Methemoglobinemia: a Puzzling Case Study

By
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Case Study

- 71 y/o male patient
- Admitted 3/7/14 for AAA repair
- Had surgery on 3/7/14 to repair 75 mm Abdominal Aortic Aneurysm
- Patient also worked up for CVA while hospitalized on 3/13/14
  - CT and MRI of brain showed hemorrhage
  - TEE ordered to rule out cardiac cause of stroke
Transesophageal Echocardiogram

COMPLICATIONS:
None.

INDICATION:
The patient is a 71-year-old male. He had a recent acute stroke. Transesophageal echocardiogram was requested to rule out cardiac source of embolism.

DESCRIPTION OF PROCEDURE:
The patient was in a non-sedated, fasting state. Informed consent was obtained. He was placed in the usual left lateral position. Hurricaine spray was administered to the posterior pharynx for topical anesthetic. A total of 2 mg IV Versed was given for IV sedation. After esophageal intubation with transesophageal echocardiogram probe, visual transgastric and transesophageal views were obtained.

- After the TEE our patient took a turn for the worse
Post TEE

- Patient became cyanotic, dyspneic
- Breathing became labored
- Tachycardic
- Transferred to the ICU
- $S_pO_2$ was very low - 40 to 80%
- Placed on oxygen via non-rebreathing mask
- ABGs were ordered
ABG Results

- High $P_aO_2$ of 393 mm Hg
- Hyperventilation with high pH and low $P_aCO_2$
- Why was patient cyanotic with a $P_aO_2$ of 393?

<table>
<thead>
<tr>
<th>Blood Gas</th>
<th>03/13 0621</th>
<th>03/13 1605</th>
<th>03/13 1817</th>
<th>03/13 1840</th>
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<tbody>
<tr>
<td>ABG pH (7.35 - 7.45)</td>
<td></td>
<td></td>
<td>7.52H</td>
<td>7.48H</td>
</tr>
<tr>
<td>ABG pCO2 at Pt Temp (34 - 45 mm Hg)</td>
<td></td>
<td></td>
<td>31L</td>
<td>35</td>
</tr>
<tr>
<td>ABG pO2 at Pt Temp (75 - 100 mm Hg)</td>
<td></td>
<td></td>
<td>393H</td>
<td>216H</td>
</tr>
<tr>
<td>ABG HCO3 (23.0 - 28.0 meq/L)</td>
<td></td>
<td></td>
<td>24.8</td>
<td>25.2</td>
</tr>
<tr>
<td>ABG O2 Saturation (93 - 100 %)</td>
<td></td>
<td></td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>ABG Base Excess (-3.0 - 3.0 meq/L)</td>
<td></td>
<td></td>
<td>2.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Patient Transferred to ICU

- Physician’s note shows:

**Reason for consult:**
Hypoxia

**Chief complaint:**
SoA

**HPI:**
71yo gentleman who is s/p AAA with repair, IPH, who was undergoing TEE today. Procedure was completed and pt oxygen saturations noted to be very low into the 40-50% range by RN. Pt noted to be cyanotic and with somewhat labored breathing. Oxygen flow increased, but pt remained hypoxic on this, therefore pt transferred to ICU.

Pt had required tubing at initial consult.

**General appearance:** awake, face symmetrical

**Head/Eyes:** PERRLA, abnl conjuctiva/sclera (mild icterus)

**ENT:** moist mucosal membranes

**Cardiovascular:** normal heart sounds, tachycardia

**Respiratory:** clear to auscultation, no distress

**Abdomen:** soft, non-tender

**Extremities:** no edema

**Skin:** dry, intact, abnormal color (cyanotic)
Intensivist Figured it Out

- Even without co-oximeter reading the physician determined the patient had methemoglobinemia.
- The physician ordered methylene blue IV at 1 mg/kg and ordered a methemoglobin test by co-oximeter after methylene blue was given.
What Happened Next

• Methemoglobin level 40 minutes after methylene blue administered was 4%
• Patient was doing much better and no longer cyanotic
• Patient recovered and was dismissed to rehab hospital on 3/17/14
  • Lab went back and looked at full results panel from blood gas machine and saw the Met-Hb was 57%
  • So why didn’t they report it?
What’s Missing from this Picture

- All blood gases at WMC are processed through a blood gas machine that has electrolyte and metabolite electrodes as well as a co-oximeter.
- However, physician orders were just for ABG, not any co-oximeter results.
  - The blood gas machine reported only ABG data for the test ordered:
    - The co-ox showed a critically high Met-Hb of 57%.
    - New policy in place to report to technician any critical co-ox data regardless of blood panel ordered.
**ARTERIAL SAMPLE**

03/13/2014  
System ID: 1265-15921  
Acc. No: 078150

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<th>Parameter</th>
<th>Value</th>
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<tr>
<td><strong>ACID/BASE</strong></td>
<td>37.0 °C</td>
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<tr>
<td>pH</td>
<td>7.521</td>
</tr>
<tr>
<td>pCO₂</td>
<td>31.0 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>393.3 mmHg</td>
</tr>
<tr>
<td>HCO₃-act</td>
<td>24.8 mmol/L</td>
</tr>
<tr>
<td>BE(B)</td>
<td>2.3 mmol/L</td>
</tr>
<tr>
<td>ctCO₂</td>
<td>25.8 mmol/L</td>
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</table>

<table>
<thead>
<tr>
<th>CO-OXIMETRY</th>
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<tr>
<td>Hct</td>
<td>29%</td>
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<tr>
<td>tHb</td>
<td>9.7 g/dL</td>
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<tr>
<td>sO₂</td>
<td>96.7%</td>
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<tr>
<td>FO₂Hb</td>
<td>41.3%</td>
</tr>
<tr>
<td>FC0Hb</td>
<td>0.3%</td>
</tr>
<tr>
<td>FMetHb</td>
<td>57.0%</td>
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<tr>
<td>FHbHb</td>
<td>1.4%</td>
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</table>

<table>
<thead>
<tr>
<th>ELECTROLYTES</th>
<th></th>
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<tbody>
<tr>
<td>Na⁺</td>
<td>137.0 mmol/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.57 mmol/L</td>
</tr>
<tr>
<td>Ca⁺⁺</td>
<td>4.6 mg/dL</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>106 mmol/L</td>
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<tr>
<td>AnGap</td>
<td>9.8 mmol/L</td>
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</table>

<table>
<thead>
<tr>
<th>METABOLITES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>127 mg/dL</td>
</tr>
<tr>
<td>Lac</td>
<td>1.16 mmol/L</td>
</tr>
<tr>
<td>pAtm</td>
<td>724 mmHg</td>
</tr>
</tbody>
</table>
What Clues Helped Physician with Diagnosis

- High $P_aO_2$ and $S_aO_2$ on the blood gas
  - However patient is cyanotic with low $S_pO_2$
- Color of blood
  - Chocolate Brown
- Patient had benzocaine topical anesthetic during TEE
  - Benzocaine is an oxidizing agent
Blood Color as a Percent of Methemoglobin

Samples of blood with varying methemoglobin levels displayed on white absorbent material.

Reproduced from: Shihana F, Dissanayake DM, Buckley NA, Dawson AH. A simple quantitative bedside test to determine methemoglobin. Ann Emerg Med 2010 55:164. Illustration used with the permission of Elsevier Inc. All rights reserved.
What is Methemoglobin?

- **Oxidized form of normal hemoglobin**, in which the iron atom in hemoglobin loses 1 electron to an oxidant, and the ferrous (Fe$^{2+}$) state of iron is transformed into the ferric (Fe$^{3+}$) state.
- Ferric hemes of methemoglobin are unable to bind with oxygen.
- Methemoglobin not only decreases the available oxygen-carrying capacity, but also increases the affinity of the unaltered hemoglobin for oxygen.
- This shifts the oxygen hemoglobin dissociation curve to the left, which further impairs oxygen delivery, leading to tissue hypoxia.
Decreased $P_{50}$ (increased affinity)

- $\downarrow$ Temperature
- $\downarrow$ $P_{CO_2}$
- $\downarrow$ 2,3-DPG
- $\uparrow$ pH

Increased $P_{50}$ (decreased affinity)

- $\uparrow$ Temperature
- $\uparrow$ $P_{CO_2}$
- $\uparrow$ 2,3-DPG
- $\downarrow$ pH
Methemoglobinemia Defined

- >1% of total hemoglobin is in the oxidized form.
- Due to imbalance due to either increased methemoglobin production or decreased methemoglobin reduction.
- High levels can lead to severe and irreversible tissue hypoxia and cell death.
What’s Wrong with Being Blue?

They Look okay to me
Causes of Methemoglobinemia

- Hereditary
  - Cytochrome b5 reductase deficiency (Met H gene)
  - Hemoglobin M disease
  - Pyruvate kinase deficiency
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
Blue Fugates of Troublesome Creek, Kentucky

- The Fugates, commonly known as the "Blue Fugates" a family who lived in the hills of Kentucky, are notable for having blue-tinged skin, caused by methemoglobinemia.
- Martin Fugate settled near Hazard, Kentucky in the early 1820’s and his skin had a blue tint.
  - His wife, Elizabeth Smith, was a member of a family clan who possessed the recessive Met-H gene.
  - Intermarriage between families in around Hazard, Kentucky led to multiple blue skinned Fugates.
Blue Fugates of Troublesome Creek, Kentucky

- Descendants with the disease gene continued to live in the area into the 20th century
- Hematologist Madison Cawein, III studied the family and published his findings in 1964
- Benjamin Stacy, born in 1975 is the last known descendant of the Fugates to have blue colored skin, but the blue faded as he grew older
Blue Fugates of Troublesome Creek, Kentucky

- The congenital form of methemoglobinemia has an autosomal recessive pattern of inheritance
Causes of Methemoglobinemia

• Acquired
  • Drug classifications that can oxidize the iron ion in the hemoglobin are:
    • Antibiotics
      • Trimethoprim, sulfonamides and dapsone
    • Local anesthetics
      • Especially ’caines - articaine, benzocaine, and prilocaine
    • Other meds
      • Aniline dyes, metoclopramide, chlorates and bromates
    • Ingestion of compounds containing nitrates
      • Fertilizer leaked into ground water
    • RT medication
      • Nitric Oxide Therapy > 20 PPM
Blood in Methemoglobinemia

- Dark-red, chocolate, or brownish to blue in color
- Does not change in color with addition of oxygen, unlike deoxyhemoglobin
Clinical Features of Methemoglobinemia

- Cyanosis – detected when methemoglobin concentration exceeds 1.5 g/dL, or 8-12% of total hemoglobin.
- Early symptoms – headache, fatigue, dyspnea, lethargy
- At higher methemoglobin levels – respiratory depression, seizures, altered consciousness, shock, death
- Erythrocytosis – rare
Clinical Features of Methemoglobinemia

<table>
<thead>
<tr>
<th>Methemoglobin Concentration</th>
<th>% Total Hemoglobin*</th>
<th>Symptoms^</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 g/dl</td>
<td>10%</td>
<td>None</td>
</tr>
<tr>
<td>1.5-3.0 g/dl</td>
<td>10-20%</td>
<td>Cyanotic skin discoloration</td>
</tr>
<tr>
<td>3.0-4.5 g/dl</td>
<td>20-30%</td>
<td>Anxiety, lightheadedness, headache, tachycardia</td>
</tr>
<tr>
<td>4.5-7.5 g/dl</td>
<td>30-50%</td>
<td>Fatigue, confusion, dizziness, tachypnea, tachycardia</td>
</tr>
<tr>
<td>7.5-10.5 g/dl</td>
<td>50-70%</td>
<td>Coma, seizures, arrhythmias, acidosis</td>
</tr>
<tr>
<td>&gt; 10.5 g/dl</td>
<td>&gt;70%</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Assumes hemoglobin = 15 g/dl. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of methemoglobin level.

^Patients with underlying cardiac, pulmonary, or hematologic disease may experience more severe symptoms for a given methemoglobin concentration.
Diagnosis

• Standard – Co-oximeter
  • Interprets all readings in 630 nm range as methemoglobin (peak absorbance at 631 nm)
  • False positives if sulfhemoglobin and methylene blue present
• Confirmatory – Evelyn-Malloy method
  • Adds cyanide and ferricyanide to measure total Hb and Met-Hb levels
Treatment of Methemoglobinemia

• Acquired Methemoglobinemia
  • Discontinue offending agents – especially if dapsone or xylocaine-related med
  • Transfusion of pRBCs if anemic
  • Activated charcoal if overdose
  • Supplemental O2
  • Methylene Blue – if severe
  • Converts Iron back from Oxidized ferric state Fe$^{3+}$ to reduced ferrous Fe$^{2+}$ state
Methylene Blue

- Usually given only if methemoglobin level > 40-50% of total hemoglobin.
- Dose of 1 to 2 mg/kg IV over 5 minutes
- Dose may be repeated in 1 hr.
- Large (>7 mg/kg) cumulative doses can cause dyspnea, chest pain, and hemolysis
- Should not be used in a pt. with G6PD deficiency b/c it may further produce hemolysis
  - Methylene blue paradoxically causes methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Ascorbic acid should be given instead
Methylene Blue

- Methylene blue is an oxidant, its metabolite leukomethylene blue is the reducing agent.
  - Therefore, large doses of methylene blue may result in higher levels of methylene blue rather than the leukomethylene blue, which will result in hemolysis.
Treatment of Methemoglobinemia

- **Hereditary Methemoglobinemia**
  - Cytochrome b5r deficiency
    - Methylene blue or ascorbic acid and dextrose
  - Methemoglobinemia due to hemoglobin M does not respond to ascorbic acid or methylene blue
    - N-Acetylcysteine, cimetidine, and ketoconazole are experimental therapies in the treatment of methemoglobinemia that have shown some promising results
  - **Exchange transfusion** is reserved for patients in whom methylene blue therapy is ineffective
  - Hyperbaric Oxygen Therapy
Take-Home Points

- Methemoglobinemia is a condition in which >1% of total Hg is in oxidized form (Fe^{3+}).
- Clinical Triad: Breathlessness, Cyanosis, Chocolate-colored blood
- Usually, if methemoglobin <40% of total Hg, can treat with O2, possibly pRBCs, and discontinuation of any offending agents
- If methemoglobin >40% of total Hg, can give methylene blue (unless G6PD deficient)
- If you are running ABGs on a machine with co-oximeter ensure that any critical value is reported regardless of test panel ordered and reported
References


- Cathy Trost. "The Blue People of Troublesome Creek". Science 82, November, 1982