

**Assessment of Pulmonary Hypertension in
Patients with Liver Disease Pre and Post Liver
Transplantation**

Thesis

Submitted for the partial fulfillment of
Master Degree in chest diseases and tuberculosis

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List of Abbreviations

ASD	Atrial septal defect.
AcT	Acceleration time.
ANCA	Antineutrophil cytoplasmic antibody.
ANA	Antinuclear antibody.
BMPR2	Bone morphogenetic protein receptor.
BNP	Brain natriuretic peptide.
CCBs	Calcium channel blockers.
CVP	Central venous pressure.
COPD	Chronic obstructive pulmonary disease.
CPLA2	Cytosolic phospholipase A2.
dPAP	Diastolic pulmonary artery pressure.
DLCO	Diffusion lung capacity of CO.
ECG	Electrocardiogram.
ENOS	Endothelial nitric oxide synthase.
ERS	European Respiratory Society.
FPAH	Familial pulmonary artery hypertension.
FEV1	Forced expiratory volume in 1 second.
FVC	Forced vital capacity.
FRC	Function residual capacity.
GP	Glycoprotein .
HPS	Hepatopulmonary syndrome .
HIV	Human immunodeficiency virus.
IPAH	Idiopathic Pulmonary Arterial Hypertension.
INR	International Normalized Ratio.
ILD	Interstitial lung disease.
KS	Kaposi's sarcoma.
L	Liter.
LT	Liver transplantation.
MPAP	Mean pulmonary artery pressure.
No	Number.
Ppa	Mean pulmonary arterial pressure.
Ppv	Mean pulmonary venous pressure.
PVOD	Pulmonary veno-occlusive disease.

List of abbreviations (Cont.)

NHLBI	National Heart , Lung and Blood Institute.
NYHA	New York Heart Association.
NOTT	Nocturnal Oxygen Therapy Trial.
NT-proBNP	N-terminal pro-brain natriuretic peptide.
OSAH	Obstructive sleep apnea-hyperpnoea.
VO2	Peak oxygen consumption.
PVR	Pulmonary vascular resistance.
PDE5	Phosphodiesterase-5.
PPHTN	Portopulmonary hypertension.
PAH	Pulmonary artery hypertension.
PASP	Pulmonary artery systolic preesure.
PCWP	pulmonary capillary wedge pressure.
PFT	Pulmonary function test.
PHTN	Pulmonary hypertension .
RF	Rheumatoid factor.
RV	Right ventricle .
RVET	Right ventricular ejection time.
Q	Right-sided cardiac output.
HS	Highly Significance.
6MWT	Six minute walk test.
SLE	Systemic lupus erythematosus.
SPAP	Systolic pulmonary artery pressure.
US	United State.
V/Q	Ventilation-perfusion.
VSD	Ventricular septal defect.
Kv	Voltage-gated potassium channel.
WHO	World health organization.

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Introduction

Patients with chronic liver disease may show two pulmonary vascular disorders that are considered mutually exclusive: on the one hand, hepatopulmonary syndrome (HPS), which is characterized by pulmonary vascular dilatations and abnormal gas exchange (**Krowka and Cortese, 1994**), and on the other, portopulmonary hypertension (PPHTN), a process defined by pulmonary hypertension associated with portal hypertension (**Hadengue et al., 1991**).

If severe, both conditions are associated with a high mortality rate. The role of liver transplantation in reversing these vascular disorders is controversial, although complete resolution of HPS and, less frequently, PPHTN, following liver transplantation have been reported (**Krowka et al., 1997**).

The pathiogenesis of these entities likely depends on an imbalance between vasoconstrictor and vasodilator substances that may also exert an effect on vascular proliferation. This imbalance results from liver dysfunction and promotes HPS if the vasodilator effect predominates or PPHTN if vasoconstriction prevails (**Schraufnagel and Kay, 1996**). Furthermore, angiogenic factors that escape hepatic metabolism and enter the pulmonary circulation through collateral shunts may also play a role in the pathogenesis of PPHTN (**Mandell and Groves, 1996**).

Pulmonary hypertension (PHTN) is a progressive disease characterized by an increased PVR and eventually right heart failure. The initial pulmonary vascular change is endothelial dysfunction that results in vasoconstriction, which

is reversible with vasodilator therapy. The histopathological changes then progress with the development of intimal proliferation, medial hypertrophy and plexogenic changes in the media causing narrowing of the vascular lumen. Microthrombosis may also be seen as a result of endothelial dysfunction. Many of these changes may be reversed with chronic vasodilator therapy but endothelial injury will make the disease more resistant to therapy.

Eventually fixed pathological changes will occur with fibrosis developing that is not responsive to therapy. Survival correlates with the ability of the RV to accommodate the increase in PVR, or increase in cardiac output, as may occur at reperfusion of a liver graft, may precipitate acute RV failure **(Ramsay, 2004)**.

Portopulmonary hypertension is defined by the presence of the following features in patients with portal hypertension: raised pulmonary arterial pressure (mean pressure determined by right-heart catheterization of >25mmHg at rest and >30mmHg during exercise) **(Rich, 1998)**, raised pulmonary vascular resistance (>240 dyne s-1cm-5) in the presence of a pulmonary arterial occlusion pressure; or a left-ventricular end diastolic pressure of less than 15mmHg. According to the current WHO classification, portopulmonary hypertension is no longer classified as secondary pulmonary hypertension but as pulmonary arterial hypertension associated with liver disease or portal hypertension **(Rich, 1998)**.

The reported frequency of hepatopulmonary syndrome in patients with liver disease is between 4% and 29 %.The differing incidence is primarily due to heterogeneity of the applied diagnostic criteria. This syndrome is a well defined

cause of hypoxaemia in patients who have liver disease due to abnormal intrapulmonary vascular dilatation, which results in an excess perfusion for a given state of ventilation. This complication is characterised by anatomical shunting and a diffusion-perfusion abnormality (**Deng et al., 2000**).

Thus, abnormal pulmonary vascular dilatation plays a central part in the hepatopulmonary syndrome, whereas abnormal vasoconstriction and obliterative vascular remodeling are the key features of portopulmonary hypertension (**Mal et al., 1999**).

Aim of The Work

Assessment of pulmonary hypertension in liver disease patients pre and post liver transplantation. Studying the impact of pulmonary hypertension on hemodynamic of the patients in hospital after liver transplantation.

Pulmonary Hypertension

Pulmonary hypertension (PHTN) is characterized by elevated pulmonary arterial pressure with or without secondary right ventricular failure. It is a life-threatening condition with a poor prognosis if untreated (**Barst et al., 2004**). In this topic review, we discuss the definition, classification, epidemiology, clinical manifestations, and prognosis of PHTN.

Patients suspected of having pulmonary hypertension (PHTN) undergo extensive diagnostic testing. The goal of diagnostic testing is to confirm that PHTN exists and to identify its underlying cause (**Simonneau et al., 2004**). The diagnostic tests used to evaluate a patient with suspected PHTN will be reviewed here.

Because the pulmonary vasculature is highly distensible it is capable of handling significant increases in blood flow with only minimal increases in pressure. The right ventricle (RV) is a thin walled chamber with very little muscle and is unable to respond to acute increases in after load by increasing its force of contraction; therefore, it will dilate and this will be followed by the right atrium causing an increase in central venous pressure (CV P) resulting in congestion of the liver. The high flow state may be further complicated by the presence of a cirrhotic cardiomyopathy, cardiac failure and volume overload and on occasion by the pathological increase in pulmonary vascular resistance (PVR). This will cause pulmonary hypertension (PHTN) (**Ramsay, 2010**).

Definitions

Pulmonary hypertension (PHTN) is defined as a mean pulmonary artery pressure greater than 25mmHg at rest or 30mmHg with exercise, as measured by right heart catheterization (**Badesch et al., 2009**).

It was previously defined as a systolic pulmonary artery pressure greater than 40mmHg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of 3.0 to 3.5 m/sec (Rich, 1998).

PHTN is a progressive disease characterized by an increased PVR and eventually right heart failure.

Classification of PHTN

Pulmonary arterial hypertension (PAH) represents Group 1 within the Pulmonary Hypertension (PHTN) WHO clinical classification system (Venice 2003 revision) and is one of five such groups. The groups are divided based on aetiology (Simonneau et al., 2004).

Table (I): WHO clinical classification system (Venice 2003 revision)

Group I	Pulmonary arterial hypertension (PAH)
	• Idiopathic (IPAH) • Familial (FPAH) • Associated with (APAH): ◦ Connective tissue disease ◦ Congenital systemic-to-pulmonary shunts ◦ <u>Portal hypertension</u> ◦ HIV infection ◦ Drugs and toxins ◦ Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy) • Associated with significant venous or capillary involvement ◦ Pulmonary veno-occlusive disease (PVOD) ◦ Pulmonary capillary haemangiomatosis

Group I	Pulmonary arterial hypertension (PAH)
	(PCH) • Persistent pulmonary hypertension of the newborn (PPHN)
Group II	1. Pulmonary hypertension associated with left heart diseases
Group III	2. Pulmonary hypertension associated with respiratory diseases and / or hypoxemia (including chronic obstructive pulmonary disease)
Group IV	Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group V	Miscellaneous group
	• eg. sarcoidosis, histiocytosis X and lymphangiomatosis

Idiopathic Pulmonary Arterial Hypertension (PAH) (IPAH), which by definition has no identifiable underlying cause, is one of the more common types of Pulmonary Arterial Hypertension (PAH). Familial PAH (FPAH) accounts for at least 6% of cases of IPAH and mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in the majority of cases of FPAH (**Lana et al., 2000**).

Pulmonary Arterial Hypertension (PAH) can also be associated with a number of conditions (Associated Pulmonary Arterial Hypertension - APAH), which together account for most other cases of Pulmonary Arterial Hypertension (PAH).

Pulmonary Arterial Hypertension (PAH) is also a rare side effect of certain anorexigenic agents, such as fenfluramine.