Pulmonary changes in liver transplant candidates with Hepatitis C Cirrhosis

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ABSTRACT

Objectives: Several studies have shown that pulmonary abnormalities are common in patients with end-stage liver disease. However, most of these studies were conducted on patients with heterogeneous etiologies. Therefore, we studied these changes in a homogenous group of hepatitis C cirrhotic patients who were potential candidates for liver transplantation.

Methods: The charts of 81 patients from King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia with hepatitis C cirrhosis who were evaluated for liver transplantation were reviewed. The following data was retrieved: echocardiography with micro-bubble study, arterial blood gases, and pulmonary function tests of 81 candidates and reviewed over 3 years from 1994 to 1997.

Results: The mean age was 53 (±9) years with male to female ratio of 1.4:1. Echocardiographic micro-bubble study, revealed 4 of 62 (7%) had an intrapulmonary shunt. Arterial blood gases results were pH of 7.44 (±0.4), partial arterial tension of carbon doxide of 33 mm Hg (±4), partial arterial tension of oxygen of 84 mm Hg (±12), and alveolar-arterial gradient of 30 mm Hg (±10). Eleven percent had obstructive airway disease, 17% had restrictive lung impairment, and 43% had reduced diffusion capacity. Seventy five percent of patients with reduced diffusion capacity had normal lung volumes. Various pulmonary function test abnormalities did not lead to significant differences in arterial blood gases.

Conclusion: Pulmonary changes were frequent in liver transplant candidates with hepatitis C virus cirrhosis with reduced diffusion capacity being the most. Apart from the effect of hepatopulmonary syndrome on arterial oxygenation, other pulmonary abnormalities were not significantly different.

Keywords: Hepatitis C virus, cirrhosis, hepatopulmonary syndrome, orthodeoxia.

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End-stage liver disease (ESLD) is associated with a variety of pulmonary changes. According to the degree of liver failure, patients with cirrhosis exhibit progressive abnormalities of the systemic and pulmonary hemodynamics which reflect a complex interaction between intrapulmonary and extrapulmonary factors.[1,2] This explains the frequent occurrence of arterial oxygenation and pulmonary function tests (PFT) abnormalities in ESLD. Intrapulmonary shunt (IPS) is another cause of significant arterial oxygenation abnormalities in ESLD. It occurs uncommonly in ESLD and can be diagnosed reliably by contrast trans-thoracic echocardiography.[3,4] These changes mandate careful pre-transplantation evaluation to avoid intra-operative or post-operative complications. Most of the studies that evaluated cardiopulmonary changes in chronic liver disease were conducted on a group of patients with different etiologies. Therefore, we evaluated the pulmonary changes in a homogenous cohort of liver transplant (LT) candidates with ESLD due to hepatitis C virus infection (HCV) with special

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emphasis on the prevalence and features of intra-pulmonary shunt.

Methods. ***Study population.*** King Fahad National Guard Hospital (KFNGH) is a tertiary care center in the Kingdom of Saudi Arabia where approximately 25-30 LTs are performed each year. From January 1994 to October 1997, 263 patients with ESLD were evaluated for possible LT. Of these, the study group consisted of 81 patients (31%) with advanced ESLD due to HCV. All patients had biopsy-proven liver cirrhosis consistent with HCV. All patients were anti-HCV positive using a 2nd generation enzyme linked immunosorbent assay (ELISA) test and the HCV infection was confirmed by the presence of hepatitis C ribonucleic acid. Comprehensive investigations were carried out to exclude other etiologies.

Pulmonary function tests. The majority of patients had pulmonary function tests (Jaeger Master lab, Germany) that included spirometry, lung volumes by either body box or helium dilution methods, and diffusion capacity. Spirometric values were calculated from the best of at least 3 trials as recommended by the American Thoracic Society criteria.[5] All PFT values were reported as a percentage of the predicted values. Forced expiratory volume in 1 second (FEV1) to forced expiratory capacity (FVC) ratio of less than 70% was considered an obstructive impairment and total lung capacity (TLC) of less than 80% of predicted was considered a restrictive lung impairment.[6] A reduced lung diffusion capacity (DLco) of less than 80% of predicted was considered abnormal when corrected DLco to alveolar volume was less than predicted.[6]

Arterial blood gases. Sixty-seven arterial blood gases (ABG) were performed on room air. The Alveolar-arterial oxygen gradient (A–a) PO_2, was calculated by the simplified version of the alveolar air equation.[6] Partial arterial tension of oxygen (PAO_2)=149-partial arterial tension of carbon dioxide ($PaCO_2$)/0.8 The (A–a) PO_2 was then obtained by calculating the difference between calculated PAO_2 and measured PaO_2. Orthodeoxia was defined as drop in PaO_2 by 10% upon standing up from lying position.[4]

Echocardiographic measurements. As part of the LT work up, all patients had a contrast trans-thoracic echocardiography (TTE) with micro-bubble study to assess cardiac structure and function and to exclude the presence of shunt. All the echocardiographs were carried out by one operator. Micro-bubble study was performed by injecting 10ml of agitated normal saline through a large peripheral vein. A micro-bubble study was considered positive for intra-pulmonary shunting if the contrast appeared in the left atrium within 4 to 6 cycles after injection.[7]

Statistical test. Numbers were expressed as mean ± standard deviation. The Mann-Whitney test was used to compare distribution of continuous variables across 2 groups. Whenever there was data in the 2x2 table, chi square test was used.

Results. Of 263 patients evaluated for LT, 81 (31%) had ESLD due to HCV (Study group). The mean age was 53 years (± 8.7). There were 47 males and 34 female with a male to female ratio of 1.4:1. Of 62 patients whom had micro-bubble study, 4 patients (7%) had intrapulmonary shunt and one (2%) had a patent foramen ovale.

Sixty seven patients (83%) had ABG measurements and they were as follows: pH of 7.44 (± 0.04), $PaCO_2$ of 32.8 mm Hg (± 4.1), $PaCO_2$ of 83.6 (± 11.8), HCO_3 of 22.4 (± 10.6), and (A–a) PO_2 of 30 (±10.0). These findings reflect a state of chronic respiratory alkalosis secondary to hyperventilation and arterial oxygenation abnormalities manifested by high (A-a) PO_2 despite normal PaO_2. Patients with IPS showed the following ABGs findings: pH of 7.40 (± 0.05), $PaCO_2$ of 33.5 mm Hg (± 3.7), PaO_2 of 59.3 (± 14.3), HCO_3 of 21.7 (± 3.5), and (A–a) PO_2 of 47 (± 5.8). These findings were remarkable for chronic respiratory alkalosis secondary to hyperventilation and significant hypoxemia. Three of 4 patients with IPS had supine and standing ABGs of which 2 had typical finding of orthodeoxia. Table 1 shows pulmonary function test characteristics of 64 LT candidates. Restrictive impairment was found in 11 (17%). Obstructive impairment was found on 7 (11%), 4 of them had a history of smoking and chronic bronchitis. Of the 37 patients who had DLco measurements, 16 (43%) had reduced DLco. In the majority (75%) of those patients with reduced DLco, the lung volumes were normal, Table 2 shows that the ABGs findings in patients with different PFT patterns were not significantly different.

Table 1 - Pulmonary function test results of 64 liver transplant candidates.

Tests	n	%	± SD
Forced expiratory volume in 1 sec	64	(92)	± 21.4
Forced expiratory capacity	64	(88)	± 19.3
Forced expiratory volume in 1 sec/ Forced expiratory capacity	64	(86)	± 10.1
Residual volume	63	(99)	± 27.6
Total lung capacity	63	(89)	± 13.3
Diffusion capacity	37	(80)	± 23.7
n=number, SD=standard deviation, sec=second			

Table 2 - Arterial blood gases and pulmonary function tests abnormalities in liver transplant candidates with different pulmonary function impairments.

ABG and PFT	Restrictive impairment n=11	Obstructive impairment n=7	Reduced diffusion capacity n=16*
pH	7.45(+0.03)	7.43(+0.03)	7.43(+0.04)
$PaCO_2$(mm Hg)	32.3(+4.65)	32.2(+3.48)	31.7(+4.9)
PaO_2(mm Hg)	83.8(+7.8)	78.8(+6.5)	83.7(+11.5)
HCO_3(mEq/L)	22.1(+3.2)	22.0(+2.73)	21.3(2.8)
(A-a) PO2(mm Hg)	23.60(+8.6)	28.8(+8.7)	27.3(+10.8)
FEV_1/FVC ratio	85.4(+8.8)	67.25(+7.6)	86.3(+9.4)
TLC (%) predicted)	69.45(+9.00)	89.25(+9.9)	83.1(+14.5)

ABG=arterial blood gases, PFT=pulmonary function test, *=36 patients had DLco measured, $PaCo_2$=partial arterial tension of carbon dioxide, PaO_2=partial arterial tension of oxygen, HCO_3=serum bicarbonate, FEV1=forced expiratory volume in one second, FVC=forced expiratory capacity, TLC=total lung capacity

Discussion. The majority of the previous studies which evaluated pulmonary changes in ESLD included patients with different etiologies. In the Kingdom of Saudi Arabia, viral hepatitis is the major etiology of cirrhosis and is the leading indication for LT, this is in contrast to the data from the western countries where ethanol abuse is a major etiology.[8,9] Hepatitis C Virus was identified as an important etiology for cirrhosis in the last decade and has been associated with a variety of extra-hepatic conditions like essential mixed cryoglobulinemia, porphyria cutanea tarda, and various types of glomerulonephritis.[10,11]

Hepatopulmonary syndrome (HPS) is defined as the triad of liver dysfunction, an increase in (A-a) gradient while breathing room air, and evidence of intrapulmonary shunt. The pulmonary features of HPS include digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia.[4] It occurs in 13%-47% of LT candidates regardless of the etiology.[12] The prevalence of HPS in our study was 7% which is lower than what has been reported in the literature and may suggest that the prevalence of this complication is lower in patients with HCV. Hepatopulmonary syndrome is considered, per se, an indication for LT as it is the only available curative treatment for HPS.[4]

Pulmonary changes have been attributed to intrapulmonary arteriovenous communication, diffusion-perfusion defects, and ventilation-perfusion inequality.[1,9,10] Although measured arterial oxygen saturation PaO_2 appears normal in the majority of these patients, such values may mask hypoxemia as a result of compensatory increase in cardiac output and minute ventilation.[13-15] Pre-transplantation pulmonary function tests also show various physiological abnormalities with reduced DLco being the most prominent.[15]

Pulmonary function abnormalities in our study were compatible with the findings by Hourani and colleagues.[15] Reduced DLco was the most frequent PFT abnormality in our patients, a finding that reflects the presence of perfusion-diffusion defects.[1] Blood gases of patients with HCV cirrhosis showed chronic respiratory alkalosis and increased (A-a) gradient hypoxemia which are attributed to a "functional lung impairment". These changes in blood gases are usually reversible within 2-3 months after LT.[16] Moreover, the degree in arterial oxygenation abnormalities and pulmonary function changes will not probably affect the decision for transplantation.

In conclusion, pulmonary changes were frequent in LT candidates with HCV cirrhosis with reduced diffusion capacity being the most. Apart from the effect of HPS on arterial oxygenation, other pulmonary abnormalities were not significantly different.

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