Pulmonary Arterial Hypertension: Diagnosis of Treatment

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PAH

• Classification
• Diagnosis
• Current treatment

Pulmonary Circulation

• Originates from the RV
• Low Pressure, low resistance circuit
• Thin-walled vessels
• High compliance
• Receives entire CO from RV
• Accommodates wide range of CO without increase in PVR

Pulmonary circulation
Pulmonary Hypertension

• Mean PAP > 25 mmHg
• Not just one disease, but a large group of diverse diseases

Classification

1. Pulmonary arterial hypertension (PAH)
   • 1.1. Idiopathic (IPAH)
   • 1.2. Heritable
     • 1.2.1 BMPR2
     • 1.2.2 ALKI Endoglin (with or without HHT)
     • 1.2.3 Unknown
   • 1.3. Drugs and Toxins
   • 1.4. Associated with (APAH):
     • 1.4.1. Collagen vascular disease
     • 1.4.2. HIV
     • 1.4.3. Portal hypertension
     • 1.4.4. Congenital Heart Disease
     • 1.4.5. Schistosomiasis
   • 1.5. Pulmonary veno-occlusive disease (PVOD)/Pulmonary capillary hemangiomatosis (PCH)
   • 1.6. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease
   2.1. Left Ventricular Systolic Dysfunction
   2.2. Left Ventricular Diastolic Dysfunction
   2.3. Valvular Disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep-disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thromboembolic
### Classification

- 5. Pulmonary Hypertension with unclear multifactorial mechanism
  - 5.1 Hematologic disorders, myeloproliferative disorders, splenectomy
  - 5.2 Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis
  - 5.3 Metabolic disorders, glycogen storage disease, Gaucher disease, thyroid
  - 5.4 Compression of pulmonary vessels tumor obstruction, fibrosing mediastinitis, Chronic renal failure

### Pulmonary Arterial Hypertension

- mean pulmonary artery pressure
  - > 25 mm Hg
  - Pulmonary artery wedge pressure <15

### Incidence of PAH

- 187 patients followed over 7 years
- Mean age at diagnosis: 36 years
- Almost 2:1 female-to-male ratio
- Incidence: ~2 cases per 100,000
- Mean survival 2.8 yrs
- Mean duration of symptoms before diagnosis: 2 years
- 647 patients in 1 yr
- Prevalence increasing: 15 cases per million
  - IPAH = 5.9 per million
- Mean delay between enrollment and diagnosis: 6 ± 86 months

### A Disease of Decline and Deterioration: IPAH Survival if Untreated

- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

Is There a Reason to Suspect PAH?

**Clinical Presentation**

<table>
<thead>
<tr>
<th>Common Initial Symptoms</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>13</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5</td>
</tr>
<tr>
<td>Leg edema</td>
<td>3</td>
</tr>
</tbody>
</table>


**Physical Exam**

- Presence of PH
  - Loud P2
  - RV lift
  - Systolic murmur (TR)
  - Diastolic murmur (PR)
  - RV S4

- Presence of RV Failure
  - JVD with V wave
  - RV S3
  - Hepatomegaly
  - Edema
  - Ascites

Chest X-Ray

Prominent Proximal Pulmonary Arteries

Peripheral Hypovascularity (Pruning)

RV Enlargement into Retrosternal Clear Space

Is There a Reason to Suspect PAH?

ECG

Diagnostic Evaluation

- Pulmonary function tests
  - Mild restrictive defects
  - Decreased DLCO
- Arterial Blood gas
  - Hypoxemia
  - Increased A-a gradient

Chest X-Ray

- Peripheral Hypovascularity (Pruning)
- RV Enlargement into Retrosternal Clear Space
- Prominent Proximal Pulmonary Arteries

Cardiovascular Evaluation

- Chamber size
- LV and RV systolic function
- LV diastolic function
- Valvular function
- TR
- Bubble study

Cardiovascular Evaluation

4.1 m/sec = 70 mmHg
RA Pressure = PA 80 mmHg
**Diagnostic Approach**

- RVE, RAE, RVSP
- Left heart disease
- VHD
- CHD

- Echocardiogram
- CXR
- ECG
- PFTs
- Sleep study

- Emphysema
- ILD
- Thoracic abnl

- Ventilation
- Perfusion scan,
- Contrast CT,
- Angiography

- Left heart disease
- VHD
- CHD

- Emphysema
- ILD
- Thoracic abnl

- Sleep disorder

- Ventilation-perfusion scan, Contrast CT, Angiography

- Autoantibody tests
- HIV test

- LFTs and clinical evidence of cirrhosis and portal htn

- Portopulmonary hypertension

- Functional test
- BNP
- RH cath
- Vasodilator test
- Scleroderma
- SLE
- RA
- Vasculitis

- Chronic thromboembolism


**Exercise testing**

- Six – minute walk
- Cardiopulmonary exercise test
  - Assessment of functional status
  - Response to therapy

**Functional Assessment**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to perform any physical activity without symptoms. Signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

**NYHA Staging / Survival in PPH**

* New York Heart Assoc./World Health Org. modification


[http://www.who.int/ncd/cvd/pph.htm](http://www.who.int/ncd/cvd/pph.htm)
Right Heart Catheterization

- Invasive measurement of:
  - Right atrial Pressure
  - Right ventricular Pressures
  - PA Pressure
  - Pulmonary capillary wedge pressure
  - Mixed venous oxygen saturation
  - Cardiac output
  - Vasodilator challenge

Image from A.D.A.M.

Pivotal Tests

- History
- Exam
- ECG
- Chest X-Ray (CXR)
- Echocardiogram
- Pulmonary Angiography
- VQ Scan
- PFT's
- TEE
- Polysomnography
- Exercise Echo
- Pulmonary Function Test (PFT's)
- TEE
- ABG's
- Overland Oximetry
- Scleroderma, SLE, RA
- Pulmonary Arterial Hypertension
- Periscleromycin
- Exercise RH Cath
- Vasodilator Test
- Exercise RH Cath
- Volume Loading
- Other CTD Serologies
- HIV Infection
- Scleroderma, SLE, RA
- Portopulmonary Hypertension
- Establish Baseline
- Prognosis
- Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response
- Exercise RH Cath

ACCF/AHA Diagnostic Algorithm

Pivotal Tests

- History
- Exam
- ECG
- Chest X-Ray (CXR)
- Echocardiogram
- Pulmonary Angiography
- VQ Scan
- PFT's
- TEE
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Mechanisms of Disease Pathology

RISK FACTORS AND ASSOCIATED CONDITIONS
- Collagen vascular disease
- Congenital heart disease
- Portal hypertension
- HIV infection
- Pregnancy
- Drugs and toxins
- Pregnancy
- Other genetic factors

VASCULAR INJURY
- Endothelial Dysfunction
- Thromboxane production
- Endothelin 1 production

DISEASE PROGRESSION
- Loss of response to short-acting vasodilator trial

Pivotal Tests

- History
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- Vasodilator Response
- Exercise RH Cath

Progression of PAH

- Pre-symptomatic/Compensated
- Symptomatic/Decompensating
- Declining/Decompensated

## Treatment

### General measures
- Supplemental oxygen
- Diuretics
- Digoxin
- Anticoagulation

### Rationale:
- Fresh intrapulmonary clots
- High risk for thromboembolic event
- Improved survival

### Treatment
- Warfarin- goal INR 1.6-2.5

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## Anticoagulation

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## Digoxin

- Inotropic effect: variable
- Used in varying number of patients in major center trials of PAH
- Short-term administration associated with an increase in cardiac output and reduced circulating catecholamines
- No long-term data available

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## Diuretics

- Majority of patients require them
- Variable response
- Follow renal and electrolyte parameters
- Individual patient assessment

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Oxygen

- Hypoxemia is detrimental: results in vaso-constriction
- Altitude and sleep may result in hypoxemia
- In congenital heart disease, probably no benefit

Other Management Issues

- Encourage exercise and activity within the limits of disease and ability to maintain O₂ levels
- Immunizations
- Contraception

Calcium Channel Blockers

Rationale:
- Rich et al NEJM 1992;327:76-81
- 64 patients with PPH
- 17 Significant vasoreactivity
  - 13 treated with Nifedipine 172mg + 41 mg/day
  - 4 treated with Diltiazem 720 + 208 mg/day
- 94% alive at 5 years

Treatment
- Diltiazem 360-900 mg/day
- Nifedipine 90-180 mg/day
- ? Amiodipine 20-40 mg/day

What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Negative

Oral CCB

Sustained Response

Yes

Continue CCB

What Is the Optimal Treatment Strategy?

"Vasodilator Response"
- Fall in mPAP ≥ 10 mm Hg
- + PAPm (absolute) < 40 mm Hg
- + Normal CO

Sustained Response
- Yes
- Continue CCB

Approved Therapeutic Targets

End points used in trials
- 6 minute walk distance
- VO2
- QOL
- Hemodynamics
- Time to clinical worsening
**Approved Therapeutic Targets**

- Endothelin Pathway
  - Pre-proendothelin
  - Endothelin-1
  - Endothelial cells
  - Arachidonic acid
- Prostacyclin Pathway
  - Prostacyclin (prostaglandin I₂)
  - Endothelial cells
  - Nitric Oxide

**Endothelin receptor Blocker**

- Ambrisentan: selective (ETₐ) antagonist
  - Approved doses: 5 mg and 10 mg qd
- Bosentan: dual (ETₐ and ETₐ) antagonist
  - Approved doses: 62.5 mg bid starting dose for 4 weeks increased to 125 mg bid maintenance dose
- Macitentan: dual (ETₐ and ETₐ) antagonist

**Endothelin receptor blockers vs Placebo in PH**

- Bosentan and Ambrisentan
  - Increased exercise capacity
  - Delayed the time to clinical worsening
  - Improved dyspnea score
  - WHO Functional Class

**Macitentan for PAH: Time To Clinical Worsening or Death**

- Mean change from baseline in 6 MWD (m)
- Time from treatment start (months)

Macitentan 10 mg: Hazard ratio=0.55; log-rank p=0.0001
Macitentan 3 mg: Hazard ratio=0.70; log-rank p=0.0108

N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous/subcutaneous prostanoids or ‘other worsening’ of PAH.

Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function
  - reversible transaminase elevations >3X ULN
  - may require dose adjustments or discontinuations
  - monthly LFTs required
- Edema
  - lower extremity edema may require diuretic adjustment
- Use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets

- Endothelin
  - Pathway
- Nitric Oxide
  - Pathway
- Prostacyclin
  - Pathway

Phosphodiesterase-5 Inhibitors

- Sildenafil
  - Approved dose: 20 mg tid
  - Approved for PAH (all classes)
- Tadalafil
  - Approved dose 40 mg once a day

PDE-5 Inhibitor

- Sildenafil Improved
  - Exercise capacity
  - Functional class
  - Hemodynamics
- Tadalafil Improved
  - Exercise capacity
  - Quality of life measures
  - Delayed clinical worsening
**Riociguat**

- It is a stimulator of soluble guanylate cyclase (sGC).
- Stimulates NO production.
- Does not require endogenous NO.
- Initiate at 1 mg taken 3 times a day and titrate by 0.5 mg every 2 weeks as tolerated to 2.5 mg.

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**PATENT-1: Riociguat for PAH**

**Change in 6MWD At Week 12**

Six-minute Walk Distance

<table>
<thead>
<tr>
<th>Week</th>
<th>Riociguat</th>
<th>Placebo</th>
<th>Observed</th>
<th>Imputed</th>
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<tbody>
<tr>
<td>0</td>
<td>n=126</td>
<td>n=112</td>
<td>n=116</td>
<td>n=116</td>
</tr>
<tr>
<td>2</td>
<td>n=121</td>
<td>n=117</td>
<td>n=118</td>
<td>n=118</td>
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<tr>
<td>4</td>
<td>n=124</td>
<td>n=119</td>
<td>n=121</td>
<td>n=121</td>
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<tr>
<td>6</td>
<td>n=125</td>
<td>n=120</td>
<td>n=122</td>
<td>n=122</td>
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<tr>
<td>8</td>
<td>n=126</td>
<td>n=121</td>
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<td>n=123</td>
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<tr>
<td>10</td>
<td>n=127</td>
<td>n=122</td>
<td>n=124</td>
<td>n=124</td>
</tr>
<tr>
<td>12</td>
<td>n=128</td>
<td>n=123</td>
<td>n=125</td>
<td>n=125</td>
</tr>
</tbody>
</table>

Placebo-corrected treatment effect = 36 m (95% CI: 20-52 m; p<0.0001)

N=445. Double-blind, placebo-controlled Phase III trial. 50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%).

Ghofrani H, et al. N=445. Double-blind, placebo-controlled Phase III trial. 50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%).

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**Approved Therapeutic Targets**

- Endothelin Pathway
- Nitric Oxide Pathway

**Prostacyclin Pathway**

- Prostacyclin (prostaglandin I2)
- Prostacyclin derivatives
- Smooth muscle cells
- Endothelial cells

**Prostacyclin Analogues:**

- Intravenous Subcutaneous, Inhaled
  - Epoprostenol (Flolan®)
  - Treprostinil (Remodulin®)

### Prostacyclin Analogues: Intravenous, Subcutaneous, Inhaled

- **Epoprostenol (Flolan®)**
- **Treprostinil (Remodulin®)**

### Prostacyclin Analogues: Intravenous, Inhaled

- **Iloprost (Ventavis®)**
- **Treprostinil (Tyvaso®)**

### Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

**Vary according to drug and route of delivery**

### Epoprostenol

- Synthetic salt of prostacyclin
- Rapid efficacy; short, 3- to 5-min half-life
- Approved for Class III and IV
- Invasive: requires continuous IV infusion
- Initiate at low dose 2ng/kg/min

*Flolan® (epoprostenol sodium) package insert. GlaxoSmithKline. Research Triangle Park, NC.*
Continuous IV Epoprostenol vs conventional therapy in IPAH

- Improved
  - Exercise Capacity
  - Hemodynamics
  - NYHA Class
  - Survival

Treprostinil

- Longer-acting prostacyclin analogue
- Subcutaneous and IV infusion;
- Approved for Class II-IV
- Efficacy slower than epoprostenol, requires higher doses

Inhalated Treprostinil

1. Inhalation device assembled
2. Measuring cup
3. One inhaled treprostinil ampule
4. Carrying case provided

Dosage delivery of 6 µg per breath.
Start at 3 breaths QID to up to 9 breaths QID

TYVASO (treprostinil) Improved Peak and Trough 6MWD at Week 12

<table>
<thead>
<tr>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO corrected: 20 m, P&lt;0.001</td>
<td>PBO corrected: 14 m</td>
</tr>
</tbody>
</table>

6MWD, 6-minute walk distance; PBO, placebo.
* Peak defined as measure between 10 and 60 minutes after dose. ** Trough defined as measure 24 hours after dose.
Iloprost

- Longer-acting prostacyclin analogue (20- to 30-min half-life)
- Aerosolized delivery system
- Approved for Class III and IV
- Requires frequent inhalations (6-9x/d)

Ventavis® (iloprost) package insert. CoTherix Inc. South San Francisco, CA.

I-neb® AAD® Once Daily Routine

At the beginning of each day, load Blue case with 6 CLEAN meshes

Administer therapy

After treatment, remove USED mesh and place it in Red case

At the end of each day, remove the USED meshes from the Red case and wash along with the mouthpiece and drug chamber in distilled water with 1 drop of liquid detergent

PAH Determinants of Risk

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MW distance</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Very elevated</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiographic findings</td>
<td>Pericardial effusion, significant RV dysfunction</td>
</tr>
<tr>
<td>Normal/near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
</table>

McLaughlin VV and McGoon M. In press.
## Treatment

**Monitoring Response to Treatment**
- 6 min walk
- Echocardiogram
- BNP
- Right heart Catheterization

## On-therapy Prognostic Indicators
- Functional Class I or II
- 6MWD > 380 m
- Hemodynamics
  - Normal cardiac index (> 2.2 L/min/m²)
  - Normal RA pressure
- Positive response to CCB
- BNP <180 pg/mL
- Tricuspid Annular plane systolic excursion > 1.8 cm


## Goal oriented therapy
- Improve functional status
- RA pressure less than 10 mmHg
- BNP less than 100
- 6 minute walk > 350 m

## Goal Oriented Therapy
- If patient does not improve, what would you do?
  - Substitute therapy
  - Add therapies
Combination Therapy in PAH

- Endothelin receptor antagonists
- Prostanoids (IV, SC, PO, PI)
- Phosphodiesterase-5 inhibitors

PACES: Change From Baseline in 6MWD after adding Sildenafil to IV Epoprostenol

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (on the left)</td>
<td>Sildenafil (on the right)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change from baseline (m)

ATS, 2006


Goal Oriented Treatment and Combination Therapy for PAH

Tadalafil Improved 6MWD in the Bosentan Treatment Subgroup

6MWD, 6-minute walk distance; NS, not significant.
**Combination Therapy in PAH**
- Endothelin receptor antagonists
- Prostanoids (IV, SC, PO, PI)
- Phosphodiesterase-5 inhibitors

**Atrial Septostomy**
- Percutaneous catheter based technique
- Allows shunting from Right to left
- Shown to improve
  - clinical status
  - Long lasting benefit
- Carries a mortality of 5-6%
- Reserved for patients with refractory right heart failure or recurrent syncope despite maximal medical therapy
- Acceptable baseline oxygenation
- Poor outcome
  - mRA > 20mmHg
  - PVRI > 55u/m²
  - Not indicated in patients with hemodynamic instability

**Transplantation**
- Symptomatic, Progressive Ds
- NYHA class III or IV
- Hemodynamic parameters
  - Cardiac index < 2L/min/m²
  - RA pressures > 15 mmHg
  - mPA pressure > 55mmHg

**1951**
"Primary Pulmonary Hypertension"
- "Runs a malignant course, characterized by right heart failure, frequently ending in sudden death"
- "There is no effective treatment"

*Dresdale DT Am J Med 1951: 11: 686-705*