Pulmonary Hypertension
Redefining Rare....

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History of Classification¹

1973

2nd world symposium - 1998

3rd world symposium - 2003

4th world symposium - 2008

5th world symposium - 2013
## WHO Classification of PH

<table>
<thead>
<tr>
<th>Group 1: Pulmonary Arterial Hypertension</th>
<th>Idiopathic, Familial, Associated (CTD, congenital, portal HTN, HIV, drugs/toxins, other, PVOD, PCH)</th>
</tr>
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<tbody>
<tr>
<td>Group 2: Pulmonary Hypertension associated with Left Heart Disease</td>
<td>Left sided atrial or ventricular disease, Left sided valvular disease</td>
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<tr>
<td>Group 3: Pulmonary Hypertension associated with Lung Disease or Hypoxemia</td>
<td>COPD, ILD, sleep disordered breathing, alveolar hypoventilation syndromes, chronic high altitude, developmental abnormalities</td>
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<tr>
<td>Group 4: Pulmonary Hypertension due to chronic thrombotic and/or embolic disease (CTEPH)</td>
<td>Thromboembolic obstruction of proximal or distal pulmonary arteries, nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
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<tr>
<td>Group 5: Miscellaneous</td>
<td>Sarcoidosis, histocytosis, LAM, compression of pulmonary vessels.</td>
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</table>
Group 1: Pulmonary Arterial Hypertension (PAH)

1.1 Idiopathic

1.2 Heritable

1.3 Drugs and Toxins induced

1.4 Associated with (APAH):
   ◦ 1.4.1 Connective Tissue Disease
   ◦ 1.4.2 Infection with Human Immunodeficiency virus
   ◦ 1.4.3 Portal Hypertension
   ◦ 1.4.4 Congenital Heart Disease
   ◦ 1.4.5 Schistosomiasis
   ◦ 1.4.6 Chronic haemolytic anaemia

1.5 Persistent Pulmonary HTN of the newborn
Definition of PAH¹

Right Heart Catheterization (RHC) showing precapillary pulmonary hypertension with a mean pulmonary artery pressure (mPAP) of >25mmHg and a normal pulmonary artery wedge pressure (PCWP) of <15mmHg

Significant changes have occurred since first classification in 1973 (only 2 categories: Primary/Secondary)
Group 2: Pulmonary HTN due to Left Heart Disease¹

- One of the most common cases of PH
- PVR is normal or near normal (<3.0 Wood units) and there is no gradient between mean PAP and pulmonary wedge pressure (transpulmonary gradient < 12mmHg)
Group 3: Pulmonary HTN due to lung disease and/or hypoxia\(^1\)

3.1 Chronic Obstructive Pulmonary Disease

3.2 Interstitial Lung Disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   ◦ Chronic bronchiectasis
   ◦ Cystic fibrosis
   ◦ Combined pulmonary fibrosis and emphysema

3.4 Sleep Disordered Breathing

3.5 Alveolar Hypoventilation Disorders

3.6 Chronic exposure to high altitude

3.7 Developmental abnormalities
Group 3: Pulmonary HTN due to lung disease and/or hypoxia

Predominant cause of PH is alveolar hypoxia as a result of either chronic lung disease, impaired control of breathing or residence of high altitude

Prevalence is unknown

In PAH associated with parenchymal lung disease, the increase of pulmonary arterial pressure is usually modest (mean PAP >35mmHg)

The pts w more severe PH were characterized by mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide

11 patients out of 998 had COPD as the only possible etiology of their PH

Genetic predisposition to PH in patients with COPD
Group 4: Chronic Thromboembolic pulmonary HTN (CTEPH)

1

Occurs in 4% of pts after an acute pulmonary embolism

Classified as Proximal CTEPH or Distal CTEPH

- No definition describing either
- Depending on the feasibility of performing pulmonary thromboendarterectomy
- Decision of surgery is facility dependent and should be sent to “expert centers”
- Indication for surgery depends on:
  - the location of the obstruction
  - Correlation between hemodynamics and the degree of obstruction assessed by angiography
  - Comorbidities
  - Willingness of the patient
  - Experience of the surgeon
- Patients who are not candidates for surgery may benefit from PAH-specific medical therapy
Group 5: PH with unclear an/or multifactorial mechanisms

5.1 Haematological disorders, splenectomy

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

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

5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
Epidemiology

Parameters associated with improved survival:
- Gender: women
- Preserved 6MWD
- Normal Cardiac Output

Data from the REVEAL registry
- 1-year survival rate = 91%

Variables associated with increased mortality:
- Pulmonary vascular resistance >32 Wood units
- NYHA functional Class IV
- Men older than 60yo
- Family History of PAH

National Registry 1980’s (187 pts w idiopathic PAH) had a median survival of 2.8 years (poor prognosis)

Recent prospective data (improved survival rates)
- 1 year survival (85.7%), 2 year survival (69.6%), 3 year survival (54.5%)
Pathophysiology

Disease which affects small pulmonary arteries

Characterized by vascular obstruction leading to progressive increase in vascular resistance
  ◦ This increases right ventricular afterload $\rightarrow$ right ventricular failure

Intima and media proliferation and its consequent pulmonary vascular obstruction are considered to be the key element in the pathogenesis of PAH

Vasoconstriction, vascular remodeling and thrombosis are factors that increase pulmonary vascular resistance
Pathophysiology

Pulmonary vasoconstriction → associated w abnormal dysfunction of potassium channels & endothelial dysfunction

- Results in decreased prod of vasodilators like nitric oxide (NO) and prostacyclin and increase production of vasoconstrictors like endothelin-1

Hypoxia inhibits one or several voltage dependent potassium channels of the pulmonary arterial smooth muscles cells → membrane depolarization and opening of voltage dependent calcium channels → increase in intracellular calcium concentration and cellular contraction

- Dichloroacetate and sildenafil increase the function of potassium channels
Clinical Signs of PH

Presentation related to right heart failure signs & symptoms
- Venous jugular distension, hepato-jugular reflux, hepatomegaly, hepatalgia, LE edema, ascites

Dyspnea on exertion is the most frequent symptom
- Present even with mild hemodynamic abnormalities

70% of pts are diagnosed when in NYHA class III to IV
- May have chest pain, lightheadedness, syncope with physical efforts

May have fatigue and weakness

Hemoptysis could be life threatening → embolization of dilated bronchial arteries

Hoarseness of voice may be due to compression of the left laryngeal nerve due to dilated pulmonary artery (Ortners Syndrome)

Auscultation – prominent S2 (systolic murmurs of tricuspid regurg), pulmonary auscultation usually normal

Raynauds syndrome common especially in PAH with CTD
Tests
Diagnostic

Trans-thoracic echocardiogram*
Right Heart Catheterization**
Chest Radiograph
Electrocardiogram (ECG) – low sensitivity
PFTS
ABGs
Exercise Testing
Ventilation/Perfusion Lung Scan
High resolution computed tomography (HRCT) of the chest
Pulmonary angiography
TTE

Estimates pulmonary artery systolic pressure (sPAP)

Estimated PAP is based on peak velocity of the jet tricuspid regurgitation
  ◦ PA systolic Pressure = tricuspid regurgitation + estimated R atrial pressure

Additional Information
  ◦ Recognize left heart valvular disease
  ◦ Myocardial disease
  ◦ Congenital heart disease with systemic to pulmonary shunts
  ◦ Identify foramen ovale or atrial septal defects
Right Heart Catheterization

Confirms the definite diagnosis of PH
- Resting mPAP of >25mmHG and Normal PCWP

No definition of PH on exercise was currently adopted

PCWP
- Allow distinction between precapillary (normal PCWP <15mmHg) and postcapillary PH (PCWP>15 mmHg)

Measurements obtained:
- PAP (diastolic, mean, systolic)
- Right atrial pressure (rap)
- PCWP
- Right ventricular pressure
- Cardiac Output

Elevated mean R atrial pressure, reduced CO, mixed venous oxygen saturation (svo2) are related to the prognosis of PAH
Chest Radiography

Abnormal in 90% of idiopathic PAH pts at time of diagnosis

Findings Include:
- Central pulmonary arterial dilatation
- Right atrial and ventricular enlargement
- May help to identify moderate to severe lung disease or pulmonary venous hypertension due to L heart abnormalities
Pulmonary Function Test & ABGs

PFT will help assess underlying lung abnormalities

Normal Forced expiration volume in 1 sec (FEV1) and total lung capacity (TLC) in idiopathic PAH

Abnormal DLCO has been reported in PAH
  ◦ More pronounced in PVOD pts

ABGs usually show mild hypoxemia and hypocapnia
  ◦ Severe hypoxemia may be a parameter of underlying PVOD or chronic lung disease
Prognosis
Assessing Disease Severity/Prognosis

NYHA functional class
Signs of right heart failure
6-MWD
Peak VO2
Echocardiograph parameters
Hyperuricemia?
Brain Natriuretic Peptide (BNP)
Troponin
REVEAL Registry Risk Score

All can predict prognosis in idiopathic PAH when assessed at baseline
NYHA Classification of Pulmonary HTN

Class I
- Patients with pulmonary HTN but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain or near syncope.

Class II
- Patients with pulmonary HTN resulting in slight limitation in physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III
- Patients with pulmonary HTN resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class IV
- Patients with pulmonary HTN with inability to carry out physical activity without symptoms. These pts manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest. Discomfort is increased by physical activity.
WHO Classification of PH

Class 1
- Has no limits. You can do regular physical activities, such as walking or climbing stairs. These activities don’t cause PH symptoms, such as tiredness, shortness of breath, or chest pain.

Class 2
- Has slight or mild limits. You're comfortable while resting, but regular physical activity causes PH symptoms.

Class 3
- Has marked or noticeable limits. You're comfortable while resting. However, walking even one or two blocks or climbing one flight of stairs can cause PH symptoms.

Class 4
- Has severe limits. You're not able to do any physical activity without discomfort. You also may have PH symptoms while at rest.
Prognosis

Patient with PVOD or PAH associated with CTD have a worse prognosis than pts with idiopathic PAH

Pts with PAH associated congenital systemic to pulmonary shunts have a more slowly progressed coughse than idiopathic PAH pts

A score has been proposed (REVEAL Registry Risk Score) to evaluate the severity of newly diagnosed PAH pts

- Based on subgroups of PAH, renal insufficiency, age>60yo, NYHA FC, systolic BP, HR, 6-MWD, BNP, pericardial effusion, DLCO, RAP, PVR
REVEAL Registry Risk factor

Multi-centered: 55 centers contributed

Diagnosis of PAH by right heart catheterization (RHC)

Requirements:
- mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise
- mean pulmonary capillary wedge pressure (Ppcw) or left ventricular end-diastolic pressure of 18 mmHg at rest
- pulmonary vascular resistance (PVR) 3 Wood units.
- Age > 3 months at time of diagnosis

Goal:
- Characterize the demographics and clinical course WHO group I: PAH
- Evaluate differences in patient outcomes according to WHO group I classification subgroups
- Identify clinical predictors of short-term and long-term outcome
Management of PAH

Pharmacologic Management
  ◦ Nonspecific v. Specific

Physical Activity/Exercise
Avoid Altitude and hypoxia
Avoid Pregnancy, need contraception
Avoid Anesthesia and surgery
Sodium Restriction Diet
Immunizations
Pharmacologic Agents
Non-Specific Agents for PAH

Anticoagulants
Diuretics
Supplemental Oxygen
Digoxin
Calcium Channel Blockers
Anticoagulation⁴

Oral Anticoagulation

Several agents are commonly used
- However, relatively little controlled trial data

Warfarin with IPAH with goal INR: 1.5 – 2.5
Warfarin with CTEPH with goal INR: 2-3
Diuretics$^{4,5}$

Indication:
- Management of right ventricle volume overload
- RV overload:
  - Elevated jugular vein distension
  - Lower extremity edema
  - Abdominal distension
  - In some cases IV diuretics are required

Physical Therapy Considerations:
- Monitoring of serum electrolytes, renal function panels (lab values)
- Can cause volume depletion; monitor for orthostatic hypotension
- Monitor for signs/symptoms of gout
Supplemental Oxygen$^{4,5}$

Indication:
- Decrease hypoxemia
  - Hypoxemia is a potent pulmonary vasoconstrictor
  - Most experts recommend oxygen saturation >90%

Physical Therapy Considerations:
- Oxygen is a drug and requires a physician's prescription
  - Know the goal for rest and exercise
  - Know your facilities protocol/standard for titration of supplemental oxygen
- Understand limitations of devices uses
Digoxin\textsuperscript{4,5}

Indication:
- Positive iontortope
- Acutely increase cardiac output in patients with right heart failure and in patients with atrial arrhythmias
- Data on effectiveness is limited

Physical Therapy Considerations:
- Monitor for signs/symptoms of digitalis toxicity
  - CNS: drowsiness, fatigue, confusion, visual disturbance
  - Cardiac: premature atrial and/or ventricular contractions, PSVT, VT, high degrees AV block, VF
  - GI: nausea, vomiting, diarrhea
Calcium Channel Blockers\textsuperscript{4,5}

Indication:
\begin{itemize}
  \item Patients with IPAH who exhibit an acute vasodilatory response to iNO, IV epoprostenol, or IV adenosine
  \item Also can be used with responders with associated forms of PAH
\end{itemize}

Most commonly used agents:
\begin{itemize}
  \item Long acting nifedipine, diltiazem or amlodipine
\end{itemize}

Physical Therapy Considerations:
\begin{itemize}
  \item Monitor for bradycardia, hypotension, AV block, CHF, peripheral edema, flushing, palpation and headache
    \begin{itemize}
      \item Non-DHP: Decrease HR and prevent HR increase response to exercise (diltizam)
      \item DHP: increased effects in the peripheral vasculature vs. non-DHP have more central cardiac effects
    \end{itemize}
\end{itemize}
Specific Agents for PAH

Prostanoids
Endothelin Receptor Antagonist
Phosphodiesterase type 5 inhibitors
Tyrosine kinase inhibitors
Soluable guanylate cyclase activators
  ◦ Riociguat
Prostacyclin receptor agonist
  ◦ selexipag
Prostanoids

Indication:
- Prostacyclin synthase is reduced in PAH patients -> inadequate production of prostacyclin I2 (vasodilator with antiproliferative effects)

Mainstay of treatment > 10 years

3 commercially available:
- Epoprostenol
- Treprostinil
- Iloprost
Epoprostenol

Indications:
- Improvements seen in functional class, exercise tolerance, hemodynamics and survival in IPAH
- Improvements with PAH with the scleroderma spectrum with exercise endurance and hemodynamics

Delivered by continuous intravenous infusion

Dosing is highly individualized
- Commonly started at a dose of 2 ng/kg/min in the hospital and up titrated based on symptoms of PAH and side effects of the drug
- Optimal range per expert opinion for chronic use is between 25 and 40 ng/kg/min for most adult patients

Side effects:
- HA, jaw pain, flushing, nausea, diarrhea, skin rash, musculoskeletal pain

Infections and infusion interruptions can be life threatening
Treprostinil⁴

Indications:
- In 2004, IV treprostinil was approved for the use in functional class II, III, IV patients who subcutaneous infusion is not tolerated

Delivered either subcutaneously or by intravenous infusion

Side effects:
- Pain or erythema at the site of subcutaneous infusion
- HA, diarrhea, rash and nausea
Iloprost

Indication:
- In 2004 was approved by the FDA for functional class III and IV PAH

Delivered by an adaptive aerosol device

Side effects:
- cough, HA, flushing and jaw pain
Endothelin Receptor Antagonists

Indications:
- Endotheian-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH
- Treats PAH with endothelin receptor blockade

Bosentan

Sitaxsentan – not avaible in US

Ambrisentan
Bosentan⁴

Indications:
- Endothelin receptor agonist
- Widely used in patients with PAH

Side Effects:
- Hepatotoxicity
  - FDA rec's that liver function tests checked monthly
- Anemia, edema, hormonal methods of birth control may be less effective
- May cause testicular atrophy and male infertility
Ambrisentan$^4$

Indication:
- Endothelin receptor agonist
- Approved in 2007 by the FDA for patients with PAH and functional class II and III symptoms

Side Effects:
- Similar to Bosentan
Phoshodiesterae Inhibitors

Sildenafil
Tadalafil
Sildenafil

A specific PDE5 inhibitor that has been utilized for erectile dysfunction

FDA approved dose is 20 mg, orally, 3 times a day; higher doses are considered "off label"

SUPER-1 (Sildenafil use in Pulmonary Arterial Hypertension)

- Randomized, double-blind, placebo controlled
- N =278
- Dosesage: 20, 40, or 80 mg 3 times a day
- Increased 6MWD in all Sildenafil groups (p <0.001)
- All dosages decreased mPAP and improved functional class

Side Effects:
- HA, flushing, dyspepsia, epistaxis
Exercise & PH
Exercise Physiology in PH$^{3,11}$

Failure to perfuse the ventilated lung, leading to an increase of physiologic dead space and ventilatory requirement

- Increased ventilation–perfusion mismatch, can decreases arterial oxygen saturation if severe enough
- Exercise-induced hypoxemia increasing the hypoxic ventilatory drive.
- The ventilatory expired gas abnormalities precipitated by PH are multifactorial and associated with disease severity.

Decreased pulmonary venous return leading to a decrease in left-sided cardiac output (CO)

Possible leftward shift in the ventricular septum; decreasing left ventricular filling capacity and further compounding the reduction in cardiac output

Failure to increase cardiac output appropriately in response to exercise, causing an early lactic acidosis, thereby increasing acid ventilatory drive

As PH disease severity progresses, RV dysfunction/deterioration progresses, which further contributes to a decline in cardiac output
Exercise Training Effects$^{3,11}$

• Upgraded to Class I, Level evidence A after the 2013 World congress in Nice.

• Improvement in muscle function
  • increase in capallarization and change in fiber type

• Influences the pulmonary vasculature
  • regulating effect on pulmonary vascular remodeling

• Improve peak oxygen consumption (VO2/kg)
  • May be due to inc. skeletal muscle capillary density

• Training may improve right ventricular function
  • may reduce RV end-diastolic pressure and increase RV capillary density
Exercise Training Effects$^{3,11}$

Improve exercise capacity
- May help improve 6MWD as much as pharmacotherapy
- 53.3-72.5 meter with ET v. 35.6 meters specific-PH med
- Improvement in capallarisation and oxidative enzymes
- Improvements in type I muscle fibers

Quality of Life (QOL)
- Improvement in SF-36 physical scores
- Improve pain scores
- Decreased fatigue
Exercise Training Effects$^{3,11}$

Improvement in cardiac function
- May reduce RV end-diastolic pressure
- Improve pulmonary artery remodeling
- Increase in peak exercise heart rate by 10 beats per min

Improvement in hemodynamics
- Reduce echo PA systolic pressure by 3.7 mmHg
- Reduced peak velocity in pulmonary artery
- Increased pulmonary blood volume post-ET
Exercise Prescription Recommendation\textsuperscript{3,11}

3 week inpatient exercise prescription followed by 12-15 week home-based exercise program

Inpatient Program
\begin{itemize}
  \item Interval training with bicycle ergometer 10-25min/day at 60-80% of heart rate max
  \item 60 minutes walking/day x 5 days/week
  \item 30 minutes of respiratory training
    \begin{itemize}
      \item PLB, stretching, strengthening of respiratory muscles
    \end{itemize}
  \item Weight training
    \begin{itemize}
      \item Major muscle groups x 30min x 5 days/week
    \end{itemize}
\end{itemize}

Home-Based Exercise Program
\begin{itemize}
  \item Bicycle ergometer x 15-30min/day x 5 days/week
  \item Continue daily respiratory exercise
  \item Resistance training with weights for 15-30min
  \item Walk 2x/week for a total of 120 minutes per week
\end{itemize}
Recommendations

Patients must be clinically stable and on optimal pharmacological agents prior to commencing any exercise training

Exercise Training should occur at least 2hrs per day x 5 days/week

Exercise training should include

- Aerobic exercise via bicycle or walking
- Weight training
- Respiratory muscle exercise
Cases


References


References


