J Gastroenterol 2006; 41:837–847
DOI 10.1007/s00535-006-1879-x

Journal of Gastroenterology

Review

Portopulmonary hypertension

Michael Halank[1], Ralf Ewert[2], Hans-Juergen Seyfarth[3], and Gert Hoeffken[1]

[1]Carl Gustav Carus University Dresden, Internal Medicine I, Fetscherstr. 74, 01307 Dresden, Germany
[2]Ernst-Moritz-Arndt University Greifswald, Internal Medicine B, Greifswald, Germany
[3]University Leipzig, Department of Pulmonary Medicine, Critical Care and Cardiology, Leipzig, Germany

Portopulmonary hypertension (PPHT) is defined as precapillary pulmonary hypertension accompanied by hepatic disease or portal hypertension. Pulmonary hypertension results from excessive pulmonary vascular remodeling and vasoconstriction. These histological alterations have been indistinguishable from those of other forms of pulmonary arterial hypertension. Factors involved in the pathogenesis of PPHT include volume overload, hyperdynamic circulation, and circulating vasoactive mediators. The disorder has a substantial impact on survival and requires focused treatment. Liver transplantation in patients with moderate to severe PPHT is associated with a significantly reduced survival rate. The best medical treatment for patients with PPHT is controversial; most authors currently regard continuous intravenous application of prostacyclin as the treatment of choice for patients with severe PPHT. There is only very limited reported experience with inhaled prostacyclin or its analog, iloprost. Increasing evidence of the efficacy of the endothelin-receptor antagonist bosentan and of the phosphodiesterase-5 inhibitor sildenafil is emerging in highly selected patients with PPHT. In the future, a combination therapy of the above-mentioned agents might become a therapeutic option. Other agents such as β-blockers seem to be harmful to patients with moderate to severe portopulmonary hypertension. Up-to-date, randomized, double-blind, controlled clinical trials are lacking and are needed urgently.

Key words: liver cirrhosis, portal hypertension, pulmonary hypertension, portopulmonary hypertension

Received: December 29, 2005 / Accepted: July 25, 2006
Reprint requests to: M. Halank

Introduction

Several extrahepatic manifestations of liver diseases are known. Glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, thrombocytopenia, agranulocytosis, aplastic anemia, and pancreatitis were described by Amarapurkar and Amarapurkar[1] in 29 (6.4%) of 448 patients with different forms of viral hepatitis. Circulating immune complexes have been implicated as causes of extrahepatic manifestations in patients with viral hepatitis.[2] Alcohol has been reported to cause immunologic abnormalities, such as elevation of immunoglobulin E, and seems to account significantly for the increased appearance of allergic skin reactions, regardless of the extent of the underlying liver disease.[3]

Two clinically distinct syndromes that represent a continuum of pulmonary vasculopathy have been defined in association with liver disease or portal hypertension: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHT).[4]

HPS and PPHT often present as dyspnea, which frequently cannot be distinguished from non-pulmonary symptoms caused by manifestations of liver disease such as anemia, ascites, hydrothorax, and muscle wasting.[4] These and other liver-related causes of dyspnea in patients suffering from liver disease or portal hypertension are listed in Table 1.[5]

From pathological and pathophysiological points of view, HPS is the opposite of PPHT.[4] HPS is a pulmonary vascular dilative and PPHT a pulmonary vascular constrictive/obliterative process resulting from liver disease or portal hypertension.[6] Patients with cirrhosis have elevated circulating levels of the vasoconstrictor endothelin-1 (ET-1) owing to increased production in the liver.[7] The pathogenesis of HPS and PPHT might depend on the balance between pulmonary 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.[8] This syndrome is defined as the clinical triad of hepatic disease, arterial oxygenation defect, and intrapulmonary vascular dilation or intrapulmonary shunts. The dilated intrapulmonary vessels can be seen by contrast-enhanced echocardiography. The clinical significance of the pulmonary transit time of erythrocytes for evaluation of arterial oxygenation in patients with HPS has recently been described in this journal.[9] If hepatic disease has been diagnosed, the alveoloarterial oxygen pressure difference (≥15 mmHg, or ≥20 mmHg for patients aged over 64 years) is elevated, and contrast-enhanced echocardiography is positive, HPS can be diagnosed, and its severity is defined as a function of the arterial oxygen partial pressure (paO_2). Orthodeoxia (i.e., decreased arterial oxygen pressure from a supine to upright position) and platypnea (dyspnea manifesting on arising from supine to upright) are hallmarks of HPS. The most frequent hepatic disorder leading to HPS is liver cirrhosis, irrespective of etiology, although HPS has also been described in many other chronic, or even acute, hepatic diseases.[4]

Apart from symptomatic treatment with oxygen, liver transplantation is the only established HPS therapy. Typical differences between HPS and PPHT are presented in Table 2. This review paper focuses on the pulmonary vascular syndrome PPHT.

Table 1. Liver-related causes of dyspnea in patients with liver disease and/or portal hypertension

Pulmonary
Vascular
Portopulmonary hypertension
Hepatopulmonary syndrome
Pulmonary hemorrhage (PBC)
Alveolar
Aspiration pneumonia
Interstitial
Cryptogenic organizing pneumonia (PBC)
Lymphocytic interstitial pneumonia (PBC)
Pulmonary edema from hepatorenal syndrome
Pleural effusions (noncardiogenic, nonrenal transudate)
Extrapulmonary
Deconditioning (immobility)
Muscle wasting
Cardiomyopathy (liver cirrhosis)
Chronotropic dysfunction (liver cirrhosis)

PBC, primary biliary cirrhosis
Modified from ref. 5

Prevalence and diagnosis

In 1951, Mantz and Craige[10] were the first to report an association between pulmonary and portal hypertension. The reported prevalence of PPHT in patients with hepatic cirrhosis varies widely between 0.25% and 4%,[11–13] and increases to 16% in patients with hepatic cirrhosis and refractory ascites.[14]

Table 2. Distinctions between portopulmonary hypertension (PPHT) and hepatopulmonary syndrome (HPS)

	PPHT	HPS
Symptoms	Progressive dyspnea Chest pain Syncope	Progressive dyspnea Platypnea
Physical examination	No cyanosis Pronounced P2 component	Cyanosis Finger clubbing
ECG characteristics	rbbb Rightward axis Right ventricular hypertrophy	Unspecific
Chest radiograph	Cardiomegaly Enlargement of central PA	Normal
Arterial blood gas	No/mild hypoxemia	Moderate/severe hypoxemia, orthodeoxia
$P(A\text{-}a)O_2$	Normal or elevated	Elevated
Pulmonary NO production	Decreased	Increased
CE-echocardiography	Only positive if cardiac shunt is present; left atrial opacification for <3 cardiac cycles after right atrial opacification	Always positive, positive for >3–6 cardiac cycles
^{99m}TcMAA shunting	<6%	≥6%
Pulmonary angiography	Extended main PA, distal PA pruning	Normal/"spongy" appearance (type I); discrete arteriovenous communications (type II)
Pulmonary hemodynamics	Increased PVR, normal PCWP	Normal/low PVR
OLT	Indicated in mild-to-moderate stages	Indicated in severe stages

ECG, electrocardiography; rbbb, right bundle-branch block; PA, pulmonary arteries; $P(A\text{-}a)O_2$, alveolar-arterial oxygen pressure gradient; NO, nitric oxide; CE, contrast-enhanced; ^{99m}TcMAA, technetium-99m-labeled macroaggregated albumin; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; OLT, orthotopic liver transplantation
Modified from ref. 4

Since the World Health Organization (WHO) consensus conference on primary pulmonary hypertension in 1998, PPHT is no longer classified as secondary pulmonary hypertension but as pulmonary arterial hypertension (PAH) in association with hepatic disease or portal hypertension.[15]

The definition of PAH involves a risk of false interpretation in patients with hepatic disease and consequently higher cardiac output. PAH is defined by a mean pulmonary arterial pressure (PAP_m) of more than 25 mmHg at rest or more than 30 mmHg while exercising and normal pulmonary capillary occlusive pressure (≤15 mmHg).[16] As the normal pressure-flow relation in the pulmonary artery is 2–2.5 mmHg l^{-1} min^{-1},[17] and patients with advanced hepatic cirrhosis often have increased cardiac output, the pulmonary arterial pressure is not infrequently above the normal range. Pulmonary vascular resistance, on the other hand, is often normal or only slightly elevated. This may be the reason, at least in some cases, that in up to 20% of patients with advanced hepatic cirrhosis the diagnosis is PAH.[18] The Mayo Clinic classification of pulmonary hypertension in the setting of portal hypertension differentiates three types.[19] The first type is characterized by a pulmonary artery high-flow state. The PAP_m rarely exceeds 35 mmHg, and pulmonary vascular resistance and pulmonary capillary wedge pressure are normal. This type is the most frequent in patients with liver disease or portal hypertension.[13] The second type is characterized by an excess pulmonary venous volume. The volume increase reflects probable excess volume or a pressure increase caused by left ventricular systolic or diastolic dysfunction. The key hemodynamic findings in this situation are increased pulmonary capillary wedge pressure and normal calculated pulmonary vascular resistance. This type is associated with alcoholic cirrhosis, familial amyloidosis, and combined liver-renal insufficiency.[20,21] The third type is characterized by portopulmonary hypertension with elevated pulmonary arterial pressure, and the key finding is clearly elevated calculated pulmonary vascular resistance. As pulmonary vascular resistance increases, right ventricular failure progresses, which is characterized by decreasing cardiac output.[4] Left heart dysfunction, a marked increase in volume, or the concomitant presence of true PPHT with excess volume may confound the interpretation of hemodynamic results.[19] Clinically, patients may be asymptomatic or develop exercise dyspnea and peripheral edema.[22] Mild hypoxemia at rest, due to ventilation–perfusion mismatch and a diffusion limitation, is a common finding in the setting of moderate to severe PPHT. Severe hypoxemia is, however, uncommon and other causes such as an intracardiac right-to-left shunt or HPS should be ruled out. Other symptoms, such as fatigue, thoracic pain, palpitations, or syncope, occur infrequently, and more often at an advanced stage. Until PAP_m is below 40 mmHg, most patients remain asymptomatic. Pulmonary vascular changes compatible with new-onset PPHT may occasionally develop within periods as short as 2 to 3 months.[23] An accentuated second heart sound and a systolic murmur, typically along the right side of the sternum at the level of the fifth interspace, are indicative of pulmonary hypertension. Edema in the legs, ascites, and hemostatic jugular veins are symptoms of both decompensated hepatic cirrhosis and right ventricular failure.

Chest radiography and electrocardiography lack sufficient sensitivity to serve as screening tools for the detection of significant pulmonary arterial hypertension.[24] Abnormalities in the chest radiograph (enlarged central pulmonary arteries, cardiomegaly) and electrocardiograph (right axis, right bundle-branch block, t-wave inversion in the anterior leads) are late findings.

Plasma levels of brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are indices of loading to the heart. Sakuma and coworkers[25] demonstrated elevated ANP and BNP levels in patients with PPHT. To date, the relevance of these peptides in patients with PPHT remains unexplained.

Two-dimensional echocardiography with an additional Doppler examination is the noninvasive diagnostic tool of choice. Typically, enlarged right cardiac cavities and pathological regurgitation in the area of the tricuspid are found.[26] The right ventricular systolic pressure is approximated by measurement of the systolic regurgitant tricuspid flow velocity and estimation of the right atrial pressure. Because the precise value is hard to ascertain, right heart catheterization is recommended to confirm a suspected diagnosis of PPHT.[23]

The older criteria for the diagnosis of PPHT are an elevated mean pulmonary arterial pressure at rest of ≥25 mmHg, an elevated resistance of pulmonary vessels of ≥120 dyn s cm^{-5}, normal pulmonary capillary occlusive pressure (≤15 mm Hg), and evidence of portal hypertension.[6,26] According to more recent studies, the pulmonary vascular resistance value for the diagnosis of PPHT should exceed 240[27] or 250 dyn s cm^{-5}.[28] Before a diagnosis of PPHT is made, other known causes of pulmonary hypertension, in particular chronic thromboembolism, interstitial or obstructive pulmonary diseases, sleep apnea, left ventricular diseases, and cardiac shunt or valvular defects, must be excluded.

For rating the severity of PPHT, we refer to the recommendations of Hoeper et al.[27] (Table 3). With mild or moderate PPHT, the cardiac index is elevated or normal and the pulmonary vascular resistance is only marginally to moderately increased.[27] With severe PPHT, on the other hand, the cardiac index is normal or reduced and pulmonary vascular resistance is clearly increased. In an unknown proportion of patients, mild or

Table 3. Criteria for distinguishing among mild, moderate, and severe portopulmonary hypertension

	Normal	Mild	Moderate	Severe
NYHA class	—	I, II	II, III	III, IV
PAP_m	15–24	25–34	35–44	>45
CI (l min^{-1} m^{-2})	2.5–4.0	>2.5	>2.5	<2.0
PVR (dyne s^{-1} cm^{-5})	<240	240–500	500–800	>800
RAP	0–5	0–5	5–8	>8

Not all factors indicate the same degree of severity in individual patients, so severity must be based on the combination of several factors viewed in clinical context
NYHA, New York Heart Association; PAP_m, mean pulmonary arterial pressure; CI, cardiac index; RAP, right atrial pressure
Modified from ref. 27

moderate PPHT progresses to severe disease. Thus, examinations should be made regularly to identify any progression to pulmonary hypertension. Biannual or annual echocardiographic examinations are advisable.[27] On average, pulmonary arterial hypertension is diagnosed 4 to 7 years after the diagnosis of portal hypertension.[29] The longer the portal hypertension persists, the higher is the risk that pulmonary hypertension will develop.[29,30] No clear relationship has been found between the level of portal venous pressure or the severity of the hepatic dysfunction and the severity of the pulmonary hypertension; in some cases the results have even been contradictory.[29] Rarely, symptoms of pulmonary hypertension appear before portal hypertension can be detected.[27]

Pathogenesis and pathophysiology

Advanced hepatic cirrhosis is characterized by changes in hepatic, peripheral, splanchnic, brain, kidney, and lung circulation. The clinical manifestations of hepatic cirrhosis result mostly from portal hypertension and its complications, such as variceal bleeding, portal hypertensive gastropathy, ascites, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, and PPHT. Generalized systemic vasodilatation is typical of hepatic cirrhosis and results in a hyperdynamic circulatory state with reduced systemic resistance and blood pressure, and raised cardiac output and cardiac rate. The cause of systemic vasodilatation and of vasodilatation in the splanchnic area is assumed to be a higher concentration of vasodilating agents or reduced sensitivity of the vascular endothelium to vasoconstrictors.

Portal hypertension results from either reduced secretion of vasodilating substances such as NO[31] or increased secretion of vasoconstricting substances such as ET-1.[32] Hepatic stellate cells (HSCs) play an important part in regulating vascular resistance in the area of hepatic flow. In hepatic cirrhosis, the HSCs show a stronger response to ET-1, which can be seen as a higher mitotic rate and increased proliferation. The leading role of ET-1 in causing increased portal vessel resistance has been proved in an animal model of portal hypertension, even in the absence of hepatic cirrhosis.[33] Despite systemic vasodilatation, patients with hepatic cirrhosis may also show renal or cerebral vasoconstriction.

Liver cirrhosis and portal hypertension may allow substances normally cleared by the liver to reach the pulmonary circulation and may induce mediator release by different cells such as macrophages, platelets, endothelium, and smooth muscle, resulting in the development of HPS or PPHT.[20] The causes of the different pulmonary manifestations are currently not fully understood. The histopathological changes in connection with portopulmonary hypertension include plexus-like arteriopathy, media hypertrophy, intimal fibrosis, adventitial proliferation, and in situ thrombosis of the minor pulmonary arteries,[11,34,35] which cannot be distinguished from other forms of PAH. Reviewing the literature, Sakuma and coworkers[25] reported that in 147 Japanese patients with PPHT, half of those with liver disease suffered from liver cirrhosis, including alcoholic cirrhosis and primary biliary cirrhosis. However, precise information about the frequency and causes of liver cirrhosis is lacking, because many cases have been reported on only in abstracts. With remarkably high frequency, nonhepatic diseases, including extrahepatic portal obstruction (11%), idiopathic portal hypertension (11%), and congenital biliary atresia (10%), for an overall frequency of more than 30%, have been reported to cause portal hypertension.[25] In Western countries, nonhepatic causes of portal hypertension seem to be less frequent, ranging between 1.5% and 20%.[20,29,36–38] In two French and one German series, alcoholic cirrhosis was reported to be the most important cause of portal hypertension in 60% and 63%, respectively, of patients with PPHT.[29,37,38] In another study of 66 patients from the United States, alcoholic cirrhosis alone was reported in 25%, hepatitis C alone in 18%, alcohol plus hepatitis C in 15%, and cryptogenic cirrhosis in 14% of patients as the most frequent etiology of PPHT.[36] Swanson and Krowka[39] (6 of 27 patients) and

Kuo and colleagues[26] (5 of 30 patients) reported that in about 20% of their patients, PPHT could most frequently be attributed to autoimmune hepatitis, and it could be attributed with high frequency to alcoholic and hepatitis C-related cirrhosis.[26,39] Other causes of PPHT such as nonalcoholic steatohepatitis,[36,39] granulomatous hepatitis,[39,40] primary sclerosing cholangitis,[36,41] and hepatitis B infection[36,40] are more rarely mentioned in the literature. Thus, most liver diseases reported in patients with PPHT are liver cirrhoses. Alcohol abuse seems to be the most important cause of cirrhosis in patients with PPHT.

The details of the development of structural pulmonary vascular changes are not well understood. Three causative factors are (1) shear stress in the vascular walls due to the increased blood flow in a hyperdynamic state of circulation; (2) a volume phenomenon as a consequence of the increased pulmonary vascular volume; and (3) vasoconstriction caused by substances from the vascular bed of the hepatosplanchnic circulation.[6]

Increased cardiac output causes higher shear forces in the pulmonary vessels with possible lesions of the vascular endothelium and the consequential release of mediators causing vasoconstriction of pulmonary vessels and vascular remodeling. It may be that hypercirculation is not the only factor responsible for the development of pulmonary hypertension, given that the shunt volume from the portal circulation is not a risk factor on its own for the development of pulmonary hypertension,[29] nor does the acute increase in the pulmonary arterial flow (due to the formation of a transjugular intrahepatic portosystemic shunt in patients with hepatic cirrhosis) induce transient PPHT.[42]

The fact that increased intravascular volume in patients with hepatic cirrhosis does not lead to pulmonary vasoconstriction but to generalized vasodilatation argues against increased volume as a causative factor.[43] These findings and the fact that only a few patients with a hyperdynamic state of circulation develop portopulmonary hypertension suggest that additional factors, not yet identified, causing proliferation of endothelial cells may be involved. Overexpression of proliferative and angiogenic mediators may lead to endothelial proliferation with subsequent plexiform vascular lesions of the pathway of pulmonary circulation.[44] In portal hypertension, increased production and release of ET-1, a potent vasoconstrictor and smooth-muscle mitogen, occur in the liver,[7] the intestines,[7,45] and the spleen.[45] ET-1 levels are significantly higher in patients with decompensated hepatic cirrhosis and PPHT than in those with decompensated hepatic cirrhosis without PPHT.[14] Two endothelin-receptor isoforms, endothelin-A (ET_A) and endothelin-B (ET_B), have been identified. Activation of ET_A receptors facilitates vasoconstriction and proliferation of vascular smooth-muscle cells. ET_B receptors are involved principally in the clearance of endothelin, particularly in the vascular beds of the lung and kidney. Activation of ET_B receptors may also cause NO release and vasodilation. In contrast to PPHT, during the onset of experimental HPS after biliary obstruction, enhanced pulmonary endothelial ET_B-receptor expression has been demonstrated, leading to ET-1-mediated endothelial NO synthase-derived NO overproduction and pulmonary vasodilation.[46] Two case reports describing the use of the nonselective ET_A and ET_B receptor blocker bosentan demonstrated a reduction of pulmonary arterial and portal pressures in patients with PPHT, underlining the possible importance of an elevated ET-1 level in the pathophysiology of PPHT.[47,48] Other vasoconstrictive mediators, such as serotonin, norepinephrine, and angiotensin II, which are produced in the splanchnicus and enter pulmonary circulation via portosystemic shunts, have been observed in connection with the development of PPHT.[49,50] Tuder and colleagues[51] found a reduced expression of prostacyclin synthase, which catalyzes the synthesis of the vasodilator prostacyclin, in the small and medium-sized pulmonary arteries of patients with severe pulmonary hypertension, and PPHT was diagnosed in four of these patients.

In addition to an imbalance between vasoconstricting and vasodilating mediators, disordered antithrombotic conditions of the pulmonary vascular endothelium with formation of in situ thrombosis are known to be associated with PPHT.[35] Furthermore, the increased prevalence of autoimmune antibodies in patients with PPHT indicates a possible autoimmune disease in some patients.[20] In patients with familial and sporadic idiopathic PAH, mutations in bone morphogenetic protein receptor II, a member of the transforming growth factor receptor family, have been identified.[52–54] So far, no genetic disposition for the development of pulmonary arterial hypertension in the presence of portal hypertension has been found. Figure 1 summarizes the most important hypotheses on the pathophysiology of PPHT.[5]

Prognosis

Information concerning the prognosis of PPHT in the literature varies widely. Yang et al.[55] suggested that PPHT is not associated with an adverse outcome, but none of the examined patients revealed pulmonary vascular resistance of more than 250 dyn s cm^{-5}. In a literature review of PPHT, Robalino and Moodie[49] reported mean and median survivals of 15 and 6 months, respectively, without specific treatment. In contrast, Sakuma and coworkers[25] recently reported a 5-year survival rate

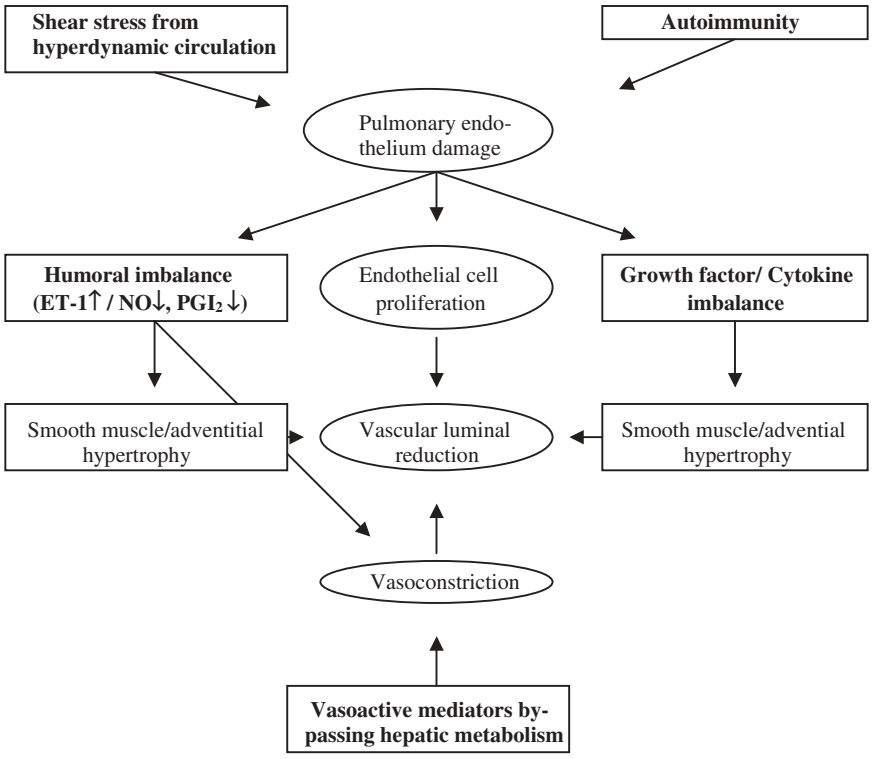

Fig. 1. Mechanisms by which portal hypertension causes pulmonary hypertension. *ET-1*, endothelin 1; *NO*, nitric oxide; *PGI2*, prostacyclin. Modified from ref. 5

of approximately 80% in ten patients with PPHT. Kawut and coworkers[40] reported 1- and 3-year survival estimates of 85% and 38% in 13 patients with PPHT of comparable severity. In 147 Japanese patients with PPHT, half of the 64 deaths were from cardiac events, including right heart failure and sudden death.[25]

Pharmacotherapy

The medicinal treatment of PPHT has been based largely on actual data from the treatment of other forms of pulmonary arterial hypertension. No specific treatment is recommended for mild pulmonary arterial hypertension according to present knowledge. A case of 30 years of mild pulmonary arterial hypertension without progression was published recently.[56] It is questionable whether patients with a mild to moderate PPHT benefit from a specific treatment—that is, intravenous epoprostenol, other oral or inhaled prostanoids, phosphodiesterase-5 inhibitors, or endothelin-receptor antagonists.[27] But specific therapy may be necessary when patients with mild to moderate PPHT require liver transplantation or other major surgery.[27] Considering its poor prognosis, severe PPHT is best treated without delay. The treatment is expensive, carries risks, and requires good patient compliance.

Because in situ thrombosis of the pulmonary circulation has been found in patients with PPHT,[35] anticoagulation might be useful in patients with Child's class A who have no relevant esophageal or gastric varices. Owing to a lack of data, general recommendations concerning anticoagulation in patients with PPHT are not possible.[27] When the risk of gastrointestinal bleeding is high, oral anticoagulant therapy is not contraindicated.[4] β-Blockers prescribed for prophylaxis of variceal bleeding are assumed to contribute to deterioration of PAH because of their negative inotropic and chronotropic effects.[4] Recently Provencher and coworkers[38] demonstrated that in the context of moderate to severe portopulmonary hypertension, withdrawing β-blockers improved exercise capacity and pulmonary hemodynamics. They concluded that β-blockers are contraindicated in patients with moderate to severe PPHT. A single study reported improvement and another deterioration in the hemodynamics with the administration of isosorbide-5′-mononitrate.[57,58] The efficacy of positive inotropic cardiac glycosides in PPHT patients is unproven. Therefore, no recommendations relating to nitrates or cardiac glycosides in PPHT patients have been made. Long-term oxygen therapy should be considered in patients with paO_2 less than 60 mmHg.[4] In patients with cirrhosis, calcium-channel blockers failed to reduce portal hypertension. Moreover, nifedipine administration increased the hepatic venous pressure gradient.[59] Owing to a lack of studies of their use in patients with PPHT, calcium-channel blockers are not recommended.[4]

Intravenous epoprostenol (synthetic prostacyclin) is a potent vasodilator with antiproliferative action. Several open-label studies reported improvement in hemodynamics and exercise capacity in patients with PPHT.[41,60,61] Epoprostenol is a recommended treatment for PPHT, but no randomized controlled studies proving its efficacy and safety exist for these patients.[62] Epoprostenol may serve as a bridge to liver transplantation in selected patients.[61] Data in a multicenter database from ten liver transplantation centers suggest an independent positive effect of intravenous epoprostenol with respect to survival in four of five liver-transplanted patients with PPHT.[36] Progressive splenomegaly with worsening thrombocytopenia and leukopenia during treatment with epoprostenol in the setting of advanced liver disease has been reported.[63] Other serious complications include catheter-related sepsis and the risk for rebound worsening with interruption of the infusion.

Alternative application pathways, such as the inhalation or subcutaneous or oral administration of prostacyclin or its derivatives iloprost, treprostinil, and beraprost, might provide another treatment option in the future. In patients with PPHT, a reduction of PAP_m after inhalation of prostacyclin or iloprost has been demonstrated in two case reports.[64,65] Although subcutaneous treprostinil and oral beraprost have been used, no fully published data demonstrate the efficacy of these drugs in patients with PPHT. Therefore, no recommendations regarding above-mentioned treatment options are possible.

Because plasma levels of ET-1 are elevated in patients with PPHT, the use of an oral endothelin-receptor antagonist might be a successful treatment alternative. So far, case reports and a retrospective case series of patients with PPHT in Child's class A have shown clinical, functional, and hemodynamic benefits without elevation of hepatic aminotransferases on treatment with the dual endothelin-receptor antagonist bosentan.[37,47,48,66] Excluding cases of PPHT, increases in hepatic aminotransferases occurred in about 10% of patients with PAH treated with bosentan. The increases were dose-dependent, and reversible after dose reduction or discontinuation.[67] Use of bosentan in patients with PPHT should be restricted to highly experienced centers.[27] To date, no data on the use of a selective ET_A-receptor antagonist in patients with PPHT have been published.

Phosphodiesterase-5 inhibitors boost the effect of endogenous NO by inhibiting breakdown of the messenger substance cGMP (cyclic guanosine monophosphate), leading to pulmonary vasodilatation and inhibition of proliferation of vascular smooth muscle. In several case reports and a recent retrospective case series of patients with PPHT, a benefit with respect to physical capacity and hemodynamics has been demonstrated,[68–71] but long-term hemodynamic parameters (12 months of follow-up) were not significantly different from baseline.[71] At this moment, no recommendation is possible.

Goal-directed therapy is a current challenge in PAH, and specific therapeutic targets might be identified with growing experience and the availability of combination therapy.[72] One patient with PPHT demonstrated cardiopulmonary recompensation after bosentan was added to intravenous prostanoid treatment.[73] In a retrospective case series of patients with PPHT, adding oral sildenafil to chronic in-haled prostanoid treatment led to significant hemodynamic and functional improvements.[71] Published placebo-controlled trials in patients with PPHT are lacking.

Table 4 summarizes the pharmacotherapy of patients with PPHT.

Liver transplantation

In up to 12.5% of all patients for whom orthotopic liver transplantation is planned, portopulmonary hypertension is diagnosed.[74] Of these patients, 60% are asymptomatic at the time of the diagnosis.[49] Depending on the severity of the pulmonary hypertension, the peri- or postoperative mortality rate increases. If pulmonary hypertension is mild or moderate, it is often reversible after liver transplantation[75–77] and does not carry a higher mortality rate.[13,78] Severe pulmonary hypertension, on the other hand, increases the mortality rate after liver transplantation markedly. A PAP_m between 35 and 50 mmHg causes an estimated 50% mortality, and this may increase to 100% if the PAP_m exceeds 50 mmHg.[79,80] Following the current recommendations of the European Respiratory Society Task Force, liver transplantation should not be considered if PAP_m is ≥45 mmHg; vasodilating treatment before liver transplantation should be considered if PAP_m is more than 35 to 45 mmHg.[4] Other reports suggest that PAP_m is not a very precise predictor of the risk of mortality and that pulmonary pressure does not serve as an independent prognostic value for the severity of disease or outcome.[81] Starkel and coworkers[81] reported that 7 of 11 patients with PAP_m ≥50 mmHg survived liver transplantation, which does not support the assumption that higher PAP_m is an absolute contraindication for transplantation. A Multicenter Liver Transplant Database report indicated no significant difference in PAP_m between 13 patients who died after liver transplantation (44 ± 8 mmHg) and 23 patients who survived (45 ± 14 mmHg).[36]

In mild to moderate PPHT, an acute volume loading test before a planned liver transplantation is recom-

Table 4. Pharmacotherapy in patients with portopulmonary hypertension

Drug class	Studies in patients with portopulmonary hypertension	References	Recommendations in severe portopulmonary hypertension	References
Anticoagulants	No studies		No recommendations in patients with low risk of gastrointestinal bleeding	4,27
β-Blockers	One prospective, open-label study	38	Contraindicated	4,38
Nitrates	Two case reports	57,58	No recommendations	
Glycosides	No studies		No recommendations	
Oxygen	No studies		Recommended in severe hypoxemia	4
Calcium channel blockers	No controlled studies		Contraindicated	4
Intravenous epoprostenol	Several open-label studies	41,60,61	Recommended	62
Prostacyclin analogs			No recommendations	
Inhaled epoprostenol	One case report	64	Use should be restricted to highly experienced centers	
Inhaled iloprost	One case report	65		
Oral beraprost	No fully published data			
Subcutaneous treprostinil	No fully published data			
Endothelin-receptor antagonists	Several case reports	47,48,66	Use should be restricted to highly experienced centers	27
Oral bosentan	One retrospective case series	37		
Phosphodiesterase-5 inhibitors			No recommendations	
Sildenafil	Several case reports	68,69,70	Use should be restricted to highly experienced centers	
	One retrospective case series	71		
Combination therapies			No recommendations. Use	
Intravenous iloprost + oral bosentan	One case report	73	should be restricted to highly experienced centers	
Inhaled iloprost + oral sildenafil	One retrospective case series	71		

mended.[82,74] First, however, aberrant left ventricular function should be excluded with a stress echocardiogram.[82] If the PAP_m before or after volume loading exceeds a threshold value of about 34–40 mmHg, or if right cardiac dysfunction is diagnosed, vasodilator therapy prior to liver transplantation should be considered.[4,74,82] To date, it is unknown which value of PAP_m should be chosen as the cutoff for initiating a specific pharmacotherapy before liver transplantation. The European Task Force[4] recommends a threshold value of ≥35 mmHg, Tan and coworkers[74] recommend ≥36 mmHg, and Kuo and coworkers[82] >40 mmHg for starting therapy with epoprostenol. It should be emphasized that PAP_m alone does not reflect the functional capacity of the right heart. The severity of PPHT depends hemodynamically on a combination of cardiac index, right atrial pressure, pulmonary vascular resistance, and PAP_m.[27] A modified version of the algorithm for diagnosis and treatment recommended by Tan et al.[74] is presented in Fig. 2. This approach has not been evaluated by evidence-based studies.

In individual cases, multiple organ transplantation can be considered for patients with severe pulmonary hypertension that cannot be treated with drugs. Both liver and lung transplantation and liver, lung, and heart transplantation have been reported.[83,84]

Transjugular intrahepatic portosystemic shunt

Placing a transjugular intrahepatic portosystemic shunt (TIPS) is an optional treatment for patients with untreatable ascites or relapsing variceal bleeding. It should be noted, however, that this procedure increases the preload of the heart and the cardiac output, whereas the systemic peripheral resistance drops.[42,85,86] This may lead to diastolic dysfunction of the hyperdynamic left ventricle with a rise of the pulmonary capillary occlusive pressure in patients with alcohol-induced hepatic cirrhosis.[42] A TIPS should not be placed in patients with PPHT.[4]

Summary

Patients with advanced hepatic disease of different causes suffer quite frequently from PPHT. Before

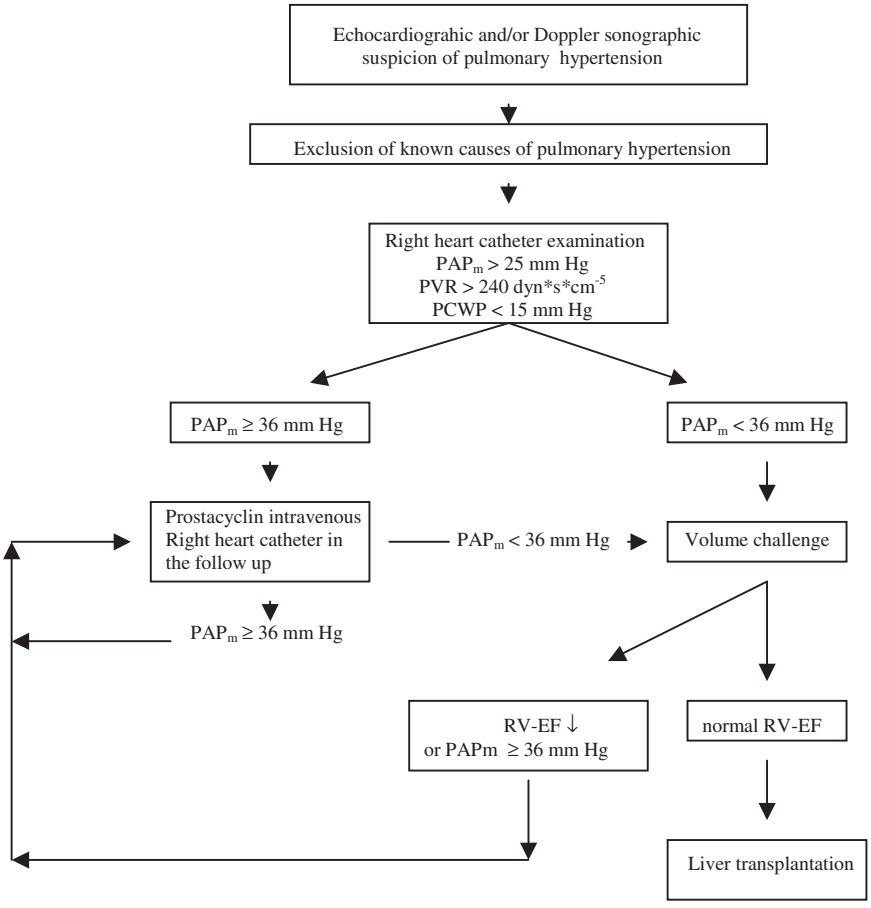

Fig. 2. Algorithm for the diagnosis and treatment of portopulmonary hypertension and evaluation of candidates for liver transplantation. *PAPm*, mean pulmonary arterial pressure; *PVR*, pulmonary vascular resistance; *PCWP*, pulmonary vascular occlusion pressure; *RV-EF*, right ventricular ejection fraction. Modified from ref. 74

PPHT is diagnosed, other known causes of pulmonary hypertension must be excluded. The etiology of pulmonary hypertension is not fully understood. Hypercirculation, volume overload, and circulating vasoconstricting mediators bypassing the hepatic circulation have all been proposed as causal factors. Pulmonary arterial vasoconstriction and vascular remodeling, which can lead to right heart failure, are characteristic features. Evidence-based studies are required to determine whether prostanoids, endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, or a combination of these agents improve survival in patients with PPHT. In certain cases, liver or liver, (heart), lung transplantation is the only possible treatment.

References

1. Amarapurkar DN, Amarapurkar AD. Extrahepatic manifestations of viral hepatitis. Ann Hepatol 2002;1:192–5.
2. Wilson RA. Extrahepatic manifestations of chronic viral hepatitis. Am J Gastroenterol 1997;92:4–17.
3. Mujagic H, Prnjavorac B, Mujagic Z, Festa G. Alcohol in liver disease is a causative factor for development of allergic skin manifestations. Med Arh 2003;57:273–8.
4. Rodriguez-Roisin R, Krowka MJ, Herve Ph, Fallon MB, ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-hepatic vascular disorders (PHD). Eur Respir J 2004;24:861–80.
5. Budhiraja R, Hassoun PM. Portopulmonary hypertension: a tale of two circulations. Chest 2003;123:562–76.
6. Krowka MJ. Hepatopulmonary syndrome versus portopulmonary hypertension: distinctions and dilemmas. Hepatology 1997;25: 1282–4.
7. Gerbes AL, Moller S, Gulberg V, Henriksen JH. Endothelin-1 and -3 plasma concentrations in patients with cirrhosis: a role of splanchnic and renal passage and liver function. Hepatology 1995; 21:735–9.
8. Cremona G, Higenbottam TW, Mayoral V, Alexander G, Demoncheaux E, Borland C, et al. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. Eur Respir J 1995;8: 1883–5.
9. Katsuta Y, Honma H, Zhang XJ, Ohsuga M, Komeichi H, Shimizu S, et al. Pulmonary blood transit time and impaired arterial oxygenation in patients with chronic liver disease. J Gastroenterol 2005;40:57–63.
10. Mantz FA Jr, Craige E. Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. AMA Arch Pathol 1951;52:91–7.
11. McDonnel PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis 1983;127:437–41.
12. Cheng E, Woehlck H. Pulmonary artery hypertension complicating anesthesia for liver transplantation. Anesthesiology 1992;77: 389–92.

13. Castro M, Krowka MJ, Schroeder R, Beck KC, Plevak DJ, Rettke SR, et al. Frequency and clinical implications of increased pulmonary pressures in liver transplant patients. Mayo Clin Proc 1996; 71:543–51.
14. 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.
15. Rich S. Primary pulmonary hypertension: executive summary from the world symposium on primary pulmonary hypertension 1998. Geneva: World Health Organization; 1998.
16. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997; 336:111–7.
17. Naeije R. Pulmonary Circulation. In: Gibson CJ, Geddes DM, Costabel U, Sterk PJ, Corris B, editors. Respiratory medicine. Vol. I. 3rd ed. London: Saunders; 2003. p. 147–57.
18. Krowka MJ. Hepatopulmonary syndromes. Gut 2000;46:1–4.
19. Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension: implications for liver transplantation. Clin Chest Med 2005;26:587–97.
20. Herve P, Lebrec D, Brenot F, Simonneau G, Humbert M, Sitbon O, et al. Pulmonary vascular disorders in portal hypertension. Eur Respir J 1998;11:1153–66.
21. Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 2002;20:1314–31.
22. Mandell MS. Critical care issues: portopulmonary hypertension. Liver Transpl 2000;6(4 Suppl 1):S36–43.
23. 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.
24. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detecting, and diagnosis of pulmonary arterial hypertension. Chest 2004;126:14S–34S.
25. 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.
26. Kuo PC, Plotkin JS, Johnson LB, Howell CD, Laurin JM, Bartlett ST, et al. Distinctive clinical features of portopulmonary hypertension. Chest 1997;112:980–6.
27. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet 2004;363:1461–8.
28. Naeije R. Hepatopulmonary syndrome and portopulmonary hypertension. Swiss Med Wkly 2003;133:163–9.
29. Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100:520–8.
30. Auletta M, Oliviero U, Iasiuolo L, Scherillo G, Antoniello S. Pulmonary hypertension associated with liver cirrhosis: an echocardiographic study. Angiology 2000;51:1013–20.
31. Shah V, Toruner M, Haddad F, Cadelina G, Papapetropoulos A, Choo K, et al. Impaired endothelial nitric oxide synthase activity associated with enhanced caveolin binding in experimental cirrhosis in the rat. Gastroenterology 1999;117:1222–8.
32. Rockey DC, Weisiger RA. Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance. Hepatology 1996; 24:233–40.
33. Kamath PS, Tyce GM, Miller VM, Edwards BS, Rorie DK. Endothelin-1 modulates intrahepatic resistance in a rat model of noncirrhotic portal hypertension. Hepatology 1999;30:401–7.
34. Mandell MS, Groves BM. Pulmonary hypertension in chronic liver disease. Clin Chest Med 1996;17:17–33.
35. Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. Liver Transpl 2000; 6:241–2.
36. 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 Transpl 2004;10:174–82.
37. Hoeper MM, Halank M, Marx C, Hoeffken G, Seyfarth HJ, Schauer J, et al. Bosentan therapy for portopulmonary hypertension. Eur Resp J 2005;25:502–8.
38. Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, et al. Deleterious effects of β-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. Gastroenterology 2006;130:120–6.
39. Swanson KL, Krowka MJ. Arterial oxygenation associated with portopulmonary hypertension. Chest 2002;121:1869–75.
40. Kawut SM, Taichman DB, Ahya VN, Kaplan S, Archer-Chicko CL, Kimmel SE, et al. Hemodynamics and survival of patients with portopulmonary hypertension. Liver Transpl 2005;11:1107–11.
41. Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. Hepatology 1999;30:641–8.
42. Huonker M, Schumacher YO, Ochs A, Sorichter S, Keul J, Rossle M. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. Gut 1999;44:743–8.
43. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. Pharmacol Ther 2001;89:221–31.
44. Tuder RM, Cool CD, Yeager M, Taraseviciene-Stewart L, Bull TM, Voelkel NF. The pathobiology of pulmonary hypertension. Endothelium. Clin Chest Med 2001;22:405–18.
45. Nagasue N, Dahr DK, Yamanoi A, Emi Y, Udagawa J, Yamamoto A, et al. Production and release of endothelin-1 from the gut and spleen in portal hypertension due to cirrhosis. Hepatology 2000;31:1107–14.
46. Ling Y, Zhang J, Luo B, Song D, Liu L, Tang L, et al. The role of endothelin-1 and endothelin B receptor in the pathogenesis of experimental hepatopulmonary syndrome. Hepatology 2004;39: 1593–602.
47. Halank M, Miehlke S, Höffken G, Schmeisser A, Schulze M, Strasser RH. Use of oral endothelin-receptor antagonist bosentan in the treatment of portopulmonary hypertension. Transplantation 2004;77:1775–6.
48. Hinterhuber L, Graziadei IW, Kahler CM, Jaschke W, Vogel W. Endothelin-receptor antagonist treatment of portopulmonary hypertension. Clin Gastroenterol Hepatol 2004;2:1039–42.
49. Robalino BD, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. J Am Coll Cardiol 1991;17:492–8.
50. Salvi SS. Alpha 1-adrenergic hypothesis for pulmonary hypertension. Chest 1999;115:1708–19.
51. 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.
52. Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips JA 3rd, Loyd JE, et al. Heterozygous germline mutations in *BMPR2*, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension: the International PPH Consortium. Nat Genet 2000;26:81–4.
53. Machado RD, Pauciulo MW, Thomson JR, Lane KB, Morgan NV, Wheeler L, et al. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. Am J Hum Genet 2001;69:92–102.
54. Thomson JR, Machado RD, Pauciulo MW, Morgan NV, Humbert M, Elliot GC, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family. J Med Genet 2000;37:741–5.

55. Yang YY, Lin HC, Lee WC, Hou MC, Lee FY, Chang FY. Portopulmonary hypertension: distinctive hemodynamic and clinical manifestations. J Gastroenterol 2001;36:181–6.
56. Halank M, Marx C, Hoeffken G. Long term survival in primary pulmonary hypertension. Heart 2004;90:e40.
57. Ribas J, Angrill J, Barbera JA, Garcia-Pagan JC, Roca J, Bosch J, et al. Isosorbide-5-mononitrate in the treatment of pulmonary hypertension associated with portal hypertension. Eur Respir J 1999;13:210–2.
58. Halank M, Miehlke S, Kolditz M, Hoeffken G. Portopulmonary hypertension (in German with English abstract). Z Gastroenterol 2005;43:677–85.
59. Ota K, Shilo H, Kokawa H, Kubara 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.
60. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997;63:604–6.
61. Plotkin JS, Kuo PC, Rubin LJ, Gaine S, Howell CD, Laurin J, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. Transplantation 1998;65:457–9.
62. Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension. Curr Treat Options Cardiovasc Med 2002;4:267–73.
63. 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
64. Schroeder RA, Rafii AA, Plotkin JS, Johnson LB, Rustgi VK, Kuo PC. Use of aerosolized inhaled epoprostenol in the treatment of portopulmonary hypertension. Transplantation 2000;70: 548–50.
65. Halank M, Marx C, Miehlke S, Hoeffken G. Use of aerosolized inhaled iloprost in the treatment of portopulmonary hypertension. J Gastroenterol 2004;39:1222–3.
66. Kuntzen C, Guelberg V, Gerbes AL. Use of a mixed receptor antagonist in portopulmonary hypertension: a safe and effective therapy? Gastroenterology 2005;128:164–8.
67. Rubin LJ, Badesch DB, Barst R, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
68. Makisalo H, Koivusalo A, Vakkuri A, Hockerstedt K. Sildenafil for portopulmonary hypertension in a patient undergoing liver transplantation. Liver Transpl 2004;10:945–50.
69. Chua R, Keogh A, Miyashita M. Novel use of sildenafil in the treatment of portopulmonary hypertension. J Heart Lung Transplant 2005;24:498–500.
70. Callejas Rubio JL, Salmeron Escobar J, Gonzalez-Calvin J, Ortego Centeno N. Successful treatment of severe portopulmonary hypertension in a patient with Child C cirrhosis by sildenafil. Liver Transpl 2006;12:690–1.
71. 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.
72. Hoeper MM, Markevych I, Spiekerkoetter W, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J 2005;26:858–63.
73. Halank M, Kolditz M, Miehlke S, Schiemanck S, Schmeisser A, Hoeffken G. Combination therapy for portopulmonary hypertension with intravenous iloprost and oral bosentan. Wien Med Wochenschr 2005;155:376–80.
74. Tan HP, Markowitz JS, Montgomery RA, Merritt WT, Klein AS, Thuluvath PJ, et al. Liver transplantation in patients with severe portopulmonary hypertension treated with preoperative chronic intravenous epoprostenol. Liver Transpl 2001;7:745–9.
75. Levy MT, Torzillo P, Bookallil M, Sheil AG, McCaughan GW. Case report: delayed resolution of severe pulmonary hypertension after isolated liver transplantation in a patient with cirrhosis. J Gastroenterol Hepatol 1996;11:734–7.
76. Schott R, Chaouat A, Launoy A, Pottecher T, Weitzenblum E. Improvement of pulmonary hypertension after liver transplantation. Chest 1999;115:1748–9.
77. Koneru B, Ahmed S, Weisse AB, Grant GB, McKim KA. Resolution of pulmonary hypertension of cirrhosis after liver transplantation. Transplantation 1994;58:1133–5.
78. Taura P, Garcia-Valdecasas JC, Beltran J, Izquierdo E, Navasa M, Sala-Blanch J, et al. Moderate primary pulmonary hypertension in patients undergoing liver transplantation. Anesth Analg 1996;83:675–80.
79. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. Liver Transpl Surg 1997;3:494–500.
80. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl 2000;6: 443–50.
81. Starkel P, Vera A, Gunson B, Mutimer D. Outcome of liver transplantation for patients with pulmonary hypertension. Liver Transpl 2002;8:382–8.
82. Kuo PC, Plotkin JS, Gaine S, Schroeder RA, Rustgi VK, Rubin LJ, et al. Portopulmonary hypertension and the liver transplant candidate. Transplantation 1999;67:1087–93.
83. Pirenne J, Verleden G, Nevens F, Delcroix M, Van Raemdonck D, Meyns B, et al. Combined liver and (heart) lung transplantation in liver transplant candidates with refractory portopulmonary hypertension. Transplantation 2002;73:140–2.
84. Dennis CM, McNeil KD, Dunning J, Stewart S, Friend PJ, Alexander G, et al. Heart-lung-liver transplantation. J Heart Lung Transplant 1996;15:536–8.
85. Azoulay D, Castaing Y, Dennison A, Martino W, Eyraud D, Bismuth H. Transjugular intrahepatic portosystemic shunt worsens the hyperdynamic circulatory state of the cirrhotic patient. Hepatology 1994;19:129–32.
86. Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Deviere J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. Hepatology 1996;23:982–7.