Pulmonary function assessment in patients with liver cirrhosis

Thesis

Submitted for partial fulfillment of Master Degree in Hepatology

BY

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LIST OF ABBREVIATIONS

A-aDO_2	Alveolar arterial oxygen difference
A-aPO_2	Alveolar-arterial oxygen gradient
ABG	Arterial blood gas
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Serum alanine transaminase
AST	Serum aspartate transaminase
ATS	American thoracic society
CBC	Complete blood count
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary diseases
CT	Computed tomography
CTP	Child-Turcotte-Pugh
DLCO	Diffusing capacity for carbon monoxide
ECM	Extracellula matrix
eNOS	Endothelial nitric oxide synthase
ERS	European respiratory society
FiO_2	Fraction of inspired O2
FVC	Forced vital capacity
FVC_1	Forced expiratory volume in first second
γ-GT	Gamma-glutamyl transpeptidase
GMP	Guanosine monophosphate
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HSC	Hepatic stellate cell
HPS	Hepatopulmonary syndrome
IHD	Ischemic heart disease
IPVD	Intrapulmonary vascular dilatations
IPS	Intrapulmonary shunt
L-NAME	N-nitro-L-arginine methyle ester
LT	Liver transplantation
MMA	Macro-aggregated albumin
MELD	Model for End Stage Liver Disease
NASH	Nonalcoholic steatohepatitis
NAFLD	Nonalcoholic fatty liver disease
NO	Nitric oxide

NOS	Nitric oxide synthase
OLT	Orthotopic liver transplantation
PaO_2	Arterial partial pressure of oxygen
PCO_2	Carbon dioxide tension
$PaCO_2$	Alveolar carbon dioxide
PBC	Primary biliary cirrhosis
P_B	Barometric pressure
PDGF	Platelet-derived growth factor
PFT	Pulmonary function test
PH	Power of hydrogen
POPH	Portopulmonary hypertension
SaO_2	Arterial oxygen saturation
TIPS	Transjugular intrahepatic portosystemic shunt
T_{LCO}	Carbon monoxide transfer factor
UNOS	United Net-work for Organ Sharing
VA/Q	Ventilation/Perfusion ratio
WBC	White blood cells
$\chi 2$	Chi-square test

INTRODUCTION

The association between liver disease and vascular abnormalities in the lung has been recognized for more than 100 years. However, it has been only over the last 15 years that specific pulmonary vascular alterations associated with the presence of liver disease and portal hypertension have been widely appreciated and submitted to investigation. These alterations include two distinct syndromes in the pulmonary vasculature: (1) the hepatopulmonary syndrome (HPS) characterized by dilatation in the microvasculature and (2) portopulmonary hypertension characterized by vasoconstriction and remodeling in the resistance vasculature. These entities may share pathogenetic mechanisms with systemic vascular alterations in liver disease and with each other, although each has unique clinical features and consequences ***(Fallon MB, 2005)***.

Hepatopulmonary syndrome is characterized by the triad of (1) liver disease complicated by (2) arterial hypoxemia (caused by intrapulmonary vascular dilatation) and (3) the absence of detectable primary cardiopulmonary disease ***(Krowka MJ, 2005)***.

Liver cirrhosis is sometimes associated with very severe hypoxemia which is thought to be the result of intrapulmonary vascular dilatations. These vascular dilatations occur close to the gas exchange units and thus diffusion of oxygen molecules to their center is impaired causing an increase in alveolar-arterial oxygen tension difference ***(Thorens JB, 1992)***.

Nitric oxide (No) is an important mediator of impaired oxygenation in patients with cirrhosis. Nitric oxide (No) is a vasodilatary substance which can abolish the local vasoconstrictive reflex to alveolar hypoxemia,

increasing the ventilation/perfusion mismatching which is one of the mechanisms of oxygenation abnormalities in cirrhosis ***(Termato S, 2000)***.

Hypoxemia is observed in about 30% of patient with liver cirrhosis irrespective of the cause of cirrhosis. Two main physiopathological mechanisms can be described: hypoxemia may be secondary to intrapulmonary vascular abnormalities or due to a regional disequilibrium of the ventilation/perfusion ratio ***(Cadranel J, 1989)***.

There is no consensus on the pathogenesis and incidence of diffusion disorder in chronic liver disease. It supposed that the pathogenic mechanisms responsible for the reduction of diffusion capacity in liver disease are multlfactorial including :ventilation-perfusion mismatching and reduced transitory time in hyperperfused lung area ***(Tulafi C, 2002)***.

Although low arterial oxygen tension (PO_2) has been claimed to occur in one to two thirds of patients with cirrhosis, hypoxemia appear to be rare in clinical practice ***(Moller S, 1998)***.

Aim of the study

This study aims to assess pulmonary function in patients with liver cirrhosis.

CIRRHOSIS

Definition:

Cirrhosis is a diffuse process characterized by extensive fibrosis and a conversion of normal architecture into structurally abnormal nodules (Figures 1 through A-D) ***(Serpaggi J et al., 2006***).

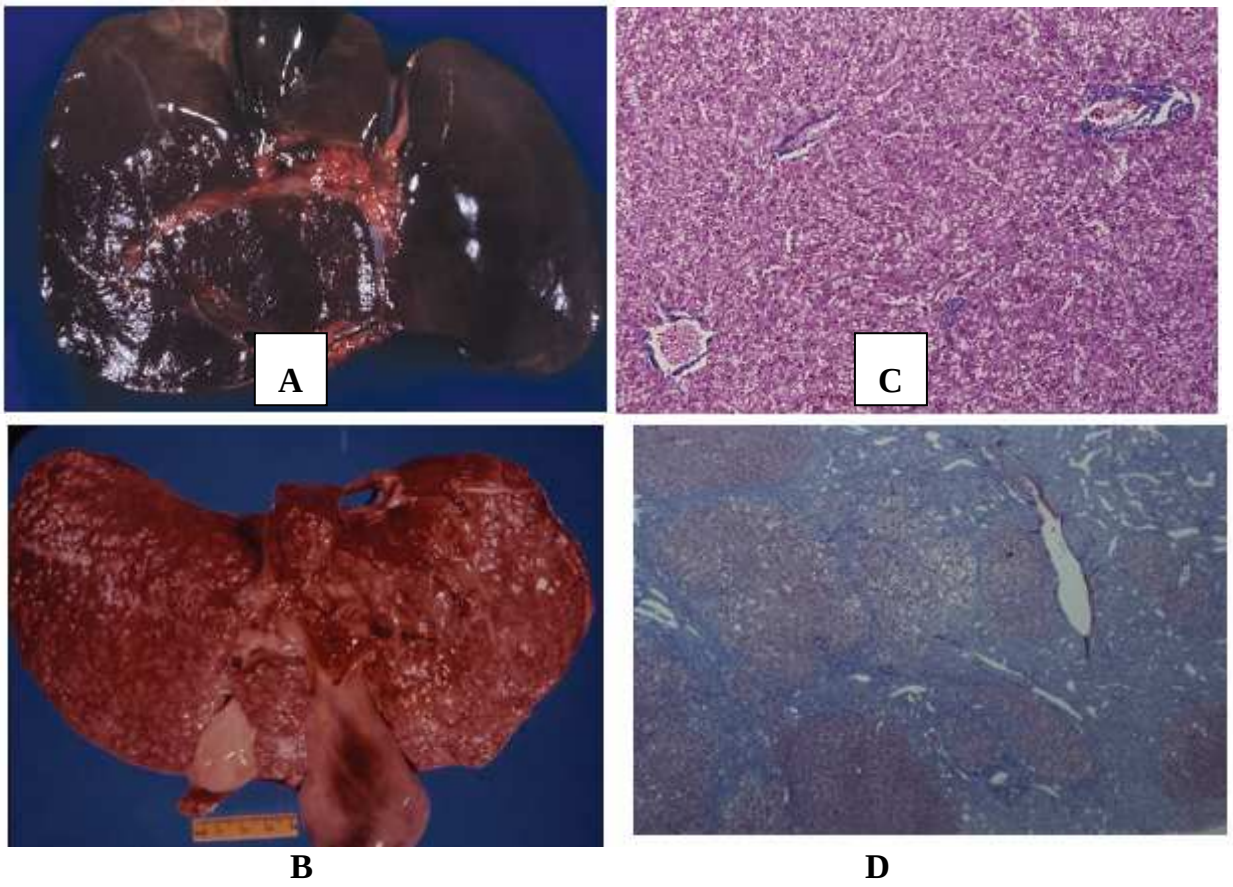


Figure I-A: Inferior surface of liver, biliary tree, and gallbladder (gross) revealing normal hepatic tissue and structure. **B:** Inferior surface of liver and gallbladder (gross) revealing cirrhotic liver. **C:** Normal hepatic tissue (microscopic, 10X, trichrome stain). **D:** Cirrhosis (microscopic, 10X, trichrome stain) ***(Michael B, 2006)***.

Epidemiology:

Cirrhosis and chronic liver failure together were the 12th most common cause of death in the United States in 2002, accounting for 27,257 deaths (9.5 per 100,000 persons), with a slight male predominance. Approximately 40 percent of patients with cirrhosis are asymptomatic, and the condition often is discovered during a routine examination with laboratory or radiographic studies, or at autopsy. In 2000, there were 360,000 U.S. hospital discharges related to cirrhosis and liver failure ***(National Center for Health Statistics, 2006)***.

According to estimates from the United Network for Organ Sharing, 75 to 80 percent of cirrhosis cases could be prevented by eliminating alcohol abuse, and approximately 3.9 million Americans have chronic hepatitis C. In August 2005, there were 17,935 persons with cirrhosis (from various etiologies) in the United States who were awaiting a liver transplant. Mortality rates in patients with alcoholic liver disease are considerably higher than in patients with other forms of cirrhosis ***(United Network for Organ Sharing, 2006)***.

The Centers for Disease Control and Prevention estimates that 75,766 deaths and 2.3 million years of potential life lost during 2001 were attributable to excessive alcohol use, an average of approximately 30 years of potential life lost for each alcohol-attributable death ***(Michael B, 2006)***.

Natural history of cirrhosis:

Cirrhosis is the end-stage of every chronic liver disease, its natural history is characterized by an asymptomatic phase, termed ‘compensated’ cirrhosis followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction termed‘ decompensated cirrhosis’ (Fig.II). In the compensated phase, portal pressure may be normal or below the threshold level identified for the development of

varices or ascites (clinically significant portal hypertension). As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy and jaundice. The development of any of these complications marks the transition from a compensated to decompensated phase. Progression may be accelerated by the development of other complications such as rebleeding, renal impairment, refractory ascites, hepatorenal syndrome, hepatopulmonary syndrome and sepsis (spontaneous bacterial peritonitis).The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage ***(D'Amico G et al., 2006)***.

Once the diagnosis has been established, up to 30% of patients die within a year from hepatic failure or complications of portal hypertension, of which bleeding esophageal varices is the most feared. In newly diagnosed cirrhotics, the chances of dying within the subsequent 2–3 years are influenced by the status of liver function (as reflected by the Child-Pugh classification), the presence of varices, and the portal pressure ***(William R , 2007)***.

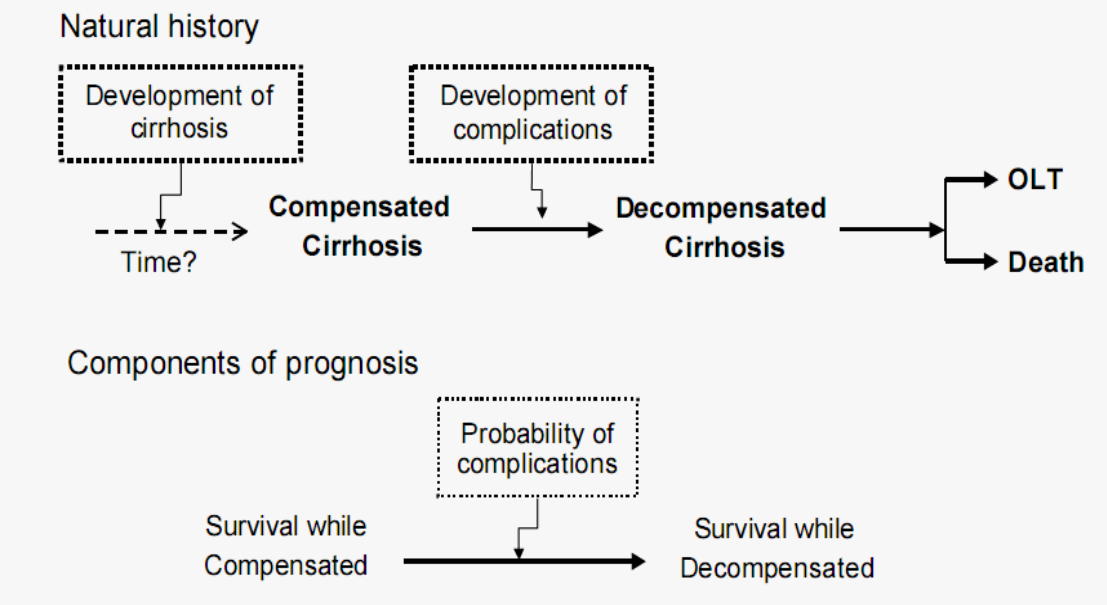


Figure II: the natural history of cirrhosis and component of prognosis ***(D'Amico G et al., 2006)***.

Pathogenesis of Cirrhosis:

Three major mechanisms are central to the onset of cirrhosis: cell death, extracellular matrix (ECM) deposition, and vascular modifications ***(Wanless IR, 2004)***.

The fibrotic process is characterized by both quantitative and qualitative changes in the composition of the hepatic ECM with excessive deposition of collagen, in particular, in the portal tracts and the replacement of low-density type IV collagen with high-density types I and III collagen in the space of Disse, causing sinusoidal capillarization. The morphogenesis of cirrhosis is related to the underlying disease and reflects the topographic distribution of the liver damage and the contribution of different cells involved in the fibrogenic process ***(Pinzani M, 2004)***.

Regardless of the cause, sinusoidal capillarization is an early event with remarkable effects on the metabolic exchanges between hepatocytes and blood circulation. Further impairment in liver function stems from the formation of novel intrahepatic vessels, via porto-portal and porto-central collaterals, that shunt the blood away from the hepatocytes. Fully developed cirrhosis has diverse morphological features, with more or less numerous, slender or broad septa and parenchymal nodules of varying sizes and shapes. It has been suggested that the severity of cirrhosis be classified according to the characteristics of the septa ***(Kutami R et al., 2000)***.

Recently, a combination of nodule size and septal thickness has been proposed for staging the severity of portal hypertension. Basing the severity of cirrhosis on histological criteria may help us to predict its potential for reversal ***(Nagula S et al., 2006)***.

The anatomic classification distinguishes between micronodular cirrhosis, (typically associated with alcohol abuse and characterized by small uniform nodules a few millimeters in size), macronodular cirrhosis (with large

bulging nodules of varying sizes) and mixed cirrhosis (typical of primary biliary cirrhosis and primary sclerosing cholangitis). Most cases of advanced cirrhosis acquire a mixed pattern, however because of the ongoing regenerative and fibrogenic process. Incomplete septal cirrhosis, characterized by slender fibrous septa that do not connect portal tracts to portal tracts and/or central veins, is regarded as a histological feature of regression of cirrhosis ***(Bortolotti F, 2007)***.

Fibrogenic cells of the liver :

Accumulating data clearly indicate that matrix accumulation originates from different types of smooth muscle alpha-actin myofibroblastic cells deriving from distinct cell populations known as activating stellate cells and hepatic myofibroblasts ***(Cassiman D, 2002)***.

In normal liver, hepatic stellate cells composed 5% - 10% of cells and are located in the subendothelial space between hepatocytes and sinusoidal endothelial cells. Following acute or chronic liver disease, they undergo phenotypic changes, switching from a quiescent vitamin A rich phenotype to myofibroblastic phenotype referred as activated hepatic stellate cell (HSC) ***(Geerts A, 2001)***.

Activated hepatic stellate cell (HSC) show de novo fibrogenic properties including proliferation and accumulation in areas of parenchymal cell necrosis, secretion of proinflammatory cytokines and chemokines and synthesis of a large panel of matrix proteins and of inhibitors of matrix degradation leading to progressive scar formation ***(Lotersztajn S, 2005)***.

Hepatic fibroblast are another source of fibrogenic cells that derive from fibroblast of portal connective tissue, perivasclular fibroblast of portal and central veins, and periductular fibroblast in close contact with bile duct epithelial cells. Activated HSCs migrate and accumulate at the sites of tissue repair, secreting large amounts of (extracellular matrix) ECM and regulating

ECM degradation. Platelet-derived growth factor (PDGF), mainly produced by Kupffer cells, is the predominant mitogen for activated HSCs. Collagen synthesis in HSCs is regulated at the transcriptional and posttranscriptional levels (fig. III through IV) ***(Bataller R, 2005)***.

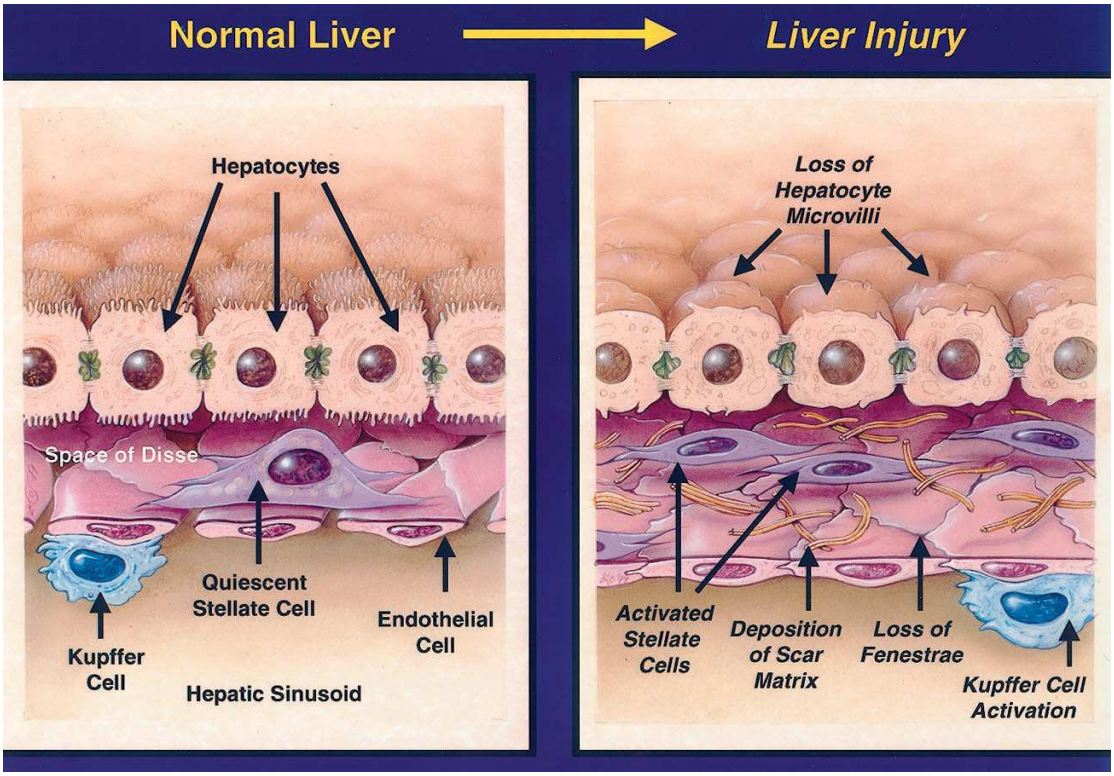


Figure III: Sinusoidal events during fibrosing liver injury. Changes in the subendothelial space of Disse and sinusoid as fibrosis develops in response to liver injury include alterations in both cellular responses and extracellular matrix composition. Stellate cell activation leads to accumulation of scar (fibril-forming) matrix. This in turn contributes to the loss of hepatocyte microvilli and sinusoidal endothelial fenestrae, which result in deterioration of hepatic function. Kupffer cell (macrophage) activation accompanies liver injury and contributes to paracrine activation of stellate cells ***(Friedman SL, 2000)***.

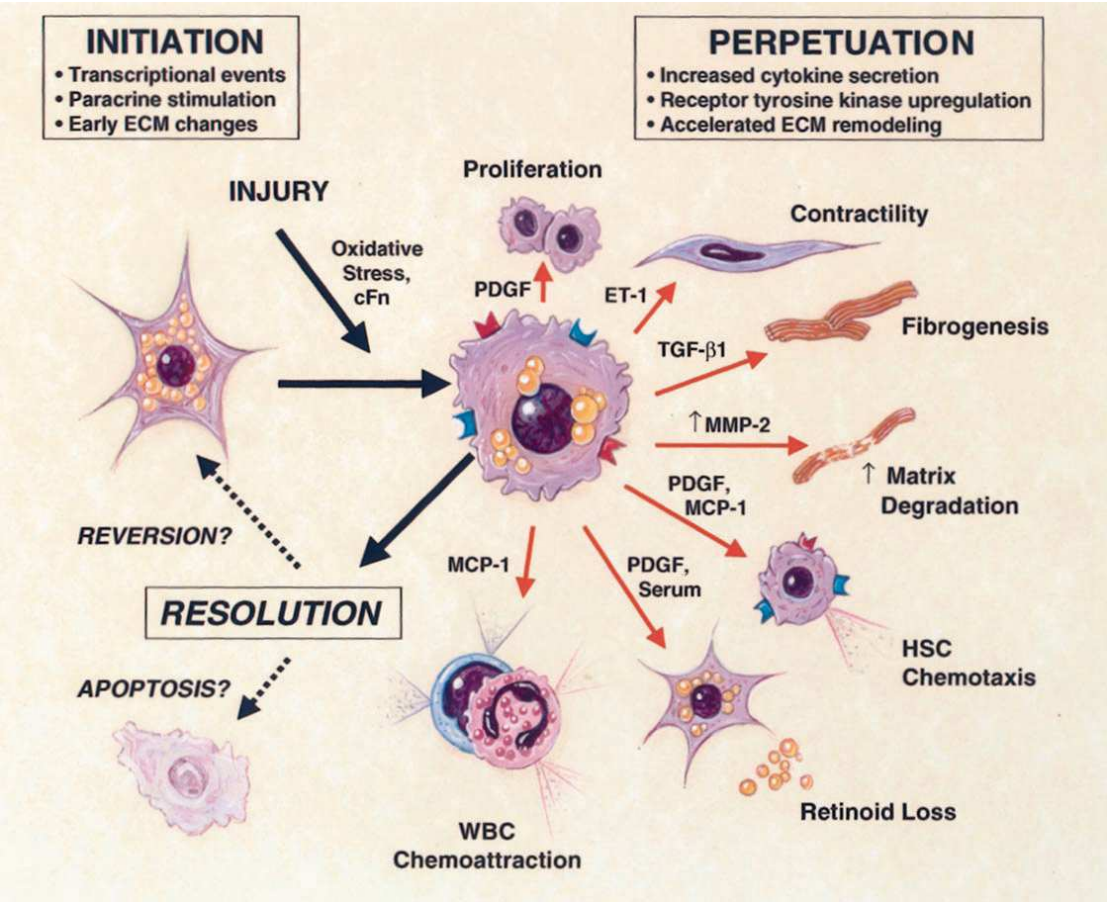


Figure IV: Phenotypic features of hepatic stellate cell activation during liver injury and resolution. Following liver injury, hepatic stellate cells (HSC) undergo "activation," which connotes a transition from quiescent vitamin A-rich cells into proliferative, fibrogenic, and contractile myofibroblasts. The major phenotypic changes after activation include proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, and white blood cell (WBC) chemoattraction. Key mediators underlying these effects are shown. The fate of activated stellate cells during resolution of liver injury is uncertain but may include reversion to a quiescent phenotype and/or selective clearance by apoptosis ***(Friedman SL, 2000)***.

Is liver cirrhosis reversible?

In contrast with the traditional view that cirrhosis is an irreversible disease, ***(Arther MJ, 2002)*** indicates that even advanced fibrosis is reversible although ***(Kumar M, 2007)*** said that depending on its duration, fibrosis may be irreversible**.**

In experimentally induced fibrosis, cessation of liver injury results in fibrosis regression ***(Issa R et al., 2004)***.

In humans, spontaneous resolution of liver fibrosis can occur after successful treatment of the underlying disease. This observation has been described in patients with nonalcoholic steatohepatitis (NASH) after weight loss ***(Dixon JB, 2004),*** iron and copper overload, alcohol-induced liver injury, chronic hepatitis C, B, and D, hemochromatosis, secondary biliary cirrhosis, and autoimmune hepatitis ***(Kumar M, 2007)***.

It may take years for significant regression to be achieved; the time varies depending on the underlying cause of the liver disease and its severity. Chronic HCV infection is the most extensively studied condition, and therapy (IFN-α plus ribavirin) with viral clearance results in fibrosis improvement ***(Bataller R, 2005)***.

Importantly, nearly half of patients with cirrhosis exhibit reversal to a significant degree but not completely ***(Cho JJ et al., 2000)***.

Whether this beneficial effect is associated with improvements in long-term clinical outcome, including decreased portal hypertension, is unknown ***(Bataller R, 2005)***.

Recently, regression of fibrosis and cirrhosis (Table1) has been documented in the entire spectrum of chronic liver diseases (ie, in autoimmune hepatitis and primary biliary cirrhosis after effective immunosuppressive therapy, in biliary obstruction after surgical decompression, in thalassemia after iron depletion, in hepatitis B after lamivudine therapy, and in hepatitis D during long-term follow-up after IFN treatment) ***(Bansal MB, 2006)*** and ***(Bortolotti F, 2007)***.

Table I: Cirrhosis reversal in relation to cause and treatment: data published in the past decade ***(Bortolotti F, 2007)***.

Study	Cause	Treatment	Reversal (n)
Dufour et al (12)	Autoimmune	Steroids+ azathioprin	8
Kaplan et al (14)	PBC	Methotrexate	3
Cotler et al (16)	HDV	IFN	1
Muretto et al (17)	Thalassemia	Bone marrow transplant	6
Kweon et al (18)	HBV	IFN	5
Lau et al (19)	Autoimmune	Steroids	1
Farci et al (20)	HDV	IFN	4
Poynard et al (122)	HCV	IFN+ribavirin	75*****
Pol et al (23)	HCV	IFN+ribavirin	7
Bortolotti et al(50)	HBV^	None	2

PBC; primary biliary cirrhosis; HDV, hepatitis D virus; HBV, Hepatitis B virus; HCV, hepatitis C virus. *Normal liver in 3 cases. ^Acquired in childhood .

Etiologies: *(Michael B, 2006),* *(Ronnie EM et al., 2006)* and *(Strickland GT, 2006)*

Table II

Etiologies of Hepatic Cirrhosis

Most common causes:

In Egypt:

- Chronic hepatitis C virus (70%-80%)
- Schistosomiasis
- Chronic hepatitis B virus (2%)
- Others

In the world:

- Alcohol (60 to 70 percent)
- Biliary obstruction (5 to 10 percent)
- Biliary atresia / neonatal hepatitis
- Congenital biliary cysts
- Cystic fibrosis
- Primary or secondary biliary cirrhosis
- Chronic hepatitis B or C (10 percent)
- Hemochromatosis (5 to 10 percent)
- NAFLD (10 %), most commonly result from obesity, also can occur after jejunoileal bypass.

Less common causes:

Autoimmune chronic hepatitis types 1, 2, and 3

Drugs and toxins

- Alpha-methyldopa (Aldomet)
- Amiodarone (Cordarone)
- Isoniazid (INH)
- Methotrexate
- Oxyphenisatin (Prulet)
- Perhexiline
- Troglitazone (Rezulin)
- Vitamin A

enetic metabolic disease

- alpha 1 -Antitrypsin deficiency
- Amino acid disorders (e.g., tyrosinemia)
- Bile acid disorders

- Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)
- Lipid disorders (e.g., abetalipoproteinemia)
- Porphyria
- Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency)
- Wilson's disease

Idiopathic/miscellaneous

- Granulomatous liver disease (e.g., sarcoidosis)
- Idiopathic portal fibrosis
- Indian childhood cirrhosis
- Polycystic liver disease

Infection

- Brucellosis
- Congenital or tertiary syphilis
- Echinococcosis
- Schistosomiasis

Vascular abnormalities

- Chronic passive hepatic congestion caused by right-sided heart failure and pericarditis
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
- Veno-occlusive disease
- Budd-chiari syndrome

Clinical Presentation:

HISTORY:

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis . Quantity and duration of alcohol consumption is an important factor in the early diagnosis of cirrhosis. Other risk factors include those for hepatitis B and C transmission (e.g., birth place in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases ***(Schiano T, 2004)***.

Early and well-compensated cirrhosis can manifest as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding from portal hypertension ***(Heidelbaugh JJ, 2006)***.

Clinical symptoms at presentation may include jaundice, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Each of these clinical findings is the result of impaired hepatocellular function with or without physical obstruction secondary to cirrhosis. Because hepatic enzyme synthesis is required for drug metabolism, heightened sensitivity and medication toxicity may occur in patients with impaired hepatic enzyme synthesis ***(Michael B, 2006)***.

Physical examination:

Physical examination of patients with cirrhosis may reveal a variety of findings that should lead to a targeted hepatic- or gastrointestinal-based work-up (Table III)(Fig. V) ***(Lidofsky SD, 2002)***.

Table III

Common Physical Examination Findings in Patients with Cirrhosis

- Abdominal wall vascular collaterals (caput medusa)
- Ascites
- Asterixis
- Clubbing and hypertrophic osteoarthropathy
- Constitutional symptoms, including anorexia, fatigue, weakness, and weight loss.
- Cruveilhier-Baumgarten murmur—a venous hum in patients with portal hypertension
- Dupuytren's contracture
- Fetor hepaticus—a sweet, pungent breath odor
- Gynecomastia
- Hepatomegaly
- Jaundice
- Kayser-Fleischer ring—brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease
- Nail changes: Muehrcke's nails—paired horizontal white bands separated by normal color and Terry's nails—proximal two thirds of nail plate appears white, whereas the distal one third is red
- Palmar erythema
- Scleral icterus

- Vascular spiders (spider telangiectasias, spider angiomata)
- Splenomegaly
- Testicular atrophy

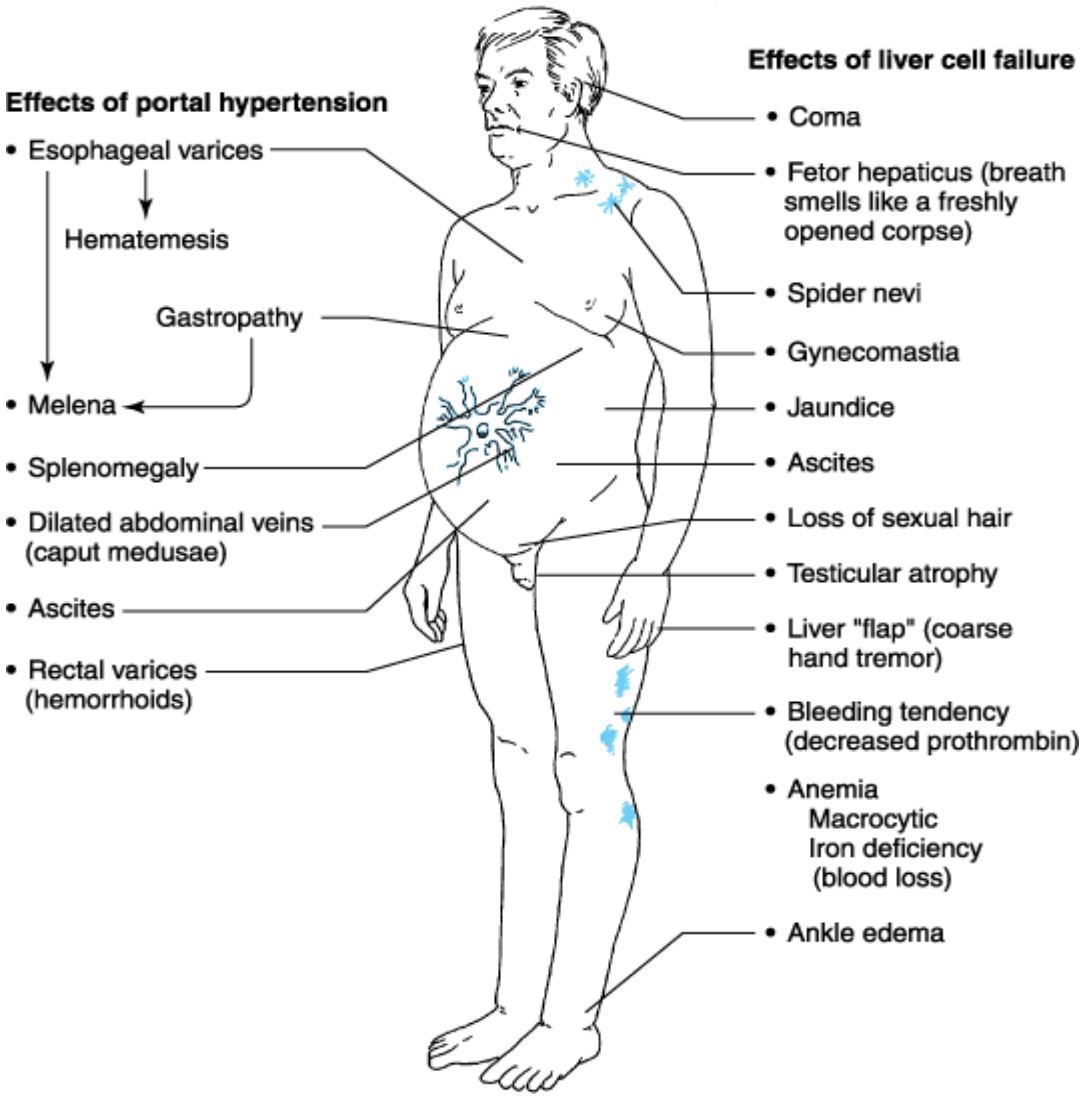


Figure V: physical signs in patient with cirrhosis.

Laboratory Evaluation:

No serologic test can diagnose cirrhosis accurately ***(Schiano T, 2004)***.

The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly ***(Lidofsky SD, 2002)***.

Although liver function tests may not correlate exactly with hepatic function, interpreting abnormal biochemical patterns in conjunction with the clinical picture may suggest certain liver diseases. When a liver abnormality is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time test should be performed ***(Dufour DR et al., 2000)***.

Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and g-glutamyl-transferase; total, direct, and indirect serum bilirubin; and serum albumin. The ALT is thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury, but like other liver function tests, it is of limited use in predicting degree of inflammation and of no use in estimating severity of fibrosis ***(Michael B, 2006)***.

Aminotransferase levels may be normal or only slightly elevated in cirrhosis ***(Edoardo G, 2005)***.

It is common in patients with liver cirrhosis to undertake the following additional laboratory investigations: full blood count, urea and electrolytes, and a liver disease screen which may include viral hepatitis screen, autoimmune antibody screen, serum ferritin and transferrin saturation (Hemochromatosis) alpha-fetoprotein (hepatocellular carcinoma) ***(Sargent S, 2006)***.

Determining serum albumin levels and assessing prothrombin time are often considered tests of liver function “This is mainly because hepatic

synthesis of albumin tends to decrease in end stage liver disease and an increase in prothrombin time depends on the decreased synthesis of liver derived coagulation factors ***(Edoardo G, 2005)***.

Radiographic studies:

Although various radiographic studies may suggest the presence of cirrhosis, no test is considered a diagnostic standard ***(Schiano T, 2004)***.

Radiologic imaging can be useful in the management of patients with suspected or established cirrhosis and it can assist in the diagnosis and in some cases when the clinical suspicion is high, can obviate the need for liver biopsy ***(Norman D, 2002)***.

The major use of radiographic studies is to detect ascites, hepatosplenomegaly, hepatic or portal vein thromboses, and hepatocellular carcinoma, all of which strongly suggest cirrhosis ***(Michael B, 2006)***.

Ultrasonography:

Ultrasonography should be the first radiographic study performed in the evaluation of cirrhosis because it is the least expensive and does not pose a radiation exposure risk or involve intravenous contrast with the potential for nephrotoxicity as does computed tomography (CT) ***(American College of Radiology, 2002)*** and ***(Agostino C et al., 2003)***.

Nodularity, irregularity, increased echogenicity, and atrophy are ultrasonographic hallmarks of cirrhosis. In advanced disease, the gross liver appears small and multinodular, ascites may be detected, and Doppler flow can be significantly decreased in the portal circulation ***(Yuko Kono, 2005)***.

The discovery of hepatic nodules via ultrasonography warrants further evaluation because benign and malignant nodules can have similar ultrasonographic appearances. A study using high-resolution ultrasonography in patients with cirrhosis confirmed with biopsy or laparoscopy found a

sensitivity and specificity for cirrhosis of 91.1 and 93.5 percent, respectively, and positive and negative predictive values of 93.2 and 91.5 percent, respectively ***(Simonovsky V , 1999)***.

CT and MRI:

CT and magnetic resonance imaging (MRI) generally are poor at detecting morphologic changes associated with early cirrhosis, but they can accurately demonstrate nodularity and lobar atrophic and hypertrophic changes, as well as ascites and varices in advanced disease ***(Michael B, 2006)***.

The classic CT scan findings of cirrhosis include small fibrotic right lobe with regenerative enlargement of the caudate and left lobe and nodularity. Evidence of portal hypertension may also be present with a portal vein diameter of greater than 1.3cm, splenomegaly, presence of portosystemic collaterals, and ascites ***(Norman D, 2002)***.

MR imaging is a sensitive means of assessing cirrhosis with the ability to identify regenerative nodules. MR imaging is superior to ultrasound and CT scanning in characterizing cirrhosis. MRI has high sensitivity and specificity in the diagnosis of liver cirrhosis ***(Kirsti N, 2005)***.

Liver Biopsy:

Referral for liver biopsy should be considered after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis, the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. The sensitivity and specificity for an accurate diagnosis of cirrhosis and its etiology range from 80 to 100 percent, depending on the number and size of the histologic samples and on the sampling method ***(Abdi W , 1979).***

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography- or CT-guided fine-needle approaches. Before the procedure, a CBC with platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding ***(Michael B, 2006)***.

Prognosis:

Cirrhosis belongs to a group of severe conditions for which survival remains the principal end-point. Thus the main objective of prognostic scores in cirrhotic patients is to estimate the probability of death within a given time interval. However, prognostic scores also represent a quantitative estimation of the 'reserve' in terms of liver function and the capacity to stand up surgery or other aggressive therapeutic interventions ***(Poynard T et al., 1999)***.

Therefore, prognostic scores are also expected to address important issues in addition to those related to life expectancy. In particular, prognostic scores are expected to help determine which therapeutic option is the most appropriate with respect to the patient's condition, whether a patient has an acceptable chance of survival after a given treatment (i.e., liver resection or arterial chemo-embolisation), and whether are source-spending therapy (such as transplantation) is justified. Child score first proposed in 1964 and modified as Child–Pugh score there after, has been widely used to address these basic issues (Table IV) ***(Durand F, 2005)***.

Among a series of new prognostic scores reported in the literature, MELD (Model for End Stage Liver Disease) score was proposed as the most promising alternative to Child–Pugh score ***(Kamath PS et al., 2001)***.

Four objective variables had a significant and independent impact on survival; namely bilirubin, creatinine, INR and the cause of cirrhosis (alcoholic and cholestatic versus other causes). For a given patient, the final risk score

(the ancestor of the current MELD score), derived from a survival function, is as follows: R= 0.957 loge (creatinine [mg/dl]) + 0.378 loge (bilirubin [mg/dl]) + 1.120 loge (INR) + 0.643 (cause of cirrhosis). 'Cause of cirrhosis' is quoted (0) if alcoholic or cholestatic and (1) for all other causes ***(Durand F, 2005)***.

Whether Child–Pugh score should be definitely abandoned for MELD score remains uncertain.

Table IV . Child Pugh score ***(Durand F, 2005)*** and ***(Pugh et al., 1973)***.

Parameters	**Numerical score**			**Child-Pugh class**	**Numerical score**
	1	**2**	**3**		
1. Encephalopathy	None	Slight to moderate	Moderate to severe	A	5-6
2. Ascites	None	Mild	Moderate to severe	B	7-9
3. Serum Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8		
4. Serum Bilirubin (mg/dL)	< 2	2-3	> 3	C	10-15
5. Prothrombin time (seconds increased)	1-3	4-6	> 6		

Complications:

1. Portal Hypertension and Variceal Bleeding:

Regardless of the etiology of cirrhosis, the development of portal hypertension is nearly universal and results from an increased resistance to portal flow secondary to scarring, narrowing, and compression of the hepatic sinusoids. When the portal pressure exceeds a certain threshold, it results in the development of varices ***(Heidelbaugh JJ, 2006)***.

Approximately esophageal varices are present in 25 to 40% of all patients with cirrhosis. Each episode of bleeding has a 10 to 30% mortality rate.

Left untreated, over 70% of patients experience a recurrent bleed within one year. Therefore, prevention of variceal bleeding is vitally important ***(Ronnie EM, 2006)***.

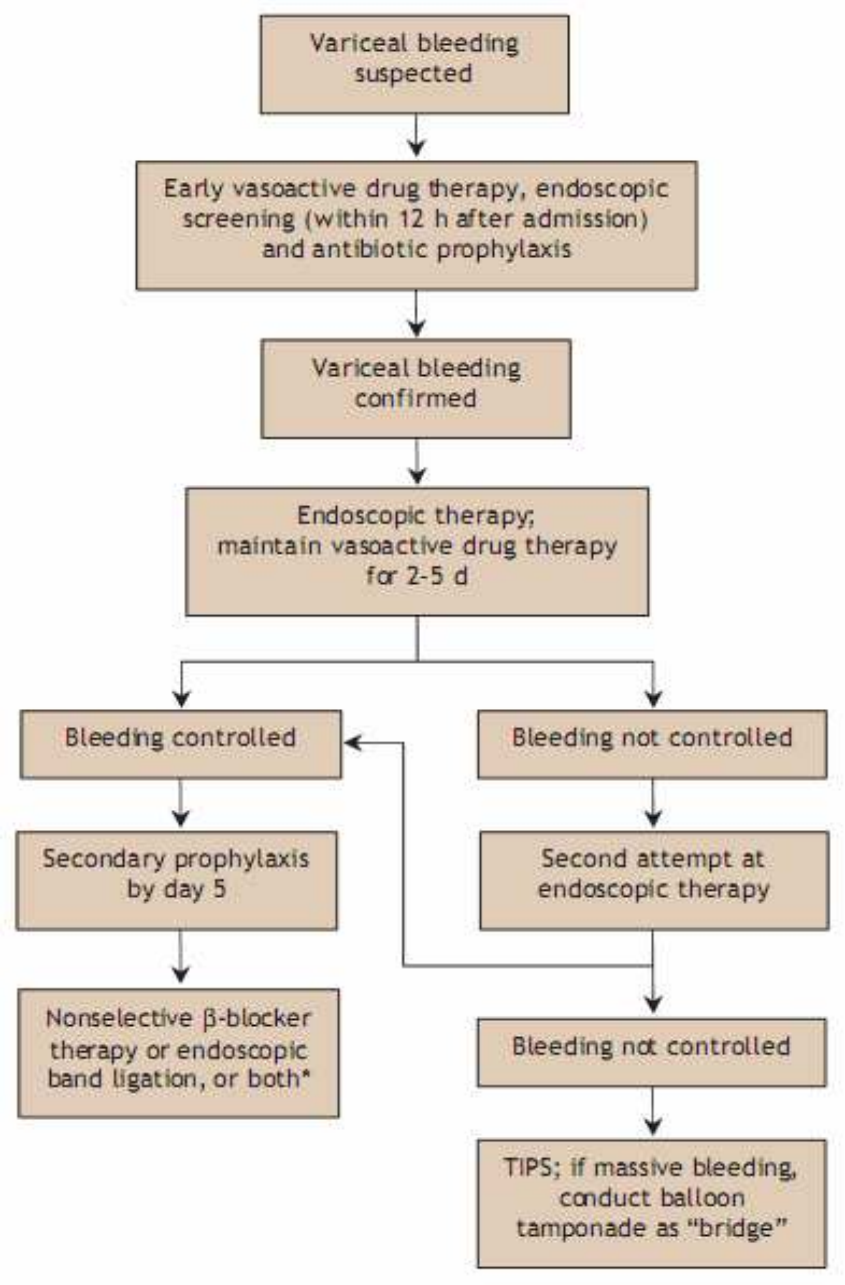


Figure VI: algorithm for the treatment of variceal bleeding. TIPS= transjugular intrahepatic portosystemic shunt ***(Nina D, 2006)***.

2. Ascites:

Ascites is the most common complication of cirrhosis, developing in nearly 60% of all patients with compensated cirrhosis within 10 years. Patients presenting with new onset ascites should undergo a diagnostic paracentesis to establish the cause of ascites and to rule out a bacterial infection. The treatment of ascites depends on the cause. A serum-ascites albumin gradient (serum albumin concentration minus ascitic fluid albumin concentration) greater then 1.1 g/dL indicates that portal hypertension is the cause of the ascites ***(Ronnie EM, 2006)***.

All patients with ascites should undergo an evaluation of ascetic fluid content to rule out spontaneous bacterial peritonitis. The evaluation should include cell count, bacterial culture in blood culture medium, measurement of protein concentration and cytologic examination in cases of suspected malignant ascites ***(Moore KP et al., 2003)***.

The use of leukocyte reagent strips has been recently proposed for the early detection of leukocytes in ascites and spontaneous bacterial peritonitis ***(Thevenot T et al., 2004)***.

For subclinical ascites detectable only by ultrasonography, no specific treatment is necessary. However, a reduction in daily sodium intake (to 90 mmol/d) is recommended. In cases of moderate ascites, renal function is usually preserved and treatment can be administered on an outpatient of basis ***(Cardenas A et al., 2004)***.

Moderate dietary sodium restriction (90 mmol sodium per day) should be imposed ***(Moore KP et al., 2003)***.

Spironolactone, an anti-mineralocorticoid, is the drug of choice at the onset of treatment because it promotes better natriuresis more often than loop diuretics. It blocks the aldosterone-dependent exchange of sodium in the distal and collecting renal tubules, thus increasing the excretion of sodium and water.

The initial dose is about 100-200 mg/d. About 75% of patients respond to treatment after only a few days. Side effects of spironolactone are gynecomastia, metabolic acidosis, hyperkalemia and renal impairment. In the presence of edema, treatment with furosemide (20-40 mg/d) may be added for a few days to increase natriuresis. Loop diuretics act by increasing sodium excretion in the proximal tubules. In cirrhosis, the effect of loop diuretic monotherapy is limited and therefore is more commonly used as an adjunct to spironolactone therapy ***(Nina D, 2006)***.

The side effects of furosemide include hypokaliemia, metabolic hypochloremic alkalosis, hyponatremia, hypovolemia and related renal dysfunction. Amiloride (5-10 mg/d) may be used when spironolactone is contraindicated or if side effects such as gynecomastia occur. It also acts in the distal tubule. Diuretic therapy should be monitored by measuring the patients weight and levels of serum electrolytes, urea and creatinine daily. Maximum weight loss should not exceed 500 g/d in patients without peripheral edema and 1000g/d in those with it. If the therapeutic effect is insufficient, urinary sodium excretion should be determined to identify nonresponsive patients (characterized by a urinary sodium excretion below 30 mmol/d) ***(Cardenas A et al., 2004)***.

Patients with severe ascites will have marked abdominal discomfort. In such cases, higher diuretic doses are needed (i.e., up to 400 mg of spironolactone and 160 mg of furosemide daily). However, in some patients, free-water excretion is impaired and severe hyponatremia may develop ***(Moore KP et al., 2003)***.

Paracentesis should be routinely combined with plasma volume expansion. If the volume of ascites removed is less than 5 L, a synthetic plasma substitute may be used. If more than 5L of ascitic fluid is removed, albumin should be given at a dose of 8 g per litre of fluid removed ***(Suzuki H, 2001)***.

Refractory ascites develops in about 10% of cases. In such cases, liver transplantation should be considered ***(Lebrec D, 2005)***.

In the meantime, therapeutic strategies can involve repeated large-volume paracentesis and plasma volume expansion with albumin or transjugular intrahepatic portosystemic shunt (TIPS) ***(Lebrec D, 2005)***.

TIPS improves renal function and sodium excretion and is more effective than paracentesis in removing ascites ***(Boyer TD, 2005)***.

TIPS has a mortality not significantly differerent from that associated with paracentesis. evertheless, a recent meta-analysis has reported a tendency toward improved survival with TIPS ***(D'Amico G et al., 2005)***.

3. Spontaneous bacterial peritonitis:

Spontaneous bacterial peritonitis, an infection of the ascetic fluid, occurs in 10% to 30% of patients with ascites ***(Rimola A et al., 2000)***.

All cases in which the neutrophil count is at least 250 x 10/L (250 cells per cubic mm or greater) in ascetic fluid should be treated empirically, since ascites culture yields negative results in about 40% of patients with symptoms suggestive of spontaneous bacterial peritonitis. Empirical treatment should also be started if leukocytes are detected in ascitic fluid at a significant level on reagent strips ***(Vanbiervliet G et al., 2002)***.

Because most cases of peritonitis are due to gram-negative bacteria (e.g., Escherichia coli), therapy with a third-generation cephalosporin is the treatment of choice (cefotaxime 2 to 4 g/d, intravenously, for 5 days) ***(Nina D, 2006)***.

Alternative treatments include combination therapy with amoxicillin and clavulinic acid (1g and 0.125 g respectively, given intravenously or orally 3 times daily) or norfloxacin (400 mg/d, orally) for 7 days ***(Lebrec D, 2005)***.

Antibiotic therapy should be used in conjunction with albumin infusion (1.5 g per kg body weight within six hours of detection and 1 g per kg on day 3) to prevent renal failure and death ***(Sort P, 1999)***.

Treatment efficacy should be assessed by means of evaluating clinical symptoms and determining the neutrophil count in ascitic fluid after 48 hours. If treatment fails, antibiotic therapy should be shifted toward a broader-spectrum drug or to one adapted to the organisms antibiogram ***(Nina D, 2006)***.

Oral ofloxacin (Floxin; 400 mg twice daily) is an alternative to intravenous medications in patients without vomiting, shock, severe hepatic encephalopathy, or a creatinine level greater than 3 mg per dL (265 µmol per L) . Patients with ascitic fluid PMNL counts less than 250 cells per mm and signs and symptoms of infection should receive empiric antibiotic therapy while awaiting culture results. Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin (Noroxin) or trimethoprim /sulfamethoxazole (Bactrim, Septrin). Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days (the drug is then discontinued) ***(Runyon BA, 2004)***.

4. Hepatic Encephalopathy:

Hepatic (portosystemic) encephalopathy represents potentially reversible decrease in neuropsychiatric function caused by acute and chronic liver disease, occurring predominantly in patients with portal hypertension. The onset often is insidious and is characterized by subtle and sometimes intermittent changes in memory, personality concentration, and reaction times. Hepatic encephalopathy is a diagnosis of exclusion, therefore all other etiologies of altered mental status must be effectively ruled out ***(Heidelbaugh JJ, 2006)***.

Hepatic encephalopathy is a complication of cirrhosis seen in 27 to 75% of all patients with cirrhosis depending on the mechanism of testing and the diagnostic criteria ***(Quero JC et al., 1996)***.

We recommend initiating treatment when patients develop any of the early symptoms of encephalopathy. The most common complaint is sleep disturbance, but patients may also complain of mood disturbance, speech difficulties, or disorientation ***(Ronnie E, 2006)***.

Treatment goals for hepatic encephalopathy include provision of supportive care, identification and removal of precipitating factors, reduction in the nitrogenous load from the gut, and optimization of long-term therapy. Therapy should be directed toward improving mental status via bowel cleansing with lactulose orally (10 to 30 mL syrup titrated up to three or four times per day) or with 300 mL retention enemas until two to four bowel movements per day and mental status improvement ***(Fitz JG, 2002)***.

5. Hepatorenal Syndrome:

Hepatorenal syndrome is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease. It is characterized by sodium and water retention in patients with renal vasoconstriction, resulting in decreased renal blood flow, glomerular filtration rate, and urinary output, which contribute to azotemia ***(Friedman S, 2000)***.

The pathogenesis of hepatorenal syndrome is not completely understood, but it is likely the result of an extreme underfilling of the arterial circulation secondary to arterial vasodilatation in the splanchnic circulation ***(Gines P, 2004)***.

The International Ascites Club consensus conference on hepatorenal syndrome defined diagnostic criteria that distinguish between two types of hepatorenal syndrome.

Type 1 hepatorenal syndrome is defined as a rapid deterioration of renal function indicated by a two-fold increase of serum creatinine to values above 2.5 mg per dL (221 µmol per L), or a decrease of creatinine clearance to values below 20 mL per minute (0.33 mL per second). This form of hepatorenal syndrome usually is precipitated by spontaneous bacterial peritonitis and occurs in approximately 25 percent of patients with spontaneous bacterial peritonitis, even with the clearance of infection. The median survival duration of these patients is less than two weeks without treatment, and almost all patients die within 10 weeks after the onset of renal failure. Patients with type 2 hepatorenal syndrome exhibit moderately increased serum creatinine levels above 1.5 mg per dL (133 µmol per L) that remain stable over a longer period, and ascites that generally is resistant to diuretics. The median survival duration in these patients is three to six months ***(Arroyo V, 1996)*** and ***(Heidelbaugh JJ, 2006)***.

The ideal treatment of hepatorenal syndrome is liver transplantation. Besides transplantation, vasoactive drug therapy in combination with albumin (20-40 g/d for 5-15 days) can be used in hepatorenal syndrome type 1 ***(Lebrec D, 2005)***.

The efficiency of terlipressin (0.5-1mg intravenously every 4-12 hours) has been reported in several uncontrolled trials ***(Ortega R et al, 2002)***.

One controlled trial demonstrated a substantial improvement in renal plasma flow, glomerular filtration rate, and urinary sodium excretion in patients with type 1 hepatorenal syndrome after 20 days of treatment with oral midodrine and parenteral octreotide compared with the use of nonpressor dose dopamine ***(Runyon BA, 2004)***.

Hemodialysis often is used to control azotemia in hepatorenal syndrome and to correct electrolyte imbalances. Nonsteroidal anti-inflammatory drugs and potentially nephrotoxic medications should be avoided. These therapies also appear to improve survival rates and may serve as a bridge to liver

transplantation. In the future, endothelins, adenosine antagonists, long-acting vasoconstrictors, and antileukotriene antagonists may play a role in preventing and treating hepatorenal syndrome ***(Moller S, 2004)***.

6. Hepatocellular Carcinoma:

The incidence of hepatocellular carcinoma (HCC) in the US has doubled in the last 20 years ***(El-serag HB et al., 2003)***.

The annual incidence of developing HCC is 1.4% in patients with compensated cirrhosis and 4% in patients with decompensated cirrhosis ***(Ronnie E, 2006)***.

To decrease this incidence, new cases of cirrhosis must be prevented. However, once patients have cirrhosis, there is a shift from prevention of HCC to early detection. As with many cancers, early detection when the primary tumor is small and localized greatly increases survival (Table V) ***(Ueno S et al., 2001)***.

Survival is improved because patients with limited stage disease may be eligible for liver transplant or resection, which are potentially curative treatment options. Resection is the preferred treatment for patients without cirrhosis and for patients with cirrhosis and well-preserved liver function. Liver transplantation provides excellent outcomes in patients with T_1 or T_2 lesions (a single nodule < 5 cm or 2 or 3 nodules, all < 3 cm), no evidence of vascular involvement, and no extrahepatic metastasis. For patients with more extensive disease, treatment options are limited ***(Liovet JM, 2005)***.

Early detection of HCC lies in an aggressive screening plan for all patients with cirrhosis. Screening options consist of following alpha-fetoprotein (AFP) levels and imaging the abdomen with ultrasound, helical CT scan, or spin-echo MR ***(Peterson MS, 2001)***.

The sensitivity, specificity, and cost vary depending on the test, with helical CT scan being the most cost-effective strategy for imaging ***(Chen VK et al., 2003)***.

Based on the current limited evidence that is available, we recommend screening all patients with cirrhosis with AFP levels and helical CT scans, MRI, or ultrasound at 6 to 12 month intervals ***(Gebo KA et al., 2002)***.

Table V. Survival rates in hepatocellular carcinoma ***(Farinati F et al., 2000)***

Stage	Median survival
T_1 : 1 lesion <2 cm	48 months
T_2 : 1 lesion < 5 cm or 2 or 3 lesions, largest <3 cm	37 months
T_3 : >T2 with no metastasis	23 months
T_4 : metastasic disease	15 months

7. SYSTEMIC CIRCULATION IN CIRRHOSIS:

Table VI: Circulatory changes in patients with cirrhosis ***(Henriksen JH, 2006)***.

Systemic circulation:

Plasma volume ↑

Total blood volume ↑

Non-central blood volume ↑

Central and arterial blood volume →↓(↑)

Cardiac output (→)↑

Arterial blood pressure →↓

Heart rate ↑

Systemic vascular resistance ↓

Heart

Left atrial volume ↑

Left ventricular volume →(↓)

Right atrial volume→↑↓

Right ventricular volume →↑↓

Right atrial pressure →↑

Right ventricular end-diastolic pressure →

Pulmonary artery pressure →↑

Pulmonary capillary wedge pressure →

Left ventricular end-diastolic pressure →

Pulmonary circulation:

Pulmonary blood flow ↑

Pulmonary vascular resistance ↓(↑)

Renal circulation:

Renal blood flow ↓

Renal vascular resistance ↑

Cerebral circulation:

Cerebral blood flow ↓ →

Cutaneous and skeletal muscle circulation:

Cutaneous blood flow →↑

Skeletal muscular blood flow →↑

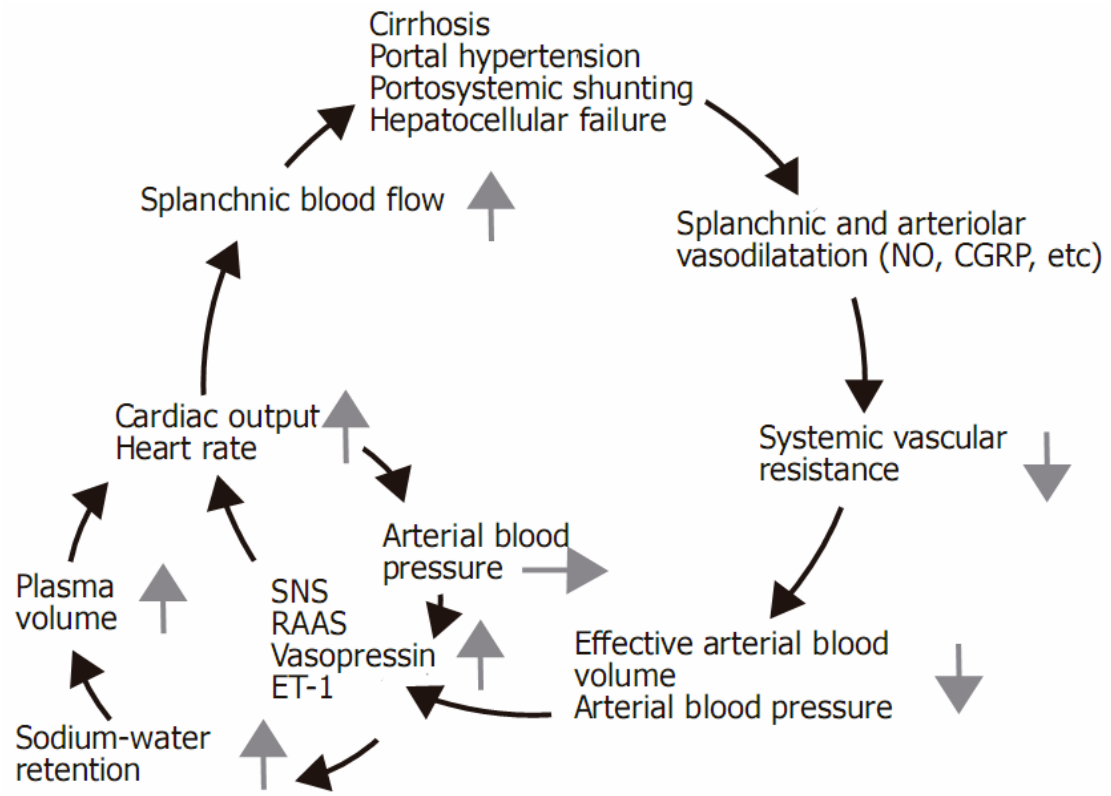


Figure VII: Pathophysiology of the splanchnic and peripheral arteriolar vasodilation and systemic hemodynamic changes in cirrhosis. Endogenous vasodilators may escape hepatic degradation, owing to portosystemic shunting and/or hepatocellular damage, and induce vasodilatation preferentially in the splanchnic vascular area. Reduced systemic and splanchnic vascular resistance leads to a reduced effective arterial blood volume, and hence to activation of vasoconstrictor systems. The hemodynamic and clinical consequences are increases in cardiac output, heart rate, and plasma volume and decreased renal blood flow, low arterial blood pressure, and fluid and water retention. The development of the hyperdynamic circulation may increase portal inflow and further aggravate the portal pressure in a vicious cycle. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ET-1, endothelin-1 ***(Moller S, 2006)***.

8. CARDIAC DYSFUNCTION IN CIRRHOSIS:

The hyperdynamic circulation in cirrhosis comprises increased cardiac output and work. In other circumstances, this would cause cardiac failure, but because of the decreased afterload as reflected by reduced systemic vascular resistance and increased arterial compliance, left ventricular failure may be latent in cirrhosis ***(Moller S, 2002)***.

Cardiac failure may become manifest under strain or treatment with vasoconstrictors. This type of cardiac dysfunction has been termed as cirrhotic cardiomyopathy and includes impaired cardiac contractility with a systolic dysfunction, diastolic dysfunction, and electromechanical abnormalities with a prolonged Q-T interval ***(Liu H, 2002)***.

Various electrophysiological mechanisms for the conductance abnormalities and impaired cardiac contractility have been put forward, including reduced beta-adrenoceptor density, post-receptor signal defects, abnormal excitation-contraction coupling, and molecular abnormalities ***(Moller S, 2001)***.

9. PULMONARY COMPLICATIONS OF CIRRHOSIS:

Cirrhotic patients occasionally experience three distinct types of pulmonary complications: (a) hepatic hydrothorax (b) hepatopulmonary syndrome and (c) portopulmonary hypertension ***(Claire F, 2007)***.

Over the last 15 years, two distinct pulmonary vascular disorders have emerged as important etiologies of pulmonary dysfunction in patients with liver disease or portal hypertension. The hepatopulmonary syndrome (HPS) occurs when intrapulmonary vasodilatation impairs arterial gas exchange and Portopulmonary hypertension (POPH) results when pulmonary arterial constriction and remodeling lead to increased pulmonary arterial pressure ***(Fallon MB, 2000)***. HPS appears to be more common than POPH ***(Budhiraja R, 2003)***.

Patients with cirrhosis often complain of dyspnea and platypnea, and arterial oxygenation is often impaired with orthodeoxia. The etiology of abnormal lung function and ventilation in cirrhosis may be multifarious 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 ***(Moller S, 2006)***.

In addition, lung function and oxygenation can be affected by edema and tense ascites, which are ameliorated after diuretic treatment and paracentesis. But independent of smoking status, patients with cirrhosis have a compromised 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 ***(Krwaka MJ, 2000)***.

Various pathophysiological factors may be involved in the reduced diffusing capacity, including an abnormal ventilation/perfusion ratio (VA/Q), the presence of arterial venous shunts, and changes in the alveolar-arterial membrane ***(Moller S, 1998)***.

a) Hepatic hydrothorax:

Hepatic hydrothorax results from the accumulation of ascetic fluid within pleural cavity through microscopic or macroscopic diaphragmatic defects. Large-volume effusions can be responsible for dyspnea and severe hypoxemia. When a salt and diuretics are inefficient, repeated thoracocentesis is needed ***(Claire F, 2007)***.

Unfortunately, thoracocentesis is poorly tolerated in cirrhotic patients, frequently resulting in pneumothorax, bleeding, or infection ***(Xiol X et al., 2001)***.

Overall, the prognosis of patients with symptomatic, large-volume, hepatic hydrothorax is poor. The efficacy of peritoneovenous jugular shunting as well as the efficacy of TIPS is limited ***(Spencer EB, 2002)***.

Similarly, chemical pleurodesis under thoracoscopy may be poorly tolerated. Liver transplantation is the only effective option ***(Lazaridis KN et al., 1999)***.

b) Portopulmonary hypertension:

Portopulmonary hypertension is even more uncommon than hepatopulmonary syndrome. It is seen infrequently in cirrhosis with an average prevalence from 1% to 4% ***(Moller S, 2006)***.

It is defined by the following criteria:(1) chronic liver disease with portal hypertension; (2) mean pulmonary artery pressure over 25 mmHg (and elevated pulmonary arterial resistance over 240 dyns/cm^5); and (3) pulmonary capillary wedge pressure below 15 mmHg ***(Herve P et al., 1998)***.

Symptoms are typically progressive and include fatigue, dyspnea, and edema ***(Fallon MB, 2000)***.

Hypoxemia is absent or only mild. Portopulmonary hypertension carries a high mortality risk and most patients die due to cardiocirculatory complications rather than other complications of cirrhosis. Treatment is nonspecific and palliative and includes vasodilators such as Continuous intravenous administration of the prostacyclin analogue, epoprostenol, calcium channel blockers and nitrate decreases pulmonary artery pressure in most cases ***(Rodriguez-Roisin R et al., 2004)***.

However, it is a demanding therapy that does not allow complete recovery. Indications for transplantation in patients with portopulmonary hypertension are not as clear as in patients with hepatopulmonary syndrome ***(Claire F, 2007)***.

Indeed, pulmonary hypertension represents a major operative risk when mean arterial pressure exceeds 35 mmHg. In addition, post-transplant reversibility is inconstant. Some patients recover whereas, in others, pulmonary hypertension relentlessly progresses after transplantation. Until now, no predictive factors for reversibility have been identified ***(Plevak DJ e al., 2000)***.

c) Hepatopulmonary Syndrome:

Definition

HPS is defined as a defect in arterial oxygenation induced by intrapulmonary vascular dilatations (IPVD) associated with hepatic disease. The vascular component characteristically includes diffuse or localized dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications. HPS associates a clinical triad characterized by (1) arterial deoxygenation (2) IPVD and (3) liver disorder or portal hypertension ***(Rodriguez-Roisin R et al., 2004)***.

Epidemiology, occurrence, and disease associations:

The reported frequency of hepatopulmonary syndrome in patients with liver cirrhosis is between 4% and 28%. The differing incidence is primarily due to heterogenecity of the applied diagnostic criteria and study population ***(Herve P et al., 2007)***.

Intrapulmonary vasodilatation is common in chronic liver disease and may be detected in over 40% of patients being evaluated for liver transplantation. As many as 8% to 20% of those with intrapulmonary vasodilatation have impaired oxygenation resulting in the diagnosis of HPS ***(Schenk P et al., 2002)***.

HPS also has been recognized in patients with portal hypertension in the absence of cirrhosis (portal vein thrombosis, nodular regenerative hyperplasia, congenital hepatic fibrosis, and Budd-Chiari syndrome ***(Gupta D et al., 2001)***.

The prevalence of HPS is about 10% in chronic viral hepatitis with or without cirrhosis, and as high as 28% in Budd-Chiari syndrome ***(Herve P et al., 2007)***.

These findings support that advanced liver disease is not required for HPS to develop ***(Regev A et al., 2001)***.

Pathophysiology:

Hypoxemia in liver disease:

A decrease in blood oxygen saturation is a symptom of many pathologic processes, but few diseases require a specific and precise numerical cutoff value to establish a diagnosis ***(Susan M, 2006)***.

Impaired arterial oxygenation is a hallmark of the hepatopulmonary syndrome. Mild hypoxemia is a frequent feature of chronic liver disease; it occurs in approximately one third of all patients and is multifactorial. In contrast, severe hypoxemia (PaO_2 < 60 mm Hg) is less common with cirrhosis alone and is unusual without associated cardiopulmonary disease. In the absence of independent lung disease (obstructive or restrictive), severe hypoxemia in the setting of liver disease suggests the possibility of the hepatopulmonary syndrome ***(Lange PA, 1995)***.

Evidence is growing rapidly that abnormal intrapulmonary vascular dilatation is linked to portal hypertension, which in itself leads to altered bowel perfusion and an increased rate of enteral translocation of gram-negative bacteria and endotoxin. This process in turn stimulates the release of vasoactive mediators, which include tumor necrosis factor α, haem-oxygenase-derived carbon monoxide, and nitric oxide ***(Carter EP et al., 2002)***.

Experimental and clinical data suggest that increased production of nitric oxide in the lung plays a central part in the pathogenesis of the hepatopulmonary syndrome ***(Liu L, 2001)***.

Increased concentrations of exhaled nitric oxide are positively correlated with the increase of alveolo-arterial oxygen difference. The constitutive and the inducible isoforms of nitric-oxide synthase have been implicated in this process ***(Nunes H et al., 2001)***.

In addition, the endothelin system, especially abnormal activation and increased expression of endothelial type B endothelin receptors, has been implicated in the pathogenesis of the hepatopulmonary syndrome ***(Schroeder RA, 2000)***.

In patients who have pulmonary hypertension, endothelin predominantly exerts vasoconstrictive and mitogenic effects due to activation of type A and type B endothelin receptors on pulmonary arterial smooth-muscle cells ***(Davie N et al., 2002)***.

By contrast, in experimental models of the hepatopulmonary syndrome, the expression of endothelial type B endothelin receptors is strikingly increased and is linked to the increased production of nitric oxide by endothelial cells (Figure VIII) ***(Luo B et al., 2003)***.

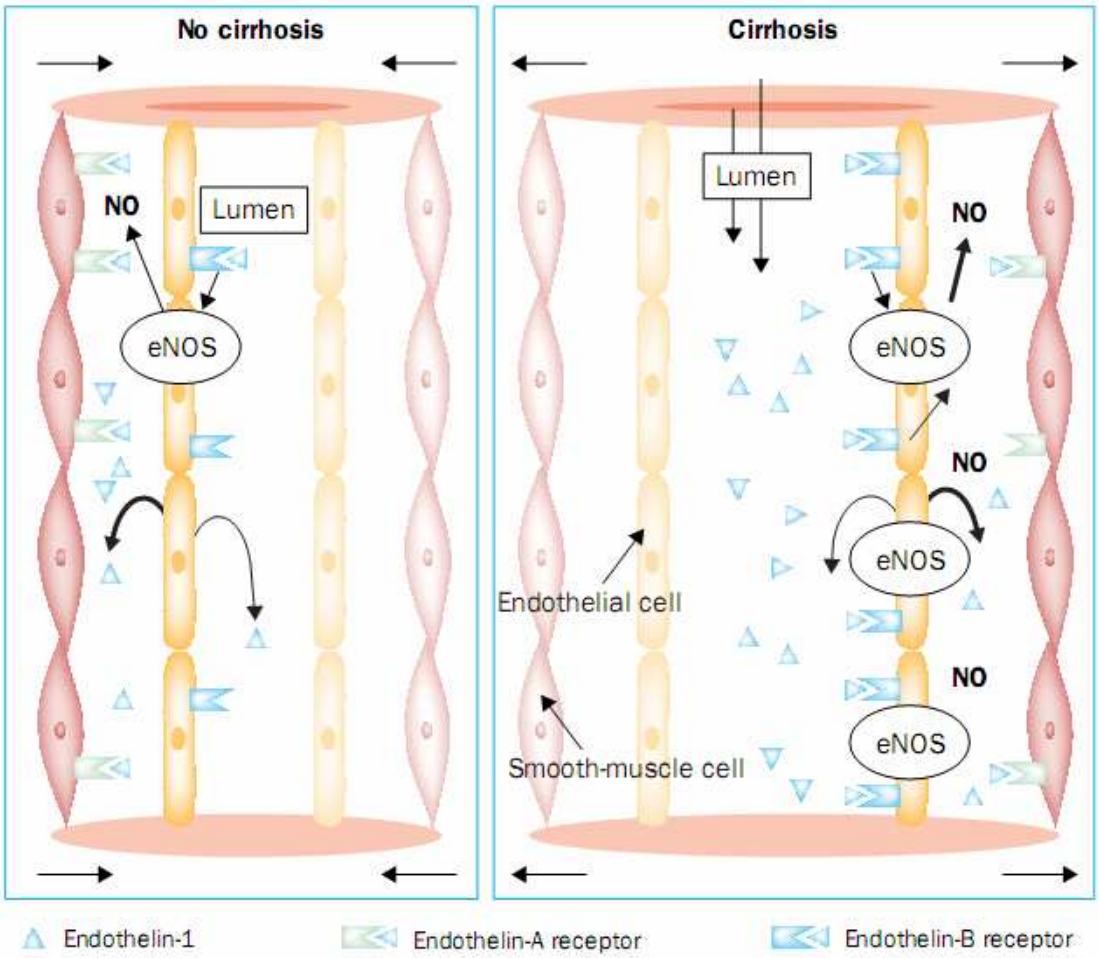


Figure VIII: Schematic illustrating hypothesis underlying pulmonary-vessel dilatation in hepatopulmonary syndrome. NO= nitric oxide. eNOS=endothelial nitric oxide synthase. **Left panel:** In absence of cirrhosis and portal hypertension, endothelin-1 is secreted, mainly luminally, where it activates vasoconstrictive endothelin type A receptors on smooth-muscle cells and contributes to maintenance of adequate vascular tone. Under physiological conditions, luminally secreted endothelin is rapidly cleared from circulation after binding to endothelial type B endothelin receptors, which stimulates production of NO, partly antagonizing vasoconstrictive effects of endothelin. **Right panel:** in presence of portal hypertension, hepatic production of endothelin-1 occurs and expression of endothelial type B receptors increase but no increase in type A receptors in pulmonary vasculature. Signaling via endothelially expressed endothelin B receptor leads to increased NO production by eNOS, with the overall effect of pulmonary vascular dilatation, which is pathognomonic of hepatopulmonary syndrome ***(Luo B et al., 2003)***.

Histological examination reveals dilated intrapulmonary arterioles and capillaries and dilated vascular channels between pulmonary arteries and veins.

The latter structures have been described as vascular spider naevi on the pleura and exhibit features of vasculogenesis ***(Marius M, 2004)***.

A typical, albeit not universal, finding in hepatopulmonary syndrome is orthodeoxia—ie, arterial deoxygenation improving in recumbency—which leads to the debilitating clinical symptom of orthodeoxia-platypnea (hypoxaemia and dyspnoea induced or worsened in the upright position). This phenomenon is explained by the worsening of diffusion-perfusion matching and an increase of the shunt fraction in the upright position because of increased perfusion of the lower lobes ***(Naeije R, 2003)***.

Mechanism of hypoxemia in hepatopulmonary syndrome:

Three physiologic mechanisms commonly used to explain why hypoxemia occurs in patients who have HPS are (1) enhanced mismatching of alveolar ventilation to pulmonary vascular perfusion (VA/Q), (2) diffusion perfusion defect, and (3) the flow of deoxygenated blood through abnormal dilated vessels that join pulmonary arteries directly to the pulmonary veins, bypassing the pulmonary-capillary alveolar surface. A significant improvement in arterial oxygenation is observed in most patients who have HPS and who are given supplemental oxygen supports the hypothesis that VA/Q is the predominant cause of hypoxemia . Some investigators suggest that hypoxemia is also caused by a ‘‘diffusion-perfusion defect’’ ***(Susan M, 2006)***.

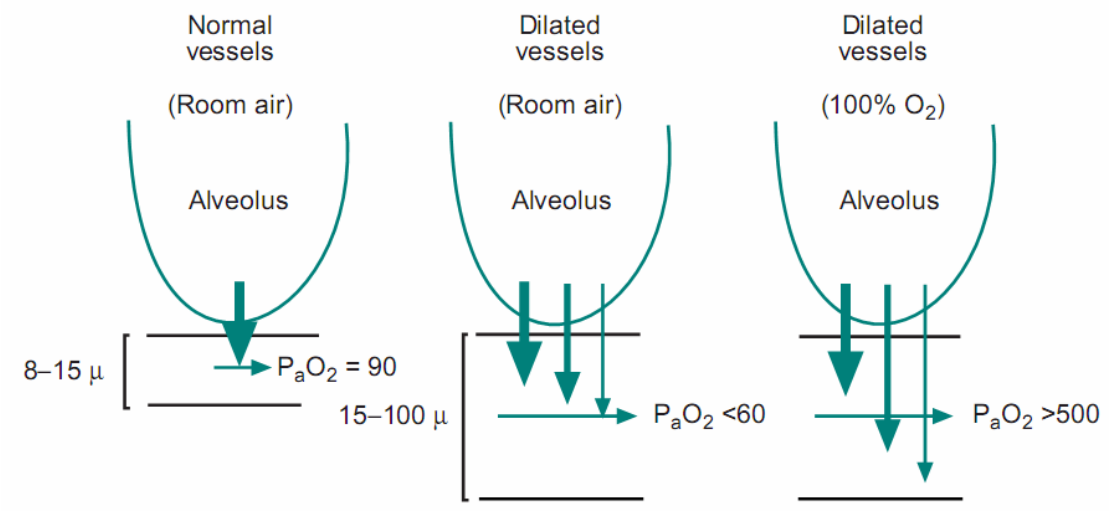


Figure IX. Diffusion-perfusion impairment. The left panel**:** shows normal transfer of oxygen across a normal blood vessel. **The middle panel:** illustrates the mechanism of diffusion-perfusion impairment across a dilated pre-capillary vessel. **The right panel:** demonstrates how this impairment can be overcome by increasing the driving pressure of oxygen across the alveolar-capillary barrier. Reproduced from Krowka and Cortese (1987, Mayo Clinic Proceedings 62: 164±173) with permission of Mayo Foundation ***(Loutfi S, 2000)***.

Investigators speculate that pulmonary blood flow is increased to such an extent in patients who have liver disease that there is insufficient time for adequate oxygen exchange at the capillary–alveolar interface ***(Katsuta Y et al., 2005)***.

Because there would be no contact between a proportion of the red blood cell mass and the alveolar surface, this condition constitutes an unconventional form of anatomic shunt ***(Susan M, 2006)***.

Positioning affects arterial oxygen saturation in all patients , but this effect is accentuated in certain patients who have HPS ***(Gomez FP et al., 2004)***.

Under normal circumstances arterial oxygenation falls in the supine position because gravity pushes the abdominal contents into the diaphragm, reducing functional residual capacity and causing venous admixture as a result

of impaired VA/Q mismatching . Oxygen desaturation in the supine position often is enhanced in patients who have liver disease because of the added effects of ascites and increased intrathoracic blood volume on functional residual capacity. In contrast, patients who have HPS often experience orthodeoxia and platypnea and deoxygenation and dyspnea in the sitting and standing position compared with the supine position . These findings are caused by the gravity-dependent redirection of pulmonary blood flow to dilated vessels in the base of the lung while in the upright position. Thus pulmonary blood is delivered preferentially to dilated vessels that are unable to regulate their diameter in response to ventilation. This failure of autoregulation enhances preexistent VA/Q mismatching, creating a physiologic shunt and venous admixture ***(Susan M, 2006).***

Some investigators suggest that orthodeoxia is a sufficiently unique observation that it can be used to confirm a diagnosis of HPS . Investigators use three common definitions for orthodeoxia associated with HPS: a decline in PaO_2 of 4% or more, of 5% or more, or of 10% or more . The values of a 4% and a 5% decline in oxygenation upon assuming the upright position were derived from studies that correlated arterial oxygenation with a measurable increase in shunt fraction; clinical impression guided the choice of the 10% value. Although these values are of interest, they await testing in study subjects to see if they are of any clinical value ***(Gomez FP et al., 2004)***.

Mechanism of intrapulmonary vascular dilatation and hyperdynamic circulation:

The hallmark of HPS is microvascular dilatation occurring within the pulmonary arterial circulation that appears to result from decreased tone in precapillary arterioles ***(Miguel R, 2005)***.

Most hypotheses have considered an imbalance between pulmonary vasodilators and vasoconstrictors. The imbalance could be a result of failure of clearance by the diseased liver of a vasodilator substance, production by the

liver of a circulating vasodilator, or inhibition of a vasoconstrictor ***(Loutfi S, 2000)***.

Many candidate humoral mediators have been proposed as circulating vasodilators in the hepatopulmonary syndrome, including vasodilating prostaglandins, vasoactive intestinal peptide, calcitonin gene-related peptide, glucagon, substance P, adrenomedullin , atrial natriuretic peptide, platelet activating factor and nitric oxide ***(LiCP et al., 1999)***.

In HPS, the vasodilatation is assumed to result from excessive vascular production of vasodilators, particularly nitric oxide (NO). This has been based on the observation that exhaled NO levels, a measure of pulmonary production, are increased in cirrhotic patients with HPS and normalize after OLT, as HPS resolves ***(Palma DT, 2006)***.

In addition, a case report revealed that acute inhibition of NO production or action with N-nitro-L-arginine methyle ester (L-NAME) or cyclic GMP inhibitor methylene blue, respectively, transiently improves HPS ***(Brussino L et al., 2003)***.

However, a recent study found that administration of inhaled L NAME did not acutely improve intrapulmonary vasodilatation, raising the possibility that factors other than NOS-derived NO effects on vascular tone contribute to HPS ***(Gomez FP et al., 2006)***.

The exact mechanisms of increased endogenous NO production and its relationship to the presence of portal hypertension, the hyperdynamic circulation and the degree of liver injury remain uncertain. In addition, whether other mediators such as hemeoxygenase-derived carbon monoxide might contribute to intrapulmonary vasodilatation and explain the lack of improvement of HPS with NO inhibition in some patients has not yet been established ***(Arguedas MR, 2005)***.

Clinical manifestations:

Patients with hepatopulmonary syndrome complain of progressive dyspnoea and can become increasingly cyanotic. Some patients develop clubbing, and cutaneous telangiectasias (spider angiomas) are typically seen in high numbers ***(Marius M, 2004)***.

the dyspnoea is insidious in onset occurring particularly on exertion but non specific. Platypnea (shortness of breath exacerbated by sitting up and improved by lying supine) and orthodeoxia (hypoxemia exacerbated in the upright position) are classically described and result from a gravitational increase in blood flow through dilated vessels in the lung bases ***(Gomez FP et al., 2004)***.

While orthodeoxia (decrease in PaO_2 >5% or >4 mmHg from the supine to upright position) has been observed in a variety of conditions, including post-pneumonectomy, recurrent pulmonary thromboemboli, and atrial septal defects (such as patent foramen ovale), it is highly specific for HPS in the setting of liver disease ***(Herve P et al., 2007)***.

The sensitivity of orthodeoxia for HPS is relatively low, but increases in cases of severe HPS ***(Martinez GP et al., 2001)***.

Cough is not a common finding in HPS. Spider angiomata are commonly reported in HPS but are frequently seen in cirrhotic patients without HPS. One study observed that patients with these cutaneous lesions had more pulmonary vasodilatation and higher alveolar-arterial oxygen gradients than those without vascular spiders (A-aPO_2: 20 mmHg versus 8 mmHg ***(Palma DT, 2006)***.

Finally, clubbing and distal cyanosis, when present in the setting of liver disease or portal hypertension, should raise suspicion for HPS ***(Fallon MB, 2000)***.

Diagnosis:

The diagnostic features of HPS include evidence of liver disease or portal hypertension, an elevated age-adjusted alveolar-arterial oxygen gradient (A-aPO_2), and evidence of intrapulmonary vasodilatation. In the presence of coexisting cardiac or pulmonary disease, establishing a diagnosis of HPS can be difficult. (Fig. X) presents an algorithm for the diagnosis of HPS. A logical evaluation of dyspnea in the patient with liver disease or portal hypertension begins with a careful history and physical examination. Such an evaluation may lead the clinician to consider alternate, more common diagnoses such as chronic obstructive pulmonary disease (COPD), CHF or myocardial ischemia. However, if the common causes of dyspnea can be excluded, and particularly if platypnea or digital clubbing is present, further evaluation for HPS is warranted ***(Herve P et al., 2007)***.

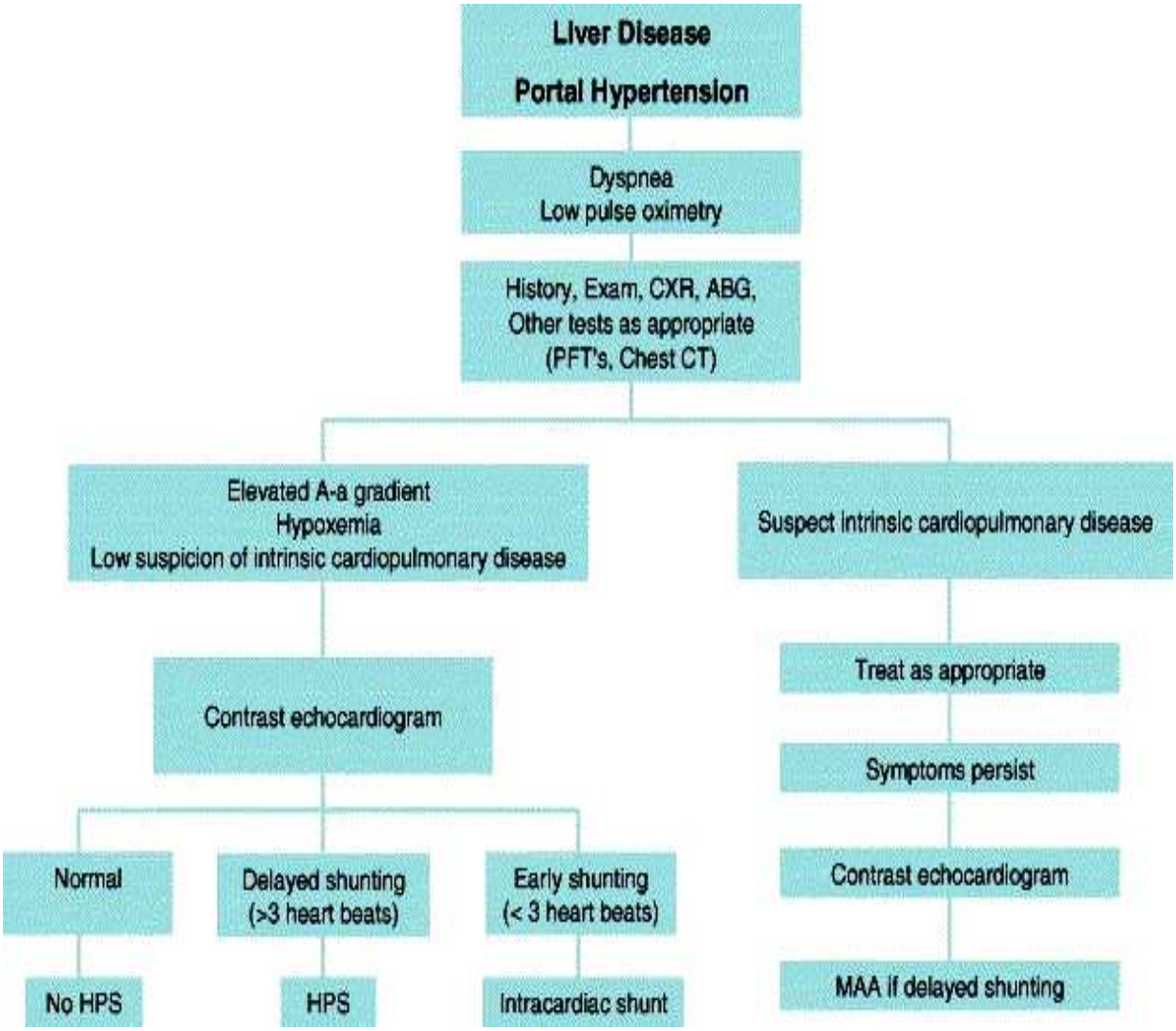


Figure X: Diagnosis of HPS ***(Palma DT, 2006)***.

1. Assessment of arterial oxygenation:

In patients with liver disease found to have dyspnea or clubbing, or in those undergoing transplant evaluation, pulse oximetry is a simple, non-invasive screening test for hypoxemia and a decreased SaO_2 should lead to arterial blood gas (ABG) analysis. However, caution must be exercised in interpreting a "normal" SaO_2 as pulse oximetry may overestimate SaO_2 in nearly one-half of patients with cirrhosis ***(Abrams GA , 2002)***.

Therefore, to reliably detect hypoxemia, ABG analysis should be considered when the SaO_2 values are 95% or less. In addition, if hypoxemia or HPS is strongly suspected based on history and physical exam, arterial blood

gas analysis should be performed while breathing room air regardless of pulse oximetry. In HPS, ABGs reveal an elevated age-adjusted A-aPO_2 with or without hypoxemia. The expected upper limit of normal for room-air A-aPO_2 at a given age (>95% confidence interval) can be calculated using the following equation: A-aPO_2 = [0.26 age − 0.43] + 10 ***(Palma DT, 2006)***.

Since orthodeoxia is a typical finding in the hepatopulmonary syndrome, blood-gas analyses should be obtained with the patient in erect and supine positions. Blood-gas analysis is also useful while the patient is breathing 100% oxygen to assess the amount of right-to-left shunting ***(Krowka MJ, 2000)***.

If gas exchange abnormalities are detected, chest radiography and pulmonary function tests are performed to evaluate for the presence of other pulmonary abnormalities. Since cardiopulmonary disorders unrelated to liver disease or those related to ascites are more common than HPS, treating these abnormalities prior to further evaluation for HPS is reasonable in the absence of significant hypoxemia (PaO_2 < 70 mmHg) ***(Palma DT, 2006)***.

2. Staging of severity:

Staging of the severity of HPS is important because severity influences survival ***(Krowka MJ, 2000)***, and is useful in determining the timing and risks of OLT ***(Schenk P et al., 2003)***.

A classification of the severity of HPS based on oxygenation abnormalities in four stages is proposed (table VII) ***(Rodriguez-Roisin R et al., 2004)***.

Table VII. Grading of severity of hepatopulmonary syndrome***(Rodriguez-Roisin R et al., 2004)***.

Stage	A–aPO_2 mmHg	PaO_2 mmHg
Mild Moderate Severe Very severe	≥15 ≥15 ≥15 ≥15	≥80 <80- ≥60 <60-≥50 <50

A-aPO_2 :alveolar –arterial oxygen tension difference; PaO_2 :arterial oxygen tension

3. Lung function tests:

Both forced spirometric results and static lung volumes are characteristically within normal limits in HPS in the absence of pulmonary co-morbid conditions. A moderately to severely reduced diffusion capacity of carbon monoxide (DLco), after adequate correction for anemia, appears to be a common functional marker of HPS ***(Herve P et al, 2007)***.

4. Contrast echocardiography

Diffusion-perfusion impairment relates to the mechanism of hypoxemia associated with intra-pulmonary vascular dilatations in the setting of HPS**.** Contrast echocardiography is considered the most useful screening test for detecting intrapulmonary shunt (IPS)**.** The contrast agent used is agitated saline solution injected through a peripheral vein. It is a safe method as long as there is no visible free air in the injection system. Gelatin solutions which give brighter contrast have been used as well ***(Rollan MJ, 2006)***.

Unlike blood, microbubbles resonate at a frequency similar to clinical transducer frequencies, which make ultrasounds to be reflected**.** Under normal circumstances, only right heart chambers are opacified and the microbubbles (mean diameter of up to 10 mm) are trapped in the pulmonary capillaries (mean diameter 8 mm). The presence of contrast in the left chamber suggests an

arteriovenous connection. Three levels of shunting can be identified : atrial septal defect, ventricular septal defect with Eisenmenger's and IPS**.** In patients with intracardiac shunts, a small amount of contrast is usually recorded in the left chambers within 1 or 2 cardiac cycles after its appearance in the right side chambers. On the contrary, late arrival of contrast in the left atrium after a time delay of 4-8 cardiac cycles is diagnostic of IPS, and is due to the time required for passage through the pulmonary circulation (Figure XI) ***(Gudavalli A, 2002)***.

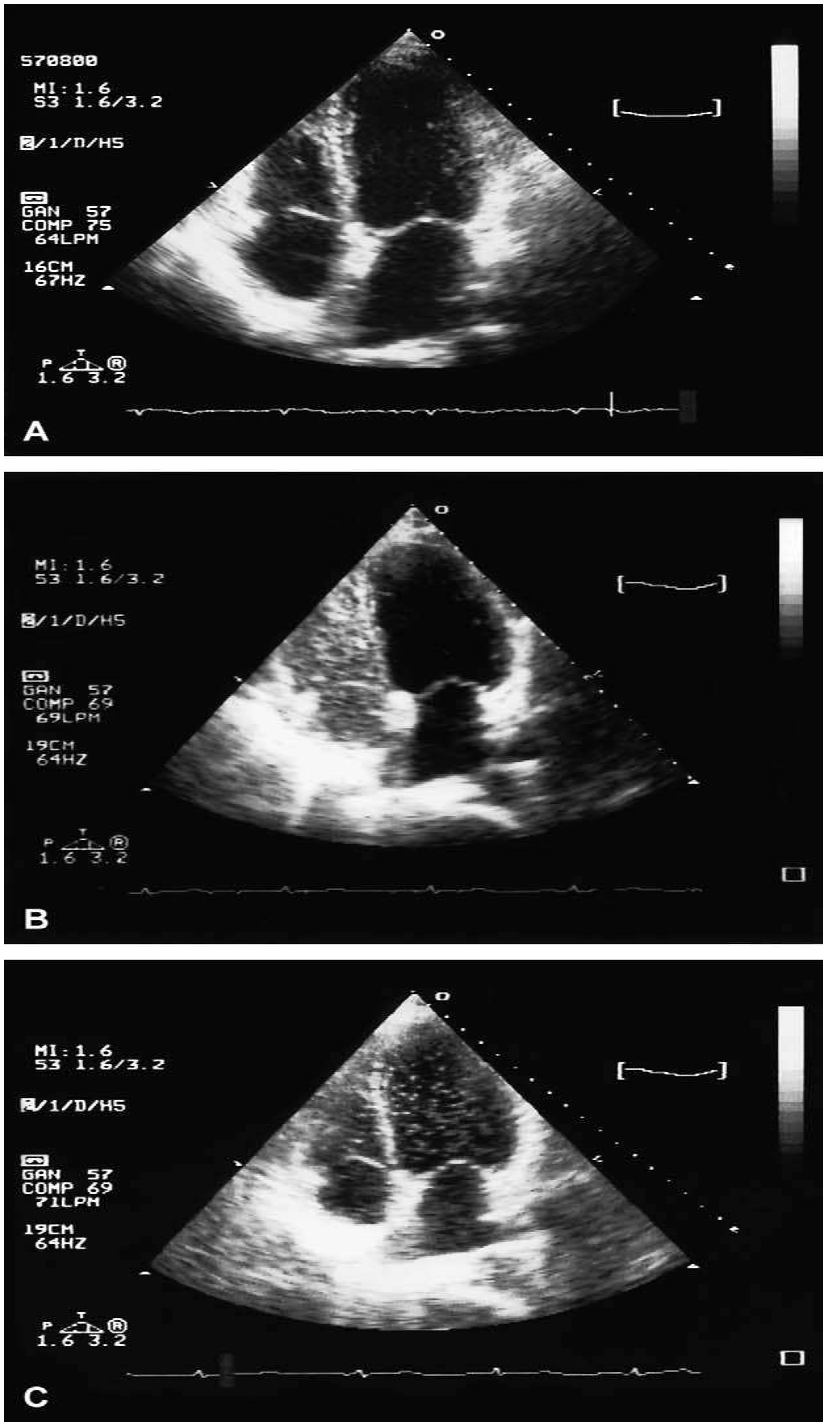


Figure XI: Contrast echocardiogram. **Panel A:** apical four-chamber view before injection of agitated saline (contrast); **Panel B:** apical four-chamber view after contrast injection showing opacification of the RA and RV. **Panel C:** apical four-chamber view showing microbubbles within the LA and LV 5 heart beats after its appearance in the right heart. LA: left atrium, LV: left ventricle, RA: right atrium, and RV: right ventricle ***(Rollan MJ et al., 2006)***.

Some studies have also shown better detection of intrapulmonary shunts with transoesophageal echocardiography compared to transthoracic echocardiography. In one study, a transoesophageal approach detected intrapulmonary shunts in 51% of patients with end-stage liver disease compared to a 32% detection rate using a transthoracic approach ***(Aller R, 1999)***.

Contrast echocardiogram is a sensitive screening test for the hepatopulmonary syndrome and for the detection of intrapulmonary shunts ***(Abrams GA, 1998)***.

However, it lacks specificity and is often positive in normoxaemic patients with cirrhosis, who therefore don't fulfill the criteria for hepatopulmonary syndrome ***(Loutfi S, 2000)***.

5. Macro-aggregated albumin scanning:

Perfusion lung scanning with technetium 99m-labelled macro-aggregated albumin is a method that allows detection of intrapulmonary vascular dilatations and shunt quantification. The injected aggregates of albumin have a diameter of 20 to 50 mm, and are normally trapped by the pulmonary capillary bed, which has a diameter of 8 to 15 mm. Detection of radionuclide uptake in the brain and kidneys, which receive a high fraction (about 39%) of the cardiac output, usually indicates shunting of blood across the pulmonary capillary bed ***(Whyte MK et al., 1998)***.

Lung perfusion scanning with macro-aggregated albumin was reported to be positive in 21 of 25 patients with moderate to severe hepatopulmonary syndrome (sensitivity 84%), and negative in cirrhotic patients without the syndrome and in patients with intrinsic lung disease (specificity 100%) ***(Abrams GA, 1998)***.

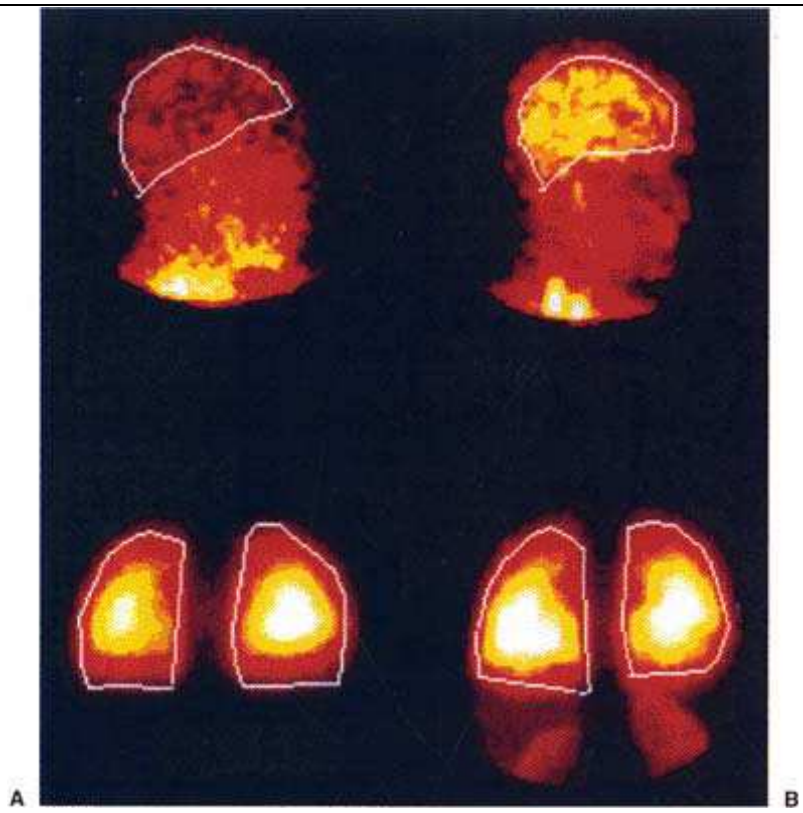


Figure XII: Technetium-99m–labeled macroaggregated albumin (99mTc MAA) scanning**. A:** A normal 99mTc MAA scan from a patient without hepatopulmonary syndrome (HPS) with regions of interest drawn around the lungs and cerebrum. In the absence of intrapulmonary vasodilatation, there is minimal passage of intravenously administered labeled albumin through the lungs and signal intensity is low in the cerebrum. Shunting is quantified by comparing the relative signal intensity in the lung and the brain. **B:** An 99mTc MAA scan in HPS demonstrates significant cerebral uptake because of passage of labeled albumin through the dilated pulmonary microvasculature ***(Abrams GA, 1998)***.

Other diagnostic techniques:

- *Pulmonary angiography*

According to Krowka, pulmonary angiography should be reserved for patients with a severe hypoxemia and a poor response to 100% inspired oxygen in whom vascular embolotherapy is a therapeutic option ***(Krowka MJ, 2000)***.

Angiographic patterns in the arterial phase vary Based on these angiographic patterns and underlying pathophysiology, HPS can be classified into two types. Type 1 HPS may present as a spectrum from minimal to

advanced angiographic changes. The angiogram may appear normal or as diffuse, small, spider-like, branches. With advanced dilatations, the diffuse pattern may appear spongy or blotchy. Individuals with minimal diffuse dilatations may experience a near normal response to 100% inspired oxygen, at least in a supine position, suggesting diffusion–perfusion impairment. With advanced diffuse vascular dilatations, however, the patient may have a poor response to 100% inspired oxygen ***(Scott VL, 1999)***.

The Type 2 pattern of HPS, which is less common, does not respond to 100% oxygen. These patients behave as if they have true shunts and are unable to raise the arterial PaO_2 to more than 150–200 mmHg. The pulmonary angiography of Type 2 HPS demonstrates anatomic arteriovenous communications or malformations similar to spider angiomata ***(Jung KR, 2003)***.

Pulmonary angiography is expensive and invasive and has a low sensitivity for detecting intrapulmonary vasodilatation. Therefore, it is not routinely utilized in the diagnosis of HPS. High-resolution chest computerized tomography (CT) and evaluation of pulmonary blood transit time are newer diagnostic modalities for assessing HPS ***(Palma DT, 2006)***.

Natural history and prognosis:

The natural history of HPS is incompletely defined, but the syndrome frequently is progressive and associated with significant morbidity and mortality ***(Arguedas MR et al., 2003)***.

(Schenck et al., 2003) presented a prospective study on the prognostic significance of HPS in cirrhotic patients awaiting liver transplantation. Among a population of cirrhotic patients they showed a significant reduction in survival of patients with HPS, which correlated not only with the severity of hypoxemia, but also with the Child-Pugh class with HPS. The results of that study, in fact, showed that patients with HPS had an average survival almost

four times less than subjects not affected by this complication (10.6 vs 40.6 months).

Cirrhotic patients with Child-Pugh class C showed a survival of 2.9 months in contrast to 14.7 months among patients without HPS whereas cirrhotic patients with Child-Pugh class B showed a survival of 35.3 months in HPS vs. 44.5 months without HPS ***(Peter S et al, 2003)***.

(Krowka MJ, 1993) observed that the mortality in cirrhotic patients at 2.5 years after the diagnosis of HPS was 41%.

(Arguedas MR et al., 2003) showed that 1 year after OLT the postoperative mortality was almost two fold greater in patients with HPS than those free of this complication (29% vs 7%).

Management:

1. Pharmacological treatment:

There are currently no effective medical therapies for HPS. Small uncontrolled studies have reported a lack of efficacy using sympathomimetic agents, somatostatin, almitrine, indomethacin, and plasma exchange . Aspirin increased arterial oxygenation in two children who had HPS and a case report and subsequent open label trial using garlic also suggested a beneficial effect. In the latter trial, garlic powder was administered for a minimum of 6 months. Six of 15 (40%) patients who had HPS had improvements greater than 10 mmHg in the PaO_2 and one subject had resolution of hypoxemia (PaO_2:46-80 mmHg) over a 1.5 year period ***(Palma DT, 2006)***.

Acute infusion of methylene blue, a dye that inhibits the effect of NO on soluble guanylate cyclase, also transiently improved oxygenation in two reports comprising a total of eight patients ***(Madl C, 2000)***.

Acute administration of inhaled N-nitro-L-arginine methyle ester (L-NAME), to inhibit nitric oxide production also transiently improved

oxygenation in one patient (PaO_2:25-70 mmHg) but failed to significantly alter oxygenation in another group of 10 patients ***(Gomez FP et al., 2006)***.

A single case report suggests that norfloxacin also may have contributed to improvement in oxygen saturation in HPS where it was hypothesized that the patient's pulmonary vascular pathology was due, in large part, to chronic elevated levels of nitric oxide (a potent vasodilator thought to be generated by endotoxin absorbed from the gut). Treatment with oral norfloxacin was initiated on the basis of data that this antibiotic reduces endotoxemia and concomitant nitric oxide production in patients with cirrhosis. Four months after initiation of treatment, the patient's hypoxia had resolved. These reports under score the need to evaluate agents targeted at likely pathogenetic mechanisms in randomized multicenter trials to determine efficacy ***(Anel RM, 2001)***.

Several uncontrolled trials using different agents have shown no effects or limited improvement in HPS, such that We therefore suggest that, the extremely safe and commonly used antidepressant medication paroxetine (Paxil) which is a potent nitric oxide synthase (NOS) inhibitor be considered for use in HPS ***(Eric Lewin A, 2004)***.

2. Non-pharmacological treatment:

- *Long-term oxygen therapy*

HPS patients with severe hypoxemia (PaO_2 <60 mmHg) at rest should receive continuous long-term low-flow oxygen therapy ***(Herve p et al., 2007)***.

Continuous long-term oxygen therapy is the only effective therapy for hypoxemia in HPS patients ***(Rodriguez-Roisin R, 2005)***.

- *Transjugular intrahepatic portosystemic shunt (TIPS)*

Portal hypertension appears to play a central role in the pathogenesis of HPS. Accordingly, a reduction in portal pressure might be beneficial in HPS.

However, TIPS neither improved nor worsened pulmonary gas exchange in patients with portal hypertension therefore the use of TIPS as a specific treatment for HPS is not supported by several studies ***(Lasch HM et al., 2001)*** and ***(Martinez-Pall et al., 2005)***.

- *Cavoplasty*

This effective decompressive treatment in patients with suprahepatic inferior vena cava obstruction causing Budd–Chiari syndrome showed promise in reversing coexistent HPS ***(Herve p et al, 2007)***.

- *Embolization*

Coil embolization (embolotherapy) in type II angiographic pattern HPS has been reported to improve arterial oxygenation (as a temporary measure) in a single case report ***(Herve P et al., 2007)***.

- *Orthotopic liver transplantation(OLT)*

In the past, HPS was considered a contraindication for liver transplantation when severe hypoxemia was present, because of an expected high post-operative mortality and because of the lack of information about long-term out come. Several case reports and case series have subsequently demonstrated that even severe hypoxemia could reverse after liver transplantation (LT), although the improvement in oxygenation may take several months or even years. The lower the pre-operative PaO_2, the longer the time to reverse hypoxaemia. HPS is presently considered as an indication for LT per se, whatever the severity of the underlying liver disease may be ***(Rolla G, 2004)***.

LT is the only possible cure for HPS. The preoperative mortality rate ranges from 9 to 16%, with 1 year mortality rate of 26% ***(Taillé C et al., 2003)***.

Improvement of oxygenation has generally been observed in the majority of patients who survived the preoperative period, even in the most severe cases. Severe hypoxemia, poor 100% oxygen response, high shunt fraction have been reported to be strong risk factors for increased post-liver transplantation mortality ***(Arguedas MR et al., 2003)*** although ***(Collisson EA et al., 2002)*** stated that none of the above factors were associated with a significant excess of mortality.

This supports the newly implemented United Net-work for Organ Sharing (UNOS) criteria that LT for HPS may be extended to include patients with PaO_2 < 60mmHg ***(Wiesner R et al., 2003)***.

Interestingly, liver transplantation reverses pulmonary vasodilatation and hypoxemia in almost all cases, even in those with profound hypoxemia at evaluation. Therefore, evidence for hepatopulmonary syndrome represents an accepted indication for transplantation, including in patients with otherwise compensated cirrhosis ***(Taillé C et al., 2003)***.

Only major hypoxemia (PaO_2 below 50mmHg on room air) significantly affects early post-transplantation survival compared with cirrhotic patients with out hypoxemia. Post-transplantation, the mean interval for a return of PaO_2 over 70 mmHg is 6 months on average; it can be longer than 1 year in some patients ***(Claire F, 2007)***.

PATIENTS AND METHODS

This study included 50 adult patients with liver cirrhosis presenting to National Liver Institute, Menoufiya University.

Inclusion criteria were :

Patients with liver cirrhosis have the ability to perform a full lung function test.

Exclusion criteria were:

1. Patients with cardiac diseases e.g Ischemic heart disease, valvular heart disease and congestive heart failure.
2. Patients with chronic intrinsic lung disease e.g chronic obstructive air way disease, bronchial asthma, pneumonia and lung fibrosis.
3. Patients with pleural effusion.
4. Patients with malignancy any where.

Informed consent was obtained from each patient.

All included Patients were subjected to the following:

- Thorough history taking and clinical examination.
- Laboratory investigations:

  Liver profile:
  - Bilirubin (total and direct).
  - Albumin.
  - Prothrombin time, concentration and INR (International normalized ratio).
  - ALT.
  - AST.

- Alkaline phosphatase.
- γ-GT (gamma-glutamyl transpeptidase).

Liver function test was done using Cobas Integra 400, Hoffman La Roche Company, Switzerland. The only exception was prothrombin time, concentration and INR which were assessed using Thromborel S, Behring fibrin timer II, Behring Inc., Germany.

- X-ray of chest: the chest radiographs were done in posteroanterior view and lateral views.
- Abdominal ultrasonography: It was done using real time ultrasound equipment with a 3.5 MHz convex array transducer with a pulsed Doppler device operating at a frequency of 3.5 MHz (Aloka SSD 680, Tokyo, Japan).
- Echocardiogram: it was done by using combined M-mode and two dimensional transthoracic echocardiography with an apical four chamber view (Hewlett Packard Sonos 2000 with a 2.5 m Hz transducer ; Hewlett Packard, Palo Alto, CA, USA).
- Arterial blood gases analysis: arterial blood gas samples were obtained by percutaneous radial artery puncture using a heparinized syringe with the subject in supine and erect positions breathing room air (FiO2: 21%), and were analyzed with a standard blood gas analyzer (BGElectrolytes; Instrumentation Lab. Inc., USA) to determine the partial pressure of oxygen (PaO_2) , carbon dioxide tension (PCO_2) and arterial oxygen saturation (SaO_2), as well as the pH of arterial blood. A-aDo_2 calculated using the modified alveolar gas equation:

$$\mathbf{A\text{-}aDo_2 = FiO_2 (P_B\text{-}47) - (PaCO_2/R) - PaO_2}$$

were $\mathbf{FiO_2}$ is the fraction of inspired O_2 (FiO_2 = 0.21), $\mathbf{P_B}$ is the barometric pressure (average, 760 mmHg), $\mathbf{PaCO_2}$ is alveolar CO_2

which was assumed to be equal to arterial (PCO_2) and **R** is the mean respiratory equotient (assumed to be o.8 while a subject is breathing room air).

The normal range of A-aDo_2 was 4-8 mmHg ***(Schiffer E et al., 2006)***. 9-14 mmHg is defined as subclinical range ***(Binay K D, 2000)***.

Normal blood gas values are, pH (7.35-7.45), PaO_2 (80-100mmgH), $PaCO_2$ (35-45 mmgH) and , SaO_2 (95-100 %) ***(Bisson J, 2006)***.

According to the PaO_2 measured in supine position, a PaO_2 of <80 mm Hg was defined as hypoxemia, in a scheme in which mild hypoxemia was defined as 70–80 mmHg, moderate hypoxemia as 60 – < 70 mm Hg, and severe hypoxemia as <60 mm Hg ***(Maruyama S et al., 2005)***.

$SaO_2 \leq 95\%$ is regarding as hypoxemia and $PaCO_2 < 35$ mmHg is regarding as hypocapnia ***(Mazzeo AT et al., 2006)***.

- Lung function test : forced expiratory volume in first second (FEV_1) and forced vital capacity (FVC) were measured using a computerized Spirometer (Quark PFT class IIa; Sensor Medics, COSMED Srl, Rome, ITALY) according to standard measures, recording the best of three attempts. All spirometric indices were expressed as percentage of the predicted values corrected for age, sex and body surface area according to respective reference equations of American thoracic society (ATS) and European respiratory society (ERS).

Single-breath carbon monoxide transfer factor (TLCO) or (Diffusing capacity, DLCO) was calculated by the single breath technique and corrected to a standard hemoglobin concentration of 14.6 g/dl. the percentage predicted values were derived from European standards.

the normal values are as follows:

DLco > 75 % of predicted.

FEV_1% > 100 % of predicted.

FVC% > 80 % of predicted,

FEV_1/FVC % > 70 % of predicted.

Normal spirometry indicated by FVC% > 80 % of predicted, FEV_1% > 100 % of predicted and FEV1/FVC % > 7o % of predicted.

The obstructive pattern is indicated as follows:

FEV_1% < 100 ≥ 70 indicate mild obstructive pattern

FEV_1% < 70 ≥ 60 indicate moderate obstructive pattern

FEV_1% < 60 indicate severe obstructive pattern

The restrictive pattern is indicated as follows:

FVC % < 80 ≥ 70 % of predicted indicate mild restrictive pattern

FVC % < 70 ≥ 60 indicate moderate restrictive pattern

FVC % < 60 indicate severe restrictive pattern.

- The grading of liver insufficiency (A, B, C) is determined according to Child Pugh score ***(Pugh et al., 1973).***

Table VIII: Child Pugh score

Parameters	**Numerical score**			**Child-Pugh class**	**Numerical score**
	1	**2**	**3**		
1. Encephalopathy	None	Slight to moderate	Moderate to severe	A	5-6
2. Ascites	None	Mild	Moderate to severe	B	7-9
3. Serum Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8		
4. Serum Bilirubin (mg/dL)	< 2	2-3	> 3	C	10-15
5. Prothrombin time (seconds increased)	1-3	4-6	> 6		

Statistical analysis

Data were analyzed using the SPSS package for Windows, version 10.0.1, SPSS Inc., Chicago, Illinois, USA. The following tests were used to test for significance:

1. **Chi-square test (χ^2):** for comparison of two or more sets of nominal qualitative data.

2. **Student t-test:** is a test of significant used for comparison between tow groups having quantitative variable.

3. **paired t-test**: is a test of significance used for comparison between two related groups having quantitative variable.

4. **Fisher's exact test:** for comparison of two or more sets of nominal qualitative data when the expected value of one cell less than five.

5. **Pearson's correlation coefficient (r):** was used to test significant correlation between 2 series of non parametric variables when they were categorized or they were not following normal distribution.

P = p value

T = t value

N = sample size

SD = standard deviation

χ2 = chi-square value

> 0.05 = no statistical significant difference

< 0.05 = statistical significant difference at 0.05

RESULTS

The present study included 50 patients presenting with liver cirrhosis. The overall age was 51.32 ± 10.78 years in the range of 30-70 years. Females represented 36.0% (18 patients) of the total number studied subjects and males represented 64.0% (32 patients). Twenty four patients had Child Pugh stage C liver disease, 16 were stage B, and 10 were stage A.

All included patients were subjected to arterial blood gas samples which were obtained by percutaneous radial artery puncture with the subject in supine and erect positions breathing room air, lung function test, single-breath carbon monoxide transfer factor (TLco) and echocardiogram.

Table (1) Figure (1) shows the personal data and Child Pugh classification in patients with liver cirrhosis. The highest percent of cirrhotic patients were males and class C Child-Pugh classification.

Table (2) Figure (2) shows the mean values of spirometric measurements of cirrhotic patients. The mean values of FEV_1 % of prediction (110.12 ± 19.51), FVC% of prediction (101.80 ± 20.46), FEV_1/FVC % of prediction (110.37 ± 6.70) and DLco corrected (69.47 ± 11.89). The mean values of spirometric measurements of cirrhotic patients were within normal range while DLco corrected was less than normal.

Table (3) Figure (3) shows correlation between pulmonary function tests and age in patients with liver cirrhosis. There was negative

correlation between age and FEV_1 (%), FVC (%) and DLco corrected in cirrhotic patients.

Table (4) Figure (4) shows the pulmonary function tests in patients with liver cirrhosis regarding gender. There was no statistically significant relationship between FEV_1 (%), FVC (%) and DLco corrected regarding gender.

Table (5) Figure (5) shows the pulmonary function tests in patients with liver cirrhosis regarding Child Pugh classification. There were statistically significant differences in FEV_1 (%), FVC (%) and DLco corrected in cirrhotic patients regarding Child Pugh classification. The FEV_1 (%) showed statistically higher significant decrease in class C than class A ($P< 0.01$) and FVC (%) showed statistically significant decrease in class C than class A ($P< 0.05$) while DLco corrected showed statistically higher significant decrease in class C than class A ($P<0.01$).

Table (6) Figure (6) shows the correlation between DLco corrected and spirometric measurements. There was no statistically significant correlation between FEV_1 (%), FVC (%) and DLco corrected in cirrhotic patients.

Table (7) Figure (7) shows the comparison between arterial blood gases (ABG) parameters in supine and erect positions in patients with liver cirrhosis. There was no statistically significant difference between arterial blood gases (ABG) parameters in supine and erect positions in patients with liver cirrhosis.

Table (8) Figure (8) shows the frequency distribution of patients with liver cirrhosis regarding spirometric measurements, DLco corrected state, ABG parameters, orthodeoxia, hypoxemia and A-aDO_2. The

highest percentage of cirrhotic patients had normal spirometric measurements, reduced DLco corrected state, respiratory alkalosis, hypocapnia, abnormal A-aDO_2 without orthodeoxia and with negative hypoxemia.

Table (9) Figure (9) shows the pulmonary function tests in patients with liver cirrhosis regarding orthodeoxia. There was statistically highly significant lower mean value of DLco corrected in cirrhotic patients with orthodeoxia than without orthodeoxia ($P<0.01$).

Table (10) Figure (10) shows the arterial blood gases (ABG) in patients with liver cirrhosis regarding position and orthodeoxia. There was statistically highly significant higher mean value of PaO_2 in supine position in cirrhotic patients with orthodeoxia than those without ($P< 0.01$) while the reverse occurred regarding PaO_2 in erect position ($P<0.001$).

There were statistically highly significant higher mean values of PaO_2, $PaCO_2$ and O_2 saturation in supine position than in erect position in cirrhotic patients with orthodeoxia ($P <0.01$).

There was statistically highly significant lower mean value of PaO_2 in supine position than in erect position in cirrhotic patients without orthodeoxia ($P< 0.001$) while the reverse occurred regarding $PaCO_2$ levels ($P <0.01$).

Table (11) Figure (11) shows the relationship between Child Pugh classification and orthodeoxia in patients with liver cirrhosis. There was no statistically significant relationship between Child Pugh classification and orthodeoxia in cirrhotic patient.

Table (12) Figure (12) shows the relationship between Child Pugh classification and degree of hypoxemia in patients with liver cirrhosis. There was no statistically significant relationship between Child Pugh classification and degree of hypoxemia in cirrhotic patient.

Table (13) Figure (13) shows the relationship between Child Pugh classification and hypoxemia in patients with liver cirrhosis. There was no statistically significant relationship between hypoxemia and Child Pugh classification in patients with liver cirrhosis.

Table (14) Figure (14) shows the relationship between hypoxemia in erect and supine positions with orthodeoxia in patients with liver cirrhosis. There was no statistically significant relationship between hypoxemia in supine and erect positions with orthodeoxia in cirrhotic patient.

Table (15) Figure (15) shows the relationship between restrictive ventilatory disorders and DLco corrected state in patients with liver cirrhosis. There was no statistically significant relationship between restrictive ventilatory disorders and DLco corrected state in cirrhotic patient.

Table (16) Figure (16) shows the relationship between the incidence of restrictive ventilatory disorders and DLco corrected state in patients with liver cirrhosis. There was statistically highly significant relationship between the incidence of restrictive ventilatory disorders and DLco corrected state in cirrhotic patient ($P < 0.0001$).

Table (17) Figure (17) shows the relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis. There was

statistically significant relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis ($P < 0.05$).

Table (18) Figure (18) shows the A-aDO_2 in patients with liver cirrhosis regarding patients position. There was statistically significant higher percent of abnormal A-aDO_2 in supine position than in erect position in cirrhotic patient ($P < 0.05$).

Table (19) Figure (19) shows the relationship between A-aDO_2 in supine and erect positions and Child Pugh classification in patients with liver cirrhosis. There was no statistically significant relationship between A-aDO_2 in erect and supine positions and Child Pugh classification in patients with liver cirrhosis.

Table (20) Figure (20) shows the relationship between A-aDO_2 and hypoxemia in patients with liver cirrhosis. There was no statistically significant relationship between A-aDO_2 and hypoxemia in erect position in patient with liver cirrhosis whereas all cases of hypoxemia had statistically highly significant abnormal A-aDO_2 in supine position in patient with liver cirrhosis ($P < 0.01$).

Table (21) Figure (21) shows the relationship between A-aDO_2 and PaO_2 in patients with liver cirrhosis. There was highly significant negative correlation between A-aDO_2 and PaO_2 in supine position in patients with liver cirrhosis.

Table (22) Figure (22) shows the relationship between A-aDO_2 and DLco corrected state in patients with liver cirrhosis. There was no statistically significant relationship between A-aDO_2 and DLco corrected state in both supine and erect positions in patients with liver cirrhosis.

Table (23) Figure (23) shows the relationship between A-aDO_2 and orthodeoxia in patients with liver cirrhosis in supine position. There was statistically significant relationship between orthodeoxia and A-aDO_2 in supine position in patients with liver cirrhosis ($P < 0.05$).

Table (24) Figure (24) shows the relationship between A-aDO_2 and orthodeoxia in patients with liver cirrhosis in erect position. There was no statistically significant relationship between orthodeoxia and A-aDO_2 in supine position in patients with liver cirrhosis.

Table (25) Figure (25) shows the relationship between A-aDO_2 and arterial blood gases (ABG) in patients with liver cirrhosis. There was no statistically significant relationship between arterial blood gases and A-aDO_2 in erect and supine positions in cirrhotic patient.

Table (1) Personal data and Child Pugh classification in patients with liver cirrhosis:

Personal data and Child Pugh classification	Patients with liver cirrhosis (No= 50) $\overline{X} \pm SD$	
Age (years)	51.32 ± 10.78	
	No	%
Gender:		
• Females	18	36.0
• Males	32	64.0
Child Pugh class:		
• A	10	20.0
• B	16	32.0
• C	24	48.0

Figure (1) Personal data and Child Pugh classification in patients with liver cirrhosis:

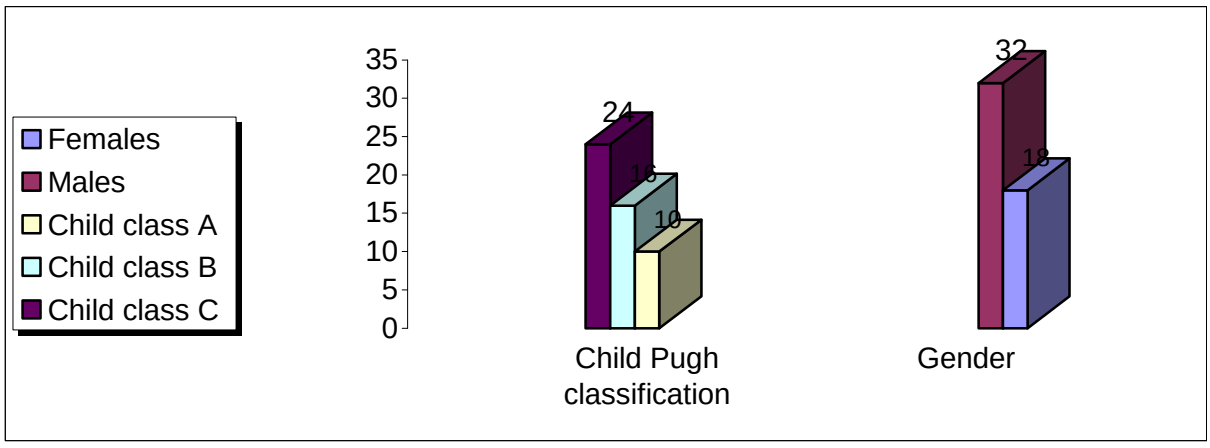


Table (2) Pulmonary function tests in patients with liver cirrhosis:

Pulmonary function tests (PFT)	**Patients with liver cirrhosis** (No = 50) $\overline{X} \pm SD$
Spirometric measurements:	
FEV_1 %	110.12 ± 19.51
FVC %	101.80 ± 20.46
FEV_1 / FVC %	110.37 ± 6.70
Diffusion capacity:	
DLco corrected	69.47 ± 11.89

Figure (2) Pulmonary function tests in patients with liver cirrhosis:

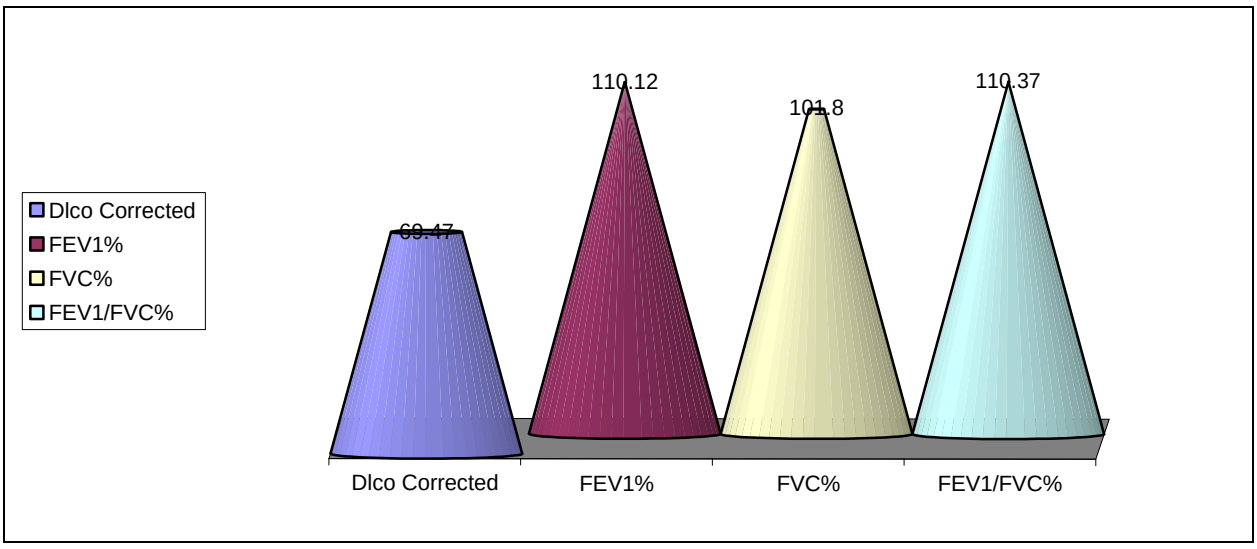


Table (3) Correlation between pulmonary function tests and age in patients with liver cirrhosis:

Pulmonary function tests (PFT)	Age (years) in patients with liver cirrhosis (No=50)	
	(r)	P
Spirometric measurements:		
FEV_1 (%)	- 0.23	> 0.05
FVC (%)	- 0.27	> 0.05
FEV_1 / FVC (%)	0.02	> 0.05
Diffusion capacity:		
DLco corrected	- 0.21	> 0.05

Figure (3) Correlation between pulmonary function tests and age in patients with liver cirrhosis:

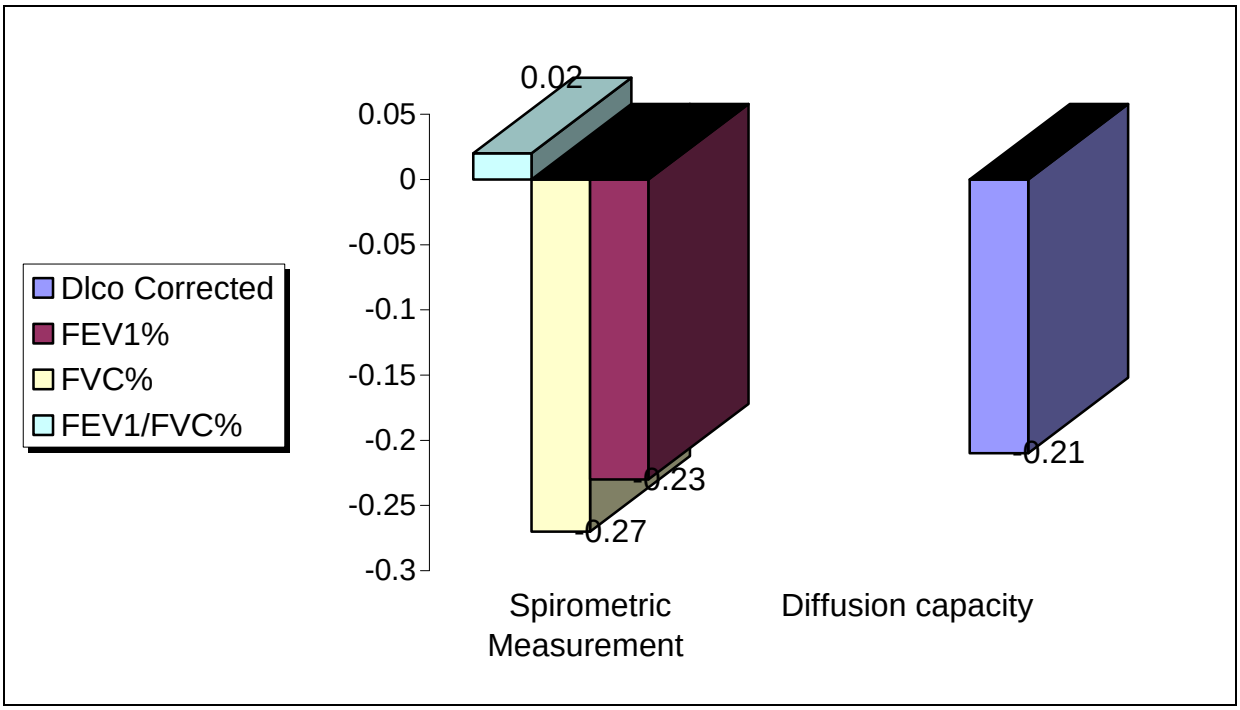


Table (4) Pulmonary function tests in patients with liver cirrhosis regarding gender:

Pulmonary function tests (PFT)	Patients with liver cirrhosis		T- test	P
	Females (No =18) $\overline{X} \pm SD$	Males (No = 32) $\overline{X} \pm SD$		
Spirometric measurements:				
FEV_1 (%)	124.04 ± 11.30	102.08 ± 18.61	0.41	> 0.05
FVC (%)	114.52 ± 12.96	104.64 ± 20.56	1.84	>0.05
FEV_1 / FVC (%)	111.30 ± 4.19	109.84 ± 7.78	0.73	> 0.05
diffusion capacity:				
DLco corrected	65.11 ± 12.11	68.92 ± 11.21	1.13	> 0.05

Figure (4) Pulmonary function tests in patients with liver cirrhosis regarding gender:

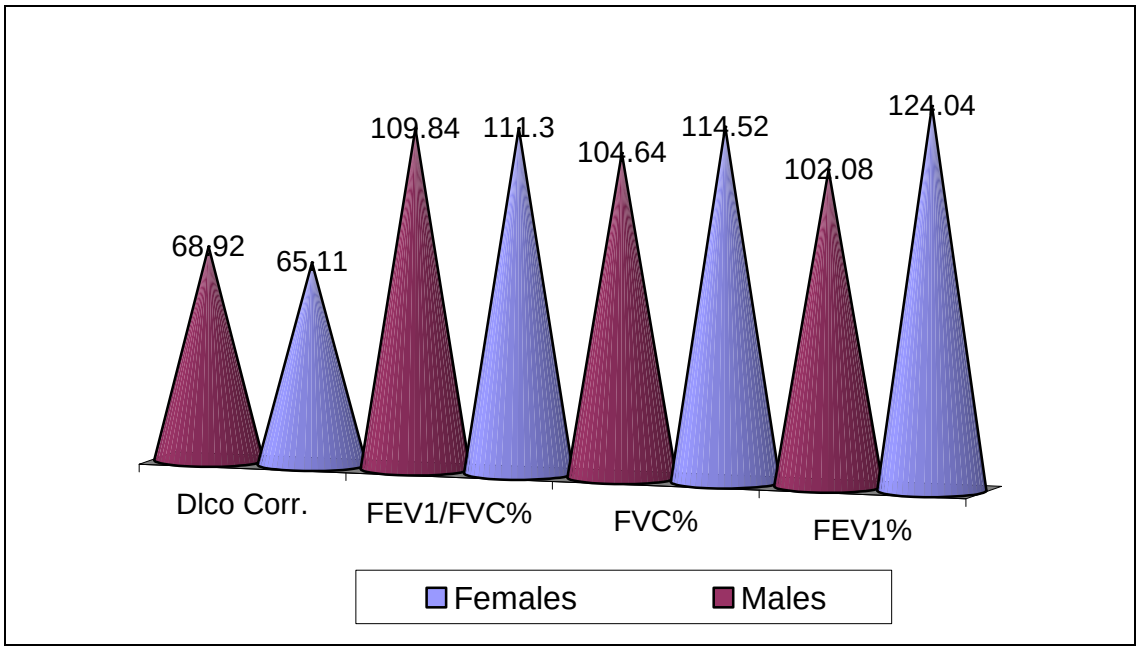


Table (5) Pulmonary function tests in patients with liver cirrhosis regarding Child Pugh classification:

Pulmonary function tests (PFT)	Child Pugh classification in patients with liver cirrhosis			F-test	P
	A (No = 10) $\overline{X} \pm SD$	B (No = 16) $\overline{X} \pm SD$	C (No = 24) $\overline{X} \pm SD$		
Spirometric measurements:					
FEV1 (%)	118.88 ± 12.19	113.92 ± 23.75	98.94 ± 9.01	4.71	< 0.01
FVC (%)	110.96 ± 19.59	105.48 ± 23.00	90.55 ± 10.64	4.33	< 0.05
FEV1 / FVC %	110.40 ± 8.35	110.78 ± 8.02	110.08 ± 5.12	0.05	> 0.05
Diffusion capacity:					
DLco corrected	10.94 ± 3.46	9.70 ± 2.43	9.44 ± 1.93	12.35	< 0.01

Figure (5) Pulmonary function tests in patients with liver cirrhosis regarding Child Pugh classification:

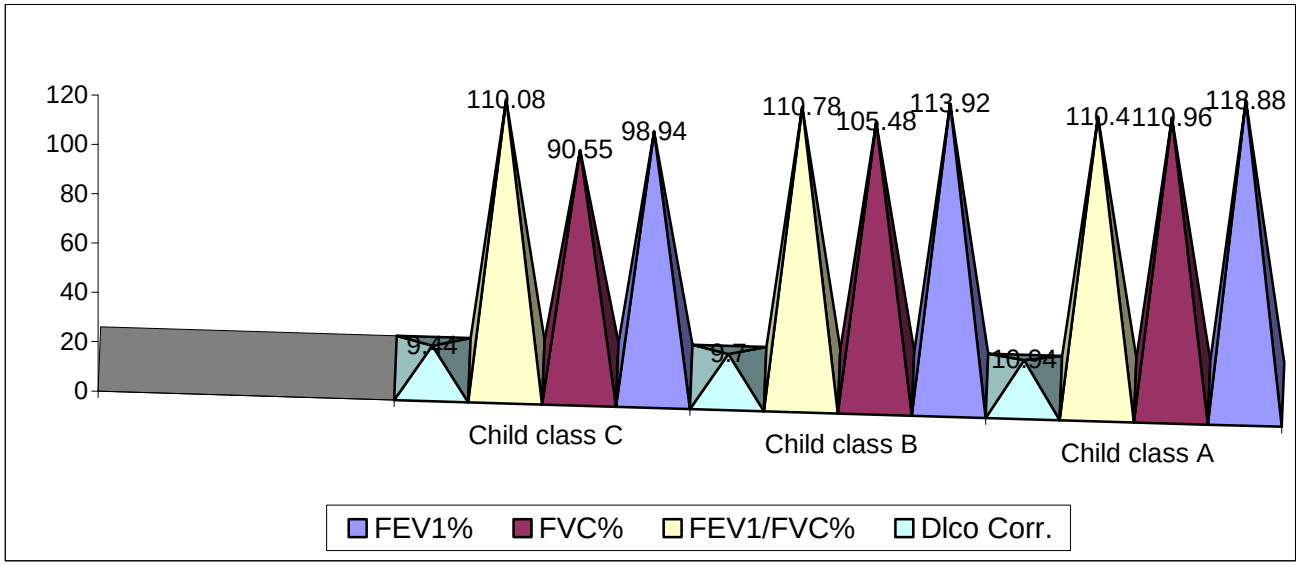


Table (6) Correlation between DLco corrected and spirometric measurements:

Spirometric measurements	DLco corrected (No=50)	
	(r)	P
FEV_1 %	0.04	> 0.05
FVC %	0.1	> 0.05
FEV_1/ FVC %	0.15	> 0.05

Figure (6) Correlation between DLco corrected and spirometric measurements:

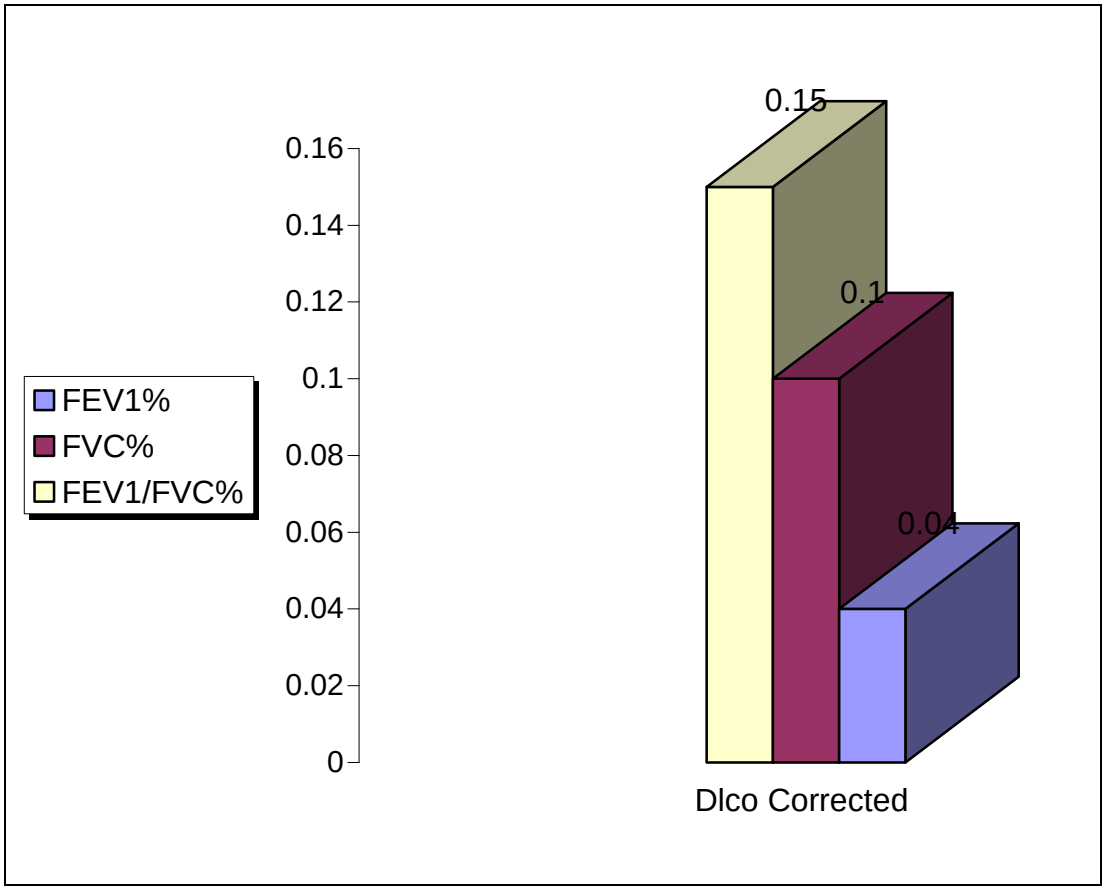


Table (7) Comparison between arterial blood gases (ABG) parameters in supine and erect positions in patients with liver cirrhosis:

ABG Parameters	Patients with liver cirrhosis (No = 50)		Mean difference	Paired T-test	P
	Supine position $\overline{X} \pm SD$	Erect position $\overline{X} \pm SD$			
PH	7.48 ± 0.05	7.47 ± 0.06	0.60	0.05	> 0.05
PaO_2 (mm Hg)	89.30 ± 18.01	85.13 ± 20.76	3.82	1.07	> 0.05
$PaCO_2$ (mmHg)	30.56 ± 3.59	29.45 ± 4.82	2.04	1.31	>0.05
O_2 sat. (%)	96.48 ± 1.89	92.38 ± 17.82	4.10	1.59	> 0.05
A-aDO_2 (mmHg)	28.33 ± 15.86	26.23 ± 19.19	2.10	7.9	> 0.05

Figure (7) Comparison between arterial blood gases (ABG) parameters in supine and erect positions in patients with liver cirrhosis:

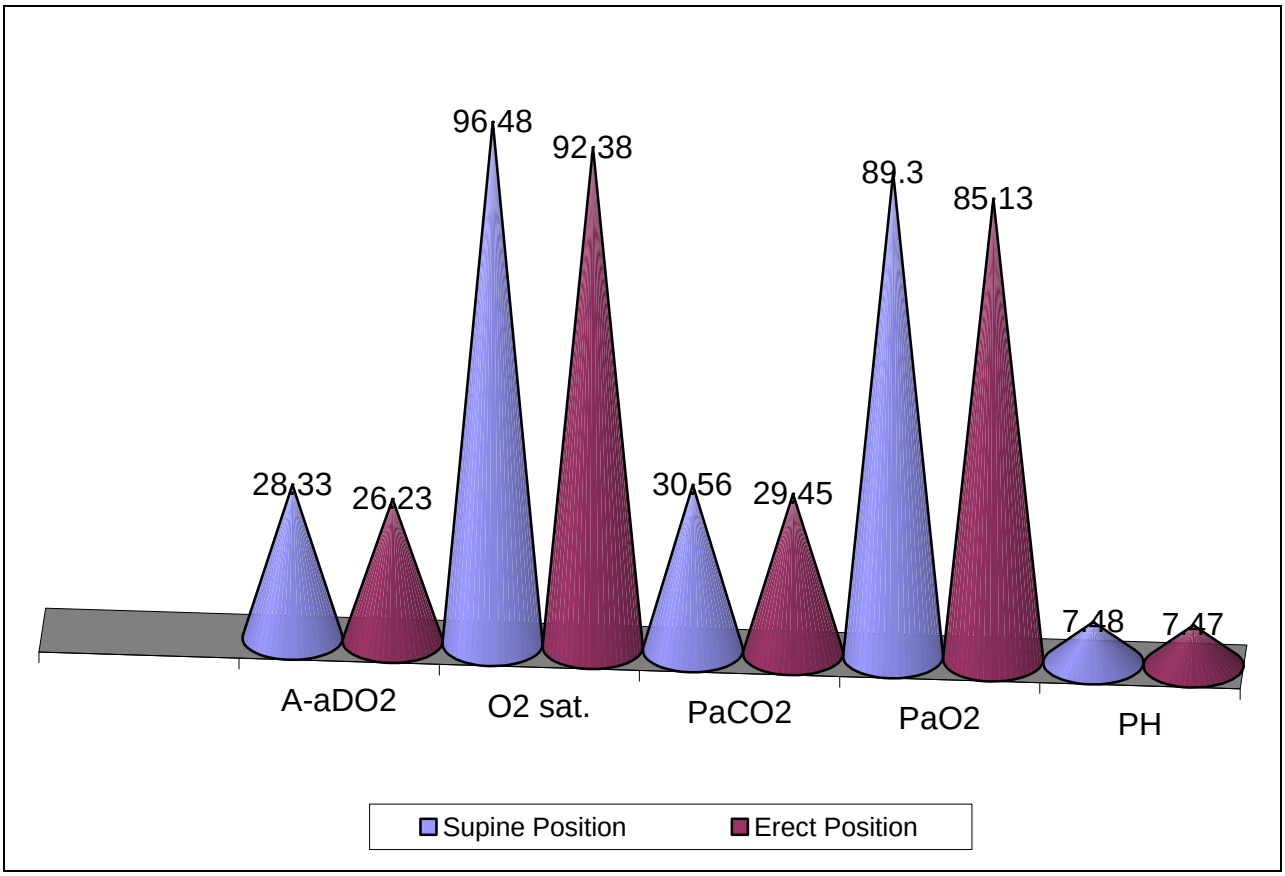


Table (8) Frequency distribution of patients with liver cirrhosis regarding spirometric measurements, DLco state, ABG, orthodeoxia, hypoxemia and A-aDO_2:

	Patients with liver cirrhosis (No= 50)	
	No	%
Spirometric measurements		
Normal	38	76.0 %
Restrictive	12	24.0 %
DLco-state		
Normal	18	36.0 %
Reduced	32	64.0 %
ABG		
R. alkalosis	44	88.0 %
M. alkalosis	6	12.0 %
Orthodeoxia		
Present	12	24.0 %
Absent	38	76.0 %
Hypoxemia		
Mild (<80%)	6	12.0 %
Moderate (<70%)	2	4.0 %
Severe (<60%)	6	12.0 %
Negative	36	72.0 %
Hypocapnia		
Positive (<35 mmgH)	38	76.0 %
Negative	12	24.0 %
A-a DO_2		
Normal (<15 mmgH)	11	22.0 %
Abnormal (≥ 15 mmgH)	39	78.0 %

Figure (8) Frequency distribution of patients with liver cirrhosis regarding spirometric measurements, DLco state, ABG, orthodeoxia, hypoxemia and A-aDO$_2$:

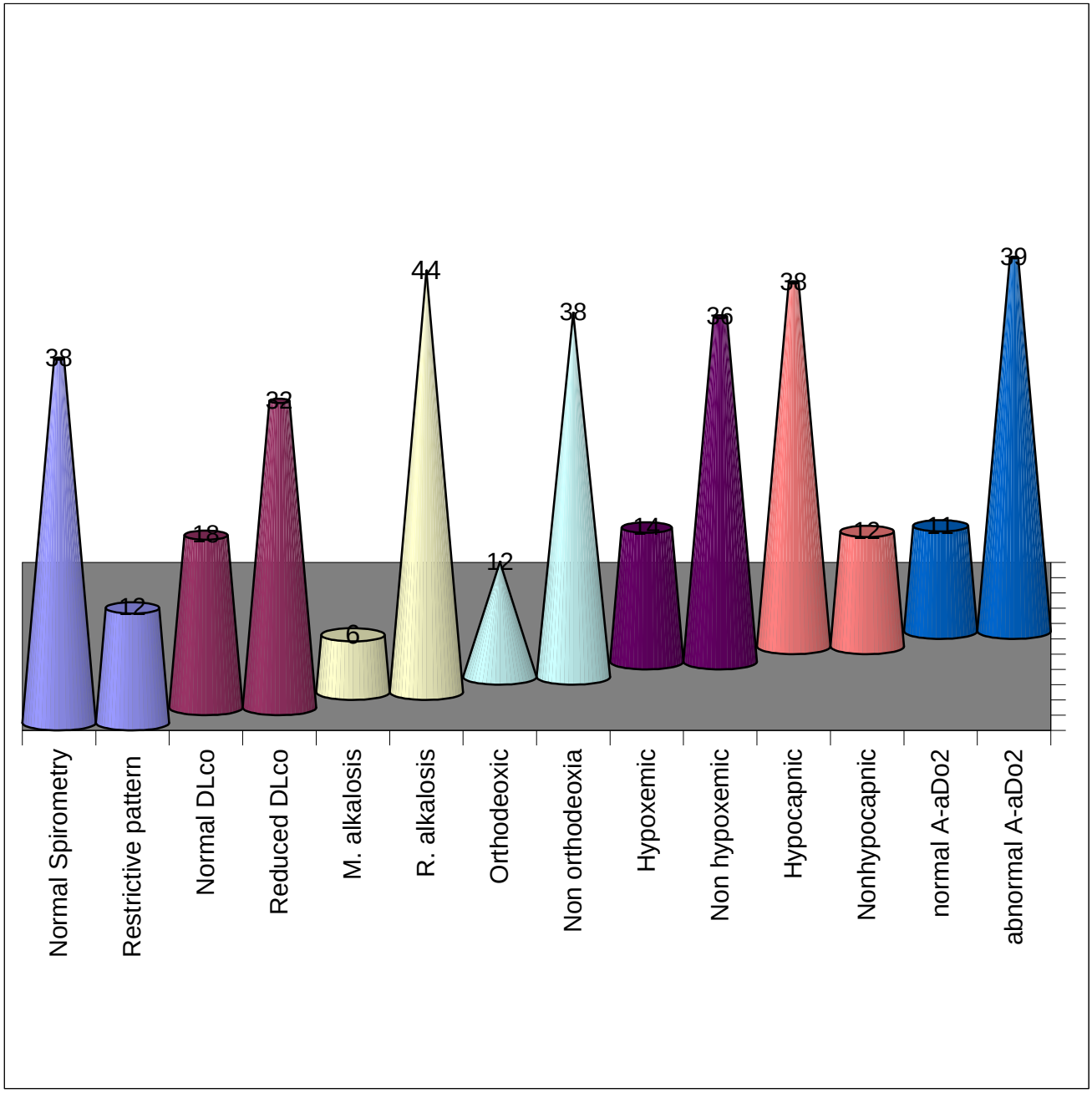


Table (9) Pulmonary function tests in patients with liver cirrhosis regarding orthodeoxia:

Pulmonary function tests	Patients with liver cirrhosis (No = 50)		T-test	P
	With Orthodeoxia (No = 12) $\overline{X} \pm SD$	Without Orthodeoxia (No= 38) $\overline{X} \pm SD$		
Spirometric measurements				
FEV_1 (%)	103.32 ± 23.22	112.62 ± 18.00	1.04	>0.05
FVC(%)	96.28 ± 21.44	103.54 ± 20.12	1.07	>0.05
FEV_1/FVC (%)	108.28 ± 5.80	111.03 ± 6.90	1.24	>0.05
Diffusion capacity DLco. corrected	62.27 ± 5.84	71.74 ± 12.44	2.54	<0.01

Figure (9) Pulmonary function tests in patients with liver cirrhosis regarding orthodeoxia:

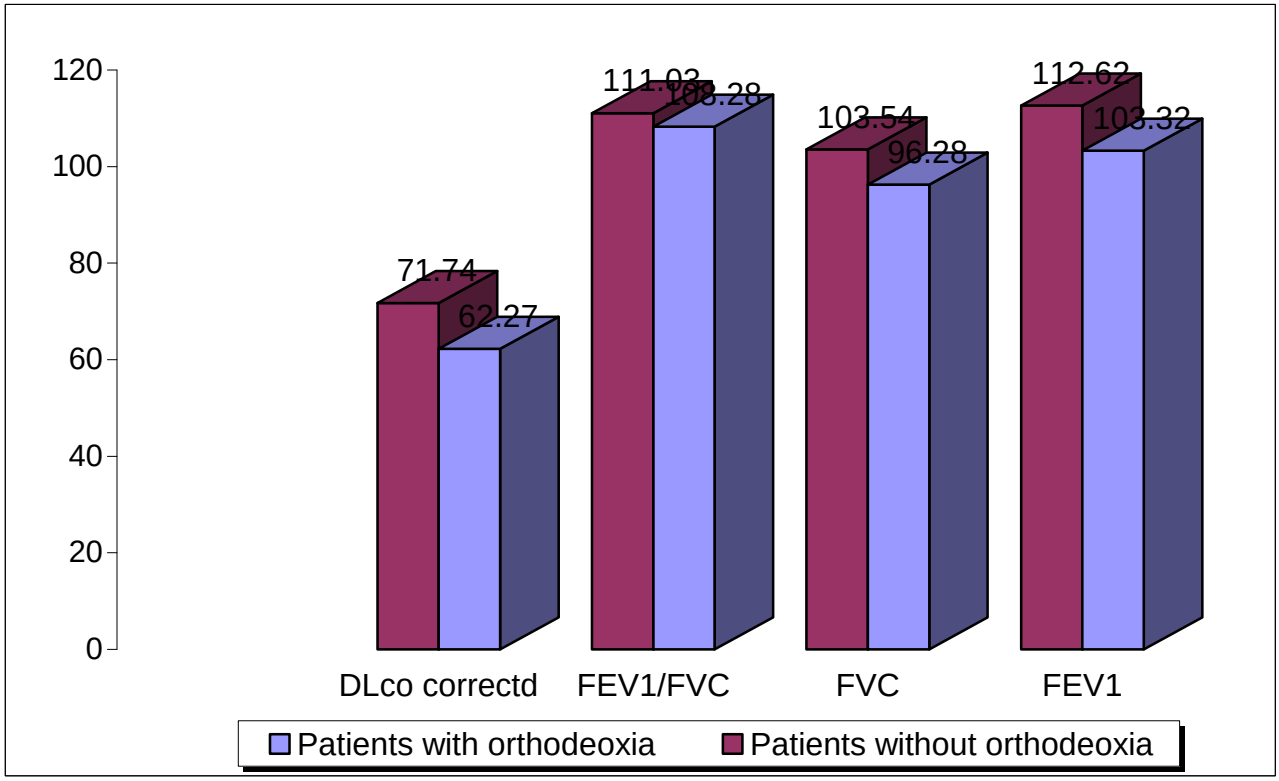


Table (10) Arterial blood gases (ABG) in patients with liver cirrhosis regarding position and orthodeoxia.

Arterial blood gases (ABG)	Patients with liver cirrhosis		Student T-Test	P
	With Orthodeoxia (No =12) $\overline{X} \pm SD$	With out Orthodeoxia (No=38) $\overline{X} \pm SD$		
PH In supine In erect	7.47 ± 0.04 7.45 ± 0.04	7.48 ± 0.06 7.49 ± 0.06	0.59 1.71	>0.05 >0.05
Paired t test	1.76	1.22		
p	> 0.05	> 0.05		
PaO_2(mmHg) In supine In erect	98.85 ± 20.86 70.23 ± 21.25	81.03 ± 14.90 95.09 ± 16.86	3.27 4.18	<0.01 <0.001
Paired t-test	4.48	5.39		
P	0.001	<0.001		
$PaCO_2$(mmHg) In supine In erect	29.68 ± 2.63 28.18 ± 3.41	30.38± 3.83 28.63 ± 5.23	0.97 0.28	>0.05 >0.05
Paired t-test	3.36	2.94		
P	< 0.01	< 0.01		
O_2 sot (%) In supine In erect	97.38 ± 1.27 92.10 ± 6.48	96.20 ± 1.87 92.47 ± 20.20	1.95 0.06	>0.05 >0.05
Paired t-test	2.92	1.11		
p	< 0.01	> 0.05		

Figure (10) Arterial blood gases (ABG) in patients with liver cirrhosis regarding position and orthodeoxia:

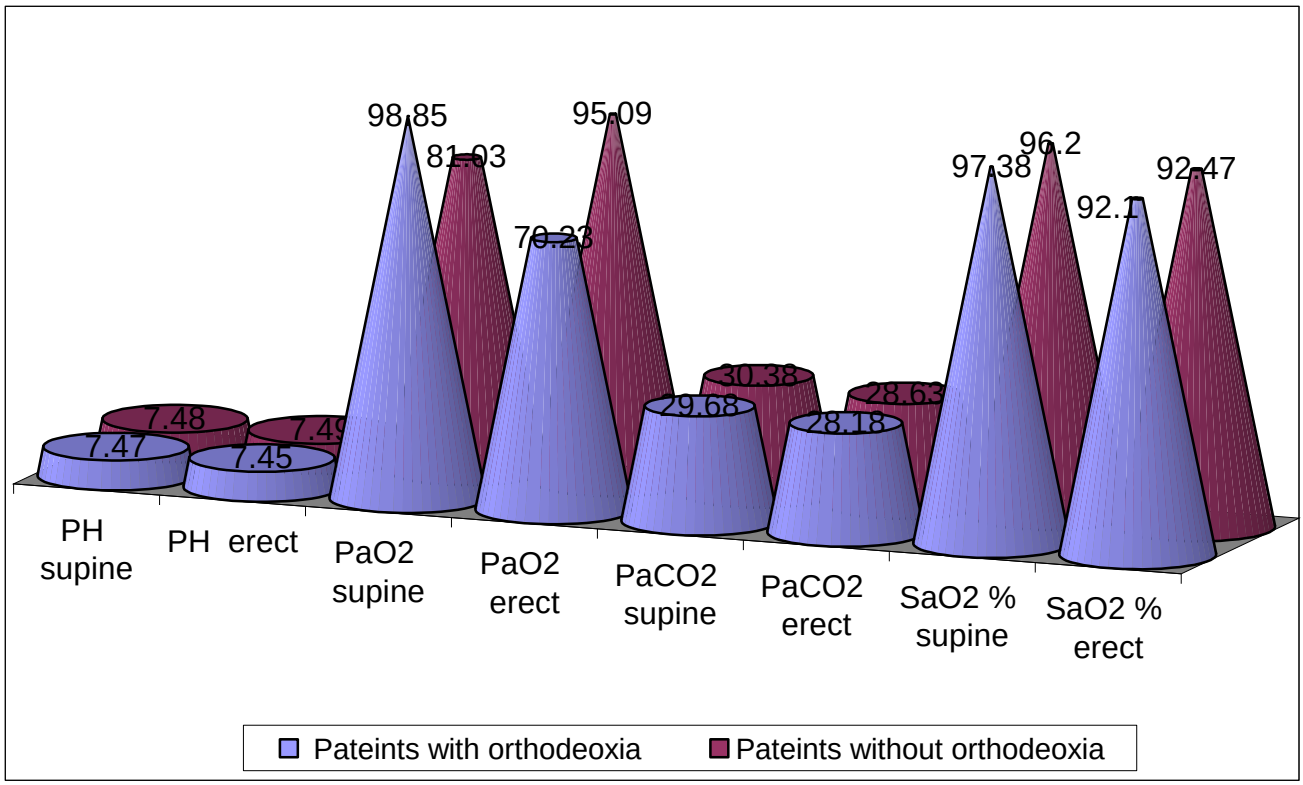


Figure (10-1) Arterial blood gases (ABG) in patients with liver cirrhosis and orthodeoxia:

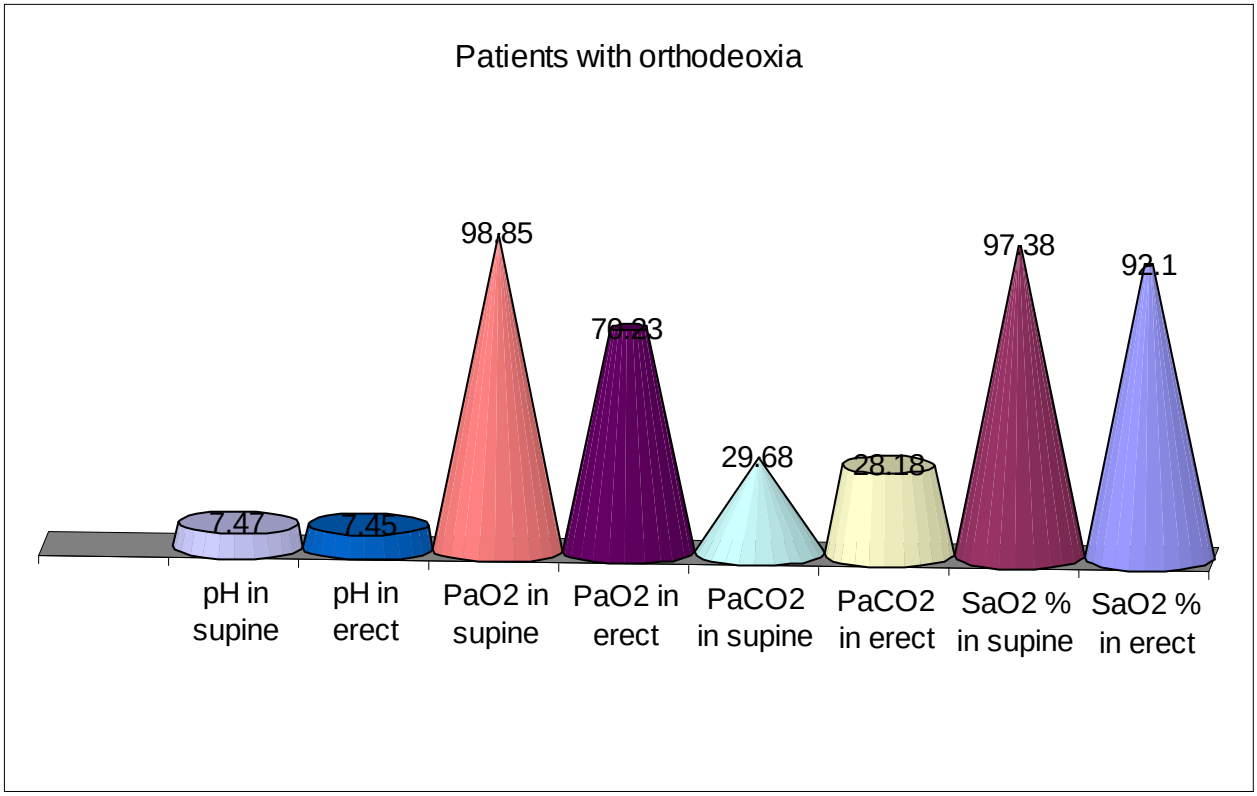


Figure (10-2) Arterial blood gases (ABG) in patients with liver cirrhosis without orthodeoxia:

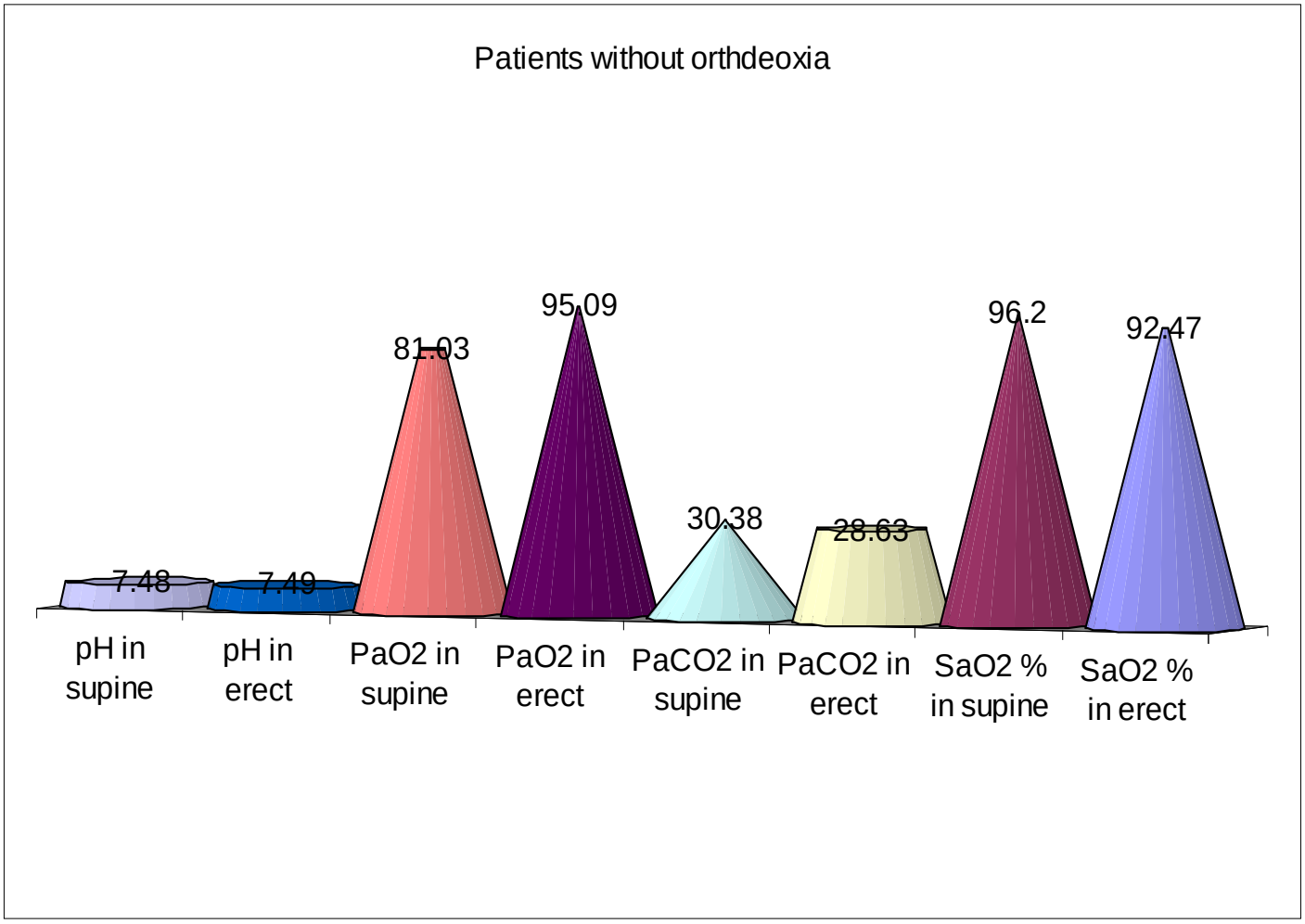


Table (11) The relationship between Child Pugh classification and orthodeoxia:

Orthodeoxia	Child Pugh classification in patients with liver cirrhosis (No=50)								
	A (No =10)		B (No =16)		C (No=24)		X^2	p
	No.	%	No.	%	No.	%		
Present	2	20.0	2	12.5	10	41.7	4.45	> 0.05
Absent	8	80.0	14	87.5	14	58.3		

Figure (11) The relationship between Child Pugh classification and orthodeoxia:

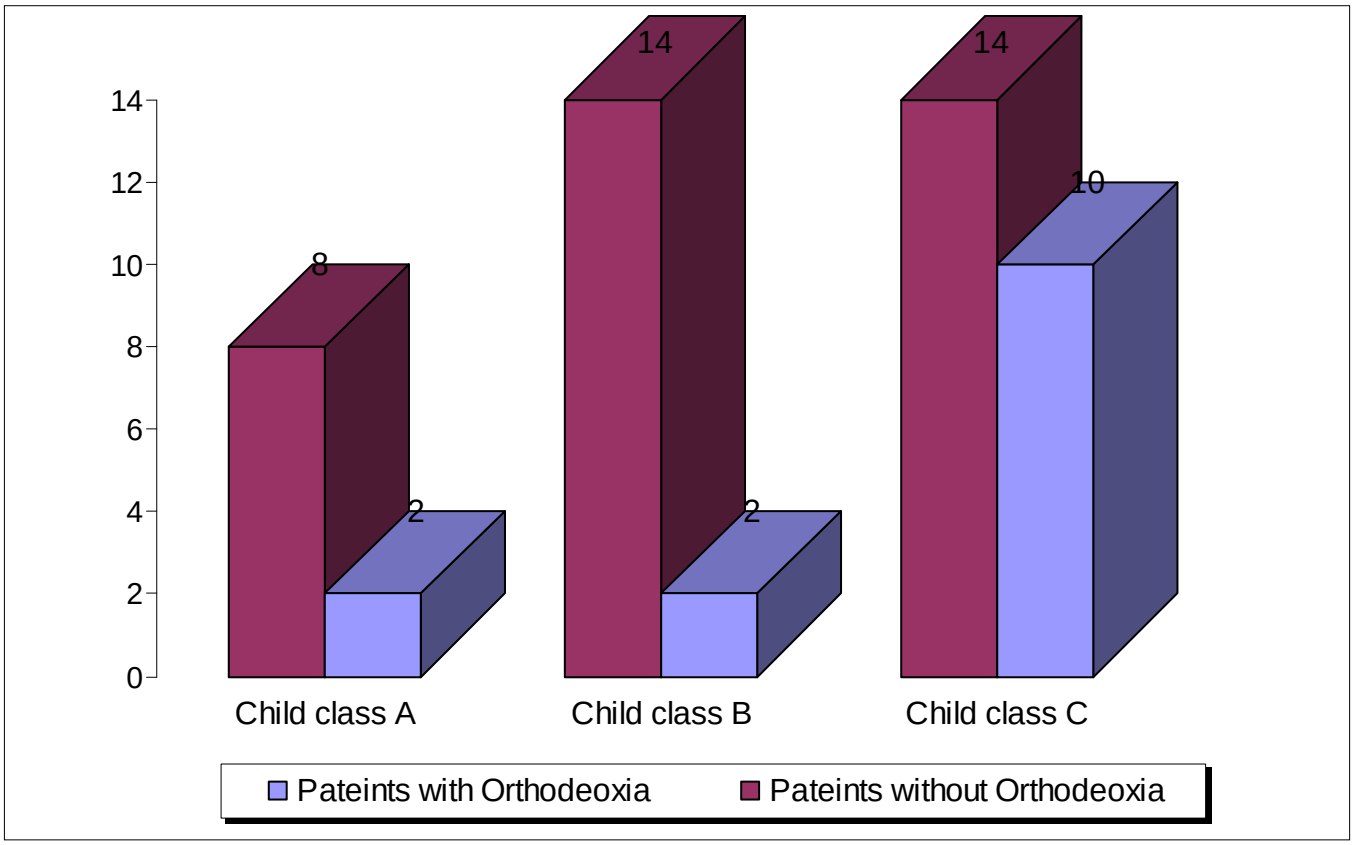


Table (12) The relationship between Child Pugh classification and degree of hypoxemia in patients with liver cirrhosis:

Hypoxemia	Child Pugh classification in patients with liver cirrhosis (No=50)							
	A (No=10)		B (No=16)		C (No=24)		X^2	p
	No.	%	No.	%	No.	%		
Mild	0	0.0	4	25.0	2	8.3	11.18	>0.05
Moderate	0	0.0	2	12.5	0	0.0		
Severe	2	20.0	0	0.0	4	16.7		
Negative	8	80.0	10	62.5	18	75.0		

Figure (12) The relationship between Child Pugh classification and degree of hypoxemia in patients with liver cirrhosis:

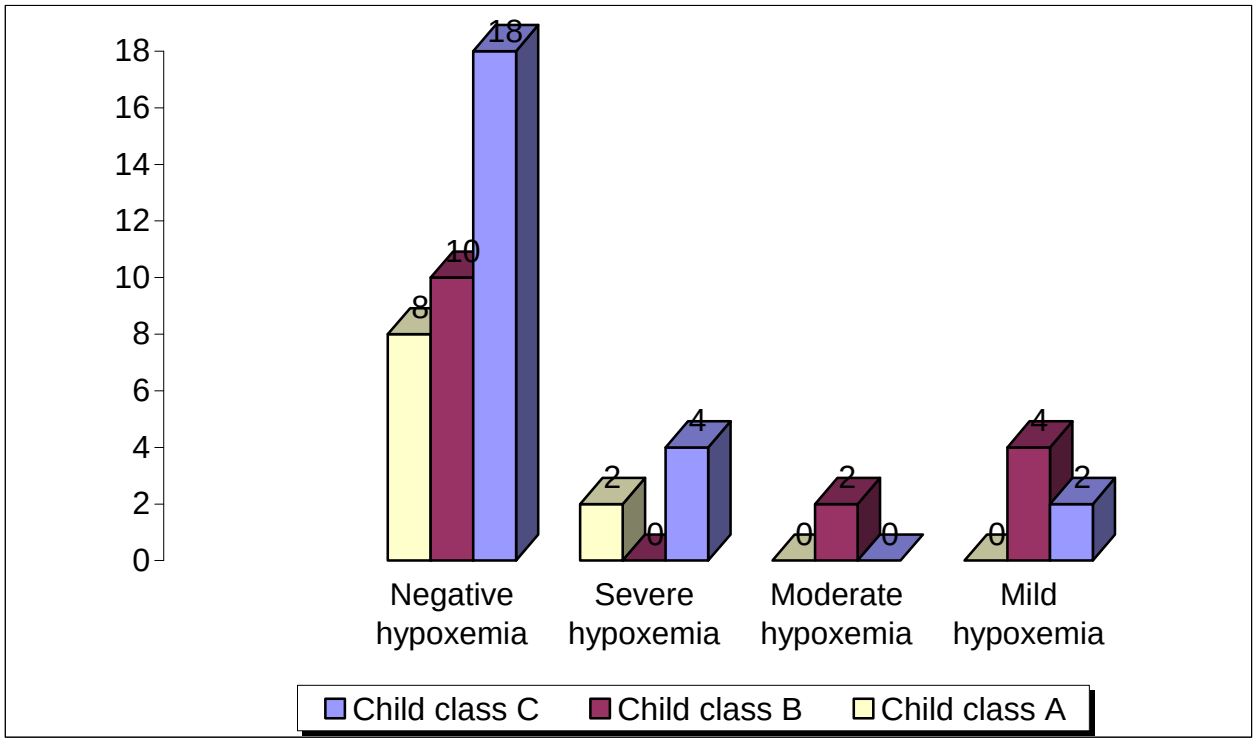


Table (13) The relationship between Child Pugh classification and hypoxemia in patients with liver cirrhosis:

Hypoxemia	Child Pugh classification in patients with liver cirrhosis (No=50)							
	A (No= 10)		B (No=16)		C (No=24)		$\times^2$	P
	No.	%	No.	%	No.	%		
Present	2	20.0	6	37.5	6	25	1.14	>0.05
Absent	8	80.0	10	62.5	18	75		

Figure (13) The relationship between Child Pugh classification and hypoxemia in patients with liver cirrhosis:

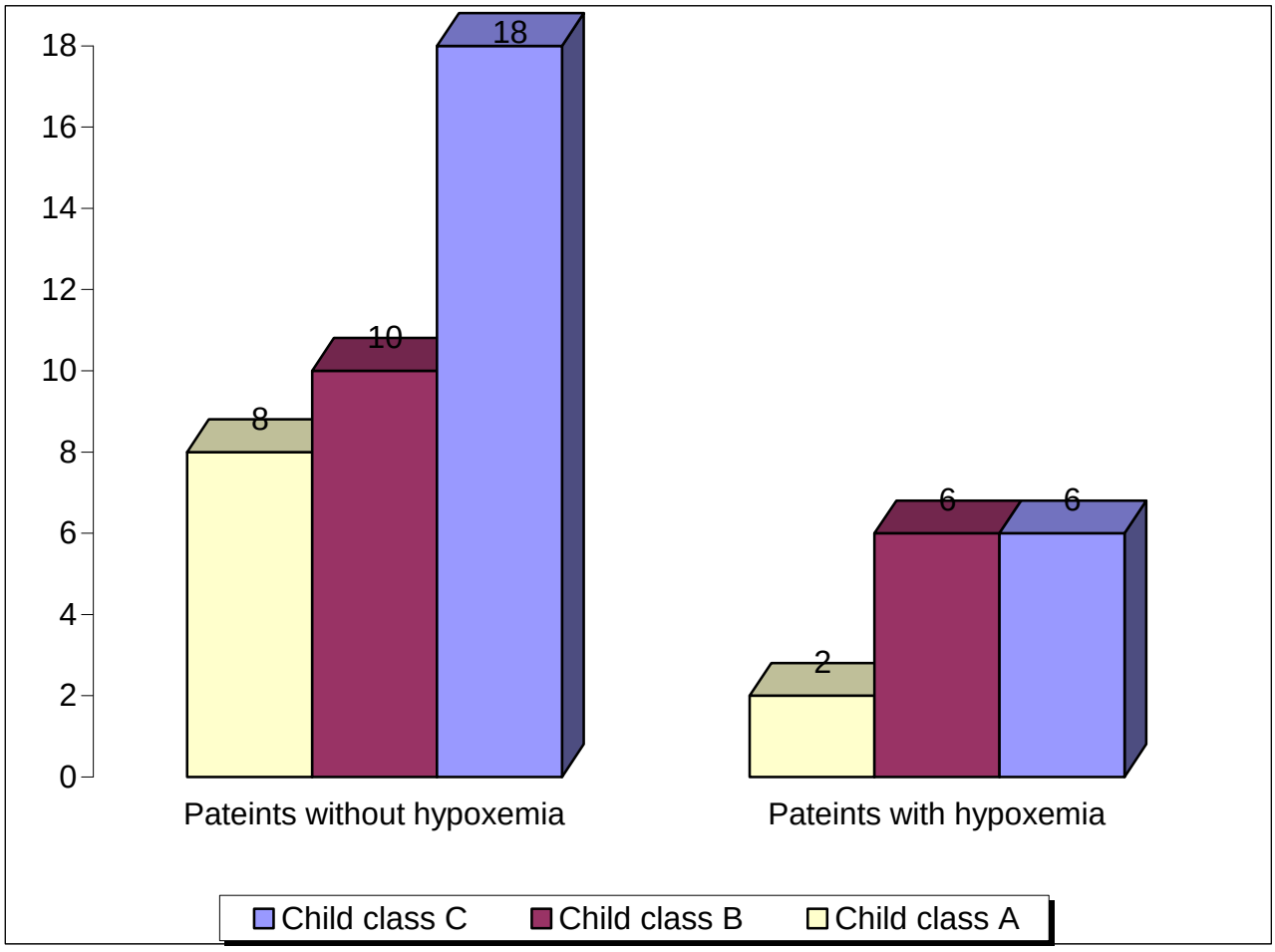


Table (14) The relationship between hypoxemia in erect and supine positions with orthodeoxia in patients with liver cirrhosis:

Hypoxemia	Patients with liver cirrhosis (No=50)					
	Patients with Orthodeoxia (No=12)		Patients without Orthodeoxia (No=38)		$\times^2$	p
	No.	%	No.	%		
Hypoxemia in supine						
• Present	2	16.7	12	31.6	1.01	>0.05
• Absent	10	83.3	26	68.4		
Hypoxemia in erect						
• Present	3	25.0	11	28.9		
• Absent	9	75.0	27	71.1	0.07	>0.05

Figure (14) The relationship between hypoxemia in erect and supine positions with orthodeoxia in patients with liver cirrhosis:

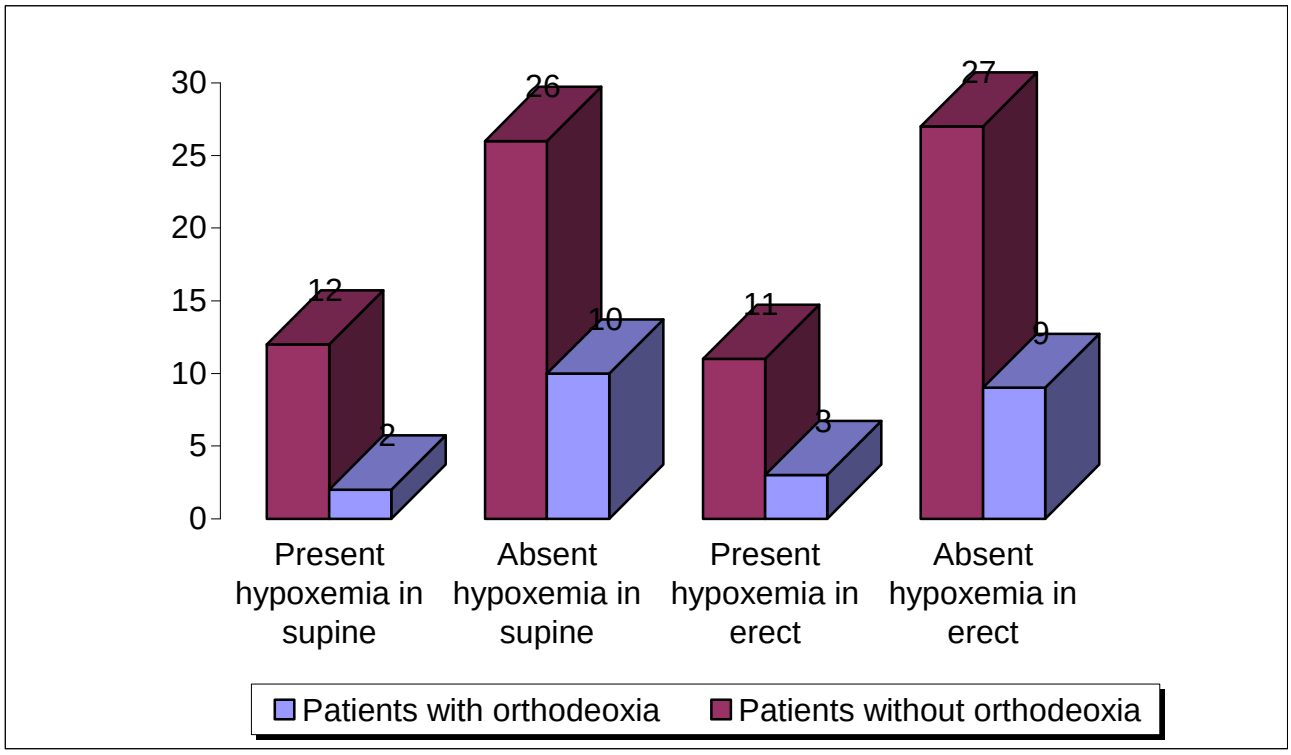


Table (15) The relationship between restrictive ventilatory disorders and DLco state in patients with liver cirrhosis:

DLco	Restrictive ventilatory disorders in patients with liver cirrhosis (No=50)					
	Present (No=12)		Absent (No=38)		$\times^2$	P
	No.	%	No.	%		
Reduced	8	66.7	24	63.2	0.05	> 0.05
Normal	4	33.3	14	36.8		

Figure (15) The relationship between restrictive ventilatory disorders and DLco state in patients with liver cirrhosis:

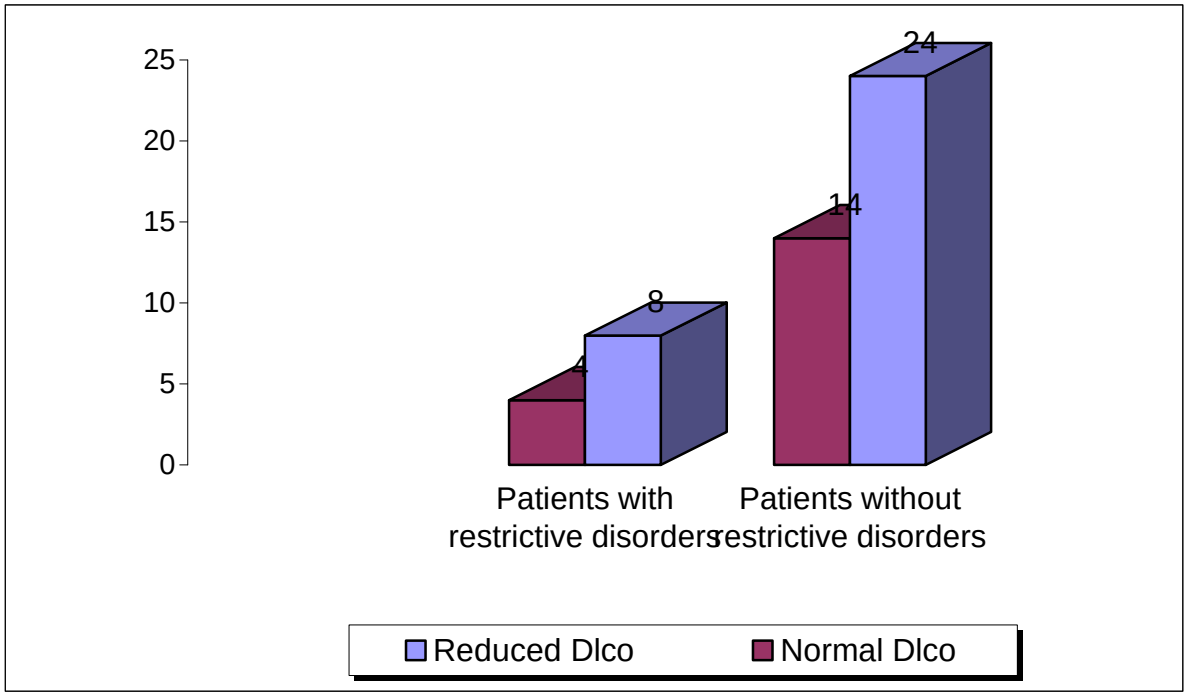


Table (16) The relationship between the incidence of restrictive ventilatory disorders and DLco corrected state in patients with liver cirrhosis:

	Patients with liver cirrhosis (No=50)					
	DLco corrected		**Restrictive disorders**		**$\times^2$**	**P**
	No.	%	No.	%		
Present	32	64	12	24	16.23	< 0.0001
Absent	18	36	38	76		

Figure (16) The relationship between the incidence of restrictive ventilatory disorders and DLco corrected state in patients with liver cirrhosis:

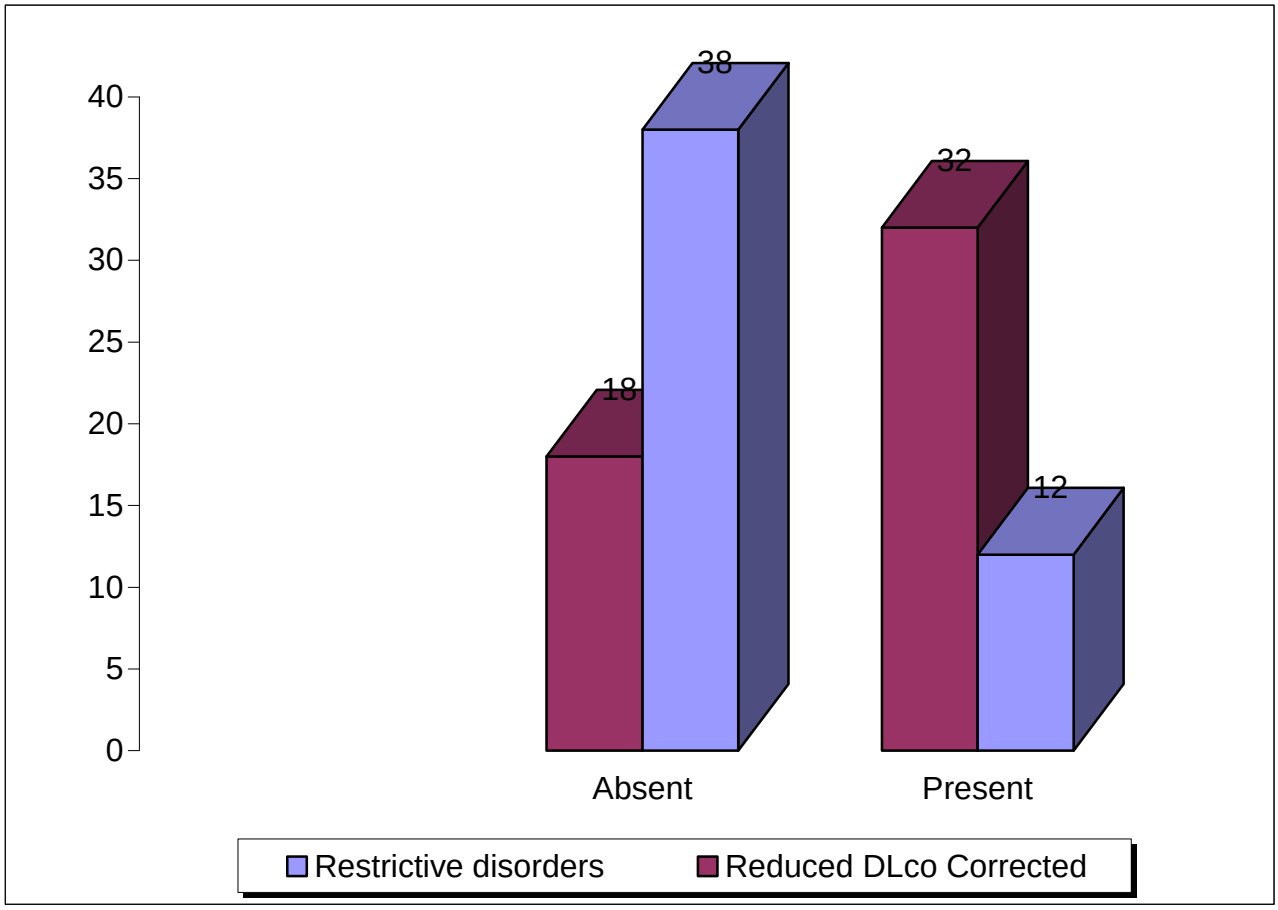


Table (17) The relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis:

Hypocapnia	Child Pugh classification in patients with liver cirrhosis (No=50)								$\times^2$	P
	A (No= 10)		B (No=16)		C (No=24)					
	No.	%	No.	%	No.	%				
Positive	4	40.0	14	87.5	20	83.4			8.97	< 0.05
Negative	6	60.0	2	12.5	4	16.6				

Table (17) The relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis:

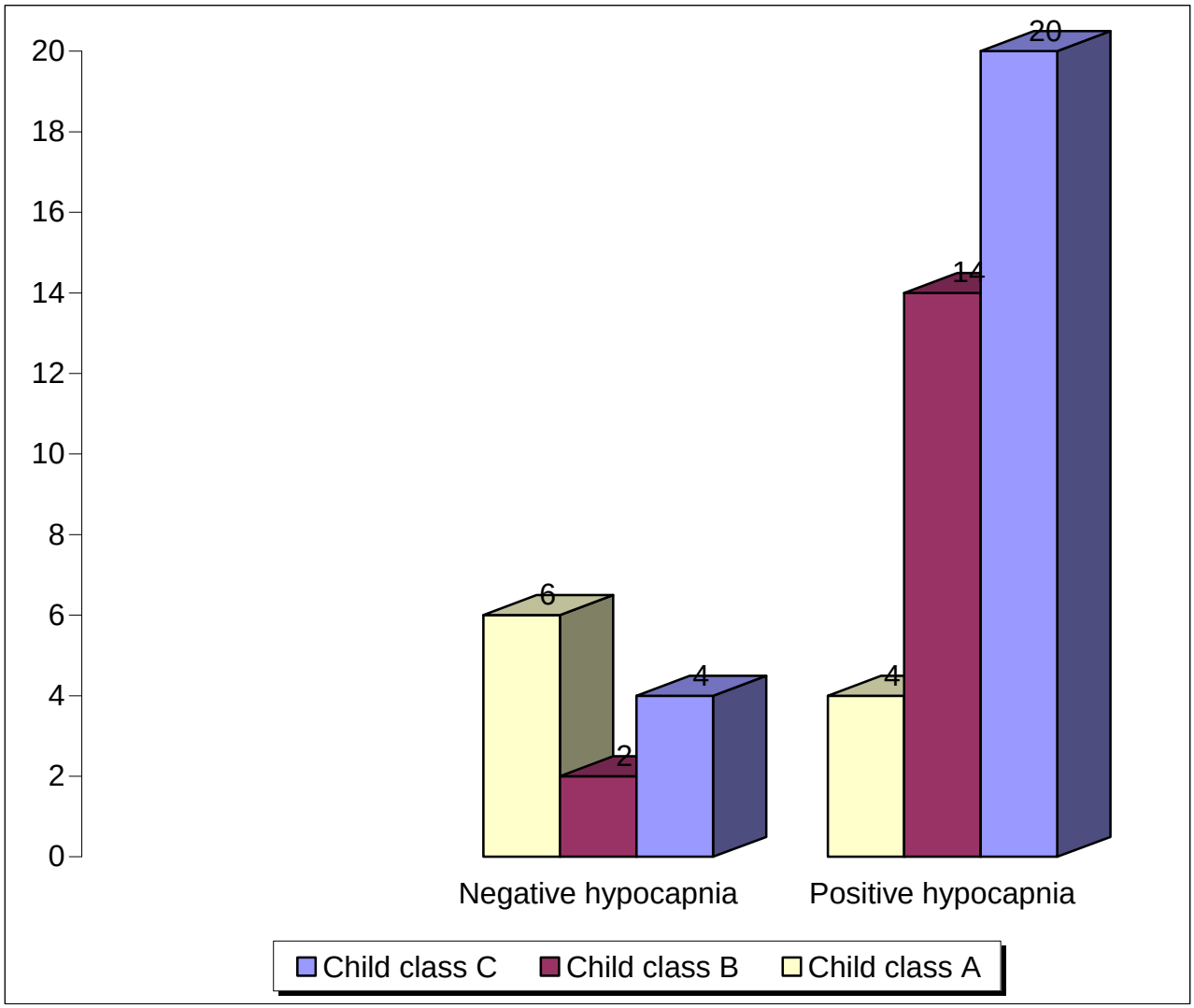


Table (18) $A\text{-}aDO_2$ in patients with liver cirrhosis regarding patients position:

$A\text{-}aDO_2$	Patients with liver cirrhosis (No=50)				$\times^2$	P
	Supine position (No=50)		Erect position (No=50)			
	No.	%	No.	%		
Normal	11	22.0	20	40	3.79	< 0.05
Abnormal	39	78.0	30	60.0		

Figure (18) $A\text{-}aDO_2$ in patients with liver cirrhosis regarding patients position:

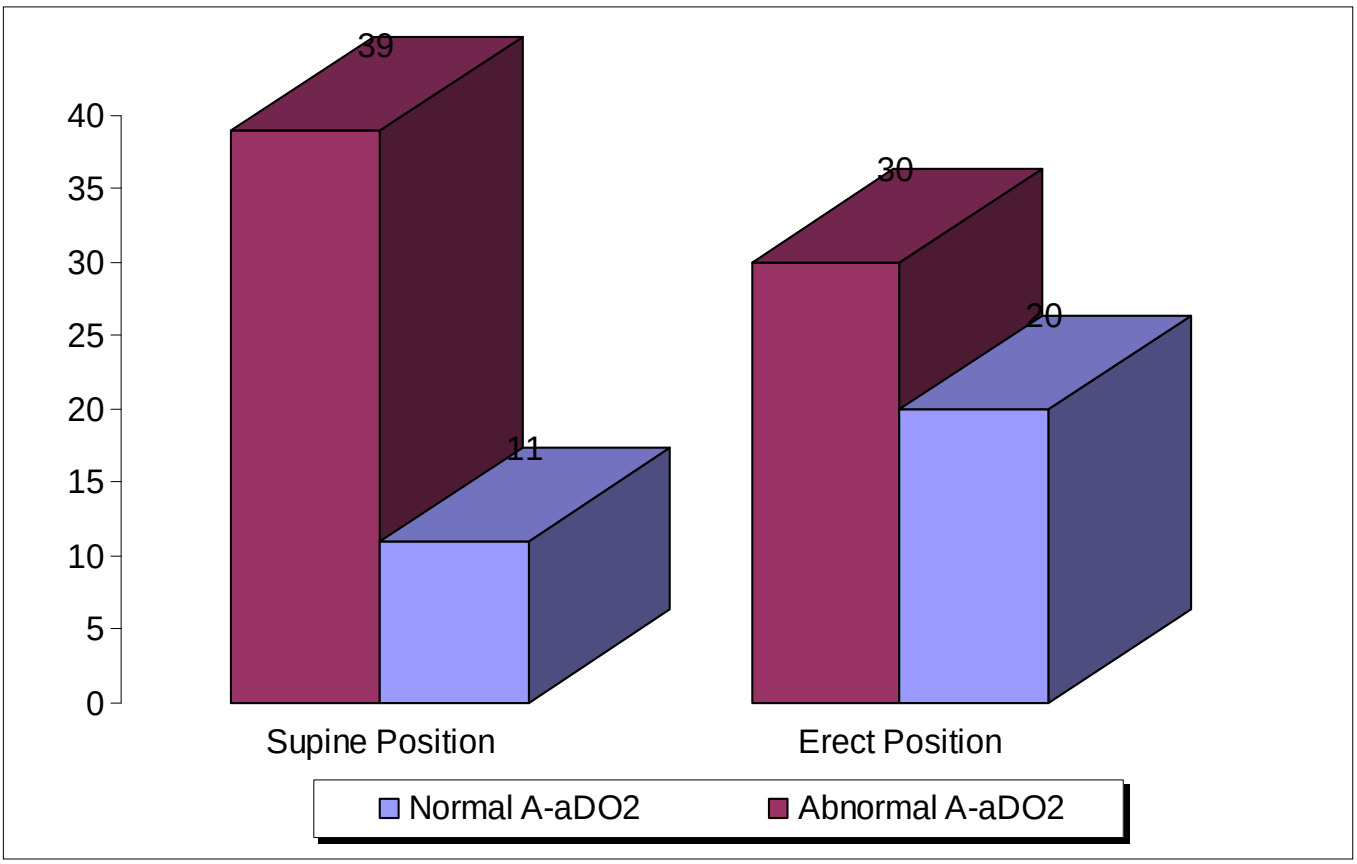


Table (19) The relationship between A-aDO$_2$ in supine and erect positions and Child Pugh classification in patients with liver cirrhosis:

A-aDO$_2$	Child Pugh classification in patients with liver cirrhosis (No=50)								
	A (No= 10)		B (No=16)		C (No=24)		χ^2	P
	No.	%	No.	%	No.	%		
In supine position								
• Normal	3	30.0	1	6.3	7	29.2		
• Abnormal	7	70.0	15	93.7	17	70.8	3.40	>0.05
In erect position								
• Normal	4	40.0	3	18.8	13	54.2	5.02	>0.05
• Abnormal	6	60.0	13	81.2	11	45.8		

Figure (19) The relationship between A-aDO$_2$ in supine and erect positions and Child Pugh classification in patients with liver cirrhosis:

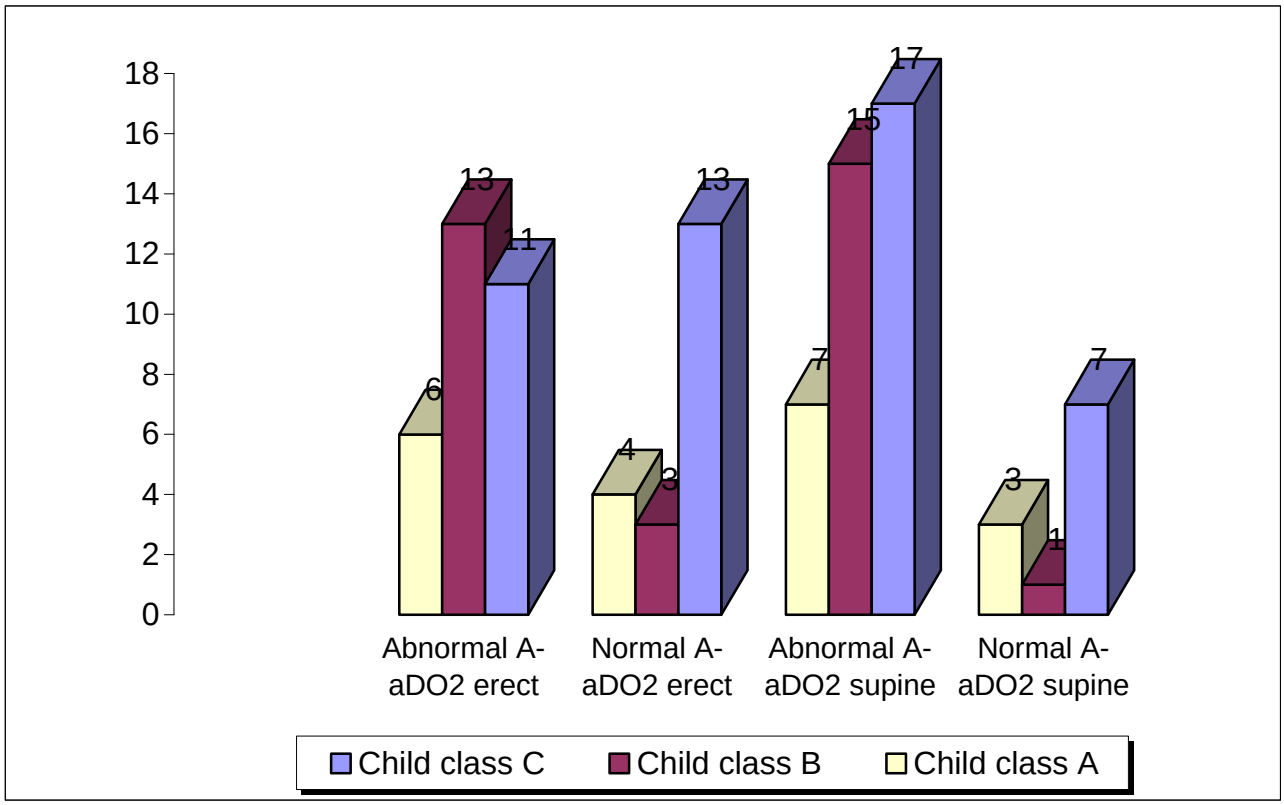
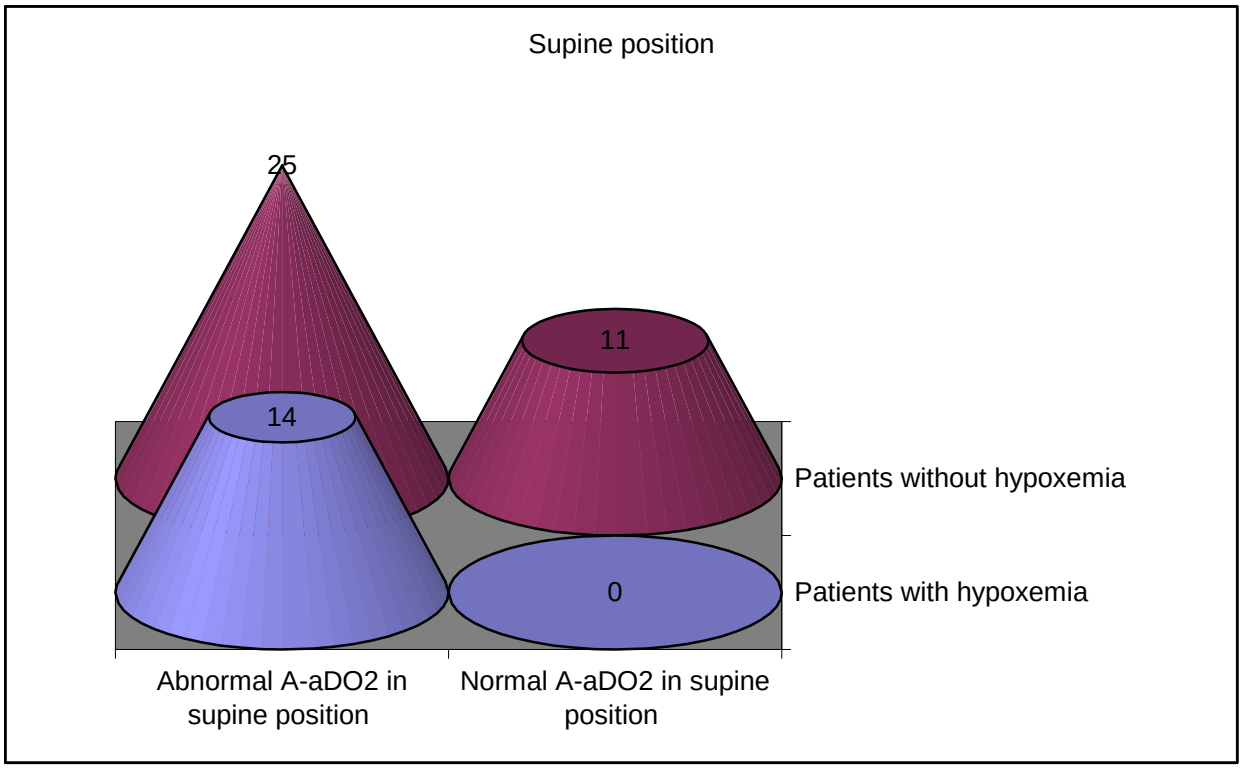


Table (20) The relationship between A-aDO_2 and hypoxemia in patients with liver cirrhosis:

Hypoxemia	A-aDO_2 in erect position in patients with liver cirrhosis (No=50)			
	Normal (No=20) No. %	Abnormal (No=30) No. %	$\times^2$	P
Present	4 20.0	10 33.33	2.21	> 0.05
Absent	16 80.0	20 66.67		
Hypoxemia	**A-aDO_2 in supine position in patients with liver cirrhosis** (No=50)			
	Normal (No=11) No. %	Abnormal (No=39) No. %	$\times^2$	P
Present	0 0.0	14 35.89	6.64	< 0.01
Absent	11 100.0	25 64.11		

Figure (20) The relationship between A-aDO$_2$ and hypoxemia in patients with liver cirrhosis:



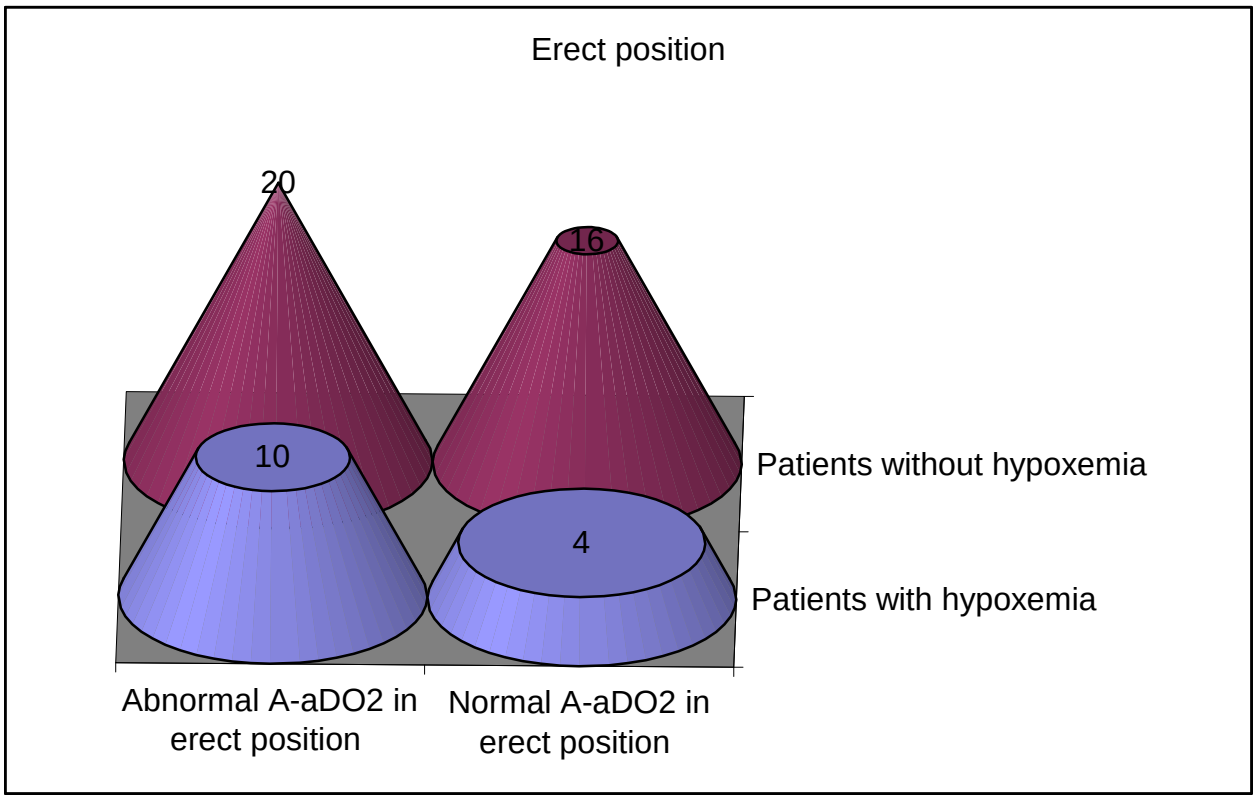


Table (21) The relationship between A-aDO$_2$ and PaO$_2$ in patients with liver cirrhosis:

A-aDO$_2$	PaO$_2$(mmHg) in patients with liver cirrhosis (No=50)			
	In erect position		In supine position	
	(r)	**P**	**(r)**	**P**
In erect position	-0.05	>o.05		
In supine position			-0.36	<0.01

Figure (21):The relationship between A-aDO$_2$ and PaO$_2$ in patients with liver cirrhosis:

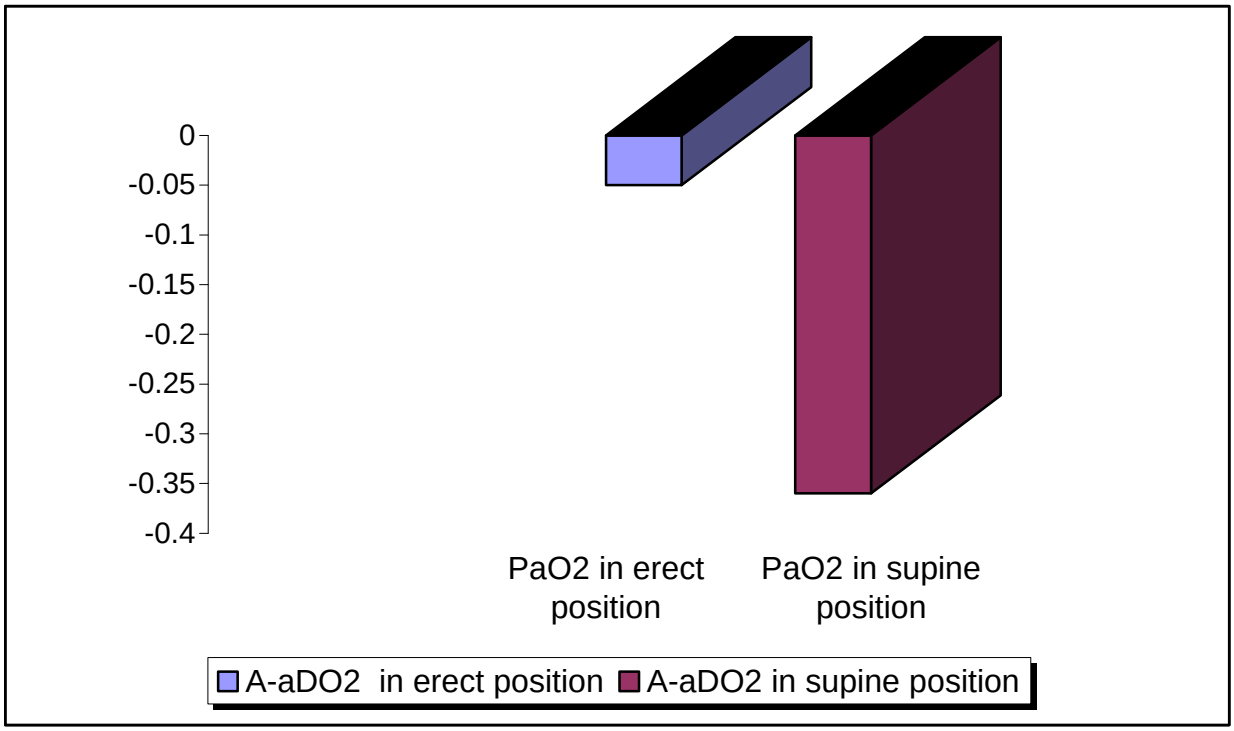


Table (22) The relationship between A-aDO$_2$ and DLco corrected state in patients with liver cirrhosis:

DLco	A-aDO$_2$ in erect position in patients with liver cirrhosis (No=50)			
	Normal (No=20) No. %	Abnormal (No=30) No. %	$\times^2$	P
Reduced	10 50.0	22 73.0	2.84	> 0.05
Normal	10 50.0	8 26.7		
DLco	**A-aDO$_2$ in supine position in patients with liver cirrhosis (No=50)**			
	Normal (No=11) No. %	Abnormal (No=39) No. %	$\times^2$	P
Reduced	8 72.7	24 61.5	0.47	> 0.05
Normal	3 27.3	15 38.5		

Figure (22-1) The relationship between A-aDO$_2$ and DLco corrected state in patients with liver cirrhosis in erect position:

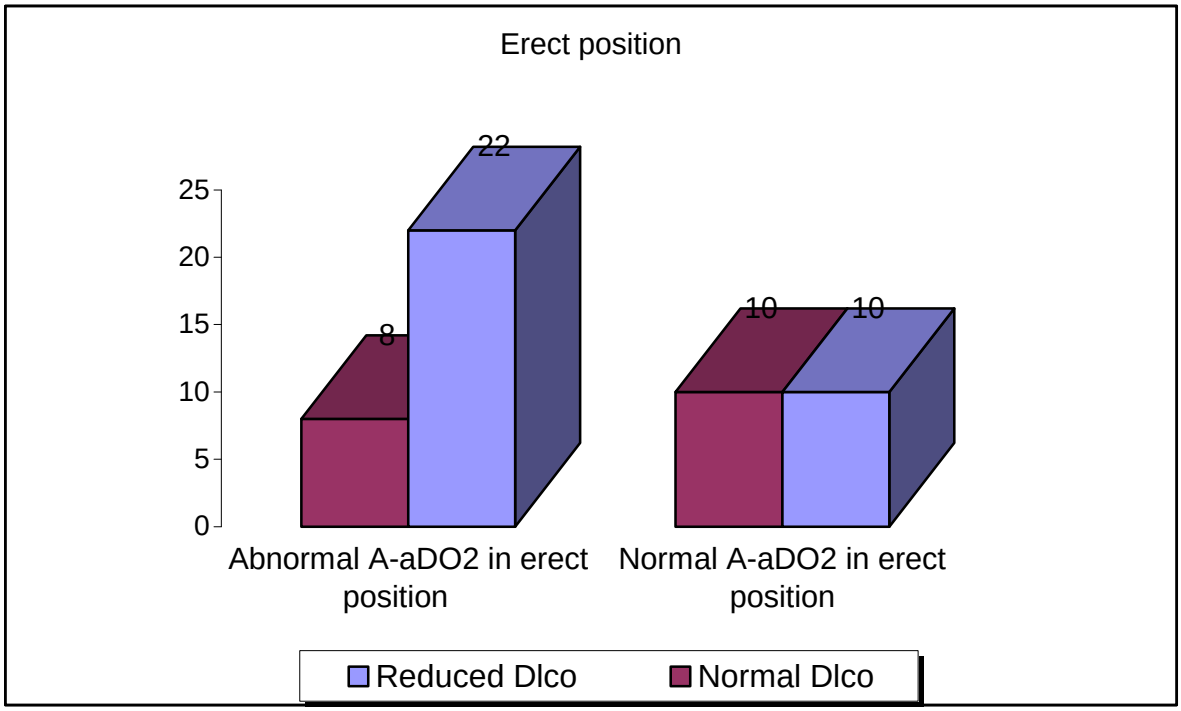


Figure (22-2) The relationship between A-aDO_2 and DLco corrected state in patients with liver cirrhosis in supine position:

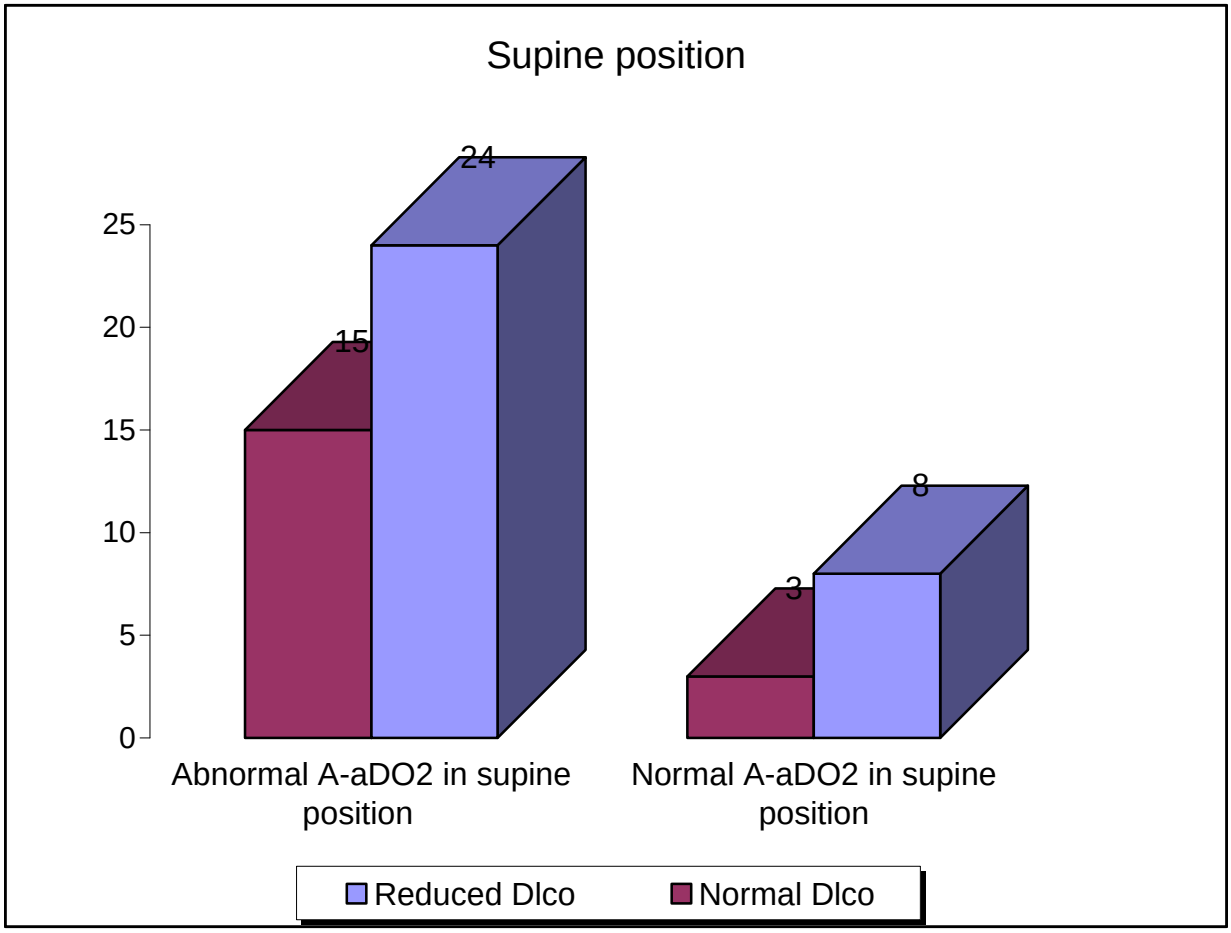


Table (23) The relationship between A-aDO$_2$ and orthodeoxia in patients with liver cirrhosis in supine position:

Orthodeoxia	A-aDO$_2$ in supine position in patients with liver cirrhosis (No=50)			
	Normal (No=11) No. %	Abnormal (No=39) No. %	×$_2$	P
In supine position				
Present	2 18.2	10 25.64	3.82	< 0.05
Absent	9 81.8	29 74.35		

Figure (23) The relationship between A-aDO$_2$ and orthodeoxia in patients with liver cirrhosis in supine position:

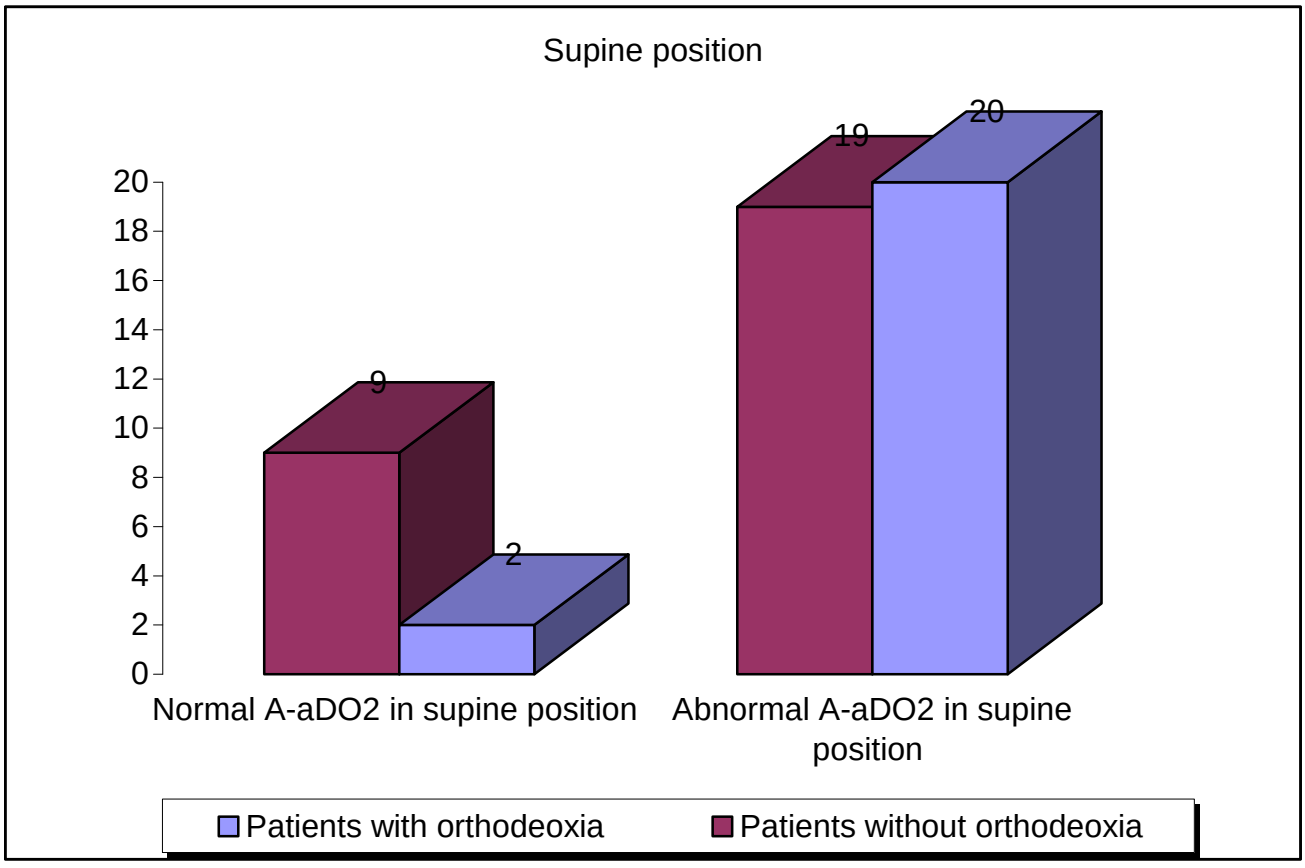


Table (24) The relationship between A-aDO$_2$ and orthodeoxia in patients with liver cirrhosis in erect position:

Orthodeoxia	A-aDO$_2$ in erect position in patients with liver cirrhosis (No=50)			
	Normal (No=20) No. %	Abnormal (No=30) No. %	$\times^2$	P
In erect position Present	5 25.0	7 23.3	0.02	> 0.05
Absent	15 75.0	23 76.7		

Figure (24) The relationship between A-aDO$_2$ and orthodeoxia in patients with liver cirrhosis in erect position:

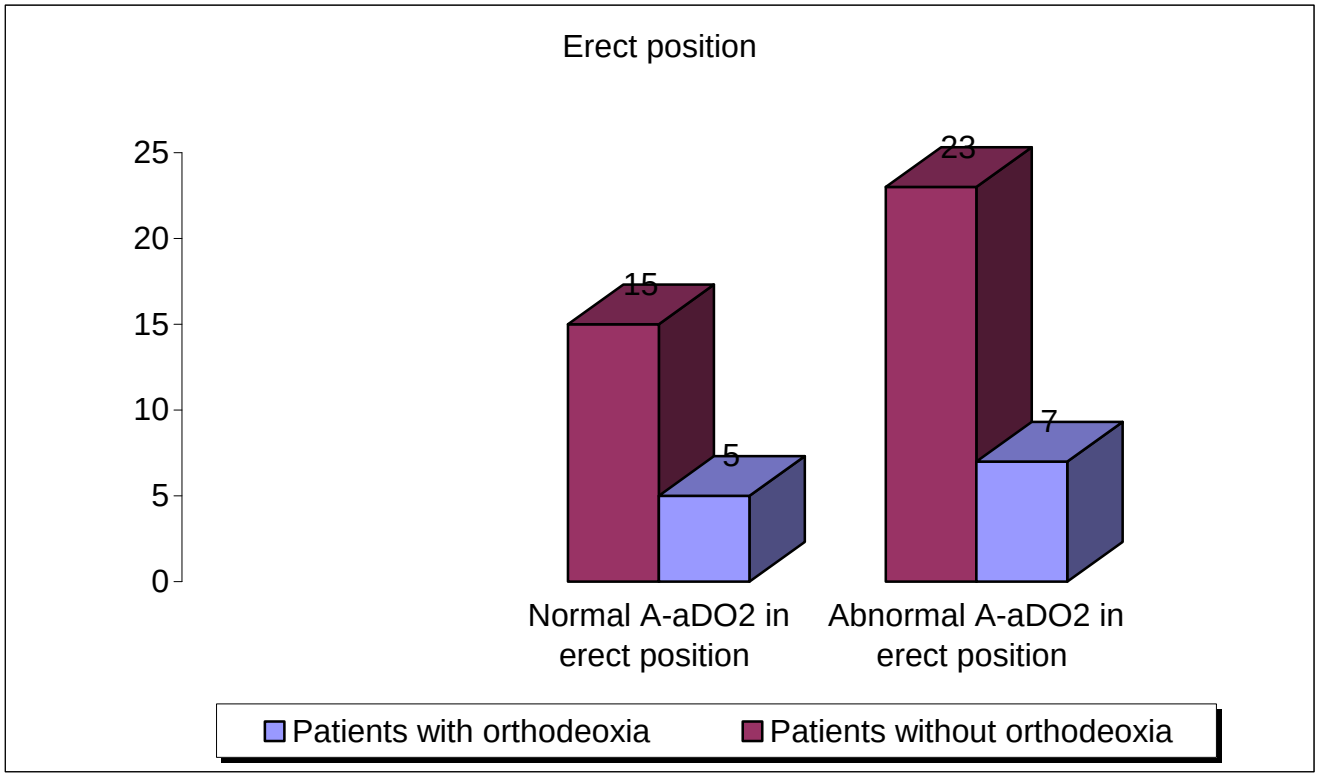


Table (25) The relationship between A-aDO_2 and arterial blood gases(ABG) in patients with liver cirrhosis:

ABG	A-aDO_2 in erect position in patients with liver cirrhosis (No=50)			
	Normal (No=20) No. %	Abnormal (No=30) No. %	$\times^2$	P
Metabolic alkalosis	4 20.0	2 6.7	3.41	>0.05
Respiratory Alkalosis	16 80.0	28 93.3		
ABG	**A-aDO_2 in supine position in patients with liver cirrhosis** (No=50)			
	Normal (No=11) No. %	Abnormal (No=39) No. %	$\times^2$	P
Metabolic alkalosis	0 0.0	6 15.4	1.92	>0.05
Respiratory Alkalosis	11 100.0	33 84.6		

Figure (25-1) The relationship between A-aDO$_2$ and arterial blood gases (ABG) in patients with liver cirrhosis in erect position:

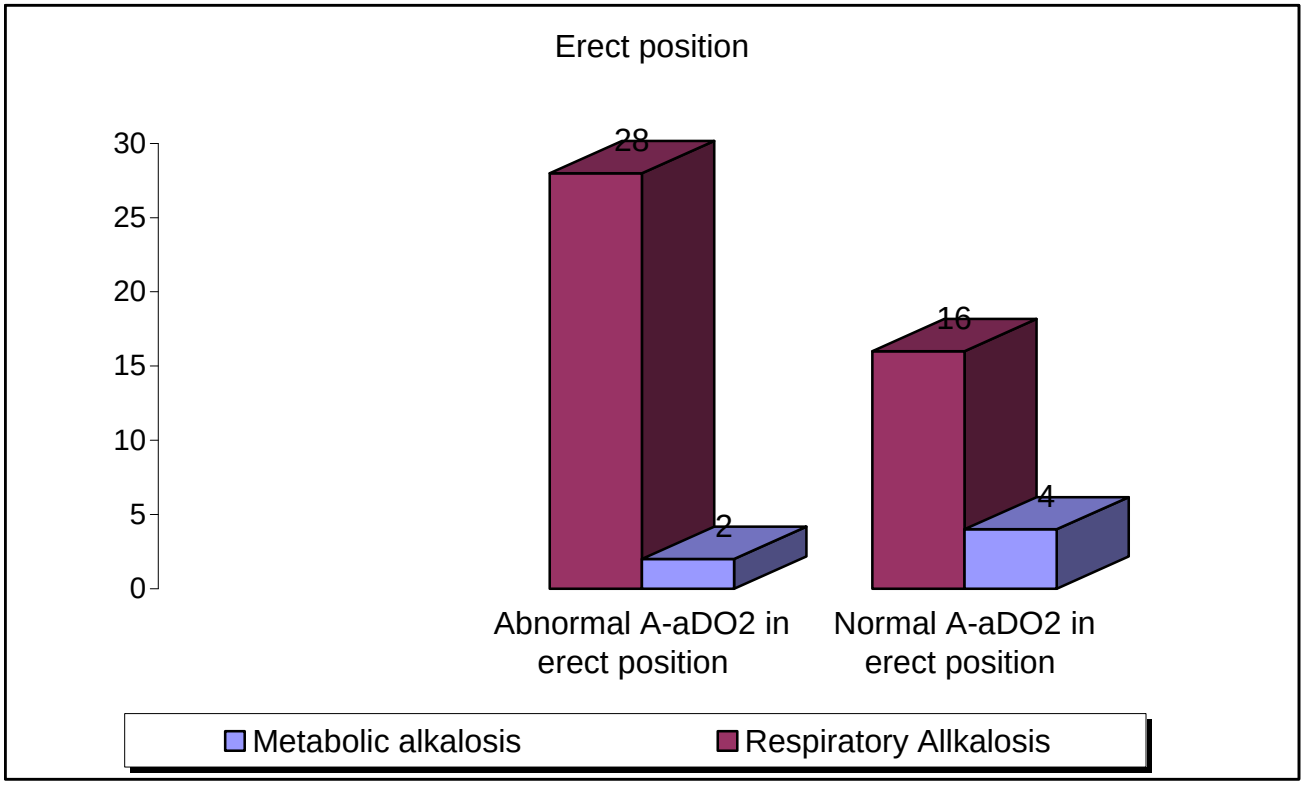
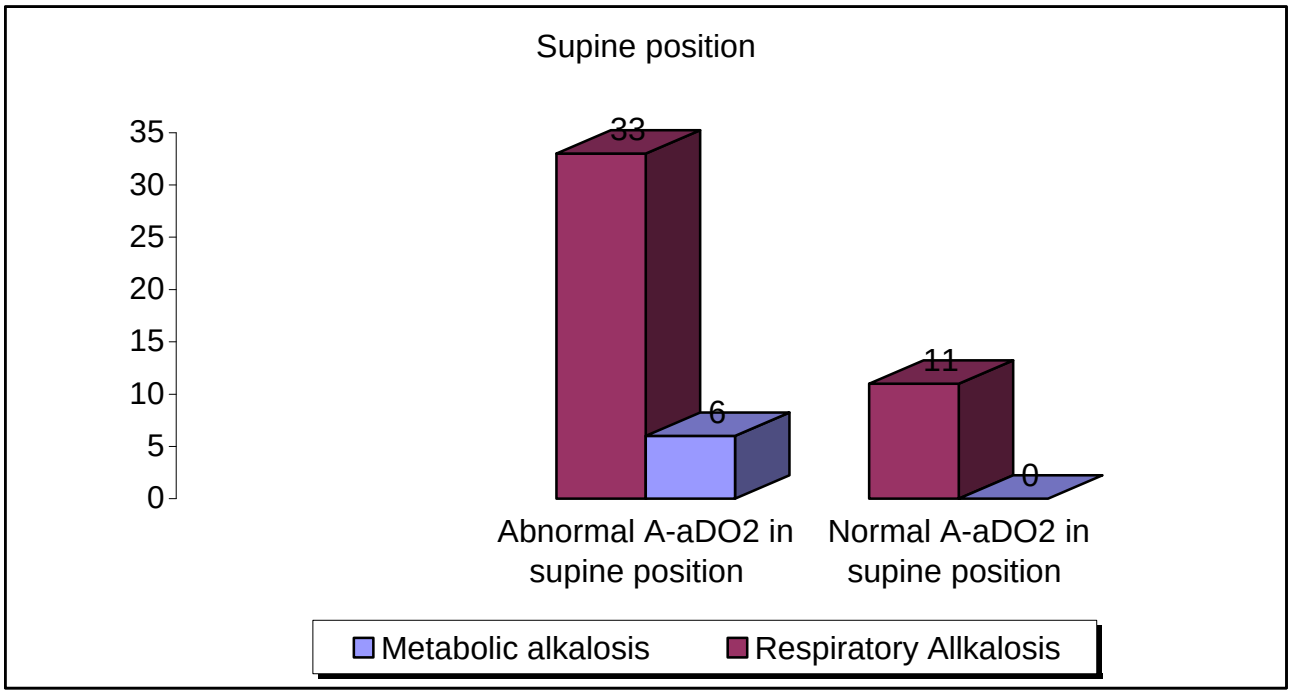


Figure (25-2) The relationship between A-aDO$_2$ and arterial blood gases (ABG) in patients with liver cirrhosis in supine position:



DISCUSSION

Over the last 15 years, pulmonary vascular abnormalities have been increasingly recognized as important clinical entities that influence survival and liver transplant candidacy in affected patients. The most common such abnormality, the hepatopulmonary syndrome (HPS), occurs when intrapulmonary vasodilatation impairs arterial oxygenation ***(Palma DT, 2006).***

The presence of HPS increases mortality in the setting of cirrhosis and may influence the frequency and severity of complications of portal hypertension ***(Schenk P et al, 2003)*** and ***(Palma DT, 2006).***

Gas exchange abnormalities are frequent in cirrhosis. The most frequent alteration is hypocapnia, which is associated with pulmonary vasodilatation. The main cause of severe hypoxemia in these patients is pulmonary function test (PFT) abnormality. Pulmonary vasodilatation is more frequent and more severe in patients with advanced hepatocellular dysfunction ***(Aller R, 1999).***

The current study was performed to assess the pulmonary functions in patients with cirrhosis attending the National Liver Institute, Menoufiya University.

It was conducted on 50 patients presenting with cirrhosis of different grades. All included Patients were subjected to arterial blood gas samples which were obtained by percutaneous radial artery puncture with the subject in supine and erect positions breathing room air, lung function test, single-breath carbon monoxide transfer factor (TLco) and Echocardiogram.

Analysis of the results revealed that the means values of the spirometric measurements of cirrhotic patients were within the normal limits, FEV_1 % of prediction (110.12 ± 19.51), FVC % of prediction (101.80 ± 20.46), FEV_1/FVC % of prediction (110.37 ± 6.70) while that of DLco corrected was reduced (69.47 ± 11.89). This in agreement with ***(Yigit I et al., 2007)*** who found normal mean values of spirometric measurements in the whole group of his patients, ***(Przybylowski T et al., 2006)*** who said that the mean values of lung function parameters for the entire group were within normal limits while the mean value of DLco in patients with liver cirrhosis was reduced, ***(Martínez GP, 2001)*** who found normal spirometry in all patients, ***(Mimidis KP et al., 1998)*** who said that the means values of lung function test were within normal range and DLco corrected was on the average mildly reduced, ***(Hedenstierna G, 1991)*** who said that spirometry was essentially normal but the transfer factor of the lung (DLco) was reduced, and ***(Furukawa et al, 1984)*** who said that spirometric data were normal in all subjects and FEV_1 % was not reduced in the cirrhotic patients.

Our study revealed that spirometric measurements were within normal range in (76%) of the patients while ventilatory restriction was noted in (24%) of patients which is in agreement with ***(Tulafi C, 2002)*** who noted normal spirometry in 72% of the patients and ventilatory restriction in 28% of patients. ***(Gupta et al., 2001)*** who found normal spirometry in 68.5% of patients and ventilatory restriction in 22.2% of patients, ***(Mimidis KP et al., 1998)*** who noted normal spirometry in (68%) of the patients, ***(Hourani JM et al., 1991)*** who noted ventilatory restriction in

25% of patients, and ***(Yao EH, 1987)*** who said that cirrhosis is associated with prominent ventilatory restriction**.**

This is on the contrary of ***(Nagral A, 1993)*** who said that pulmonary functions are impaired in cirrhosis and ascites causes further deterioration and ***(Behera D, 1998)*** who said that most pulmonary functions were abnormal (low) in cirrhosis and the most affected parameter was FEV_1.

The ventilatory restriction demonstrated in our study can be explained by the presence of tense ascites as most our patients were Child class B (no= 16, 4 of them have restrictive disorders) and C (no= 24, 8 of them have restrictive disorders) where the pattern of restrictive lung disease is expected in the patient whose tense ascites mimics abdominal loading in which the upward displacement of the hemidiaphragms reduces both the static lung volumes and the dynamic airflow indices and this in agreement with ***(Byrd , 1996)***.

Diffusing capacity of carbon monoxide (DLco) was reduced in 64% of patients in cirrhotic patients. This is in agreement with ***(Przybylowski T et al., 2006)*** who found reduced diffusing capacity of carbon monoxide in 77.9% of patients, ***(Tulafi C, 2002)*** who noted reduced diffusing capacity of carbon monoxide in 54% of patients, ***(Mohamed et al., 2002)*** who noted reduced (DLco) in (51%) of the patients, ***(Gupta et al., 2001)*** who noted the presence of reduced diffusing capacity of carbon monoxide in (66.6%) of the patients, ***(Martínez GP, 2001)*** who noted the presence of reduced diffusing capacity of carbon monoxide in (69%) of the patients ***(Krowka MJ et al., 2000)*** who

noted reduced (DLco) in (94%) of the patients, ***(Mimidis KP et al., 1998)*** who noted reduced diffusing capacity of carbon monoxide in (56%) of patients and ***(Hourani JM et al., 1991)*** who noted reduced diffusing capacity of carbon monoxide in 48% of patients.

This may be attributed to the increased diffusion distance for carbon monoxide (and oxygen) from the alveoli to the erythrocyte in the centre of the capillary blood stream, resulting in a decrease in diffusion capacity ***(Mimidis KP et al., 1998)*** that is exaggerated by the inordinately high cardiac output, resulting in a shorter transit time of the red blood cell, and contributes to diffusion-perfusion impairment ***(Martínez GP, 2001)*** or due to intrapulmonary vascular dilatations {pulmonary vasodilatations could account for the decreased DLco because this vasodilatations would be lead to decrease perfusion to the upper parts of the lung thereby reducing the effective surface area available for gas exchange ***(Silvereo M, 1977)***}, or due to diffuse interstitial lung disease, pulmonary vaso-occlusive disease and/or ventilation-perfusion imbalance ***(Hourani JM et al., 1991)***.

There was negative correlation between age and FEV_1 (%) values ($r = -0.23$, > 0.05) and FVC (%) values ($r = -0.27$, > 0.05) and DLco corrected values ($r = -0.21$, > 0.05) in cirrhotic patients. This is in agreement with the well known believe that respiratory functions decline with aging ***(Hansen J, 2006)*** ***(Katsuta Y et al., 2005)***, ***(Ostowski S et al., 2005)*** and ***(Guenard H, 2004)*** where the decrease in the ratio of FEV_1 to FVC with age is 0.2 per year ***(Cardús J et al., 1997).***

(Amra B et al., 2006) said that age presented a moderate negative correlation with the diffusing capacity.

The effect of aging on the normal lung has received considerable attention over the years. Elastic recoil is progressively reduced ***(Colebatch HJ, 1979)***, ***(Rossi A, 1996)*** and ***(Janssens JP, 1999)*** vital capacity decrease ***(Rossi A, 1996)*** and maximal expiratory flow rates fall ***(Knudson, 1977)***, closing volume is increased and FVC and FEV_1 diminish with advanced age ***(Janssens JP, 1999),*** and PaO_2 diminishes ***(Rossi A, 1996)***. Since $PaCO_2$ does not rise, the decrease in PaO_2 must indicate an increase in the alveolar–arterial PO_2 difference (A-aPO_2) ***(Cardús J et al., 1997)***.

Therefore the negative correlation of age with FEV_1(%), FVC (%) and DLco corrected values in our study could be anticipated because ageing is related to a decline in the total area of the alveolocapillary membrane and the capillary operating volume and to an increase in the closing capacity of the small airways (i.e. closing volume plus RV) ***(Amra B et al., 2006)*** such that in older subjects some airways are closed during normal tidal breathing, reducing local ventilation and hence producing (V/Q) mismatching ***(Cardús J et al., 1997)***.

The current study has also revealed no significant relationship between FEV_1 (%), FVC (%) and DLco corrected regarding gender.

This is in agreement with ***(Amra B et al., 2006)*** who observed that DLco corrected values were not significantly

different between the genders but no studies compared spirometric measures with gender.

There was statistically significant difference in FEV_1 (%) ($P < 0.01$), FVC (%) ($P < 0.05$) and DLco corrected ($P < 0.01$) in cirrhotic patients regarding Child Pugh classification, the highest levels presented in class A and the lowest in class C. This is in agreement with ***(Przybylowski T et al., 2006)*** who found that DLco in stage C patients was lower compared with stage B and A patients but he said that no differences were found when other lung function tests were analyzed by Child-Pugh classification which is on the contrary of our results whereas ***(Byrd, 1996)*** found that dynamic airflow and the static lung volumes are reduced in cirrhotic patients with child class B and C, ***(Krowka et al, 1992)*** found the lowest values of diffusion capacity in patients with grade C, ***(Mimidis KP et al., 1998)*** who said that reduced diffusion capacity was more prominent with advancing stage of liver disease**,** ***(Drenth JP et al., 2002)*** who found that DLco was significantly attenuated in patients with liver cirrhosis. Compared to patients with only mild disease, patients with severe disease had a more profound impaired diffusing capacity as there was a significant (negative) correlation between Child classification and DLco but on the contrary of ***(Tulafi C, 2002)*** who noted no statistically significant difference between these values regarding Child Pugh score and ***(Mohamed et al, 2002)*** who said that DLco correlated poorly with severity of liver damage assessed by the Child Pugh score**.**

This may be due to that intrapulmonary vasodilatation and shunting, occurring in liver cirrhosis and causing diffusion

impairment, are related to the degree of liver dysfunction as measured by Child Pugh classification ***(Alonso Martinez JL et al., 2004)*** and patients in Child class C are more likely to have intrapulmonary shunting than those with class A and B ***(Santo-Cruz RA et al., 2005)***. In the addition to the presence of tense ascites in Child class C and B patients than Child class A patients ***(Nagral A, 1993)*** and ***(Byrd, 1996)*** which compromise lung functions and gas exchange by the immobilized ***(Drenth JP et al., 2002)*** and upward displacement of diaphragm ***(Byrd, 1996)***.

Our study revealed that no correlation between FEV_1 (%), FVC (%) and DLco corrected in cirrhotic patients. No studies compared the spirometric measures with DLco corrected.

Our study revealed that the mean values of PaO_2 (89.30 ± 18.01) and O_2 % saturation (96.48 ± 1.89) are within the normal limits while the mean values of PH (7.48 ± 0.05) and A-aDo_2 (28.33 ± 15.86) are elevated and that of $PaCO_2$ (30.56 ± 3.59) is reduced in supine position without significant difference between the mean values of arterial blood gases parameters in supine and erect position in patients with liver cirrhosis although there is some reduction in the erect position but without statistic significance. This is in agreement with ***(Yigit I et al., 2007)*** who found normal mean values of PaO_2 and O_2 % saturation, reduced $PaCO_2$, elevated PH, ***(Przybylowski T et al., 2006)*** who found that the mean PaO_2 (86.9 ±12.9) was within normal limit, the mean value of $PaCO_2$ was reduced (34.8 ±4.3) and that of PH is in the upper limit of normal (7.45 ±0.03) but he did not compare supine to upright values, ***(Katsuta Y et al., 2005)*** found normal mean PaO_2, normal mean $PaCO_2$, elevated mean value of A-aDo_2 and the

PH was in the upper limit of normal in the supine position but he did not compare supine to upright values, ***(Mimidis KP et al., 1998)*** who observed that all patients included in his study had normal mean value of PaO_2, reduced mean value of $PaCO_2$ and PH mean value was in the upper normal limit in the supine position but he did not compare supine to upright values and ***(Marichal I, 1991)*** who observed no difference in arterial blood gases at upright and recumbent positions with low values in the upright position but without statistic significance. This is on the contrary of ***(Krowka MJ et al., 2000)*** who found that Standing oxygenation (PaO_2) was significantly worse compared with supine oxygenation.

Our study revealed the highest percent of cirrhotic patients were with normal spirometric measures **(76%)**, reduced DLco corrected State (64%), respiratory alkalosis (88%), hypocapnia (76%), abnormal A-aDo_2 (78%) with mean value (28.4) mmHg, in supine position, table (8) without orthodeoxia (24%) and without hypoxemia (28%) whereas restrictive disorders present in (24%), diffusion impairment (reduced DLco corrected) was accompanied by restrictive disorders in (8/12) (66.7%) table (15) and by an abnormal widened alveolar oxygen gradient in (61%) (24/39) table (22). This is in agreement with most studies which mentioned that normoxemia with hypocapnia, respiratory alkalosis and reduced DLco corrected State have frequently been reported in cirrhosis ***(Aller R, 1999)***, ***(Martínez GP, 2001), (Mohamed et al., 2002)*** and ***(Katsuta Y et al., 2005).***

(Hourani JM et al., 1991) found restrictive disorders in (25%) and diffusion impairment was accompanied by restrictive

disorders in 35% and by an abnormal widened alveolar oxygen gradient in (60%), and reported a widened alveolar-arterial oxygen gradient in (45%) of candidates for liver transplantation (n =46) with a mean value of 36.7 mmHg, ***(Przybylowski T et al., 2006)*** who observed abnormal widened alveolar oxygen gradient more than 20 mmHg in (41.7%) of the (n=96) patients with a mean value of 34.7 mmHg in hypoxemic patients and 16.3 mmHg in normoxemic patients, ***(Schiffer et al., 2006)*** who reported abnormal A-aDO_2 more than 20 mmHg in (31%) of the patients, ***(Loenzo-Zuniga V et al., 2005)*** who said that the most prevalent gas exchange abnormality in cirrhosis was the alteration of alveolar-arterial oxygen tension gradient***, (Mohamed et al., 2002)*** who found abnormal widened alveolar oxygen gradient more than 20 mmHg in (35%) of the patients, ***(Colle I et al., 2002)*** who observed an abnormal Aa-O_2 gradient > 20 mmHg in 60% (mean 32.9±1.8), ***(Battaglia et al., 1997)*** who found abnormal A-aDO_2 more than 15 mmHg in (50%) of the patients, ***(Eahy JV, 1992)*** who found that 69% of candidates for liver transplantation (n =207) had an elevated alveolar-arterial oxygen gradient, ***(Naeije R, 1985***) found a mean alveolar-arterial oxygen gradient of 34.4 mmHg in a group of candidates for portocaval shunt and ***(Bashour FA, 1966)*** who found a mean alveolar-arterial oxygen gradient of 44.8 mmHg in 26 patients with cirrhosis.

The higher percentage regarding accompaniment of diffusion impairment and restrictive disorders and the higher incidence of abnormal A-aDO_2 in our study is may be due to small sample (50 patients), most patients are child B (42%) and C (48%), both have moderate to tense ascites which causes more

ventilation-perfusion impairment and increases the incidence of elevated alveolar-arterial oxygen gradient ***(Amir HM et al, 2006)***, or due to the different cutoff values of A-aDO_2 used in different studies in which we used the threshold value of 15 mmHg whereas ***(Przybylowski T et al., 2006)***, ***(Mohamed et al., 2002)***, ***(Schiffer et al., 2006)*** used the threshold value of 20 mmHg and may be because most of patients included in the study are elderly (mean age is 51.32 ± 10.78) where age associated with progressive reduction in elastic recoil of the lung, vital capacity and maximal expiratory flow rates and increase in A-aDO_2 ***(Rossi A, 1996)*** and ***(Janssens JP, 1999)*** because pulmonary ventilation–perfusion inequality, but not intrapulmonary shunting, does indeed increase with age leading to decrease in PaO_2 and since $PaCO_2$ does not rise, the decrease in PaO_2 must indicate an increase in the alveolar–arterial PO_2 difference (A-aDO_2) ***(Cardús J et al, 1997)***.

Therefore cirrhosis and age may interact together to produce these higher results in our study.

Our study demonstrated that hypoxemia was presented in (28%) of patients ranging from mild to severe . This is in agreement with ***(Furwaka T, 1984)*** who observed hypoxemia in (30%) of the patients, ***(Naeije R, 1985)*** who found mild to severe hypoxemia in (28%) of patients, ***(Behera D, 1998)*** who noted the presence of hypoxemia in (26.7%) of patients, ***(Maruyama S, 1999)*** who found hypoxemia in (38%) of his patients, ***(Gupta et al., 2001)*** who noted the presence of hypoxemia in (24%) of patients, ***(Mazzeo AT et al., 2006)*** who found hypoxemia in (20%) of patients, ***(Yigit I et al., 2007)*** who found hypoxemia in (33.3%)

of patients, but on the contrary of ***(Gomez et al., 2004)*** who noted the presence of moderate to severe hypoxemia in (70%) of patients, ***(Vachiery F et al., 1997)*** who noted the presence of hypoxemia in 14% of patients and ***(Charalabopoulos K et al., 2007)*** who found hypoxemia in all patients with cirrhosis including in his study.

The prevalence of hypoxemia in this study was in agreement with most studies and with disagreement with others.

Although the reasons for this difference are unclear but it may be that the heterogeneity of the patients studied in which smokers and patients from an intensive care unit who had more severe cirrhosis and thus hypoxemia were included as in ***(Gomez et al., 2004)*** study or they were grade B or C Child-Pugh score as in ***(Charalabopoulos K et al., 2007)*** or it may be due to the different threshold values used for establishing the presence of hypoxemia or the different characteristics of patients populations in different studies.

Hypoxemia can be explained by the presence of intrapulmonary vascular abnormalities, these vessels which are normally 8-15 µm in diameter have been demonstrated to dilate to 15-500 µm, ***(Singh, S, 2007)*** or due to a regional disequilibrium of the ventilation/perfusion ratio ***(Cadranel J, 1989)*** in which pulmonary vasodilatation in the dependent parts of the lungs could increase perfusion relative to ventilation and thereby contribute to hypoxemia ***(Silvereo M, 1977).*** While ascites, increase in airway closure, or impaired hypoxic pulmonary vasoconstriction have been suggested as possible mechanisms of ventilation/perfusion

and pulmonary arteriovenous fistulas would explain the presence of intrapulmonary right to-left shunting ***(Andrivet P et al., 1993).***

Arterial 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 ***(Charalabopoulos K et al., 2007).***

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 VA/Q inequality ***(Charalabopoulos K et al., 2007).***

(Charalabopoulos K et al., 2007) 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.

Ascites by elevating the diaphragm and confounding the ventilation/perfusion might lead to mild hypoxemia in most patients with chronic hepatic involvement, not regarding the etiology ***(Amir HM et al., 2005).***

Our study revealed that respiratory alkalosis was observed in (88%) of patients, metabolic alkalosis in (12%) and hypocapnia was the most frequent observed alteration in gas exchange (76%) and all patients have a more alkaline pH. This is in agreement with the ***(Aller R, 1999)*** who noticed hypocapnia in (73.4%) of

patients with a more alkaline blood pH, ***(Katsuta Y et al., 2005)*** who found hypocapnia in 50% of patients, alkalosis in 43.8% of patients and respiratory alkalosis in 87.5% of patients (n=16), ***(Gomez et al., 2004)*** who noted the presence of hypocapnia in all patients (100%) (n=20), ***(Charalabopoulos K et al., 2007)*** who observed respiratory alkalosis in (44.89 %), metabolic alkalosis in (14.28 %), and hypocapnia was most frequently found in (73%) of cirrhotic patients and all the patients have more alkaline pH, ***(Bernardi M, 2005)*** who found respiratory alkalosis in (38%) and metabolic alkalosis in (13%) of the patients and ***(Mimidis KP et al, 1998)*** who found that all his patients had hypocapnia but with normal blood pH, ***(Furukawa T, 1984)*** who found hypocapnia in 52.4% of the patients.

The highest percentage of respiratory alkalosis in our study is explained by the presence of high proportion of patients in Child class B (n=16) and C (n=24) who have more advanced disease and ascites where both of them play important role in the development of respiratory alkalosis (see below). In the study of ***(Katsuta Y et al., 2005)*** the number of patients was 16, Child class A and B, while in the study of ***(Charalabopoulos K et al., 2007)*** although the number of patients was 104 but most of them Child A=40, B=42 whereas child C=23

The incidence of hypocapnia in our study was close to that was seen by ***(Aller R, 1999)*** and ***(Charalabopoulos K et al., 2007)*** but higher than that reported by ***(Katsuta Y et al., 2005)*** and ***(Bernardi M, 2005)*** and lower than that reported by ***(Mimidis KP et al., 1998)*** and ***(Gomez et al., 2004).***

This is because the degree of hypocapnia in patients with cirrhosis was found to be correlated with levels of progesterone and oestradiol, suggesting that the respiratory alkalosis of liver dysfunction is due to increased levels of those hormones from impaired liver metabolism ***(Lustik SJ et al., 1997).***

The derangement of sex hormone serum levels in cirrhotic patients is well-delineated, and increased levels of progesterone and estradiol have been associated with hyperventilation in cirrhotic patients ***(Aller R et al., 2002).***

In cirrhosis, increased ammonia and progesterone, two respiratory stimulants are believed to contribute to hyperventilation ***(Javaheri S et al, 2005).***

One suggested mechanism is an increased ventilatory effect (hyperventilation) due to altered blood brain barrier in cirrhosis. However, earlier research suggests a heightened sensitivity of peripheral chemoreceptor to hypoxia. Metabolic alkalosis is the second most frequent acid base disturbance in patients with cirrhosis ***(Loutfi S, 2000)*** and this is in agreement with our study.

Hyperventilation can also be the result of hypoxemia secondary to hepatopulmonary syndrome and porto-pulmonary hypertension, as well as restrictive lung dysfunction because of massive ascites ***(Bernardi M, 2005)*** which cause increased abdominal pressure leading to cephalad displacement of the diaphragm ***(Huffmyer JL, 2007).***

Therefore hypocapnia could be a compensatory mechanism or the result of the activation of central respiratory centers by non-depurated substances by the liver ***(Lorenzo-Zuniga V et al., 2005)***

Another metabolic abnormality, which can lead to pH changes in cirrhosis is represented by the reduced synthesis of proteins and, mainly, albumin. In fact, reduced plasma concentrations of albumin, which is a weak acid, has an alkalinizing effect on plasma and would predispose to alkalosis (hypoalbuminic alkalosis) ***(Funk et al., 2007), (Bernardi M, 2005)*** and ***(Fencl V et al., 2000)*** which can explain the higher incidence of alkalosis in our study.

The incidence of metabolic alkalosis in our study is close that seen in other studies. This is can be explained by the impaired efficiency of the urea cycle in cirrhosis which reduces bicarbonate utilization ***(Haussinger D, 1990)*** and impaired hepatic bicarbonate disposal from the lack of functioning hepatocytes in cirrhosis ***(Funk et al., 2005)*** leading to metabolic alkalosis ***(Bernardi M, 2005)*** which occur also in cirrhotic patients on loop diuretics.

Our study also revealed the presence of orthodeoxia in (24%) of patients (orthodeoxia is defined as a fall in $PaO_2 \geq 5$ % at upright position) and 76% was non orthodeoxic. All orthodeoxic patients have significantly higher PO_2 in supine position than those without (both two groups show no hypoxemia) while in erect position all orthodeoxic patients have significantly lower PO_2 (hypoxemia) than those without. This is somewhat in agreement with ***(Gomez et al., 2004)*** who noticed OD in 25% of patients but OD patients were hypoxemic at both positions on the

contrary of our results, ***(Amir HM et al., 2006***) who found orthodeoxia in 31.5% of patients**,** and on the contrary of (***Lange Ap, 1995***) who mentioned that ***(Robin ED et al., 1975)*** and ***(Krowka MJ, 1985)*** found orthodeoxia in 5% of cirrhotic patients.

There were significantly higher mean values of PaO_2 /$PaCO_2$ and o_2 sat. in supine than in erect position in cirrhotic patients with orthodeoxia while in cirrhotic patients without orthodeoxia, there were significantly lower PaO_2 in supine than in erect position and $PaCO_2$ levels was higher in supine position than erect position. Therefore compared to supine, both OD and non-OD patients showed at erect a small but significantly decrease in $PaCO_2$. this is in agreement with ***(Gomez et al., 2004)*** who noticed the same results and ***(Edell ES, 1989)*** who found improvement in PaO_2 in supine position in patients with orthodeoxia and ***(Krowka, 1993)*** who found the mean PaO_2 was statistically lower in the standing position than in supine position in patients with orthodeoxia.

The prevalence of orthodeoxia in this study was in agreement with some studies and with disagreement with others.

Whether the differences between earlier and more recent work reflect methodological differences or differences in subject selection cannot be answered.

The previously demonstrated findings can be explained by the fact that in patients with liver cirrhosis, when the patient is standing, blood flow follows gravity to the bases of the lungs, which has true anatomic intrapulmonary vascular dilatations. These abnormally dilated capillary blood vessels at the lung bases

are situated far away from the alveolar epithelium. This decreases the oxygenation of blood in these segments, which become more intensified in an upright position**.** In other words, in normal seated subjects, the ventilation to the apical alveoli is roughly half that of the dependent alveoli. This distribution pattern is determined almost entirely by the gravity-dependent pleural pressure gradient down the lungs acting in combination with the nonlinear volume elasticity of the lungs. In the patients with liver cirrhosis, the distribution of a breath taken from resting lung volume (FRC) was not preferential to the lower lung zones, but there was a marked reduction in lower zones ventilation (reduction in PaO_2). This was associated in some patients with a somewhat reduced lower zones perfusion ***(Ruff f, 1971)***.

Therefore the further decrease in the arterial PO_2 occurring in OD patients in the upright position can be explained by further increase in magnitude of the shunt ***(Silverio M, 1977)*** when a sudden gush of blood into the lower lobes of the lungs caused by gravity when the position is changed from supine to standing result in increased intrapulmonary shunt inducing orthodeoxia and tachypnea and hence lead to more ventilation/perfusion mismatch (reduction in PaO_2 and O_2 saturation) and hyperventilation (reduction in $PaCo_2$) ***(Gupta et al., 2001)*** and on assuming the supine position, O2 sat. revert to normal or near normal where the shunt decrease or reverse ***(Abhash et al., 1998).***

The notion that OD in cirrhotic patients is related to an increased intrapulmonary shunt points to a more altered pulmonary vascular tone inducing more heterogeneous gravitational pulmonary blood flow redistribution to dependent

lung zones, possibly with more pronounced vascular dilatations and more ventilation/perfusion mismatch ***(Gomez et al., 2004)***.

In non-OD patients, V_A/Q imbalance improved at upright in the face of increased minute ventilation and decreased cardiac output, both of which tend to reduce intrapulmonary shunt, hence increasing PaO_2 ***(Gomez et al., 2004)***. On the contrary, compared to non-OD patients, those with OD deteriorated V_A/Q inequality despite similar changes in minute ventilation and cardiac output, resulting in more intense arterial and mixed venous hypoxemia. It is therefore conceivable that the redistribution of pulmonary blood flow in OD patients is more heterogeneous throughout the pulmonary vasculature and more dependent gravitationally than in non-OD patients, hence favoring further V_A/Q imbalance ***(Gomez et al., 2004)***.

Our study revealed the presence of significantly lower mean values of DLco corrected in cirrhotic patients with orthodeoxia than with out orthodeoxia. This is on the contrary of ***(Gomez et al., 2004)*** who noticed no significant difference between the OD and non-OD regarding DLco corrected state .

This is can be attributed to that OD is related to an increased intrapulmonary shunt ***(Gomez et al., 2004)*** leading to the increased diffusion distance for carbon monoxide from the alveoli to the erythrocyte in the centre of the capillary blood stream, resulting in a decrease in diffusion capacity ***(Mimidis KP et al., 1998)***.

Our results showed no significant relationship between Child Pugh classification and orthodeoxia in cirrhotic patients.

This is in agreement with ***(Mohamed et al., 2002)*** who found no significant correlation between PaO_2 gradient (orthodeoxia) and Child Pugh score.

There was no significant relationship between Child-Pugh classification and hypoxemia or degree of hypoxemia in cirrhotic patient. This is in agreement with ***(Lorenzo-Zúñiga V et al., 2005)*** who said that hypoxemia was observed without differences with Child-Pugh classification**,** ***(Mohamed et al., 2002)*** who noticed the same results, ***(Maruyama S, 1999)*** who said hypoxemia was not associated with the Child- Pugh grade, ***(Lange PA, 1995)*** who found no consistent relationship between hypoxemia and Child-Pugh classification and ***(Krowka MJ, 1993)*** who found that hypoxemia was not related to the severity of cirrhosis**, ,** but on the contrary of ***(Vachiery F et al., 1997)*** who found among patients with hypoxemia, the proportion of Grade C patients was significantly greater than the proportion of Grade A or Grade B patients and ***(Charalabopoulos K et al., 2007)*** who found a weak relationship between PaO_2 and Child-Pugh score in his patients .

One explanation for these discrepant results is that our study and other studies which show no significance were performed in a small series of selected patients who were not compared to non-hypoxemic patients with cirrhosis.

There was no significant relationship between hypoxemia in supine and erect position with orthodeoxia in cirrhotic patients. This is in agreement with ***(Gomez et al., 2004)*** who said that OD was not related to supine nor to upright PaO_2 level but on the

contrary of ***(Culafic Dj, 2000)*** who said that orthodeoxia was confirmed in all patients with hypoxemia in supine position.

So not all hypoxemic cirrhotic patients in supine position have orthodeoxia on getting upright. This is because orthodeoxia is due to increased intrapulmonary shunt in the upright position worsening hypoxemia if it has been already present but not induce it whereas hypoxemia per se is multifactorial in origin including changes in the affinity of hemoglobin for oxygen, intrapulmonary and portopulmonary shunt, alveolar capillary diffusion limitation, ventilation-perfusion inequality, and combinations of these factors ***(Lange PA, 1995)***.

There was no significant relationship between restrictive ventilatory disorders and DLco state in cirrhotic patient but the incidence of reduced DLco was more significant than the incidence of restrictive disorders. This is in agreement with ***(Tulafi C, 2002)*** who noted the same results.

So not all cirrhotic patients with restrictive ventilatory disorders have reduced DLco. This is because reduced DLco is attributed to the increased diffusion distance for carbon monoxide from the alveoli to the erythrocyte in the centre of the capillary blood stream, resulting in a decrease in diffusion capacity ***(Mimidis KP et al., 1998)*** whereas restrictive ventilatory disorders is due to tense ascites which compromise lung functions and gas exchange by the immobilized diaphragm ***(Drenth JP et al., 2002)***. The incidence of reduced DLco was more significant than the incidence of restrictive disorders, because restrictive disorders

affect those with moderate to severe ascites (class B and C) whereas reduced DLco affect all child class classification.

There was significant relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis **.** This is in agreement with ***(Mohamed et al., 2002)*** who found a weak but significant inverse correlation between $PaCO_2$ and child Pugh score and ***(Lorenzo-Zúñiga V et al., 2005)*** who observed that hypocapnia was significantly more evident in Child C than in A and B .

this is can be explained by the fact that hypocapnia in patients with cirrhosis was found to be correlated with levels of progesterone and oestradiol, which are increased in cirrhotic patients due to impaired liver metabolism leading to hyperventilation ***(Lustik SJ et al., 1997)*** and ***(Loutfi S, 2000).***

As liver cirrhosis become more advanced, liver metabolism become more impaired and the level of these hormones increased more leading to more hyperventilation and more hypocapnia.

(Aller R et al., 1999) found that gas exchange abnormalities are frequent in cirrhosis and the most frequent alteration is hypocapnia which is associated with pulmonary vasodilatation that is more severe and more frequent in patients with advanced hepatocellular dysfunction.

Our studies revealed the presence of significantly higher percent of abnormal $A\text{-}aDO_2$ in supine position than in erect position in cirrhotic patient and all cases of hypoxemia have significantly abnormal $A\text{-}aDO_2$ in supine position in patients with

liver cirrhosis. This is in agreement with ***(Colle I et al., 2002)*** who found 60% of the patients included in his study having abnormal A-aDO_2 > 20 mmHg and are hypoxemic, ***(Katsuta Y et al., 2005)*** who found that hypoxemia was significantly observed in patients with an alveolar-arterial oxygen difference of more than 15 mmHg (A-aDO_2) and ***(Vachiery F et al., 1997)*** who said that hypoxemic patients have significantly higher alveolar-arterial oxygen gradient than normoxemic patients.

Also our study revealed that there is significantly negative correlation between A-aDO_2 and PaO_2 in supine position in patients with liver cirrhosis.

The previously observed findings can be explained by that abnormal A-aDO_2 is mainly due to a diffusion-perfusion (or "diffusion-like") impairment of oxygenation as a result of intrapulmonary vascular dilations ***(Vachiery F et al., 1997)*** which are so dilated that diffusion of oxygen molecules to their centre is impaired, causing an increase in alveolar-arterial oxygen tension difference (A-aDO_2) ***(Thorens JB, 1992).*** In other words in hepatic cirrhosis there are low V/Q areas in the dependent lung zones which must contribute substantially to decreased arterial oxygen tension and increased alveolar-arterial oxygen tension differences ***(Ruff f, 1971)*** and this explain why all cases of hypoxemia have significantly abnormal A-aDO_2 in supine position in patients with liver cirrhosis.

At upright position, V_A/Q imbalance improved in the face of increased minute ventilation and decreased cardiac output, both of which tend to reduce intrapulmonary shunt so improving A-

aDO_2 ***(Gomez et al., 2004)***. Therefore the incidence of abnormal A-aDO_2 are more in supine than erect position which in agreement with our study.

Since $PaCO_2$ does not rise but on the contrary it is reduced in cirrhosis, therefore any decrease in PaO_2 must be associated with an increase in the alveolar–arterial PO_2 difference (A-aPO_2) ***(Cardús J et al, 1997)***.

Our study also revealed no significant relationship between A-aDO_2 in erect and supine position and Child Pugh classification in patients with liver cirrhosis. This is in agreement with ***(Krowaka MJ et al., 2000)*** who said that no difference was found when A-aDO_2 was analyzed by CP classification, ***(Colle I et al., 2002)*** who said that there was no correlation between A-aO_2 gradient changes and Child-Pugh grade changes, ***(Katsuta Y et al., 2005)*** who said that the Child Pugh score of the patients with abnormal A-aDo_2 was higher than the score in those with normal A-aDo_2 values but no significant difference but on the contrary of ***(Lorenzo-Zúñiga V et al., 2005)*** who said that, the most prevalent gas exchange abnormality in cirrhosis was the alteration of alveolar-arterial oxygen tension gradient, directly correlated with hepatocellur dysfunction and ***(Przybylowski T et al., 2006)*** who found significant correlation between A-aDO_2 and Child Pugh score.

We have found that, no significant relationship between A-aDO_2 and DLco corrected state in both supine and erect positions in patients with liver cirrhosis. this is in agreement with ***(Tufali C, 2002)*** who found no significant difference, (***Mohamed***

et al., 2002) who found no correlation between A-aDo_2 and DLco. This is because the cause of either one is different from another.

Our study revealed significant relationship between orthodeoxia and A-aDO_2 in supine but not in erect positions in patients with liver cirrhosis in which patients who had an increased A-aDO_2 in the supine position showed significant orthodeoxia. This is in agreement with ***(Katsuta Y et al, 2005)*** who found significant relationship.

This can be explained by the presence of impairment and/or a defective pressor response of the pulmonary vasculature (i.e., hypoxic vasoconstriction) ***(Agusti AG, 1996)*** and the widespread pulmonary vasodilatation (particularly in the lung bases) in patients with advanced cirrhosis ***(Schraufnagel DE, 1996)***.

The pulmonary vascular bed is a low-pressure system with a mean pressure below 25 mmHg, and it tends to be greatly influenced by gravity. In the bases of the upright lungs, physiological alveolar ventilation is minimal (i.e., the smallest ventilation-perfusion ratio), while blood flow is increased and the hydrostatic pressure rises due to the effect of gravity. In patients with chronic liver disease who show orthodeoxia, therefore, sitting up should provoke and/or augment vasodilatation and increase blood flow in these regions because of the poor resistance to a rise in hydrostatic pressure, leading to a further reduction of the ventilation-perfusion ratio ***(Katsuta Y et al, 2005)***. Thus, it is possible that the orthodeoxia observed in our patients indirectly indicates deterioration of the pressor response of the pulmonary vasculature and/or the existence of IPVD.

We did not find any significant relationship between acid base disturbance in cirrhosis and A-aDO_2 in erect and in supine position in cirrhotic patient.

This is on the contrary of ***(Katsuta Y et al., 2005)*** who found that respiratory alkalosis was significantly observed in patients with an alveolar-arterial oxygen difference of more than 15 mmHg (A-aDO_2).

I will try to find a logical explanation for ***(Katsuta Y et al., 2005)*** finding and try to rule it out.

(Katsuta Y et al., 2005) finding may be due to hypocapnia in patients with cirrhosis that was found to be correlated with levels of progesterone and oestradiol, which are increased in cirrhotic patients due to impaired liver metabolism ***(Lustik SJ et al, 1997)*** where they are respiratory stimulant causing hyperventilation and respiratory alkalosis. These hormones have a well-known role in the regulation of vascular tone and they are related to pulmonary vasodilatation in cirrhotic patients ***(Aller R et al., 2002)*** causing oxygen molecules diffusion impairment resulting in an increase in alveolar-arterial oxygen tension difference (A-aDO_2) ***(Thorens JB, 1992)*** .

We disagree with the previous study and it's explanation because hyperventilation causing respiratory alkalosis is multifactorial in origin other than progesterone and oestradiol including elevated ammonia, altered blood brain barriers and tense ascites. In addition ***(Ordiales JJ et al., 1996)*** found no relationship between hyperventilation and the circulating level of progesterone.

SUMMARY AND CONCLUSIONS

This study was done to assess the pulmonary function in patients with liver cirrhosis.

The study included 50 patients with liver cirrhosis of different grades presented to National Liver Institute, Menoufiya University.

Inclusion criteria:

Patients with liver cirrhosis.

Exclusion criteria:

5. Patients with cardiac diseases e.g ischemic heart disease (IHD), congestive heart failure (CHF) and valvular heart disease.
6. Patients with chronic intrinsic lung disease e.g chronic obstructive pulmonary disease (COPD), bronchial asthma, pneumonia and lung fibrosis.
7. Patients with pleural effusion.
8. Patients with malignancy any where.

All included patients were subjected to the following:

1. Thorough history taking and physical examination.

2. Laboratory investigations: liver function test including albumin, prothrombin time and bilirubin.

3. X-ray of chest: posteroanterior view and lateral view.

4. Abdominal ultrasound.

5. Echocardiogram to exclude cardiac diseases.

6. Arterial blood gases in supine and setting position to calculate the alveolar-arterial oxygen gradient and orthodeoxia.
7. Diffusion capacity for carbon monoxide to measure diffusion parameters.
8. Spirometry to measure forced expiratory volume in first second (FEV1) and forced vital capacity (FVC) to determine ventilatory disorders.
9. The grading of liver insufficiency (A, B, C) is determined according to Child Pugh score.

It was found that:

- The highest percentage of cirrhotic patients were with normal spirometric measures, reduced DLco corrected state, respiratory alkalosis, hypocapnia, abnormal A-aDO_2 without orthodeoxia and with negative hypoxemia.

- Reduced DLco corrected State is the single most common affected lung function test.

- There is negative correlation between age and FEV1 (%), FVC (%) and DLco corrected in cirrhotic patients but no statistically significant relationship between FEV1 (%), FVC (%) and DLco corrected regarding gender.

- There are statistically significant differences in FEV1 (%), FVC (%) and DLco corrected in cirrhotic patients regarding Child Pugh classification, the highest levels presented in class A and the lowest in class C.

- Respiratory alkalosis was the commonest metabolic abnormalities among cirrhotic patients.

- The most prevalent gas exchange abnormality in cirrhosis was the alteration of alveolar-arterial oxygen tension gradient (A-aDO_2) and hypocapnia.

- The incidence of abnormal A-aDO_2 was significantly higher in supine position than in erect position in cirrhotic patients.

- All cases of hypoxemia have statistically abnormal A-aDO_2 in supine position in patient with liver cirrhosis.

- In patients with liver cirrhosis, hyperventilation is present that can be multifocal in origin leading to respiratory alkalosis and hypocapnia.

- Cirrhotic patients with orthodeoxia have significantly higher PaO_2 in supine position than those without while the reverse occurred regarding PaO2 in erect position where orthodeoxic patients showed hypoxemia whereas nonorthodeoxic showed improvement in PaO_2 level.

- There are significantly higher mean values of PaO_2, $PaCO_2$ and O_2 sat. in supine than in erect position in cirrhotic patients with orthodeoxia.

- The incidence of reduced DLco corrected is more significant than the incidence of restrictive disorders.

- There is significant relationship between hypocapnia and Child Pugh classification in patients with liver cirrhosis where the incidence is more among patients with Child class C than B than A.

- There is significantly negative correlation between A-aDO_2 and PaO_2 in supine position in patients with liver cirrhosis.

- There is significant relationship between orthodeoxia and A-aDO_2 in supine position in patients with liver cirrhosis.

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Recommendations

Patients With liver cirrhosis who shows signs of hypoxemia in the absence of cardiopulmonary abnormalities should be subjected to arterial blood gas analysis in the supine position looking for abnormal A-aDO_2, if present, arterial blood gas analysis in the erect position should be obtained looking for orthodeoxia, if present, it is highly specific for HPS, therefore DLco should be the next investigation, if it is abnormal, the patient may have HPS, and more specific and diagnostic investigation for HPS should be done.

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تقييم وظائف الرئتين في مرضى التشمع الكبدي

مقدمه

إن مرضى التشمع الكبدي في خطر متزايد لتغيرات معينة في ميكانيكية التهوية الرئوية وكذلك في نفاذية الغازات خلال الرئتين . فعلى الرغم من أن الارتباط بين مرض الكبد والتغيرات الوعائية الرئوية قد عرفت منذ أكثر من مائة عام إلا أن هذه التغيرات قد خضعت للبحث والدراسة خلال السنوات الخمسة عشرة الاخيرة فقط حيث تم ربطها بمرض التشمع الكبدي وارتفاع ضغط الدم في الوريد البابى.

هذه التغيرات تتضمن متلازمتين متميزتين:

1. متلازمة الكبد الرئوية والتي تتميز بتوسع الأوعية الدموية الرئوية الدقيقة.
2. ارتفاع ضغط الدم الرئوي البابى والذي يتميز بتضيق الأوعية الدموية الرئوية.

فبالرغم من أن كلٍ من هاتين المتلازمتين تمتلك مميزاتٍ ونتائج سريرية فريدة إلا أنهما قد تشتركان في بعض الأليات المسببة للمرض.

إن حالة اعتلال وظيفة الرئة الأكثر شيوعاً في مرضى مرحلة نهاية التليف الكبدي هي قدرة الانتشار الناقصة لأول أكسيد الكربون.

لا يوجد إجماع على سبب الأصابة باعتلال نفاذية الغازات في مريض الكبد المزمن ويفترض بأن الآليات المرضية المسئولة عن تخفيض قدرة الانتشار في أمراض الكبد متعددة العوامل وتتضمن اختلال التناسق بين الارواء الدموي والتهوية الرئوية.

إن الأكسيد النتريكى وسيط مهم لضعف الأكسدة في مريض تشمع الكبد وهو ماده موسعة للأوعية الدموية التي يمكن أن تلغى رد الفعل المحلى القابض للأوعية الدموية الناتج عن نقص فى وصول الأكسجين إلى الحويصلات الرئوية مما يؤدى الى ازدياد الإخلال فى التناسق بين الإرواء الدموي والتهوية الرئوية.

بالرغم من أن إنخفاض ضغط الأكسجين الشرياني يمكن رصده فى ثلث إلى ثلثين من مرضى التشمع الكبدي فإن نقص وصول الأكسجين إلى أنسجة الجسم يبدو نادراً فى الممارسة السريرية.

كما أن متلازمة الكبد الرئوية تعتبر واحده من التعقيدات الخطيرة التي تتميز بثلاثية مرض الكبد ونقص أوكسجين الدم الشرياني و التوسعات الوعائية الرئوية فى غياب الأمراض القلبية والرئوية الأساسية القابلة للكشف.

الهدف من البحث

تهدف هذه الدراسة الى تقييم وظائف الرئتين لدى مرضى التشمع الكبدي.

خطة البحث

شمل البحث خمسين مريضا بتشمع الكبد من الذين ُادخلوا إلى قسم طب الكبد في معهد الكبد القومي.

معايير الإدراج

مرضى تشمع الكبد بمختلف مراحله.

معايير الاستثناء

المرضى المصابين بأمراض قلبية مثل قصور الشريان التاجي ومرضى فشل القلب الإحتقانى.

- المرضى المصابين بأمراض الرئة المزمنة والحادة مثل مرضى انتفاخ الرئة ومرضى الربو الشعبي ومرضى تشمع الرئة ومرضى الأ لتهاب الرئوي ومرضى إلتهاب القصابات الحاد والمزمن.
- مرضى إرتشاح الغشاء البللورى.
- المرضى المصابين بالسرطان أياً كان مكانه فى الجسم.

سوف يتم عمل الأتي لكل المرضى الذين يشملهم البحث:

- استقراء التاريخ المرضى لكل حاله
- فحص طبي شامل
- عمل فحوصات معملية تشمل وظائف الكبد كاملة و إختبار الدم الشرياني لقياس غازات الدم.
- عمل أشعه صدر أمامي وجانبي .
- عمل أشعه بالموجات فوق الصوتية للبطن.
- عمل أشعه بالموجات فوق الصوتية للقلب.
- قياس قدرة الإنتشار لغاز أول أكسيد الكربون.
- قياس وظائف التنفس.
- تصنيف درجة تشمع الكبد طبقاً لتصنيف تشايلد بوف.

و قد تبين الآتي:

- النسبة المؤوية الأعلى لمرضى التشمع الكبدي تميزت بوظائف تنفس طبيعية , انخفاض فى قدرة الانتشار لغاز أول أكسيد الكربون , قلوية تنفسية, انخفاض فى مستوى ثاني أكسيد الكربون فى الدم, توتر أوكسجين حويصلى شرياني شاذ, بدون نقص فى وصول الأكسجين إلى أنسجة الجسم, بدون انخفاض فى نسبة الاوكسجين عند التحول من وضع الرقود الى وضع القيام.

- إن قدرة الإنتشار لغاز أول أكسيد الكربون كانت أكثر وظائف الكبد تأثرا لدى مرضى التشمع الكبدي.
- وجود ارتباط سلبي بين العمر ووظائف التنفس وقدرة الإنتشار لغاز أول أكسيد الكربون فى مرضى التشمع الكبدي ولكن لا توجد علاقة بين هذه المقاييس والجنس.
- وجود اختلافات ملحوضة فى وظائف التنفس و قدرة الإنتشار لغاز أول أكسيد الكربون فى مرضى التشمع الكبدي بخصوص تصنيف تشايلد بوف حيث كان المستوى الأعلى لهذه المقاييس فى التصنيف (أ) والمستوى الأدنى فى التصنيف (ج).
- إن القلوية التنفسية كانت أكثر حالات الشذوذ الأيضي لدى مرضى التشمع الكبدي.
- إن أكثر شذوذ التبادل الغازي لدى مرضى التشمع الكبدي كان التغير فى معدل توتر الأوكسجين الحويصلى الشرياني وانخفاض معدل ثاني أكسيد الكربون فى الدم.
- إن حوادث وجود التغير فى معدل توتر الأوكسجين الحويصلى الشرياني لدى مرضى التشمع الكبدي كان أعلى بصورة ملحوضة فى وضع الرقود أكثر منه فى وضع الانتصاب.
- كل حالات نقص وصول الأكسجين إلى أنسجة الجسم لديها تغير فى معدل توتر الأوكسجين الحويصلى الشرياني فى وضع الرقود فى مرضى التشمع الكبدي.

- وجود زيادة فى معدل التنفس لدى مرضى التشمع الكبدي والذي يمكن إن يكون نتيجة أسباب عدة مؤديا الى قلوية الدم التنفسي وانخفاض معدل ثاني أكسيد الكربون فى الدم.
- أن مرضى التشمع الكبدي الذين يعانون من انخفاض نسبة الأوكسجين عند التحول من وضع الرقود الى وضع القيام (الاورثوديوكسيا) لديهم توتر أوكسجين شرياني فى وضع الرقود أعلى من مرضى التشمع الكبدي الغير مصابين بالاورثوديوكسيا بينما العكس حدث بخصوص توتر الأوكسجين الشرياني فى وضع القيام حيث عانى المرضى المصابين بالاورثوديوكسيا من نقص وصول الأكسجين إلى أنسجة الجسم فى حين أن المرضى الغير مصابين بالاورثوديوكسيا أظهروا تحسننا ملحوظا فى توتر الأوكسجين الشرياني.
- وجود قيم متوسطة عالية لتوتر الأوكسجين الشرياني وتوتر ثاني أكسيد الكربون الشرياني ونسبة تشبع الاوكسجين فى الدم فى وضع الرقود أكثر منه فى وضع القيام لدى مرضى التشمع الكبدي المصابين بالاورثوديوكسيا.
- إن معدل الحالات المصابة بنقص قدرة الإنتشار لغاز أول أكسيد الكربون كانت أعلى بصورة ملحوظة من معدل الحالات المصابه باعتلالات الرئة التقييدية.
- وجود علاقة هامة بين انخفاض ثاني أكسيد الكربون فى الدم وتصنيف تشايلد لدى مرضى التشمع الكبدي حيث أن معدل

الانخفاض أعلى فى مرضى التصنيف (ج) أكثر منه فى التصنيف (أ).

- وجود ارتباط سلبي ملحوظ بين توتر الأوكسجين الشرياني ومعدل توتر الأوكسجين الحويصلى الشرياني فى وضع الرقود فى مرضى التشمع الكبدي.
- وجود علاقة هامة بين الاورثوديوكسيا و معدل توتر الأوكسجين الحويصلى الشرياني فى وضع الرقود فى مرضى التشمع الكبدي كون كل المرضى المصابين باعتلال معدل توتر الأوكسجين الحويصلى الشرياني فى وضع الرقود لديهم الاورثوديوكسيا فى وضع القيام.

تقييم وظائف الرئتين فى مرضى التشمع الكبدي

رسالة

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