Suspecting Pulmonary Hypertension in the Dyspneic Patient: Who, When, and How

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Faculty Disclosures

• Has no financial conflicts to disclose.
The **Pulmonary Hypertension Association (PHA)** is the leading non-profit organization for PH research, public awareness, and services. The organization has over 16,000 members, including patients, family members, and medical professionals.

www.PHAssociation.org
Let’s get started...
PH Lessons

1. Pulmonary Hypertension Is Common
2. WHO Group I PAH Is Rare but Deadly—Make the Diagnosis Early
3. Know the PH Clinical Clues in the Dyspneic Patient
4. Look Beyond the PA Pressure on Echocardiography
5. Definitive Diagnosis of PAH Requires Invasive Hemodynamic Testing
PH Lessons (cont’d)

6. Always Look for the Underlying Cause of PH

7. Treatment of PH—Get the Diagnosis Correct and Determine Functional Status

8. Lack of Response to Acute Vasodilator Challenge in PAH ≠ Untreatable

9. First Do No Harm—Learn to Differentiate WHO Group I PAH From Other Forms of PH

10. Appropriate, Timely, and Collaborative Care: Key to Early and Effective Treatment of PH in the Dyspneic Patient
Case Presentations

2 Women With Dyspnea
2 Women With Dyspnea

Patient 1

Patient 2
2 Women With Dyspnea

**Patient 1**

**Age:** 57 years

**Comorbidities:**
- HTN
- Diabetes
- CKD
- Atrial fibrillation

**Patient 2**

**Age:** 48 years

**Comorbidities:**
- HTN
- CKD
- Systemic sclerosis
2 Women With Dyspnea

Patient 1

NYHA Class III
- BP: 172/65 mm Hg
- JVP elevated
- Irregularly irregular
- Loud P2
- 2/6 murmur (holosystolic, left sternal border)
- 2+ leg edema

Patient 2

NYHA Class III
- BP: 120/84 mm Hg
- JVP elevated
- Regular rate, rhythm
- Loud 2
- 3/6 murmur (holosystolic, left sternal border)
- 2+ leg edema
What do we do?

Does this patient have pulmonary hypertension (PH)?

If PH, does this patient have pulmonary arterial hypertension, PAH?

PAH versus PH, why should I care?
Pulmonary Arterial Hypertension (PAH): Key Points

• Average 14-mo delay from initial presentation to diagnosis: need to diagnose early

• Evaluation must be methodical and include echocardiography and right heart catheterization

• To treat effectively and avoid harm, PAH must be differentiated from pulmonary venous hypertension

• Prognosis improves with therapy, but PAH remains a progressive fatal disease

• Therapies and management strategies continue to evolve
Pulmonary Hypertension = abnormally high pressure in the pulmonary arteries
Pulmonary Hypertension = abnormally high pressure in the pulmonary arteries
5th World Symposium on PH: Hemodynamic Definition of PH/PAH

**PH**
Mean PAP $\geq 25$ mm Hg at rest during RHC

**PAH**
Mean PAP $\geq 25$ mm Hg \textit{plus}
PAWP $\leq 15$ mm Hg \textit{plus}
PVR $> 3$ Wood units

Look for 6th World Symposium Update
End of 2018

5th World Symposium on PH: Classification

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
     1.2.1 BMPR2
     1.2.2 ALK1, ENG, Smad 9, CAV1, KCNK3
     1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
     1.4.1 Connective tissue disease
     1.4.2 HIV infection
     1.4.3 Portal hypertension
     1.4.4 Congenital heart diseases
     1.4.5 Schistosomiasis

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1”. Persistent PH of the newborn

2. PH due to left heart disease
   2.1 LV systolic dysfunction
   2.2 LV diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases

4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH


Look for 6th World Symposium Update End of 2018
Lesson 1

Pulmonary Hypertension Is Common
PH in the Community: PASP and Survival

- **All Participants** (N=1413)
  - Overall Log Rank $p < 0.001$

- **No Cardiopulmonary Disease** (N=778)
  - Overall Log Rank $p = 0.002$

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**Time (yr)**

**Cumulative survival**

**PASP quintile**
- 1: 15-23 mm Hg
- 2: 24-25 mm Hg
- 3: 26-29 mm Hg
- 4: 30-32 mm Hg*
- 5: 34-66 mm Hg*

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**PASP tertile**
- 1: 15-24 mm Hg
- 2: 24-28 mm Hg
- 3: 28-43 mm Hg*

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*Bonferroni-adjusted $p < 0.05$ in pairwise comparison with lowest tertile.

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**Up to 20% of the US population has echo evidence of PH**
PH Is Common in Elderly Patients With Heart Failure With Preserved EF

• PH by echo in a community-based sample:
  – heart failure with preserved EF: 83% with PH
  – HTN but no CHF (control): 8% with PH

• Patients with PH:
  – older
  – higher systolic BP
  – larger LA size
  – higher E/e’ ratio

Epidemiology of PH by Echo

- Single echo lab / Australian community of 165,450
- Etiology of PH noted on echocardiogram

N=936 of 10,314 patients with echo PASP >40 mm Hg.
Lesson 2

WHO Group I PAH Is Rare but Deadly—
Make the Diagnosis Early
Idiopathic PAH: Survival If Untreated

- Incidence: 2-6 cases per million in US
- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

Schematic Progression of PAH

Presymptomatic/Compensated
Symptomatic/Decompensating
Declining/Decompensated

CO= \frac{TPG}{PVR}

TPG= transpulmonary gradient.
Advanced Functional Class at Diagnosis Common and Indicates Delayed Recognition

- Approximate prevalence: 15 cases/million
- More common in women
- Spans broad age range
- Delay in diagnosis persists
- Most patients diagnosed with late symptoms
- Poor prognosis if untreated (median survival <3 yr)

REVEAL Registry (N=1831)  NIH Registry (N=187)  French Registry (N=674)

Lesson 3

Know the PH Clinical Clues in the Dyspneic Patient
Patient Presentation: Nonspecific Symptoms

- Dyspnea
- Fatigue
- Near syncope/syncope
- Chest pain
- Palpitations
- Edema

Median Time From Symptom Onset to Diagnosis

- NIH Registry (1981 to 1985) 1.3 years
- REVEAL Registry (2006 to 2007) 1.1 years

Is There a Reason to Suspect PAH?

**Clinical Presentation**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam (PH)</th>
<th>Exam (RV Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea (86%)</td>
<td>Loud P2 (listen at apex)</td>
<td>JVD; increased A wave, V wave; hepatojugular reflex</td>
</tr>
<tr>
<td>Fatigue (27%)</td>
<td>RV lift (left parasternal – fingertips)</td>
<td>Pulsatile liver</td>
</tr>
<tr>
<td>Chest pain (22%)</td>
<td>RV S3, S4</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Edema (22%)</td>
<td>Systolic murmur (TR; inspiratory augmentation)</td>
<td>Edema</td>
</tr>
<tr>
<td>Syncope (17%)</td>
<td>Early systolic click</td>
<td>Ascites</td>
</tr>
<tr>
<td>Dizziness (15%)</td>
<td>Midsystolic ejection murmur</td>
<td>Low BP, low PP, cool extremities</td>
</tr>
<tr>
<td>Cough (14%)</td>
<td>Diastolic murmur (PR)</td>
<td></td>
</tr>
<tr>
<td>Palpitations (13%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is There a Reason to Suspect PAH?

*Risk Factors*

- Family history
- Connective tissue disease
- Congenital heart disease
- Portal hypertension—orthotopic liver transplant candidate
- Environmental/drug factors
- HIV
Is There a Reason to Suspect PAH?

ECG

Right Axis

RVH

RV Strain

Right Atrial Enlargement
Is There a Reason to Suspect PAH?

Chest X-ray

Normal

Abnormal

Peripheral hypo-vascularity (pruning)

Prominent central pulmonary artery

RV enlargement into retrosternal clear space

Is There a Reason to Suspect PAH?

Echo

- RV enlargement
- RA enlargement
- Septal straightening
- Loss of IVC inspiratory collapse
- Tricuspid regurgitation
- Pericardial effusion
- Decreased RV systolic dysfunction
  - TAPSE (tricuspid annular plane systolic excursion)


Relatively preserved RV function

RV dysfunction

TAPSE 2.3 cm

TAPSE 1.5 cm
Is There a Reason to Suspect PAH?

VQ Scan

Idiopathic Pulmonary Arterial Hypertension

Perf

Vent

Chronic Pulmonary Embolism

Perf

Vent
Chronic Thromboembolic PH (CTEPH)

Not a PAH subgroup, but:

• Should never be missed
• Is potentially curable with thromboendarterectomy (PEA)
• 3% to 4% of acute PE do not entirely resolve
• One half of those with CTEPH do not have an apparent history of acute PE
• Normal VQ scan excludes chronic PE
• CT angiogram can detect chronic clot (experienced radiologist is required)

CTEPH: CT Angiogram

- Stenosis
- Recanalization
- Fresh thrombus
- Retraction with partial obstruction
- Retraction with total obstruction

Disturbed resolution of thrombus*

*Less subtle thrombus

Is There a Reason to Suspect PAH?  

**Pulmonary Function**

- Underlying lung disease (diagnostic group III)
- Abnormalities consistent with PH

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**IPAH and CTEPH**

- 20% have an isolated reduction in DLCO
- DLCO mildly reduced (60%-80% predicted NIH registry)
- PVR correlates with reduction in DLCO

**Systemic Sclerosis**

- 20% have an isolated reduction in DLCO
- Severity predicts future PAH
- DLCO correlates inversely with PASP

DLCO = diffusing capacity of the lungs for carbon monoxide
Is There a Reason to Suspect PAH?  
**Overnight Oximetry**

- Hypoxia may signal underlying sleep apnea
- In patients with obstructive sleep apnea (OSA), pulmonary artery pressures (PAP) are reported to decrease in response to CPAP therapy
- Untreated—response to other treatment likely to be less effective

## Screening Guidelines: Patients With Known PAH Risk

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Further Assessment</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known BMPR2 mutation</td>
<td>Echo yearly; RHC if echo shows evidence of PAH</td>
<td>Early PAH detection; 20% chance of developing PAH</td>
</tr>
<tr>
<td>Systemic sclerosis*</td>
<td>Echo yearly; RHC if echo shows evidence of PAH</td>
<td>8% prevalence of PAH</td>
</tr>
<tr>
<td>HIV</td>
<td>Echo if symptomatic; RHC if echo shows evidence of PAH</td>
<td>0.5% prevalence of PAH</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Echo if OLT considered; RHC if echo shows evidence of PAH</td>
<td>4% prevalence of PAH; predictive of poor outcome</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Echo and RHC at diagnosis; consider repair of L-R shunt defect</td>
<td>High PAH probability if unrepaired (Eisenmenger)</td>
</tr>
</tbody>
</table>

*Systemic sclerosis: consider echocardiogram if \( \frac{\% \text{ FVC}}{\% \text{ DLCO}} > 1.6 \) or unexplained declining DLCO.

Diagnostic Algorithm for PH

• Identical for local practitioners and PH specialists

• Requirements:
  – thorough evaluation
  – high quality studies and interpretation

  • Establish a suspicion of PAH
  • Confirm the diagnosis (right heart catheterization)
  • Classify the type of PH (Group I-V)
  • Determine the disease severity
  • Select the appropriate treatment for patients with PAH

## Echocardiography in PH

### Strengths
- Best screening tool for PH
- Inexpensive, portable, readily available, non-invasive, no radiation
- Allows for serial assessment
- Provides clues to other diagnoses (eg, LHD, CHD)

### Limitations
- Experienced techs/MDs essential
- Imaging quality suboptimal in patients with poor windows (eg, lung disease, obesity)
- Right ventricle not imaged adequately in some labs
- TR jet inadequate to determine RVSP in 10%–25% of patients

Lesson 4

Look Beyond the PA Pressure on Echocardiography
PAH: RV Changes

TTE apical 4-chamber view

Normal

PH
Key Features of PAH on Echo

- Enlarged RV with normal or small LV
- RA, RV, and PA enlargement
- RV dysfunction
- Increased RVSP
- Interventricular septal flattening during systole ± diastole
- Mitral E/A wave ratio <1.0

Essential Components of the Echocardiogram in PH

• Doppler estimate of RVSP
• Assess biventricular size and systolic function
• Look for interventricular septal shift
• Discriminate between pulmonary arterial and pulmonary venous causes of PH (if possible)
• Assess for congenital heart shunt lesions
• Document pericardial effusion

Estimation of RV Systolic Pressure (RVSP)

RVSP = 4(velocity of TR)^2 + RA pressure

= 4(4)^2 + 20

= ~84 mm Hg
Definitive Diagnosis of PAH Requires Invasive Hemodynamic Testing
Catheterization is required when pulmonary arterial hypertension is suspected.

Diagnostic Cardiac Catheterization

- Establish the presence of PH
- Make the diagnosis of PAH
  - measure wedge pressure and/or LVEDP
- Determine severity and prognosis of disease
- Exclude congenital heart disease
- Perform acute vasodilator test

Catheterization is required when pulmonary arterial hypertension is suspected.
PH: Define the Lesion
(mean PAP ≥25 mm Hg)

- **Post-capillary PH**
  - PCWP >15 mm Hg
  - PVR <3 Wood units

- **Mixed PH**
  - PCWP >15 mm Hg
  - PVR ≥3 Wood units

- **Pre-capillary PH**
  - PCWP <15 mm Hg
  - PVR ≥3 Wood units

- **Other:**
  - High CO
  - PCWP <15 mm Hg
  - PVR <3 Wood units
Lesson 6

Always Look for the Underlying Cause of PH
Lesson 7

Treatment of PH—Get the Diagnosis Correct and Determine Functional Status
PAH Treatment Goals

- Improve survival
- Improve quality of life
- Improve exercise capacity
  - 6MWD
  - WHO functional classification
- Improve hemodynamics

- Fewer/less severe symptoms
- Prevent clinical worsening
  - escalation of therapy
  - hospitalization
  - lung transplantation
  - death
Chronic Adjuvant Treatment

**Digoxin**

- Variable inotropic effect and use
- No long-term data; need to balance unproven benefits with known risks

**Oxygen**

- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt

Chronic Adjuvant Treatment

**Diuretics**
- Most patients need
- Hypotension not a contraindication
- Renal function and electrolytes must be monitored closely

**Anticoagulation**
- Recommended in IPAH and CTEPH
- Observational data only
- Need to balance unproven benefits with known risks
- INR goal 1.5 – 2.5

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PAH Therapy

(+) Vasodilator Response—ONLY IF RESPONDER

• Calcium channel blockers

(−) Vasodilator Response or Non-sustained Vasodilator Response

• Endothelin receptor antagonists
• Phosphodiesterase-5 inhibitors
• sGC stimulator
• Prostanoids

Mechanisms of Action of Approved Therapies for PAH

Choice of Therapy

**Local Practitioners**
- Knowledge and management of comorbid illnesses
- Geographically close to patients
- Established therapeutic relationship

**PH Centers**
- Experience with therapy escalation
- Knowledge of drug-drug interactions; eg, PDE-5 inhibitors and antiretroviral therapy
- Nursing support for management of parenteral medications
- Relationships with other subspecialists; eg, lung transplant centers
Initial Therapy: Making the Right Decision

- Make sure the patient truly has PAH and not another type of PH (especially pulmonary venous hypertension)
- Severity of disease
- Patient preference
- Trying to weigh the data (evidence-based)
- When “comparing” trials, examine objective baseline characteristics (6MWD, hemodynamics)
# 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 of symptoms</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>6MWD</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak VO$_2$ &gt;10.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO$_2$ &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg; CI &gt;2.5 L/min/m$^2$</td>
<td>Hemodynamics</td>
<td>RAP &gt;20 mm Hg; CI &lt;2.0 L/min/m$^2$</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

5th World Symposium on PH: PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

Expert Referral (I-C)

Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
  - APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

VASOREACTIVE

WHO FC I-III CCB (I-C)

Sustained response (WHO FC I-II)

Continue CCB

NON-VASOREACTIVE

INITIAL THERAPY WITH PAH-APPROVED DRUGS

Approved Therapeutic Targets

Endothelin Pathway
- Pre-proendothelin → Proendothelin
  - Endothelin receptor A
  - Endothelin receptor B

Endothelin-1
- Endothelin receptor antagonists
  - Vasoconstriction and proliferation

Endothelial cells

Nitric Oxide Pathway
- L-arginine → L-citrulline
- Nitric Oxide
- sGC stimulator
  - Phosphodiesterase type 5
  - Vasodilation and antiproliferation
  - Prostacyclin (prostaglandin I₂)

Endothelial cells

Prostacyclin Pathway
- Arachidonic acid → Prostaglandin I₂
- Prostacyclin derivatives
  - Vasodilation and antiproliferation

Smooth muscle cells

# PDE-5 Inhibitor Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiol Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| SUPER-1 Oral sildenafil* vs placebo | 278 PAH I-IV | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics |
| PHIRST-1 Oral tadalafil § vs placebo | 405 PAH I-IV | Double-blind 16-week | • 6MWD  
• Delay clinical worsening  
• Hemodynamics  
• HRQoL |

*Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.  
§Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.

PDE-5 Side Effects

- Nose bleed
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes

*Contraindicated with use of nitrate*
# sGC Stimulator Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiol Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| PATENT-1 Oral riociguat* vs placebo | 443 PAH I-IV  | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics  
• Delay clinical worsening |
| CHEST-1 Oral riociguat vs placebo | 261 CTEPH I-IV | Double-blind 16-week | • 6MWD  
• Symptoms  
• Hemodynamics |

*Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.

sGC Stimulator Side Effects

- Headache
- Dizziness
- Dyspepsia/gastritis
- Nausea
- Diarrhea
- Hypotension
- Vomiting
- Anemia
- Gastroesophageal reflux
- Constipation

Contraindicated in pregnancy, with use of nitrates or NO donors in any form, or with use of PDE inhibitors
# Endothelin Receptor Antagonists: Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BREATHE-1</strong> Oral bosentan* vs placebo</td>
<td>213 PAH III, IV</td>
<td>Double-blind 16-week</td>
<td>• 6MWD&lt;br&gt;• Delay clinical worsening&lt;br&gt;• Symptoms</td>
</tr>
<tr>
<td><strong>EARLY</strong> Oral bosentan vs placebo</td>
<td>185 PAH II</td>
<td>Double-blind 6-month</td>
<td>• Delay clinical worsening&lt;br&gt;• Hemodynamics</td>
</tr>
<tr>
<td><strong>ARIES-1&amp;2</strong> Oral ambrisentan § vs placebo</td>
<td>394 PAH II, III</td>
<td>Double-blind 12-week</td>
<td>• 6MWD&lt;br&gt;• Delay clinical worsening</td>
</tr>
<tr>
<td><strong>SERAPHIN</strong> Oral macitentan† vs placebo</td>
<td>742 PAH II,III</td>
<td>Double-blind Event-driven morbidity/mortality</td>
<td>• Delay disease progression&lt;br&gt;• 6MWD&lt;br&gt;• Symptoms</td>
</tr>
</tbody>
</table>

*Bosentan = Tracleer®. Approved for FC II-IV. 62.5-125 mg po bid.

§ Ambrisentan = Letairis®. Approved for FC II-III. 5-10 mg po qd

†Macitentan = Opsumit®. Approved for FC II-III. 10 mg po qd.

Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function*
  - monthly LFTs required for bosentan
- Anemia
  - monitor CBC quarterly
- Edema
  - lower extremity edema may require diuretic adjustment
- Teratogenic
  - use requires dual contraceptive methods (hormonal plus barrier)

*PHA Scientific Leadership Council recommends LFT testing at onset of all treatments for PAH and periodically thereafter, at prescriber’s discretion.
Prostacyclin Analogues: Intravenous, Implanted, Subcutaneous, Inhaled, or Oral

Epoprostenol (Flolan® or Veletri®)
Treprostinil (Remodulin®)

Treprostinil (Remodulin®)

Treprostinil (Orenitram®)
Selexipag (Uptravi®)

Iloprost (Ventavis®)
Treprostinil (Tyvaso®)

Epoprostenol IV: FC III-IV, 2 ng/kg/min titrated to desired clinical response in 1-2 ng/kg/min increments.
Treprostinil IV / SC: FC II-IV, 1.25-2.5 ng/kg/min/wk. IV=diluted. Inhaled: FC III, to 54 mcg, 4 inh/d. Oral: FC II-III, starting at 0.25 mg bid and titrated in 0.25 mg increments as tolerated. Selexipag: FC II-III, starting at 200 mcg bid, and titrated as tolerated up to 1600 mcg bid. Iloprost Inhaled: FC III-IV, 2.5-5 mcg, 6-9 inh/d. Treprostinil Implanted: FC II-IV, same as patient's current IV dose.
## Prostacyclin Analogues: Pivotal Trials for IV and SC Formulations

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol / Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV epoprostenol vs conventional Rx</td>
<td>81 IPAH/FPAH III,IV</td>
<td>Open-label 12-week</td>
<td>• 6MWD • Symptoms • Hemodynamics • <strong>Survival</strong></td>
</tr>
<tr>
<td>IV epoprostenol vs conventional Rx</td>
<td>111 APAH SSc III,IV</td>
<td>Open-label 12-week</td>
<td>• 6MWD • Hemodynamics • Symptoms</td>
</tr>
<tr>
<td>TRUST</td>
<td>44 PAH III</td>
<td>Double-blind, placebo-controlled 12-week</td>
<td>• 6MWD • Symptoms</td>
</tr>
<tr>
<td>SC treprostinil vs SC placebo</td>
<td>470 PAH II-IV</td>
<td>Double-blind 12-week</td>
<td>• 6MWD • Symptoms • Hemodynamics</td>
</tr>
</tbody>
</table>
**Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations**

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol / Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIR</strong>&lt;br&gt;Inhaled iloprost vs placebo</td>
<td>203&lt;br&gt;PH III-IV</td>
<td>Double-blind 12-week</td>
<td>• Composite end point&lt;br&gt;• 6MWD&lt;br&gt;• Symptoms&lt;br&gt;• Hemodynamics</td>
</tr>
<tr>
<td><strong>TRIUMPH 1</strong>&lt;br&gt;Inhaled treprostinil vs placebo§</td>
<td>235&lt;br&gt;PAH III-IV*</td>
<td>Double-blind 12-week on background oral Rx</td>
<td>• 6MWD</td>
</tr>
<tr>
<td><strong>FREEDOM-M</strong>&lt;br&gt;Oral treprostinil vs placebo</td>
<td>228&lt;br&gt;PAH II-III</td>
<td>Double-blind, placebo-controlled 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td><strong>GRIPHON</strong>&lt;br&gt;Oral selexipag vs placebo</td>
<td>1156&lt;br&gt;PAH II-III</td>
<td>Double-blind, naïve or on background ERA and/or PDE5I, event-driven morbidity/mortality</td>
<td>• Time to first morbid or mortality event</td>
</tr>
</tbody>
</table>

* Approved for class III only. § Included background therapy with ERA or PDE5-I.

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension

- Dizziness
- Syncope
- Rebound PH if interruption of epoprostenol delivery (due to short half-life)
- Delivery site complications (pain, infection, cough, thrombosis, infusion)

Vary according to drug and route of delivery
Sequential Combination Therapy (I-A)

- ERAs
- Prostanoids +
- PDE-5 I or sGCs

Inadequate Clinical Response on Maximal Therapy

Balloon Atrial Septostomy (IIa-C)

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

Initial Therapy with PAH-Approved Drugs

Combination Therapy

sGC Stimulators

Patent-1*

Triumph Step

Seraphin†

Griphonγ

Endothelin Receptor Antagonists

Prostanoids

Phosphodiesterase Inhibitors

*53% on background ERA for PHIRST, 50% on background ERA or prostanoid for PATENT-1
†64% on background PDE-5I or prostanoid in SERAPHIN. 84% on background ERA and/or PDE-5I in GRIPHON
Lesson 8

Lack of Response to Acute Vasodilator Challenge in PAH ≠ Untreatable
Acute Vasodilator Trial

• Purpose:
  – identify vasodilator “responders” who are candidates for CCB therapy

• Short-acting vasodilators
  – inhaled nitric oxide is preferred

• Definition of response
  – decrease in mPAP by ≥10 mm Hg down to mPAP of ≤40 mm Hg
  – with *improvement or maintenance* of cardiac output

Rubin LJ. *Chest*. 2004;126:4S-6S.
Lesson 9

First Do No Harm—Learn to Differentiate WHO Group I PAH From Other Forms of PH
Is It Left Heart Disease?

**Symptoms**
- paroxysmal nocturnal dyspnea
- orthopnea

**History**
- diabetes
- hypertension
- obesity
- coronary artery disease
- metabolic syndrome

**ECG**
- atrial fibrillation
- absence of right axis deviation

**Echo**
- left atrial enlargement
- left ventricular hypertrophy
- normal RA, RV
- abnormal diastolic filling
Problems With Incorrect Treatment

- **WHO Group 1 PAH: True PAH**
  - incorrect treatment with systemic vasodilators could lead to profound hypotension, death

- **WHO Group 2 PH: PH due to LHD**
  - incorrect treatment with pulmonary vasodilators could lead to pulmonary edema, CHF exacerbation

- **WHO Group 3 PH: PH due to hypoxemia/lung disease**
  - incorrect treatment with pulmonary vasodilators could lead to increased V/Q mismatch, worsening hypoxemia

- **WHO Group 4 PH: CTEPH**
  - treating with pulmonary vasodilators likely not harmful, but don’t delay referral for potentially curative surgical thromboendarterectomy (if indicated)
Lesson 10

Appropriate, Timely, and Collaborative Care: Key to Early and Effective Treatment of PH in the Dyspneic Patient
Goals of Collaborative Care

Clinical Practice Guidelines

Local Practitioners
PH Specialists

Best Practice

Clinical Trial Evidence
Collaborative Care With PH Centers: Initial Steps

Local Care
- Diagnostic dilemmas
- Diagnostic cath/vasodilator trial
- Fluid management
- Acute issues
- PAH-specific therapies
- Side effects
- Hospitalizations
- Transplant
- Clinical trials

PH Center
Collaborative Care With PH Centers: Ongoing Care

- Symptom evaluation
- Titrate diuretics
- Monitor Rx
- Need to change Rx
- Manage SEs
- ? Transplant
- Evaluate acute issues
- Acute hospital care
- Emotional support
Timing of Referral to a PH Center

- Dependent on a local physician’s level of comfort
- Referral can occur at multiple junctures

1. Abnormal symptoms, exam, and initial screening (echo) → PH Center
2. Pivotal tests (without RHC) → PH Center
3. Diagnosis (RHC with vasodilator challenge) → PH Center
4. Treatment → PH Center
5. Treatment escalation → PH Center
Case Resolutions

2 Women With Dyspnea
## 2 Women With Dyspnea

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echo</strong></td>
<td><strong>Echo</strong></td>
</tr>
<tr>
<td>• LV: EF 65%</td>
<td>• LV: EF 58%</td>
</tr>
<tr>
<td>• Grade 3 diastolic dysfunction</td>
<td>• Grade 1 diastolic dysfunction</td>
</tr>
<tr>
<td>• RV: ↑ size</td>
<td>• RV: ↑↑↑ size</td>
</tr>
<tr>
<td>• Normal RV function</td>
<td>• 3+ RV dysfunction</td>
</tr>
<tr>
<td>• PASP: 60 mm Hg</td>
<td>• PASP: 76 mm Hg</td>
</tr>
<tr>
<td>• RA: 10 mm Hg</td>
<td>• RA: 10 mm Hg</td>
</tr>
<tr>
<td>• 1+ TR</td>
<td>• 2+ TR</td>
</tr>
</tbody>
</table>
2 Women With Dyspnea

**Patient 1**

**Invasive Hemodynamics**
- RA: 15 mm Hg
- mPAP: 42 mm Hg
- PCWP: 29 mm Hg
- CO: 6.7 L/min
- PVR: 1.8 Wood units
- BP: 172/65 mm Hg
- Vasodilator challenge with iNO: *not indicated* (high PCWP)

**Patient 2**

**Invasive Hemodynamics**
- RA: 12 mm Hg
- mPAP: 41 mm Hg
- PCWP: 10 mm Hg
- CO: 2.6 L/min
- PVR: 11.9 Wood units
- BP: 93/69 mm Hg
- Vasodilator challenge with iNO: *non-responder*
2 Women With Dyspnea

Patient 1
Final Diagnosis
- WHO Group II—pulmonary venous hypertension (PVH)
- Heart failure with preserved EF (HFpEF)

Patient 2
Final Diagnosis
- WHO Group I—pulmonary arterial hypertension (PAH)
- PAH due to connective tissue disease
2 Women With Dyspnea

**Patient 1: PVH**

Clinical Course

- Carvedilol
- Furosemide
- Co-managed with nephrology
- Improved symptoms
- NYHA II

**Patient 2: PAH**

Clinical Course

- PDE-5 inhibitor: no improvement
- ERA added
- ↑ symptoms over time
- Now on parenteral prostanoid with improved symptoms
- NYHA II
Summary: PH Lessons

1. PH is common, but most often due to LHD or chronic lung disease: selective pulmonary vasodilators are not proven in these patients

2. PAH is rare but deadly: outcomes have improved but not as much as we would like; diagnosis must be made earlier

3. Know the PH clinical clues in the dyspneic patient

4. Know the limitations of echo, and look beyond PA pressure to the RV to evaluate size/function

5. Definitive diagnosis of PH requires heart cath
Summary: PH Lessons (cont’d)

6. **Identify underlying cause of PH:** *etiology important = prognostic and Rx implications*

7. **Treatment** of PH is **based on correct diagnosis and functional status**

8. **Lack of response** to **acute vasodilator challenge** in PAH **does not mean the patient is untreated**

9. **Learn to differentiate Group I PAH from other forms of PH:** *when in doubt, ask for help*

10. **Collaborative care:** key to early and effective treatment of PH in the dyspneic patient
Final Housekeeping

- Hand in CME evaluation form and be sure you signed in at the registration desk
- Bring your PHA information home
- Expect an email from WUSM with a link to access your CME certificate
Thank you for your participation!

For more information on upcoming PHA Medical Education Programs, please visit:

www.PHAssociation.org