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Pulmonary Arterial Hypertension: An Overview

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1. Introduction

Pulmonary hypertension (PH) is a hemodynamic state defined by a resting mean pulmonary artery pressure (PAP) at or above 25 mm Hg.[1] with normal left ventricular filling pressure (mean pulmonary wedge pressure) 15 mmHg or less.

Pre-capillary PH is defined as mean PAP ≥25 mm Hg in association with PAOP ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units. This include group 1, 3, 4 and 5 (Table 1). [2] Post-capillary PH (group 2 as shown in Table 1) is characterized by a mean PAP ≥25 mm Hg in association with PAOP >15 mm Hg and PVR ≤3 Wood units.[3] This differentiation in pre- and post-capillary PH is important as it narrows the differential diagnosis and also has treatment implications.

1. Pulmonary arterial hypertension (PAH)

1.1. Idiopathic PAH

1.2. Heritable

1.2.1. BMPR2

1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)

1.2.3. Unknown

1.3. Drug- and toxin-induced

1.4. Associated with

1.4.1. Connective tissue diseases

1.4.2. HIV infection

1.4.3. Portal hypertension

1.4.4. Congenital heart diseases

1.4.5. Schistosomiasis

1.4.6. Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn

1=. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease

2.1. Systolic dysfunction

2.2. Diastolic dysfunction

2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases 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 thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

5.1. Hematologic disorders: myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure

on dialysis.

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

Adapted from Simonneau et al. Updated clinical Classification of pulmonary hypertension. J Am Coll Cardiol 2009; Vol. 54 (1): S43–54

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Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

2. Epidemiology

Pulmonary arterial hypertension (PAH) is a rare disease, with an estimated prevalence of 15-50 cases per million.[4] Idiopathic PAH (IPAH) has an annual incidence of 1-2 cases per million people in the US and Europe and is 2-4 times as common in women as in men.[5], [6] The REVEAL Registry demonstrates a 4.1:1 female-to-male ratio among patients with IPAH, and a 3.8:1 ratio among those with associated pulmonary arterial hypertension (APAH). [4] The mean age at diagnosis is around 45 years.[7] IPAH accounts for at least 40% of cases of PAH, with APAH accounting for the majority of the remaining cases. [8]

The REVEAL Registry population tends to be overweight, with a BMI of 29 kg/m^{2}; hence, obesity may be a risk factor for the development of PAH. A variety of comorbid conditions

were identified, including systemic hypertension, obstructive lung disease, sleep apnea, and prior venous thrombo-embolism, which were not believed to represent the principal cause for the patients' pulmonary hypertension. [6]

The median interval from symptom onset to diagnosis remains unacceptably high at 1.1 years in current registry data, [6] unchanged from the experience from the 1980's.[9] Overall survival has improved somewhat, with 3-year survival of 48% in the NIH registry [10], compared to 67% in both US [11] and French [12] contemporary registries.

3. Etiology

Pulmonary arterial hypertension (PAH) is comprised of idiopathic, heritable and associated forms. IPAH was previously referred to as primary pulmonary hypertension. During the 4th World Symposium on pulmonary hypertension in 2008 at Dana Point, California, USA, the group updated the Evian –Venice classification of 2003 of pulmonary hypertension based upon mechanism. [2] (Table 1)

4. Pathophysiology

PAH is a proliferative vasculopathy which is histologically characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, fibrosis and in-situ thrombi of the small pulmonary arteries and arterioles.[13], [14]

Genetic mutations — Predisposition to pulmonary vascular disease may be related to genetic mutations in the bone morphogenetic protein receptor type II (BMPR2), activin-like kinase type 1, and/or 5-hydroxytryptamine (serotonin) transporter (5HTT) genes. Abnormal BMPR2 may play an important role in the pathogenesis of IPAH, with up to 25 percent of patients with IPAH having abnormal BMPR2 structure or function. [15], [16], [17]

5. Pathobiologic basis of therapy

The pathophysiology of IPAH is not fully elucidated An elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to vascular wall remodeling.

Three major pathobiologic pathways (nitric oxide, endothelin, and prostacyclin) play important roles in the development and progression of PAH.

5.1. Nitric Oxide (N.O)

The endothelium-derived relaxing factor nitric oxide (NO), a potent pulmonary vasodilator, is produced in high levels in the upper and lower airways by nitric oxide synthase II (NOSII)

and affects the pulmonary vascular tone in concert with the low NO levels that are produced by nitric oxide synthase III (NOSIII) in the vascular endothelium. NO causes smooth muscle relaxation and proliferation, maintaining the normal pulmonary vascular tone. Patients with IPAH have low levels of NO in their exhaled breath, and the severity of the disease inversely correlates with NO reaction products in bronchoalveolar lavage fluid. [18], [19]

5.2. Endothelin-1

Endothelin-1 is a peptide produced by the vascular endothelium that has potent vasoconstrictive and proliferative paracrine actions on the vascular smooth muscle cells. The pulmonary circulation plays an important role in the production and clearance of endothelin-1, and this physiologic balance is reflected in the circulating levels of endothelin-1. Patients with pulmonary hypertension, IPAH in particular, have an increased expression of endothelin-1 in pulmonary vascular endothelial cells, and serum endothelin-1 levels are increased in patients with pulmonary hypertension.[20], [21]

5.3. Prostacyclin

The endothelium also produces prostacyclin (PGI2) by cyclooxygenase metabolism of arachidonic acid. Prostacyclin causes vasodilation throughout the human circulation and is an inhibitor of platelet aggregation by its action on platelet adenylate cyclase. The final enzyme in the production of PGI2 is prostacyclin synthase. The remodeled pulmonary vasculature in lung tissue obtained from patients with severe IPAH expresses lower levels of prostacyclin synthase when compared with normal lung tissue. [22]

5.4. Remodeling

In IPAH, pulmonary vascular smooth muscle cells that normally have a low rate of multiplication undergo proliferation and hypertrophy. Those smooth cell changes arise from the loss of the antimitogenic endothelial substances (e.g., PGI2 and NO) and an increase in mitogenic substances (e.g., endothelin-1). Other stimuli arise from locally activated platelets, which release thromboxane A2 and serotonin; thromboxane A2 and serotonin act as growth-promoting substances on the vascular smooth muscle cells. Both are vasoconstrictors and serotonin also promotes smooth muscle cell hypertrophy and hyperplasia. In addition to the smooth muscle cell proliferation, abnormalities in extracellular matrix contribute to the medial hypertrophy in PAH.[3] These lead to intimal narrowing and increased resistance to blood flow.

An abnormal proliferation of endothelial cells occurs in the irreversible plexogenic lesion. The plexiform lesions in IPAH have been considered an abnormal growth of modified smooth muscle cells. These lesions are glomeruloid structures forming channels in branches of the pulmonary artery. These may result from a deregulated growth of endothelial cells. [23]

Because the plexiform lesions bear some resemblance to the neovascularization induced by malignant gliomas at both the morphological and immunohistochemical level, one might hypothesize that the plexogenic vessels also represent a unique form of active angiogenesis.

Vascular endothelial cell factor (VEGF) promotes endothelial cell proliferation and is identical to the tumor factor responsible for inducing increased vascular permeability. Lung and brain express high levels of VEGF messenger RNA, and hypoxia triggers the production of VEGF. Furthermore, the presence of inflammatory cells in the perimeter of structurally altered vessels suggests that inflammatory cell-derived cytokines and growth factors may participate in the pathogenesis of PPH. Based on these results PPH may also represent a disorder of endothelial cell differentiation and growth. [23]

5.5. Thrombosis

Blood thrombin activity is increased in patients with pulmonary hypertension, indicating activation of intravascular coagulation, whereas soluble thrombomodulin, a cell membrane protein that acts as an important site of thrombin binding and coagulation inactivation, is decreased. In addition, PGI2 and NO, both inhibitors of platelet aggregation, are decreased at the level of the injured endothelial cell. Circulating platelets in patients with PAH seem to be in a continuous state of activation and contribute to the prothrombotic milieu by aggregating at the level of the injured endothelial cells.[3]

5.6. Other Factors contributing to PAH

• Vasoactive intestinal peptide (VIP) (systemic vasodilator, decreases pulmonary artery pressure and pulmonary vascular resistance, inhibits platelet activation and vascular smooth muscle cell proliferation)

• Vascular endothelial growth factor (VEGF) & receptors (participate in angiogenesis, appears to be disordered in PAH)
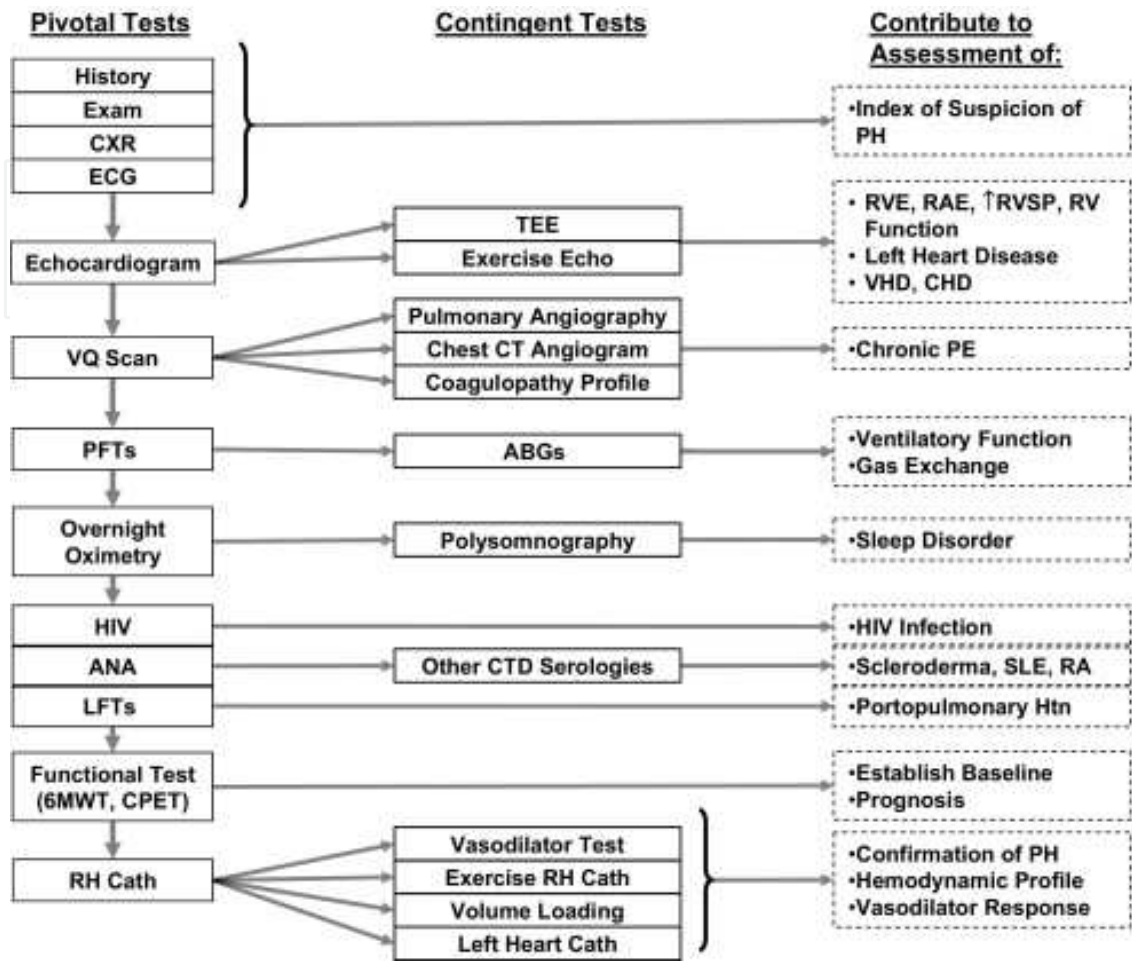
6. Signs and symptoms

Early symptoms are nonspecific. The most common symptoms include dyspnea, weakness and recurrent syncope. Other symptoms include fatigue, angina, and abdominal distention. Symptoms at rest are reported only in very advanced cases.[1], [24]

The physical signs of pulmonary hypertension include left parasternal lift, loud pulmonary component of the second heart sound (P_2), pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, and right ventricular S_3. Jugular vein distention, hepatomegaly, peripheral edema, ascites, central cyanosis and cool extremities may be seen in patients with advanced disease. [25] The lung examination is usually normal.

7. Investigations

Diagnostic approach is summarized in Figure 1.[25]

Figure 1. Diagnostic Approach to Pulmonary hypertension. 6 MWD indicates 6-minute walk test; ABGs, arterial blood gases; ANA, antinuclear antibody serology; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CT, computerized tomography; CTD, connective tissue disease; CXR, chest X-ray; ECG, electrocardiogram; HIV, human immunodeficiency virus screening; Htn, hypertension; LFT, liver function test; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; RAE, right atrial enlargement; RH Cath, right heart catheterization; RVE, right ventricular enlargement; RVSP, right ventricular systolic pressure; SLE, systemic lupus erythematosus; TEE, transesophageal echocardiography; VHD, valvular heart disease; and VQ Scan, ventilation-perfusion scintigram.

7.1. Electrocardiography

ECG results are often abnormal in patients with PAH, revealing right atrial enlargement, right axis deviation, right ventricular hypertrophy, or large P wave and characteristic ST depression and T-wave inversions in the anterior leads. [26] However, a normal ECG does not exclude a diagnosis of PAH.

7.2. Chest radiography

Radiographic signs of pulmonary hypertension include cardiomegaly or prominent central pulmonary arteries. [26]

7.3. Computed tomography and lung scanning

High-resolution chest CT scanning and ventilation-perfusion (V/Q) lung scanning are frequently obtained to help exclude interstitial lung disease and thromboembolic disease.

Radiographically, PH is said to be more likely when the main pulmonary artery diameter (MPAD) is > 29 mm (sensitivity 69%, specificity 100%) [27], [28] and/or the ratio of the main pulmonary artery to ascending aorta diameter is >1 [29]. The most specific CT findings for the presence of PH were both a MPAD > 29 mm and segmental artery-to-bronchus ratio of >1:1 in three or four lobes (specificity 100%) [30]. An additional feature of PH is rapid tapering or "pruning" of the distal pulmonary vessels.

7.4. Echocardiography

Echocardiography is extremely useful for assessing right and left ventricular function, estimating pulmonary systolic arterial pressure, and evaluating for congenital anomalies and valvular disease. [1],[24],[31], [32]

Systolic pulmonary artery pressure is estimated using tricuspid insufficiency jet velocity based on the simplified Bernoulli's equation:

$$[4 \times (TRV)^2 + RA\ pressure]$$

Normal velocity is 2.0 – 2.5 m/s and a higher velocity indicates pulmonary hypertension, especially if there is associated dilation or dysfunction of the right ventricle.

7.5. Right heart catheterization

Right heart catheterization measures right atrial pressure, mean pulmonary artery pressure (mean PAP), pulmonary artery occlusion pressure (PAOP), cardiac output (CO) by thermo-dilution / indirect Fick and mixed venous oxygen saturation. Right heart catheterization provides data to calculate the pulmonary vascular resistance (mPAP-PAOP)/CO and trans-pulmonary gradient (mPAP-PAOP). In addition right heart catheterization evaluates pulmonary vasoreactivity and helps in the diagnosis of left-to-right intracardiac shunts (e.g. ASD, VSD and PDA).

The normal resting mean PAP is 14 ± 3 mm Hg. The normal PAOP is from 6-12 mmHg. The normal pulmonary vascular resistance is 0.3-1.6 Wood Units. Transpulmonary gradient is normally ≤ 12 mmHg. Pulmonary hypertension (PH) is present when mean pulmonary artery pressure (PAP) is greater than 25 mm Hg. The severity of PH is further classified on the basis of mean pulmonary artery pressure as mild (25 to 40 mm Hg), moderate (41 to 55 mm Hg), or severe (> 55 mm Hg) [33] or mild to moderate when PVR is between 2.5 and 4.9 Wood units; and severe when PVR > or =5.0 Wood units. [34]

7.6. Exercise testing

This is very helpful to assess the efficacy of therapy. Severe exercise-induced hypoxemia should cause consideration of a right-to-left shunt. Cardiopulmonary exercise assessment with a widely available 6-minute walk test is commonly used to assess and track functional capacity. [1],[10], [24],[35],[36] However, it lacks specificity in that it cannot be used to discern between several causes of an impaired ability to walk.[10]

Additional Workup: includes:

- Pulmonary function testing with diffusing capacity (DLCO): Elevated pulmonary artery pressure causes restrictive physiology. In patients with PAH, the diffusing lung capacity for carbon monoxide (DLCO) is reduced to approximately 60% to 80% of that predicted.

- Overnight oximetry or polysomnography is useful in detecting obstructive sleep apnea

- Ventilation/perfusion (VQ) scanning Patients with PAH may reveal a relatively normal perfusion pattern or diffuse, patchy perfusion abnormalities

- Pulmonary angiography performed to further evaluate or better define the anatomy in the setting of chronic thromboembolic disease

- Rheumatologic serologies to look for auto-immune diseases.

- Thyroid function testing: There is an increased incidence of thyroid disease in patients with PAH, which can mimic the symptoms of right ventricular failure. Consequently, it is advised that thyroid function tests be monitored serially in all patients.

- B-Type Natriuretic Peptide (BNP): Brain natriuretic peptide (BNP) levels are elevated in patients with pulmonary hypertension and correlate with the pulmonary artery pressure.

- Anti-HIV

- If chronic arterial oxygen desaturation exists, polycythemia should be present. Hyper-coagulable states, abnormal platelet function, defects in fibrinolysis, and other abnormalities of coagulation are found in some patients with PAH.

8. Treatment

Despite advances in various treatments, there is no cure for pulmonary hypertension. The goals of treatment for pulmonary hypertension are to treat the underlying cause, to reduce symptoms and improve quality of life, to slow the growth of the smooth muscle cells and the development of blood clots; and to increase the supply of blood and oxygen to the heart, while reducing its workload.

An algorithm for treatment is shown in Figure 2. [37]
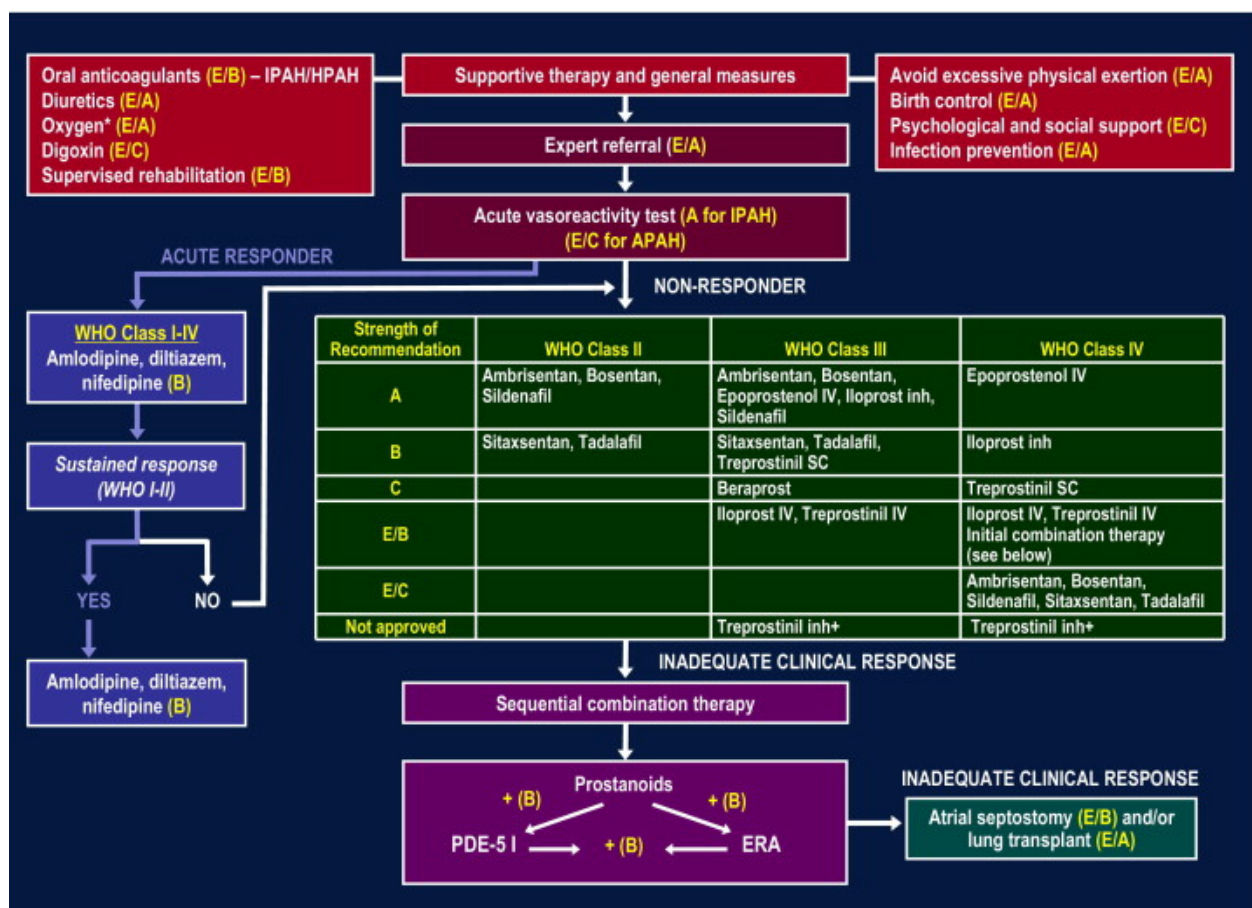
Adapted with permission from ELSEVIER (ref 33)
Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol. 2009 Jun 30;54(1 Suppl):S78-84.

Figure 2. Evidence-Based Treatment Algorithm. (Drugs within the same grade of evidence are listed in alphabetical order and not order of preference). APAH = associated pulmonary arterial hypertension; ERA = endothelin receptor antagonist; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; SC = subcutaneous; WHO = World Health Organization.

8.1. Medical treatment

8.1.1. General measures

- Oral anticoagulation improves survival in IPAH and is recommended in all these patients unless there is a contraindication. [26]

- Supplemental oxygen should be used to maintain oxygen saturation greater than 90%, especially because hypoxemia is a major cause of pulmonary vasoconstriction. Consider supplemental oxygen for PAH patients who are planning air travel, as mild hypobaric hypoxia can start at altitudes between 1500 and 2000 m, and commercial airliners are pressurized to the equivalent of an altitude between 1600 and 2500 m.[31]. Results suggest

travelers with PH, who will be traveling on long flights or those with a history of oxygen use, should be considered for supplemental in-flight oxygen.[32]. A flight simulation test before the flight can help determine oxygen needs at altitude.[24],[35]

- Diuretics are indicated for right ventricular volume overload

- Digoxin is reserved for patients with refractory right ventricular failure and for rate control in atrial flutter or fibrillation. [24],[35],[37]

- No specific diet is recommended; however, a low-sodium and low-fluid diet is recommended in patients with significant volume overload due to right ventricular failure.

- Exercise training is well tolerated and improves quality of life, WHO functional class, peak oxygen consumption, oxygen consumption at the anaerobic threshold, and achieved workload.[38] Patients with pulmonary hypertension and heart failure should perform mild symptom-limited aerobic activity and avoid complete bed rest. Isometric exercises (weight lifting) are contraindicated.

- Vaccination against influenza and pneumococcal pneumonia and avoidance of pregnancy.

9. Pulmonary vascular reactivity testing and vasodilator therapy

Diagnostic catheterization followed by pharmacological testing of vasodilator therapy response is required to test the pulmonary vasoreactivity in patients with IPAH before prescribing a vasodilator. The most commonly used drugs are: iv prostacyclin, iv adenosine, inhaled nitric oxide and inhaled iloprost. Oxygen, nitroprusside, and hydralazine should not be used as pulmonary vasodilator testing agents. A complete right heart catheterization and an invasive monitoring of the systemic pressures are mandatory. The increased pulmonary vascular resistance results from extensive vascular changes and vasoconstriction. Therefore, in pulmonary hypertension true pulmonary vasodilation is only present if, in addition to a decreased pulmonary vascular resistance, reductions in the transpulmonary gradient and the mean pulmonary artery pressure are achieved.

A positive test or 'responder to vasodilator' is defined as a drop in mPAP of ≥ 10 mmHg to an absolute level < 40 mmHg. A positive test is observed in 10-15% of patients with IPAH. However half of these patients will have a long-term response to calcium channel blockers (CCB). [39]

Only patients with an acute vasodilator response to an intravenous or inhaled pulmonary vasodilator challenge (eg, with adenosine, epoprostenol, nitric oxide) derive any long-term benefit from CCBs. Such patients constitute less than 15% of patients with IPAH and probably less than 3% of patients with other forms of PAH. [24], [35], [39]

Patients who do not have an acute vasodilator response to a vasodilator challenge have a worse prognosis on long-term oral vasodilator therapy compared with those who have an initial response. These non-responders are those who have no significant change of the mean

pulmonary vascular pressure or symptomatic systemic hypotension and no change or a reduction of cardiac index (by more than 10 %), possibly accompanied by an increase in right atrial pressure (by more than 20 – 25 %). However, the absence of an acute response to intravenous or inhaled vasodilators does not preclude the use of intravenous vasodilator therapy. In fact, continuous intravenous vasodilator therapy is strongly suggested for these patients because CCBs are contraindicated. [40]

10. Calcium Channel Blocker therapy (CCB)

These drugs are thought to act on the vascular smooth muscle to dilate the pulmonary resistance vessels and lower the pulmonary artery pressure. The use of CCBs should be limited to patients without overt evidence of right-sided heart failure. In patients with IPAH (or any other form of PAH), a cardiac index of less than 2 L/min/m^2 or a right atrial pressure above 15 mm Hg is a contraindication to CCB therapy, as these agents may worsen right ventricular failure in such cases.

10.1. Specific vasodilator therapy

These drugs in general work by dilating the pulmonary arteries and, therefore, by reducing the pressure in these blood vessels and some help prevent the excessive overgrowth of tissue in the blood vessels (that decrease remodeling of the vessels). Common side effects include cough, flushing, and headache. Inhaled therapies may be useful as an adjunct to oral therapy.

There are three major classes of drugs used to treat pulmonary arterial hypertension:

10.2. Prostacyclins

Prostacyclin dilates systemic and pulmonary arterial vascular beds. These short acting drugs include epoprostenol [41] (Flolan), treprostinil (Remodulin), iloprost [42] (Ventavis), Treprostinil (Tyvaso). Parenteral vasodilators are used for patients whose IPAH fails to respond to calcium channel blockers or who cannot tolerate these agents and who have New York Heart Association (NYHA) type III or IV right-sided heart failure.

Long-term treatment with intravenous PGI2 improves exercise capacity, hemodynamics, and survival in most patients with PPH in NYHA functional class III or IV. Despite these favorable outcomes, continuous intravenous infusion of PGI2 is not ideal due to its cost and side effects such as flushing, headache, jaw pain, diarrhea and incidence of catheter-related infections. Survival of patients with PPH treated with epoprostenol depends on the severity at baseline, as well as the three-month response to therapy. Lung transplantation should be considered in a subset of patients who remain in NYHA functional class III or IV or in those who cannot achieve a significant hemodynamic improvement after three months of epoprostenol therapy, or both. [40]

10.3. Phosphodiesterase type 5 Inhibitors (PDE5i)

PDE5 inhibitors such as sildenafil [43] (Revatio, Viagra) is an orally active pulmonary vaso-dilators. (The dosing is much different when these drugs are used for erectile dysfunction). These drugs promote selective smooth muscle relaxation in lung vasculature by inhibiting PDE5 thereby stabilizing cyclic guanosine monophosphate (cGMP, the second messenger of nitric oxide), allowing a more sustained effect of endogenous nitric oxide, an indirect but effective and practical way of using the NO-cGMP pathway. Sildenafil improves exercise capacity, World Health Organization (WHO) functional class, and hemodynamics in patients with symptomatic pulmonary arterial hypertension. The main side effects of Sildenafil include headache, flushing, dyspepsia, nasal congestion, and epistasis Nitrates should be avoided in patients taking PDE5 inhibitors because the additive effects of the drugs may cause severe systemic hypotension. [44]

10.4. Endothelin Receptor Antagonists (ERAs)

Endothelin-1 is a 21–amino acid peptide that plays a key role in the pathobiology of PAH,[45], [46] exerting vasoconstrictor and mitogenic effects by binding to 2 distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin A and B receptors.[47] Endothelin B receptors also are present in endothelial cells, and their activation leads to release of vasodilators and antiproliferative substances such as nitric oxide and prostacyclin that may counterbalance the deleterious effects of endothelin-1.[47]

Bosentan is effective in patients with FC III / IV [48] but more recently bosentan was demon-strated to increase the 6 MWD from baseline in FC II patients as well [49]. Sitaxentan, a selective endothelin (ET)-A receptor antagonist, has negligible inhibition of the beneficial effects of ET_B stimulation, such as nitric oxide production and clearance of ET from circulation. In clinical trials, the efficacy of sitaxentan has been much the same as bosentan with reduced hepatotox-icity. [50] Dosing is once daily, as opposed to twice daily for bosentan.

Ambrisentan is a nonsulfonamide, propanoic acid– based, A-selective endothelin receptor antagonist with a bioavailability and half-life that allow once-daily dosing. In the ARIES study [51], Ambrisentan showed improvements in 6-minute walk distance in patients with WHO functional class II and III symptoms. It is well tolerated and is associated with a low risk of aminotransferase abnormalities. The most frequent side effects of ambrisentan are fluid retention (ranging from swelling of the extremities to heart failure), nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain and constipation.

ACCP guidelines recommend using the patient's New York Heart Association (NYHA) functional class to guide the choice of vasodilator therapy.[52] Grade A recommendations for vasodilator therapy by functional class from the ACCP are as follows:

- Functional class II - Sildenafil

- Functional class III - Endothelin-receptor antagonists (bosentan), sildenafil, IV epoprostenol, or inhaled iloprost

- Functional class IV - Intravenous epoprostenol.

10.5. Combination therapy

Patients with PAH may experience clinical and hemodynamic deterioration despite treatment with a single agent. This circumstance requires the addition on a second agent to slow disease progression and aid in clinical improvement.[35],[37] Different combinations have been tried, however current guidelines do not favor a particular combination over others. Several studies are on-going to compare the efficacy of single agent versus combination therapy. Failure of combination therapy requires consideration for parenteral therapy and surgical intervention such as lung transplantation.

10.6. Surgery

10.6.1. Atrial septostomy

Atrial septostomy is a palliative procedure that may afford some benefit to patients whose condition is deteriorating in the setting of severe disease with recurrent syncope or right heart failure (or both) despite maximal medical therapy. The procedure can also be used as a bridge to lung transplantation. The rationale for its use is that the controlled creation of an atrial septal defect would allow right-to-left shunting, leading to increased systemic output and systemic oxygen transport despite the accompanying fall in systemic arterial oxygen saturation. The shunt at the atrial level would also allow decompression of the right atrium and right ventricle, alleviating signs and symptoms of right heart failure. Balloon atrial septostomy is a high-risk procedure and should be performed only in experienced centers to reduce the procedural risks. [35],[37]

10.6.2. Lung transplantation

Lung transplantation has been used in treatment for pulmonary hypertension since the 1980s, even before current medical therapies were available. It is indicated in PAH patients with advanced disease that is refractory to available medical therapy. A single- or double-lung transplant is indicated for patients who do not respond to medical therapy. Simultaneous cardiac transplantation may not be necessary even with severe right ventricular dysfunction; however, this depends on the transplant institution. The 3- and 5- year survival rates after lung and heart-lung transplantation are approximately 55% and 45%, respectively. [35],[37]

10.6.3. Pulmonary thromboendarterectomy

Pulmonary thromboendarterectomy provides a potential surgical cure and should be considered in all patients with chronic thromboembolic PAH (CTEPH) affecting central pulmonary arteries. Pulmonary angiography is required to confirm surgical accessibility of chronic thromboemboli. The procedure requires cardiopulmonary bypass and involves dissecting well-organized thromboembolic material as well as part of the intimal layer of the pulmonary arterial bed. Patients with suspected CTEPH should be referred to centers experienced in the procedure for consideration of this procedure. In patients with operable CTEPH, pulmonary

thromboendarterectomy is the treatment of choice because it improves hemodynamics, functional status, and survival. [35],[37]

11. Considerations for special populations

11.1. Surgery

Elective surgery involves an increased risk in patients with PAH. The increased risk is proportionate to the severity of the disease. It is not clear which type of anesthesia is advisable, but probably local and regional anesthesia are better tolerated than general anesthesia. Surgery preferably is performed at referral centers with experienced anesthesia and pulmonary hypertension teams that can deal with potential complications.[36],[53] Anticoagulant treatment should be interrupted for as short a period as possible. In patients with CTEPH, bridging with heparin is recommended to minimize the time off anticoagulation.

11.2. Pregnancy

Although successful pregnancies have been reported in PAH patients, pregnancy and delivery in PAH patients are associated with an increased mortality rate of 30% to 50%, and pregnancy should be avoided or terminated. An appropriate method of birth control is highly recom‐ mended in all women with pulmonary hypertension who have childbearing potential. Unfortunately, there is no current consensus on the most appropriate birth control method in PAH patients. Because of the increased risk of thrombosis with estrogen-based contraception, some experts suggest the use of estrogen-free products, surgical sterilization, or barrier methods.[24], [35]

12. Natural history and prognosis

PAH has no cure. However, the rate of progression is highly variable and depends upon the type and severity of the PAH. Untreated PAH leads to right-sided heart failure and death.

Prior to the 1990s, therapeutic options were limited. The emergence of prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and other novel drug therapies has greatly improved the outlook for patients with PAH.

For untreated IPAH, the estimated 3-year survival rate is approximately 41%. In one study of long-term continuous intravenous prostacyclin therapy, 3-year survival increased to approx‐ imately 63%. [54] With newer therapies, perhaps in combination, these figures are expected to improve further.

Less symptomatic patients in WHO class II/III, with normal right atrial and ventriclar size and pressure and can walk more than 400 meters on 6 minute walk distance (MWD) are considered lower risk group of patients for morbidity and mortality. While symptomatic patients in WHO

class IV with signs of right heart failure, enlarged right atria and ventricle with right ventricular dysfunction and cannot walk more than 300 meters on 6 MWD testing are considered high risk group of pattients with pulmonary hypertension. [25], [55]

The one-year survival of patients with newly diagnosed group 1 PAH can be predicted using a risk score derived from the Registry to Evaluate Early and Long-term PAH Disease Management (i.e. the REVEAL registry). This risk score was validated by a prospective cohort study of 504 patients with a mean 6-minute walk testing (6 MWD) of 308 m and 61.5 percent classified as WHO functional class III, which found that a risk score of 1 to 7, 8, 9, 10 to 11, and ≥ 12 correlated with one-year survival of 95, 92, 89, 72, and 66 percent, respectively. [56]

Severity of PAH – Patients with severe PAH or right heart failure (i.e., cor pulmonale) die sooner without treatment (usually within one year) than patients with mild PAH or no right heart failure. As an example, patients with IPAH and a mean right atrial pressure ≥ 20 mmHg have a median survival of approximately one month.[10]

In conclusion, age, PAH etiology, World Health Organization functional class, pericardial effusion, 6MWT distance, the need for oxygen during the 6MWT, and brain natriuretic peptide are predictors of prognosis in patients PAH receiving specific therapy and might help identify a group that could benefit from aggressive upfront therapy. [57]

Since survival in patients who fall into NYHA classes III or IV is poor (9-18 months), patients with severe symptoms and evidence of impaired cardiac function, which is refractory to conventional therapy or epoprostenol infusion should be considered for lung transplantation.

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