Pulmonary Arterial Hypertension

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University of Utah
Outline

- Causes of elevated pulmonary artery (PA) pressures
- Diagnosis of pulmonary hypertension (PH)
- Classifications of PH
- Treatment of PAH
  - Meds
  - Rehab
Elevated Pulmonary Artery Pressures

- Pulmonary hypertension (PH)

  Mean pulmonary artery pressure ≥ 25 mmHg
Causes of Elevated PA Pressures

Ohm’s Law: \( PAP - LAP = PVR \times CO \) or \( PAP = PVR \times CO + LAP \)
Pulmonary Arterial Hypertension (PAH)

- Right heart catheterization

Mean pulmonary artery pressure $\geq 25$ mmHg

Pulmonary capillary wedge pressure $\leq 15$ mmHg
Pulmonary Arterial Hypertension

• Pulmonary hypertension (PH) is an elevation of mean pulmonary artery pressure ≥ 25 mmHg on right heart catheterization

• Pulmonary arterial hypertension (group 1 PH) requires that the
  • Mean pulmonary artery pressure ≥ 25 mmHg
  • PCWP is < 15 mmHg
  • Pulmonary vascular resistance is > 3 WU
PAH Background

• Rare disease (orphan designation) of the pulmonary microvasculature affecting 15 to 50 people per million inhabitants in the Western world
  – Affects all races
  – Affects all ages; however, most prevalent in 4th and 5th decades of life
  – Higher prevalence in females (80%)

• Global burden of PAH may be underestimated because of:
  – Underdiagnosis (eg, nondescript symptoms)
  – Misdiagnosis (eg, asthma, left-heart disease)
  – Increasing risk factors (eg, HIV infection, chronic liver disease, stimulant use, schistosomiasis)
21% of PAH patients experienced symptoms for > 2 years before PAH was diagnosed.
Pulmonary Vascular Disease

- **Group 1. Pulmonary *arterial* hypertension**

  Mean pulmonary artery pressure $\geq 25$ mmHg
  Pulmonary capillary wedge pressure $\leq 15$ mmHg
  Pulmonary vascular resistance $> 3$ Wood units

- **Idiopathic PAH**
- **Heritable**
- **Drug and toxin-induced**

- **Associated with:**
  - Connective tissue disease
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Chronic hemolytic anemia
Classifications of Pulmonary Hypertension

Group 1: Pulmonary arterial hypertension (PAH)

- Collagen vascular disease
- HIV
- Drugs and toxins
- Portopulmonary hypertension
- Congenital heart disease
- Heritable
- Pulmonary veno-occlusive disease
- Idiopathic
- Other
Classifications of Pulmonary Hypertension

- **Group 2. PH due to left heart disease**
  - Systolic dysfunction
  - Diastolic dysfunction
  - Valvular disease

- **Group 3. PH due to lung diseases and/or hypoxia**
  - COPD
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental abnormalities
Classifications of Pulmonary Hypertension

**Group 4: Chronic thromboembolic pulmonary hypertension**

**Group 5: Unclear multifactorial mechanisms**
- Sarcoidosis
- Post-splenectomy
- Hematologic disorders
- Metabolic disorders
Classification Debates

- Pulmonary arterial hypertension

   ‘Out of proportion’ to:

   left-sided heart disease
   lung disease (obstructive lung disease, pulmonary fibrosis)
Intrinsic Pulmonary Vascular Disease
Diagnosis

Nonspecific symptoms

- Dizziness and/or fainting (syncope)
- Shortness of breath (dyspnea)
- Chest pain (angina)
- Feeling tired or worn out (fatigue)
- Swollen ankles and legs (edema)
Diagnosis

- **Pulmonary Function Tests** → **Obstructive Lung Disease**
  - Low DLCO

- **Ventilation-Perfusion Scan** or **Chest CT-Angiogram** → **Chronic Pulmonary Embolism**
  - Lung Parenchyma

- **Echocardiogram** (with agitated saline) → **Shunt**
  - Structural and Functional Changes

- **Laboratory Tests** → **Collagen Vascular Disease**
  - Liver disease
  - HIV

- **Sleep Study** → **OSA**
Common Findings

Enlarged cardiac silhouette
Enlarged pulmonary arteries

Right axis deviation
Right atrial enlargement
Right ventricular strain
Pulmonary Function Tests

- **Decreased DLCO**
  - Out of proportion to any restriction

\[
\left( \frac{\% \text{ FVC}}{\% \text{ DLCO}} \right) \geq 1.6
\]

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Ref</th>
<th>(LLN-ULN)</th>
<th>Pre</th>
<th>%Ref</th>
</tr>
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<tbody>
<tr>
<td>FVC Liters</td>
<td>2.47</td>
<td>(1.9-3.1)</td>
<td>1.87</td>
<td>76</td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>1.87</td>
<td>(1.4-2.4)</td>
<td>1.47</td>
<td>78</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>77</td>
<td>(66.8-86.4)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>FEF25-75% L/sec</td>
<td>1.74</td>
<td>(0.7-2.8)</td>
<td>1.58</td>
<td>91</td>
</tr>
</tbody>
</table>

Diffusing Capacity (Hb 13.8)

| DLCO ml/mmHg/min   | 20.1  | (14.1-26.1)| 9.9 | 49   |
| DL Adj ml/mmHg/min | 20.1  | (14.1-26.1)| 9.8 | 49   |
Echocardiography

Echocardiographic findings concerning for PH

- Elevated RVSP
- Right atrial enlargement
- Right ventricular enlargement
- Decreased right ventricular systolic function
- Pericardial effusion

Tricuspid jet velocity > 2.8 m/sec

\[
4(\text{TRV})^2 + \text{RAP}
\]
Echocardiography
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure</td>
<td>6 mmHg</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>44/22 (29) mmHg</td>
</tr>
<tr>
<td>PCWP</td>
<td>10 mmHg</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>5.4 L/min</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance</td>
<td>3.5 Wood units</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure</td>
<td>20 mmHg</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>68/40 (49) mmHg</td>
</tr>
<tr>
<td>PCWP</td>
<td>13 mmHg</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>2.8 L/min</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance</td>
<td>12.9 Wood units</td>
</tr>
</tbody>
</table>
CTPA: Chronic Thromboembolic Disease

Courtesy of Bill Auger UCSD
Right Heart Catheterization

• Required to diagnose pulmonary hypertension
  • *Mean* pulmonary artery pressure ≥ 25 mmHg

• Pulmonary arterial hypertension
  • Mean pulmonary artery pressure ≥ 25 mmHg
  • Normal pulmonary capillary wedge pressure

• Pulmonary vascular resistance > 3 WU
# Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
<th>Abnormal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right Atrial Pressure</strong></td>
<td>&lt; 8 mmHg</td>
<td>9 mmHg</td>
<td>12 mmHg</td>
<td>12 mmHg</td>
</tr>
<tr>
<td><strong>Mean Pulmonary Artery Pressure</strong></td>
<td>&lt; 20 mmHg</td>
<td>40 mmHg</td>
<td>32 mmHg</td>
<td>32 mmHg</td>
</tr>
<tr>
<td><strong>Pulmonary Capillary Wedge Pressure</strong></td>
<td>&lt; 15 mmHg</td>
<td>18 mmHg</td>
<td>29 mmHg</td>
<td>8 mmHg</td>
</tr>
<tr>
<td><strong>Cardiac Output</strong></td>
<td>≈ 5 L/min</td>
<td>13.7 L/min</td>
<td>4.5 L/min</td>
<td>3.2 L/min</td>
</tr>
<tr>
<td><strong>Pulmonary Vascular Resistance</strong></td>
<td>&lt; 3 WU</td>
<td>1.6 WU</td>
<td>1 WU</td>
<td>7.5 WU</td>
</tr>
</tbody>
</table>

**Liver Disease**

**Left Heart Disease**

**Pulmonary Arterial Hypertension**
Right Heart Catheterization

- **Vasoreactivity**
  
  Selective vasodilator of the pulmonary vasculature (smooth muscle relaxation)
  
  Decrease in mean PA pressure by 10 mmHg to a level < 40 mmHg; no loss of cardiac output

  ![Diagram](image)

  - Pulmonary hypertension primarily due to vasoconstriction (reversible)*
    
    Responds to calcium channel blockers (Nifedipine)

  - Pulmonary hypertension primarily due to cell proliferation (irreversible)

  iNO
  
  20 ppm for 15 minutes
Definition of Vasoreactivity

Mean pulmonary artery pressure (mmHg)

Baseline  Post vasodilator

10 mmHg
Survival Based on Vasoreactivity

Cumulative Survival

Years

0 2 4 6 8 10 12

0 0.2 0.4 0.6 0.8 1

vasoreactive

not vasoreactive
Differential Diagnosis of PAH: Algorithm

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

**Echocardiogram**

- Chest x-ray
- PFTs

- HIV test
- Autoantibody tests

- LFTs and clinical evidence of cirrhosis and portal HTN
  - PoPH
    - Functional test
    - RH catheterization
    - Vasodilator test

- COPD
- ILD
- Thoracic abnl

- Sleep disorder
- Sleep study
- Ventilation-perfusion scan, angiography
- Chronic thromboembolism

- Scleroderma
- SLE
- RA
- Vasculitis

Evaluation of Possible PH

1. **Echocardiogram**
   - 6-12 month
     - yes: Liver disease, Collagen vascular disease, HIV
     - no: **Routine Follow Up**

2. **Abnormal?**
   - no: **Routine Follow Up**
   - yes: **Risk Factor?**

3. **Risk Factor?**
   - no: **Routine Follow Up**
   - yes: Liver disease, Collagen vascular disease, HIV

4. **Left Heart Disease?**
   - yes: Cardiology Consult
   - no: **Standard PH Work Up**

   **Standard PH Work Up**
   - Systolic dysfunction, Diastolic dysfunction, Valvular disease
Treatment

FDA-Approved for PAH
Risk stratification is primary determinant of therapy

<table>
<thead>
<tr>
<th>Phosphodiesterase Inhibitors (oral)</th>
<th>Endothelin Receptor Antagonists (oral)</th>
<th>Prostanoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>Iloprost (INH)</td>
</tr>
<tr>
<td>WHO I to IV</td>
<td>WHO II, III &amp; IV</td>
<td>WHO III &amp; IV</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Ambrisentan</td>
<td>Epoprostenol (IV)</td>
</tr>
<tr>
<td>WHO I to IV</td>
<td>WHO II &amp; III</td>
<td>WHO III &amp; IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treprostinil (IV, SQ, INH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO II to IV</td>
</tr>
</tbody>
</table>
## Determining Therapy

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

# WHO Functional Classification

<table>
<thead>
<tr>
<th>WHO</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with PAH but without resulting 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>Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea or fatigue may even be present at rest. Discomfort is increased by any physical activity</td>
</tr>
</tbody>
</table>
Functional Class at Diagnosis

% of Newly Diagnosed Patients

Class I | Class II | Class III | Class IV
---|---|---|---
21 | 94 | 208 | 42

Note: Newly diagnosed subjects are those whose diagnostic right heart catheterization (RHC) fell within 90 days prior to enrollment. Patients whose confirmatory diagnostic RHC occurred after consent date will be considered newly diagnosed.
Hemodynamic Changes Over Time

- Pulmonary Vascular Resistance
- Pulmonary Artery Pressure
- Cardiac Output
Choice of Therapy

RHC

Vasoreactive?

Yes

CCB

No

Sustained Response?

Yes

Low

Risk?

High

Epoprostenol or Treprostinil (IV)
Iloprost (INH)
ERA, PDE-5 (oral)
Treprostinil (SC)

Deterioration?

No

Yes

Low

Epoprostenol or Treprostinil (IV)
Iloprost (INH)
Treprostinil (SC)

Combination Therapy
Investigational Protocols
Atrial Septostomy
Lung Transplant

McLaughlin V et al. J. AM Coll Card 2009;30:1573-1619
Vasoactive mediators involved in PAH

**Abnormalities**
- Nitric oxide deficiency
- Prostacyclin deficiency
- Endothelin overexpression

**Therapies**
- **PDE-5 inhibitors**: Block the activity of PDE-5, restoring vasodilation through an increase in cGMP.
- **Prostacyclin**: Supplement the deficiency in PGI₂, resulting in vasodilation and inhibition of platelet aggregation.
- **ERAs**: Block the binding of ET-1 to its receptors, preventing vasoconstrictor effects of ET-1.

Parenteral Prostanoids

Arachidonic Acid

Cyclooxygenases

PGH₂ (endoperoxides)

PGI₂ Synthase

PGI₂ (prostacycline)

CAMP

Epoprostenol

Treprostinil
Oral Therapies for PAH

• Phosphodiesterase-5 inhibitors

O₂ \rightarrow \text{L-Arginine} \rightarrow \text{Nitric Oxide Synthase} \rightarrow \text{Nitric Oxide} \rightarrow \text{L-Citrulline} \rightarrow \text{Nitric Oxide}

\text{cGMP} \rightarrow \text{PDE-5} \rightarrow \text{Degraded cGMP}

Hypotension
Headache
GERD
Oral Therapies for PAH

• Endothelin receptor antagonists

Pre-Proendothelin → Pro-endothelin-1 → Endothelin-1
Oral Therapies for PAH

• Endothelin receptor antagonists

Pre-Proendothelin

Pro-endothelin-1

Endothelin-1

BOSENTAN
AMBRISENTAN

Fluid Retention
Liver Dysfunction
Teratogenic
Inhaled Therapies for PAH

• Candidates
  • Unable to manage parenteral prostanoids
  • Underlying lung disease

• Treprostinil
  • Nine breaths 4 times daily

• Iloprost
  • Treatments 6 to 9 times daily

Cough
Headache
Throat Irritation
PAH Pharmacotherapies

266 (11%) patients were not on PGI, PDE5-Inh, or ETRA

N = 2,438

CHEST 2010; 137: 376-387
Pulmonary Rehabilitation in PAH

• Cardiopulmonary rehab effective for COPD and CHF patients, why not PAH patients?

• Historically exercise discouraged in PAH patients because of safety concerns
  – Inducing hypoxemia
  – Arrhythmia
  – Precipitous rise in PA pressure resulting in worsening right heart failure

• ACCP/AACVPR practice guidelines state that rehab may be beneficial in PAH but offers no explicit recommendations
Study Design

- 30 patients with group I and group IV PH randomly assigned to control or intense training group
- 15 week program (inpatient for 3 weeks)
- Primary end points: change in 6-minute walk and quality of life score
### Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=15)</th>
<th>Primary Training Group (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>5/10</td>
<td>5/10</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>53±14</td>
<td>47±12</td>
<td>0.39</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166±5</td>
<td>171±11</td>
<td>0.24</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78±18</td>
<td>75±13</td>
<td>0.91</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>...</td>
<td>...</td>
<td>0.50</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Cause of pulmonary hypertension, n (%)</td>
<td>...</td>
<td>...</td>
<td>0.54</td>
</tr>
<tr>
<td>PAH</td>
<td>11 (73.3)</td>
<td>13 (86.6)</td>
<td>...</td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>4 (26.7)</td>
<td>2 (13.3)</td>
<td>...</td>
</tr>
<tr>
<td>Walking distance at 6 min, m</td>
<td>411±86</td>
<td>439±82</td>
<td>0.38</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>49.6±12.3</td>
<td>49.5±17.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyne · s · cm⁻⁵</td>
<td>901.8±358.0</td>
<td>968.7±444.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Cardiac index, L · min⁻¹ · m⁻²</td>
<td>2.1±0.5</td>
<td>2.3±0.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>7±5</td>
<td>6±4</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Pulmonary Rehabilitation in PAH

111 m increase in 6-minute walking distance between control and primary training group (P< 0.001)

Circulation 2006; 114:1482-1489
Study Design

- 22 patients with group I and group IV PH randomly assigned to control or exercise training group
- 12 week program with 24 1-hour sessions of exercise training
- Primary end points: change in 6-minute walk and peak VO$_2$
Pulmonary Rehabilitation in PAH

Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Rehabilitation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (n)</strong></td>
<td>11 (6M/5F)</td>
<td>11 (1M/10F)</td>
<td>.063</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>46 ± 4.5</td>
<td>57 ± 3.7</td>
<td>.14</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>65 ± 9.4</td>
<td>74 ± 6.5</td>
<td>.49</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>115 ± 4</td>
<td>111 ± 4</td>
<td>.59</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>75 ± 4</td>
<td>68 ± 3</td>
<td>.36</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>13.0 ± 0.9</td>
<td>12.5 ± 0.7</td>
<td>.65</td>
</tr>
<tr>
<td><strong>PAH diagnosis (n)</strong></td>
<td></td>
<td></td>
<td>.167</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>6</td>
<td>4</td>
<td>.67</td>
</tr>
<tr>
<td>Endothelin antagonists</td>
<td>7</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>5</td>
<td>3</td>
<td>.65</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>4</td>
<td>8</td>
<td>.11</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Historic cardiac catheterization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>45 ± 5</td>
<td>57 ± 6</td>
<td>.6522</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>11.8 ± 3.1</td>
<td>13.5 ± 1.7</td>
<td>.33</td>
</tr>
<tr>
<td>CI (L min⁻¹ m⁻²)</td>
<td>3.4 ± 0.9</td>
<td>2.03 ± 0.25</td>
<td>.09</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>8 ± 2</td>
<td>8 ± 1</td>
<td>.702</td>
</tr>
</tbody>
</table>
Pulmonary Rehabilitation in PAH

58 m increase in 6MWD in exercise group c/w controls (P = 0.003); also significant increase in peak VO\textsubscript{2}
Pulmonary Rehabilitation in PAH

Study Design

• 23 patients with group I PAH randomly assigned to education or education/exercise combined

• 10 week exercise program with 24-30 sessions of treadmill walking for 30-45 min per session

• Primary end points: change in 6-minute walk, peak work rate and quality of life score
## Pulmonary Rehabilitation in PAH

### Table 1—Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EXF Group (n = 10)</th>
<th>EDU Group (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.0 (13.0)</td>
<td>55.5 (8.5)</td>
<td>.295</td>
</tr>
<tr>
<td>Female patient, No. (%)</td>
<td>10 (100.0)</td>
<td>13 (100.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td>.195</td>
</tr>
<tr>
<td>White</td>
<td>6 (60.0)</td>
<td>3 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (30.0)</td>
<td>6 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (10.0)</td>
<td>2 (15.4)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.2 (7.0)</td>
<td>31.8 (7.4)</td>
<td>.307</td>
</tr>
<tr>
<td>Supplemental O₂, No. (%)</td>
<td>4 (40.0)</td>
<td>4 (30.8)</td>
<td>.665</td>
</tr>
<tr>
<td>WHO group 1 PAH etiology, No. (%)</td>
<td></td>
<td></td>
<td>.643</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2 (20.0)</td>
<td>3 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Drug-induced</td>
<td>0</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Associated with connective tissue diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>5 (50.0)</td>
<td>5 (38.5)</td>
<td>.376</td>
</tr>
<tr>
<td>Lupus</td>
<td>1 (10.0)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>1 (10.0)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed connective tissue disorder</td>
<td>1 (10.0)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>NYHA/WHO functional classification, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1 (10.0)</td>
<td>0</td>
<td>.376</td>
</tr>
<tr>
<td>Class II</td>
<td>4 (40.0)</td>
<td>6 (46.2)</td>
<td>.298</td>
</tr>
<tr>
<td>Class III</td>
<td>4 (40.0)</td>
<td>5 (38.5)</td>
<td>.299</td>
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<tr>
<td>Class IV</td>
<td>1 (10.0)</td>
<td>0</td>
<td>.191</td>
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<tr>
<td>Drug combination therapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>5 (50.0)</td>
<td>2 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Dual therapy</td>
<td>1 (10.0)</td>
<td>5 (38.5)</td>
<td></td>
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<tr>
<td>Triple therapy</td>
<td>4 (40.0)</td>
<td>5 (38.5)</td>
<td></td>
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<tr>
<td>Cardiac catheterization</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>40.3 (13.8)</td>
<td>43.8 (14.2)</td>
<td>.291</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>8.6 (7.2)</td>
<td>6.0 (6.4)</td>
<td>.298</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>9.9 (2.8)</td>
<td>9.4 (2.9)</td>
<td>.348</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes/cm²/m²</td>
<td>506 (293)</td>
<td>553 (406)</td>
<td>.299</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>3.3 (1.6)</td>
<td>2.9 (0.7)</td>
<td>.402</td>
</tr>
<tr>
<td>Pulmonary function test</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FVC, % predicted</td>
<td>74.3 (17.4)</td>
<td>65.6 (11.3)</td>
<td>.060</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>72.4 (15.8)</td>
<td>63.5 (13.1)</td>
<td>.050</td>
</tr>
<tr>
<td>Ratio FEV₁/FVC, %</td>
<td>81.5 (13.6)</td>
<td>75.5 (7.7)</td>
<td>.107</td>
</tr>
<tr>
<td>Performance measures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6MWT distance, m</td>
<td>411 (73)</td>
<td>377 (97)</td>
<td>.153</td>
</tr>
<tr>
<td>CPET variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to exercise intolerance, min</td>
<td>11.1 (3.1)</td>
<td>9.7 (3.3)</td>
<td>.151</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>17.6 (5.7)</td>
<td>14.7 (5.1)</td>
<td>.111</td>
</tr>
<tr>
<td>Peak WR, W</td>
<td>102 (41)</td>
<td>87 (50)</td>
<td>.229</td>
</tr>
<tr>
<td>Peak MET</td>
<td>5.3 (1.3)</td>
<td>4.8 (1.6)</td>
<td>.247</td>
</tr>
<tr>
<td>Time at AT, min</td>
<td>4.4 (2.2)</td>
<td>4.2 (2.3)</td>
<td>.386</td>
</tr>
</tbody>
</table>
45 m increase in 6 MWD in exercise group c/w education only group; no significant increase in peak VO2
Significant improvement in QOL measures
No adverse events

Chest 2013; 143:333-343
Pulmonary Rehabilitation in PAH

• Limited evidence but rehab in PAH is safe and effective – improvement in exercise capacity generally exceeds that observed in drug trials

• Optimal patient population and rehab protocol are not well defined
Summary

- Pulmonary hypertension (PH) is an elevation of mean PA pressure to ≥ 25 mmHg on right heart catheterization.
- PAH (group 1 PH) requires that the PCWP is < 15 mmHg and the pulmonary vascular resistance is > 3 WU.
- Symptoms of pulmonary hypertension are nonspecific:
  - Dyspnea
  - Fatigue
- Echocardiogram is the best screening tool.
- Oral and parenteral therapies are available.
- Exercise training and pulmonary rehabilitation is beneficial.