Pulmonary Hypertension, Obstructive Sleep Apnoea and the Endothelium in Sickle Cell Disease

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Patient History

27 yr old HbSS female presents to establish care. She notes a 1-2 year history of increased dyspnea on exertion, now cannot walk 1-2 blocks.

She notes occasional chest pain with exertion and LE edema

She reports a history of snoring, daytime somnolence and witnessed apneas
Physical Exam

Morbidly obese female in NAD
BMI 43, $O_2$ sat on RA 85% BP 163/87
Neck – Elevated JVP
Chest – Clear
COR – RRR, normal S1, loud P2, II/VI systolic murmur at LSB

Labs – WBC 18.1, Hb 7.1, LDH 705, BNP 66, Creat 0.9. No proteinurea
Polysomnography (PSG)

OSA Grading Scale
- Mild: 5-15 episodes/hr
- Mod: 15-30 episodes/hr
- Severe: >30 episodes/hr
Sleep Study

• There were 122 obstructive apneas, 0 hypopneas, 6 central apneas, and 0 mixed apneas.

• The Apnea-Hypopnea Index was 71.6 events per hour. The supine AHI was 71.5, and the non-supine AHI was 71.6.

• $O_2$ sats as low as 53% on RA noted

• Diagnosis: Severe Obstructive Sleep Apnea
Echocardiogram

Left ventricle - Normal size with mildly increased wall thickness (11 mm) and normal LV systolic function. LVEF 65%. Normal diastolic function.

Right ventricle - Normal in size and systolic function.

Severely enlarged left atrium (54 mL/m2). Right atrium appears at least moderately enlarged.

Trace MR. Mild (1+) TR. Trace PR.

Estimated PASP at least 42 mmHg, assuming RA pressure of 3 mmHg (TRV 3.1 m/sec).

IVC is normal in size, No pericardial effusion.
Diagnosing Pulmonary Hypertension (PH) in SCD

Right Heart Catheterization

- RA/CVP: 2
- RV: 27/1
- PA: 25/11, mean 13
- PAOP: 6
- CO: 8.27
- CI: 3.66
- SVR: 619
- PVR: 68

<table>
<thead>
<tr>
<th></th>
<th>PH (n=56)</th>
<th>No PH (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP (mmHg)</td>
<td>10 ± 5</td>
<td>6 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>36 ± 9</td>
<td>19 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>16 ± 5</td>
<td>12 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>8 ± 3</td>
<td>9 ± 2</td>
<td>0.14</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>0.063</td>
</tr>
<tr>
<td>PVR (dyne.sec/cm⁵)</td>
<td>229 ± 149</td>
<td>74 ± 38</td>
<td>&lt;0.001</td>
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</table>

What can we say about this patient’s future cardiopulmonary risk?
Possible Etiologies of PH in SCD

- Increased hemolysis
- Reduced NO bioavailability/Increased ET-1 expression
- Vascular remodeling from chronically elevated left-sided pressures
- Dysregulated Inflammation/Redox Biology
- Thrombosis – in situ and VTE
- Intermittent hypoxia
- Anemia related cardiomyopathy

Pulmonary Vasculopathy
Hypoxia in SCD

- Under-recognized and historically, under-treated
- Frequent de-saturations with exercise and sleep
- Impaired diffusion capacity, rightward shift of Hb-O$_2$ dissociation curve,
  hypoventilation, anemia
  intra- and extra-cardiac shunts

Sleep Disordered Breathing (SDB) Overview

- Two major forms – Obstructive and Central Sleep Apnea
- Obstructive Sleep Apnea (OSA): Pharyngeal collapse, upper airway obstruction
  Risk factors: Obesity, short neck, narrow oropharynx, male sex, older age

- Central Sleep apnea (CSA): Abnormal brainstem function – cessation of respiratory effort
  - $pCO_2$ increases $\rightarrow$ hyperventilation $\rightarrow$ $pCO2$ decreases $\rightarrow$ apnea

- Features of both can be present
OSA, Hypoxia and Pulmonary Hypertension

Sickle Cell Disease
Abnormal Rheology
Inflammation
Oxidative stress
Endothelial dysfunction
Morbidity
Pulmonary Hypertension, Stroke, Pain/ACS
Early Mortality
SDB (OSA, Nocturnal hypoxemia)

SDB as a Vascular Modulator in SCD
#### Sleep-Disordered Breathing (SDB) in SCD

<table>
<thead>
<tr>
<th></th>
<th>Obstructive Sleep Apnea</th>
<th>Nocturnal Hypoxemia</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Pedi: Up to 79% (most studies 30-40%)</td>
<td>Up to 40% of pediatric SCD patients</td>
</tr>
<tr>
<td></td>
<td>Adult: 44% of 32 HbSS adults</td>
<td>Daytime hypoxemia</td>
</tr>
<tr>
<td><strong>Associations</strong></td>
<td>Tonsillar/Adenoid Hypertrophy in some</td>
<td>Increased vasoocclusive events, priapism and enuresis</td>
</tr>
<tr>
<td><strong>Sickle Cell Disease complications</strong></td>
<td>Increased vasoocclusion</td>
<td>Increased vasoocclusive events, priapism and enuresis</td>
</tr>
</tbody>
</table>

Hypotheses

1) SDB is common in SCD adolescents and adults
2) SDB has adverse impacts on endothelial function and cardiopulmonary outcomes
3) Screening for SDB can identify a modifiable risk factor for morbidity and mortality across the lifespan of SCD patients

Retrospective chart review of BMC patients

Prospective study at Howard University
Stable SCD Patients aged 21-30

Informed Consent History and physical Echo

Arrive at 6 pm at GCRU

Epworth Sleepiness Scale
SF-36
Facit Fatigue Scale
ASCQ-Me Questionnaire

Blood draw for labs/biomarkers
6 minute walk test

Next Morning

Overnight sleep study
# SDB in a Screening Study of SCD Adults

<table>
<thead>
<tr>
<th></th>
<th>AHI &lt; 5 (n=10)</th>
<th>AHI &gt; 5 (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>25 (23-27)</td>
<td>28 (22-28)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>19.8 (18.5-24.4)</td>
<td>23.8 (20.7-27.6)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>50</td>
<td>30</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>HbSS (%)</strong></td>
<td>8</td>
<td>8</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td><strong>Snore index</strong></td>
<td>0.0 (0.0-0.1)</td>
<td>0.8 (0.0-2.1)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure</strong></td>
<td>103 (99-120)</td>
<td>114 (111-130)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>HRQoL</strong></td>
<td>50 (46-53)</td>
<td>39 (31-46)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>6MWD (m)</strong></td>
<td>401 (360-438)</td>
<td>358 (322-383)</td>
<td>0.06</td>
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45 Patients with Sickle Cell Disease Referred for Sleep Study

Obstructive Sleep Apnea (14)  Both (3)  Nocturnal Hypoxemia (8)

22 Adults
OSA (12)  Both (3)  NH (4)

23 Children
OSA (2)  NH (2)
In Males, OSA Increases Linearly with Age

Obstructive Sleep Apnea May Be Different in SCD

- Typical risk factors for OSA: obesity, symptoms of daytime somnolence, snoring

**In our cohort:**
- Median BMI 25.5 (adults), 17.8 (pediatric)
- Epworth sleepiness scale scores do not correlate with AHI (r=-0.06, p=0.78)
- Moderate-severe snoring more common in those with AHI > 5 but not present in all

Sleep-Disordered Breathing

• OSA - Not associated with obesity, but associated with age, particularly in males, HbSC genotype, reduced 6MWD and elevated SBPs

• % of sleep time with hypoxemia inversely correlated with daytime resting $O_2$ sat and Hb, directly correlated with WBC, AST and retic count

Unanswered Questions in the Field

• How prevalent is SDB in children and adults with SCD?
• What does its presence mean in terms of disease severity?
• Does treatment of SDB improve outcomes?
• Planning a multi-center study of SDB and cardiopulmonary dysfunction in adolescents and adults with SCD
How to Approach Sleep-Disordered Breathing in SCD in 2017

• NHLBI SCD Guidelines: Screen for symptoms of SDB Only study if present
• Classic paradigms are likely incorrect
• Need to better understand the true frequency in children and adults and who needs to be evaluated
• Be hyper-vigilant for hypoxia/oxygen de-saturation – particularly inpatients on IV opiates
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