Pulmonary Hypertension in Sickle Cell Disease

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Patient Presentation

• 28F with SCD, genotype SS.
• Presented to UWMC ER with 1 month progressive DOE and several days of chest pain
• Could climb 3 stairs at home before becoming dyspneic. SOB worse with lying flat.

  – Pain is different than vaso-occlusive crisis pain
  – No fevers, chills, cough
  – BP: 144/94
Patient Presentation

• PMH:
  – Multiple vaso-occlusive pain crises over the past 8 months
  – Right atrial clot 11/12
  – Acute chest syndrome 8/12
  – CVA 6/12
  – Hypertension

• Medications:
  – Hydroxyurea, Folate, Warfarin, Amlodipine, Oxycontin, Vicodin
Patient Presentation

- CT Chest: diffuse, bilateral centrilobular ground-glass opacities, no focal consolidation, no PE. RV and pulmonary trunk enlargement.

- PFTs: no airflow obstruction, decreased FEV1 and FVC with preserved FEV1/FVC consistent with restrictive lung disease pattern (DLCO not measured)

- TTE (4m prior): TRV 3.6 m/s, PASP 57-62, and increased RV size with low normal RV function. LV function preserved at 55-60% with evidence of diastolic dysfunction.

- V/Q scan (5m prior): low probability of pulmonary emboli
Patient outcome (hospital course)

- Treated initially with ABX, IVF, oxygen, and pain control
- On D3, patient went into acute respiratory failure requiring intubation. HbS = 42%.
- Underwent RBC exchange that night with improvement in her respiratory status and was subsequently extubated on D4 and transferred to the floor
- On D7, patient noted to be tachycardic in the evening. No change in dyspnea.
- Several hours later, patient found unresponsive and pulseless. CPR attempted and unsuccessful.
Pulmonary Hypertension

- **PH**: mean pulmonary artery systolic pressure > 25mmHg at rest on right heart catheterization

- On TTE, a TRV of 2.5-2.8 m/s is suggestive and ≥ 2.8 m/s is highly indicative of pulmonary hypertension

- **Right heart catheterization is necessary to confirm diagnosis, identify mechanism, and perform vasoreactivity testing to guide therapy**

Nef et al. Heart 2010
## Classification of Pulmonary Hypertension

1. **Pulmonary arterial hypertension**
   - Idiopathic PAH
   - Heritable
     - BMPR2
     - ALK1, endoglin
     - unknown
   - Drugs and toxins induced
   - Associated with:
     - Connective tissue diseases
     - HIV infection
     - Portal hypertension
     - systemic to pulmonary shunts
     - Schistosomiasis
     - Chronic haemolytic anaemia

2. **Pulmonary hypertension due to left heart disease**
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. **Pulmonary hypertension due to lung diseases and/or hypoxia**
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Chronic exposure to high altitude
   - Broncho pulmonary dysplasia (BPD)
   - Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary Hypertension with unclear and/or multifactorial mechanisms**
   - Haematologic disorders
     - myeloproliferative disorders; splenectomy
   - Systemic disorders
     - Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.
   - Metabolic disorders
     - Glycogen storage disease, Gaucher disease, thyroid disorders
   - Congenital heart disease
     - other than systemic to pulmonary shunt
   - Others: obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis

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**Figure 1** Updated clinical classification of pulmonary hypertension according to the proposals of the 4th World Symposium on Pulmonary Hypertension held in Dana Point 2008.

Nef et al. Heart 2010
# Pulmonary Hypertension Classification and Sickle Cell Disease

<table>
<thead>
<tr>
<th>Group and Typical Hemodynamic Features</th>
<th>Examples of Associated Conditions</th>
<th>Aspects of Sickle Cell Disease Potentially Related to PH</th>
</tr>
</thead>
</table>
| 1 - Idiopathic pulmonary artery hypertension (PAH), including pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis  
  mPAP ↑ (often 50-60 mmHg)  
PVR ↑  
PCWP normal (<15 mmHg)  
CO normal or low | • Heritable  
• Drugs and toxins induced  
• Associated with  
  - Connective tissue diseases  
  - HIV Infection  
  - Portal Hypertension  
  - System to pulmonary shunts  
  - Schistosomiasis  
  - Chronic hemolytic anemia | Vasculopathy (remodeling)  
Hemolysis  
Limited NO Bioavailability |
| 2 - PH due to left heart disease  
mPAP ↑  
PVR normal  
PCWP ↑  
CO normal or low | • Systolic dysfunction  
• Diastolic dysfunction  
• Valvular disease | Chronic anemia with left ventricular hypertrophy/dysfunction |
| 3 - PH due to lung disease and/or hypoxia  
mPAP ↑ (often 25-40 mmHg) | • Chronic obstructive pulmonary disease  
• Interstitial lung disease  
• Sleep-disordered breathing  
• Chronic exposure to high altitude | Parenchymal pulmonary changes (fibrosis, infarction) |
| 4 - Chronic thromboembolic PH (CTEPH) | | Pulmonary embolism  
Coagulation activation |
| 5 - PH with unclear and/or multifactorial mechanisms | • Hematologic disorders e.g.  
  - Myeloproliferative disorders  
  - Splenectomy  
• Systemic disorders e.g.  
  - Vasculitis  
  - Sarcoidosis  
• Metabolic disorders e.g. Gaucher’s  
• Congenital heart disease  
• Chronic renal failure on dialysis | Auto- or surgical splenectomy  
End-stage renal disease |

mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; PCWP = pulmonary capillary wedge pressure; CO = cardiac output.
Pathophysiology of PAH in SCD: Hemolysis associated?

- Impaired vasodilation
- Increased vaso-constriction
- Hyperplasia/Proliferation
- Increased platelet activation
- Increased adhesion molecules
- Uncoupled NOS

Left Ventricular Dysfunction and PH in SCD

• Chronic anemia creates a hyperdynamic state with an elevated cardiac output -> LV remodeling and diastolic dysfunction

• These findings are associated with a relative systemic hypertension and increased TRV
Left Ventricular Dysfunction and PH in SCD

- Increased mortality was independent of, but additive to TRV
- Patients with diastolic dysfunction had a statistically significant higher SBP (137 mmHg vs 119 mmHg)

Figure 2 Kaplan-Meier Survival Curve According to Both TR Jet Velocity and E/A Ratio

Patients were classified as low risk if they had a tricuspid regurgitation (TR) jet velocity of <2.5 m/s and an E/A ratio of ≥1.0. The high-risk group of patients had either a TR velocity of ≥2.5 m/s or an E/A ratio of <1.0 or both. Mortality was significantly increased in the group having one or both risk factors (p < 0.0001).

Sachdev et al J Am Coll Cardiol. 2007
Pulmonary dysfunction and PH in SCD

• 310 adults with SCD evaluated

• 90% had abnormal PFTs, with the most common abnormality being a restrictive pattern with a decreased DLCO (74%)

• Given high prevalence of restrictive lung disease, routine pulse oximetry monitoring indicated with clinical visits


<table>
<thead>
<tr>
<th>TABLE 2. SUMMARY OF PULMONARY FUNCTION TEST RESULTS</th>
<th>All Patients (n = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of PFT results</td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>82.80</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>83.03 ± 16.06</td>
</tr>
<tr>
<td>FVC</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>83.62</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>84.37 ± 16.01</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC, %</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>98.61</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>98.36 ± 9.15</td>
</tr>
<tr>
<td>TLC</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>69.79</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>70.20 ± 14.69</td>
</tr>
<tr>
<td>RV</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>78.04</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>88.60 ± 60.88</td>
</tr>
<tr>
<td>D&lt;sub&gt;LCO&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53.74</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>56.57 ± 20.11</td>
</tr>
<tr>
<td>Adjusted D&lt;sub&gt;LCO&lt;/sub&gt;*</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61.74</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>64.54 ± 19.93</td>
</tr>
</tbody>
</table>

Subclassification based on PFTs

| Normal, n (%)                                      | 31 (10)               |
| Isolated low D<sub>LCO</sub>, n (%)                | 40 (13)               |
| Mixed O/R, n (%)                                   | 5 (2)                 |
| Obstructive, n (%)                                 | 4 (1)                 |
| Restrictive, n (%)                                 | 230 (74)              |

Definition of abbreviations: D<sub>LCO</sub> = diffusion capacity for carbon monoxide; O/R = obstructive/restrictive; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity.

* Adjusted for hemoglobin concentration.
Thromboembolic Disease and PH in SCD

V/Q scans are more sensitive for detecting chronic thromboembolic events than CT scans

Prevalence of PH in SCD

- Previous studies had suggested a prevalence of PH of 30% based on echocardiographic findings of an elevated TRV\(^1\)

- Prevalence based on right heart catheterization was 6%

- Positive Predictive Value 25%

- 13 patients had post-capillary PH and 11 had pre-capillary PH, suggesting that PH in the sickle cell disease population is multifactorial

\(^1\)Gladwin et al. NEJM 2004
\(^2\)Parent et al. NEJM 2011
Additional diagnostics for evaluation of PH in SCD

• 6 Minute Walk Distance Test
  – Patients with RHC-proven PH had a shorter 6 minute walk distance (320m vs. 435m, \(p=0.002\))^1
  – Non-cardiopulmonary limitations such as avascular necrosis limits utility on some patients with SCD

• Brain Natriuretic Peptide (NT-pro-BNP)
  – One study demonstrated a PPV of 78% when level \(\geq 160\) for when definition utilized for PH was TRV \(\geq 2.5\) m/s on echocardiography^2
  – Never studied in RHC diagnosed pulmonary hypertension

^1 Anthi et al Am J Resp Crit Care Med 2007
^2 Machado et al JAMA 2006
Work-Up for Pulmonary Hypertension in SCD

- Echocardiography -> Right Heart Catheterization
- Pulmonary Function Tests with 6-minute walk test
- CT scan vs. V/Q scan
- Sleep Study (as clinically indicated)
- HIV, ANA, ANCA, RF, LFTs (as clinically indicated)
Prognosis of Pulmonary Hypertension in SCD

Gladwin et al. JAMA 2012
Treatment

• Hydroxyurea: Goal ANC 2.0 and Plts 80,000
• Exchange transfusions as necessary
• Treat conditions contributing to PH:
  – LV dysfunction: BP control
  – Chronic thromboembolism
  – Restrictive lung disease and hypoxemia
  – Asthma
  – OSA
Treatment – PAH directed trials

- ASSET-1 and ASSET-2\(^1\)
  - RCTs of bosentan (endothelial receptor antagonist) vs. placebo in PAH (ASSET-1) and post-capillary PH (ASSET-2)
  - Both closed early secondary to poor accrual
- Walk-PHaSST\(^2\)
  - RCT of sildenafil (PDE-5 inhibitor) vs. placebo in any form of PH (based on TRV \(\geq 2.7\)m/s and decreased 6MWD)
  - Study stopped early secondary to more serious adverse events in treatment group (46% vs. 22%), most frequently hospitalization for pain crisis
  - Analysis of available data did not demonstrate any observed improvement in primary efficacy measure of 6MWD in treatment group
- Arginine
  - 5 days of oral arginine decreased PASP on echo by 15.2\(^3\)
  - Follow-up longer duration studies have failed to show benefit in functional capacity and TRV

\(^1\)Barst et al. Br J Haematol. 2010  
\(^2\)Machado et al. Blood 2011  
\(^3\)Morris et al. Am J Respir Crit Care Med 2003
Conclusions

• Pulmonary hypertension in sickle cell disease is heterogeneous and the cause can be multifactorial

• Echocardiography has a high false positive rate and is not dependable for making a diagnosis of pulmonary hypertension

• All sickle cell disease patients should have a right heart catheterization to make definitive diagnosis

• TRV is an independent risk factor of increased mortality regardless of presence or absence of PH for unclear reasons

• Prognosis is poor and treatment should be directed at decreasing hemolysis and the underlying cause