Pulmonary Hypertension: Update and Exercise Implications

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Improving People's Lives through innovations in personalized health care

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Disclosures and Conflicts

- I have no relationships to disclose with any pharmaceutical or device company.
- I have participated in COPD research funded by the NIH and by the Flight Attendant Medical Research Institute (FAMRI).
- I have developed and participated in programming for the COPD Alliance and Midwest COPD Network.
Objectives

1. To review treatment strategies and outcomes in pulmonary hypertension
2. To identify the effects of exercise on the pulmonary circulation.
3. To understand the evidence supporting pulmonary rehabilitation for patients with pulmonary hypertension.
Case Presentation

- 33 year-old woman presents with a 6 month history of gradually progressive shortness of breath with exertion. She had lightheadedness and near-syncope while climbing steps on one occasion.

- Her vital signs were normal, lungs were clear, and cardiac exam showed a slightly prominent second heart sound and a systolic murmur.

- A initial diagnosis of exercise-induced asthma was made and she was prescribed an inhaled bronchodilator.
Case Presentation

- The pt’s symptoms continued for the next 3 months.
- A CXR showed mild cardiomegaly and slightly prominent pulmonary arteries.
- PFTs showed mild reduction in DLCO.
- EKG showed right-axis deviation and possible RVH.
- Echocardiogram confirmed RVH, RAE, flattening of the interventricular septum, and moderate TR with a calculated right ventricular systolic pressure of 78 mmHg.
Pulmonary Hypertension: Definition

- Pulmonary hypertension is characterized by an elevated pulmonary arterial pressure which often results in secondary right ventricular failure.
- Mean pulmonary artery pressure > than 25 at rest.
  - mean PAP = diastolic PAP + 1/3 (pulse pressure)
- For PAH, must have a PCWP less than 15 and no lung disease, thromboembolic disease, or systemic disorders.
Pathogenesis

- Microvascular dysfunction with restriction of pulmonary circulation and attenuation of cardiac function.
Pulmonary Hypertension
Presenting Symptoms and Prevalence

- Dyspnea
- Fatigue
- Near syncope/syncope
- Chest pain
- Palpitations
- LE edema

- Pulmonary hypertension is relatively common
- PAH thought to be 5-15 cases per million so relatively uncommon
Pulmonary Hypertension: Classification

- **Group 1 – Pulmonary arterial hypertension (PAH)**
  - Idiopathic, familial or due to connective tissue disease, congenital heart disease, HIV or liver disease
- **Group 2 – PH due to left heart disease**
- **Group 3 – PH due to lung disease or hypoxemia**
- **Group 4 – Chronic thromboembolic PH**
- **Group 5 – multifactorial mechanisms**
  - Sarcoid, myeloproliferative disorders, or miscellaneous
Baseline Assessment

World Health Organization (WHO) functional classification for pulmonary hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>WHO functional classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.</td>
</tr>
</tbody>
</table>
Diagnostic Testing

- CXR – prominent pulmonary arteries and cardiomegaly with RV enlargement

- ECG – RV strain or hypertrophy
  - Right axis deviation, increased P wave

- 6 minute walk test
  - Healthy subjects 365 – 700 m (1200 – 2200 feet)
  - Determines functional class and provides prognostic indicator
Diagnostic Testing
Diagnostic Testing

- Pulmonary Function Testing
  - Decreased DLCO
- V/Q scan
  - Evaluate for thromboembolic disease
- Lab tests
  - HIV, LFTs, ANA, RF, ANCA
- Sleep Study
  - When there is clinical suspicion of OSA
Diagnostic Testing - Echocardiogram

- Order for screening when clinical suspicion exists
- Increased sPAP / TR jet
- Right atrial and ventricular hypertrophy
- Flattening of interventricular septum
- Small LV dimension
- Dilated PA
- Pericardial effusion
Diagnostic Testing - RHC

- Right Heart Catheterization
  - Gold standard for firm diagnosis
  - Helps to rule out PH in people that do not have it!
- Vasoreactivity testing – predicts CCB response
  - NO, Flolan, Adenosine - drop in mPAP by 10 mmHg and to value < 40 mmHg
Treatment Considerations

- **Medical**
  - Diuretics
  - Coumadin (IPAH, Anorexigen)
  - Oxygen
  - PAH specific therapy
- **Surgical therapy**
  - Atrial septostomy
  - Lung transplantation
Treatment

Pulmonary hypertension (NYHA functional class II, III, or IV)

Conventional therapy (oral anticoagulant ± diuretics ± oxygen)

Acute vasodilator response?

Yes

Oral calcium-channel blockers

Sustained response?

Yes

Continue calcium-channel blockers

No

Class II

Ambrisentan, or Bosentan, or Sildenafil, or Tadalafil

Class IV

Preferred: Epoprostenol
Acceptable: Treprostinil IV

No improvement or deterioration

Consider combination therapy

Atrial septostomy or Lung transplantation

Class III

Ambrisentan, or Bosentan, or Epoprostenol IV, or Inhaled Iloprost, or Sildenafil, or Treprostinil IV or SC, or Tadalafil
### Characteristics of medications used in the treatment of pulmonary hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose range, adult</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol*</td>
<td>Continuous IV</td>
<td>1 to 20 ng/kg/min</td>
<td>3 to 5 min</td>
</tr>
<tr>
<td>Treprostinil*</td>
<td>Continuous SC/IV</td>
<td>0.625 to 1.25 ng/kg/min</td>
<td>4 to 5 hr</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Inhaled</td>
<td>2.5 to 5 mcg, 6 to 9 times/day</td>
<td>1 to 2 hr</td>
</tr>
<tr>
<td>Treprostinal</td>
<td>Inhaled</td>
<td>6-18 mcg, 4 times daily</td>
<td>4 hr</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Oral</td>
<td>62.5 to 125 mg, 2 times/day</td>
<td>5 hr</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Oral</td>
<td>5 to 10 mg/day</td>
<td>9 hr</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Oral</td>
<td>20 mg, 3 times/day</td>
<td>4 hr</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Oral</td>
<td>40 mg/day</td>
<td>35 hr</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>Oral</td>
<td>30 to 240 mg/day</td>
<td>2 to 5 hr</td>
</tr>
<tr>
<td>Diltiazem*</td>
<td>Oral</td>
<td>120 to 900 mg/day</td>
<td>2 to 4.5 hr</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Oral</td>
<td>2.5 to 20 mg/day</td>
<td>30 to 50 hr</td>
</tr>
</tbody>
</table>

* The dose range shown is for a short-term infusion; higher doses are required for long-term infusions (range often exceeds 100 to 150 ng per kg per minute).

* The half-life shown refers to immediate-release preparations; however, sustained-release preparations that can be administered once daily are available and preferred for maintenance.
Advanced Therapy Considerations

- **Group 1 PAH** – Advanced therapy often needed because there are no effective primary therapies.

- **Group 2 PH** – For most patients advanced therapy should be avoided because it may be harmful.

- **Group 3 PH** – Advanced therapy is not approved by the FDA for patients with group 3 PH. Several guideline panels recommend against its use in this population, except in the context of a clinical trial.

- **Group 4 PH** – Advanced therapy can be considered for patients who remain WHO functional class III or IV even after anticoagulation or thromboendarterectomy. Pharmacologic therapy can also act as a bridge to surgical intervention.

- **Group 5 PH** – Small studies have addressed the role of advanced therapy for patients with PH related to sarcoidosis.
Advanced Therapy - Epoprostenol

- Most studies of advanced therapy
- Delivered continuously through catheter with infusion pump.
- Improves hemodynamics, functional capacity and survival in IPAH

Side effects: headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, anxiety and catheter complications
Advanced Therapy - Treprostinil

- Administered IV or SQ or inhaled
- Longer half-life and no need for refrigeration
- Improves hemodynamics, symptoms, and functional capacity in IPAH.
Advanced Therapy - iloprost

- Inhaled frequently (6-9 times a day)
- Longer half-life and no need for refrigeration
- Improved walk distance.
Advanced Therapy - ERAs

- Endothelin receptor antagonists
  - Potent teratogenics
- Bosentan – nonselective oral agent
  - Improves hemodynamics, exercise capacity and delays time to clinical worsening.
  - Monitor liver function
- Ambrisentan – selective type A ERA
  - Improves exercise tolerance, hemodynamics, functional class and quality of life

215 patients: 70% IPAH, 92% Class III

Week 16: 36 meter improvement and 44 meter treatment effect

Advanced Therapy - PDE5 Inhibitors

- Prolong vasodilator effect of nitric oxide
  - Improve hemodynamics and exercise capacity
- Sildenafil
- Tadalafil
- Vardenafil

- 278 patients\(^1\)
  - 65% IPAH
  - 40% Class II and 56% Class III
- Treatment effect \(\sim 45\) meters
- No difference in 6 MWD between doses

Treatment Outcomes – Following Response

- Six minute walk test
- Echocardiogram
- Right heart catheterization
- BNP
- Functional class
Case Presentation - update

- Initial evaluation 6MW of 305 m (1000 feet).
- RHC
  - Pulmonary arterial pressure 65/30 (mean 42 mmHg)
  - RAP of 12 mmHg
  - Pulmonary capillary wedge pressure of 6 mmHg
  - Cardiac output of 3.2 L/min
  - No response to vasodilators
- No other factors so thought to have idiopathic PAH and WHO class III on the basis of her symptoms.
- Treatment options were discussed with the pt, including medical therapy, diet, exercise, travel, altitude exposure, and pregnancy.
Case Presentation - update

- Patient was treated with bosentan and follow up echo 3 months later showed a RVSP of 55 mmHg and 6MW distance increased by 30 m with improved dyspnea and greater activity tolerance.

- She had regular follow up did well, but two years later reported increasing dyspnea on exertion, ankle edema, and an episode of near-syncope. 6MW results were worse compared with baseline.

- RHC showed PAP 75/36 mmHg (mean 48 mmHg)
  - RAP was 13 mmHg, PCWP was 7 mmHg, CO was 2.7 L/min

- An indwelling central venous catheter was placed, and long-term intravenous epoprostenol therapy was initiated.

- 3 months later symptoms significantly improved and she asks about exercise.
Pulmonary Anatomy

- Pulmonary circuit
  - Pulmonary veins
  - Pulmonary arteries
  - Right atrium
  - Right ventricle
  - Left atrium
  - Left ventricle

- Lung
- Capillaries
Normal Pulmonary Response to Exercise

- Increased minute ventilation and increased cardiac output
- Vasodilation of pulmonary vascular bed and recruitment of unused vascular units
Exercise Physiology in PH

- Transition from high flow/low resistance state to low flow/high resistance.
- Inability to vasodilate and few unused vascular units.
- V/Q mismatch and dead-space ventilation
- 20% will develop right to left shunt across PFO
- Skeletal muscle has decreased oxygen extraction
- Left ventricular dysfunction may contribute
Rationale for Exercise in PH

- Historically, exercise discouraged.
- Advances in exercise therapy in COPD and heart failure.
- Improved medical therapy resulted in improved hemodynamics.
- However, patients still have dyspnea, decreased HRQOL and skeletal muscle dysfunction.
Safety of Exercise in PH

- Several small case reports and case series in early 2000’s looking at safety of exercise in PH
- Mereles in 2006 performed largest study
  - Crossover trial: 73% Class III, 7% Class IV
  - Randomly assigned 30 patients who were receiving advanced therapy for severe PH to either an exercise training group or a sedentary control group.
  - 15 week rehabilitation program (inpatient first 3 weeks then 12 weeks outpatient).
  - 7 day a week program (60 minutes walking, 30 minutes bike, and resistance).
  - Given a cycle ergometer to use at home.
Safety of Exercise in PH

### TABLE 2. Medical Treatment With PH-Targeted Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Control Group (n=15)</th>
<th>Primary Training Group (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>11</td>
<td>8</td>
<td>0.22</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Illoprost inhaled</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Beraprost</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

**Drug combination therapy**

- Monotherapy: 7, 6
- Dual therapy: 5, 5
- Triple Therapy: 3, 4

The 2 groups did not differ with respect to medical therapy. Values represent mean±SD. Probability values were adjusted by χ² test.
Safety of Exercise in PH

- After 15 weeks, the mean six-minute walk distance increased in the exercise training group and decreased in the sedentary group (+96 versus -15 meters).
- Following crossover, the sedentary group also improved their mean six-minute walk distance (+74 meters).
- The improved distances exceed those described for all types of advanced therapy.
- Exercise training improved the WHO functional class and peak oxygen consumption.
- Despite the functional benefits, exercise training did not improve hemodynamic abnormalities, measured as the Doppler-derived pulmonary artery systolic pressure.

Exercise in PH

- 2009 de Man et al published outpatient exercise program in 19 patients
- Used exercise protocol for rehab in CHF
- Class II and III with mean PAP = 53
- Increased exercise endurance time by 89% but did not increase 6 MW distance.
Exercise in PH

- 2011 Fox et al reported in Journal of Cardiac Failure on 22 PAH class II and III subjects
- Twice weekly outpatient rehab for 12 weeks.
- Treadmill walking, cycling and stair climbing and added resistance after 6 weeks.
- Increased 6 MW distance by 32 meters and control group dropped by 26 m.
Exercise in PH

- 183 patients with PH (75% class III)
- 3 week in-hospital intensive exercise training
- Given cycle ergometer on discharge
- 6MW distance improved 68 m at 3 weeks and 78 m at 15 weeks.

Grunig et al ERJ 2012
Exercise in PH – adverse events

- 25 patients had adverse events during 3 weeks
- 2 had syncope several hours after exercise (one upon standing in the middle of the night)
- 6 presyncope – only one linked to exercise
- 2 episodes of SVT that were self-limiting
- 15 complications related to URI’s
- No adverse events during home exercise
Exercise in PH

- Chan et al, Chest February 2013
- Group 1 PH, no Class 1 and had to walk less than 400 m and more than 50 m on initial testing.
- 24-30 supervised sessions of treadmill walking over 10 weeks.
Exercise in PH

302 Individuals screened for eligibility

276 Excluded
- 187 Did not meet inclusion criteria
- 43 Declined to participate
- 40 Met exclusion criteria
- 6 Unable to walk

Enrollment

26 Randomized

13 Allocated to Exercise and Education
- 0 Lost to follow-up
- 3 Discontinued intervention
  - 2 Medication change
  - 1 Adherence < 80%
- 10 Included in analysis
- 3 Excluded from analysis

Allocation

13 Allocated to Education only
- 0 Lost to follow-up
- 0 Discontinued intervention

Follow-Up

Analysis

13 Included in analysis
- 0 Excluded from analysis
Figure 2. Distribution of the improvement observed in the 6MWT distance for both groups. Black bars represent patients in the education/exercise combined (EXE) group and gray bars represent patients in the education only (EDU) group. Dashed black line represents the minimally important difference for 6MWT distance in patients with pulmonary hypertension.\(^{48}\) 6MWT = 6-min walk test.
Exercise in PH

- Increase in 6MW distance of 56 m in exercise group with increased work rate and improvement on SF-36
- No improvement in education only group.
- No adverse events noted.
What to tell PH patients about Exercise

- Exercise is not harmful and very likely helpful.
- Patients with PAH should speak with their MD before starting an exercise program.
- Patients with PAH should not over-exercise.
- Light resistance training and moderate aerobic activity are recommended.
- Consider starting exercise in a supervised program.
Conclusion

- A thorough diagnostic evaluation of pulmonary hypertension helps differentiate the cause.

- A hemodynamic assessment is needed to make the diagnosis and determine therapy.

- Treatment based outcomes in PH center around the 6 MW test

- Exercise can be safely performed in pulmonary hypertension patients with the appropriate supervision and training program.