THE RELATIONSHIP BETWEEN SEVERITY OF LIVER CIRRHOSIS AND PULMONARY FUNCTION TESTS

Thesis

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(ويسألونك عن الروح قل الروح من أمر ربي وما أوتيتم من العلم إلا قليلا)

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Abstract

Liver cirrhosis is a progressive disease that involves inflammation and fibrosis. Pulmonary complications include hypoxemia, hepatopulmonary syndrome and portopulmonary hypertension. The aim is to investigate impairment in PFT and hypoxemia to determine relation to severity of liver cirrhosis. **Methods**: 100 patients with liver cirrhosis aged from 18years to 60years. Not smokers or have cardiac diseases or any pulmonary problem. Patients subjected to history taking, clinical examination, chest X-ray, Complete Blood picture, Fasting Blood Glucose, Liver Profile, hepatitis markers for B and C virus, Abdominal U/S, and Pulmonary function tests (Arterial Blood Gases and Spirometry). **Results:** the study revealed that 30% of the patients had hypoxia which more common in child C and patients with ascites. Restrictive Pulmonary function present in 46% of the patients and more common in patients with ascites.

Conclusion: patients suffering from severe liver cirrhosis and ascites, presented with reduction in PaO_2 and SaO_2 in association with restrictive pulmonary function pattern (up to 88.2% of patients with massive ascites). As a result, pulmonary resistance is impaired and patients are more likely succumb to infection and adult respiratory distress syndrome. Thus prognosis in those patients is poor on the basis of both hepatic and pulmonary disease.

Keywords: Liver cirrhosis. Hypoxia. Pulmonary function tests.

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Contents

List of abbreviations

ABG: Arterial blood gases
ANA: Antinuclear antibodies
ANCA: Antineutrophil cytoplasmic antibodies
COX: Cyclooxygenase
ECM: Extracellular matrix
ET: Endothelin
FVC: Forced vital capacity
FEV1: Forced expiratory volume in first second
FEF25-75%: Forced expiratory flow at 25 to 75% Forced vital capacity
HPS: Hepatopulmonary syndrome
IPVD: Intrapulmonary vascular dilatation
MMP: Matrix metalloproteinase
MT1-MMP: Mmbran-type matrix metalloproteinase 1
NASH: Non alcoholic steatohepatitis
NO: Nitric oxide
NOS: Nitric oxide synthase
NSAID: Non steroidal anti-inflammatory drugs
PAI-1: Plasminogen activator inhibitor 1
PDGF: Platelet derived growth factor
PFT: Pulmonary function tests
POPH: Portopulmonary hypertension
PVR: Pulmonary vascular resistance
TGFb: Transforming growth factor b
TGFb1: Tissue growth factor b1
TIMPs: Tissue inhibitors of metalloproteinases
TIPS: Trans jugular intrahepatic Porto systemic shunt
TPO: Thrombopoietin
UPA: Uroplasminogen activator

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INTRODUCTION

Liver cirrhosis is slowly progressive disease, causing irreversible scarring and nodularity of the liver in response to chronic injury from a variety of causes**(Rimola A, et al.,2000)**. This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupt the biochemical functions of the liver **(Mathews RE, et al., 2006).**

Patients with cirrhosis develop complication affecting multiple organs including the lung, the heart and the kidney (**La villa G, et al., 2001).** Pulmonary complications such as hepatopulmonary syndrome and Porto pulmonary hypertension are observed frequently in cirrhotic patients **(Memik F, et al., 2005).**

varying degrees of pulmonary findings including dyspnea , cyanosis, clubbing, Platypnea due to dilatations in the intrapulmonary vasculature and hypoxemia are seen in patients with hepatopulmonary syndrome**(Lima BLG, et al., 2004).**

Patients with cirrhosis have a compromised lung function with a reduced transfer factor and ventilation / perfusion abnormalities and arterial hypoxia is seen in 30% - 70% of patient with chronic liver disease, depending on the severity **(Fallon MB., 2005)**. 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(**Martinez G, et al ., 2001**).In addition, lung function and oxygenation can be affected by edema and tense ascites, which are ameliorated after treatment with diuretic and paracentesis (**Herve P, et al., 1998) .**

The aim of the study

In our study the aim is to investigate impairment in PFT and hypoxemia and to determine its relation to the severity of liver failure in patients with liver cirrhosis.

Anatomy and Physiology of The Liver

The liver is among the most complex and important organ in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver function leads to death within minutes, demonstrating the liver's importance **(Marieb EN., 2001).**

General Description of the Liver:

The liver is the largest gland in the human body, weighting approximately 3 pounds, and occupying a large region mostly on the right side of the body, below the diaphragm and behind the ribs 5 through 10.

The liver has many functions, primarily including:

- Acting as a gatekeeper between the digestive system and the circulatory system.
- Processing toxic substances before they enter general circulation.
- Storing and converting nutrients for future use.
- Synthesizing most plasma proteins.
- Secreting bile into small intestine to break down fats ***(*Marieb EN., 2001).**

Gross Anatomy:

The liver is divided into four lobes which are right, left, caudate, and quadrate. The right and left lobes are the largest, while the caudate and quadrate are smaller and located posteriorly. Two ligaments are visible anteriorly. Superiorly, the falciform ligament separates the right and left lobes. Inferior to the falciform ligament is the round ligament, which protrudes from the liver slightly. Also visible anteriorly on the most inferior portion of the right lobe is the gall bladder. The caudate lobe is located superiorly, approximately between the right and left lobes. Adjacent to the caudate lobe is the sulcus for the inferior vena cava. Just inferior to the caudate lobe is the porta hepatis, where the hepatic artery and hepatic portal vein enter the liver. The portal vein carries nutrient laden blood from the digestive system. Inferior to the porta hepatis is the bile duct which leads back to the gallbladder. Finally, the hepatic vein, where post-processed blood leaves the liver, is found inferior and adjacent to the sulcus for the inferior vena cava. The liver is held on place by a system of mesenteries posteriorly, and is also attached to the diaphragm via the falciform ligament. Additionally, most of the liver is covered by visceral peritoneum **(Heuman Dm., 1997).**

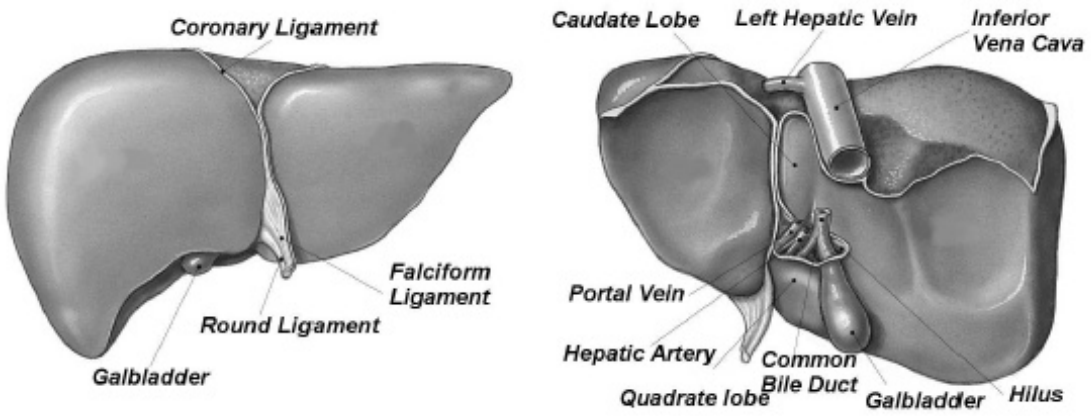

Figure (1) show anatomy of the liver. **(Heuman Dm., 1997)**

Microscopic Anatomy:

The basic functional unit of the liver is the liver lobule. A single lobule is about the size of a sesame seed and is roughly hexagonal in shape. The primary structures in a lobule include:

- Plates of hepatocytes form the bulk of the lobule
- Portal triads at each corner of hexagon
- Central vein
- Liver sinusoids that run from the central vein to the portal triads
- Hepatic macrophages (Kupffer cells)
- Bile canaliculi ("little canals") – formed between walls of adjacent hepatocytes
- Space of Disse – a small space between the sinusoids and the hepatocytes

The portal triads consist of three vessels: a hepatic portal arteriole, hepatic portal venule, and a bile duct. The blood from the arteriole and the venule both flow in the same direction through the sinusoids toward the central vein, which eventually leads to the hepatic vein and the inferior vena cava. Secreted bile flows in the opposite direction through the bile canaliculi away from the central vein, toward the portal triad, and exiting via the bile duct. As blood flows through the sinusoids and the space of Disse toward the central vein, nutrients are processed and stored by the hepatocytes. Moreover, worn out blood cells and bacteria are engulfed by the Kupffer cells **(Stevens A, et al., 1997).**

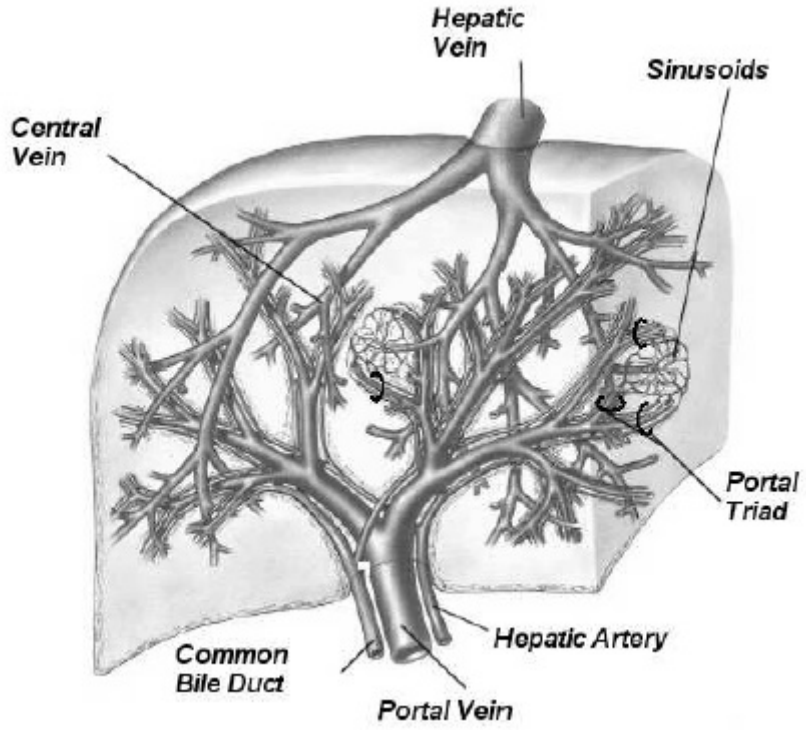

Figure (2) show the functional anatomy of hepatic lobule **(Heuman DM., 1997).**

Interrelationships with Other Organ:

The liver interacts with many other organs. Following the flow of blood, the liver receives its arterial blood supply from the hepatic arteries. The hepatic arteries are originating from abdominal aorta distal to the celiac trunk. Thus the liver receives its oxygenated blood supply from the heart. Nutrient laden blood from the digestive system and blood leaving the spleen enters the liver through the hepatic portal vein. Processed blood leaving the liver through the hepatic veins drains into the inferior vena cava, completing the connection to the heart. The liver affects digestion through its formation of bile, which is secreted into the small intestine. The gallbladder is essentially an overflow area for the liver's bile duct. The liver is full of lymph glands, which provide fluid drainage and immune system support. The liver synthesizes many blood proteins, showing its relation to that "organ". Finally, liver disease often causes

problems in the renal system, demonstrating a relationship with the kidneys. **(Marieb EN.,2001).**

Cell Types:

The liver has 5 cell types: hepatocytes, Kupffer cells, sinusoidal endothelial cells, bile duct epithelial cells, and Ito cells. Hepatocytes represent 60% of the liver's cells, and about 80% of the liver's total cell mass. Hepatocytes are arranged in plates only a single cell thick. Blood flowing toward the hepatic vein within the space of Disse passes both exposed surface areas of the hepatocyte plates. Toxins and nutrients within the blood are extracted by the hepatocytes **(Stevens A, et al.,1997).**

Kupffer cells are macrophages that reside in the sinusoids. These cells help clear out old red blood cells and bacteria. They also break down heme (the iron-containing pigment in hemoglobin) into bilirubin, which then becomes one of the chief pigments of bile. A later by-product of bilirubin gives feces its characteristic brown color. Sinusoidal endothelial cells are fenestrated (Latin for "windows"), meaning they have large pores that allow most proteins to pass freely through the sinusoidal endothelium into the space of Disse, where they can make direct contact with hepatocytes. The pores are also bi-directional, meaning that proteins created by the liver and other substances stored or processed by the liver can also be passed back into the blood. Bile duct epithelial cells line the interlobular bile ducts within the portal triads. Ito cells are found in the space of Disse. They are important because when the liver is injured, the Ito cells transform into cells that produce collagen, which leads to liver fibrosis. If this occurs on a large scale, it can lead to cirrhosis of the liver **(Lanza RP., 2000)**.