CF patient with hypoxia

David Shoseyov MD
D.G.

- 14 years old with CF and PI
- Portal hypertension
- Esophageal varices and repeated banding
- Decrease synthetic liver function (INR=1.5->1.7)
- Thrombocytopenia
- Hypoxemia
- FEV1=60-70%
- SaO2= 89% on RA
- Sputum culture- PA once but usually MSSA
D.G.

- **Blood Gasses** –
  - **RA**: pH-7.374, SaO₂-69.0, PaO₂-37.6 PaCO₂-45.2 Bic-25.8 BE-0.2
  - **FiO₂ 100%**: pH-7.454, SaO₂-99.7, PaO₂-196 PaCO₂-34 Bic-23.5 BE-0.2

Echo – 2009 – Normal M/P
D.G.

• PE –
  – Lung sounds usually normal
  – Liver and Spleen are enlarged
  – Clubbing of fingers++
  – Heart Normal sounds and rhythm
  – No spiders
Chest CT (Jan 2012)
HRCT (Jan 2012)
Why is he hypoxic?

- The physiological mechanisms that induce hypoxemia include:
  - High altitude
  - Hypoventilation
  - Diffusion defects
  - Shunts
  - Ventilation–perfusion defects.
Why is he hypoxic?

- Although the differential diagnosis of hypoxemia is broad, it can be refined by defining the **duration** of hypoxemia and the underlying **physiological mechanism** (Central Vs Peripheral).

- We need information:
  - **Duration** – Clubbing of fingers, elevated hemoglobin and hematocrit values.
  - **ABG**
  - Calculate A-a difference
  - Other tests like ECHO (why?)
**A-a Gradient**

A normal A-a gradient for a young adult non-smoker breathing air, is between 5-10 mmHg.

\[
Aa\ Gradient = \left( F_iO_2(P_{atm} - P_{H_2O}) - \frac{P_aCO_2}{0.8} \right) - P_aO_2
\]

At Sea level A-a Gradient = (21%*(746 - 40) - 5/4(PCO2)) - PaO2

Approximately

At Sea level A-a Gradient = 147 - 5/4(PCO2)) - PaO2

In Jerusalem A-a Gradient = (21%*(700 - 40) - 5/4(PCO2)) - PaO2
Why is he hypoxic?

High Altitude (JERUSALEM)

- The value for the partial pressure of oxygen should improve with oxygen therapy.
- Altitude is not a concern in this case, since he is hypoxic in Jerusalem which is not too high from sea level.
- It improves with oxygen and CO2 is often low due to hyperventilation.
Why is he hypoxic?

- **Hypoventilation** - failure of the central respiratory center or abnormalities of the peripheral nerves and muscles.
- Hepatic Encephalopathy - unlikely
- The PaO$_2$ depressed and that of PaCO$_2$ is **elevated**.
- There is a normal alveolar–arterial (A-a) gradient and a robust response to oxygen, unlike the findings in this case.
<table>
<thead>
<tr>
<th>Finding</th>
<th>Response to 100% Oxygen</th>
<th>Partial Pressure of Carbon Dioxide</th>
<th>Alveolar–Arterial Oxygen Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation</td>
<td>Yes</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Diffusion defect</td>
<td>Yes</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Shunt</td>
<td>No</td>
<td>Increased or normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Ventilation–perfusion mismatch</td>
<td>Yes</td>
<td>Decreased, increased, or normal</td>
<td>Increased</td>
</tr>
</tbody>
</table>


Why is he hypoxic?

- **Diffusion defects** - arise when the distance that oxygen must travel from the alveolus to the hemoglobin in the pulmonary capillary is altered.

- Such defects result in hypoxemia with exercise (6 min walk test etc) or at altitude but rarely at rest.

- This type of hypoxemia responds to inhaled oxygen.

- *DG response to 100% O₂ was partial and insufficient*
Where is the Shunt?

- **Shunting** of blood through intracardiac defects or abnormal intrapulmonary intrapulmonary vessels is a frequent cause of hypoxemia.
- **The hallmarks of shunting** are a poor response to inhaled oxygen therapy and an increased alveolar–arterial gradient.
- In some cases, there may be a partial response to oxygen therapy.
- The most frequent cause of hypoxemia is a ventilation–perfusion (V/Q) mismatch, which can lead to clinically significant hypoxemia but is responsive to oxygen therapy (like in Bronchiolitis).
Intra cardiac Shunt

• They occur in approximately 20 % of patients with congenital heart disease.
• Conditions that could cause such a shunt in the age group of the patient include:
  – Tetralogy of Fallot,
  – Eisenmenger’s syndrome (with an ASD, VSD or PDA)
  – Pulmonary artery hypertension with a PFO
Intrapulmonary Shunt

• Chronic intrapulmonary shunts are unusual, and the differential diagnosis includes two conditions:
  – Pulmonary arteriovenous malformations (AVM)
  – Hepatopulmonary syndrome.
Pulmonary arteriovenous malformations (AVM)

• Such malformations are rare, detected in only 2 of 15,000 consecutive autopsies.
• They occur twice as often in females as in males and are rarely identified in infancy but are increasingly identified with advancing age.
• Approximately **two thirds** of pulmonary AVM occur in the context of hereditary hemorrhagic telangiectasia, also known as the:  
Hepatopulmonary syndrome

- The unique striking pathological feature of HPS is:
  - gross dilatation of the pulmonary precapillary and capillary vessels (15 to 100 μm in diameter when the patient is at rest), coupled with an absolute increase in the number of dilated vessels.
The unique striking pathological feature of hepatopulmonary syndrome is gross dilatation of the pulmonary precapillary and capillary vessels (to 15 to 100 μm in diameter when the patient is at rest).
Hepatopulmonary syndrome

• The hepatopulmonary syndrome is suspected in any patient with known liver disease who reports dyspnea.

• Arterial blood gases should be measured on room air in patients with clinically significant symptoms.
Hepatopulmonary syndrome

A useful diagnostic test is contrast echocardiography.

*Intravenous microbubbles (>10 μm in diameter) from agitated normal saline that are normally obstructed by pulmonary capillaries (normally <8 to 15 μm) rapidly transit the lung and appear in the left atrium of the heart within 7 heart beats.*
Hepatopulmonary syndrome

- Similarly, intravenous technetium-99m–labeled albumin may transit the lungs and appear in the kidney and brain.
- Pulmonary angiography may reveal diffusely fine or blotchy vascular configuration. The distinction has to be made with an intracardiac right-to-left shunt.
Hepatopulmonary syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation defect</td>
<td>Partial pressure of oxygen &lt;80 mm Hg or alveolar–arterial oxygen gradient ≥15 mm Hg while breathing ambient air</td>
</tr>
<tr>
<td>Pulmonary vascular dilatation</td>
<td>Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (&gt;6%) with radioactive lung-perfusion scanning</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Portal hypertension (most common) with or without cirrhosis</td>
</tr>
<tr>
<td>Degree of severity†</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥80 mm Hg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥60 to &lt;80 mm Hg</td>
</tr>
<tr>
<td>Severe</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥50 to &lt;60 mm Hg</td>
</tr>
<tr>
<td>Very severe</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen &lt;50 mm Hg (&lt;300 mm Hg while the patient is breathing 100% oxygen)</td>
</tr>
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DG echo bubble
D.G.

• Blood Gasses –
  – RA: pH-7.374, SaO$_2$-69.0, PaO$_2$-37.6 PaCO$_2$-45.2 Bic-25.8 BE- 0.2
  – FiO$_2$ 100% : pH-7.454, SaO$_2$-99.7, PaO$_2$-196 PaCO$_2$- 34 Bic-23.5 BE- 0.2

In Jerusalem A-a Gradient = (134 - 5/4(PCO$_2$)) - PaO$_2$

A-a Gradient = (134 - 5/4(45.2)) – 40

A-a Gradient – 42.6  High

Severe  HPS
Hepatopulmonary Synd – Clinical Presentation

• **Dyspnea on exertion, at rest, or both** is the predominant presenting symptom, usually after years of liver disease.

• There are no signs, symptoms, or hallmarks of the HPS on physical examination.

• However, the presence of:
  – spider nevi
  – digital clubbing
  – Cyanosis
  – severe hypoxemia (partial pressure of oxygen, <60 mm Hg)
  
  **strongly suggests Hepatopulmonary syndrome**
Hepatopulmonary Synd – Clinical Presentation

- **Orthodeoxia** - arterial blood O2 decreases by 5% or more or by 4 mm Hg (0.5 kPa) or more when the patient moves from a supine to an upright position.

- Worsening dyspnea (**platypnea**) related to further ventilation–perfusion mismatch.
Lab finding

- **A decrease in the DLCO** is the only routine pulmonary-function test that is consistently abnormal in patients with the hepatopulmonary syndrome.

- The CXR is **frequently nonspecific**, with a mild interstitial pattern in the lower lung that may reflect the existence of diffuse pulmonary vascular dilatation.
Chest angio CT
PREVALENCE AND NATURAL HISTORY

• The term “hepatopulmonary syndrome,” which was probably coined in 1977, was preceded by compelling descriptions based on autopsy and clinical findings.

• An autopsy study in patients with liver cirrhosis, reported in 1966 by Berthelot et al. first suggested that marked pulmonary vascular dilatation may play a role in this condition.

• Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. Chest 1977; 72:305-309
PREVALENCE AND NATURAL HISTORY

- Survival was significantly worse among patients with a partial pressure of oxygen of less than 50 mm Hg at the time of diagnosis.
- Patients with HPS (Not candidates for liver Tx)
  - median survival of 24 months and a 5-year survival rate of 23%.
- Patients without the HPS matched for the cause and severity of liver disease
  - median survival of 87 months, with a 5-year survival rate of 63%.
Management

• **Pharmacological treatment.**
• A small number of small uncontrolled trials:
  – somatostatin analogue,
  – β-blockers,
  – cyclooxygenase inhibitors,
  – glucocorticoids and immunosuppressors (cyclophosphamide)
  – pulmonary vasoconstrictors (almitrine),
  – NO inhibitors, inhaled NO,
  – antimicrobials
  – garlic preparation.
• None of the studies demonstrated consistent improvement due to inadequate size to test efficacy.
• In addition, rare spontaneous recovery has been observed in HPS
Management

• Long-term oxygen therapy. No data are available,

• Transjugular intrahepatic portosystemic shunt (TIPS).
  – Only a few case reports using TIPS for HPS have been published, and have shown variable short-term effects on pulmonary gas exchange.
  – **Our single experience was a failure.**

• Cavoplasty. Venous decompression by abscess drainage resolved HPS in a **single case** with Budd-Chiari syndrome.

• Embolisation. Coil embolisation in type II angiographic pattern HPS has been reported to improve arterial oxygenation (as a temporary measure) in a single case report.
Management

• Orthotopic liver transplantation *
• Complete resolution of HPS following OLT has been observed in >80% of reported cases,
• Many centers currently view HPS as an indication for OLT, particularly in the pediatric population.

* Orthotopic liver transplantation refers to a procedure in which a failed liver is removed from the patient's body and a healthy donor liver is transplanted
Algorithm for screening and therapeutic decisions in hepatopulmonary syndrome (OLT: orthotopic liver transplantation CEE: Contrast Enhanced Echocardiography; MAA: macroaggregated albumin)

Add on

• The correlation between the degree of hepatic dysfunction and portal hypertension and the prevalence and severity of the hepatopulmonary syndrome remains controversial.

• Rare congenital cardiac disorders without liver injury in which either hepatic venous blood flow does not reach the lung or portal venous blood reaches the inferior vena cava without passing through the liver (i.e., the type 1 Abernethy malformation) have clinical similarities to the hepatopulmonary syndrome.

• This provides support for the hypothesis that blood from the gut must cross the liver to prevent pulmonary vascular dilatation.
Abernethy Malformation a rare cause of HPS. The first account of congenital absence of the portal vein (CAPV) was given by John Abernethy in 1793.
Which animal suffers frequently from Abernethy malformation?

Patellar luxation and *portosystemic shunt*, can often be identified early. Parents can be screened for retinal dysplasia, and their histories should reveal any epilepsy or collapsing trachea.

Though *pancreatitis* is not actually a hereditary disease, the fact that the Yorkshire terrier, along with a few other breeds, shows a higher occurrence rate than among dogs in general.