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Portopulmonary Hypertension

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Abstract

Portopulmonary hypertension (PPH) is characterized by the development of pulmonary arterial hypertension (PAH) associated with portal hypertension, with or without liver disease. It is defined as a mean pulmonary artery pressure (MPAP) greater than 25 mmHg, pulmonary vascular resistance (PVR) above 240 dynes.s.cm^{-5}, pulmonary artery occlusion pressure (PAOP) normal when less than 15 mmHg or transpulmonary gradient (TPG) > 10 mmHg. In the pulmonary hypertension classification PPH is classified in Group I. Pulmonary arterial hypertension in association with cirrhosis and portal hypertension is underdiagnosed. Epidemiological studies estimated that about 2–6% of patients with portal hypertension develop PPH. Mortality is directly proportional to measured MPAP and PVR. Mean pulmonary artery pressure is an independent predictor of mortality, and many centers consider that values greater than 50 mmHg is an absolute contraindication to liver transplantation (LT). The aim of the review is to explore the current aspects of PPH relative to concept, diagnosis, and treatment.

Keywords: pulmonary hypertension, portal hypertension, portopulmonary hypertension, diagnosis, liver transplantation

1. Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure greater than or equal to 25 mmHg at rest, and above 30 mmHg during exercise, measured by right heart catheterization (RHC) [1].

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Pulmonary arterial hypertension (PAH) is a complex clinical entity, classified as Group I from the classification of PH. It may be idiopathic (formally called primary pulmonary hypertension), hereditary, induced by drugs or toxins, or associated with connective tissue diseases, human immunodeficiency virus, portal hypertension, congenital heart disease, schistosomiasis, and others [1–3].

Portal hypertension is a hemodynamic disorder that usually results from chronic liver disease or cirrhosis. Portal blood flow in adults is about 1000–1200 mL/min, creating a normal intraportal pressure of 7 mmHg. In the normal liver, the gradient between the portal vein and hepatic veins or the right atrium usually does not exceed 5 mmHg. Portal hypertension is defined by a gradient greater than 6 mmHg. When pressure gradients reach 10–12 mmHg, portal blood flow is shunted into the systemic circulation, resulting in the development of esophageal varices, ascites, and splenomegaly. Diagnosis can be made by abdominal ultrasonography and endoscopy [4].

Portopulmonary hypertension (PPH) is a form of pulmonary hypertension, associated with portal hypertension, with or without advanced liver disease [5–9].

In liver transplantation (LT) candidates, a large deconstructed pulmonary vasculature can occur. Vasculature alteration may range from hepatopulmonary syndrome (HPS), characterized by pulmonary vascular dilatation to portopulmonary hypertension, with pulmonary vascular resistance elevated, causing severe clinic hypoxemia, right heart failure, and death [5, 10, 11].

Mantz and Craige were the first to describe an association between pulmonary hypertension and portal hypertension in 1951. Those authors reported a case of a 53-year-old patient diagnosed with axial portal vein thrombosis and spontaneous portocaval shunt. Autopsy revealed changes in the pulmonary arterial vascular bed and reduction in portal vein diameter with normal liver parenchyma [12, 13].

Since the 1980s, PPH has gained recognition and importance, following the evolution of liver transplantation. In some cases, LT can be beneficial for the disease [6, 11].

In 1983, the National Institutes of Health Consensus Development Conference concluded that LT should be considered a therapeutic procedure for patients with chronic and end-stage liver disease lack of alternative treatment [14].

PPH was classified as a subtype of primary pulmonary hypertension in 1981 by the National Institute of Health Registry for Characterization of Primary Pulmonary Hypertension [8].

PPH was classified as secondary pulmonary hypertension in 1993, and since then it has become known as portopulmonary hypertension [5, 11, 15].

The Second World Pulmonary Hypertension Symposium was held in Evian (France) in 1998, where pulmonary hypertensive diseases were classified into five groups according to similarities in pathophysiologic mechanisms, clinical presentation, and therapeutic options [2].

At the Third World Pulmonary Hypertension Symposium in 2003 in Venice (Italy) and the Fourth World Symposium in 2008 in Dana Point (California, USA), PPH was categorized into Group I Pulmonary Hypertension [1, 2, 16, 17].

During the Fifth World Pulmonary Hypertension Symposium held in 2013 in Nice, France, the consensus was to maintain the general disposition of previous classification, with some modifications and updates [18], as seen in **Table 1**.

Group I. Pulmonary arterial hypertension

- Idiopathic

- Hereditary: mutation in the bone morphogenetic protein receptor type 2 (BMPR2), activin type I receptor kinase-like gene (ALK-1), endoglin (ENG), mothers against decapentaplegic 9 (SMAD9), caveolin 1 (CAV1), gene encoding potassium channel superfamily K member 3 (KCNK3) or unknown causes

- Drug and toxin induced

- Associated with: connective tissue disease, congenital heart disease, acquired immunodeficiency syndrome,**portal hypertension**, schistosomiasis

1′-Veno-occlusive pulmonary disease and/or pulmonary capillary hemangiomatosis

1″-Persistent pulmonary hypertension of the newborn (PPHN)

Group II. Pulmonary hypertension due to left heart disease

- Systolic dysfunction, diastolic dysfunction, valvular disease, congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group III. Pulmonary hypertension due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease, interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive pattern, sleep disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, developmental lung diseases

Group IV. Chronic thromboembolic disease (CTEPH)

Group V. Pulmonary hypertension with unknown multifactorial mechanisms

Table 1. Classification of pulmonary hypertension—2013 Nice/France [18].

Based on diagnostic criteria, PPH can also be defined as: an increase in mean pulmonary artery pressure (MPAP) > 25 mmHg, increased pulmonary vascular resistance (PVR) > 240 dynes.s.cm^{-5}, and a mean pulmonary artery occlusion pressure (PAOP) normal < 15 mmHg, in patients with portal hypertension and no other causes of pulmonary hypertension. These hemodynamic criteria are consistent with the definitions and classification proposed by the Third World Pulmonary Hypertension Symposium, according to the European Respiratory Society (ERS) Task Force on Pulmonary-Hepatic Vascular Disorders (PHD). Furthermore, a transpulmonary gradient (TPG) > 10 mmHg was finally recommended by the ERS Task Force on PHD [19], as seen in **Table 2**.

1. Portal hypertension (with and without cirrhosis)

2. Abnormal pulmonary hemodynamics

    a. MPAP > 25 mmHg

    b. PVR > 240 dynes.s.cm^{-5}

    c. PAOP < 15 mmHg

MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PAOP, pulmonary artery occlusion pressure.

Table 2. Diagnostic criteria for portopulmonary hypertension (according to ERS Task Force on PHD) [19].

The addition of transpulmonary gradient,TPG (MPAP-PAOP), was suggested because it can distinguish between excess volume (TPG < 10 mmHg) and vascular abnormalities (TPG > 10 mmHg) [19].

Approximately 30–50% of patients with cirrhosis have a high-flow circulatory state, owing to splanchnic vasodilation and hyperdynamic circulation, and this may cause an increase in MPAP, despite lack of pulmonary vasculature remodeling. The hyperdynamic circulation is characterized by a high cardiac output (CO), a low systemic vascular resistance (SVR), and a low PVR [6, 20]. Therefore, the proposed classification for severity of PPH was based on MPAP [19, 21], as described in **Table 3**.

Severity rate	Mean pulmonary artery pressure (mmHg)
Mild	25 to < 35
Moderate	35 to < 45
Severe	≥ 45

Table 3. Classification of severity of portopulmonary hypertension based on MPAP (mean pulmonary artery pressure) [19].

Mild PPH appears to have no impact on outcomes following LT. However, significant increases in pulmonary artery pressures are associated with high mortality rates. MPAP > 50 mmHg is associated with 100% mortality in patients undergoing LT. Mortality is 35–40% in MPAP ranging from 35 to 50 mmHg and from zero to 17% in MPAP < 35 mmHg [22].

2. Prevalence and survival

The first autopsy studies were carried by McDonnell et al. in 1983. Those authors reported a prevalence of 0.13% in PAH non-cirrhotic patients compared to 0.73% in patients with cirrhosis and portal hypertension. In biopsies of other clinical studies, the prevalence of PAH ranged from 0.61% to 2% in cirrhotic patients [8, 23, 24].

Hemodynamic data from prospective studies revealed that approximately 2–6% of patients with portal hypertension develop PPH [25, 26].

The incidence of PPH in patients undergoing LT ranges from 4 to 6%, while some studies show percentages as high as 8.5–12.5% [13, 25, 27, 28].

In a study involving 362 patients from 1985 to 1993, Castro et al. [27] used the criteria MPAP > 25 mmHg and PVR > 120 dynes.s.cm^{-5} for diagnosis of PPH. Those authors concluded that increased MPAP is common in patients with advanced liver disease (20%), although PPH occurred in only 4% of patients (15 patients).

Ramsay et al. [28] reviewed severe PH in patients with advanced liver disease in a study from Baylor University Medical Center. Those authors evaluated 1205 consecutive LTs, between December 1984 and October 1995. The incidence of PPH was 8.5% (102 patients with MPAP > 25 mmHg, and 6.72% in the mild form, 1.16% in the moderate form, and 0.58% in the severe form), using the same criteria. Mortality was 30% in three years in mild to moderate PPH, 42% in nine months in severe PPH, and 71% at three years post-LT.

In 1990, Robalino et al. [29] found that patients suffering from PAH associated with portal hypertension had a 15-month survival mean and a 50% mortality rate within six months of diagnosis, compared to those with primary pulmonary hypertension who survived two to three years and had a 57% survival rate within two years of diagnosis.

In a retrospective cohort study (data collection from 1997 to 2001 at the University of Pennsylvania, with a 3-year follow-up), Kawut et al. [30] compared survival and hemodynamics in patients with PPH (n=13) and PAH (n=33, pulmonary arterial hypertension was idiopathic, familial or associated with anorexics). Many of those patients were treated with epoprostenol. Those authors concluded that death risk in patients with PPH increased two fold compared to patients with PAH. Estimates of 1-year and 3-year-survival rates were 85% and 38% for patients with PPH, 82% and 72% for patients with PAH respectively. Although PPH patients had a higher cardiac index and lower PVR than PAH, patient outcome was worse, and could be attributed to complications of portal hypertension.

In a retrospective analysis of 154 PPH patients diagnosed from 1984 to 2004 and referred to the French Center for Pulmonary Arterial Hypertension, Le Pavec et al. [31] found a survival rate of 88%, 75%, and 68% at one, three, and five years, respectively. In this study, mortality was related to cirrhosis severity (higher in patients with Child-Turcotte-Pugh class B and C) and to low cardiac index.

In another French study (data obtained from the 2002/2003 National Registry including 17 university hospitals), Humbert et al. [25, 32] evaluated 674 cases diagnosed with PAH, showing that 10.4% of this population had PPH. Among all causes, PPH was the fourth cause of PAH, following idiopathic PAH (39.2%), PAH associated with connective tissue disease (15.3%), and PAH associated with congenital heart disease (11.3%). At diagnosis, 75% of patients were New York Heart Association (NYHA) class II or IV. Diagnosis was made following diagnostic criteria, according to RHC. Survival rate of PAH was 88% within one year.

In a retrospective Mayo Clinic study, Swanson et al. [33] reviewed 74 patients with PPH, between 1994 and 2007. Using current diagnostic criteria, hemodynamic data (averages and ranges) were: MPAP= 49 mmHg (27–86); PVR = 515 dynes.s.cm^{-5} (241–1285); PAOP = 12 mmHg (3-29); TPG = 36 mmHg (14-77). Patients were categorized into three subgroups: (I) 19 patients without therapy for PAH or LT represented the natural history of the disease, (II) 43 patients with therapy for PAH, and (III) 12 patients with therapy for PAH and LT. In subgroup (I), the 5-year survival rate was 14%, and 54% of patients had died within one year of diagnosis. In subgroup (II), the five-year survival rate was 45% and 12% of the patients had died within one year of diagnosis. In subgroup (III), the 5-year survival rate was 67% in nine patients under-going LT and therapy for PH, and 25% in patients undergoing only LT. The authors concluded that mortality was not related to baseline hemodynamic variables, type of liver disease or severity of liver dysfunction. Medical therapy for PPH should be considered in all patients with PPH. However, its effects and impact on potential LT candidates deserve further study.

In a recent research study carried out by REVEAL (Registry to Evaluate The Early and Long-Term PAH Disease Management), Krowka et al. [34] conducted an observational study of 174 patients with PPH, compared to 1392 patients with idiopathic PAH and 85 patients with familial PAH. Survival in patients with PPH was 67% within two years and 40% within five years, and 85% and 64% in patients with PAH, respectively. The authors concluded that despite better hemodynamics, survival was worse in PPH. A delay in diagnosis, different treatment patterns, late onset of treatment of pulmonary hypertension, and liver-related complications had an impact on survival in PPH patients. However, further controlled studies are needed to elucidate this issue. Those authors concluded that PPH accounted for 7–10% of Group I pulmonary hypertension cases.

Nowadays with the advent of better patient selection for LT and appearance of new drugs, it is hoped that this limited scenary will be changed.

2.1. Pathophysiogenesis

The development of PPH is independent on the cause of portal hypertension and severity of underlying liver disease. It is weakly correlated with the Child-Turcotte-Pugh [35] classification and is associated with mortality beyond that predicted by the MELD score (Model End-Stage Liver Disease) [16, 36].

The pathogenesis mechanisms of PPH remain unclear, and the knowledge on its development comes from PAH because of features similarity. Both disorders are characterized by obstruction of pulmonary arterial blood flow with increased PVR. The lesions detected are: medial hypertrophy, intimal proliferation and fibrosis of muscular pulmonary arteries, thickening of the adventitia, and *in situ* thrombosis. Plexiform lesions are typically found in small muscular arteries, adjacent to a larger parent vessel, and large arterial vasodilatation. Necrosis of muscular arteries cause leakage of plasma proteins into the arterial wall, resulting in necrotizing inflammatory arteritis, a probable precursor of plexiform lesions [8, 19, 37].

All these changes lead to increased pulmonary vascular resistance with vasoconstriction, arterial wall remodeling, and *in situ* microthrombosis, among other angiogenic factors

investigated, such as genetic susceptibility, increased production of inflammatory mediators, and neurohormones [19].

It is believed that hyperdynamic circulation with high cardiac output can cause PPH, which are influenced by hepatic dysfunction caused by liver cirrhosis. This condition of increased pulmonary blood flow seen in patients with portal hypertension determines an increase shear stress at the level of vasculature, that may lead to endothelial injury and dysfunction with vasoconstriction and progressive vascular remodeling [25, 38].

Investigators have postulated that high concentrations vasoactive substances secondary to an imbalance between vasoconstrictor and vasodilator factors could reach the pulmonary circulation due to portosystemic shunts or defective hepatic metabolism, and initiate the pulmonary vascular injury present in PPH [19, 25].

The mediator substances envolving in this process may be ET-1A, tromboxane A2, interleukin-1, interleukin-6, angiotensin-1, glucagon, and serotonin. PPH patients showed elevated ET-1 and interleukin levels compared to patients with cirrhosis without PPH [38, 39].

ET-1 is produced by the pulmonary endothelium and liver, and binding ET-1A and ET-1B receptors on smooth muscle cells results in vasoconstriction and mitogenesis [19].

In a prospective multicenter case-control study of 175 patients with liver disease, Kawut et al. [40] identified 34 patients with PPH. Those authors demonstrated that the risk of developing PPH was higher in females and patients suffering from autoimmune hepatitis, and lower in those with hepatitis C virus.

In a recent study, Roberts et al. [41] showed that genetic variation in estrogen signaling and cell growth regulators is associated with PPH.

In another study, the same authors demonstrated that serotonin transporter polymorphism is not associated with PPH [42].

The fact that the presence of a high cardiac output, can result in a degree of pulmonary hypertension with normal or near normal pulmonary vascular resistance, which might have led to erroneous interpretation and overestimation of the incidence of PPH [43].

2.2. Clinical presentation

Patients with PPH usually have symptoms similar to those observed in other forms of PAH [1, 25].

Symptoms produced by the disease may be nonspecific. The most common symptoms are dyspnea, fatigue, and chest pain. Syncope, palpitations, and peripheral edema are less commonly observed. Symptoms arise when mean pulmonary artery pressure exceeds 40 mmHg [5, 44].

Clinical symptoms of liver disease and portal hypertension may be present [25, 45].

A prospective study by Hadengue et al. showed that 60% of patients with PPH were asymptomatic and 40% had exertional dyspnea [11, 35].

Investigating a small number of patients with PPH, Robalino and Moodie found that symptomatic patients had a higher incidence of dyspnea (81%), followed by syncope (26%), chest pain (24%), asthenia (15%), hemoptysis (12%), and orthopnea (12%) [29].

Regarding cardiac auscultation, an increased pulmonic component of the second heart sound (P2) occurred in 82% of cases. A systolic murmur of tricuspid regurgitation was present in 69%, edema in 35%, and signs suggestive of right heart failure in 34% [22, 29].

Differences between hepatopulmonary syndrome and portopulmonary hypertension are described according to Rodriguez-Roisin et al., as seen in **Table 4** [6, 19, 43, 46].

	HPS	PPH
Symptoms	progressive dyspnea	progressive dyspnea, chest pain, syncope
Clinical examination	cyanosis, finger clubbing, spider angiomas	no cyanosis, RV heave, pronounced P2 component
ECG	none	RBBB Rightward axis RV hypertropy
Arterial blood gas	moderate/severe hypoxaemia	no or mild hypoxaemia
Chest radiograph	normal	cardiomegaly hilar enlargement
CEE	always positive, left atrial opacification for > 3-6 cardiac cycles after RA opacification	usually negative
Pulmonary angiography	normal/spongy appearence (type I) elevated PVR Discrete AVC (type II)	large main pulmonary arteries
^{99m}TcMAA	≥6%	<6%
Hemodynamics	normal/ low PVR	elevated PVR/ normal PAOP
OLT indicated	even in severe stages	only in mild/ moderate stages

Abbreviations: RV, right ventricle; P2, hyperphonesis of the pulmonic component of the second heart sound; ECG, electrocardiography; RBBB, right bundle-branch block; CEE, contrast-enhanced echocardiography; RA, right atrium; PVR, pulmonary vascular resistance; AVC, arteriovenous comunication; ^{99m}TcMAA, technetium^{99m} labelled macroaggregated albumin; PAOP, pulmonary artery occlusion pressure; OLT, orthotopic liver transplantation. Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-hepatic vascular disorders (PHD). Eur Respir J 2004; 24 (5):873 [19].

Table 4. Differences between hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH).

2.3. Diagnosis

PPH is usually diagnosed after a diagnosis of portal hypertension is made. The mean interval between diagnoses of both conditions is 28 ± 38 months, according to a prospective study by Hadengue et al. [35]. Those authors reported that 40% of dyspneic patients were overlooked on clinical examination.

According to currently established and recognized diagnostic criteria, the American Association for the Study of Liver Disease (AASLD) has proposed transthoracic echocardiography screening of all LT candidates for noninvasive identification of any form of PH and patient selection for RHC [47].

Transthoracic echocardiography (TTE) provides a number of variables that correlate with right heart hemodynamics, including pulmonary artery pressure. Estimated pulmonary artery pressure (PAP) is based on maximum tricuspid regurgitant jet velocity. The simplified Bernoulli equation describes the relationship between tricuspid regurgitant jet velocity and peak tricuspid regurgitant pressure gradient is equal to 4X (tricuspid regurgitant jet velocity)^2. This equation allows us to estimate systolic pulmonary artery pressure (SPAP), taking into account right atrial pressure (RAP):

SPAP = (tricuspid regurgitant pressure gradient) + estimated RAP (which is equal to 5 or 10 mmHg), or *Equation (1):*

$$SPAP = [4x(tricuspid\ regurgitation\ jet\ velocity)^2 + meanRAP] \tag{1}$$

In patients with severe tricuspid regurgitation, calculation of SPAP may be underestimated, thus the pulmonary hypertension is not precisely defined by Doppler for a threshold value of SPAP obtained [1].

Doppler TTE is a sensitive method for detection of PH, despite its low positive predictive value. Consequently, pulmonary hemodynamics should be measured by RHC in positive cases to substantiate diagnosis [1, 19, 46, 47].

In a recent study, Raevens et al. [48–50] analyzed the accuracy of TTE in the detection of all forms of PPH for different cutoff values of SPAP. In SPAP values of 30 mmHg, those authors found a sensitivity of 100%, a specificity of 54%, a positive predictive value of 10%, and a negative predictive value of 100%. In SPAP values of 38 mmHg, findings were: 100% sensitivity, 82% specificity, 22% positive predictive value, and 100% negative predictive value. In SPAP values of 50 mmHg, 86% sensitivity, 95% specificity, 46% positive predictive value, and 99% negative predictive value were found.

The authors incorporated the presence or absence of right ventricle dilatation, concluding that TTE is a highly sensitive screening test for PPH detection. Currently, in the performance of RHC to confirm or rule out PPH, an SPAP cutoff of 30 mmHg may produce a high number of false-positive tests, resulting in low specificity, and low positive predictive values. An SPAP of 38 mmHg was associated with a lower number of false-positive tests and higher specificity,

ensuring a negative predictive value of 100%, safely reducing the number of patients referred to RHC. An SPAP of 50 mmHg is associated with a decreased sensitivity of 86% and a risk of canceling LT at the time of surgery.

Right heart catheterization is the gold standard for diagnostic confirmation of pulmonary arterial hypertension, including PPH. RHC measures pressure, flow, and resistance, provides assessment of severity of hemodynamic impairment, and is useful for vasoreactivity testing of the pulmonary circulation. The following variables are measured systolic, diastolic and mean pulmonary artery pressure, RAP, PAOP, right ventricular pressure (RVP), cardiac output (CO) by thermodilution or by the Fick method, allowing calculation of pulmonary vascular resistance [19, 48]. The PVR is calculated using following formula, *Equation (2):*

$$PVR = \frac{MPAP - PAOP \times 80}{CO} \tag{2}$$

In PPH, the vasoreactivity test should be performed to determine disease severity and identify which patients could benefit from vasodilator therapy. A acute vasodilator testing should be commonly performed using intravenous epoprostenol (IV) or inhaled nitric oxide (NO). The test is considered positive when MPAP decreases by ≥ 10 mmHg to an absolute value of MPAP ≤ 40 mmHg with increased or no change in CO [1, 19].

MPAP may increase in different situations. First, many patients with advanced liver disease present a hyperdynamic, high-flow circulatory state, resulting from splanchnic vasodilation caused by portal hypertension, leading to a marked increase in MPAP and CO. However, PVR remains normal or decreased. Second, elevation of MPAP is due to increased central blood volume due to left ventricular (LV) abnormalities measured by PAOP, which reflects end-diastolic LV volume, resulting in varying effects on PVR. Traspulmonary gradient (TPG = MPAP - PAOP) can distinguish between excess volume (TPG < 10 mmHg) and vascular pulmonary abnormalities (TPG > 10 mmHg) [19]. Third, MPAP is elevated regardless of disease severity, due to increased PVR caused by changes in the pulmonary vascular bed with progressive obliteration to pulmonary arterial blood flow from the right ventricle (RV) to the lungs [19, 36].

Type	MPAP	PAOP	CO	PVR
1. Hyperdynamic circulatory state	↑	N or ↓	↑↑	↓
2. Excess volume	↑	↑↑↑	↑	NA
3. Portopulmonary hypertension	↑↑↑	↓	↑follow by ↓	↑↑↑

MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; PVR, pulmonary vascular resistance; N, normal; NA, no alteration.

Table 5. Hemodynamic data obtained by right heart catheterization in advanced liver disease [19].

In all patients with pulmonary hypertension, RHC is essential for diagnostic confirmation and assessment of disease severity [1, 19, 36].

Diagnostic confirmation of cirrhosis by liver biopsy may strengthen the diagnosis of PPH [5, 8].

Pulmonary artery catheterization obtained the following hemodynamic data [19, 36], as observed in **Table 5**.

2.4. Treatment

Specific treatment of PAH are use in PPH and includes different classes of vasodilators, such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors [19, 25, 38].

The goal of therapies is to improve haemodynamics by reducing mean pulmonary artery pressure and pulmonary vascular resistance, to improve the haemodynamic right ventricle, thus creating possibility for patients to become eligible for LT [51, 52].

These drugs are used only after diagnostic confirmation of the disease by RHC, and patients meet diagnostic criteria for PPH, according to the ERS Task Force on PHD [16, 19].

A decrease of > 20% in MPAP and PVR indicates that patients are responsive to vasodilators [11]. Publications and reports of a recent small case series have indicated that use of these drugs before and after LT results in clinical improvement. However, further studies are needed [53–55].

2.4.1. Prostacyclins

Prostacyclin analogs (prostanoids), such as epoprostenol, beraprost, iloprost.

Epoprostenol is administered by continuous intravenous infusion. It is a potent pulmonary and systemic vasodilator, it has antiproliferative effects, and potent inhibitor of platelet aggregation. The drug also reduces MPAP, and probably improves exercise tolerance and hemodynamic parameters, but common adverse effects and complications are attributable to this drug: jaw pain, headache, diarrhea, nausea, and vomiting; others effects are described as infecction in infusion line, ascites, right heart failure, splenomegaly, severe thrombocytopenia, and leukopenia [1, 19, 25, 56].

2.4.2. Endothelin receptor antagonists

Bosentan, ambrisentan, and sitaxentan.

Endothelin are endogenous vasoconstrictors with a major role in the pathogenesis of PAH.

Bosentan is an orally active dual antagonist of endothelin 1A and 1B that reduces PVR, improving exercise capacity, functional class, pulmonary and cardiac hemodynamics, and even prevents clinical deterioration. It can elevate liver enzymes despite limited experience in PPH [1, 19].Bosentan use should be avoided in patients with moderate to severe liver dysfunction and elevated liver enzymes.

Ambrisentan is a selective ET-1A with minimal effect on liver function and sitaxentan was withdrawn from the market due fatal liver injury registration [38].

2.4.3. Phosphodiesterase inhibitors (PDE 5 inhibitors)

Sildenafil, vardenafil, tadalafil.

These drugs block cyclic GMP degradation. Cyclic GMP is a second messenger for nitric oxide, thereby prolonging vasodilator mediation of NO, producing lower MPAP and PVR [1]. These should be use cautiously because it may increase portal hypertension by splanchnic vasodilation [38].

Reichenberger et al. [16, 57] used sildenafil in 14 patients with PPH for 12 months. Of these patients, six received inhaled iloprost or treprostinil. Hemodynamics improved significantly within three months and was maintained at 12 months, when diagnosed by RHC. Other small studies have shown clinical improvement after safe and effective use of this drug.

Yamashita et al. [58] reported cases of two patients with advanced liver disfunction and thrombocytopenia who were successfully treated with a combination of two oral vasodilators, ambrisentan and tadalafil. They concluded that it may be a safe and effective option for selected patients with severe and rapidly progressing PPH.

Retrospective studies involving postoperative liver transplant have stated that PPH was an absolute contraindication to transplantation because of high perioperative mortality. It is currently known that better preoperative evaluation, early initiation of drug, and improved anesthetic and surgical conditions offer new treatment possibilities.

PPH can thus become more common in liver transplantation centers [1, 5, 19, 56, 59].

2.5. Liver transplantation

Liver transplantation is a highly complex procedure, since the organ is responsible for multiple functions in the body. The first unsuccessful attempt at orthotopic LT in humans was carried out in the United States in 1963 by Thomas Earl Starzl and staff. Starzl was named the father of modern transplantation. The first successful case was recorded in 1967. By the end of the 1960s, 33 transplants had been described worldwide. Subsequently, other teams started performing this surgery with a low survival rate [14].

PPH patients have a high mortality rate related to right heart failure. There are few treatment options and LT has become an attractive therapy with a potential for cure. The role of LT in the treatment of PPH has evolved over the past 15 years [16]. Over time, better results will be achieved by advances in the understanding of new immunosuppressive drugs, biologic drug activity, metabolism, surgical technique, evaluation and intraoperative monitoring in anesthesiology and intensive care [14]. The anesthesiologist has an important role in managing these high risk patients [60].

Perioperative mortality risk is 100% in patients with a MPAP above 50 mmHg. However, a patient with MPAP ≤ 35 mmHg, observed in intraoperative period, can safely undergo LT. An

MPAP ranging from 35 to 50 mmHg poses a dilemma if these values are associated with PVR > 240 dynes.s.cm^{-5}, mortality rate hovers around 50% [61–63].

Studies have proved successful in practice, with the introduction of pulmonary arterial vasodilators after PPH diagnosis, lower pulmonary artery pressure, and improving right ventricular function obtained for patient referral to LT [16, 19, 64].

Kwo et al. [65] reported that four patients with severe PPH showed a marked reduction in MPAP and PVR after long-term use of epoprostenol, providing better results for LT candidates.

Mair et al. [66] described a poor outcome in a case report. The patient received epoprostenol for eight months before LT. PVR was reduced from 12 units to 3 Wood units, but the patient developed right heart failure unresponsive to conventional inhaled therapy in the LT perioperative period, and died 28 days later.

LT is a special case of right ventricular stress with a sharp 5–10% increase in CO during reperfusion. However, an increase in CO is unpredictable and may reach up to 300%, precipitating right heart failure in a RV that is already under strain [61, 67]. Increased CO probably results from removal of blood flow obstruction through the portal vein in the diseased liver, associated with systemic vasodilatation caused by acid rain, and other metabolites originating from the new graft. There is a significant decrease in myocardial contractility, chronotropy, and systemic vascular resistance [61, 68]. Once this occurs, a patient suffering from pulmonary hypertension is at great risk [61].

2.6. Study justification

We believe that understanding the aspects and nuances of this severe disease may raise awareness about the issue and increase scientific knowledge. Following recommendations proposed by the international scientific community will certainly contribute to solidify work done by a multidisciplinary team to decrease morbidity and mortality in PPH patients undergoing liver transplantation.

2.7. Nomenclature

ALK 1   Activin-like receptor kinase-1

AASLD   American Association for the Study of Liver Disease

BMPR2   Bone morphogenetic protein receptor type 2

CAV1   Caveolin-1

CO   Cardiac output

ENG   Endoglin

ERS   European Respiratory Society

ET-1A   Endothelin-1A

ET-1B	Endothelin-1B
cGPM	Cyclic guanosine monophosphate
HPS	Hepatopulmonary syndrome
IV	Intravenous
KCNK3	Gene encoding potassium channel
LT	Liver transplantation
LV	Left ventricle
MELD	Model end-stage for liver disease
MPAP	Mean pulmonary artery pressure
NO	Nitric oxide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAOP	Pulmonary artery occlusion pressure
PAP	Pulmonary artery pression
PDE	Phosphodiesterase
PH	Pulmonary hypertension
PHD	Pulmonary hepatic vascular disorders
PPH	Portopulmonary hypertension
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RHC	Right heart catheterization
RV	Right ventricle
SPAP	Systolic pulmonary artery pressure

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