INTRODUCTION

Hepatopulmonary syndrome (HPS) is defined as a clinical triad characterised by an oxygenation defect induced by the presence of pulmonary vasodilation observed in patients with liver disease or portal hypertension ***(Gonçalves-Macedo et al., 2017).***

Portopulmonary hypertention definition has evolved over time, specifically with regard to the cutoff for pulmonary vascular resistances (PVR), therefore the current consensus diagnostic criteria for PPHTN include mean pulmonary artery pressure (MPAP) > 25 mmHg, PVR > 240 dyn·s·cm−5, and pulmonary artery occlusion pressure (PAOP) <15 mmHg ***(Luigi et al., 2013),*** with presence of portal hypertension (either concluded from the presence of splenomegaly, thrombocytopenia, portosystemic shunts, oesophageal varices or portal vein abnormalities, or confirmed by haemodynamic measurements) but not necessarily the presence of cirrhosis. Confirmed by haemodynamic measurements from right heart catheterization (RHC) including mean pulmonary artery pressure (mean Ppa) >25 mmHg at rest, mean pulmonary capillary wedge pressure (mean Ppcw) < 15 mmHg, and pulmonary vascular resistance (PVR) > 240 dyn·s·cm−5 ***(Porres-Aguilar et al., 2012).***

Transthoracic echocardiography (TTE) is the most accessible noninvasive diagnostic procedure for the initial

assessment of pediatric pulmonary hypertension (PH) ***(Martin et al., 2016).***

For the initial assessment and follow-up of children with suspected or confirmed pulmonary hypertention, transthoracic echocardiography (TTE) is the noninvasive diagnostic method of choice TTE allows a detailed description of cardiovascular anatomy, ventricular function, and flow determination and carries low risk and wider availability, compared with cardiac magnetic resonance ***(Ploegstra et al., 2015; Von et al., 2015).***

Aim of the Work

The aim of this study is to assess screening of hepatopulmonary syndrome and portopulmonary hypertension in cholestatic patients versus non cholestatic patients.

Chapter One

HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome (HPS) is defined as a clinical triad characterised by an oxygenation defect induced by the presence of pulmonary vasodilation observed in patients with liver disease or portal hypertension ***(Gonçalves-Macedo et al., 2017).***

It is distinguished by three specific clinical entities consisting of liver disease and/or portal hypertension, disturbance of alveolar-arterial oxygen gradient, and intrapulmonary vascular dilatations (IPVD) ***(Raevens et al., 2015)***.

The relationship between pulmonary disorder and liver disease has been recognized for more than 100 years. Despite years of research, diagnosing HPS is still difficult due to the existence of other comorbidities and unclear clinical presentation. Moreover, the only proven therapy for HPS is liver transplantation (LT) ***(Fallon and Zhang, 2013; Fritz et al., 2013).*** HPS is defined by the existence of liver disease, disturbance of arterial oxygenation marked by elevated room air alveolar-arterial oxygen gradient [P(A-a)O2] >15 mmHg or arterial partial pressure oxygen (PaO2) < 80 mmHg during room air breathing without other identifiable cause, and IPVD diagnosed by contrast transthoracic echocardiography or other accepted modality ***(Tumgor, 2014; Raevens et al., 2015).***

However, it is now known that HPS could manifest in patients with portal hypertension despite having no liver cirrhosis. Moreover, many studies have failed to establish a clear link between the severity of liver disorder and the presence of HPS. Consequently, clinical symptoms such as dyspnea, cyanosis, digital clubbing, orthodeoxia, and platypnea will have more diagnostic value in establishing a more reliable definition ***(Grace and Angus, 2013; Shah et al., 2014).***

Epidemiology and risk factors

The prevalence of HPS in pediatric patients with cirrhosis with portal hypertension have not been well characterized, especially in children aged <2 years. In addition, few studies have reported on outcomes of pediatric patients with HPS after liver transplantation. In adults, the reported prevalence of HPS is approximately 4%-47% of patients with cirrhosis evaluated for liver transplantation ***(Cosardereliogluet al., 2016).***

The estimated prevalence of HPS is 4% to 32% among chronic liver disease patients. The cause of this wide range of prevalence is the variation of diagnostic criteria and study population. IPVDs were found in 38% of cirrhotic patients using biopsy in conjunction with microbubble transthoracic echocardiography (MTTE), but only 17.5% of cirrhotic patients had an arterial oxygenation defect as detected by blood gas

analysis. However, other studies found a wide range of IPVDs prevalence (13-80%) in LT candidates ***(Kim et al., 2004)***.

Pathophysiology

The hallmark of HPS is intrapulmonary vasodilatation. The most remarkable anatomic abnormality is dilatation at both the pre-capillary and capillary level of the pulmonary circulation (50-80 μm; normal diameter range is 8–15 μm), especially in the lower lobes as figure (1). Less frequently, discrete arteriovenous anastomoses unrelated to the alveolar-capillary unit may be identified, as well as porto-pulmonary anastomoses ***(Porres-Aguilar et al., 2012).***

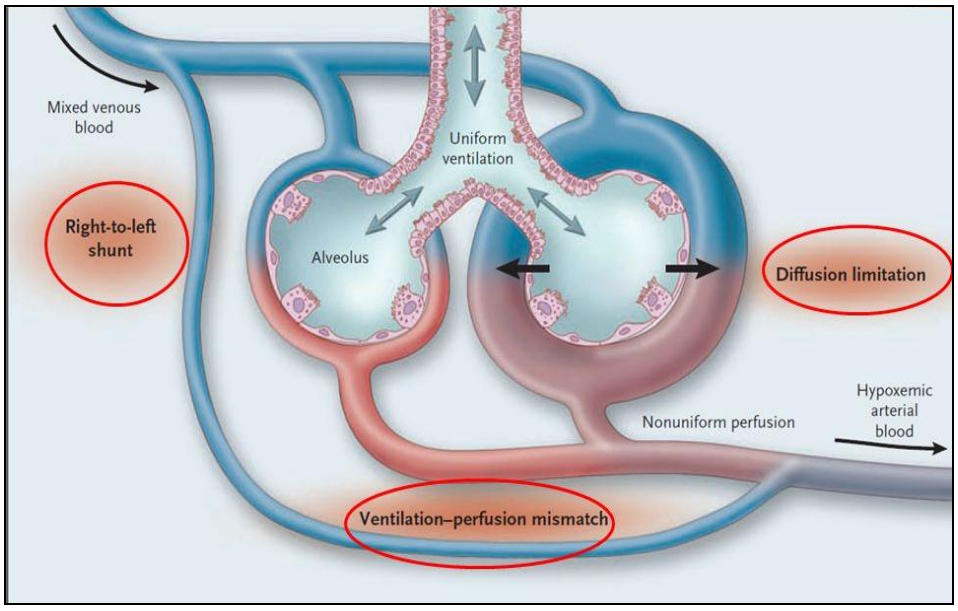

Figure (1): Mechanisms of Arterial Hypoxemia in hepatopulmonary syndrome ***(Rodríguez-Roisin et al., 2008).***

The consequence of the intrapulmonary vasodilatation is arterial deoxygenation by three mechanisms: ventilation/ perfusion V′/Q′mismatch, intrapulmonary shunting, and limitation of oxygen diffusion. The main mechanism seems to be related to a low V′/Q′, a hypothesis strongly supported by improvement of partial pressure of oxygen PaO2 while breathing 100% O2 in the majority of affected patients. The hyperdynamic circulation present in patients with cirrhosis causes a decrease in the transit time of erythrocytes through the alveolar-capillary unit, further compromising oxygen diffusion ***(Porres-Aguilar et al., 2012).***

The definitive cause of HPS has not been clearly determined. Some clinical studies have suggested that reduced pulmonary vascular tone and advanced liver disorder are the main causes. Other studies have also found that exhaled NO level is elevated in cirrhotic patients with HPS compared to control, providing a clue of the role elevated pulmonary nitric oxide (NO) production has in causing HPS. Another contributing factor in elevated NO levels is the increased expression of inducible NO synthase (iNOS) due to increase in phagocytosis caused by bacterial endotoxin. This event could occur in portal hypertension, which will eventually result in intestinal perfusion disturbance and increased rate of gram-negative bacteria and enteral endotoxin translocation. Moreover, it also induces the release of vasoactive mediators including NO ***(Grace and Angus, 2013; Tumgor, 2014)***.

Plasma endothelin-1 (ET-1) could give rise to NO-associated vasodilatation through activation of endothelin B receptors (ETBR) on endothelial cells. ET-1 levels were found to be elevated in cirrhosis and IPVD cases ***(Feng and Rong, 2014).*** Macrophages could also induce vasodilatation due to hemeoxygenase (HO-1) production that resultes in increased production of carbon monoxide (CO) ***(Thenappan et al., 2011).*** Furthermore, gene polymorphisms also played a role in the angiogenesis that had been linked with advanced HPS as shown in figure (2) ***(Roberts et al., 2010).***

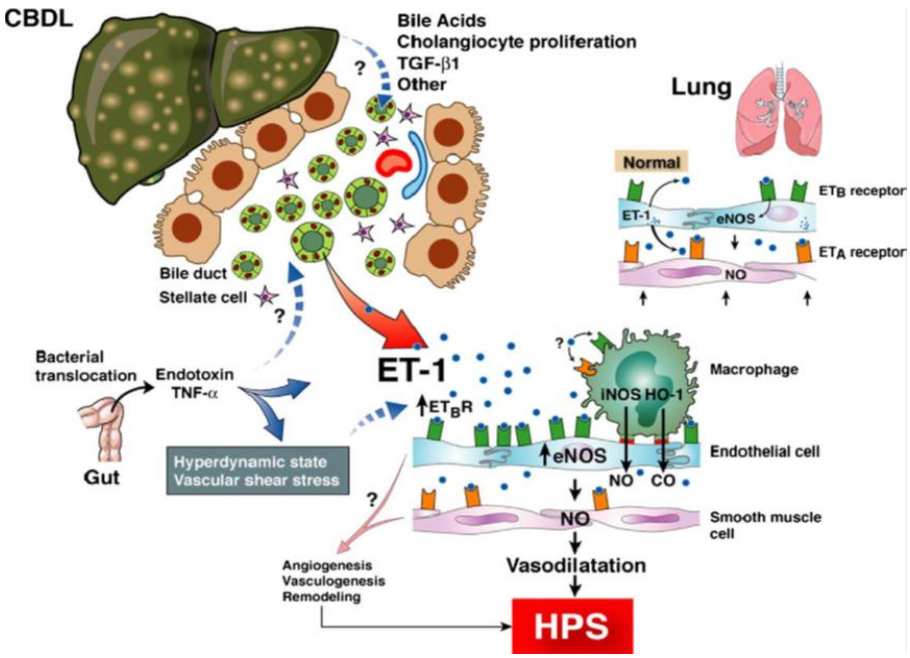

Figure (2): Pathophysiology of HPS ***(Palma and Fallon, 2008).***

The aforementioned conditions lead to diffusion-perfusion flaw, ventilation perfusion (V/Q) mismatch, and direct arteriovenous shunt. Diffusion-perfusion flaw is caused

by an increase of alveolar capillary diameter that expandes the binding space between oxygen molecules with hemoglobin. The combination of the aforementioned conditions with increased cardiac output and reduction of transit time that is usually seen in cirrhosis cause the red blood cells to leave the pulmonary capillaries before oxygen equilibrium is reached. It could also be aggravated by hypoxic pulmonary vasoconstriction. Lastly, direct arteriovenous shunt could lead to hypoxemia due to mixture of arterial and venous blood ***(Feng and Rong, 2014; Tumgor, 2014).*** Studies of HPS in animal models have identified a number of pathological changes consisting of decreased tidal volume, minute ventilation, lung airway resistance, and mean inspiratory flow, accompanied by elevated chest wall pressure dissipation and viscoelastic pressure. The amount of collagen volume in the vasculature was elevated by 29% in HPS animal models. In addition, cirrhotic patients also showed an increased level of lipopolysaccharide (LPS). Cirrhotic animal models that had been given extra LPS revealed abnormalities of lung anatomy and functions, such as reduction of cell density, expanded alveolar wall, constricted alveolar space, and obliteration of type 1 cell membrane solidity, along with a series of inflammatory reaction and interstitial pulmonary edema. These impairments lead to extensive dilatation of alveolar capillaries and increased permeability of vasculature ***(Melo-Silva et al., 2011).***

Clinical manifestations

Dyspnea, digital clubbing, cyanosis and spider angiomata are characteristic features in patients with HPS. Dyspnea on exertion may lack specificity as it does not occur more frequently in the setting of HPS, probably being confounded by physical deconditioning and fatigue, which are very common among patients with cirrhosis ***(Arguedas et al., 2007).*** Platypnea and orthodeoxia, the increase in dyspnea or deoxygenation while in the standing position, are classically described in HPS. These occur as the change from supine to standing position exacerbate the V′/Q′ mismatch through decreased perfusion of the highly ventilated lung apices, and the opposite effect in the bases, driven by changes in hydrostatic pressure and the predominance of pulmonary dilatations in the lung bases. However, these are not pathognomonic features and actually orthopnea seems to be a more frequent manifestation in HPS ***(Fallon et al., 2008).***

Other physical stigmata of cirrhosis and portal hypertension can be seen in patients with HPS ***(Porres-Aguilar et al., 2012).***

Table (1): Diagnostic criteria for HPS:

Diagnostic Criteria of HPS	
Oxygenation defect:	Partial pressure of oxygen equals or below 80 mmHg or alveolar-arterial oxygen gradient ≥ 15 mmHg while breathing ambient air.
Pulmonary vascular dilatation:	Positive findings on contrast enhanced echocardiography or abnormal uptake in the brain with radioactive Lung Perfusion Scan.
Liver disease:	Portal Hypertension (most common) with or without cirrhosis.

(Tumgor, 2014; Raevens et al., 2015)

Table (2): Degree of Severity of HPS

Degree of severity	
Mild	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ 80 mmHg.
Moderate	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen ≥ (60-80) mmHg.
Severe	Alveolar-arterial oxygen gradient ≥15 mmHg, partial pressure of oxygen ≥ (50-60) mmHg.
Very Severe	Alveolar-arterial oxygen gradient ≥ 15 mmHg, partial pressure of oxygen < 50 mmHg

(Tumgor, 2014; Raevens et al., 2015)

Diagnostic evaluation

1) Oxygen saturation in room air is screened by percutaneous pulse oximetry in sitting position which is a well-established method for noninvasive evaluation of arterial oxygenation ***(Birnbaum, 2009)***.

The threshold for identifying hypoxemia was defined as SO2 <97% ***(Noli et al., 2008).***

2) Measurement of Arterial Blood Gases (ABGs) is the gold standard for identifying arterial deoxygenation and classifying HPS according to the degree of hypoxemia. PaO2 is the main prognostic determinant for HPS, although, because of the reflex hyperventilation (increased alveolar oxygen tension), it underestimates the oxygenation defect. Thus, A-aDO2 is the most important parameter for the early diagnosis of HPS ***(Porres-Aguilar et al., 2012).***

The European Respiratory Society Task Force recommends alveolar–arterial oxygen tension difference (aA-aDO2) ≥15 mmHg for the diagnosis of HPS, whereas PaO2 is used to classify the severity of HPS ***(Rodriguez-Roisin et al., 2008).***

ABGs are usually obtained while the patient is sitting and breathing room air, but two characteristic features linked to the pathophysiology of HPS can be also studied with ABGs:

A- Orthodeoxia, which manifests as a decrease inPaO2 of ≥ 4 mmHg or ≥ 5% from the supine to the upright position.

Orthodeoxia is a consequence of the increased V′/Q′ mismatch and decreased cardiac output following the change from the supine to the upright position ***(Gonçalves-Macedo et al., 2017).***

B- The increase in PaO2 while breathing 100% oxygen, which should reach > 300 mmHg ***(Rodriguez-Roisin et al., 2008; Montani et al., 2010).***

Marked hypoxemia during sleep has been described in HPS and it is recommended to assess overnight pulse oximetry ***(Palma et al., 2008).***

3) Chest radiographs are usually normal in patients with HPS but can manifest as increased interstitial pattern in the bases, an effect usually caused by arteriovenous shunts in severe HPS ***(Porres et al., 2012).*** The hyperdynamic circulation of cirrhosis can also lead to left atrial enlargement in the absence of any specific cardiac disease ***(Zamirian et al., 2007).***

4) High-Resolution Computed Tomography (HRCT) can identify dilatation of the peripheral pulmonary vessels in the lung bases at early stages of HPS, although the clinical usefulness of this finding is uncertain at the present time ***(Koksal et al., 2002).***

5) Pulmonary functions test is associated with decreased diffusion capacity of oxygen observed in HPS, also the

diffusing capacity of the lung for carbon monoxide can be found to be low ***(Zamirian et al., 2007).***

6) Contrast Enhanced Trans-esophageal Echocardiogram (CETEE) has become the most commonly used test for identifying the intravascular vasodilatation of HPS. Contrast is usually accomplished by injecting 10 mL of normal saline that has been hand-agitated, producing micro-bubbles (≤ 90 μm in diameter). This opacifies the left atrium four or more beats after the initial appearance of contrast in the right atrium in patients with HPS, whereas those with a cardiac right-to-left shunt (*i.e.* atrial septal defect) will show opacification of the left atrium within the first three beats ***(Lenci et al., 2009).***

(CE-TEE) is rarely needed, but it may define probable cases of inter-atrial communication. However, CE-TEE is more expensive, requires sedation and has a low risk of complications with variceal bleeding. A recent report with a small number of patients proposed performing the CE-TTE in the upright position as another measure to increase the sensitivity of the test ***(Lenci et al., 2009).***

7) Agitated saline contrast enhanced transthoracic echocardiogram.

Transthoracic echocardiography with contrast enhancement (CE-TTE) provides a sensitive, noninvasive and qualitative screening approach for the detection of IPVD, the central defining structural characteristic feature of HPS, and is

considered the gold standard for the diagnosis of HPS. It is commonly accomplished by hand agitation of 10 mL normal saline, resulting in microbubbles (90 μm in diameter), which are injected into an upper extremity vein. Detection of microbubbles within the left atrium is considered positive CE-TTE. Microbubbles are physiologically trapped and absorbed by normal alveoli during the first pass and should not appear in the left atrium. Following microbubble appearance in the right atrium, immediate appearance in the left atrium (within less than three cardiac cycles) suggests an intra-atrial right-to-left communication, whereas delayed appearance in the left heart cavities (within greater than three cardiac cycles) implies definite IPVD. ***(Neuberger and Steeds, 2009).***

8) Lung perfusion scanning with Macro-Aggregated Albumin (MAA scan) provides a quantitative assessment of the severity of the intrapulmonary vasodilatation. In this method the signal of 99mTc-radiolabelled MAA (>20 μm in diameter) is abnormally detected outside of the lungs (in the brain by convention), as these particles should remaine trapped within the lungs in the absence of intrapulmonary vasodilatation. Even though an MAA scan is not necessary for the diagnosis of HPS, it can help to identify clinically significant pulmonary vasodilatation, especially in patients with intrinsic lung disease in whom it is difficult to establish the contribution of HPS to hypoxemia ***(Porres-Aguilar et al., 2012).***