Pulmonary Arterial Hypertension: The OTHER Hypertension: What do you need to know?

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Potential Conflicts of Interest

- Actelion Ltd.
- Encysive
- Glaxo-Wellcome
- Myogen (Gilead)
- Pfizer
- ICOS
- INO Therapeutics
- United Therapeutics
- Aztra-Zeneca
Really Useful Things to Remember About PAH

• Classification Dictates Treatment
  – Pulmonary hypertension is an observation not a diagnosis

• Diagnosis is Critical and Difficult
  – Echocardiography is best for screening but lacks specificity
  – Alternate and unusual diagnoses are the rule.
  – V/Q scan is important to exclude chronic thromboembolism
  – Right (possibly with Left) heart catheterization is the standard of care for diagnosis.

• Therapy
  – Calcium channel blockers are the best drugs nobody will ever use
  – Current therapy consists of risk stratified use of prostacyclins, endothelin receptor antagonists and phosphodiesterase inhibitors

• Future Therapies and Concepts are Rapidly Evolving
What is an abnormal pulmonary pressure?
Mean PAP greater than:

- 25 mm Hg at rest
- 30 mm Hg during exercise,

<table>
<thead>
<tr>
<th>Pulmonary Arterial Pressure (mm Hg)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>18 - 25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>6 - 10</td>
</tr>
<tr>
<td>Mean</td>
<td>12 - 16</td>
</tr>
<tr>
<td>PCWP</td>
<td>6 - 10</td>
</tr>
<tr>
<td>PVR (dynes-sec-cm⁻⁵)</td>
<td>60 - 120</td>
</tr>
<tr>
<td>I. Pulmonary Arterial Hypertension</td>
<td>III. Pulmonary Hypertension Associated with Disorders of the Respiratory System/Hypoxia</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>- Hypoventilation/OSA</td>
</tr>
<tr>
<td>- Familial</td>
<td>- COPD</td>
</tr>
<tr>
<td>- Associated with CTD, Portal HTN, HIV, Drugs*</td>
<td>- Pulmonary Parenchymal Disease</td>
</tr>
<tr>
<td>- With Venous Involvement</td>
<td>- High Altitude Exposure</td>
</tr>
<tr>
<td>- Pulmonary Hypertension of the Newborn</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>II. Pulmonary Venous Hypertension</td>
<td>Pulmonary Hypertension Associated with Chronic Thromboembolism</td>
</tr>
<tr>
<td>- Left Ventricular Dysfunction (Systolic or diastolic)</td>
<td></td>
</tr>
<tr>
<td>- Valvular Disease</td>
<td></td>
</tr>
<tr>
<td>- Pulmonary Vein Disease or Anomaly</td>
<td></td>
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<tr>
<td>- Pericardial Constriction</td>
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<td>------------------------------------------------------------------------</td>
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What is the estimated prevalence of pulmonary arterial hypertension in United States?

- **Population**
  - **Idiopathic**  
    - 1-4:500,000  
    - 3000 cases
  - **Familial**  
    - (6-26% of IPAH)
  - **Connective Tissue**  
    - 10%-20%  
    - 7500-30000 cases
  - **HIV**  
    - 1:5000  
    - 200 cases
  - **Portal Pulmonary**  
    - 5-8:1000  
    - 8000 cases
  - **Anorexigen**  
    - 1:25000
  - **Congenital Heart Disease**  
    - 100% of unrepaired  
    - ?3000-10000 cases
  - **CTEPH (600,000 PE)**  
    - 3:100  
    - 18000 cases

**Overall prevalence independently estimated at 50-100000 cases.**

**France prevalence**  
What distinguishes PAH from other elevations of pressures in the lungs?

- Pathology
- Progressive, fatal course
- Magnitude of pressure elevations in symptomatic patients
- Hemodynamic limitation of exercise
- Treatment
Pathophysiology in 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
   - Vascular Smooth Muscle Dysfunction
   - Impaired Voltage-Gated Potassium Channel (Kv1.5)

3. **DISEASE PROGRESSION**
   - Loss of Response to Short-Acting Vasodilator Trial

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

- **FLOW**
  - Adventitia
  - Media
  - Intima

- **SMOOTH MUSCLE HYPERTROPHY**
  - Early Intimal Proliferation

- **VASOCONSTRICTION**

- **ADVANCED VASCULAR LESION**
  - Adventitial and Intimal Proliferation
  - In situ Thrombosis
  - Plexiform Lesion

Gaine, JAMA, 2000
Idiopathic Pulmonary Arterial Hypertension: Overall Survival Without Treatment

Est. Median survival: 2.8 yrs (95% CI, 1.9 to 3.7 years)

Survival by Functional Class in IPAH

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Symptoms</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
<td>58.6 months</td>
</tr>
<tr>
<td>II</td>
<td>Ordinary Activity</td>
<td>31.5 months</td>
</tr>
<tr>
<td>III</td>
<td>Less than Ordinary Activity</td>
<td>31.5 months</td>
</tr>
<tr>
<td>IV</td>
<td>Rest</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Impact of Functional Class at Period 1 on Subsequent Survival

“Typical” Pulmonary Pressures in Patients with Various Disorders

Mean PAP (mm Hg)

- Normal
- COPD
- OSA
- SCD
- IPF
- PAH (CTEPH)

PAP = 25mm Hg
Typical Hemodynamic Picture of Pulmonary Arterial Hypertension

Key Elements in Classification

• All pulmonary hypertension is not the same.
• Pulmonary arterial hypertension is uniquely fatal and progressive.
• Pathogenesis involves endothelial dysfunction and dysregulation of growth with important genetic susceptibilities for some cases of idiopathic diseases
Diagnosis
When should the diagnosis of PAH be considered?

- Patients with unexplained exercise limitation
- Patients with clinical signs consistent with right heart dysfunction
- Patients with abnormal right ventricular findings on radiography, echocardiography or electrocardiography
- Patients with systemic disease known to be associated with PAH
Pulmonary Arterial Hypertension: Detection and Diagnosis

Is there a reason to suspect PAH
Clinical history (symptoms, risk factors, family Hs.), Exam, CXR, ECG

No further evaluation for PAH

Is PAH likely?
Echo

Is PAH due to LH disease?
Echo

Is PAH due to CHD?
Echo with contrast

Is PAH due to CTD, HIV?
Serologies

Is chronic PE suspected?
VQ scan

Is PAH due to LH disease?
yes

Is PAH due to CHD?
no

Is PAH due to CTD, HIV?
yes

TRV to measure RVSP; RVE; RAE; RV Dysfunction:

Rationale

Dx LV systolic, diastolic dysfunction; valvular disease: Appropriate treatment and further evaluation if necessary, including R&LHC

Dx abnormal morphology; shunt:
Surgery. Medical treatment of PAH or evaluation for further definition or other contributing causes, including R&LHC if necessary

Dx Scleroderma, SLE, other CTD, HIV: Medical treatment of PAH and further evaluation for other contributing causes, including RHC

Pulmonary Arterial Hypertension: Detection & Diagnosis

Is chronic PE suspected?
  VQ scan

no      yes

Is PAH due to lung disease or hypoxemia?
PFTs, arterial saturation

no      yes

Is chronic PE confirmed and operable?
Pulmonary angiogram

no      yes

Anatomic definition (CT, MRI may provide additional useful but not definitive information):
Thromboendarterectomy if appropriate or medical treatment; clotting evaluation; a/c

Dx parenchymal lung disease, hypoxemia, or sleep disorder:
Medical treatment, oxygen, positive pressure breathing as appropriate, and further evaluation for other contributing causes, including RHC if necessary

Document exercise capacity regardless of cause of PH:
Establish baseline, prognosis and document progression/response to treatment with serial reassessments

Document PA and RA pressures, PCWP (LV or LA pressure if PCWP unobtainable or uncertain), transpulmonary gradient CO, PVR, SvO₂, response to vasodilators:
Confirm PAH, or IPAH if no other cause identified
Discuss genetic testing and counseling of IPAH

What limitations are caused by the PAH?
Functional class; 6-minute walk test

What are the precise pulmonary hemodynamics?
RHC

Alternative Diagnoses of Patients Referred to PAH Specialty Clinic

N = 268, all patients referred to PAH specialty center.
# Pulmonary Hypertension: Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
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<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>Jugular vein distention</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Prominent right ventricular impulse</td>
</tr>
<tr>
<td>Syncope</td>
<td>Accentuated pulmonic valve component (P_2)</td>
</tr>
<tr>
<td>Anginal chest pain</td>
<td>Right-sided third heart sound (S_3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Tricuspid insufficiency murmur</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
</tr>
</tbody>
</table>

Nauser TD, Stites SW. *Am Fam Physician* 2001;63(9):1789-98
Findings on Electrocardiogram

- RVH, RAE, RAD, RBBBD
Findings in PH Chest Radiography

- Cardiac enlargement
- Prominent proximal PA
- “Pruning” of distal PA
Echocardiography in PAH

- T R
- RVE
- RAE
- RVH
- Flattening of IVS
- Dilated IVC
Accuracy of PH Diagnosis by Echocardiography in Advanced Lung Disease

317 patients with RHC & Doppler less than 30 days apart
Chronic Thromboembolic Disease
Pulmonary Endarterectomy
Misclassification of PAH Due to Use of PCWP Rather Than LVEDP

Concordance of PCWP and LVEDP in Patients with Pulmonary Hypertension N=4666

- Concordant PVH: 85%
- Concordant PAH: 6%
- Discordant PVH: 3%
- Discordant PAH: 14%

Key Elements and Pitfalls in PH Workup

- PAH in a differential diagnosis should be considered frequently but is a rare diagnosis.
- Echo RVSP estimates can be unreliable.
- Chronic thromboembolism is an important consideration among patients with PH.
- Be suspicious of cases which do not fit “typical” patient presentations.
- All patients getting treatment for PAH deserve right heart cath (and perhaps left heart cath).
Targets for Therapy in PAH

General Supportive Therapy for PAH

- Oxygen
- Diuretics
- Digoxin
- Anticoagulation
- Contraception
- Avoid anemia
General Points on Therapy of Pulmonary Hypertension

- The vast majority of data reflect IPAH patients and is abstracted to PAH.
- Experience and data (when available) does not support the use of patients that do not have the diagnosis of PAH.
Why are calcium channel antagonists like Brooke Shields?

• Both have gotten significant attention while offering very little to very few!
Definitions for Calcium Channel Antagonist Therapy

- Acute challenge with inhaled NO, intravenous epoprostenol or intravenous adenosine.
- Positive Response:
  - $>10\text{mm mean PAP decrease and}$
  - $<40\text{mm final mean PAP}$
  - Unchanged or increased CI
- Sustained Response to CCB:
  - Attainment of NYHC I or II with normal or near normal hemodynamics after several months of therapy.
Prostacyclin Therapy

Multiple Potential Therapeutic Actions

- Vasodilation
- Antiproliferative
- Antiplatelet
- Increase NO
- Decrease ET-1
- Inonotrope

Epoprostenol (Flolan®)

Iloprost (Ventavis®)

Treprostinil (Remodulin®)
Epoprostenol Delivery System

- Continuous IV infusion
- Short $t_{1/2}$ & chemical instability
- Adverse outcomes related to delivery system
- Initial dosing 4-8 ng/kg/min
- Ultimate dosing frequently 40-60 ng/kg/min
- Expensive ($25,000-125,000/year)
- Difficult to manage follow-up
- Improves:
  - exercise capacity
  - hemodynamics
  - survival
Treprostinil SC Delivery System

- A stable prostacyclin analog
- Longer $t_{1/2}$
- Subcutaneous delivery
- Similar SE profile compared to epoprostenol*
- Site pain
Ventavis® (iloprost) Inhalation Solution:

**Dosage and Administration**

- Indicated for inhalation via the Prodose® AAD® system only
- 6-9 inhalations daily during waking hours
  - No more than once every two hours
- Dose: maximum of 2.5 or 5 mcg per treatment
  - 2.5 mcg initial dose
  - If well tolerated, increase to 5 mcg and maintain.
  - If 5 mcg dose not tolerated, reduced to 2.5 mcg and maintain.
ET-1 ACTIVITIES ARE MEDIATED BY ETA AND ETB RECEPTORS

ET-1 binding to ETB stimulates NO/PGI2 production and clears ET-1.

ETA and ETB receptors play a crucial role in the regulation of vascular tone and smooth muscle cell function.

Studies suggest that the blockade of the ETB receptor contributes to the imbalance of the L-arginine/NO pathway.

Endothelin Antagonist Therapy

- Dual or semi-selective antagonism of endothelin receptors
- High bioavailability
- Once or twice daily dosing
- Different patterns of drug interaction
- Side effects/Adverse effects
  - Liver Toxicity – requires monthly monitoring
  - Teratogen
  - Anemia
  - Edema

Bosentan (Tracleer®)

Ambrisentan (Letaris®)

Sitaxsentan (Thelin®)
Phosphodiesterase Inhibitors

- Selective phosphodiesterase E5 inhibitor
  - Vasodilation
  - Antiproliferative
- Should not be given with nitrates, caution with alpha blockers
- Can have hypotension and edema formation
- Well tolerated overall
- No blood level monitoring
- No LFT abnormalities

Sildenafil (Revatio®)

Tadalafil (®)
Transplantation for PAH

- Reserved for patients that have failed medical management
- Double lung transplant typically heart-Lung NOT NEEDED
- Early referral of appropriate candidates to a transplant center still reasonable
Algorithm for the Management of PAH

Anticoagulants + Diuretics + Oxygen + Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Sustained Response NYHC I or II?

Yes

Continue Oral CCB

No

Lower Risk

ERA’s or PDE-5 (oral)
Epoprostenol or Treprostinil (IV)
Iloprost (Inhaled)
Treprostinil (SC)

Investigational Protocols
Combination Therapies

Higher Risk

Epoprostenol or Treprostinil (IV)
ERA’s or PDE-5
Iloprost (Inhaled)
Treprostinil (SC)

Investigational Protocols
Combination Therapies

Atrial Septostomy
Lung Transplantation

*Reassess at 1-3 month intervals:
Are Goals of Therapy Met?

Adapted from McLaughlin VV, McGoon MD Circulation 2006 114:1417-1431
# Prognostic Factors for Risk of PAH Disease Progression


<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>
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</table>
Current Treatment and Follow-up

- Consider coumadin, digoxin, diuretics and oxygen
- Goal directed therapy (Walk +/- hemodynamics +/- FC)
- Frequent follow-up with exercise and imaging proportional to need, risk and expected drug action
- Recath with vasodilator testing at 6-12 mo, with changes in therapy and consideration cath yearly
Sobering Facts About Current Therapy

- Medical therapy will statistically fail in almost all patients at some time.
- Statistical failure is different for different therapies and only partially defined.
- We usually have no clear indication of which agents are best for any given patient.
- Optimal combination therapy is unknown.
- Current experience suggests that many combinations are not likely optimal.
Future Directions in PAH: Potential New Therapeutic Targets

- Prostacyclin Analogs
  - Oral and inhaled treprostinil
- Endothelin Antagonists
  - Sitaxsentan
- NO Augmentation
  - C-GMP phosphodiesterase inhibitors (tadalafil)
- Tyrosine kinase/growth factor receptor inhibitors
  - Imatinib, sorafenib
- Vasoactive intestinal peptide (VIP)
- Serotonin transporter agonists
- Adrenomedullin
- Rho-kinase inhibitors
- Cicletanine
- Endothelial progenitor cells
- Gene therapy
  - Vectors expressing prostacyclin synthase, endothelial NOS, or vascular endothelial growth factor
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  - Pulmonary hypertension is an observation not a diagnosis

- **Diagnosis is Critical and Difficult**
  - Echocardiography is best for screening but lacks specificity
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- **Therapy**
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  - Current therapy consists of risk stratified use of prostacyclins, endothelin receptor antagonists and phosphodiesterase inhibitors

- **Future Therapies and Concepts are Rapidly Evolving**
QUESTIONS?

You have a very rare condition we call "Good Health." Cigarettes & fast food should take care of it fairly quickly & we'll see you again in six months.