State-of-the-Art Management of Pulmonary Hypertension: Based on an Understanding of the Various Etiologies

Vallie V. McLaughlin, MD, FACC, FAHA
Kim A Eagle MD Endowed Professor of Cardiovascular Medicine
Director, Pulmonary Hypertension Program
University of Michigan Health System
Disclosures

• Has served as a consultant and/or advisor for Actelion Pharmaceuticals US, Inc., Bayer, Gilead Sciences, Inc., and United Therapeutics Corporation

• The University of Michigan has received research funding from Actelion Pharmaceuticals US, Inc., Bayer, Ikaria, Norvartis, and United Therapeutics Corporation
5th World Symposium on PH: Modified Classification of PH

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 (update)
       1.4.5 Schistosomiasis
       1.4.6 Chronic hemolytic anemia

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 (update)

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

Echocardiogram
PFT's
Polysomnography
VQ Scan
• Sleep Disorder
• Chronic PE
Functional Test (6MWT, CPET)
Pivotal Tests
History
Exam
CXR
ECG
VQ Scan
PFT's
Overnight Oximetry
HIV
ANA
LFT's
Other CTD Serologies
Contingent Tests
TEE
Exercise Echo
Pulmonary Angiography
Chest CT Angiogram
Coagulopathy Profile
ABG's
Polysomnography
Vasodilator Test
Exercise RH Cath
Volume Loading
Left Heart Cath
Contribute to
Assessment of:
• Index of Suspicion of PH
• RVE, RAE, ↑RVSP, RV Function
• Left Heart Disease
• VHD, CHD
• Ventilatory Function
• Gas Exchange
• Sleep Disorder
• HIV Infection
• Scleroderma, SLE, RA
• Portopulmonary Htn
• Establish Baseline
• Prognosis
• Confirmation of PH
• Hemodynamic Profile
• Vasodilator Response

Diagnosis of PAH Is Often Late

Mean time between symptom onset and diagnosis: 27 months

REVEAL Registry

French National Registry

Patients (n)

Functional Class at Diagnosis

Functional Class at Presentation

French Registry: Kaplan-Meier Survival Estimates in Combined PAH Population vs NIH-predicted

Survival (%)

Observed

Predicted (NIH Registry)

No. at risk:
All patients 56 69 98 113 120 127 133

Time (mo)

Key Pathways Implicated in PAH Pathogenesis

**Endothelin Pathway**
- Pre-proendothelin → Proendothelin
- Endothelin-1
- Endothelin receptor A
- Endothelin receptor B
- Vasoconstriction and proliferation

**Nitric Oxide Pathway**
- L-arginine → L-citrulline
- Nitric Oxide
- Phosphodiesterase type 5
- Vasodilation and antiproliferation

**Prostacyclin Pathway**
- Arachidonic acid → Prostaglandin I₂
- Prostacyclin (prostaglandin I₂)
- cAMP
- Vasodilation and antiproliferation

## Prostacyclin Analogues: Pivotal Trials

<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></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Inhaled iloprost vs placebo | 203 PH III-IV | Double-blind 12-week | • Composite end point  
• 6MWD  
• Symptoms  
• Hemodynamics |
| **TRIUMPH 1** | | | |
| Inhaled treprostinil vs placebo § | 235 PAH III-IV* | Double-blind 12-week on background oral Rx | • 6MWD |
| SQ treprostinil vs SQ placebo | 470 PAH II-IV | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics |
| **TRUST** | | | |
| IV treprostinil vs placebo | 44 PAH III | Double-blind, placebo-controlled 2-week | • 6MWD  
• Symptoms |
| IV epoprostenol vs conventional Rx | 81 IPAH/FPAH III,IV | Open-label 12-week | • 6MWD  
• Symptoms  
• Hemodynamics  
• Survival |
| IV epoprostenol vs conventional Rx | 111 APAH SSSc III,IV | Open-label 12-week | • 6MWD  
• Hemodynamics  
• Symptoms |

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

# Endothelin Receptor Antagonists: Pivotal Trials

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

# PDE-5 Inhibitor Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>N</th>
<th>Etiol</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.

### SGC Stimulator Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>N Etiol Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
</table>
| **PATENT-1**<br>Oral riociguat*<br>vs placebo | Oral riociguat | 278 PAH I-IV | Double-blind 12-week | • 6MWD  
• Symptoms  
• Hemodynamics  
• Delay clinical worsening |
| **CHEST-1**<br>Oral riociguat<br>vs placebo | Oral riociguat | 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.

5th World Symposium on PH: 2013 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

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

Expert Referral (I-C)

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

VASOREACTIVE

WHO FC I-III
CCB (I-C)

Sustained response (WHO FC I-II)

NO

YES

Continue CCB

NON-VASOREACTIVE

INITIAL THERAPY WITH PAH-APPROVED DRUGS

### INITIAL THERAPY WITH PAH-APPROVED DRUGS

**YELLOW:** Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

Level of evidence based on WHO-FC of majority of patients of studies

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>A or B</td>
<td>• Ambrisentan, Bosentan, Macitentan, Riociguat, Sildenafil, Tadalafil</td>
<td>• Ambrisentan, Bosentan, Epoprostenol IV, Iloprost inh, Macitentan, Riociguat, Sildenafil, Tadalafil, Treprostinil SC, inh</td>
<td>• Epoprostenol IV</td>
</tr>
<tr>
<td><strong>IIa</strong></td>
<td>C</td>
<td></td>
<td>• Iloprost IV*, Treprostinil IV</td>
<td>• Ambrisentan, Bosentan, Iloprost inh and IV*, Macitentan, Riociguat, Sildenafil, Tadalafil, Treprostinil SC, IV, Inh*</td>
</tr>
<tr>
<td><strong>IIb</strong></td>
<td>B</td>
<td></td>
<td>• Beraprost*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td><strong>Initial Combination Therapy</strong></td>
<td><strong>Initial Combination Therapy</strong></td>
</tr>
</tbody>
</table>

**5th World Symposium on PH: 2013 PAH Treatment Algorithm**


*Not approved in US.*
5th World Symposium on PH: 2013 Treatment Algorithm Caveat

- Since 5th World Symposium, oral treprostinil has been approved by FDA for treatment of PAH (WHO Group 1) to improve exercise capacity\(^1\)
- Study that established effectiveness included predominantly patients with WHO FC II-III symptoms and etiologies of IPAH or heritable PAH (75%) or CTD-associated PAH (19%)
- As sole vasodilator, effect on exercise is small
- Oral treprostinil has not been shown to add to other vasodilator therapy

At time of 5th World Symposium, treatment working group had examined clinical evidence published at that time and noted\(^2\):
  - oral treprostinil had been evaluated in 2 RCTs in PAH patients on background therapy with bosentan and/or sildenafil and, in both, primary endpoint of 6MWD did not reach statistical significance\(^3,4\)
  - additional RCT in PAH-naive patients showed improvement in 6MWD by 26 m at peak dose\(^5\)

---
INITIAL THERAPY WITH PAH-APPROVED DRUGS

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Sequential Combination Therapy (I-A)

ERAs ➔

Prostanoids ➔

PDE-5 I or SGCs

Inadequate Clinical Response on Maximal Therapy

Referral for Lung Transplantation (I-C)

Balloon Atrial Septostomy (IIa-C)

### 5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>I or II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function (RAP &lt; 8 mm Hg and CI &gt; 2.5-3.0 L/min/m²)</td>
</tr>
<tr>
<td>Echocardiography/MRI</td>
<td>Normal/near normal RV size and function</td>
</tr>
<tr>
<td>BNP level</td>
<td>‘Normal’</td>
</tr>
<tr>
<td>6-MWD</td>
<td>380-440 m, may not be aggressive enough</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO₂ &gt; 15 mL/kg/min&lt;br&gt;VE/VCO₂ @ AT &lt; 45</td>
</tr>
</tbody>
</table>

5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
     1.2.1 BMPR2
     1.2.2 ALK1, ENG, SMAD9, 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 (update)
     1.4.5 Schistosomiasis
     1.4.6 Chronic hemolytic anemia

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 (update)

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

## Differentiating PAH and HFpEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PAH More Likely</th>
<th>HFpEF More Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Comorbidities - DM, HTN, CAD, obesity (metabolic syndrome)</strong></td>
<td>Often absent</td>
<td>Often multiple present</td>
</tr>
<tr>
<td><strong>Symptoms - PND, orthopnea</strong></td>
<td>Often absent</td>
<td>Often present</td>
</tr>
<tr>
<td><strong>Cardiac Examination</strong></td>
<td>RV heave, loud P2, TR murmur</td>
<td>Sustained LV impulse, RS4,</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>Clear lung fields</td>
<td>Pulmonary vascular congestion, pleural effusions, pulmonary edema</td>
</tr>
<tr>
<td><strong>Chest CT</strong></td>
<td>Often clear lungs</td>
<td>Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>RAD, RVE</td>
<td>LAE, LVE, Atrial Fibrillation, no RAD</td>
</tr>
<tr>
<td><strong>Naturetic peptides</strong></td>
<td>Often elevated</td>
<td>Often elevated</td>
</tr>
<tr>
<td><strong>Echo-LAE, LVH</strong></td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td><strong>Echo-diastolic dysfunction</strong></td>
<td>Grade 1 common</td>
<td>Grade 2, 3 common</td>
</tr>
<tr>
<td><strong>Echo-RV</strong></td>
<td>Often enlarged, may share the apex</td>
<td>Often normal, mildly enlarged</td>
</tr>
<tr>
<td><strong>Echo-pericardial effusion</strong></td>
<td>Sometimes</td>
<td>Rare</td>
</tr>
</tbody>
</table>
# Cardiopulmonary Circulation in Patients With Tight Mitral Stenosis With and Without Pulmonary Vascular Disease

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Tight mitral stenosis (Without PVD)</th>
<th>Tight mitral stenosis (With PVD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>RV</td>
<td>5</td>
<td>45/5</td>
<td>70/20</td>
</tr>
<tr>
<td>PA</td>
<td>20/5</td>
<td>45/25 (32)</td>
<td>68/33 (53)</td>
</tr>
<tr>
<td>PC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>4.0 cm²</td>
<td>1.0 cm²</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>5</td>
<td>45/25 (32)</td>
<td>68/33 (53)</td>
</tr>
<tr>
<td>RV</td>
<td>5</td>
<td>20/5</td>
<td>70/20</td>
</tr>
<tr>
<td>PA</td>
<td>20/8 (12)</td>
<td>45/25 (32)</td>
<td>68/33 (53)</td>
</tr>
<tr>
<td>PV</td>
<td>6</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>PC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>4.0 cm²</td>
<td>1.0 cm²</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>6</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>LV</td>
<td>6</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Ao</td>
<td>6 120/6120/8</td>
<td>25 120/5</td>
<td>24 110/5</td>
</tr>
<tr>
<td>FLOW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PAH-Specific Therapies: Studies On PH-LV Dysfunction: Adverse Effects Trump Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>↓PVR, ↓SVR, ↓PAWP, ↑CO</th>
<th>↑Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil²⁻⁸</td>
<td>↓PVR, ↓PAWP, ↓MPAP, ↑CO</td>
<td>Lower PAP, Improved endothelial function and exercise tolerance</td>
</tr>
<tr>
<td>Bosentan⁹⁻¹¹</td>
<td>↓PVR</td>
<td>↑Transaminases, ↑Fluid Retention</td>
</tr>
<tr>
<td>Darusentan¹²⁻¹³</td>
<td>↓SVR</td>
<td>No Benefits</td>
</tr>
<tr>
<td>Tezosentan¹⁴</td>
<td>↓PVR, ↓SVR, ↓PAWP, ↑CI</td>
<td>No Benefits</td>
</tr>
</tbody>
</table>

No therapies that are approved for WHO Group 1 PAH are FDA approved for PH resulting from left heart failure.

HFpEF treatment algorithm

• Step 1: Diagnose HFpEF accurately
  – Remember that HFpEF is extremely common
  – Make sure you’re not dealing with a “zebra”
  – Low threshold for cardiac catheterization, CAD eval

• Step 2: Treat the underlying cause of HFpEF

• Step 3: Treat BP, fluid overload

• Step 4: Treat comorbidities aggressively

• Step 5: Exercise training, CHF education, chronic disease management program

• Step 6: Enroll in clinical trials
5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK1, ENG, SMAD9, 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 (update)
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia

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 (update)

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

### 5th World Symposium on PH: Modified Classification of PH

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
<th>3. PH due to lung diseases and/or hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
<td>3.1 COPD</td>
</tr>
<tr>
<td>1.2 Heritable PAH</td>
<td>3.2 Interstitial lung disease</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3</td>
<td>3.4 Sleep-disordered breathing</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
<td>3.5 Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>1.3 Drug- and toxin-induced</td>
<td>3.6 Chronic exposure to high altitude</td>
</tr>
<tr>
<td>1.4 Associated with</td>
<td>3.7 Developmental lung diseases (update)</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</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 heart diseases (update)</td>
<td></td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
<td></td>
</tr>
<tr>
<td>1.4.6 Chronic hemolytic anemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</th>
<th>4. Chronic thromboembolic PH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. PH due to left heart disease</th>
<th>5. PH with unclear multifactorial mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 LV systolic dysfunction</td>
<td>5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>2.2 LV diastolic dysfunction</td>
<td>5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis,</td>
</tr>
<tr>
<td>2.3 Valvular disease</td>
<td>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td>2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
<td>5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH</td>
</tr>
</tbody>
</table>

- 3-4% of acute PE do not entirely resolve
- ½ of those with CTEPH do not have an apparent history of acute PE
- Normal or very low probability VQ essentially excludes chronic PE
- CTEPH should be excluded, even when another explanation for PH is present

CTEPH: A “Curable” Form of PH
Not to Be Missed
Collaborative Care With PH Centers:

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