Friday General Session

Pulmonary Arterial Hypertension for the Primary Care Provider

Dustin Fraidenburg, MD
Assistant Professor of Medicine
Director of the Pulmonary Hypertension Program
Division of Pulmonary, Critical Care, Sleep and Allergy
University of Illinois at Chicago
Chicago, Illinois

Educational Objectives
By the end of this educational activity, participants should be better able to:
1. Identify appropriate diagnostic approaches for early detection and referral of PAH patients.
2. Evaluate the latest evidence-based recommendations for the management and monitoring of PAH patients.
3. Discuss the role of primary care providers as part of the interprofessional healthcare team in the long-term management of patients with PAH.

Speaker Disclosure
Dr. Fraidenburg has disclosed that he is on the advisory board for United Therapeutics.

Supporter Disclosure
This educational activity is supported by an educational grant from Actelion Pharmaceuticals. It has been planned and produced by VemCo MedEd with Texas Academy of Family Physicians strictly as an accredited continuing medical education activity.
ACTIVITY DESCRIPTION

Target Audience
This continuing medical education activity is planned to meet the needs of primary care providers who can contribute to early detection of disease and who are responsible for the long-term management of patients with PAH.

Learning Objectives
At the conclusion of the educational activity, the learner should be able to:
• Identify appropriate diagnostic approaches for early detection and referral of PAH patients.
• Evaluate the latest evidence-based recommendations for the management and monitoring of PAH patients.
• Discuss the role of primary care providers as part of the interprofessional healthcare team in the long-term management of patients with PAH.

FACULTY AND DISCLOSURE

Dustin Fraidenberg, MD
Assistant Professor
Director, Pulmonary Hypertension Program
Department of Medicine
Division of Pulmonary, Critical Care, Sleep and Allergy
University of Illinois at Chicago
Chicago, IL

Dr. Dustin Fraidenberg, MD has the following relevant financial relationships with the commercial interests:
Advisory Board: United Therapeutics

Dr. Fraidenburg does not intend to discuss any off-label uses.

No (other) speakers, authors, planners or content reviewers have any relevant financial relationships to disclose.

Content review confirmed that the content was developed in a fair, balanced manner free from commercial bias.
Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation, but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

Clinical Case: 27 y/o Woman with Chest Pain

She reports that one day prior to presentation she developed sharp, substernal chest pain during a walk with her son. This resolved after resting. Pain was 8 out of 10 without radiation and she had never experienced this previously. Chest pain was associated with shortness of breath and palpitations. She went to the clinic the following day and was referred to the hospital for complete evaluation.

Troponin was elevated at 0.16 and she was admitted to the hospital.

Outline

• Case presentation
• Pulmonary Hypertension definition and classification
• Clinical suspicion and screening for pulmonary hypertension
• Diagnostic strategy for PAH
• Basics of PAH management

Clinical Case (cont.)

• Past Medical History:
  – Raynaud’s syndrome
  – Migraine HA
  – Anemia
  – Gestational DM Type 2
• Past Surgical History:
  – C-section last year
  – Appy 7 years ago
• Allergies:
  – PCN: Facial swelling
• Meds:
  – None
• Family History:
  – Father: DM, HTN
  – Mother: Healthy
  – Brother: DM
• Social History:
  – Lives with husband and 3 children
  – Works in daycare
  – Never smoker
  – Denies EtOH or illicit
Physical Exam

Temp 97.7/36.5  BP 103/77  HR 107  RR 20  SpO2 100% RA
Gen: NAD, alert and cooperative
HEENT: EOMI, PERRL, moist oral mucosa
Neck: Soft, NT, DF, +/−
Ext: No LE edema, 2+ distal pulses
Skin: No rashes
Neuro: AOA3, sensation and strength intact grossly
ECG: Sinus tachycardia, nonspecific T wave inversion in infralateral leads

Plan: Admit to hospital, trend troponin, CT PE protocol, Echocardiogram

What is Pulmonary Hypertension

Diagnosed by RHC with mPAP ≥ 25mmHg
Normal mPAP ≤ 20mmHg at rest
Borderline (21-24) prognostic significance in lung disease and CTD2.3
PVR >3 WU (PVR = ∆Pressure/CO)
  – Normal PVR in some secondary PH
PAH defined with PAWP ≤15mmHg
  – Normal ≤ 12 mmHg


6th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drug- and toxin-induced PAH
   1.4 Connective tissue disease
   1.5 PAH associated with
      1.5.1 Connective tissue disease
      1.5.2 HIV infection
      1.5.3 Portal hypertension
      1.5.4 Congenital heart disease
   1.6 PAH with unclear multifactorial mechanisms
   1.7 PAH long-term responders to calcium channel blocker therapy
   1.8 Persistent PH of the newborn syndrome

2. PH due to LHD
   2.1 PH due to heart failure with preserved LVEF
   2.2 PH due to heart failure with reduced LVEF
   2.3 Valvular disease
   2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to lung disease and/or hypoxia
   3.1 Obstructive lung disease
   3.2 Restrictive lung disease
   3.3 Mixed obstructive and restrictive pattern
   3.4 Hypoxia without lung disease
   3.5 Developmental lung disease

4. PH due to pulmonary artery obstructions
   4.1 Chronic thromboembolic PH
   4.2 Developmental lung disease

WHO Functional Classification

Class Description Example
I No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, chest pain, fatigue or other symptoms.
  The patient with no symptoms of PAH with exercise, regular daily activity, or at rest
II Slight limitations of physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
  The patient may be slightly limited by normal activities such as housecleaning, walking or climbing stairs; but generally, not enough to avoid activities
III Marked limitation of physical activity, less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
  The patient is generally substantially limited by normal activities and may need to take frequent breaks or avoid certain activities
IV Unable to perform any physical activity without symptoms. Dyspnea and/or fatigue present at rest; symptoms are increased by almost any physical activity
  The patient is severely limited with normal activity and most often has symptoms while at rest.

Updated Hemodynamic Definitions of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, chest pain, fatigue or other symptoms.</td>
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<td>The patient is generally substantially limited by normal activities and may need to take frequent breaks or avoid certain activities</td>
</tr>
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<td>Unable to perform any physical activity without symptoms. Dyspnea and/or fatigue present at rest; symptoms are increased by almost any physical activity.</td>
<td>The patient is severely limited with normal activity and most often has symptoms while at rest.</td>
</tr>
</tbody>
</table>

Burden of PAH

- Pulmonary arterial hypertension (PAH) is a serious and rapidly progressive cardiopulmonary disease
- Difficult to diagnose, symptoms are often non-specific
- Sustained PAH leads to right heart failure, the leading cause of death in this population
- Associated with 1-year mortality of 10–15%
- Rare disease, affects 15 to 26 people per million
- More common in women
- True burden may be underestimated:
  - Under-diagnosis
  - Misdiagnosis

Reference:
**Pathogenesis of PAH**

- TNFα, TGF-β, Endothelin (ET-1)
- Smooth Muscle Hypertrophy
- Endothelial Hypertrophy

**Clinical Course of PAH**

- Pre-clinical
- Symptomatic
- Decompensated

**Evaluation**

- Clinical Suspicion of PH
- Echocardiography for Screening
- Echocardiography Use in PH

**Clinical Suspicion of Pulmonary Hypertension**

- Syncope
- JVD
- Chest pain
- Dypnea
- Weakness
- Fatigue
- Parasternal lift
- Loud P2
- S3 and S4
- TR murmur
- Hepatomegaly
- Peripheral edema
- Mottled cyanosis

**Echocardiography for Screening**

- Noninvasive technique to evaluate cardiac structure and function

<table>
<thead>
<tr>
<th>Echo diagnosis</th>
<th>Tricuspid regurgitation velocity</th>
<th>PA systolic pressure</th>
<th>Additional Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely</td>
<td>≤2.8 m/s</td>
<td>≤36 mmHg</td>
<td>None</td>
</tr>
<tr>
<td>Possible</td>
<td>≥2.8 m/s</td>
<td>≥36 mmHg</td>
<td>Yes</td>
</tr>
<tr>
<td>Likely</td>
<td>≥3.4 m/s</td>
<td>≥50 mmHg</td>
<td>Yes or No</td>
</tr>
</tbody>
</table>


Ghio et al. *Int J Cardiol.* 2010; 140: 272–278.
Back to Clinical Case:
27 y/o Woman with Chest Pain

Echocardiogram is performed and pulmonary consulted following results.

Echocardiography

Chest Radiograph
Can suggest PH and help elucidate underlying cardiopulmonary diseases

CT Thorax
PA: Ao ratio > 1

Back to Clinical Case:
27 y/o Woman with Chest Pain

Cardiac MR
Cardiac MR

- Best use is for evaluating RV size and function i.e. RVEF\(^1\)
- Ratio of RV:LV mass shown to predict PH\(^2\)
- Elevated RV end-diastolic volume associated with mortality\(^3\)
- Myocardial enhancement associated with fibrosis/scar – may be related to RV dysfunction\(^4\)


V/Q Scan

- Sensitivity better than CT for CTEPH\(^1\)
  - 97.4% vs 51%
- Can delineate proximal vs distal disease
- Several mismatched defects are common
- Normal perfusion excludes operable CTEPH


Right Heart Catheterization

- Necessary to diagnosis of PAH
- Prognostic value
  - RAP, CO, PVR
- Important for therapeutic decisions
  - Vasoreactivity testing
- Important that data is accurate
  - Review tracings


Back to Clinical Case:
27 y/o Woman with Chest Pain

Concern for pulmonary hypertension given elevated PASP and RV dysfunction; referred for RHC.

RA: 10/8/7  (a/v/end diastolic)
RV: 60/13  (s/d/m)
PA: 73/30/46  (s/d/m)
PAPW: 9/7/7  (a/v/end diastolic)
Fick CO 2.69  Fick Cl: 1.72
AO sat: 96  Pa Sat: 48
PVR: 12 Woods units

Clinical Case (cont.)

Work-up completed for PAH associated conditions:
- No history/evidence of congenital heart disease
- HIV negative
- Liver function tests normal, RUQ U/S normal
- No history using agents associated with drug/toxin associated PAH
- Anti-Sci70 and Anti-centromere antibody neg
- ANA positive with 1:640 titer
- Anti-RNP and Anti-Ro positive

Diagnosed withMixed connective tissue disease and started on hydroxychloroquine
I have diagnosed PAH, now what do I do?

Therapeutic Targets for PAH

PAH Approved Therapies

- PDE-5 inhibitors
  - Sildenafil, Tadalafil
- Endothelin Receptor Antagonists
  - Bosentan, Ambrisentan, Macitentan
- Prostacyclin Analogs
  - Epoprostenol, Treprostinil (oral, inhalation, subQ, IV)
  - IP receptor agonist – Selexipag
- Soluble Guanylate Cyclase Stimulator
  - Riociguat

Our First Therapy – Epoprostenol

The Evolution of PAH Therapy
The Dawn of Event-Driven Studies in PAH

- 742 subjects randomized
- 1:1:1 placebo vs. macitentan 3mg or 10mg
- FC II - III - IV
- PVR ~ 12 WU
- 64% on background therapy
- 61% PDE-5i, 5% oral or inh prostacyclin
- Combined primary outcome
  - Event related to PAH worsening
  - Death

Combination Therapy

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


- All PAH except PoPH
- FC II-III
- mPAP ~ 50 mmHg, PVR ~ 10 WU

AMBITION: Effect of Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening

Additional Combination Therapy Evidence

SERAPHIN
- Event-driven phase 3 trial evaluating long-term effects of macitentan in patients on "background therapy" compared to placebo
  - 97.4% on PDE-5i and 5.4% inh or inh prostacyclin
  - Combined primary outcome
  - Background therapy: macitentan had 37% RR in mortality/morbidity events

GRIPHON
- 1156 patients randomized to placebo (n=562) or selexipag (n=574)
  - 20% naïve, 47% on ERA or PDE-5i; 33% on ERA+PDE-5i
  - 376 pts on dual combo tx had treatment effect consistent with overall population 37% RR in mortality/mortality events
Clinical Course of PAH

Pre-clinical | Symptomatic | Decompensated
--- | --- | ---
NYHA |  |  
CO |  |  
PAP |  |  
PVR |  |  

Time

Special Circumstances
- Warfarin considered for IPAH/HPAP
  - no clear data in other PAH
- Digoxin rarely used
- ERA class are teratogens
- Do not use riociguat with PDE-5
- IV/SC prostacyclin most potent therapy
  - Goal is highest tolerable dose

Goals of Therapy
- Symptomatic improvements
- Improved functional class
  - FC I-II better prognosis than III-IV
- Longer walk distance
  - Prognostic cutoffs of 250, 332, and 380 m
- Normalized RV function
  - RAP < 8mmHg and C.I. > 2.5 mg/kg/min
- Improving / normalized BNP

Impact of Medication Adherence
- Medication adherence is critical!
- Non-adherence can result in:
  - Potential for rebound PAH or uncontrolled symptoms
  - Hospitalizations
  - Potential unnecessary escalation in therapy
  - Increased oxygen use
  - Worsening disease/progression
  - Death
Back to Clinical Case:
27 y/o Woman with Chest Pain

- Patient started on combination PDE-5 inhibitor and ERA as well as diuretics.
- Functional class improved from 3 -> 2
- Walk distance increased by 107 meters
- RVSP 54 mmHg -> 33 mmHg
- RV dysfunction improved

Conclusions

- The symptoms and signs of PH are often subtle, requiring high level of suspicion for diagnosis
- PAH diagnosis requires exclusion of associated syndromes i.e. non-Group 1 classes
- Therapy choice depends on functional class and RV function / dysfunction
- Goal of therapy is to improve symptoms, FC, walk distance and RV function
  – This ultimately slows PAH progression and improves morbidity and mortality

THANK YOU