

Research Paper

Alterations in Arterial Blood Parameters in Patients with Liver Cirrhosis and Ascites

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Received: 2006.09.08; Accepted: 2007.03.01; Published: 2007.03.06

In cirrhotic patients, in addition to hepatocytes and Kupffer cells dysfunction circulatory anatomic shunt and ventilation/perfusion (V_A/Q) ratio abnormalities can induce decrease in partial pressure of oxygen in arterial blood (PaO_2), in oxygen saturation of hemoglobin (SaO_2) as well as various acid-base disturbances. We studied 49 cases of liver cirrhosis (LC) with ascites compared to 50 normal controls. Causes were: posthepatic 37 (75.51%), alcoholic 7 (14.24%), cardiac 2 (4.08%), and cryptogenic 3 (6.12%). Complications were: upper gastrointestinal bleeding 24 (48.97%), hepatic encephalopathy 20 (40.81%), gastritis 28 (57.14%), hepatoma 5 (10.2%), renal hepatic syndrome 2 (4.01%), HbsAg (+) 24 (48.97%), and hepatic pleural effusions 7 (14.28%). Average PaO_2 and SaO_2 were 75.2 mmHg and 94.5 mmHg, respectively, compared to 94.2 mmHg and 97.1 mmHg of the control group, respectively (p value in both PaO_2 and SaO_2 was $p < 0.01$). Respiratory alkalosis, metabolic alkalosis, metabolic acidosis, respiratory acidosis and metabolic acidosis with respiratory alkalosis were acid-base disturbances observed. In conclusion, portopulmonary shunt, intrapulmonary arteriovenous shunt and V_A/Q inequality can induce a decrease in PaO_2 and SaO_2 as well as various acid-base disturbances. As a result, pulmonary resistance is impaired and patients more likely succumb to infections and adult respiratory distress syndrome.

Key words: liver cirrhosis, ascites, acid base disturbances, hepatopulmonary syndrome

1. Introduction

The arterial blood of some patients with cirrhosis is not fully saturated with oxygen, probably as a result of an admixture of venous with arterial blood and under-ventilation of some alveoli [1]. There are well known right-to-left anatomic shunts demonstrable between vessels that carry venous blood and those that carry oxygenated blood in the lungs. Arteriovenous shunt may be congenital e.g. in hereditary hemorrhagic teleangiectasia (Rendu Osler Weber disease) where the lesion is transmitted as a simple non-sex-linked dominant and the disorder is observed in the lungs as single or multiple lesions, or may be acquired [2]. Intrapulmonary arteriovenous shunt and portopulmonary shunt may be acquirably observed in patients with chronic liver disease [3, 4, 5, 6].

Hepatopulmonary syndrome refers to the triad of liver disease, pulmonary vascular dilation, and reduced arterial oxygenation [7]. While marked manifestations of the syndrome are unusual in patients with chronic liver disease, more subtle abnormalities of oxygenation are common. The abnormalities have been attributed to right-to-left shunts through pul-

monary arteriovenous fistulas and development of bronchial varices in association with pulmonary hypertension. The syndrome occurs in chronic liver disease of all types and is more common in those with severe liver disease. Furthermore, portopulmonary shunt is another mechanism inducing blood gas alterations observed in patients suffering from severe chronic liver cirrhosis with ascites [8]. It is well known that portal hypertension has an important role in the formation of ascites by raising hydrostatic pressure within the splanchnic capillary bed. Ascites is most frequently encountered in patients with cirrhosis and other forms of severe liver disease. The clinical course of patients with advanced cirrhosis is often complicated by a number of important sequelae that are independent of the etiology of the underlying liver disease. These include portal hypertension with its consequences (e.g. gastroesophageal varices and splenomegaly), ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, hepatocellular carcinoma as well as some other sequelae. In some patients with massive ascites, pleural effusion is

common but even without it, pulmonary collapse and atelectasis may lead to arterial undersaturation since some alveoli are underventilated or not ventilated at all.

As a result of all those above described abnormalities the prognosis is poor on the basis of both the pulmonary and hepatic disease in patients with severe liver cirrhosis and ascites.

2. Methodology

Forty-nine (49) patients without any cardiopulmonary disease with liver cirrhosis and ascites (35 males, 14 females, ratio 2.5:1 and average mean age 65 years with age range 42-81 years) were enrolled in the study. A group of fifty (50) healthy individuals consisted the control group. Cirrhosis had been diagnosed by history, clinical examination, laboratory findings, and liver biopsy, which all patients underwent. From a clinical point of view the patients' conditions varied from moderate to severe according to the Child-Pugh classification (B, C class). None of the patients complained of dyspnea. Patients with parenchymal lung disease were excluded from the study. Furthermore, none of them presented diagnostic criteria for asthma, chronic bronchitis, or emphysema according to the American Thoracic Society Directions.

Since classification of the various types of cirrhosis based on either etiology or morphology alone is unsatisfactory, we usefully classified the studied patients by a mixture of etiologically and morphologically defined entities based on clinical, pathological, and other data as follows: posthepatic 37 cases (75.51%), alcoholic 7 cases (14.24%), cardiac 2 cases (4.08%), and cryptogenic 3 cases (6.12%). The term posthepatic, synonymously to postnecrotic or multilobular cirrhosis, has been used in cases of cirrhosis resultant to viral hepatitis or infectious diseases, autoimmune hepatitis, inherited and metabolic disorders, as well as to drugs and toxins. In particular, based on epidemiologic and serologic evidence (HBsAg, HBeAg, anti-HbC, HBV-DNA) the vast majority of posthepatic cases was due to viral hepatitis (35 cases, 94.59%), due mostly to type B (26 cases, 74.28%), or type C (7 cases, 20%), and concomitant presence in 2 cases (5.71%). Similarly, the term cryptogenic cirrhosis has been used in cases in which the etiology of the cirrhosis was unknown.

Complications observed in the patients studied were: upper gastrointestinal (UGI) bleeding in 20 cases (48.97%), hepatic encephalopathy 20 cases (40.81%), gastritis 28 cases (57.14%), hepatoma 5 cases (10.2%), hepatorenal syndrome 2 cases (4.01%), HbsAg (+) 24 cases (48.97%), and hepatic pleural effusions 7 cases (14.28%). Table 1 and table 2 summarize patients classification and complications observed.

Partial pressure of oxygen in arterial blood (PaO₂), oxygen saturation of hemoglobin (SaO₂) as well as various acid-base disturbances were determined in all patients and normal controls as well. Arterial blood samples were taken while patients were breathing room air (FiO₂: 21%) in a half seated position. They

underwent a puncture from the radical artery. PaO₂ was immediately measured as well as carbon dioxide tension (PaCO₂) and oxyhemoglobin saturation (SaO₂).

Table 1. Classification of patients of the study.

<i>Etiology of the disease</i>	Nr	%
posthepatic	37	75.51
alcoholic	7	14.24
cardiac	2	4.08
cryptogenic	3	6.12
Total	49	100

Table 2. Complications of the cirrhotic patients under study.

	Nr	%
UGI bleeding	24	48.97
Hepatic encephalopathy	20	40.81
Gastritis	28	57.14
Hepatoma	5	10.2
Hepatorenal syndrome	2	4.01
Hbs Ag +	24	48.97
Hepatic pleural effusion	7	14.28
<i>Accompanied acid base disturbances</i>		
Respiratory alkalosis	22	44.89
Metabolic alkalosis	7	14.28
Metabolic acidosis	3	6.12
Respiratory acidosis	3	6.12
Metabolic acidosis + respiratory alkalosis	4	8.16
Normal acid base balance	10	20.4

3. Results

A PaO₂ of equal or less than 80mmHg was defined as hypoxemia values. Values taken from the patients group were as low as below 80 mm Hg with an average PaO₂ of 75.2 mm Hg while that in fifty healthy controls was 94.2 mm Hg.

Statistically, a significant difference was found ($p < 0.01$) between those compared groups. SaO₂ values were in average 94.5 mm Hg and 97.1 mm Hg, respectively, showing also a statistically significant difference ($p < 0.01$). Furthermore, a weak relationship between PaO₂ and Pugh score was found in the patients group. Mean arterial PaCO₂ in the patients group was 33.9 ± 1.5 mmHg with hypocapnia most frequently found.

Acid-base disturbances observed were: respiratory alkalosis in 22 cases (44.89 %), metabolic alkalosis in 7 (14.28 %), metabolic acidosis in 3 (6.12 %), respiratory acidosis in 3 (6.12 %), and metabolic acidosis with respiratory alkalosis in 4 (8.16 %). Normal acid base balance was observed in 10 (20.40 %). Breath rate frequency in all patients studied, was within the normal rates; thus, acid-base disturbances could not be attributed solely to breath frequency abnormalities (e.g. respiratory alkalosis in patients with tachypnea).

Tables 1 and 2 show the classification of patients regarding the etiology of their disease as well as complications and acid based disturbances observed. None of the complications observed was attributed to drugs administered.

4. Discussion

Mild hypoxemia occurs in approximately one-third of patients with chronic liver disease. Arte-

rial venous anastomoses and communications between the portal and arterial circulation as well as between bronchial and pulmonary veins are more likely to be functional in patients with cirrhosis and account for hypoxemia, as well as for perfusion defects seen on lung scan in patients with cirrhosis [9].

Shunts observed in patients with severe liver disease resulting in blood gas alterations may be contributed to portopulmonary shunt due to the portal hypertension development as well as to intrapulmonary arteriovenous shunt and V_A/Q inequality. Hepatopulmonary syndrome, an infrequent complication of chronic liver disease usually associated with portal hypertension and cirrhosis, is manifested by dyspnea, platypnea and orthopnea and nowadays is more widely diagnosed occurring in chronic liver disease of all types and mainly in severe suffering patients [4, 9, 10, 11].

Liver cirrhosis is often accompanied by arterial hypoxemia in the absence of cardiopulmonary disease but the natural history of this syndrome is unknown. This fact was initially thought to be associated with the severity of the liver disease [12]. None of the patients enrolled in our study presented dyspnea and/or chronic lung disease according to the American Thoracic Society Directions. However, spirometric tests performed in all patients studied, confirmed the issue under discussion. Although putative mechanisms of hypoxemia include an intra- or extrapulmonary shunt, ventilation - perfusion inequality, and alveolar capillary diffusion limitation, there is a lack of agreement on which factors are the most important [13]. To the majority of cirrhotic patients that present dyspnea, this appears to be a consequence of ascites, hepatic hydrothorax or cardiopulmonary diseases. A wide spectrum of pulmonary gas exchange abnormalities may be found in patients with advanced liver disease [14]. The most frequent alteration of gas exchange in cirrhosis is hypocapnia observed in approximately 73% of cirrhotic patients which is associated with pulmonary vasodilatation. We hypothesize that hypocapnia, in association with vasodilating substances such as nitric oxide (NO) and endothelins, may contribute- at least in part- in the induction of hypoxemia. Pulmonary vasodilatation is even more frequent and severe in patients with advanced hepatocellular dysfunction. Intrapulmonary vasodilatation found in cirrhosis is thought to be at least partly involved in the development of hypoxemia, though some studies are arguing whether or not hypoxemia develops in patients with intrapulmonary vasodilatation [15, 16]. In our study all of patients with cirrhosis (Child-Pugh B and C) had hypoxemia.

Contradictory, according to another study, the factor mostly inducing hypoxemia in liver cirrhosis is not the disease severity or the abnormal pulmonary circulation but rather the alcoholic etiology of cirrhosis [16]. Furthermore, according to similar studies the smoking status frequently coexisting in alcoholics had no significant effect on pulmonary functions in patients with liver diseases [16, 17]. Hypoxemia observed

in alcoholic cirrhosis does not seem to be caused by alcohol induced disorders in the extrahepatic organs. It seems rather to be associated with an accelerated hyperdynamic and hypermetabolic circulatory state that favors hypoxemia [18, 19]. All patients with alcoholic cirrhosis studied, herein, (7 out of 49, 14.24%) were in a hypoxemic state. Several studies support this assumption suggesting that an increased oxygen demand due to excess alcohol consumption is the primary cause of hypoxemia in alcoholic patients [19]. Moreover, in these series of patients none presented with dyspnea or clinical signs of hepatopulmonary syndrome. These findings confirm previous clinical investigations that illustrated hypoxemia is a common finding in patients with cirrhosis particularly in those with Child-Pugh grade C, (grade < 14), in whom, furthermore, clinical manifestations were rare [20-23]. According to previously published studies, concerning patients with liver cirrhosis, the incidence of hypoxemia appeared to be high in Child-Pugh grade C, presenting a slight difference with those patients classified as grade A or B [12, 23]. Results of the present study coincide with these reports published earlier. The weak link between PaO_2 and Pugh score found herein, suggests that other mechanisms apart from PaO_2 , are involved in the cirrhosis associated hypoxemia mechanisms.

Chronic liver disease, arterial deoxygenation and widespread intrapulmonary vasodilatation characterize the hepatopulmonary syndrome [22]. In decompensate cirrhotic patients, there is an increased arteriovenous shunt for oxygen in the lower extremities that is associated with increased arterial blood flow, decreased systemic vascular resistance and worsening of the liver function. This shunt is due at least partly to the opening of arteriovenous precapillary connections [24]. No any treatment is clinically useful, thus, at present the only treatment resulting to the resolution of the syndrome with simultaneous correction of the blood gas oxygenation alterations is the orthotopic liver transplantation.

Fluid in the chest (pleurisy) may be found in at least 10 percent of patients with cirrhosis, being more common on the right side influencing when in large quantities the V_A/Q ratio. In the present study 7 patients (14.28%) presented pleurisy. Hypoxemia usually appears to be worse in standing than in supine position. Oxygen administration improves dyspnea but does not reverse the defects in some patients [25]. Embolization of shunts if it is possible may be useful.

Gastrointestinal hemorrhage, in the type of variceal bleeding represents a common complication of chronic liver disease and is associated with a high mortality. Studies carried out in a cirrhotic rat model suggested that blood volume restitution following hemorrhage, produce an increase in portal pressure above the limit of the basal values in animals with high portal systemic shunting [26]. Additionally, a number of studies have shown that patients with alcoholic liver disease are known to have a variable and occasionally extensive degree of portosystemic shunting ranging from 5-70% [25, 26]. It must be mentioned that all pa-

tients' medicines were always administered with caution, especially those eliminated or modified through hepatic metabolism or biliary pathways. In particular, care was taken in order to avoid precipitating complications of cirrhosis due to overzealous use of drugs such as vigorous treatment of ascites with diuretics that might result in electrolyte abnormalities or hypovolemia. Similarly, sedatives even in modest doses were not used in the patients; so that encephalopathy observed in some patients studied herein, could not be attributed to such a use.

5. Conclusions

In conclusion, in patients suffering from severe liver cirrhosis and ascites, portopulmonary shunt, intrapulmonary shunt and V_A/Q inequality may induce a decrease in PaO_2 and SaO_2 in association with various acid-base disturbances. As a result, pulmonary resistance is impaired and patients more likely succumb to infections and adult respiratory distress syndrome. Thus, prognosis in those patients is poor on the basis of both hepatic and pulmonary disease.

Conflict of interest

The authors have declared that no conflict of interest exists.

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