Feeling Blue?

Aaron St-Laurent
Montreal Children’s Hospital – Pulmonology
Cross Canada Rounds
FEELING BLUE
Sometimes it's more than just a feeling
Case 1

Identification & chief complaint

• 8 year-old patient with hypoxemia on overnight oximetry

• Found to have Pulmonary arterial hypertension associated with congenital heart disease

   **Eisenmenger Syndrome**
# Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥25 mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>PAPm ≥25 mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤15 mmHg</td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>PAPm ≥25 mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt;15 mmHg</td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Isolated post-capillary PH (lpc-PH)</td>
<td>DPG &lt;7 mmHg and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR ≤3 WU&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH (Cpc-PH)</td>
<td>DPG ≥7 mmHg and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR &gt;3 WU&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

<sup>a</sup> All values measured at rest; see also section 8.0.

<sup>b</sup> According to Table 4.

<sup>c</sup> Wood Units are preferred to dynes.s.cm<sup>−5</sup>.

Pulmonary Htn Classification


<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comprehensive clinical classification of pulmonary hypertension (updated from Simoneau et al. 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Pulmonary arterial hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 Idiopathic</td>
<td></td>
</tr>
<tr>
<td>1.2 Heritable</td>
<td></td>
</tr>
<tr>
<td>1.2.1 BMPR2 mutation</td>
<td></td>
</tr>
<tr>
<td>1.2.2 Other mutations</td>
<td></td>
</tr>
<tr>
<td>1.3 Drugs and toxins induced</td>
<td></td>
</tr>
<tr>
<td>1.4 Associated with:</td>
<td></td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>1.4.2 Human immunodeficiency virus (HIV) infection</td>
<td></td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
<td></td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease (Table 6)</td>
<td></td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
<td></td>
</tr>
<tr>
<td><strong>I’. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>I”’. Persistent pulmonary hypertension of the newborn</strong></td>
<td></td>
</tr>
</tbody>
</table>

| **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 |
| 2.5 Congenital / acquired pulmonary veins stenosis |

| **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 (Web Table III) |

| **4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions** |
| 4.1 Chronic thromboembolic pulmonary hypertension |
| 4.2 Other pulmonary artery obstructions |
| 4.2.1 Angiosarcoma |
| 4.2.2 Other intravascular tumors |
| 4.2.3 Arteritis |
| 4.2.4 Congenital pulmonary arteries stenoses |
| 4.2.5 Parasites (hydatidosis) |

| **5. Pulmonary hypertension with unclear and/or multifactorial mechanisms** |
Diagnosis

Pediatric PAH: Diagnostic Evaluation

Suspected PH

ECG

Yes

Chest X-Ray

Echocardiogram normal?

No

Echocardiogram indicates Left Heart Disease With PH

Yes

Evaluate for left heart and valvular disease

No

Pulmonary Function Tests

Normal (aside from low DLCO)

Plus Polysomnography

No

Extensive evaluation for lung diseases, connective tissue disease, neuromuscular disease or chest wall restrictive disease, others

Yes

Ventilation-perfusion scan

normal or low probability

Yes

Cardiac Catheterization With Acute Vasodilator Testing

Prior to initiation of PH-specific Drug Therapy

↔

Extensive work-up to diagnose connective tissue disease, hypercoagulability, HIV, liver disease, hemoglobinopathies, others

6-min walk test, cardiopulmonary exercise test

Eisenmenger Teaching

- Eisenmenger’s syndrome (ES):
  - Large intra- & extra-cardiac defects
    - VSD, PDA, ASD (adults)
  - Begin as systemic-to-pulmonary shunts
  - Progress to severe elevation of PVR and to reversal or bidirectional shunting
  - Cyanosis, erythrocytosis, and multiple organ involvement are usually present.

Operability of Shunt Lesions

ES = non-operable - PVR/SVR > 0.3.

Eisenmenger – Presentation

• Most common:
  – Dyspnea, fatigue, syncope
  – Exercise intolerance*

• At risk of:
  – Hemoptysis, stroke, PE, brain abscess, coagulopathy, sudden death
Eisenmenger – Diagnosis

• Suggestion: ECHO

• Confirmation: Catheterization

• ECHO may miss PDA
  – 2 / 8 patients with diagnosis of iPAH found to have PDA on repeat ECHO

Eisenmenger Treatment

Table 25: Recommendations for pulmonary arterial hypertension associated with congenital heart disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome</td>
<td>I</td>
<td>B</td>
<td>200,322</td>
<td>If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is &gt;65%</td>
</tr>
<tr>
<td>Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome</td>
<td>IIa</td>
<td>C</td>
<td>223,314,323,324</td>
<td>The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels</td>
</tr>
<tr>
<td>In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure</td>
<td>IIb</td>
<td>C</td>
<td></td>
<td>Combination drug therapy may be considered in patients with Eisenmenger syndrome</td>
</tr>
<tr>
<td>The use of supplemental O₂ therapy should be considered in cases in which it produces a consistent increase in arterial O₂ saturation and reduces symptoms</td>
<td>IIa</td>
<td>C</td>
<td>179</td>
<td>The use of CCBs is not recommended in patients with Eisenmenger syndrome</td>
</tr>
</tbody>
</table>

-Bosentan therapy reduced PVR and mPAP and increased 6MWD by 53.1 m without worsening gas exchange.

Case II

Identification

• 8 year-old of South Asian origins
  – Known for mild Asthma.
  – Presenting with fever and non-bilious emesis
  – Found to have oxygen requirement
Differential Diagnosis

- Hypoventilation
  - Central
  - Obstructive

- V/Q mismatch
  - Asthma, ABPA
  - Infection
  - Pneumonitis
  - Pulmonary edema
  - Pulmonary hyptertension
  - Pulmonary embolus

- Other:
  - Low inspired oxygen
  - Technical error
  - Hemoglobinopathy

- Shunt
  - Intracardiac,
  - Intrapulmonary
    - Pulmonary AVM / HHT
    - Complete atelectasis, airway obstruction

- Diffusion abnormality
  - Interstitial Lung Disease
    - IPF
    - Connective Tissue disease
    - Sarcoidosis
    - chILD
    - IIP
      - COP
Diagnosis?

• Heterozygous Hb-Rothschild mutation
  – Reduced oxygen affinity
Oxygen-Hgb Dissociation Curve

- Normal p50: 27mmhg
- Left Shift (↓ O2 delivery)
  - ↑ pH
  - ↓ pCO2
  - Temp
  - ↓ DPG
- Right shift (↑ O2 delivery)
  - ↓ pH
  - ↑ pCO2
  - Temp
  - ↑ DPG

Oxygen-Hgb Dissociation Curve

Hemoglobin variants
- HbS – Right
- HbF – Left
- MetHb – Right
- CoHb – Left
- Rothschild, Chico, Basset – Right
Oxygen-Hgb Dissociation Curve

• Normal p50: 27mmhg

• MM: VBG
  – PaO2 32.8
  – SaO2 46.0%

• Patient’s p50: 34
  – Right-shift
Hemoglobin Variants and Desaturation

Mechanism of Low SpO2 Readings:

• True, low affinity Hb-variants
  – Rothschild, Bassett, Canebiere

• Absorption spectra of variant hemoglobins
  – Bonn, Cheverly, Koln
  – Methemoglobin

Algorithm

Figure 2. Algorithm for evaluation of low SpO2. MetHb = methemoglobin. # Arterial blood gas should be done on room air and with simultaneous SpO2 measurement. * Investigations could include hemoglobin analysis by various methods, and if necessary, DNA-based genotyping. [Color figure can be viewed in the online version of this article.]
The Saturation Gap

• “Saturation Gap”
  – SaO2 – SpO2 ≥ 5%.
  – Suggests abnormal hemoglobin
    • Carbon Monoxide poisoning
    • Methemoglobinemia
    • Sulfhemoglobinemia
    • Other hemoglobin variants

Absorption spectra of variants

Pulse oximetry calculates hemoglobin oxygen saturation based on light absorption at only two wavelengths

Figure 3. Hemoglobin extinction curve of normal adult oxyhemoglobin and normal adult deoxyhemoglobin. Figure from Sinex [36].

Absorption spectra of variants

- Variant hemoglobins with abnormal absorption spectra compromise accuracy

- Methemoglobin
  - High absorption at 660, 940 nm → Unreliable

- Carboxyhemoglobin
  - Similar 660nm absorption, falsely elevated saturations

Low Affinity Variants

• ↓SpO2, ↓SaO2
• Normal PaO2
• Right shifted p50

• Oxygen delivery NOT adversely affected
  – Right-shift: ↑ O2 delivery
  – Appropriate low-normal hemoglobin levels
• Desaturation α [Variant Hb]
Hemoglobin Rothschild

- Beta-chain mutation: Trp → Arg$^9$
- Low-oxygen affinity variant
- P50: 34.75 – 35 mmHg$^{10}$

**Demonstration of Left Shift$^{11}$**

| TABLE I. Effect of increased F$_1$O$_2$ on PaO$_2$, SaO$_2$ and predicted SaO$_2$ |
|------------------|------------------|------------------|------------------|
| F$_1$O$_2$ (%)   | PaO$_2$ (mmHg)   | Measured SaO$_2$ (%) | Predicted SaO$_2$ (%) |
| 21               | 94               | 84.2             | 97               |
| 50               | 169              | 91.3             | 99.4             |
| 100              | 589              | 96.1             | 100              |


Hemoglobin Rothschild

• Cannot be diagnosed via HPLC
  – Similar profile as Hemoglobin-D variant

Hemoglobin Rothschild

• Presentation:
  – Desaturation
  – Low-normal Hb
    • Appropriate vs. shorter $t_{1/2}$

• Natural History:
  – Unknown
  – Presumed normal life expectancy
Clinical Take Home Points

• Routine pulse oximetry
  – Record where oximetry is taken from

• Low SpO2 should be followed

• Do not ignore low SpO2 out of keeping with clinical picture
ANY QUESTIONS??