Determinants of Hypoxemia in Cirrhosis

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Abstract

Background and Objectives: Mechanisms of the development of hypoxemia in cirrhosis are still not well understood. In this study, we aimed to investigate and determine the factors contributing to hypoxemia in patients with cirrhosis.

Patients and Measurements: A total of 52 biopsy proven cirrhotic patients without any cardiopulmonary disorder and encephalopathy were studied prospectively. Blood gases were measured in supine, sitting positions and also while inhaling 100% O_2. for 15 minutes. In the supine position, PaO_2 values between 79-60 mmHg were evaluated as mild to moderate hypoxemia and any value below 60 mmHg as severe. Hemoglobin, albumin, AST and ALT levels, prothrombin time, presence of orthodeoxia, ascites, results of spirometric tests, duration of the disease and smoking habits were recorded in all patients. Contrast echocardiography (CE) was also performed in all patients. The results of these parameters were analysed to elucidate the determinants of hypoxemia in cirrhosis.

Results: Twenty-one of the patients (43.8%) were found to be hypoxemic. Hypoxemia was mild to moderate in 18 patients (mean 72.3 mmHg) and severe in 3 patients (mean 52.2 mmHg). All patients responded well to 100% O_2 inhalation with expected elevations in PaO_2, thus excluding real anatomic and portopulmonary shunts as the causes of hypoxemia. Hypoxemic patients showed significant differences from normoxemic patients with cirrhosis in frequency of ascites ($p<0.001$) and AST levels (relatively lower levels) ($p<0.05$). Positive CE findings and orthodeoxia (a sign representatives of hepatopulmonary syndrome) showed an association with severe hypoxemia ($p<0.001$ and $p<0.01$ respectively).

Conclusion: Presence of ascites and relatively low levels of serum AST appear to be predictors of hypoxemia in cirrhotic patients without cardiopulmonary disorder or encephalopathy. We suggest that all cirrhotic patients meeting one or both of these criteria be routinely investigated for hypoxemia.

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Key Words: *Cirrhosis, hypoxemia, ascites, hepatopulmonary syndrome*
Abbreviations: ALT: *Serum Alanine Transaminase,* **AST:** *Serum Aspartate Transaminase,* **PT:** *Prothrombin Time,* **CE:** *Contrast Echocardiography,* **HPS:** *Hepatopulmonary Syndrome*

Introduction

The occasional association between liver cirrhosis and hypoxemia has been known for over a century (1). Snell and co-workers were the first to attempt to provide a satisfactory explanation for this association (2). Since then, there have been many reports on the pathogenesis and treatment modalities of this process (3-11).

The hypoxemia occurring in cirrhotic patients is usually mild to moderate, rarely severe and its frequency has been reported as 20-50% (12-15). Numerous mechanisms have been suggested to explain this association and some of these, such as a rightward shift of

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the oxyhemoglobin curve (16), a blunting of the hypoxic vasoconstriction of the pulmonary vessels [6] and occurrence of true portopulmonary shunts (17), lost their popularity over time. Today we know that there is no simple mechanism to explain this association and that probably many factors have a role in its pathogenesis. Although none of them have been proven as the sole reason, nevetheless ascites (18), hepatopulmonary syndrome (13-19), increased closing volume, low albumin levels (20), anaemia (21), respiratory muscle weakness and extreme hepatomegaly (22) are still considered among the factors implicated in the pathogenesis of hypoxemia in cirrhosis.

The purpose of this present investigation was to establish the determinants of hypoxemia in biopsy proven cirrhotic patients who had no cardiopulmonary disorders or encephalopathy.

Patients and Methods

Seventy-nine consecutive and biopsy proven cirrhotic patients were enrolled in the study. Informed consent was obtained from the patients and the study protocol was approved by the Medical Ethics Committee of the Turgut Özal Medical Center Research Hospital.

The patients' smoking history, duration of the disease and ascites were recorded. To exclude patients with cardiopulmonary disorders, all patients underwent detailed questioning for past medical history and a detailed physical examination, standard 12 lead ECG, echocardiography and chest X-ray. In all patients abdominal ultrasonography was done for evaluation of ascites. Blood analyses for hemoglobin, albumin, serum AST and ALT levels, and PT values were also performed. Since patients with encephalopathy were not included in the study, Child's classification was not used.

All patients underwent contrast echocardiography (CE) examination by two dimensional echocardiography (Sonos 1000-Hewlett Packard) to detect the presence of any sign of hepatopulmonary syndrome (presence of micro air bubles of irritated serum physiologic in the left cardiac chambers 4 to 6 beats after appearance in the right atrium) and to exclude intra-cardiac shunts with rapid intravenous injection of irritated physiologic saline in supine position.

Table 1. Clinical and biochemical/hematological characteristics of the normoxemic and hypoxemic patients

	Normoxemic (n:31)	Hypoxemic (n:21)	p
Mean age (years)	49.8±19.7	53.2±10.9	>0.05
Mean duration of disease (years)	4.1±3.6	3.2±2.1	>0.05
Number of the smoking patients	9	8	>0.05
Number of the patients with ascites	8	18	**<0.001**
ALT (IU/L) (mean level)	108.4±104.8	68.9±53.4	>0.05
AST (IU/L) (mean level)	119.8±113.7	58.4±50.2	**<0.05**
Albumin (g/dl) (mean level)	2.9±0.6	2.7±0.4	>0.05
PT (sec) (mean level)	13.1±0.8	13.3±0.8	>0.05
Hemoglobin (g/dl) /mean level)	11.1±2.2	11.6±2.1	>0.05

Spirometric evaluation of the patients was done with a Vmax 20c-Sensor Medics Spirogram and FVC, FEV_1, FEV_1/FVC and FEF_{25-75} values were noted. Arterial blood gas analysis were done for PaO_2 from a catheter in the radial artery while breathing room air both in supine and sitting positions and also while inhaling 100% O_2 with a mouthpiece and a nose clip for 15 minutes. While breathing room air in the supine position, patients with PaO_2 values between 79-60 mmHg were accepted to have mild to moderate hypoxemia and patients with PaO_2 levels below 60 mmHg were accepted to have severe hypoxemia. By measuring PaO_2 in the sitting position, we intended to detect the orthodeoxia sign which represents strong evidence for hepatopulmonary syndrome (HPS) in patients with hepatic cirrhosis. By increasing FiO_2 we aimed to differentiate HPS from anatomic real shunts which respond less to inhalation of increased FiO_2.

The data are expressed as mean and standard deviation values. Correlations among multiple parameters described above and hypoxemia were analysed using Fischer's exact test and Mann-Whitney U test. Differences were considered statistically significant when p values were <0.05.

Results

Twenty seven patients were excluded from the study because of cardiopulmonary disorders (chronic obstructive pulmonary disease: 7, cardiac disorders: 11, pleural effusion: 7), 11 because of encephalopathy and 3 because of consent withdrawal (n: 3). In 8 of these patients there were more than one cause for exclusion. Fifty-two patients (35 male, 17 female, mean age 50.8±15.1 years) completed the study and 21 of these were found hypoxemic (43.8%). Eighteen patients (female: 7, male: 14) were evaluated to have mild to moderate hypoxemia and 3 patients were

Table 2. Arterial blood gases, spirometric measurements, contrast echocardiography and orthodexia results in the normoxaemic and hypoxaemic patients

	Normoxemia (n:31)	Hypoxemia (n:21)	P
PaO_2 supine (mmHg)	90.6±7.2	69.4±8.6	—
PaO_2 erect (mmHg)	93.6±9.1	72.4±11.3	—
FVC (%)	104±19.8	103.1±16.7	>0.05
FEV_1 (%)	99.9±24.2	94.7±21.1	>0.05
FEV_1/FVC (%)	78±9.8	73.6±10.1	>0.05
FEF_{25-75} (%)	72.5±18.5	68.3±27.5	>0.05
Number of the patients with positive CE	1	3	>0.05
Number of the patients with orthodexia	0	2	>0.05

severely hypoxemic. Mean age of the normoxemic group was 49.8±19.7 years and that of the hypoxemic group was 53.2±10.9 years (p>0.05). Seventeen cirrhotic patients were chronic smokers and of these, 8 were in the hypoxemic group (p>0.05). Mean duration of disease was 4.1±3.6 and 3.2±2.1 years in normoxemic and hypoxemic groups respectively (p>0.05). The patients' characteristics are presented in Table 1.

Ascites detected by abdominal ultrasonography was present in 26 (50%) patients and 18 of these patients were hypoxemic (p<0.001). ALT values ranged from 10 to 468 IU/L (mean 108.4±104.8) in the normoxemic group and from 16 to 240 IU/L (mean 68.9±53.4) in the hypoxemic group. AST values were between 13-440 IU/L (mean 119.8±113.7) in the normoxemic group and between 11-249 IU/L (mean 58.4±50.2) in the hypoxemic group. Serum transaminase levels in the hypoxemic patients were above normal but markedly lower compared to the normoxemic group and this situation was statistically significant for AST (p<0.05) (p= 0.07 for ALT). In normoxemic and hypoxemic patients mean serum albumin, hemoglobin and PT levels were 2.9±0.6g/dl and 2.7±0.4g/dl; 11.1±2.2g/dl and 11.6±2.1g/dl; 13.1±0.8 sec and 13.3±0.8 sec respectively (Table 1). Any correlation between hypoxemia and each of these parameters could not be established (p>0.05).

Spirometrically, in normoxemic patients mean results of FVC, FEV_1, FEV_1/FVC and FEF_{25-75} measurements in percentages were 104±19.8, 99.9±24.2, 78±9.8 and 72.5±18.5 respectively. The same measurements for hypoxemic patients were 103.1±16.7, 94.7±21.1, 73.6±10.1 and 68.3±27.5 respectively. All mean spirometric values studied were within normal limits and the differences between hypoxemic and normoxemic patients were not statistically significant (p>0.05) (Table 2).

Mean values of PaO_2 in supine and sitting position for normoxemic patients were 90.6±7.3 mmHg and 93.6±9.1 mmHg respectively. The same values for hypoxemic patients were 69.4±8.7 mmHg and 72.4±11.3 mmHg (Table 2). All patients responded well to 100% O_2 inhalation with expected elevations in PaO_2. PaO_2 increased over 350 mmHg in all patients on inhaling 100% O_2 (p>0.05). CE with irritated physiologic saline revealed positive results in 4 patients (8%). Except for one normoxemic patient, these patients were severely hypoxemic and no intracardiac shunt was visualised during CE procedure. Orthodeoxia (worsening or development of the hypoxemia with a more than 10 mmHg fall in PaO_2 in erect position) was present in 2 of the CE positive severely hypoxemic patients (-10.2 mmHg and -14.7 mmHg) (Table 3). Frequencies of positive CE results and orthodeoxia sign were significantly higher in the patients with severe hypoxemia (p<0.001 and p<0.01 respectively).

Discussion

In this study which comprised cirrhotic patients who had no other predisposing factors for hypoxemia, significant correlations were found between hepatic cirrhosis and hypoxemia regarding two parameters; namely, presence of ascites and serum AST level. It was also confirmed that hepatopulmonary syndrome was the most important reason in the development of severe hypoxemia.

Traditionally, hypoxemia has not been seriously evaluated in cirrhotic patients and is usually perceived as an occasional event during the course of the disease (8). Its early detection, if it could be corrected, might be of some help in better control of symptoms and prevention of subsequent complications. Many reports are found in the medical literature on mechanisms of development of hypoxemia in cirrhosis. Ascites by itself has been assumed to cause hypoxemia mechanically by restricting diaphragmatic movements leading to pulmonary effusion, by increasing closing volumes and by interfering with diffusion of alveolar O_2 content as a result of the interstitial oedema. However, these mechanisms have not been studied in large groups (18, 23, 24). In clinical practice, it is usually believed that pleural effusion by progression of ascites is the major determinant of hypoxemia in

Table 3. Reevaluation of the contrast echocardiography results and orthodexia after subdividing the patients according to presence of severe hypoxemia.

	Normoxemia/mild to moderate hypoxemia (n:49)	Severe hypoxemic (n:3)	P
Number of the patients with positive CE	1	3	<0.001
Number of the patients with orthodexia	0	2	<0.01

cirrhotic patients. In our study group, none of the patients with ascites had accompanying pleural effusion, but at the same time, a high correlation was found between hypoxemia and ascites ($p<0.001$). We believe this is the first time that such a relationship has been documented. This situation implicates that pleural effusion is not imperative for the development of hypoxemia and hence the presence of ascites by itself may be regarded as an early indicator of hypoxemia.

The term, hepatopulmonary syndrome (HPS), first suggested by Kennedy and Knudson (19), denotes the intrapulmonary vascular dilations causing hypoxemia by permitting the shunting of unoxygenated blood from right to left in patients with hepatic dysfunction. Despite different study protocols and patient groups in previous studies, HPS seems to be an important cause of hypoxemia in hepatic cirrhosis (13-19,25-27). Suspected causes of HPS are accumulation of vasodilator substances in blood by the impaired clearance, inhibition of vasoconstrictors and production of a vasodilator by a damaged liver (1, 13, 22, 28-32). Diagnosis of HPS is simple and can tentatively be made by detecting platypnea (dyspnea in erect position) and orthodeoxia during physical examination and by arterial blood gas analysis. Absolute diagnosis necessitates exclusion of true right to left shunts and demonstration of right to left shunting of unoxygenated blood via dilated alveolar capilleries by using any of the imaging techniques such as perfusion lung scanning (33), pulmonary arteriography (13) and CE (transoesophageal being superior to transthoracic), which is the most sensitive and least invasive among all these techniques (34, 35). Despite these technical advancements, uncertainty about the cause and the treatment of hepatopulmonary syndrome still persists (1, 13).

Low albumin levels may contribute to hypoxemia in cirrhosis by causing subtle interstitial oedema leading to hypoxemia by interfering diffusion of alveolar O_2 content, and/or by increasing the ascites. Smoking, reduced hemoglobin levels (below 10mg/dl), respiratory muscle weakness and extreme hepatomegaly are the other implicated minor contributors of hypoxemia in liver cirrhosis, factors which should always be considered in critically ill patients. None of these factors are expected to cause hypoxemia alone, but there is no doubt that they exert some additive effect on its development (23).

On the other hand, cirrhotic patients are usually hyperkinetic and in some patients, the expected hypoxemia may be surprisingly compensated by hyperventilation and increased circulation (7, 13). No demonstrable cause of hypoxemia can be established in some cirrhotic patients with hypoxemia, raising the suspicion that some unknown mechanisms still exist in the pathogenesis of the hypoxemia (7, 13, 19, 33, 36). Our study has demonstrated that classic mechanisms of hypoxemia do not operate in cirrhotic patients with no cardiopulmonary disorder and encephalopathy. Due to opposing or compensatory mechanisms described above, the level of the hypoxemia is kept within a reasonable range and severe hypoxemia is rare, as also noted in our study (6%) (12-15). Whatever its prevalence or degree, hypoxemia itself worsens the clinical condition of cirrhotic patients which already may be in critical balance.

Among the parameters that were assessed in this study, age, sex, duration of the disease, smoking habit, respiratory function tests (FVC, FEV_1, FEV_1/FVC, FEF_{25-75}), PT and levels of serum albumin, hemoglobin and ALT did not show any correlation with presence of hypoxemia. In our overview of the literature we were also unable to find evidence for any biochemical marker correlating with hypoxemia. In the present study, serum AST levels were found to be lower in hypoxaemic patients ($p<0.05$). Despite the fact that mean levels of serum AST in hypoxemic patients were above normal, these levels were distinguishably low when compared with those of normoxemic patients with hepatic cirrhosis. The same was true for serum ALT levels, but not at the statistical significance level. ($p= 0.07$). There was no satisfactory explanation for the lower value of serum AST in hypoxemic patients. However, as

speculated earlier, a relatively less damaged liver may be producing a still unidentified circulating substance leading to hypoxemia (13). This situation remains to be clarified and requires further investigations.

All hypoxemic patients, including severely hypoxemic ones, responded well to the 100% O_2 inhalation. This finding also confirms the fact that true right to left shunts in cirrhosis are exceptional since hypoxemia due to true shunts cannot be corrected by increasing fractional O_2 concentration (FiO_2). The shunt observed in severely hypoxemic patients is indeed not anatomic but functional and resulting from capillary dilations in pulmonary vasculature (1,13). However, after subdividing the patients into two groups as severe hypoxemia and the others, CE positivity (4 patients) and orthodeoxia sign (2 patients), findings which are assumed to be almost representative of hepatopulmonary syndrome (1,13, 25, 37), were found to be associated with severe hypoxemia ($p<0.001$ and $p<0.01$ respectively) ($p<0.001$ and $p<0.01$, respectively) (Table 3). Only 1 patient with CE positivity did not have hypoxemia and 2 patients with orthodeoxia overlapped with CE positive hypoxemic patients. In previous studies the rate of hypoxemia in CE positive patients with hepatic cirrhosis was reported to be around 90% (38). This finding suggests that either compensatory mechanisms mentioned above may be operating in some patients or the presence of subtle intrapulmonary vascular dilations are as yet insufficient to cause hypoxemia.

To our knowledge, this is the first large population based study presenting a statistically significant correlation between hypoxemia and presence of ascites and lower AST values in cirrhotic patients who have no other cardiopulmonary disorder or encephalopathy. Our study also revealed that in these patients, hepatopulmonary syndrome is the most important cause of severe hypoxemia. We suggest that all cirrhotic patients meeting either or both of these criteria should be routinely investigated for the early detection of hypoxemia, so that its correction, if possible, may contribute to the prevention of subsequent complications.

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