Pulmonary Hypertension

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No Disclosures
The PH Consult...

52 yo WM with COPD, HTN presents with progressive DOE

- LABA/LAMA x 5 years
- ACE-I x 1 year

- 2 exacerbations in last year
- 2LPM oxygen x 6mo
- An echo is ordered…

<table>
<thead>
<tr>
<th>Pulmonary Function Testing</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>3.79 (75%)</td>
<td>3.87 (77%) +2</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.39 (62%)</td>
<td>2.56 (66%) +7</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>TLC</td>
<td>7.01 (103%)</td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>3.05 (136%)</td>
<td></td>
</tr>
<tr>
<td>DLCO (adj)</td>
<td>7.01 (23%)</td>
<td></td>
</tr>
</tbody>
</table>
The COPD-PH Consult...

- Biatrial enlargement
- RV dilated
- LV EF normal
- Elevated PASP – 59mmHg +RAP
- Decreased RV Function – TAPSE = 1.5
When to Consider Pulmonary Vascular Disease

Pulmonary Consult
- Moderate obstructive lung disease stable.
- Abnormal echo.
- Continue present management of COPD

Cardiology Consult
- Normal left ventricular systolic function
- Abnormal PFTs
- Continue present management of HTN

IT’S NOT THE HEART
IT’S THE LUNGS

IT’S NOT THE LUNGS
IT’S THE HEART
Pulmonary Hypertension Objectives

- Epidemiology/Classification
- Presenting Symptoms
- Screening/Diagnosis
- Treatment
How Common is Pulmonary Hypertension?

WHO Group I PAH:

- Prevalence 10-20 cases/million population*
- US population 311 million
- US cases of PAH: 4,665 (orphan disease < 200K in U.S.)
- Worldwide population: 6 billion
- Worldwide cases of PAH: 90,000

**WHO Group I PAH is a rare, orphan disease**

- *But PH is not…*

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How Common is Pulmonary Hypertension?

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>Estimated US prevalence (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (PAH)</td>
<td>4,665</td>
</tr>
<tr>
<td>Group II (PVH)</td>
<td>millions</td>
</tr>
<tr>
<td>Group III (PH due to ↓O2)</td>
<td>&gt;200,000</td>
</tr>
<tr>
<td>Group IV (chronic PE)</td>
<td>90,000</td>
</tr>
</tbody>
</table>

All sites accessed on May 11, 2011
# How Common is Pulmonary Hypertension?

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>Estimated US prevalence (n)</th>
<th>Pubmed citations* (n)</th>
<th>Google hits** (n)</th>
<th>Clinical trials† (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N=330)</td>
</tr>
<tr>
<td>Group I (PAH)</td>
<td>4,665</td>
<td>36,629 (6,134)</td>
<td>1.18 million (586,000)</td>
<td>140 (42%)</td>
</tr>
<tr>
<td>Group II (PVH)</td>
<td>millions</td>
<td>4,724</td>
<td>64,900</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Group III (PH due to ↓O2)</td>
<td>&gt;200,000</td>
<td>5,186</td>
<td>355,000</td>
<td>74 (22%)</td>
</tr>
<tr>
<td>Group IV (chronic PE)</td>
<td>90,000</td>
<td>3,129</td>
<td>38,100</td>
<td>33 (10%)</td>
</tr>
</tbody>
</table>


All sites accessed on May 11, 2011
Pulmonary Hypertension: A Global Health Problem

Bursi et al. JAAC 2012
Graham et al. Chest 2010
Butrous et al. Circulation 2008

Other conditions: OSA, ILD, and HFpEF where prevalence of PH between 10-40%
Presenting Symptoms of PAH

**Symptoms Are Often Non-Specific**

- Progressive onset exertional dyspnea: 60%
- Syncope: 10%
- Pre-syncope: 13%
- Chest pain or discomfort: 17%
- Fatigue: 19%
- Palpitations: 5%
- Ornery Syndrome: <1%

**REVEAL Registry**

- **Number Pts**: 2525
- **% Female**: 79.5
- **Age, yr (range)**: 50.1 ± 14.4
- **NYHA III-IV (%) At diagnosis**: 73.6
- **NYHA III-IV (%) At enrollment (25mo)**: 55.6
- **Time from Symptom to RHC (mo)**: 34.1 ± 1.2

Badesch D et al; PAH: Baseline Characteristics From REVEAL Registry. CHEST 2010; 137;376-387
### WHO Clinical Classification of PH
#### Nice Guidelines 2013

<table>
<thead>
<tr>
<th>Group 1—PAH</th>
<th>Group 2—PH owing to left heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
<td>2.1 Systolic dysfunction</td>
</tr>
<tr>
<td>1.2 Heritable</td>
<td>2.2 Diastolic dysfunction</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
<td>2.3 Valvular disease</td>
</tr>
<tr>
<td>1.2.2 ALK-1, endoglin, SMAD 9, CAV-1, KCNK3</td>
<td></td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
<td></td>
</tr>
<tr>
<td>1.3 Drug- and toxin-induced</td>
<td></td>
</tr>
<tr>
<td>1.4 PAH associated with:</td>
<td></td>
</tr>
<tr>
<td>1.4.1 Connective tissue diseases</td>
<td></td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
<td></td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
<td></td>
</tr>
<tr>
<td>1.4.4 Congenital systemic to pulmonary shunts</td>
<td></td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
<td></td>
</tr>
<tr>
<td>1’ Persistent pulmonary hypertension of newborn</td>
<td></td>
</tr>
<tr>
<td>1” Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis</td>
<td></td>
</tr>
</tbody>
</table>
Where is the lesion?
Pathogenesis of Pulmonary Arterial Hypertension

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

- Advenitia
- Media
- Intima
- Flow
- Smooth Muscle Hypertrophy
- Early Intimal Proliferation
- Vasoconstriction
- Advanced Vascular Lesion
- Adventitial and Intimal Proliferation
- Thrombosis
- Plexiform Lesion
PAH: A Progressive Disease

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

CO
PAP
PVR

Symptom Threshold
Right Heart Dysfunction

Time

Work Up

- CBC
- CMP
- BNP
- HIV
- TSH
- RA/Anti-CCP
- ANA with reflex
- B-HCG

- 6 minute walk
- EKG
- CXR & V/Q scan
- CT chest
- PFTs
- Echo
- Right Heart Cath
Work Up

- CBC
- CMP
- BNP
- HIV
- TSH
- RA/Anti-CCP
- ANA with reflex
- B-HCG
- 6 minute walk
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- CXR & V/Q scan
- CT chest
- PFTs
- Echo
- Right Heart Cath
Echocardiographic Features of PAH vs PVH

### Pulmonary Arterial Hypertension

**2-D echo:**
- Normal LA, LV size; small LV (< 3.5 cm)
- No LVH
- Normal to high ejection fraction
- Septal bowing (systole> diastole)
- Pericardial effusion

**Doppler:**
- Variable PASP
- No MR
- Grade 1 diastolic dysfunction (E<A)

### Pulmonary Venous Hypertension

**2-D echo**
- Dilated LA
- Usually dilated LV ± LVH
- Variable LV EF
- RV/LV ratio < 1
- LV remains round in short axis

**Doppler**
- Variable PASP
- > 2+ MR
- E>A diastolic dysfunction (Grade 2-3)
Echo Based Pulmonary Pressures

- RA pressure estimated from IVC
- RVSP calculated from TR jet
- \( \text{PASP} = \text{RA} + \text{RVSP} \)
- \( \text{PASP} \geq 40\text{mmHg} \) is concerning for pulmonary hypertension
Echocardiographic Features of PAH vs PVH

Pulmonary Arterial Hypertension

Pulmonary Venous Hypertension
Right Heart Catheterization

- Obtain Hemodynamics
- Can run shunt studies
- Look for vasoreactivity
Right Heart Catheterization

- Obtain Hemodynamics
- Can run shunt studies
- Look for vasoreactivity (in appropriate patients)
  - Inhaled nitric oxide
  - IV adenosine
  - IV epoprostenol
- PA gram for CTEPH
- Exercise/fluid challenge
  - Gray area as to interpretation
Ca++ Channel Blockers in IPAH

**Methods:**
- 64 patients (26% responders to vasodilator challenge)
- Treatment for up to 5 years for responders

**Treatment:**
- Nifedipine (172 mgs daily);
  Diltiazem (720 mgs)
- Warfarin (55% patients)

Clinical Classification of Pulmonary Hypertension

**Class 1: PAH**
- mPAP at rest: ≥ 25mmHg
- PCWP: ≤ 15mmHg
- PVR: >3 Wood

**Class 2: PVH**
- mPAP at rest: > 25mmHg
- PCWP: > 15mmHg

**Class 3: PH associated with lung disease**
- mPAP at rest: > 25mmHg
- Underlying chronic lung disease:

**Class 4: PH CTEPH**
- mPAP at rest: > 25mmHg
- PCWP: ≤ 15mmHg
- Evidence of chronic perfusion defects
6th World Symposium Hemodynamic Definition of PH/PAH

**PH**  Mean PAP $> 20$ mm Hg

**PAH**  Mean PAP $> 20$ mm Hg \textit{plus}  
PCWP/LVEDP $\leq 15$ mm Hg \textit{plus}  
PVR $> 3$ Wood Units

Simmoneau et al. ERJ 2019
Lead Time Bias?
PAH Still a Progressive Disease

Rich et al, CHEST 2010
“Nevertheless, a change in the haemodynamic definition of PH due to PVDs does not imply treating these additional patients, but highlights the importance of close monitoring in this population. Prospective trials are required to determine whether this PH population might benefit from specific management.”
<table>
<thead>
<tr>
<th>Determinants of prognosis (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope*</td>
<td>Repeated syncope**</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165–440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt;15 ml/min/kg (&gt;65% pred.) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO₂ slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l  NT-proBNP &lt;300 ng/l</td>
<td>BNP 50–300 ng/l  NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm² No pericardial effusion</td>
<td>RA area 18–26 cm² No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm² pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>
Treatment of PH

- WHO Group 1
  - PAH
    - Pulmonary Vasodilator Therapy
      - Primary Indication
1891

1941 “PPH”

1973

1998

2002

2003

2008

2013

Classifications

NIH Registry

Natural history

2nd WHO Conference (Evian, France)

3rd World Conference Venice, Italy

4th World Conference Dana Point, CA

5th World Conference (Nice, France)

• Right Ventricle
• Exercise PH
• End-Points

1992 CCB

1996 IV PGI2

PPH1 2000

Treprostinil

AIR

Breathe-1

BREATH-2

STRIDE1

Beraprost

SUPER

SERAPH

STEP

COMBI

PHIRST

TRIUMPH

IMATINIB

ARIES1/2

EARLY

PACES

FREEDOM-C

ATHENA-1

Genetics/Genomics

Modern medical therapy

Romberg (PH-autopsy)

Dresden
Treatment of Group 1 PAH

Ambrisentan (Letairis)
Bosentan (Tracleer)
Macitentan (Opsumit)

Sildenafil (Revatio)
Tadalafil (Adcirca)
Riociguat (Adempas)

Epoprostenol (Flolan)
Treprostinil (Remodulin - IV/SQ) (Tyvaso – Inhaled) (Orenitram – Oral)
Iloprost (Ventavis – Inhaled)
Selexipag (Uptravi)
A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

Barst et al, NEJM 1996
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

- Published NEJM 2015
- Randomized double blinded in 2:1:1 ratio
  - Tadalafil + Ambrisentan
  - Tadalafil + Placebo
  - Ambrisentan + Placebo
- N=500 patients with FC II-III symptoms
- Primary end point: Time to clinical worsening
A Combination Therapy vs. Pooled Monotherapy

Participants with No Event (%)

Hazard ratio, 0.50 (95% CI, 0.35–0.72)
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Combination therapy</th>
<th>Pooled monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>253</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td>229</td>
<td>209</td>
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<td>36</td>
<td>25</td>
</tr>
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<td></td>
<td>4</td>
<td>5</td>
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</table>
Treatment of PH

- **WHO Group 1**
  - PAH
  - Pulmonary Vasodilator Therapy
  - Lung Transplant

- **WHO Group 2**
  - PVH
  - Optimize heart failure medications
  - Diuresis
  - What about pulmonary vasodilators?
### Pulmonary Vasodilators in Group 2: PVH

- Theoretical risk of pulmonary edema

<table>
<thead>
<tr>
<th>Prostacyclin</th>
<th>ERA</th>
<th>Trial</th>
<th>Outcome</th>
<th>Trial</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td></td>
<td>Incr. Mortality</td>
<td></td>
<td>VERITAS</td>
<td>Lack of eff.</td>
</tr>
<tr>
<td>ENABLE</td>
<td></td>
<td></td>
<td></td>
<td>ENABLE</td>
<td>Incr heart failure adm.</td>
</tr>
<tr>
<td>ENCOR</td>
<td></td>
<td></td>
<td></td>
<td>ENCOR</td>
<td>Trend incr. mort</td>
</tr>
<tr>
<td>EARTH</td>
<td></td>
<td></td>
<td></td>
<td>EARTH</td>
<td>Lack of eff.</td>
</tr>
</tbody>
</table>
Pulmonary Vasodilators in Group 2: PVH

- PDE5 inhibitors:
  - Most promising
  - small trials with encouraging results

<table>
<thead>
<tr>
<th>PDE-5 Inhibitor</th>
<th>TRIAL</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lewis et al Circ 2007</td>
<td>Improved exercise cap and QOL in systolic HF with PH</td>
</tr>
<tr>
<td></td>
<td>Guazzi et al JACC 2007</td>
<td>Improved exercise capacity, improved PAP, decreased hospitalization</td>
</tr>
</tbody>
</table>
Treatment of PH

WHO Group 1
PAH

Pulmonary Vasodilator Therapy

WHO Group 2
PVH

Optimize heart failure medications
Diuresis
No role for ERA
No role for prostacyclin
?Perhaps role for PDE-5?

WHO Group 3
PH lung dz

Optimize lung disease medications
Reverse hypoxia
Pulmonary Vasodilators in Group 3: PH lung disease

- Theoretical risk of increasing VQ mismatching and worsening hypoxemia

PH-ILD

No clear benefit from PAH specific therapy
Trend towards increased oxygen requirements*

* Pavec JL et al Systemic sclerosis related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies; Arthritis & Rheumatism 2011
Pulmonary Vasodilators in Group 3: PH

- PH- COPD
  - Multiple small studies, poorly defined patients
  - Prostacyclins
    - IV showed worsening oxygenation*
    - Inhaled showed improved oxygenation**
  - ERA showed trends towards worsening oxygenation, decline in 6MWT, and worse QOL**
  - PDE-5 well tolerated, attenuated exercise induced rise in mPAP+

* Archer CHEST 1996, ** Dernaika Resp 2010, ** Tamm et al; A randomised controlled trial of bosentan in severe COPD, ERJ 2008 32 619-628
Five Things Physicians and Patients Should Question

Don’t routinely offer pharmacologic treatment with advanced vasoactive agents approved only for the management of pulmonary arterial hypertension to patients with pulmonary hypertension resulting from left heart disease or hypoxemic lung diseases (Groups II or III pulmonary hypertension).

Evidence and clinical practice guidelines have not established benefits of vasoactive agents (e.g., prostanoids, phosphodiesterase inhibitors, endothelin antagonists) for patients with pulmonary hypertension resulting from left heart disease or hypoxemic lung diseases. Moreover, the use of these agents may cause harm in certain situations and incurs substantial cost and resource utilization. Patients should be carefully assessed (including at a minimum right heart catheterization, echocardiography, chest CT, six minute walk test and pulmonary function testing) to confirm that they have symptomatic pulmonary arterial hypertension prior to having approved agents initiated.
Treatment of PH

WHO Group 1
PAH

WHO Group 2
PVH

Optimize heart failure medications
Diuresis

No role for ERA
No role for prostacyclin
?Perhaps role for PDE-5?

WHO Group 3
PH lung dz

Optimize lung disease medications
Reverse hypoxia

No role for ERA
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Treatment of PH

WHO Group 1
PAH

Pulmonary Vasodilator Therapy

Optimize heart failure medications
Diuresis

No role for ERA
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WHO Group 2
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Optimize lung disease medications
Reverse hypoxia

No role for ERA
? role for inh prostacyclin?
?Perhaps role for PDE-5?

WHO Group 3
PH lung dz

Anticoagulate
Pulmonary Vasodilators
Referral for Thromboendarterectomy

WHO Group 4
CTEPH
Pulmonary Vasodilators in Group 4: CTEPH

- Anticoagulation is the backbone
- Clear role for pulmonary vasodilators in non-operative candidates

Thromboendarterectomy is treatment of choice as it offers a durable cure.
Surgical Options

- Lung Transplant
- PTE/BPA
- Atrial Septostomy
- RVAD
Temporary Right Ventricular Assist Devices

Anderson et al, J Heart Lung Transplant 2015
Recover Right Study

Cardiac Index

Central Venous Pressure

Anderson et al, J Heart Lung Transplant 2015
RVAD as Destination Therapy

Device Flow vs PAP

Rosenzweig et al, Journal of Heart and Lung Transplantation 2016
Conclusions

- Pulmonary Hypertension is a complex comorbid condition with many potential treatment pathways.
- Hemodynamic distinctions
- Pathologic distinctions
- Treatment distinctions as data to guide decision making outside of WHO Group 1 PAH and CTEPH is limited
Questions?
Peter.Hountras@cuanschutz.edu