Pulmonary Hypertension/Right Heart Failure: Update and Developing a Rural PH Practice

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MN Statewide CV Summit
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Disclosures

Consultant with Edwards Lifesciences
Objectives

1. Review updated pulmonary hypertension (PH) definition.

2. Differentiate Group 1 (PAH) versus Groups 2-5 PH.

3. Compare PH prevalence in rural MN to national registries
What is Pulmonary Hypertension?

• ↑Pressure in pulmonary vasculature

• Progressive RV failure & subsequent death

• Why it matters → PAH 85%-91% 1 yr survival -- 58% 5-yr survival

• Median 2.7 years from symptoms to diagnosis

Figure 1. Symptoms encountered most often in patients with pulmonary arterial hypertension. Y-axis shows percent of respondents. SOB: shortness of breath.
PAH Evaluation and Workup
Approach to PH Evaluation

**Pivotal Tests**
- History
- Exam
- CXR
- ECG
- Echocardiogram
- VQ Scan
- PFTs
- Overnight Oximetry
- HIV
- ANA
- LFTs
- Functional Test And Biomarkers
- RH Cath

**Contingent Tests**
- TEE
  - Exercise Echo
- Pulmonary Angiography
  - Chest CT Angiogram
  - Coagulopathy Profile
- ABGs
- Polysomnography
- Vasodilator Test
  - Exercise RH Cath
  - Volume Loading
  - Left Heart, Coronary

**Contribute to Assessment of:**
- Index of Suspicion of PH
- RVE, RAE, \( \uparrow \text{RVSP} \), RV Function
- Left Heart Disease
- VHD, CHD
- Chronic PE
- Ventilatory Function
- Gas Exchange
- Sleep Disorder
- HIV Infection
- Scleroderma, SLE, RA
- Portopulmonary Htn
- Establish Baseline
- Prognosis
- Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response
- r/o LMCA Compression
Echo is a Screening Test

• Normal RV pressure < 30 mmHg

• Estimate RVSP with modified Bernoulli equation
  – Can over or underestimate

• RV size and function: TAPSE, S’, FAC

Anatomy - Pulmonary Hypertension

- Increased flow: High output/shunt
- Protective vasoconstriction
- Irreversible Plexiform lesions
- Elevated left sided pressures
- Aortic valve disease
- Mitral valve disease
- HFrEF or HFpEF

Modified slide from Rick Nishimura MD
Right Heart Catheterization

- Right atrial pressure: 0-8 mm Hg
- Right ventricular pressure:
  - Systolic: 20-30 mm Hg
  - Diastolic: 0-8 mm Hg
- Pulmonary artery pressure:
  - Systolic: 20-30 mm Hg
  - Diastolic: 8-15 mm Hg
- Pulmonary artery wedge pressure: 8-12 mm Hg
Right Heart Catheterization

- Gold standard for diagnosis

**PAH = Mean PA pressure > 20 mm Hg**
  - In PAH → PAWP ≤ 15 mm Hg
  - PVR ≥ 3.0 Wood Units

- Vasodilator response

**Positive Vasodilator Test:**
1. mPAP ↓ by ≥ 10 mmHg
2. mPAP < 40 mmHg
3. Normal or ↑ in CO
4. 4.5-10% of patients

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**Table 7. Agents for Acute Vasodilator Testing**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Epoprostenol</th>
<th>Adenosine</th>
<th>Nitric Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Titration</td>
<td>Intravenous infusion</td>
<td>Intravenous infusion</td>
<td>Inhaled</td>
</tr>
<tr>
<td>Dose Range</td>
<td>2 ng/kg/min every 10 to 15 min</td>
<td>50 mcg/kg/min every 2 min</td>
<td>None</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Headache, nausea, lightheadness</td>
<td>Dyspnea, chest pain, AV block</td>
<td>Increased left heart filling pressure in susceptible patients</td>
</tr>
<tr>
<td>Definitions</td>
<td>Characteristics</td>
<td>Clinical Groups</td>
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<td>----------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>• mPAP &gt;20 mmHg</td>
<td>1, 3, 4, &amp; 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PAWP ≤15 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PVR ≥3 WU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>• mPAP &gt;20 mmHg</td>
<td>2 &amp; 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PAWP &gt;15 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PVR &lt;3 WU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined pre &amp; post-capillary PH</td>
<td>• mPAP &gt;20 mmHg</td>
<td>2 &amp; 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PAWP &gt;15 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PVR ≥3 WU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frost A et al. ERJ, 2019;53(1).
PH Classification

The 5 Groups
# Table 1: Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK-1, 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
      1.4.5 Schistosomiasis
1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1”’. Persistent pulmonary hypertension of the newborn (PPHN)

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

3. Pulmonary hypertension 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

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4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic 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 WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.

BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin;
HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.
PAH Epidemiology

• Idiopathic & heritable PAH incidence: estimated at 5-15 per million

• 10-15% of patients with Scleroderma

• 3-10% of patients with congenital heart disease (shunts)

• 2-16% of patients with portal hypertension

PH as a Comorbidity = \( \uparrow \) Mortality in HFpEF & HFrEF

Guazzi M. Circ, 2012; 126:975-90.
Chronic Thromboembolic PH
CTEPH = Group 4 PH

- 1-5% incidence after PE
- 25% pts w/ no PE history
- 96% sensitivity of VQ scan vs. 51% w/ CT

Figure 1. Cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after a first episode of pulmonary embolism without prior deep vein thrombosis. Reproduced by permission from Reference 30.

CTEPH Treatment

- **Proximal disease** = surgery (PTEA)
  - 11-35% of pts will have residual PH
- **Distal disease** = Medication
  - Anticoagulation
  - PH-directed meds
  - Balloon pulmonary angioplasty

PAH Pathophysiology
Irreversible

Adventitial fibrosis and inflammation
Formation of plexus channels
Disintegration of the elastic laminae
Neointimal fibrosis

Reversible

Apoptosis Resistance Apoptosis
Proliferation Apoptosis
Apoptosis-Resistance

Medial hypertrophy
Intimal hyperplasia

Normal

Disturbed Flow Flow Genes

Apoptosis
Neomuscularization

Presymptomatic/compensated
Symptomatic/decompensating
Declining/decompensated

CO
Symptom threshold
PAP
PVR
NYHA
I
II
III
IV

CO = cardiac output; NYHA = New York Heart Association functional class; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance
PH Research

Rural vs. Urban Population
Rural vs. Urban PH

- Different demographics & socioeconomic pressures than urban communities
- >25% of MN in rural communities (1.38+ million people)
- Lack of access to specialist physicians:
  - 30 specialists/100,000 pts vs. 263 per 100,000 pts
Rural vs. Urban PH

• PH registries heavily weighted to urban population
• PH classification & prevalence is underreported in rural areas
Rural vs. Urban PH

• Retrospective consecutive pts w/ RVSP ≥ 50 mmHg or PH symptoms

• PAH = mPA ≥ 25mmHg & PAWP ≤ 15 with PVR > 3.0 WU

• Consecutive patients -- 1/1/2010-3/31/2020
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All pts (n=229)</th>
<th>Group 1 (n=56)</th>
<th>Group 1* (n=41)</th>
<th>Non-group 1 (n=132)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>123 (54)</td>
<td>38 (68)</td>
<td>22 (54)</td>
<td>63 (48)</td>
<td>0.041</td>
</tr>
<tr>
<td>BMI @ first consult Mean ± SD</td>
<td>32±8.9</td>
<td>29.1±7.6</td>
<td>30.8±7.4</td>
<td>33.6±8.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Age at RHC Mean ± SD</td>
<td>72.2±11.9</td>
<td>68.5±14.1</td>
<td>74.6±10.5</td>
<td>73±10.9</td>
<td>0.023</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>101 (44)</td>
<td>18 (32)</td>
<td>16 (39)</td>
<td>67 (51)</td>
<td>0.056</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>111 (48)</td>
<td>15 (26.8)</td>
<td>28 (68)</td>
<td>68 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Connective tissue disease (%)</td>
<td>6 (3)</td>
<td>2 (4)</td>
<td>2 (5)</td>
<td>2 (2)</td>
<td>0.377</td>
</tr>
<tr>
<td>BNP median (IQR)</td>
<td>280.5 (137.5, 505.8)</td>
<td>316 (148, 801)</td>
<td>186.5 (112, 725.8)</td>
<td>287 (139.5, 443.5)</td>
<td>0.548</td>
</tr>
</tbody>
</table>
Age matters

Kaplan-Meier survival estimates

Proportion Surviving

Time (years)

Number at risk

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 80</td>
<td>169</td>
<td>146</td>
<td>126</td>
<td>112</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>58</td>
<td>42</td>
<td>36</td>
<td>30</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>
No difference in 2 year survival with PAH, Cpc PH or Non Group 1 PH.

*Kaplan-Meier survival estimates*
Prevalence of PH in Rural Minnesota

- **Cass County, MN**
  - Population: 28,567
  - PAH: 560/million
  - Group 1*+2: 420/million

- **Aitkin County, MN**
  - Population: 62,500
  - PAH: 370/million
  - Group 1*+2: 1543/million

- **Crow Wing County, MN**
  - Population: 16,202
  - PAH: 368/million
  - Group 1*+2: 1360/million
Conclusions

• PAH prevalence in rural Minnesota appears significantly higher than the estimated 15-50 cases/million compared to national data.

• Why? Lower socioeconomic area, access to care, environmental exposures? Or Nationwide trend of underrecognition?
Take Home Messages

• 5 groups for PH (Group 1 = PAH)
  – RHC is gold standard

• PH = mean PA pressure >20 mmHg
  – PAH = PAWP ≤ 15 & PVR ≥ 3.0 Wood Units

• PH is underreported in rural population
Questions