Pulmonary Arterial Hypertension and Scleroderma Treatment Options

Jean M. Elwing, M.D.
Associate Professor of Medicine
Director, University of Cincinnati Pulmonary Hypertension Program
Pulmonary, Critical Care and Sleep Medicine
University of Cincinnati College of Medicine
Is this a familiar feeling?
Normal Heart and Blood Vessels

4 Chambers

- Right
- Left

Atrium (top)
Ventricle (bottom)
Normal Airways and Blood Vessels
Pulmonary Arteries and Veins
Lung Blood Vessels in Pulmonary Hypertension

Pulmonary arterial hypertension occurs in susceptible patients as a result of an insult to the pulmonary vascular bed resulting in an injury that progresses to produce the characteristic pathological features. HIV indicates human immunodeficiency virus; BMPR2, bone morphogenetic protein receptor II gene.
Lung Blood Vessels in Pulmonary Hypertension

- Plexiform Lesion
- Thickening of the Wall
- Small pulmonary arteries

http://pathhsw5m54.ucsf.edu/image63.html
Lung Blood Vessels in Pulmonary Hypertension
Symptoms

- Other symptoms
  - Fatigue
  - Chest pain or discomfort
  - Palpitations
  - Dizziness and light-headedness
  - Nearly fainting
  - Fainting

Physical Exam

- Clinical signs
  - Loud P2
  - Tricuspid regurgitation murmur
  - Right ventricular heave
  - Jugular venous distention
  - Signs of right heart failure
Testing

- **Noninvasive Testing**
  - Electrocardiogram (EKG)
  - Chest Radiograph (CXR)
  - Transthoracic Echocardiogram (TTE)
  - Possible future use of MRI

- **Confirmatory Testing for PH**
  - Right Heart Catheterization (RHC)
Chest radiograph (CXR)

- Dilated central pulmonary arteries
- Attenuation of distal arteries
- Dilated right atrium and ventricle
Echocardiogram

Right sided chambers enlarged
Left sided chambers compressed

Peak TR velocity of 4.68 m/s
RVSP = RAP + 4v^2
RVSP = 98 mmHg

Severe Tricuspid Regurg
Apical Four Chamber View
Systole

Chest CT Scan

- Enlargement Main Pulmonary Artery
- Right Atrial and Ventricular Enlargement
Right heart catheterization (RHC)

- **Diagnosis**
  - Noninvasive testing is part of the initial evaluation but is not confirmatory of PAH
  - RHC is necessary for a confirmed diagnosis of PAH

- **Severity assessment**

- **Vasodilator challenges are performed in patients with PAH to assess for possible use of calcium channel blocker therapy**
Right Heart Catheterization
Right Heart Catheterization
Detection of Pulmonary Hypertension

RA 65%
RV 64%

110/62 Art 93%
PA 68%

CO/CI 8.4/3.5
PVR 476
Definition of Pulmonary Hypertension

- **Definition of Pulmonary Hypertension (PH)**
  - Mean pulmonary artery pressure (mPAP) $\geq 25$ mmHg at rest

- **Hemodynamic Characteristics of Pulmonary Arterial Hypertension (PAH)**
  - PH associated with pulmonary artery wedge pressure (PWP) $\leq 15$ mmHg
  - Pulmonary vascular resistance (PVR) $\geq 3$ mmHg/L/min (Wood units) or 240 dynes/sec/cm$^5$
Pulmonary Hypertension

PH Owing to Left Heart Disease

PAH

PH Owing to Lung Disease

Multifactorial Mechanisms

Chronic Thromboembolic Disease
Pulmonary Hypertension

Group 1
Pulmonary Arterial Hypertension
PAH

Group 2
Pulmonary Venous Hypertension
PVH

Group 3
Pulmonary Hypertension associated with Lung Disease

Group 4
Pulmonary Hypertension associated with Clots
CTEPH

Group 5
Misc.

The WHO Groups
Pulmonary Arterial Hypertension
WHO Group I

Reveal Registry Demographic

“A Primary” No clear cause on extensive evaluation

Pulmonary Arterial Hypertension
WHO Group I

Reveal Registry Demographic

Pulmonary Arterial Hypertension

WHO Group I

- Connective tissue disease associated PAH
  - Systemic sclerosis
    - ~ 10%
  - Mixed connective tissue disease
  - Systemic lupus erythematosus

McLaughlin V. theheart.org

Imbalance in Pulmonary Blood Vessels

- Excessive of vasoconstriction
- Lack of vasodilation
Progression of PAH

CO=cardiac output; PAP=pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure.

Symptomatic Pulmonary Arterial Hypertension

General Therapies for PAH/RHF

RHC with Vasodilator Challenge

Responder

Trial of CCB’s

Septostomy
Lung Transplant
Comfort Care

Failure of PAH Therapy

PAH Specific Therapies Should Be Used

Treatment Choices Based of Severity of PAH and RHF
Treatment – General Measures

- Physical activity
  - In general, encourage physical activity
  - Limit if chest pain, severe dyspnea, syncope results

- Travel/altitude
  - Avoid air travel if possible
  - Air travel may increase pulmonary hypoxic vasoconstriction
  - Recommend the use of supplemental oxygen if air travel
Treatment – General Measures

- Infectious Disease
  - Vaccinate for Influenza and Strep Pneumonia
  - Promptly treat pulmonary infections

- Pregnancy
  - American Heart Association recommends avoidance or termination of pregnancy in patients with PH

- Contraception
  - Recommended
  - No consensus on safest form
General Pharmacological Therapy in PH

- **Oral Anticoagulant Treatment**
  - Goal International Normalized Ratio (INR) 1.5-2.0

- **Diuretics**
  - Institute in patients with right heart failure (RHF)
  - Use with caution due to pre-load dependence

- **Oxygen**
  - Supplement oxygen to keep saturations > 90%

- **Inotropic Agents**
  - Consider digoxin for RHF and/or tachyarrhythmias
## Treatment Algorithm for Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Higher Risk</th>
<th>Lower Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of RV failure</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Gradual</td>
</tr>
<tr>
<td>WHO class</td>
<td>IV</td>
<td>II, III</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>&lt;325 m</td>
<td>&gt;380 m</td>
</tr>
<tr>
<td>Brain natriuretic peptide</td>
<td>&gt;180 pg/mL</td>
<td>&lt;180 pg/mL</td>
</tr>
<tr>
<td>Echo findings</td>
<td>Pericardial effusion; significant RV dysfunction</td>
<td>Minimal RV dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
<td>Normal/near normal RAP and CI</td>
</tr>
</tbody>
</table>
Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials

Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials

Endothelin-1 (ET-)1 Receptor Antagonists

- Bostentan (Tracleer)
- Ambrisentan (Letairis)
- Macitentan (Opsumit)
Endothelin-1 (ET-)1 Receptor Antagonists

- Bosentan
  - Oral Endothelin-1 Blocking Agent
  - Improved exercise capacity, functional class, hemodynamics, echocardiographic measurements and time to clinical worsening
  - Elevated hepatic aminotransferases occurred in 10%
  - Bosentan has been approved in 2001 for NYHA class III and IV PAH; NYHA class II 2009

Endothelin-1 (ET-1)1 Receptor Antagonists

- Ambrisentan
  - Oral Endothelin-1 Blocking Agent
  - Improved exercise capacity, hemodynamics, and time to clinical worsening
  - Elevated hepatic aminotransferases occurred in 3%
  - Ambrisentan has been approved in 2007 for NYHA class II and III PAH
Endothelin-1 (ET-1) Receptor Antagonists

- Macitentan
  - Oral Endothelin-1 Blocking Agent
  - Delay in progression of disease
  - Improved morbidity / mortality, exercise capacity, hemodynamics
  - Anemia 13%
  - Macitentan was been approved in 2013 for NYHA functional class II-IV PAH
Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials

Nitric Oxide
Type 5 Phosphodiesterase (PDE) Inhibitors
Soluble Guanylate Cyclase Stimulators

- Inhaled Nitric Oxide
- Sildenafil (Revatio)
- Tadalafil (Adcirca)
- Riociguat (Adempas)
Type 5 Phosphodiesterase (PDE) Inhibitors

- **Sildenafil**
  - Orally-active medication and intravenous (IV)
  - Selective inhibitor of cyclic guanosine monophosphate (cGMP)-PDE type 5
  - Induces smooth muscle relaxation
  - Antiproliferative effects on vascular smooth muscle cells
  - Improvement in 6MWT and hemodynamics
  - FDA approved in 2005 for NYHA II-IV PAH

Type 5 Phosphodiesterase (PDE) Inhibitors

- Tadalafil
  - Orally-active medication
  - Selective inhibitor of cyclic guanosine monophosphate (cGMP)-PDE type 5
  - Induces smooth muscle relaxation
  - Antiproliferative effects on vascular smooth muscle cells
  - Improvement in 6MWT
  - Improved time to clinical worsening
  - FDA approved in 2009 for PAH

Soluble Guanylate Cyclase Stimulator

- Riociguat
  - Stimulator of the NO receptor soluble guanylate cyclase
  - Orally active medication
  - Indicated for the treatment of adults WHO Group 1 PAH
  - Improve exercise capacity, WHO functional class and to delay clinical worsening

Ghofrani H, et al. PATENT-1 - Riociguat for the Treatment of Pulmonary Arterial Hypertension
Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials

Prostacyclin Therapy

- Epoprostenol
  - RTS Option
  - Continuous IV Infusion

- Treprostinil
  - SQ or IV
  - Inhaled
  - Oral

- Iloprost
  - Inhaled
Epoprostenol
Continuous IV Infusion

- Used frequently in advanced disease
  - Delivered by continuous intravenous infusion
  - Half life 3-5 minutes
  - Epoprostenol (Flolan) must be maintained at 2-8°C
  - Epoprostenol for Injection (Veletri) is stable at room temperature
  - Interruption may cause serious deterioration or fatal
- FDA approved in 1995 for NYHA class III and IV IPAH
- FDA approved in 2000 for PAH associated with scleroderma
- FDA approved room temperature stable epoprostenol in 2010.
Epoprostenol
Continuous IV Infusion
Improves Survival in IPAH

- Prospective, randomized, multi-center, open trial
  - 12 weeks
  - 81 IPAH patients
  - NYHA FC III - IV
  - Epoprostenol vs. conventional therapy

Improvement in symptoms, hemodynamics and survival

Treprostinil
Continuous SQ or IV Infusion

- Half-life 3-4 hrs
- Absorbed completely with subcutaneous administration
- Stable at room temperature
- Stable at a neutral pH
- FDA approved in 2002 for NYHA II-IV PAH patients

Iloprost
Intermittent Inhaled Prostanoid

- Stable analogue of prostacyclin
  - Delivered via a I-neb AAD specialized nebulizer
  - 5mcg inhaled 6-9 times daily
  - 60 to 90 minutes duration of action
- Improved a composite endpoint consisting of exercise tolerance, symptoms and lack of deterioration
- Studied as monotherapy
- FDA approved in 2005 for NYHA III-IV PAH

Inhaled Treprostinil
Intermittent Inhaled Prostanoid

- Stable analogue of prostacyclin
  - Delivered via the Optineb device
  - Goal of 9 breaths 54mcg inhaled 4 times daily
  - Approximately 4 hour duration of action
- Improves exercise tolerance
- Studied as combination therapy with an oral PAH therapy
- FDA approved in 2009 for NYHA III PAH

Oral Treprostinil Extended-Release Tablets

- Oral treprostinil
  - Improve exercise capacity.
  - Functional class II-III symptoms
  - Etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%)
  - As the sole vasodilator, the effect on exercise is small. Oral treprostinil has not been shown to add to other vasodilator therapy.

Combination Therapy

Original Article

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Class</th>
<th>Indication (PI)</th>
<th>Route</th>
<th>FC</th>
<th>Goal of Therapy (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan (Tracleer)</td>
<td>ERA</td>
<td>WHO Group 1</td>
<td>PO</td>
<td>II-IV</td>
<td>*EC and decrease rate of clinical worsening</td>
</tr>
<tr>
<td>Macitentan (Opsumit)</td>
<td>ERS</td>
<td>WHO Group 1</td>
<td>PO</td>
<td>II-IV</td>
<td>Improve morbidity</td>
</tr>
<tr>
<td>Ambrisentan (Letairis)</td>
<td>ERA</td>
<td>WHO Group 1</td>
<td>PO</td>
<td>II-III</td>
<td>*EC and delay clinical worsening</td>
</tr>
<tr>
<td>Sildenafil (Revatio)</td>
<td>PDE-I 5</td>
<td>WHO Group 1</td>
<td>PO / IV</td>
<td>II-IV</td>
<td>*EC</td>
</tr>
<tr>
<td>Tadalafil (Adcirca)</td>
<td>PDE-I 5</td>
<td>WHO Group 1</td>
<td>PO</td>
<td>II-IV</td>
<td>*EC, delay clinical worsening</td>
</tr>
<tr>
<td>Riociguat (Adempas)</td>
<td>GC</td>
<td>WHO Group 1, 4</td>
<td>PO</td>
<td>II-IV</td>
<td>EC</td>
</tr>
<tr>
<td>Epoprostenol (Flolan, Veletri)</td>
<td>Prostacyclin</td>
<td>IPAH and PAH w/ Scleroderma</td>
<td>IV</td>
<td>III-IV</td>
<td>*EC and Survival IPAH, *EC Scleroderma</td>
</tr>
<tr>
<td>Treprostinil (Remodulin)</td>
<td>Prostacyclin</td>
<td>WHO Group 1</td>
<td>IV, SQ, PO</td>
<td>II-IV</td>
<td>Decrease PAH symptoms related Exercise</td>
</tr>
<tr>
<td>Iloprost (Ventavis)</td>
<td>Prostacyclin</td>
<td>WHO Group 1</td>
<td>Inhaled</td>
<td>III-IV</td>
<td>*EC, Improve *FC, delay deterioration</td>
</tr>
<tr>
<td>Inhaled Treprostinil (Tyvaso)</td>
<td>Prostacyclin</td>
<td>WHO Group 1</td>
<td>Inhaled</td>
<td>III</td>
<td>*EC</td>
</tr>
</tbody>
</table>

*EC = Exercise Capacity, FC = Functional Class
## PAH Treatment Goals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO functional class (FC)</td>
<td>I or II</td>
</tr>
<tr>
<td>Echocardiography/CMRI</td>
<td>Normal/near-normal RV size and function</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function</td>
</tr>
<tr>
<td></td>
<td>• RAP &lt; 8 mm Hg and</td>
</tr>
<tr>
<td></td>
<td>• CI &gt; 2.5 to 3.0 L/min/m²</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO$_2$ &gt; 15 mL/min/kg and EqCO$_2$ &lt; 45 L/min/L/min</td>
</tr>
<tr>
<td>B-type natriuretic peptide</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Extremely Important

- Avoid any interruption in PAH therapy
  - May result in significant worsening and RHF
- PAH therapy should be continued pre, intra and postoperatively
- Patient may be unable to continue a specific PAH therapy
  - Critical illness
  - Surgery
  - Malabsorption
  - Mental status changes
  - An alternative therapy must be considered immediately
- Contact the prescribing physician to discuss situation
Finding the Right Plan of Care for YOU

- Many factors are considered
  - Symptoms, examination and test results
  - Your goals for therapy
  - Your response to medications for PAH
  - Side effects

- Collaborative effort with your PAH team with you as the MVP
Thank You

Questions?