Pulmonary Hypertension - The Other Hypertension

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Pulmonary Hypertension

Pulmonary Arterial Hypertension

Pulmonary Venous Hypertension
COPD, IPF, OSA

HTN

CTEPH, PAH
Pulm Stenosis

Normal PCWP, Elevated PVR

Elevated PCWP, normal PVR

PV, LA, LV, Ao

Elevated PCWP, normal PVR

PVOD

DCM, HCM, LVDD

Elevated PCWP, normal PVR

Normal PCWP, Elevated PVR

PV

LA

LV

Ao

Pulmonary Capillary Bed
Pulmonary arterial hypertension (PAH) is a progressive, incurable disease of the small pulmonary arteries characterized by vascular cell proliferation, aberrant remodeling, and thrombosis *in situ*.
Pulmonary Arterial Hypertension (PAH)

<table>
<thead>
<tr>
<th>Mean pulmonary artery pressure (mPAP)</th>
<th>≥25 mm Hg</th>
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<tr>
<td>And</td>
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<tr>
<td>Mean pulmonary artery wedge pressure (PAWP)</td>
<td>≤15 mm Hg</td>
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<tr>
<td>With</td>
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<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>&gt;3 Wood units</td>
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</table>

As measured by right-heart catheterization.

Pulmonary Vascular Histopathology

Normal Pulmonary Artery

Idiopathic PAH

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Pathogenesis of PAH

1. **RISK FACTORS AND ASSOCIATED CONDITIONS**
   - Collagen Vascular Disease
   - Congenital Heart Disease
   - Portal Hypertension
   - HIV Infection
   - Drugs and Toxins
   - Pregnancy

2. **VASCULAR INJURY**
   - Endothelial Dysfunction
     - ↓Nitric Oxide Synthase
     - ↓Prostacyclin Production
     - ↑Thromboxane Production
     - ↑Endothelin 1 Production
   - Smooth Muscle Dysfunction
     - Impaired Voltage-Gated Potassium Channel (Kv1.5)

3. **DISEASE PROGRESSION**
   - Loss of Response to Short-Acting Vasodilator Trial
   - Smooth Muscle Hypertrophy
   - Adventitial and Intimal Proliferation
   - In situ Thrombosis
   - Plexiform Lesion
   - Advanced Vascular Lesion

- **SUSCEPTIBILITY**
  - Abnormal BMPR2 Gene
  - Other Genetic Factors

- **NORMAL**
- **REVERSIBLE DISEASE**
- **IRREVERSIBLE DISEASE**
Pulmonary Hypertension WHO Group 1

- Group 1 Pulmonary Arterial Hypertension (PAH)
  - Idiopathic (IPAH)
  - Heritable (HPAH)
    - BMPR2
    - ALK-1, endoglin, SMAD9, CAV1, KCNK3
    - Unknown
  - Drugs and toxins induced
  - Associated with
    - Connective Tissue Diseases- Scleroderma, SLE
    - HIV Infection
    - Portal Hypertension
    - Congenital Heart Diseases
    - Schistosomiasis

- Group 1’ Pulmonary Veno Occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatotis (PCH)

- Group 1” Persistent pulmonary hypertension of the newborn (PPHN)

Pulmonary Hypertension WHO Group 2-4

- **Group 2 -- Pulmonary Hypertension Due to Left Heart Disease**
  - Left Ventricular Systolic Dysfunction
  - Left Ventricular Diastolic Dysfunction
  - Valvular disease
  - Congenital / acquired left heart inflow / outflow tract obstruction

- **Group 3 -- Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia**
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude

- **Group 4 – Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**

Pulmonary Hypertension WHO Group 5

Group 5 – Pulmonary Hypertension with Unclear Multifactorial Mechanisms

- Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
- Systemic disorders: Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
- Others: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Symptomatic profile</th>
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<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension 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.</td>
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<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
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</table>
Examination Findings Suggestive of PH/PAH

Lungs: CTA w/o wheeze / crackles

Liver: Hepatomegaly Pulsatile liver

Abdomen: Ascites

Joint: Changes c/w CTD

Digits: Cool, Cyanotic

Neck: HJR, JVD

Skin: Changes c/w CTD

Heart: Heave, RRR, Increased P2, TR SM

Extremities: Edema

Liver: Hepatomegaly Pulsatile liver

Abdomen: Ascites

Joint: Changes c/w CTD

Digits: Cool, Cyanotic

Neck: HJR, JVD

Skin: Changes c/w CTD

Heart: Heave, RRR, Increased P2, TR SM

Extremities: Edema
EKG signs of RH Strain

- Non sinus rhythms
- Incomplete or complete RBBB
- S1Q3T3
- Twave inversions in V1,V2, V1-V3, or V1-V4
Figure 1. Sample ECG with Signs of Pulmonary Hypertension

PAH, pulmonary arterial hypertension; RAD, right axis deviation; RVH, right ventricular hypertrophy; RV, right ventricle.
S1Q3T3

S-waves in lead I

Q-waves in lead III

Inverted T-waves in lead III
Right ventricular strain?

T-wave inversion in the right precordial leads (V1-V3)
Large, but "pruned" proximal pulmonary artery

Prominent pulmonary artery segment
Mild PAH

Systole in short-axis view

Diastole in short-axis view

Apical 4-chamber view

TR Jet
Severe PAH and RV Failure

Systole

Apical 4-Chamber View

Diastole

TR Jet
Echocardiogram in PH/PAH

- Echocardiogram findings in PH
  - RA/RV
    - RAE, RV dilation
    - RV dysfunction
    - Elevated PAP

- Echocardiogram findings in PH associated with left heart disease
  - LAE, LVH, LV dilation
  - LV systolic dysfunction
  - Grade II/III diastolic dysfunction
  - Mitral/aortic valvular disease
Important data: RAP, RV, PAP, PCWP, TPG, CO/CI, PVR, and Saturations of Vena cava, RA, RV and PA
RHC distinguishes:
Left Heart Disease
PAH
CTEPH
High output
Fever, anemia.
Why should YOU care?
Because you may see some people with PAH

- Cautions with medications
- What not to give
- What not to stop
- Who to be afraid of
PH Clinic Increasing in Size at GHS

- Approximately 150 patients
- 75-80 patients on PH drugs
- 20-25 on prostacyclins
- Regional Center
- Several recent visits to the ED/OR
Pharmacologic Treatment

- Diuretics (Lasix, Demadex, Bumex)
- Spironolactone
- Anticoagulation
- PAH focused therapy
- Treatment of RHF
- Management of other Comorbid conditions
PAH specific FDA-approved Therapies (in U.S.)

Route
- Oral
- Inhaled
- Subcutaneous
- Intravenous

Mechanism of Action
- Phosphodiesterase Inhibitors
- Endothelin Receptor Antagonists
- Stimulator of soluble guanylate cyclase (sGC)
- Prostacyclins/Prostanoids
- Prostacyclin Receptor Agonist
Eight Oral Therapies

**Endothelin Receptor Antagonists**
- **Ambrisentan** - improvements in 6MW, time to clinical worsening, functional class
- **Bosentan** - improvements in 6MW, time to clinical worsening, functional class, hemodynamics
- **Macitentan** - improvements in 6MW, time to clinical worsening

**Phosphodiesterase Inhibitors**
- **Sildenafil** - improvements in 6MW, functional class, hemodynamics
- **Tadalafil** - improvements in 6MW, functional class, time to clinical worsening

**OTHERs**
- **Riociguat** - improvement in 6MW, functional class
- **Oral treprostinil**
- **Selexipag (Uptravi)**
Growth Factors
Thrombin
Cytokines

Angiotensin II
Shear stress
Hypoxia

endothelial cells

Prepro-ET → Big ET-1 → ECE → ET-1

ET-1

ET-1

ETA

ETB

Ca^{++}

release

Vasoconstriction
Cell proliferation
Inflammation

Clearance of ET-1

Vasodilation

smooth muscle cells
ERAs

- Bosentan = Tracleer
- Ambrisentan = Letairis
- Macitentan = Opsumit
Endothelin Receptor Antagonists: Side Effects

- Can worsen diastolic dysfunction/edema
- Liver function abnormalities
- Anemia
- Teratogenicity
- Headache, nasal congestion, flushing, and nausea
Bosentan/Macitantantan

- Decreases cyclosporine, glibenclamide, simvastatin, and warfarin by up to 50% via induction of CYP3A4 and/or CYP2C9
- Renders hormone-based contraception ineffective
- Ketoconazole doubles the exposure to bosentan via inhibition of CYP3A4
- Co-administration of bosentan and sildenafil, a decrease in sildenafil
Ambrisentan

- Only significant interaction with cyclosporine A, with a twofold increase in ambrisentan concentration
PDE5 Inhibitors- Side Effects

- Hypotension
- Sudden Hearing Loss
- Anterior optic neuropathy
- Dizziness, flushing, dyspepsia, nasal congestion or rhinitis
PDE5 Inhibitors for PH

- Sildenafil = Revatio
- Tadalafil = Adcrica
PDE5 Drug Interaction

- Nitrates
- Alpha blockers
- Riociguat
- HIV protease inhibitors, ketoconazole, itraconazole, any cytochrome P450 enzyme CYP3A4 inhibitor or activator
Riociguat (Adempas): Side Effects

- Hypotension
- Bleeding
- Epistaxis
- Teratogenicity
- Anemia
- Headache, vomiting, GERD, dizziness, gastritis
Riociguat-Interactions

- PDE5 Inhibitors
- Nitrates
- Antacids
- Strong inducers of CYP3A
- Smoking- reduction of serum levels
Selexipag

- Strong CYP2C8 inhibitors- increase selexipag
- Headache, Diarrhea, Jaw pain, Nausea, Myalgia, Vomiting, Pain in Extremity, Flushing, Arthralgia, Anemia, Decreased appetite
IV, SQ and Inhaled Therapies

**Parenteral therapies**
- Epoprostenol - improvements in survival, 6MW, hemodynamics
- Treprostinil (subcutaneous also) - improvement in 6MW, hemodynamics

**Inhaled therapies**
- Iloprost - improvement in 6MW, hemodynamics
- Treprostinil - improvement in 6 MW, hemodynamics
Prostacyclins

- IV Epoprostenol = Flolan and Veletri
- IV and SQ Treprostinil = Remodulin
- Inhaled Iloprost = Ventavis
- Inhaled Treprostinil = Tyvaso
- Oral Treprostinil = Orenitram
Pumps
Side Effects Prostacyclins

- Headache, flushing, hypotension, thrombocytopenia, anemia, teratogenic
- Flushing, jaw pain, rash, line infection/malfunction
- Nausea, vomiting, diarrhea, tachycardia, paresthesia,
- Bleeding: INHIBITOR of platelet aggregation
IV therapy

- Continuous infusion
- Flolan/Veletri t ½ 3-5 minutes
- ALWAYS dedicated IV access
- NEVER flush line
- Line needs to be PRIMED
- PLEASE DO NOT STOP OR CHANGE DOSE without talking to us
SQ therapy

- Continuous infusion
- Remodulin $t \frac{1}{2}$ 4 hours
- Site pain, erythema, induration
- Continue as long as you can
Inhaled Prostacyclins

- 4-9 times a day
- Have their own nebulizers
- Can cause cough, bronchospasm
- Short half life
Non-Pharmacologic Treatments

- Oxygen
- CPAP/BiPAP
- Salt/water intake/dietary counseling
- Side Effects of Medications
- Symptoms of concern
  - Lightheadedness, dizziness, syncope
  - Fullness, early satiety
  - Swelling, ascites
Non-Pharmacologic Treatments

- Disability
- Exercise - avoid heavy lifting and vagal maneuvers
Pharmacologic Treatment

- Diuretics
- Spironolactone
- PAH focused therapy
- Treatment of RHF
- Management of other Comorbid conditions
Avoidance of pulmonary hypertensive crisis

- Avoid hypoxic pulmonary vasoconstriction
- Avoid hypercarbia, acidosis and hypothermia
- Avoid high airway pressures
- Optimize right ventricular preload
- Reduce right ventricular afterload
- Maintain coronary blood flow
- Maintain sinus rhythm
- Maintain arterial blood pressure and cardiac output
<table>
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<tr>
<th>Chronic PH</th>
<th>Pulmonary</th>
<th>Vascular</th>
<th>Cardiac</th>
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<tr>
<td></td>
<td>Pulmonary hypertension associated with lung disease or hypoxemia</td>
<td>Pulmonary arterial hypertension</td>
<td>Pulmonary hypertension secondary to left heart dysfunction</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension secondary to chronic vascular obstruction</td>
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<tr>
<td>Perioperative factors acutely increasing PVR</td>
<td><strong>CPB-related myocardial or pulmonary injury</strong></td>
<td><strong>Mechanical obstruction</strong>&lt;br&gt;- Thromboembolus&lt;br&gt;- Air, fat, or tumor emboli</td>
<td><strong>Myocardial dysfunction</strong>&lt;br&gt;- RV myocardial infarct&lt;br&gt;- Anesthesia-related decrease in myocardial contractility&lt;br&gt;<strong>Fluid overload</strong>&lt;br&gt;- Left heart dysfunction&lt;br&gt;- Tricuspid regurgitation&lt;br&gt;- Pulmonary valve regurgitation</td>
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<td><strong>Mechanical ventilation</strong>&lt;br&gt;- Alveoli overdistention&lt;br&gt;- Respiratory acid-base disturbances</td>
<td><strong>Acute vasoconstriction</strong>&lt;br&gt;- Hypoxemia&lt;br&gt;- Hypercapnia&lt;br&gt;- Acidosis&lt;br&gt;- Pain&lt;br&gt;- Hypothermia</td>
<td></td>
</tr>
<tr>
<td>Perioperative factors increasing risk of RV dysfunction</td>
<td><strong>Changes in intrathoracic pressure limiting coronary blood flow</strong></td>
<td><strong>Systemic hypotension</strong>&lt;br&gt;- Anesthesia&lt;br&gt;- Sepsis</td>
<td><strong>Reduced coronary perfusion</strong>&lt;br&gt;- Inadequate preload&lt;br&gt;- LV dysfunction</td>
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<td></td>
<td><strong>Hypovolemia</strong>&lt;br&gt;- Acute blood loss&lt;br&gt;- Fluid depletion&lt;br&gt;- Fluid shifts</td>
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IV Prostacyclin management & changeout

• DEDICATED long-term single lumen tunneled catheter (Hickman)

  • Initially must be primed with medication
  • Catheter length, pump infusion rate, half-life of medication all factor in
  • Pharm D’s, ICU nursing, MD’s responsible for this

• NEVER flush the line, NEVER stop the infusion
IV Prostacyclin management & changeout

• Catheter removal or in case of catheter malfunction
  • Alternative IV access must be obtained first
    • Ensures continuous prostacyclin delivery, avoids acute rebound PH due to short half-life of med
  • Central venous access (including PICC lines) preferred over PIV’s
    • If multiple lumens, DEDICATE and LABEL lumen through which prostacyclin is being infused
    • NEVER flush the dedicated prostacyclin lumen
      • Bolus of these potent, quick acting medications can have lethal effects

• New catheter must be primed as above
Contact Information

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Thank you