Eugenia Hopps MD
Amelia Valenti MD
Gregorio Caimi MD

Department of Internal Medicine, Cardiovascular Disease and Nephrology, Policlinico Universitario di Palermo, Palermo, Italy

Portopulmonary Hypertension

Abstract

Portopulmonary hypertension (PPHT) is a respiratory complication of portal hypertension, defined as an increase in mean pulmonary artery pressure (PAP) of > 25 mmHg with an increase in pulmonary vascular resistance of > 240 dyn.s/cm⁵ and a normal pulmonary capillary wedge pressure (< 15 mmHg), which often occurs in subjects with liver cirrhosis. Histopathological features of PPHT are endothelial and smooth-muscle cell proliferation and fibrosis leading to luminal obstruction in the resistance arteries. The pathogenesis of PPHT may result from an imbalance between vasoconstrictor and vasodilating factors. The most common pulmonary symptom is exertional dyspnea; fatigue, chest pain and syncope occur more often at an advanced stage. Edema, ascites and prominent jugular veins are signs of both decompensated hepatic cirrhosis and right ventricular failure. Right heart catheterisation is the gold standard for the diagnosis and defines PPHT in mild disease with PAP less than 35 mmHg, moderate disease with PAP between 35 and 45 mmHg, and severe disease with PAP of 45 mmHg or higher. The medical treatment of portopulmonary hypertension is based on the treatment of other forms of pulmonary arterial hypertension, including vasomodulating pharmacologic agents. Liver transplantation is accompanied by high risk of mortality, generally due to acute right ventricular failure and cardiovascular collapse. The prognosis of PPHT is poor with mean survival of 15 months.

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Correspondence to:

Dr. Eugenia Hopps
Via del Vespro, 129 – 90127 Palermo, Italy
E-mail: cuhopps@libero.it

Portopulmonary hypertension (PPHT) is a vascular disorder reported in 0.6% to 8.5% of patients with portal hypertension, often associated with liver cirrhosis. PPHT is defined as an increase in mean pulmonary artery pressure (PAP) of > 25 mmHg with an increase in pulmonary vascular resistance of > 240 dyn.s/cm⁵ and a normal pulmonary capillary wedge pressure (<15 mmHg) in subjects with portal hypertension, in absence of alternative causes of pulmonary arterial hypertension [1,2,3] (Table 1). Females seem to have a higher risk of developing PPHT [4]. Regarding the etiology of liver disease, patients with autoimmune hepatitis have a higher risk of PPHT and patients with C hepatitis have a lower risk of developing this clinical condition in comparison with patients with

other causes of liver disease [4]. Hormone profiles and a tendency to autoimmune processes may explain the higher prevalence of PPHT among females [4]. No correlation is evident between mean PAP and model for end-stage liver disease (MELD) score, so PPHT is not associated with cirrhosis severity [5]; but if untreated, PPHT can lead to progressive right ventricular failure with increased mortality. Extrahepatic portal hypertension has been found in up to 10% of patients with PPHT [6].

Pulmonary hypertension results from excessive pulmonary vascular remodelling and vasoconstriction [7]. The histopathological alterations of PPHT are characterized by endothelial and smooth-muscle cell proliferation and fibrosis, leading

TABLE 1. Clinical classification of pulmonary hypertension.

1. Pulmonary arterial hypertension	1.1 Idiopathic	
	1.2 Heritable	1.2.1 BMPR2
		1.2.2 ALK1, endoglin
		1.2.3 Unknown
	1.3 Drugs and toxins induced	
	1.4 Associated with (APAH)	1.4.1 Connective tissue disease
		1.4.2 HIV infection
		1.4.3 Portal hypertension
		1.4.4 Congenital heart disease
		1.4.5 Schistosomiasis
	1.4.6 Chronic hemolytic anemia	
1.5 Persistent pulmonary hypertension of the newborn		
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis		
2. Pulmonary hypertension due to left heart disease	2.1 Systolic dysfunction	
	2.2 Diastolic dysfunction	
	2.3 Valvular disease	
3. Pulmonary hypertension due to lung disease and/or hypoxia	3.1 Chronic obstructive pulmonary disease	
	3.2 Interstitial lung disease	
	3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern	
	3.4 Sleep-disordered breathing	
	3.5 Alveolar hypoventilation disorders	
	3.6 Chronic exposure to high altitude	
	3.7 Developmental abnormalities	
4. Chronic tromboembolic pulmonary hypertension		
5. PH with unclear and/or multifactorial mechanisms	5.1 Haematological disorders: myeloproliferative disorders, splenectomy	
	5.2 Systemic disorders: sarcoidosis, pulmonary Langherans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis	
	5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	
	5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis	

Modified from *Guidelines for the diagnosis and treatment of pulmonary hypertension*. (The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society, endorsed by the International Society of Heart and Lung Transplantation, European Heart Journal 2009)

to luminal obstruction in the resistance arteries, as seen in other forms of pulmonary arterial hypertension⁸. In liver disease or portal hypertension, the pulmonary vascular endothelium can be directly injured by substances produced in the liver or in the portal system and this may explain the frequent pulmonary vascular abnormalities associated with these diseases [8]. PPHT and hepato-pulmonary syndrome (HPS) are two different pulmonary complications of portal hypertension. Even if both conditions often occur as dyspnea, PPHT is different from HPS (Table 2), which is characterized by hypoxemia secondary to intra-pulmonary vascular shunts [3]. From a pathophysiological point of view, HPS is a pulmonary vascular dilative disease, while PPHT is the result of a pulmonary vascular constrictive/obliterative process [7]. It has been suggested that the pathogenesis of HPS and PPHT might involve an imbalance between pulmonary endothelin-1 (ET-1) and nitric oxide (NO) production. Increased pulmonary production of the vasodilator NO seems to be responsible for dilatation of intrapulmonary vessels in cases of HPS, while ET-1 is the vasoconstrictor most often implicated in the genesis of PPHT [7].

Pathophysiology

The pathogenetic mechanisms involved in PPHT development are complex and include (1) the production of vasoconstrictor substances, (2) an increase in pulmonary blood flow leading to endothelial damage and vascular remodelling and (3) probably

repeated microthrombosis [1]. Pulmonary hypertension results from an imbalance in vasoactive substances such as ET-1, angiotensin II, thromboxane, NO and prostacyclin [9]. Among these vasoconstrictor molecules, the role of ET-1 is the most well described. It is produced primarily by endothelial cells and induces strong and long-acting pulmonary vasoconstriction. ET-1 plasma levels are elevated in patients with liver cirrhosis and correlated with the degree of the liver disease. ET-1 levels are significantly higher in patients with decompensated hepatic cirrhosis and PPHT in comparison with patients with decompensated hepatic cirrhosis without PPHT [7]. ET-1 regulates the expression of various genes¹⁰ and promotes fibrosis and cell proliferation [10]. Hepatic stellate cells, during cirrhosis, show a stronger response to ET-1, which induces a higher mitotic rate and an increased proliferation [7]. Investigating the localization of ET-1, ET receptors and NO synthase (NOS) in liver tissue, a significantly higher expression of ET-1 and ET receptors in cirrhotics than in either normal controls or idiopathic portal hypertension (IPH) patients has been observed [11]. NOS expression is poor in both cirrhotic and IPH patients [11]. It seems that porto-systemic shunts in patients with portal hypertension can cause an increased concentration of ET-1 in pulmonary circulation, starting vascular remodeling [9].

Two endothelin-receptor isoforms, endothelin-A (ETA) and endothelin-B (ETB), have been identified. Activation of ETA receptors promotes vasoconstriction and proliferation of

TABLE 2. Differences between HPS and PPHT.

	HPS	PPHT
Dyspnea	Yes	Yes
Chest pain	No	Yes
Hypoxiemia	Yes	In rare cases
PAP	=	>
PVR	<	>
ECG	Non typical features	Right axis, right bundle-branch block, T-wave inversion in the anterior leads
Echocardiography	Presence of enhanced bubbles injected intravenously in the left heart cavities (shunts)	Enlarged right cardiac cavities, pathological tricuspid regurgitation
Qs/Qt	>	=
P(a-A) O ₂	>	>
Pathogenesis	Dilatation of the pulmonary precapillary and capillary vessels, intra-pulmonary vascular shunts	Pulmonary vasoconstriction, thrombosis, vessels obliteration
Etiology	Increased NO	Increased endothelin-1
Diagnostic criteria	PO ₂ < 70 mmHg, pulmonary vascular dilatation and portal hypertension	Pulmonary arterial hypertension, increased PVR and portal hypertension
Treatment	OLT	Medical treatment, OLT

vascular smooth muscle cells while activation of ETB receptors may cause NO release and vasodilation. Bosentan, a dual antagonist for receptor A and B of ET-1, decreases the systemic and pulmonary resistances with great beneficial effect in patients with PPHT [10,11].

Other vasoconstrictive molecules, such as serotonin, norepinephrine and angiotensin II, produced in the splanchnic circulation are released into pulmonary vessels via portosystemic shunts and are associated with the development of PPHT [7]. The lung is usually protected from the action of serotonin by normal hepatic metabolism and platelet storage. Portal hypertension is characterized by decreased platelet count and increased levels of circulating serotonin [6]. A serotonin transporter polymorphism is associated with some forms of pulmonary hypertension, but not with PPHT [13]. Genetic variation of estrogen receptor 1, aromatase, phosphodiesterase and angiopoietin 1 are instead related to the risk of PPHT [14].

In contrast to what has been found in HPS, production of sinusoidal NO in PPHT subjects is reduced and unable to counteract the elevation of vascular tone in the portal venous system and the platelet aggregation. Thus, platelet aggregation leads to vasoconstriction and to *in situ* thrombosis within pulmonary and portal vessels [9]. The frequent observed *in situ* thrombosis has been attributed to reduced local endothelial thrombolytic activity or to a hypercoagulable state with platelet activation [6].

Prostacyclin dysregulation has been observed in patients with portal hypertension [9]. Tudor and colleagues [15] found reduced expression of prostacyclin synthase in the small and medium-sized pulmonary arteries of patients with severe pulmonary hypertension, some of whom exhibited PPHT.

Hyperdynamic circulation and a high cardiac output are present in almost all the patients who have early stage PPHT: the splanchnic volume overload and the bowel-wall congestion leads to the release of endotoxins and cytokines into the splanchnic circulation [16]. Increased cardiac output causes higher shear stress in the pulmonary vessels with possible lesions of smooth muscle and endothelial cells and the consequent release of mediators causing vasoconstriction of pulmonary vessels and vascular remodelling [16]. Endotoxin flow to the liver promotes the activation of the macrophages adhering to the pulmonary endothelium, leading to the release of cytokines, including TNF α , and growth factors, which are implicated in the development of pulmonary vascular disease [6]. A recent study showed higher ET-1 and IL-6 plasmatic concentrations in patients with PPHT compared with

patients with hyperdynamic circulation or cirrhosis, suggesting a role for cytokines in PPHT pathogenesis [17].

The Mayo Clinic classification of pulmonary hypertension under portal hypertension differentiates three types [7]. The first is characterized by an increased pulmonary blood flow, with a mean PAP often < 35 mmHg and with normal pulmonary vascular resistance and capillary wedge pressure. This type is frequently seen in patients with liver disease or portal hypertension. The second type is characterized by an elevated pulmonary venous volume. The volume increase reflects an increase in volume and/or pressure, caused by left ventricular systolic or diastolic dysfunction. In this clinical condition, increased pulmonary capillary wedge pressure (PCWP) and normal calculated pulmonary vascular resistance are present. This type of pulmonary hypertension is associated with alcoholic cirrhosis, familial amyloidosis, and combined hepatorenal insufficiency. The third type is characterized by normal PCWP and elevated pulmonary arterial pressure and vascular resistances, leading to right ventricular failure. This increased resistance is due to vascular remodelling that, as we mentioned before, is characterized by endothelial and smooth-muscle cell proliferation and fibrosis leading to luminal obstruction in PPHT.

Clinical presentation

Patients with PPHT may be asymptomatic (until the pulmonary arterial pressure is below 40 mmHg) [7] or may present with symptoms of portal hypertension, pulmonary hypertension, or both. The most common pulmonary symptom is exertional dyspnea; there is a poor correlation between mean PAP and degree of the dyspnea [9]. Fatigue, chest pain and syncope occur more often at an advanced stage; however, presentation with only pulmonary symptoms is infrequent. There may be signs of right ventricular failure, a loud second heart sound and a pansystolic tricuspid regurgitation murmur that increases with inspiration. Edema in the legs, ascites and prominent jugular veins are signs of both decompensated hepatic cirrhosis and right ventricular failure. Patients with PPHT often have pericardial effusions, but the clinical implications of this condition are unknown [4].

Chest radiography may indicate cardiomegaly and enlarged central pulmonary arteries with rarefied peripheral vessels. The electrocardiogram (ECG) may show right ventricular hypertrophy, right axis deviation and a right bundle branch block, features of right heart stress [3,18]. A restrictive ventilatory pattern is found in 33% of patients and a reduced diffusing capacity of the lung for carbon monoxide (DLCO) can be showed in 60% of the patients [8]. Arterial blood gas analysis

may indicate mild-to-moderate hypoxiemia and decreased PaCO₂. Conventional lung perfusion scanning may show 'mosaic' perfusion but other segmental perfusion abnormalities should prompt evaluation for pulmonary emboli [8].

Diagnosis

Before a diagnosis of PPHT is made, other causes of pulmonary hypertension, including chronic thromboembolism, interstitial or obstructive lung diseases, sleep-related breathing disorders and cardiac shunt or valvular defects, must be excluded [7]. Increased cardiac output and a hyperdynamic circulation can be observed in almost all the patients with PPHT.

The common diagnostic tests of PPHT include electrocardiogram (ECG), echocardiography, chest radiography or computed tomography, ventilation-perfusion scanning or pulmonary angiography, autoantibody testing, human immunodeficiency virus (HIV) testing and liver function testing. Abnormalities in the chest radiograph and in the electrocardiograph (right axis, right bundle-branch block, t-wave inversion in the anterior leads) can be observed. Sakuma and co-workers [19] demonstrated elevated atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels in PPHT patients. Two-dimensional echocardiography with an additional Doppler examination is a useful non-invasive screening exam. Typically, enlarged right atrium and ventricle and tricuspid regurgitation are found. The right ventricular systolic pressure (RVSP) can be approximated by measurement of the systolic regurgitant tricuspid flow velocity and estimation of the right atrial pressure. An RVSP greater than 40 mmHg has a sensitivity of 37% to 63% and specificity of 91% to 100% for identifying patients with pulmonary hypertension, confirmed by RHC in patients undergoing orthotopic liver transplantation (OLT) [20]. Cut off threshold values of the RVSP ranging from 30 to 50 mmHg have been proposed to guide the decision concerning the need for right heart catheterisation (RHC) in patients with PPHT who are being evaluated for OLT [9]. A retrospective analysis showed that screening Doppler echocardiography (RVSP > 50 mmHg) identifies essentially all patients who should proceed to right heart catheterisation⁶. Echoardiography does not differentiate patients with increased PVR (PPHT) from patients with high pulmonary artery pressure and normal PVR (hyperdynamic states) measuring only systolic arterial pressure, so it has a poor positive predictive value for the diagnosis of PPHT, while it has a high negative predictive value [21].

RHC is the gold standard for the diagnosis of PPHT [6]. RHC is recommended to confirm a questionable diagnosis [7]

and is the only technique able to distinguish PPHT from an elevated PAP [21]. This is necessary because PPHT, but not elevated PAP in hyperdynamic circulation, is associated with an increased incidence of adverse events after liver transplantation [21]. Pulmonary artery pressure, right atrial pressure and pulmonary capillary wedge pressure are performed using a Swan-Ganz catheter. Usual hemodynamic criteria to diagnose PPHT include mean pulmonary arterial pressure greater than 25 mmHg at rest or greater than 30 mmHg during exercise, with a PCWP less than 15 mmHg and PVR greater than 3 mmHg/L/min (240 dyn.s/cm⁵) [22]. RHC estimates pressures and flow and provides assessment of disease severity, right heart function and potential acute vasoreactivity [6]. The classification of the severity of PPHT based on RHC defines mild disease when PAP is less than 35 mmHg, moderate when PAP is between 35 and 45 mmHg, and severe when PAP is 45 mmHg or greater [22].

An acute vasodilating test is usually performed with either i.v. epoprostenol or inhaled NO [2,23-25]. Significant acute pulmonary vasodilation has been shown in PPHT using higher concentrations of NO [24,25]; however, the acute vasodilatory effect of i.v. epoprostenol in PPHT seems to be greater than that obtained with NO. In patients with PPHT tested with both agents, the proportion of haemodynamic responders was greater when using i.v. epoprostenol than inhaled NO⁶. However, the percentage of PPHT patients who responded is generally not very high [6].

Splanchnic hemodynamic parameters may be measured via a catheter inserted into the right hepatic vein, but these parameters are rarely assessed. In a study by Colle and workers, no correlation between PAP and hepatic venous pressure was found [21]. Diagnosis of PPHT is confirmed when (1) pulmonary hypertension is evident, (2) pulmonary vascular resistance (PVR), calculated from the transpulmonary gradient during RHC, is increased and (3) portal hypertension, as indicated by an elevated hepatic venous pressure during hepatic vein catheterisation, is evident [3].

When the diagnosis of PPHT has been established, the definition of mild, moderate, or severe pulmonary hypertension is helpful for prognostic and treatment considerations. Patients who have mild PPHT frequently have no symptoms and signs of pulmonary vascular disease. In these cases, specific treatment of pulmonary hypertension is not generally required [16]. Regular follow up, including biannual to annual echocardiographic examinations, are advisable to monitor the potential progression of pulmonary disease. Patients who show no evidence of PPHT and are waiting for OLT, should annually undergo echocardiography, whereas those with PPHT may

need to be followed more frequently, at least twice or three times every year [6].

Medical treatment

The treatment of PPHT remains problematic and is based on the treatment of other forms of pulmonary arterial hypertension. No specific treatment is recommended for mild pulmonary hypertension, while specific therapy may be necessary when patients with moderate to severe PPHT needing liver transplantation or major surgery [16]. In patients with PPHT, *in situ* thrombosis of pulmonary circulation is often found, so anticoagulation, such as that recommended for patients with other causes of pulmonary arterial hypertension, might be useful in Child's class A patients with no relevant esophageal or gastric varices [7]. Long-term anticoagulation with warfarin is contraindicated when there is an elevated risk of bleeding due to the underlying liver disease or to an associated coagulopathy [26]. Diuretics decrease pulmonary arterial pressure in hypervolemic patients by reducing pulmonary venous pressure [9] and decrease intravascular volume and hepatic congestion that occur in subjects with right heart failure. Furosemide and/or spironolactone should be prescribed with caution [26]. Oxygen supplementation is useful to prevent worsening of pulmonary pressure. Beta-blockers are commonly used to minimize the risk of bleeding from varices; however, withdrawal of beta-blockers seems to improve cardiac output with no change in mean PAP and with a significant decrease in PVR [27] so beta-blocker treatment must be used judiciously in patients with moderate to severe PPHT [9]. Calcium channel blockers are not recommended in patients with portal hypertension as they may increase the hepatic venous pressure gradient [28,29].

Available treatment options for PPHT include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and vasodilators, such as prostacyclin analogues [30]. Endothelin receptor antagonists, such as bosentan, block the vasoconstrictor activity of ET-1. Hoeper and colleagues [31] showed survival rates of 94% at 1 year and 89% at both 2 and 3 years with bosentan monotherapy in severe PPHT patients. In almost 10% of patients, bosentan can cause elevations in serum aminotransferase, alkaline phosphatase, and bilirubin levels, which must be checked regularly [32]. Irreversible hepatic toxicity is uncommon; in most cases, liver function abnormalities return to baseline levels when the medication is stopped. The presumed mechanism is an impairment of bile-salt transporters, leading to bile-salt accumulation in the liver [32]. Phosphodiesterase type 5 inhibitors, such as sildenafil, increase the activity of NO-dependent cGMP-mediated vasodilation by inhibit-

ing the degradation of cGMP [33]. It has been demonstrated that patients with severe PPHT, who were treated with oral sildenafil monotherapy or with combination therapy including prostacyclin analogues, showed an improvement in clinical and hemodynamic features within three months [34]. Prostacyclin analogues stimulate the production of cAMP and inhibit the growth of vascular smooth muscle even as platelet aggregation is reduced [9]. Epoprostenol, treprostinil, and inhaled iloprost approved by FDA for treatment of severe pulmonary hypertension have been used successfully in PPHT. The use of intravenous epoprostenol, which has a positive impact on long-term survival in patients with idiopathic pulmonary hypertension [35], could potentially impair portal hypertension in patients with severe liver diseases [36].

Hoeper *et al.* [31] reported survival rates of 77% at 1 year, 62% at 2 years, and 46% at 3 years in patients with severe PPHT and well preserved liver function who were treated with inhaled iloprost monotherapy. So, as in patients with idiopathic pulmonary hypertension, inhaled iloprost may be used with oral bosentan and sildenafil to reduce pulmonary arterial pressure and to facilitate the decision to proceed with liver transplantation [37].

The natural history of untreated portopulmonary hypertension varies with the degree of liver disease and the severity of pulmonary hypertension. A single-centre study reported that 58% died within one year of the PPHT diagnosis [6]. Le Pavée *et al.* [38] demonstrated that the presence and severity of cirrhosis and the cardiac index are major independent prognostic factors. The prognosis of the portopulmonary hypertension is poor with mean survival of 15 months [6]. Causes of death were equally distributed between complications of liver disease and right heart failure [3].

Liver transplantation

The role of liver transplantation for the treatment of PPHT is controversial. OLT may be beneficial in a highly selected group of patients. Severe pulmonary hypertension, such as a PAP > 50 mmHg, which does not respond to medical management, is a contraindication to liver transplantation [32]. Subjects with mean PAP 35-50 mmHg have high mortality risk and may benefit for prolonged treatment for pulmonary hypertension [32]. A small subset of patients, who cannot undergo liver transplantation because of a severe mean PAP, may be considered for medical treatment to reduce pulmonary vascular resistance and improve pulmonary hemodynamic and thus become possible candidates for OLT [32].

Patients with portopulmonary hypertension may develop hemodynamic instability during liver transplantation [39] and

in the immediate postoperative period. The increase in blood flow following reperfusion or necessary fluid challenges may exacerbate pulmonary hypertension, resulting in worsening right heart function.

Transplantation has been successful in patients who respond to therapy and many, although not all, are able to wean off or reduce the vasodilator therapy over the first six months [5]. Krowka *et al.* observed a beneficial outcome for patients with PPHT who underwent OLT [40], although the improvement in pulmonary hemodynamics is more clear in patients with HPS than PPHT. Pre-OLT mean PAP and PVR may be helpful to determine if the patients can successfully undergo transplantation, but in hospital mortality (36%) remains high [40].

Conclusion

Portopulmonary hypertension is a lung complication occurring in 0.6% to 8.5% of patients with portal hypertension, often associated with liver cirrhosis. An imbalance between vasoconstricting and vasodilating factors produces an increase in mean pulmonary artery pressure and pulmonary vascular resistance with a normal pulmonary capillary wedge pressure. Patients often present with dyspnea, fatigue, and chest pain as with other forms of pulmonary hypertension. Early diagnosis with transthoracic echocardiography and right heart catheterisation allows the determination of PPHT severity and to select the patients who may benefit from liver transplantation or from medical therapy only. Regardless of the type of treatment, the prognosis of PPHT is poor, with high mortality within one year from diagnosis.

References

1. Benjaminov FS, Prentice M, Sniderman KW, Siu S, Liu P, Wong F. Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *GUT* 2003; 52:1355-62.
2. Fallon MB. Portopulmonary hypertension: new clinical insights and more questions on pathogenesis. *Hepatology* 2003; 37:253-5.
3. Umeda N, Kamath PS. Hepatopulmonary syndrome and portopulmonary hypertension. *Hepatol Res* 2009; 39:1020-2.
4. Kawut SM, Krowka JR, Trotter JF, Roberts KE, Benza RL, Badesch DB, et al. Clinical risk factors for portopulmonary hypertension. *Hepatology* 2008; 48:196-203.
5. Wells JT, Runo JR, Lucey MR. Portopulmonary hypertension. *Hepatology* 2008; 48:13-5.
6. Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB; ERS (European Respiratory Society) Task Force-PHD Scientific committee. Highlights of the ERS task force on pulmonary-hepatic vascular disorders. *J Hepatol* 2005; 42: 924-7.
7. Halank M, Ewert R, Seyfarth HJ, Hoefken G. Portopulmonary hypertension. *J Gastroenterol* 2006; 41:837-47.
8. Herve P, Le Pavec J, Sztrymf B, Decante B, Savale L, Stibon O. Pulmonary vascular abnormalities in cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; 21:141-59.
9. Nayak RP, Li D, Matuschak GM. Portopulmonary hypertension. *Curr Gastroenterol Rep* 2009; 11:56-63.
10. Keller S, Karaa A, Paxian M, Clemens MG, Zhang JX. Inhibition of endothelin-1-mediated up-regulation of iNOS by bosentan ameliorates endotoxin-induced liver injury in cirrhosis. *Shock* 2006; 25:306-13.
11. Hinterhuber L, Graziadei IW, Kahler CM, Jaschke W, Vogel E. Endothelin-receptor antagonist treatment of portopulmonary hypertension. *Clin Gastroenterol Hepatol* 2004; 2:1039-42.
12. Ohara N, Futagawa S, Watanabe S, Fukasawa M, Takamori S. Clinical investigation of endothelin-1 and nitric oxide in patients with portal hypertension focusing on plasma levels and immunohistological staining of liver tissues. *Hepatol Res* 2001; 21: 40-54.
13. Roberts KE, Fallon MB, Krowka MJ, Benza RL, Knowles JA, Badesch DB et al. Serotonin transporter polymorphism in patients with portopulmonary hypertension. *Chest* 2009; 135:1470-5.
14. Roberts, KE, Fallon MB, Krowka MJ, Brown RS, Trotter JF, Peter I, et al. Genetic risk factors for portopulmonary hypertension in patients with advanced liver disease. *Am J Respir Crit Care Med* 2009; 179:835-42.
15. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999; 159:1925-32.
16. Hoepfer MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet* 2004; 363:1461-8.
17. Pellicelli AM, Barbaro G, Puoti C, Guarascio P, Lusi EA, Bellis L et al. Plasma cytokines and portopulmonary hypertension in patients with cirrhosis waiting for orthotopic liver transplantation. *Angiology* 2010 [epub ahead of print].
18. Yang YY, Lin HC, Lee WC, Hou MC, Lee FY, Chang FY, et al. Portopulmonary hypertension: distinctive hemodynamic and clinical manifestations. *J Gastroenterol* 2001; 36: 181-6.
19. Sakuma M, Souma S, Kitamukai O, Demachi J, Takahashi T, Suzuki J, et al. Portopulmonary hypertension—hemodynamics, pulmonary angiography, and configuration of the heart. *Circ J* 2005; 69: 1386-93.
20. Pilatis ND, Jacobs LE, Rerkpattanapipat P, Kotler MN, Owen A, Manzarbeitia C et al. Clinical predictors of pulmonary hypertension in patients undergoing liver transplant evaluation. *Liver Transpl* 2000; 6:85-91.

21. Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology* 2003; 37:401-9.
22. Rodriguez-Roisin R, Krowka MJ, Herve P. Pulmonary-hepatic vascular disorders. *Eur Respir J* 2004; 24:861-80.
23. Morales-Blanhir J, Santos S, de Jover L, Sala E, Parè C, Roca J et al. Clinical value of vasodilator test with inhaled nitric oxide for predicting longterm response to oral vasodilators in pulmonary hypertension. *Respir Med* 2004; 98:225-34.
24. Whittle BJ, Moncada S. Nitric oxide: the elusive mediator of the hyperdynamic circulation of cirrhosis? *Hepatology* 1992; 16:1089-92.
25. Findlay JF, Harrison BA, Plevak DJ, Krowka MJ. Inhaled nitric oxide reduces pulmonary artery pressures in portopulmonary hypertension. *Liver Transpl* 1999; 5:381-7.
26. Bosch J, D'Amico G, Garcia-Pagan JC. Portal hypertension. In: Schiff ER, Dorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver*. 9th Ed Philadelphia. Lippincott Williams & Wilkins, 2003; 429-86.
27. Provencher S, Hervé P, Jais X, Lebrec D, Humbert M, Simonneau G et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterology* 2006; 130:120-6.
28. Ota K, Shilo H, Kokawa H, Hubara K, Kim T, Akiyoshi N et al. Effects of nifedipine on hepatic venous pressure gradient and portal vein blood flow in patients with cirrhosis. *J Gastroenterol Hepatol* 1995; 10:198-204.
29. Navasa M, Bosch J, Reichen J, Bru C, Mastai R, Zysset T et al. Effects of verapamil on hepatic and systemic hemodynamics and liver function in patients with cirrhosis and portal hypertension. *Hepatology* 1988; 8:850-4.
30. Golbin JM, Krowka MJ. Portopulmonary hypertension. *Clin Chest Med* 2007; 28:203-18.
31. Hoeper MM, Seyfarth HJ, Hoefken G, Wirtz H, Spiekerkoetter E, Pletz MW et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. *Eur Resp J* 2007; 30: 1096-102.
32. Swanson KL, Krowka MJ. Screen for portopulmonary hypertension, especially in liver transplant candidates. *Cleveland Clin J Med* 2008; 75: 121-32.
33. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004; 351:1655-65.
34. Reichenberger F, Voswinckel R, Steveling E, Enke B, Kreckel A, Olschewski H et al. Sildenafil treatment for portopulmonary hypertension. *Eur Respir J* 2006; 28:563-7.
35. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40:780-8.
36. Findlay JY, Plevak DJ, Krowka MJ, Sack EM, Porayko MK. Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension. *Liver Transpl Surg* 1999; 5: 362-5.
37. Austin MJ, McDougall NI, Wendon JA, Sizer E, Knisely AS, Rela M et al. Safety and efficacy of combined use of sildenafil, bosentan, and iloprost before and after liver transplantation in severe portopulmonary hypertension. *Liver Transpl* 2008; 14:287-91.
38. Le Pavec J, Souza R, Herve P, Lebrec D, Savale L, Tcherakian C et al. Portopulmonary hypertension: survival and prognostic factors. *Am J Respir Crit Care Med* 2008; 178:637-43.
39. Acosta F, Sansano T, Palenciano GC, Domenech P, Falcon L, Robles R et al. Portopulmonary hypertension and liver transplantation: hemodynamic consequences at reperfusion. *Transplant Proceed* 2005; 37: 3865-66.
40. Krowka MJ, Mandell MS, Ramsay MAE, Kawut SM, Fallon MB, Manzarbeitia C et al. Hepatopulmonary Syndrome and Portopulmonary Hypertension: A Report of the Multicenter Liver Transplant Database. *Liver Transplant* 2004; 10: 174-82.