Pulmonary Hypertension
Redefining Rare....

CSM 2017
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About us...
Objectives

1. Classify the types of pulmonary hypertension (PH) based on recommendations from the World Symposium on PH and the World Health Organization (WHO) classification systems.
2. Understand the pathophysiology of PH and the resultant signs and symptoms.
3. Understand the required tests needed to confirm the diagnosis of PH.
4. Review and understand the pharmacotherapy available for PH and their effect on physical therapy management.
5. Utilize the evidence to determine appropriate exercise prescription and interventions to progress patients with PH safely and effectively.

Classification
History of Classification

- 1st International Conference on primary PH – Geneva, Switzerland - 1973
- 2nd World Symposium – Evian, France - 1998
- 3rd World Symposium - Venice, Italy - 2003
- 4th World Symposium – Dana Point, Ca - 2008
- 5th World Symposium – Nice, France – 2013
- 6th World Symposium – Nice, France - 2018

Incidence & Prevalence

- Pulmonary Hypertension (PH) is a rare disease
  - Estimated prevalence ranging from 10 to 52 cases per million
  - Registries report 70–80% female PAH patients
  - Most commonly reported cases
    - PAH (39-61%)
    - PAH associated with CTD (7-12%), CHD (1%) or portopulmonary HTN (10%)
    - Group 2 PH due to left heart disease is the most common cause of PH (36% of all PH)
    - Chronic Thromboembolic pulmonary HTN 3.2 cases per million per year
  - In the US National Institutes of Health (NIH) registry in the 1980s PAH was typically diagnosed in young adults
    - More recent registry data depict diagnosing PAH in older patients
**Epidemiology**

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

- Recent prospective data from 2002 to 2003 (improved survival rates)
  - 1 year survival (85.7%), 2 year survival (69.6%), 3 year survival (54.5%)

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

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**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>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>Group 4: Chronic Thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions</td>
<td>Thromboembolic obstruction of proximal or distal pulmonary arteries, nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
</tr>
<tr>
<td>Group 5: Miscellaneous</td>
<td>Sarcoidosis, histocytosis, LAM, compression of pulmonary vessels.</td>
</tr>
</tbody>
</table>
Group 1: Pulmonary Arterial Hypertension (PAH)\(^1,15,18\)

- 1.1 Idiopathic (IPAH)
- 1.2 Heritable (6%)
- 1.3 Drugs and Toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective Tissue Disease
  - 1.4.2 Infection with Human Immunodeficiency Virus (HIV)
  - 1.4.3 Portal Hypertension
  - 1.4.4 Congenital Heart Disease
  - 1.4.5 Schistosomiasis (4.6%)
  - 1.4.6 Chronic hemolytic anemia
- 1.5 Persistent Pulmonary Hypertension of the Newborn
- 1’ Pulmonary veno-occlusive disease (PVOD) & Pulmonary Capillary Hemangiomatosis (PCH)

Group 3’
Pulmonary Veno-occlusive Disease (PVOD) & Pulmonary Capillary Hemangiomatosis (PCH)

- Uncommon conditions
- Increasingly recognized as a causes for PAH
- Similar characteristics with IPAH
- Distinctive Characteristics:
  - Crackles
  - Clubbing,
  - CT: ground glass opacities, septal thickening
  - Lower DLCO and PaO\(_2\)
  - Parenchymal changes (interstitial edema)
- Worse outcomes than IPAH, familial or drug

Definition of PAH\(^1\)

- Must be confirmed by Right Heart Catheterization (RHC)
- Mean pulmonary artery pressure (mPAP) of >25mmHg
- Normal pulmonary artery wedge pressure (PCWP) of <15mmHg
  - Precapillary pulmonary hypertension

Definition of PH\(^{26}\)

- Must be confirmed by Right Heart Catheterization (RHC)
- Mean pulmonary artery pressure (mPAP) >25mmHg
- If pulmonary artery wedge pressure >15mmHG
  - Post-capillary pulmonary hypertension
  - Group 2: Left Heart Disease
Group 2: PH due to left heart disease\textsuperscript{1,7,16}

- One of the most common causes of PH
- Pulmonary Arterial Pressure >25mmHg
- Pulmonary artery wedge pressure >15mmHG
- PVR is normal or near normal (<3.0 Wood units)

Group 3: PH due to lung disease and/or hypoxemia\textsuperscript{1}

- 3.1 Chronic Obstructive Pulmonary Disease (COPD)
- 3.2 Interstitial Lung Disease (ILD)
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Chronic bronchiectasis
  - Cystic fibrosis
  - Combined pulmonary fibrosis and emphysema (CPFE)
- 3.4 Sleep Disordered Breathing
- 3.5 Alveolar Hypoventilation Disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities
Group 3: PH due to lung disease and/or hypoxemia\(^1\)

- Predominant cause of PH is alveolar hypoxemia
  - chronic lung disease
  - impaired control of breathing
  - residence of high altitude
- Parenchymal lung disease, the increase of pulmonary arterial pressure is usually modest (mPAP 25-35mmHg)
- More severe PH were characterized by mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low DLCO
- Prevalence is unknown
- No specific therapy

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)\(^{1,24}\)

- Occurs in 4% of pts after an acute pulmonary embolism
- Disease of pulmonary artery remodeling
  - Consequence of major vessel thromboembolism
  - Mismatched perfusion defects on lung scan
- Classified as Proximal or Distal CTEPH
  - “Expert centers”
  - Feasibility of performing pulmonary thromboendarterectomy
  - 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 PH-specific medical therapy
  - Riociguat
Group 5: PH with unclear and/or multifactorial mechanisms

- 5.1 Hematological disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histocytosis, 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
Pathophysiology

1. Small Pulmonary Arteries
2. Vascular Obstruction
3. RV Failure
4. Increase PVR
5. Increase in RV Afterload

PAH

Pathophysiology

1. Intimal proliferation and fibrosis
2. Medial hypertrophy
3. Vascular remodeling
4. Vasoconstriction
5. Plexiform lesions
6. Thrombosis
Pulmonary Vasorestriction

Abnormal Potassium Channels
- Inc. Can Concentration
- Inc. Cellular Contraction
- Sildenafil
- Inc. function of potassium channels

Endothelial Dysfunction
- Decrease Prostacyclin
- Decrease NO
- Increase Endothelin-1
- Potent Vasodilator
- Decrease Platelet aggregation

Open voltage dependent Ca+ channels

Inc. Ca+ Concentration

Thickening of vascular walls, abnormal proliferation → plexiform lesions

3 Pathways

Pulmonary Vasorestriction

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- Inc. Can Concentration
- Inc. Cellular Contraction
- Sildenafil
- Inc. function of potassium channels

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Open voltage dependent Ca+ channels

Inc. Ca+ Concentration

Thickening of vascular walls, abnormal proliferation → plexiform lesions

3 Pathways
Clinical & Physical Signs of PH$^{1,26}$

- Dyspnea on exertion
- Shortness of breath
- Fatigue
- Weakness
- Angina
- Syncope
- Dry-cough
- Exercise-induced nausea/vomiting
- Lower extremity edema
- Ascites
- JVD
- Hepatomegaly
- Hemoptysis
- Hoarseness of voice
- Prominent S2 sound
- Pansystolic murmur of tricuspid regurgitation
- Cool extremities

Functional Class
NYHA Functional Classification of PH

• 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 Functional 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

**US REVEAL Registry**$^{6,19,20}$

- Multi-centered: 55 centers contributed
- Diagnosis of PAH by right heart catheterization (RHC)
- Requirements:
  - WHO Group 1: PAH
  - Mean pulmonary artery pressure $>25$ mmHg at rest or $>30$ mmHg with exercise
  - Mean pulmonary capillary wedge pressure (PCWP) $<18$ mmHg at rest
  - Pulmonary vascular resistance (PVR) $>3$ Wood units.
  - Age $>3$ months at time of diagnosis
- Goal:
  - Characterize the demographics and clinical course of PAH
  - Evaluate and compare patient outcomes
  - Identify clinical predictors of short-term and long-term outcomes
  - Report trends in treatments and outcomes for newly diagnosed patients
  - Collect timely and relevant data for the evolving research needs
### REVEAL (PAH) Risk Score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Predicted 1-year survival</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td>95-100%</td>
</tr>
<tr>
<td>Average Risk</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>90-95%</td>
</tr>
<tr>
<td>Moderate High Risk</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>85-90%</td>
</tr>
<tr>
<td>High Risk</td>
<td>10-11</td>
</tr>
<tr>
<td></td>
<td>70-85%</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>&gt;12</td>
</tr>
<tr>
<td></td>
<td>&lt;70%</td>
</tr>
</tbody>
</table>

### Characteristics

- **WHO group I subgroup**
  - CTD-APAHI: +1
  - PoPH-APAHI: +2
  - FPAHI: +2
- **Demographics and comorbidities**
  - Renal insufficiency: +1
  - Males aged >60 yrs: +2
- **NYHA/WHO functional class**
  - I: -2
  - III: +1
  - IV: +2
- **Vital signs**
  - SBP <110 mmHg: +1
  - HR >92 beats min⁻¹: +1
- **6MWD**
  - ≥400 m: -1
  - <165 m: +1
- **BNP**
  - <50 pg mL⁻¹: -2
  - <180 pg mL⁻¹: +1
- **Echocardiogram**
  - Pericardial effusion: +1
- **PFT**
  - D L co 80% pred: -1
  - D L co 32% pred: +1
- **RHC**
  - P H <20 mmHg in 1 yr: +1
  - PVR >32 Wood units: +2

**Sum of above**

+ 6

= Risk score

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### Lower Risk → Good Prognosis

- **Evidence of RV failure**
  - No
- **Progression of Symptoms**
  - Gradual
- **NYHA/WHO Class**
  - II, III
- **6 MWT distance**
  - > 400 m
- **Peak VO2**
  - >10.4 ml/kg/min
- **CPET**
- **Echo**
  - Minimal RV dysfunction
- **Hemodynamics**
  - RAP < 10 mmHg
  - CI >2.5 L/min/m²
- **BNP**
  - Minimally elevated
Higher Risk → Poor Prognosis

- Evidence of RV failure
- Progression of Symptoms
- NYHA/WHO Class
- 6 MWT distance

Yes
Rapid
IV
< 300 m

CPET
Echo
Hemodynamics
BNP

Peak VO2 <10.4 ml/kg/min
Pericardial effusion
RAP > 20 mmHg
BNP Significantly elevated

Rapid
Significant RV enlargement/ dysfunction
CI < 2.0 L/min/m2
Right atrial enlargement

Tests
Diagnostic

- Trans-thoracic Echocardiogram
- Right Heart Catheterization
- Chest Radiograph
- Pulmonary Function Tests
- Arterial Blood Gases
- Vasodilatory Testing

Abdominal Ultrasound Scan

- Should be performed in all pts with PH to assess for portal hypertension or liver disease
- When portal HTN is suspected the diagnosis can be confirmed during RHC measurement of an increased gradient between the free and occluded hepatic vein pressure

Doppler Echocardiography

- Trans Thoracic Echocardiography (TTE)
  - Used for screening when PH is suspected
  - Can provide an estimate of:
    - pulmonary artery systolic pressure
    - right ventricle size, thickness, and function
  - Can identify possible causes of PH
- Common echocardiographic finding in PAH
  - Right atrial enlargement
  - Right ventricular enlargement
  - Flattening or reverse curvature of the IV septum
  - Underfilled left heart chambers
  - Presence of pericardial effusion
Right Heart Catheterization

- Invasive hemodynamic assessment
- Confirms the definite diagnosis of PH
  - PAH = resting mPAP of >25mmHg and Normal PCWP(<15 mmHg)
  - PH = resting mPAP of >25mmHg
- No definition of PH on exercise was currently adopted
- PCWP
  - Allow distinction between
    - Precapillary PH: normal PCWP <15mmHg
    - Postcapillary PH: PCWP>15 mmHg
- Measurements obtained:
  - Pulmonary artery pressure (PAP) (systolic, diastolic and mean)
  - Right atrial pressure (RAP)
  - Pulmonary capillary wedge pressure (PCWP)
  - Right ventricular pressure (RVP)
  - Cardiac output (CO)
  - Cardiac index (CI)
  - Mixed venous oxygen saturation (SvO₂)
- Elevated mean RAP, reduced CO, reduced SvO₂ are related to the poor prognosis of PAH

Chest Radiography

- May help to identify
  - Moderate to severe lung disease
  - Pulmonary venous hypertension due to left heart abnormalities
- Abnormal in 90% of idiopathic PAH pts at time of diagnosis
- Findings Include:
  - Central pulmonary arterial dilatation
  - Right atrial and right ventricular enlargement
Pulmonary Function Test &
Arterial Blood Gases

- **Pulmonary Function Test (PFT)**
  - Assists in identification of underlying lung abnormalities (obstructive vs restrictive)
  - IPAH: Normal Forced Expiration Volume in 1 sec (FEV1) and Total Lung Capacity (TLC)
  - Abnormal DLCO has been reported in PAH
    - More pronounced in PVOD pts
    - Poorer predictor for survival

- **Arterial Blood Gases (ABG)**
  - Usually show mild hypoxemia and hypocapnia
  - Severe hypoxemia may be a parameter of underlying PVOD or chronic lung disease

Acute Vasodilatory Testing

- **Rational for acute vasodilatory testing is based on 2 factors**
  - Acute vasodilatory responsiveness identifies patients with a better prognosis
  - Responders are more likely to have a substantial benefit to oral calcium channel blockers than non-responders

- **Agents used:**
  - The ideal vasodilator is selective to the pulmonary circulation and has a rapid on set and off set effect
  - iNO, intravenous epoprostenol, or IV adenosine

- **Definition of responders to acute vasodilatory testing in PAH**
  - Definition presented: 20% fall in both PAP and PVR
  - European Society of Cardiology and the ACCP guidelines proposed: a decrease in mPAP by at least 10 mmHg to an absolute level of less than 40 mmHg without a drop in cardiac output/cardiac index
Management of PAH

- Pharmacologic Management
  - Nonspecific v. Specific

- Physical Activity/Exercise

  - Avoid altitude and hypoxemia
  - Avoid pregnancy, need contraception
  - Avoid anesthesia and surgery
  - Sodium restriction diet
  - Immunizations
    - Flu, pneumococcal pneumonia

Pharmacologic Agents
Non-Specific Agents for PAH

Anticoagulants
Diuretics
Supplemental Oxygen
Digoxin
Calcium Channel Blockers

Anticoagulation

• Indication:
  • Group 4 CTEPH
  • Group 1
  • Rational
    • Decrease this risk of intrapulmonary vascular thrombosis
    • May be warranted for other risk factors requiring anticoagulation

• Anticoagulation is usually avoided in:
  • Systemic Sclerosis
  • Portopulmonary HTN

• Delivered: Oral, IV, Sub Q

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

• Goal INR:
  • Warfarin with CTEPH with goal INR: 2-3
  • Warfarin with IPAH with goal INR: 1.5 – 2.5

• Physical Therapy Considerations:
  • Know the therapeutic range for your patient population
  • Evaluate the patient for risk of falling
  • Monitor for signs/symptoms of bleeding
  • Monitor for mental status changes
Diuretics\textsuperscript{4,5}

- **Indication:**
  - Management of right ventricle volume overload
    - RV overload:
      - Jugular venous distension (JVD)
      - 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\textsuperscript{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 SpO2 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 inotrope
  - 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, high degrees AV block, VT, VF
  - GI: nausea, vomiting, diarrhea

Calcium Channel Blockers\textsuperscript{4,5}

- **Indication:**
  - Patients with IPAH who exhibit an acute vasodilatory response
  - Can be used with responders with associated forms of PAH
  - Most commonly used agents:
    - Long acting nifedipine
    - Diltiazem
    - Amlodipine

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

**Prostanoids**
- **Indication:**
  - Prostacyclin synthase is reduced in PAH patients → inadequate production of prostacyclin I2 (vasodilator with antiproliferative effects)
- **Mainstay of treatment > 10 years**
- **4 commercially available:**
  - Epoprostenol (Flolan, IV)
  - Remodulin (IV, SQ)
  - Treprostinil (Tyvaso, inhaled)
  - Iloprost (Ventavis, inhaled)
  - Selexipag (oral)
Epoprostenol (Flolan, Veletri)\textsuperscript{4,32}

- Indication:
  - WHO Group 1
  - 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:
  - 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:
  - Headache, jaw pain, flushing, nausea, diarrhea, skin rash, musculoskeletal pain

- Physical Therapy Considerations:
  - Infusion interruptions can be life threatening
  - Infections can be life threatening
  - Short half life 3-5 min

Treprostinil (Remodulin, Tyvaso)\textsuperscript{4,29,30}

- Indication:
  - WHO group 1
  - In 2004, IV treprostinil was approved for the use in functional class II, III, IV patients who subcutaneous infusion is not tolerated
- Delivered
  - Remodulin:
    - Subcutaneous infusion
    - Intravenous infusion
  - Tyvaso: inhalation
- Side effects:
  - Pain or erythema at the site of subcutaneous infusion
  - Headache, diarrhea, rash, nausea, hypotension

- Physical Therapy Considerations:
  - Infusion interruptions can be life threatening
  - Infections can be life threatening
  - Consider timing of inhaled dosages of medication prior to activity
Iloprost (Ventavis)\(^4,31\)

- **Indication:**
  - WHO Group 1
  - In 2004 was approved by the FDA for functional class III and IV PAH
- **Delivered**
  - Inhaled via adaptive aerosol device
- **Side effects:**
  - Cough, headache, flushing, jaw pain, dizziness, lightheadedness, fainting, bronchospasm, flushing, hypotension, nausea
- **Physical Therapy Considerations:**
  - Monitor vitals and adverse signs/symptoms
  - Consider the timing of activity based on the \(\frac{1}{2}\) life (20-30 min) of the pulmonary vasodilatory effect

Endothelin Receptor Antagonists\(^4,22\)

- **Indications:**
  - Endothelain-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH
  - Treats PAH with endothelin receptor blockade
- **Agents available:**
  - Bosentan
  - Ambrisentan
  - Macitentan
  - Tracleer
  - Letairis
Bosentan (Tracleer), Ambrisentan (Letairis)\textsuperscript{4,34,35}

**Bosentan:**
- **Indication:**
  - WHO group 1
  - Endothelin receptor antagonist
- **Delivered:** oral tablet
- **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:**
- **Indication:**
  - WHO group 1
  - Endothelin receptor antagonist
  - Approved in 2007 by the FDA for patients with PAH and functional class II and III symptoms
- **Delivered:** oral tablet
- **Side Effects:**
  - Similar to Bosentan
- **Physical Therapy Considerations:**
  - Monitor for side effects
  - Check lab vaules (liver function tests), increased risk for bleeding

**Phoshodiesterase Type 5 Inhibitors**\textsuperscript{4,22,33,36}
- **Prolong the vasodilatory effect nitric oxide**
- **Delivered:** oral tablet
- **Side Effects:**
  - HA, dizziness, indigestion, peripheria edema, n/v
- **Agents avaiable:**
  - Sildenafil
  - Tadalafi
  - Revatio
  - Adcirca
Sildenafil (Revatio) & Tadalafil (Adcirca)\textsuperscript{4,33,36,37}

- **Indication:**
  - A specific PDE5 inhibitor that has been utilized for erectile dysfunction (Viagria)
  - 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
  - $n = 278$
  - Doses: 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:**
  - Headache, flushing, dyspepsia, epistaxis, hypotension, lightheadedness

**Physical Therapy Considerations:**
- Monitor vitals and for side effects of medication

Soluble Guanylate Cyclase Stimulant\textsuperscript{22,28}

- **Indication:**
  - WHO Group 4
  - WHO Group 1
  - Stimulators of the nitric oxide receptor, soluble guanylate cycle (sGC) have a dual mode of action:
    - Increase sensitivity to of cGC to endogenous nitric oxide
    - Directly stimulate the receptor to mimic the action of NO
- **Delivered:** oral tablet
- **Agent Available:**
  - Riociguat
  - Adempas
Exercise & PH

Normal Pathophysiology of Exercise\(^3\)

- Pulmonary artery system significantly distends and recruits a greater proportion of the vascular network during exercise
  - Accommodates for the multifold increase in cardiac output
    - \(\approx 3\)–4-fold or greater at maximal exercise

- During low-intensity aerobic exercise
  - No substantial rise in PAP, decrease in PVR

- At higher intensities of exercise
  - Increase in PAP, which lags behind the rise in cardiac output secondary to the drop in PVR
Exercise Pathophysiology in PH\(^3,11,12,23,24\)

- Failure to perfuse the ventilated lung \(\rightarrow\) leads to an increase of physiologic dead space and ventilatory requirement
  - Increased V-Q mismatch \(\rightarrow\) decreases arterial oxygen saturation
  - Exercise-induced hypoxemia \(\rightarrow\) increases the hypoxic ventilatory drive
- Decreased pulmonary venous return \(\rightarrow\) 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 during exercise \(\rightarrow\) early lactic acidosis
- As PH disease severity progresses \(\rightarrow\) RV dysfunction progresses \(\rightarrow\) contributes to a further decline in cardiac output
Change in Recommendation!!$^{2,3,11,25}$

- Previously
  - Exercise should be limited or contraindicated in PAH

- Upgraded to Class I, Level evidence A after the 2013 World Symposium in Nice, France

- 2016 ESC-ERS Guidelines & Review by Chia and colleagues state exercise training evidence is Grade IIa, Level B
Exercise Training Effects²,³,¹¹,¹²,²³,²⁴,²⁵

- Improvement in muscle function
  - Increase in capillarization and oxidative enzymes
  - Change in fiber type (increase type I)

- Influences the pulmonary vasculature
  - Regulating effect on pulmonary vascular remodeling

- Improve peak oxygen consumption (VO2/kg)
  - Inconsistent in PH trials
  - May be due to inc. skeletal muscle capillary density

Exercise Training Effects²,³,¹¹,¹²,²³,²⁴,²⁵

- 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

- Quality of Life (QOL)
  - Improvement in SF-36 physical scores
  - Improve pain scores
  - Decreased fatigue
Exercise Training Effects\textsuperscript{2,3,11,12,23,24,25}

- Improvement in cardiac function
  - May improve right ventricular function → reduce RV end-diastolic pressure and increase RV capillary density (animal studies)
  - 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{2,3,9,11,25}

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

Inpatient Program
  - Interval training with bicycle ergometer 10-25min/day at 60-80% of heart rate max
  - 60 minutes walking/day x 5 days/week
  - 30 minutes of respiratory training
    - Pursed lip breathing, stretching, strengthening of respiratory muscles
  - Weight training
    - Major muscle groups x 30min x 5 days/week
    - 500g-1000g (1.1 -2.2 lbs)

Home-Based Exercise Program
  - Bicycle ergometer x 15-30min/day x 5 days/week
  - Continue daily respiratory exercise
  - Resistance training with weights for 15-30min
  - Walk 2x/week for a total of 120 minutes per week
Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: A preliminary study. Inagaki et al.27

• Methods:
  • Eight patients with inoperable or residual CTEPH, WHO functional class II-III
  • mean pulmonary artery pressure: 47±13 mmHg
  • stable x 3months and receiving disease-targeted medications
  • Participated in a 12-week home-based pulmonary rehabilitation program
  • 1 supervised in-hospital session each week
    • muscle strength training, respiratory exercises, and walking
  • Supervised hospital sessions from March 2012 to January 2014.

• Results:
  • Improved 6MWD (33.3±25.1 m)
  • Improved St. George Questionnaire activity Score
  • Improved quadriiceps force
  • Improved 7-day physical activity level

Outcomes of Exercise Recommendations2,21

• Increase in life expectancy
• Decrease in healthcare cost
• Decrease in WHO functional class
• Improvement in 6MWD
• Improvement in skeletal muscle function
• Improvement in peak VO2
• Improvement in QoL
Recommendations from Literature$^{2,3,27}$

- Patients must be clinically stable and on optimal pharmacological agents
- Contraindicated: pts with recent syncope on exertion, decompensated RHF, recent history of chest pain$^{2,3}$
- Exercise Training should occur at least 1-2hrs per day x 5 days/week
- Low to moderate exercise is safe
- Avoid workloads that elicit abnormal physiologic response
- Exercise training should include
  - Aerobic exercise via interval walking, bicycle, arm ergometer
  - Weight training with concentration on main muscle groups
  - Respiratory muscle exercise

General Considerations for Exercise with PH

- Discussion with PH team/physicians
- Close Monitoring
- Avoidance of valsalva maneuver
- Avoidance of head down positions or bending over
- Avoid oxygen destauation
  - Know SpO2 goal for patient
- Avoid exercise immediately after a meal
- Assess Lab Values: BNP
Follow-up Considerations

- Best Practice Exercise Guidelines for PH
- Cardiac Rehab v. Pulmonary Rehab
- Further research on exercise in the acute PH patient
  - Mobilizing intubated patients with PH
- Expert Consensus

Case Studies
Case #1

- 29 y/o female seen in acute care hospital setting
  - Admitted for CF exacerbation (increased cough and shortness of breath) and lung transplant work up
  - PMH: cystic fibrosis, pseudomoneous pneumonitis, CF related diabetes, pulmonary HTN, kyphoscolosis with Harrington rod placement, anxiety, depression
  - Referral to PT for: Pulmonary Rehabilitation, increase strength
  - Social: lives with parents, 4 STE, 12 steps to basement
  - Airway Clearance Routine: frequencer, aerobika; vibrolung when in house
  - Supplemental O2 needs: baseline: 2L during sleep, none at rest
  - Pulmonary Rehab 2x/week as OP
  - FEV1: 26%

Case #1 Continued

- Chest Exam
  - Observation: thin, + clubbing of digits, right posterior rib hump, thoracic kyphosis, forward head posture, rounded shoulders, upper trap activation, 1:1 IE ratio, + accessory muscle activation (SCM, scalences), abdominal distension, mediport on right chest
  - Auscultation: diminished breath sounds throughout
- Measurements
  - 9/15: 5 time sit <> stand: 11.12 seconds
- Function
  - Independent with bed mobility, sit <> stand transfers without use of UE, independent with ambulation >700 feet with 3 standing rest breaks (~60 seconds – 90 seconds)
- Vitals (initial PT eval)
  - Pre: HR 102, BP 121/82, SpO2 97% on 2L via NC, RPD 0.5/10, RPE 8/20
  - During: HR 125, BP 139/86, SpO2 90-98% on 2L via NC, RPD 3-4/10, RPE 11/20
  - Post: 104, BP 119/87, SpO2 98% on 2L via NC, RPD 0.5/10, RPE 8/20
- 6 Minute Walk Test: 232 meters
- PH Medications: supplemental O2, team considering adding Sildenafil
- Additional medcial tx aimed at underlying lung disease
Case #1 Questions:

- What WHO Group would this patient fall under?
- What WHO or NYHA functional class is this patient presenting as?
- What PT plan of care should be created?
  - Additional examination techniques?
  - What interventions should be selected?
  - What patient considerations effect the prognosis?
  - What additional information would be good to know?
  - What goals would be appropriate for this patient?

Case #2

- 45 y/o female
  - Admitted with shortness of breath and pneumonia
  - PMH: idiopathic pulmonary hypertension, pulmonary embolism, total knee arthroplasty
  - Social: lives with husband, on disability (previously a nursing supervisor), 4 STE home, 15 steps to 2nd floor bedroom and bathroom
  - PLOF: household ambulator, supervision on stairs, requires assist with ADLs
  - Supplemental O2 needs: baseline: 3-4 L at rest, 4L with activity; currently vapotherm 80% FiO2 at 40L
  - Pulmonary Rehab: was told she was not a candidate 2/2 arthritis
Case #2 Continued

- Chest Exam:
  - Observation: obesity, telemetry, foley, on vapootherm, sleeping upon arrival, IE ratio: 1:2, + accessory muscle use with deep breath, 4-5 word dyspnea at rest, Remodulin pump, Lasix gtt, 1+ pitting edema at (B) LE
  - Auscultation: inspiratory crackles at (B) lung bases posteriorly
- Function
  - Modified independent with bed mobility with HOB elevated and use of UE, increased time to complete; required EOB sitting x 5 min d/t dizziness, min assist +1 for sit -> stand to no device and HHA, mod assist +1 to take 4 side steps to chair, min assist for stand -> sit with decreased eccentric control, tolerated 1 hour OOB
- Vitals response (initial PT eval)
  - Pre: HR 98, BP 112/76, SpO2 100%, RPD 1/10
  - During: HR 114, BP 100/67 (at EOB) - after 5 min 115/80, RPD 2/10
  - Post: HR 105, BP 110/82, RPD 2/10
  - + fatigue 7-8/10 post transfer

Case #2 Questions:

- What WHO Group would this patient fall under?
- What WHO or NYHA functional class is this patient presenting as?
- What PT plan of care should be created?
  - Additional examination techniques?
  - What interventions should be selected?
  - What patient considerations effect the prognosis?
  - What additional information would be good to know?
  - What goals would be appropriate for this patient?
Case #3

• 77 y/o male veteran
  • Admitted with Acute on chronic pulmonary embolism resulting in acute hypoxic respiratory failure and severe RV failure and secondary erythrocytosis present on admission likely due to chronic unrecognized hypoxia potentially related to underlying development of CTEPH.
  • PHI: initially admitted to the VA MICU for acute hypoxic respiratory failure on 1/17 secondary to submassive PE. Was transferred to the floor on 1/20, then back to MICU (1/22) for new onset frank hemoptysis with clots and worsening hypoxia 85% on 6L NC.
  • PMH: DVT 2012 (s/p 6 months warfarin), DVT/PE May 2016 s/p 6 months rivaroxaban), obesity (BMI 35), OSA (no longer using CPAP), DM2, Hyperlipidemia, Chronic venous insufficiency
  • PLOF: Independent with ADLS, IADLS and ambulation without an AD.
  • Supplemental O2 needs: Previously on RA at home

Case #3

• Labs: D-dimer 2071, Troponin I - 0.49, ABG - 7.48/28/56, lactate 2.2

• Echo 5/2016: Normal LV size and function, Markedly dilated RV w severe systolic dysfunction, Aortic dilatation at the level of sinuses Valsalva (42mm), Tricuspid valve: structurally normal, no tricuspid stenosis or regurgitation. Lack of TR jet preclude assessment of PA systolic pressure

• Bedside TTE 1/2017: Suspicious for RV pressure overload & RV dilatation w/o RV failure.

• CXR: No acute abnormalities are seen. There is no evidence of congestion, consolidation, mass, effusion, or pneumothorax.

• EKG: Sinus tachycardia. T-wave inversions in V2-V3 stable from previous EKG. submillimeter ST depressions in leads I, V, V5, with 1mm ST elevation in lead aVR. Q-waves in V1 previously present.

• V-Q scan 1/17/17: The perfusion scan shows multiple, large perfusion defects in both lungs, with near-absence of perfusion to the LUL, and large perfusion defects in RML and RLL as well as LLL.
Case #3

Initial PT Eval:
- Initial Chest Exam:
  - Observation: + obese belly, I:E ratio 1:1, 1-2 word dyspneic, on 3L NC on approach, poor diaphragm recruitment, + accessory mm. use (primarily upper traps)
  - Minimal lateral costal movement
  - Auscultation: bibasilar crackles, + egophony and bronchophony of left posterior left lung fields
  - Function: SBA sit to stand. Ambulated x 50ft with no AD and O2 tow on 3L NC with continuous pulse-ox monitoring.
- Vitals response
  - Vitals at rest: BP: 115/75 (88), HR: 82, spO2: 93-97% on 3L NC
  - Vitals after amb#1: spO2: 77% on 3L NC, HR: 87
  - Vitals after amb#2: spO2: 67-74% on 4L NC, HR: 87-95, on return to room
  - required ~5min of PLB and lat costal breathing to increase >90%
- Plan: Admitted to our CLC for 2-3 weeks for inpatient pulmonary rehab. Pulmonary team on board with this plan due to high O2 needs and poor hemodynamic response with minimal symptoms.
Case #3 Questions

• What WHO Group would this patient fall under?
• What WHO or NYHA functional class is this patient presenting as?
• What PT plan of care should be created?
  • Additional examination techniques?
  • What interventions should be selected?
  • What patient considerations effect the prognosis?
  • What additional information would be good to know?
  • What goals would be appropriate for this patient?

References


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