INTRODUCTION

Liver transplant is a successful treatment for patients with acute liver failure and end-stage liver cirrhosis, but the procedure carries with it risks for morbidity and mortality. Postoperative pulmonary complications contribute to the morbidity and mortality in liver transplant recipients; however, the risk factors related with these complications have not been completely defined ***(Savas et al., 2008).***

Low-level exposures to environmental toxins may partially explain the increasing problem of liver disease in U.S. adults. Among the chemicals studied were lead, mercury, and organochlorine pesticides and, so from this list, we found several chemicals associated with a dose-dependent increased risk for abnormal liver enzymes ***(Doheny, 2009).***

Increased consumption of fatty foods, addiction to alcohol, tobacco and qat, besides lack of cleanliness and poor hygiene in our daily life are other factors that contribute to the spread of liver diseases ***(Siraj, 2010).***

Cigarette smoking is associated with a higher risk for developing vascular complications, especially arterial complications after liver transplantation. Cigarette smoking cessation at least 2 years before liver transplantation can significantly reduce the risk for vascular complications. Cigarette smoking cessation should be an essential requirement for liver transplantation candidates to decrease the morbidity arising from vascular complication after liver transplantation ***(Pungpapong et al., 2002).***

Pulmonary complications, particularly pleural effusion and atelectasis, have a significant effect on mortality and morbidity of patients following orthotopic liver transplant. In addition, by prolonging the length of stay in the hospital and in the intensive care unit as well as the duration of intubation, higher hospital costs result. Patients at risk of pulmonary complications such as smokers, those with prolonged duration of hospitalization, and positive results on deep tracheal aspirate culture should be followed closely after surgery. Invasive and noninvasive diagnostic methods should be used early; pulmonary function test results and arterial blood gas results should not be the sole preoperative criteria for determining risk for undergoing liver transplant. To decrease pulmonary complications after surgery, liver transplant should be planned before multisystem involvement is seen ***(Savas et al., 2008).***

Although the incidence of pneumonia in liver recipients was relatively low, the mortality rate in patients who developed this complication was high. High-risk patients undergoing liver transplantation thus require early diagnosis and intensive treatment to diminish the morbidity and mortality associated with pulmonary complications ***(Hong et al., 2006).***

AIM OF THE WORK

This work aims to:

1- Determine enviromental risk factors associated with pulmonary complications in liver transplant patients.

2- Identify the relationship between mortality and exposure to risk factors.

3- Find any dose-response relationship between exposure to risk factors and occurance of pulmonary complications.

4- Early detection of pulmonary complications in patients exposed toenviromental risk factors for further intervention.

HEPATOPULMONARY SYNDROME

Definitions:

Rodriguez-Roisin defined Hepatopulmonary syndrome (HPS) as the triad of advanced liver disease, hypoxemia (PaO_2 < 70mmHg or increased alveolar-arterial oxygen gradient > 20mmHg) while breathing room air (at an inspired oxygen fraction of 0.21), and evidence of intrapulmonary vascular dilatations (IPVDs) resulting in an excess perfusion for a given state of ventilation irrespective of the presence or absence of cardiopulmonary disease, and the absence of arterial CO_2 retention ***(Rodrı´guez-Roisin et al., 2004).***

While ***Tzovaras*** and his colleagues defined HPS as a widened age-corrected alveolar-arterial oxygen gradient at room air with or without hypoxemia that occurs because of intrapulmonary vasodilatation in the presence of hepatic dysfunction or portal hypertension ***(Tzovaras et al., 2006).***

The vascular component characteristically includes diffuse or localized dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications. Overall, HPS encompasses a clinical triad characterized by arterial deoxygenation, IPVD, and liver disorder ***(Lucey et al., 1997).***

This syndrome is frequently underdiagnosed, due to the fact that most of the affected patients are either asymptomatic or present vague complaints of dyspnea and fatigue ***(Mandell, 2004).***

Pulmonary physiology:

Pulmonary vascular endothelium:

The lungs contain the largest expanse of endothelium in the body. This lining of the pulmonary circulation is engaged in a variety of vital functions (Table1-1). Some, such as pulmonary vasodilatation, are served by local mediators, such as nitric oxide and prostacyclin. Countering these effects are local vasoconstrictors, such as the endothelins. As noted above, other products, such as angiotensin II, exert their effects on remote functions (e.g., in the regulation of systemic blood pressure).

Table (1-1): The processing of certain vasoactive substance by the lungs

Metabolized at the luminal surface
Angiotensin I
Bradykinin
Adenine nucleotides
Uptake by endothelium and then metabolized
Serotonin
Norepinephrine
Prostaglandin E and F
Released by endothelium
Lipoprotein lipase
Heparin
Prostacycline
Kallikrein
Leukotrienes
Unaffected in traversing the lungs
Angiotensin II
Epinephrine
Dopamine
Vasopressin
Prostaglandin A
Vasoactive intestinal polypeptide
Oxytocin
The Generation of Vasoactive substances by the Lungs
Endothelins
Nitric oxide
Prostacyclin
Hyperpolarizing factor

(Fishman et al., 1998)

Pulmonary changes complicating chronic hepatocellular disease:

The etiology of abnormal lung function and ventilation in cirrhosis may be multifactorious and is often a combination of the presence of cardiac dysfunction, heavy smoking, and chronic obstructive lung disease, which is common in patients with alcoholic cirrhosis In addition, lung function and oxygenation can be affected by edema and tense ascites, which are ameliorated after diuretic treatment and paracentesis. However, independent of smoking status, patients with cirrhosis have acompromised lung function with a reduced transfer factor and ventilation/perfusion abnormalities and arterial hypoxemia is seen in 30-70% of patients with chronic liver disease, depending on the severity Various pathophysiological factors may be involved in the reduced diffusing capacity, including an abnormal ventilation/perfusion ratio (V_A/Q), the presence of arterial venous shunts, and changes in the alveolar-arterial membrane (Figure1- 1).

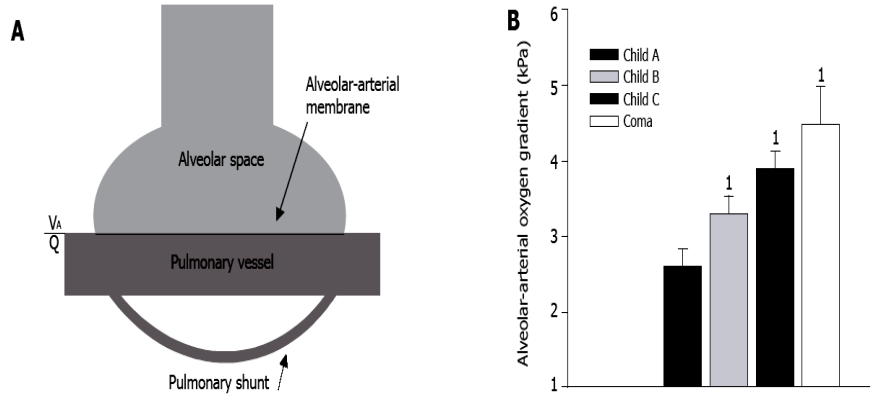

Figure (1-1): Panel A: Lung diffusion and blood oxygenation depend on the diffusion properties of the alveolar-arterial membrane, the degree of arterial-venous shunting through pulmonary shunts, and the degree of ventilation-perfusion inequality (V_A/Q). **Panel B:** The alveolar-arterial oxygen gradient increases with the severity of liver disease e.g. graduated according to the Child-Turcotte classification with the highest values in patients with hepatic coma. It denotes significant difference from Child classes A patients ***(Moller et al., 1998).***

Pulmonary changes in chronic hepatocellular disease are:

a. Hypoxia
b. Intra-pulmonary shunting
c. Ventilation-perfusion mismatch
d. Reduced transfer factor
e. Pleural effusion
f. Raised diaphragm
g. Basal atelectasis
h. Primary pulmonary hypertension
i. Portopulmonary shunting
j. Chest X-ray mottling

(Sherlock et al., 2002)

Table (1-2): Causes of Pulmonary Abnormalities in Chronic Liver Disease.

Intrinsic cardiopulmonary disease
Chronic obstructive pulmonary disease
Congestive heart failure
Pneumonia
Asthma
Specific to liver disease
Associated with specific liver diseases
Panacinar emphysema: α_1- antitrypsin deficiency
Fibrosing alveolities, pulmonary granuloms: primary biliary cirrhosis
Fluid retention complicating portal hypertension
Ascites
Hepatic hydrothorax
Pulmonary vascular abnormalities
hepatopulmonary syndrome
Portopulmonary hypertension

(Fallon and Abrams, 2000)

Ventilatory responses to hypoxia in liver cirrhosis:

Liver cirrhosis, and the accompanying portal hypertension, is often associated with striking changes in the pulmonary circulation, some of these changes appear to be diametrically opposite. Thus, on one hand the minute vessels of the lungs often show evidence of vasodilatation in the

pulmonary microcirculation (e.g., dilated arterioles and capillaries), whereas on the other hand the pulmonary microcirculation may be affected in obliterative vascular disease. Three aspects of the lung-liver relationship in liver cirrhosis have received special attention: pulmonary vasomotor control, pulmonary vasodilatation, and pulmonary hypertension ***(Mandelli et al., 1996).***

Hypoxic pulmonary vasoconstriction is blunted in patients with chronic liver disease, indicating a defect in intrinsic autonomic control. This blunting is in the face of the characteristic high-cardiac-output state that is a feature of patients with liver cirrhosis. The mechanism responsible for both the high-output state and the blunted hypoxic pulmonary pressor response is under research. Nitric Oxide is the most blamed candidate to explain the high output state associated with liver cirrhosis ***(Rydell et al., 1956).***

Mild arterial hypoxemia is found in 30 to 70 percent of patients with hepatic cirrhosis. This arterial hypoxemia is attributable to "anatomic" venous admixture i.e., to anatomic shunts or to their equivalent: the rapid passage of unoxygenated blood past the gas-exchanging surfaces of the lungs. This abbreviated transit time is, in turn, due to a combination of high cardiac output and dilation of the pulmonary precapillaries and capillaries ***(Rodriguez-Roisin et al., 1987).***

Inexplicably, the blood vessels on the pleural surface are more affected by dilatation than are the intrapulmonary vessels the *spider nevi* on the pleural surface are fed by the pulmonary circulation. They are composed of short vessels, less than 1 mm in diameter, and are generally

quite conspicuous. Although anatomic dilatation of intrapulmonary microvessels has often been seen at autopsy, as a rule such dilatation is rare compared to that on the surface of the lungs ***(Schraufnagel et al., 1996).***

Circulatory adaptations in liver cirrhosis:

Also patients with cirrhosis and portal hypertension exhibit characteristic cardiovascular changes. A vasodilatory state and a hyperdynamic circulation affecting the cardiac functions dominate the circulation. That is defined *cirrhotic cardiomyopathy* may affect systolic and diastolic functions, and imply electromechanical abnormalities. In addition, the baroreceptor function and regulation of the circulatory homoeostasis is impaired ***(Abrams et al., 1995).***

Investigations on circulatory changes and reactivity from the upright to the supine position, and vice versa, suggest that the patients are mostly hyperdynamic in the supine position ***(Bernardi et al., 1995).*** On the other hand, the pressor systems are relatively deactivated in the supine position and it is noticed that sodium-water excretion is higher in the supine position than in the upright position ***(Laffi et al., 1996).***

Dilatation of microvessels in liver cirrhosis is not confined to the lungs. Instead, it occurs throughout the body, including the skin and kidneys. In the fingers, it contributes to the rare occurrence of clubbing in patients with liver cirrhosis ***(Ring-Larsen et al., 1986).***

Haemodynamics in cirrhosis with portal hypertension:

An understanding of pulmonary haemodynamics in liver disease with portal hypertension is important to study the pulmonary vascular disorders seen in this setting. A hyperdynamic circulatory state with high cardiac output, low systemic vascular resistance, and low PVR is present in 30-50% of patients with cirrhosis . Compared with healthy subjects **(Figure 1-2)**, patients with portal hypertension have a lower median PVR value with a much wider range of PVR, extending from low levels consistent with the development of HPS to the high levels seen in portopulmonary hypertension .

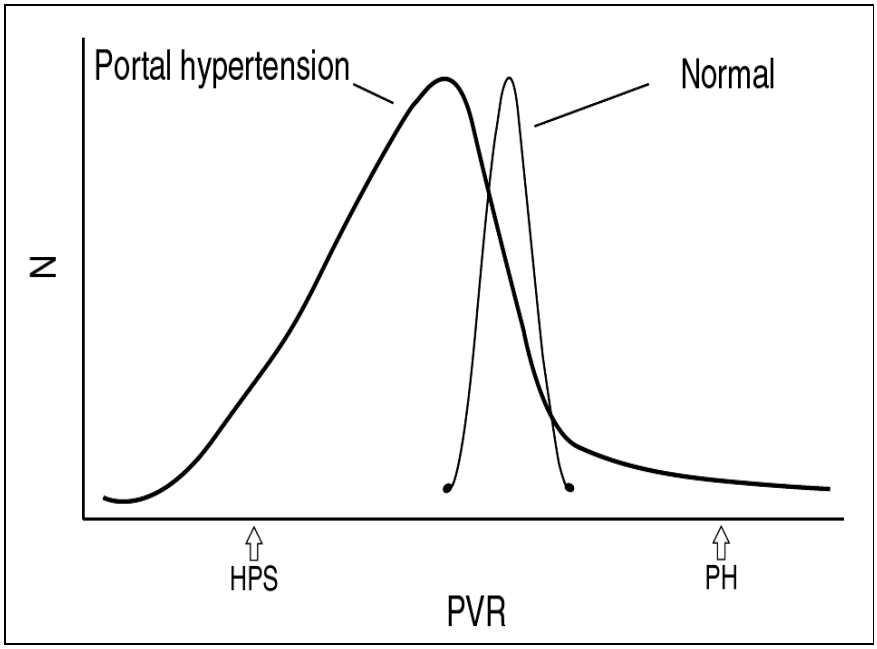

Figure (1-2): Schematic distribution of pulmonary vascular resistance (PVR) in patients with portal hypertension and in normal subjects (N). Compared with healthy subjects, patients with portal hypertension have a lower median PVR value (arrow) with a much wider range of PVR, extending from low levels consistent with the development of hepatopulmonary syndrome (HPS) to the high levels seen in portopulmonary hypertensions ***(Herve et al., 1998).***

HPS and portopulmonary hypertension; distinctions, similarities and association:

The wide spectrum of pulmonary vascular disorders in liver disease and portal hypertension ranges from the hepatopulmonary syndrome characterized by intrapulmonary vascular dilatations, to pulmonary hypertension (portopulmonary hypertension), in which pulmonary vascular resistance is elevated. Portopulmonary hypertension and HPS are characterized by distinct pulmonary microvascular

remodeling, which occurs at different anatomical sites of the pulmonary microcirculation ***(Chávez-Tapia et al., 2007).***

HPS and POPH are unique pulmonary vascular complications of liver disease and/or portal hypertension that may cause significant morbidity and influence survival and liver transplantation candidacy. HPS occurs in approximately 20% and POPH occurs in approximately 6% of patients with cirrhosis being evaluated for liver transplantation ***(Chávez-Tapia et al., 2007).***

Since hepatopulmonary syndrome and portopulmonary hypertension have been reported in patients with nonhepatic portal hypertension, the common factor that determines their development must be portal hypertension. The pathogenesis of pulmonary vascular abnormalities in HPS and POPH is an area of ongoing investigation, and similar mechanisms may play a role in each syndrome. Dilatation in pulmonary microvasculature is an important event that leads to hypoxemia and symptoms in HPS. Vasoconstriction in resistance vessels occur in portopulmonary hypertension and may lead to right-sided cardiac dysfunction as shown in **figure (1-3).**

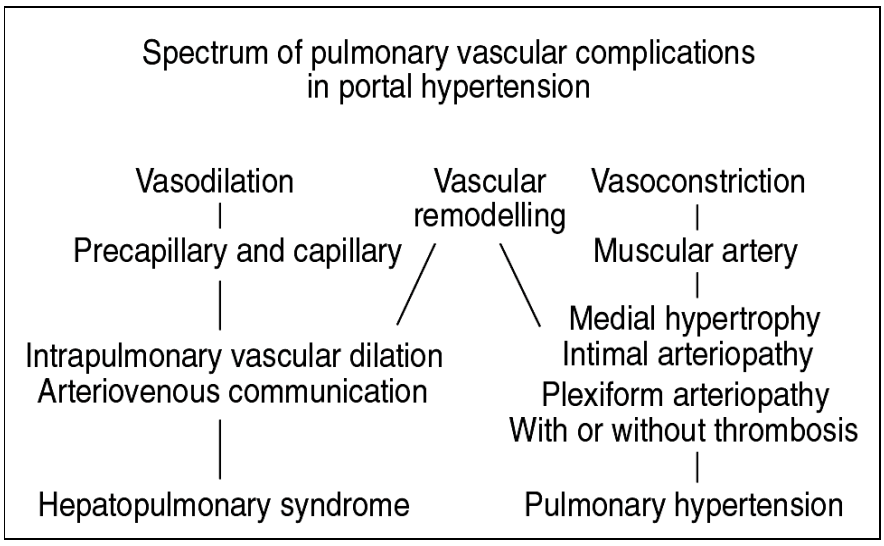

Figure (1-3): Schema of the spectrum of vascular disorders in portal hypertension *(Herve et al., 1998).*

The clinical presentations are very different, with gas exchange impairment in the hepatopulmonary syndrome and haemodynamic failure in portopulmonary hypertension. The severity of hepatopulmonary syndrome seems to parallel the severity of liver failure, whereas no simple relationship has been identified between hepatic impairment and the severity of portopulmonary hypertension ***(Herve et al., 1998).***

There are no effective medical therapies for HPS, but liver transplantation can reverse the syndrome in most patients. In contrast, there are symptomatic medical therapies for POPH, but for many patients liver transplantation is contraindicated or controversial. Transplantation carries increased mortality in both severe HPS and POPH.

Table (1-3) summarizes the differences and similarities between HPS and portopulmonary hypertension ***(Krowka, 1997).***