_2$ levels and significant direct correlation with $P(A\text{-}a)O_2$.

Carter *et al.* (2002) had found that in experimental HPS induced by common bile duct ligation in the rat, intravascular macrophages accumulate in the lung, overexpress HO-1 and are associated with increased arterial COHb levels as HPS progresses. In human, similar results have been reported, as arterial COHb levels were increased significantly in patients with HPS compared with patients without HPS. Arterial COHb levels did not correlate with severity of liver disease. However, the correlation between arterial COHb levels and arterial PaO_2 levels and alveolar-arterial oxygen gradients was modest (Arguedas *et al.*, 2005).

In the present study, we found that using COHb% alone ≥ROC-derived threshold in non-smoking cirrhotic patients has low sensitivity in detection of HPS, but using a combined SpO_2 ≤94% and COHb% ≥2.2 as an index for screening HPS in cirrhotic patients had a higher diagnostic accuracy and increase the specificity of diagnostic detection of HPS.

CONCLUSION

Study results demonstrate that pulse oximetry is a simple and reliable screening tool for the detection and follow up of HPS. Arterial COHb levels increase in HPS and correlate inversely with both SpO_2 and PaO_2 and could be used as screening for HPS in selected non smoking patients. Using COHb level more than ROC-derived threshold as a combined index with pulse oximetry for screening of HPS can provide a better clinical implication for HPS detection, better diagnostic accuracy and improve the performance of the test. Multicentre study on a larger number of patients is recommended for validation of the results and to find a reliable non invasive method for COHb measurement is recommended in future studies.

REFERENCES

Abrams, G.A., C.C. Jaffe, P.B. Hoffer, H.J. Binder and M.B. Fallon, 1995. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology, 109: 1283-1288.

Abrams, G.A., N.C. Nanda, E.V. Dubovsky, M.J. Krowka and M.B. Fallon, 1998. Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: A new approach. Gastroenterology, 114: 305-310.

Abrams, G.A., M.K. Sanders and M.B. Fallon, 2002. Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates. Liver Transplant., 8: 391-396.

Arguedas, M., G.A. Abrams, M.J. Krowka and M.B. Fallon, 2003. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology, 37: 192-197.

Arguedas, M.R., B.B. Drake, A. Kapoor and M.B. Fallon, 2005. Carboxyhemoglobin levels in cirrhotic patients with and without hepatopulmonary syndrome. Gastroenterology, 128: 328-333.

Arguedas, M.R., H. Singh, D.K. Faulk and M.B. Fallon, 2007. Utility of pulse oximetry screening for hepatopulmonary syndrome. Clin. Gastroenterol. Hepatol., 5: 749-754.

Barzilai, B., A.D. Waggoner, C. Spessert, D. Picus and D. Goodenberger, 1991. Two dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am. J. Cardiol., 68: 1507-1510.

Carter, E.P., C.L. Hartsfield, M. Miyazono, M. Jakkula and K.G. Morris *et al*., 2002. Regulation of heme oxygenase-1 by nitric oxide during hepatopulmonary syndrome. Am. J. Physiol., 283: L346-L353.

De Las Heras, D., J. Fernandez, P. Gines, A. Cardenas and R. Ortega *et al*., 2003. Increased carbon monoxide production in patients with cirrhosis with and without spontaneous bacterial peritonitis 1. Hepatology, 38: 452-459.

Dollinger, M.M., 2006. Pulmonary complication in liver disease. Schweiz Rundsch Med. Prax., 95: 1539-1542.

Fuhrmann, V., C. Madl, C. Mueller, U. Holzinger and R. Kitzberger *et al*., 2006. Hepatopulmonary syndrome in patients with hypoxic hepatitis. Gastroenterology, 131: 69-75.

Harris, E., A. Kenyon, H. Nisbet, E. Seelye and R. Whitlock, 1974. The normal alveolar-arterial oxygen-tension gradient in man. Clin. Sci. Mol. Med., 46: 89-104.

Hira, H.S., J. Kumar, S.K. Tyagi and S.K. Jain, 2003. A study of hepatopulmonary syndrome among patients of cirrhosis of liver and portal hypertension. Indian J. Chest Dis. Allied Sci., 45: 165-171.

Hopkins, E.W., A.D. Wagoner and B. Barzilai, 1992. Frequency and significance of intrapulmonary right to left shunting in end stage hepatic disease. Am. J. Cardiol., 70: 516-519.

Jensen, L., J. Onyskiw and N. Prasad, 1998. Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. Heart Lung, 27: 387-408.

Krowka, M.J., A.J. Tajik, E.R. Dickson, R.H. Wiesmer and D.A. Cortese, 1990. Intrapulmonary vascular dilatation (IPVD) in liver transplant candidates. Screening by two-dimensional contrast-enhanced echocardiography. Chest, 97: 1165-1170.

Krowka, M.J., E.R. Dickson and D.A. Cortese, 1993. Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. Chest, 104: 515-521.

Krowka, M.J. and D.A Cortese, 1994. Hepatopulmonary syndrome. Current concepts in diagnostic and therapeutic considerations. Chest, 105: 1528-1537.

Krowka, M., G. Wiseman, O. Burnett, J. Spivey and T. Therneau *et al*., 2000. Hepatopulmonary syndrome: A prospective study of relationships between severity of liver disease, PaO_2 response to 100% oxygen and brain uptake after 99mTc MAA lung scanning. Chest, 118: 615-624.

Krowka, M.J., M.S. Mandell, M.A. Ramsay, S.M. Kawut and M.B. Fallon *et al*., 2004. Hepatopulmonary syndrome and portopulmonary hypertension: A report of the multicenter liver transplant database. Liver Transplant., 10: 174-182.

Lima, B.L., A.V. Franca, A. Pazin-Filho, W.M. Araujo and J.A. Martinez *et al*., 2004. Frequency, clinical characteristics and respiratory parameters of hepatopulmonary syndrome. Mayo Clin. Proc., 79: 42-48.

Martinez, G.P., J.A. Barbera, J. Visa, A. Rinola and J.C. Pare *et al*., 2001. Hepatopulmonary syndrome in candidates for liver transplantation. J. Hepatol., 34: 651-657.

McAdams, H.P., J. Erasmus, R. Crockett, J. Mitchell and J.D. Godwin *et al*., 1996. The hepatopulmonary syndrome: Radiologic findings in 10 patients. AJR. Am. J. Roentgenol., 166: 1379-1385.

Meltzer, R.S., Z. Vered and J. Roelandt, 1983. Systematic analysis of contrast echocardiogram. Am. J. Cardiol., 52: 375-382.

Morse, D. and A.M. Choi, 2002. Heme oxygenase-1: The emerging molecule has arrived. Am. J. Respir. Cell Mol. Biol., 27: 8-16.

Muller, C. and P. Schenk, 1999. Hepatopulmonary syndrome. Wien Klin Wochenschr, 111: 339-347.

Pauwels, R., A.S. Buist, P. Ma, P.M. Calverley, C.R. Jenkins, S.S. Hurd and GOLD Scientific Committee, 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am. J. Respir. Crit. Care Med., 163: 1256-1276.

Roberts, D.N., M.R. Arguedas and M.B. Fallon, 2007. Cost-effectiveness of screening for hepatopulmonary syndrome in liver transplant candidates. Liver Transplant., 13: 206-214.

Rodriguez-Roisin, R., M.J. Krowka, P.H. Herve, M.B. Fallonz and ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee, 2004. Pulmonary-Hepatic vascular Disorders (PHD). Eur. Respir. J., 24: 861-880.

Schenk, P., V. Fuhrmann, C. Madl, G. Funk and S. Lehr *et al*., 2002. Hepatopulmonary syndrome: Prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. Gut, 51: 853-859.

Schenk, P., M. Schoniger-Hekele, V. Fuhrmann, C. Madl and G. Silberhumer *et al*., 2003. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology, 125: 1042-1052.

Stevenson, D.K. and H.J. Vreman, 1997. Carbon monoxide and bilirubin production in neonates. Pediatrics, 100: 252-259.

Swanson, K., R. Wiesner and M. Krowka, 2005. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. Hepatology, 41: 1122-1129.

Vachiery, F., R. Moreau, A. Hadengue, A. Gadeno and T. Soupison, 1997. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. J. Hepatol., 27: 492-495.

Varghese, J., H. Ilias-Basha, R. Dhanasekaran, S. Singh and J. Venkataraman, 2007. Hepatopulmonary syndrome-past to present. Concise Review. Ann. Hepatol., 6: 135-142.

West, J.B., 1990. Respiratory Physiology-the Essentials. 4th Edn. Williams and Wilkins, Baltimore, ISBN: 0683089420 .

Zhang, J., Y. Ling, B. Luo, L. Tang and C. Stockard *et al*., 2003. Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. Gastroenterology, 125: 1441-1451.