

# PULMONARY CARE

## Methemoglobinemia: A Case Study

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**M**ethemoglobinemia is a life-threatening condition that can be congenital or acquired. It is characterized by the inability of hemoglobin to carry oxygen because the ferrous part of the heme molecule has been oxidized to a ferric state. Acquired methemoglobinemia is due to medications or chemicals that cause the rate of methemoglobin formation to exceed its rate of reduction.<sup>1-9</sup> These chemicals and drugs include nitrites, aniline, dapsone, phenazopyridine, and topical anesthetics such as benzocaine and lidocaine.<sup>2-9</sup>

The case study (shaded box) describes the development of acquired methemoglobinemia in a 73-year-old woman after transesophageal echocardiography in which a topical anesthetic containing benzocaine was used.

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### ACQUIRED METHEMOGLOBINEMIA Pathophysiology

Hemoglobin consists of 4 heme groups, each containing an iron atom. Each atom is capable of binding with oxygen only if the iron is in the reduced or ferrous state ( $\text{Fe}^{2+}$ ). Removal of an electron (oxidation) from a reduced iron atom produces the ferric state ( $\text{Fe}^{3+}$ ; Figure 1), and methemoglobin results. This abnormal hemoglobin (ie, methemoglobin) is incapable of binding with oxygen.<sup>1-9</sup>

Normally, during the reaction between oxygen and hemoglobin, small amounts of methemoglobin ( $<.01$ ) are formed. The methemoglobin usually is rapidly converted back to hemoglobin by internal mechanisms within the red blood cell: the nicotinamide adenine dinucleotide reductase system, primarily via cytochrome- $\text{b}_5$  reductase.<sup>1-9</sup> Within this pathway, cytochrome  $\text{b}_5$  gains an electron from nicotinamide adenine dinucleotide in the presence of cytochrome- $\text{b}_5$  reductase and donates the negative charge to an ion of ferric iron, reducing the ion to the ferrous form.<sup>5</sup> Certain drugs, including nitrites and topical anesthetics (Table 2), may cause an increase in the oxidation of hemoglobin that overwhelms these internal mechanisms.<sup>1-9</sup>

### CASE STUDY

D.G. was a patient in the surgical intensive care unit after repair of a thoracic aortic aneurysm. Vocal cord paralysis prevented weaning from mechanical ventilation and necessitated a tracheostomy on postoperative day 6. D.G. had a pulmonary artery catheter and a radial arterial catheter in place for hemodynamic monitoring, and the results of pulse oximetry were monitored continuously. Her medical history included diabetes mellitus, asthma, hypertension, hypothyroidism, and a thoracic aortic aneurysm. She had no reported allergies or drug sensitivities. She had no significant surgical history.

Her medications included metoprolol, nifedipine, hydrocortisone, levothyroxine, quinapril, theophylline, docusate sodium, iron, multivitamins, ranitidine, oxycodone, alprazolam, cefotetan, levofloxacin, regular human insulin, albuterol, ipratropium, and beclomethasone. She was not taking nitrates.

D.G. was progressing well until postoperative day 12, when severe respiratory distress and loss of breath sounds on the left side developed. A chest radiograph revealed a large left-sided pleural effusion; a chest tube was inserted, and 500 mL of serous fluid was drained. D.G. tolerated the procedure, and her respiratory status improved. Later in the day, transesophageal echocardiography was used to rule out valvular vegetation as a possible cause of her steadily increasing white blood cell count, from  $17 \times 10^9/\text{L}$  on postoperative

The oxidized hemoglobin is then unable to carry oxygen because methemoglobin cannot bind and transport oxygen.<sup>1-9</sup> Consequently, the hemoglobin that

day 11 to  $25 \times 10^9/L$  on postoperative day 12.

The echocardiography was done in the surgical intensive care unit at approximately 6 PM after D.G. was given 50 mg of meperidine and 2 mg of midazolam intravenously. Her pharynx was anesthetized with a topical anesthetic spray containing 14% benzocaine; the amount of benzocaine administered was not noted in her chart. D.G. was in normal sinus rhythm with a heart rate of 78 beats/min, blood pressure 102/48 mm Hg, respirations 16/minute, and oxygen saturation by pulse oximetry ( $SpO_2$ ) 97%. Her most recent arterial blood gas analysis revealed the following: pH 7.52,  $Paco_2$  36 mm Hg, bicarbonate 29 mmol/L,  $Pao_2$  100 mm Hg, arterial oxygen saturation ( $Sao_2$ ) 97%; the ventilator settings had been adjusted accordingly to tidal volume 700 mL/kg, synchronized intermittent mandatory ventilation 4 breaths/min (from 6 breaths/min), positive end-expiratory pressure 5 cm  $H_2O$ , fraction of inspired oxygen ( $FiO_2$ ) 0.50, and pressure support 10 cm  $H_2O$ . The echocardiograms revealed mild aortic insufficiency.

Approximately 1 hour after the echocardiography, during the 7 PM change-of-shift report, D.G. again experienced respiratory distress. Values were as follows: respirations 33/min to 36/min,  $SpO_2$  91% on an  $FiO_2$  of 0.50, heart rate 90/min, and blood pressure 166/68 mm Hg. Her skin was gray with a deep circumoral cyanosis. She was immedi-

ately repositioned to semi-Fowler's position and manually given 100% oxygen. Auscultation revealed bilateral breath sounds, and fine rales were noted at both lung bases. The chest tube in the left pleura was intact to a thoracic drainage system at -20 cm  $H_2O$  suction, without air leaks or kinks. A stat chest radiograph revealed no abnormalities. D.G.'s neurological status alternated between agitation and lethargy, but she was able to follow simple commands.

A sample of blood obtained at 7:15 PM from the catheter in the left radial artery was brown-black, and arterial blood gas analysis revealed the following: pH 7.48,  $Paco_2$  41 mm Hg, bicarbonate 31.1 mmol/L,  $Pao_2$  424 mm Hg,  $Sao_2$  99.9%. However, D.G. was now profoundly cyanotic, and her  $SpO_2$  value decreased to 85% to 87%. Arterial blood gas analysis was repeated immediately; the results were essentially the same as the previous results. Additionally, analysis of a sample of mixed venous blood obtained from the pulmonary artery catheter revealed the following: pH 7.47; partial pressure of carbon dioxide, mixed venous, 44 mm Hg; bicarbonate 32.7 mmol/L; partial pressure of oxygen, mixed venous, 15 mm Hg; and mixed venous oxygen saturation 24.1%.

Because of the disparity between the results of pulse oximetry and calculated oxygen saturation, a co-oximetry panel was determined. The results were as follows: methe-

moglobin level 0.49 (normal levels < 0.01-0.02), deoxyhemoglobin 0.001 (0-0.05), total hemoglobin 101 g/L, oxyhemoglobin 0.51 (0.94-0.97), and carboxyhemoglobin 0 (0-0.02).

D.G.'s medications were reviewed, and none of her routine medications could be implicated as the cause of methemoglobinemia. However, a topical anesthetic spray containing benzocaine, tetracaine, and butyl aminobenzoate had been used 2 hours before her respiratory distress during the transesophageal echocardiographic procedure.

Methylene blue, 200 mg in 100 mL of isotonic sodium chloride solution, was infused intravenously during 30 minutes, and the methemoglobinemia rapidly resolved (Table 1). A sample of arterial blood obtained 30 minutes after the methylene blue infusion was bright red, and arterial blood gas analysis revealed the following: pH 7.49,  $Paco_2$  43 mm Hg, bicarbonate 33.4 mmol/L,  $Pao_2$  365 mm Hg,  $Sao_2$  99.8% on 100% oxygen. The methemoglobin level was 0.09.

D.G. had no further respiratory distress, and she was transferred to the surgical step-down unit 24 hours later. She and her family were notified of the adverse reaction. A note was placed in her chart, and an "allergy band" was placed on her wrist to advise healthcare providers to avoid topical and injectable "caine" anesthetics in the future. D.G. and her family were also given information about the anesthetics.

does bind successfully with oxygen increases its affinity, causing a shift to the left in the oxyhemoglobin dissociation curve<sup>8</sup> (Figure 2). Therefore, less oxygen is available

for tissues. This inability to transport oxygen causes the clinical manifestations of methemoglobinemia: cyanosis, hypoxia, dizziness, nausea, stupor, coma, metabolic

acidosis, and eventually cardiovascular collapse. The color of blood is notably chocolate-brown because of the increased concentration of methemoglobin (>0.15).<sup>1-9</sup>

**Table 1** Clinical findings in development and treatment of methemoglobinemia\*

Variable (reference range)	Time					
	4:30 PM	7:30 PM	8 PM	9-9:30 PM	11 PM	1 AM
Respirations, breaths/min	16	33	31	14	12	14
Heart rate, beats/min	78	90	88	89	82	88
Blood pressure, mm Hg	102/48	166/68	139/57	112/47	167/73	152/72
Cardiac output, L/min (4-8)	3.9	5.6			4.6	
Cardiac index <sup>†</sup> (2.8-4.2)	2.2	3.1			2.5	
Systemic vascular resistance, dynes s cm <sup>-5</sup> (700-1600)	1004	871			1529	
Fraction of inspired oxygen	0.50	1.00	1.00	1.00	1.00	0.50
pH (7.35-7.45)	7.52	7.48	7.49		7.49	7.51
PaO <sub>2</sub> , mm Hg (75-100)	100	424	491		365	146
Paco <sub>2</sub> , mm Hg (35-45)	36	41	41		43	39
Arterial oxygen saturation, % (95-98)	98.1	99.9	99.9		99.8	99
Partial pressure of oxygen, mixed venous, mm Hg (38-42)			15			27
Mixed venous oxygen saturation, % (60-80)			24.1			52.8
Oxygen saturation by pulse oximetry, %	97	91	87	88	98	98
Methemoglobin, proportion of total hemoglobin (0-0.15)			0.48		0.02	0.02
Oxyhemoglobin, proportion of total hemoglobin (0.94-0.97)			0.51		0.97	0.97

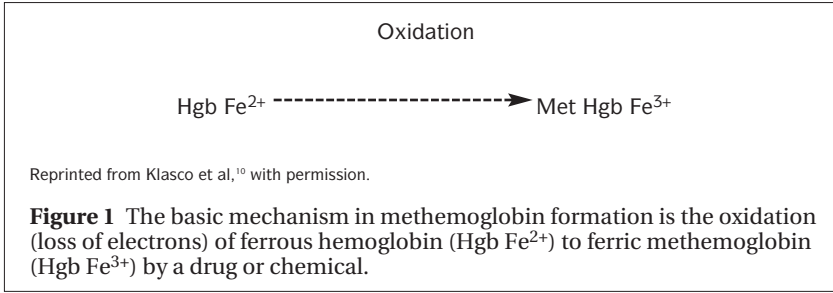
\*In preparation for transesophageal echocardiography, the patient had her pharynx anesthetized with a spray containing benzocaine at 6 PM. Methylene blue, 200 mg in 100 mL of isotonic sodium chloride solution, was administered from 9 PM to 9:30 PM. Empty cells indicate not determined.  
<sup>†</sup>Calculated as cardiac output in liters per minute divided by body surface area in square meters.

## Clinical Manifestations

Signs and symptoms of acquired methemoglobinemia usually occur within 20 to 30 minutes of drug administration.<sup>6</sup> At

methemoglobin levels greater than 0.15, cyanosis is apparent.<sup>1,2</sup> Symptoms such as weakness, headache, and dizziness occur at methemoglobin levels of 0.30 to

0.40; at levels greater than 0.45, dyspnea, acidosis, cardiac arrhythmias, heart failure, seizures, and coma ensue; death occurs at levels greater than 0.70.<sup>1-5</sup> The unusual



dark or chocolate-brown color of the patient's blood is useful in diagnosing methemoglobinemia<sup>1-3,6,7</sup> (Table 3).

**Diagnosis**

The diagnosis of methemoglobinemia is based on clinical

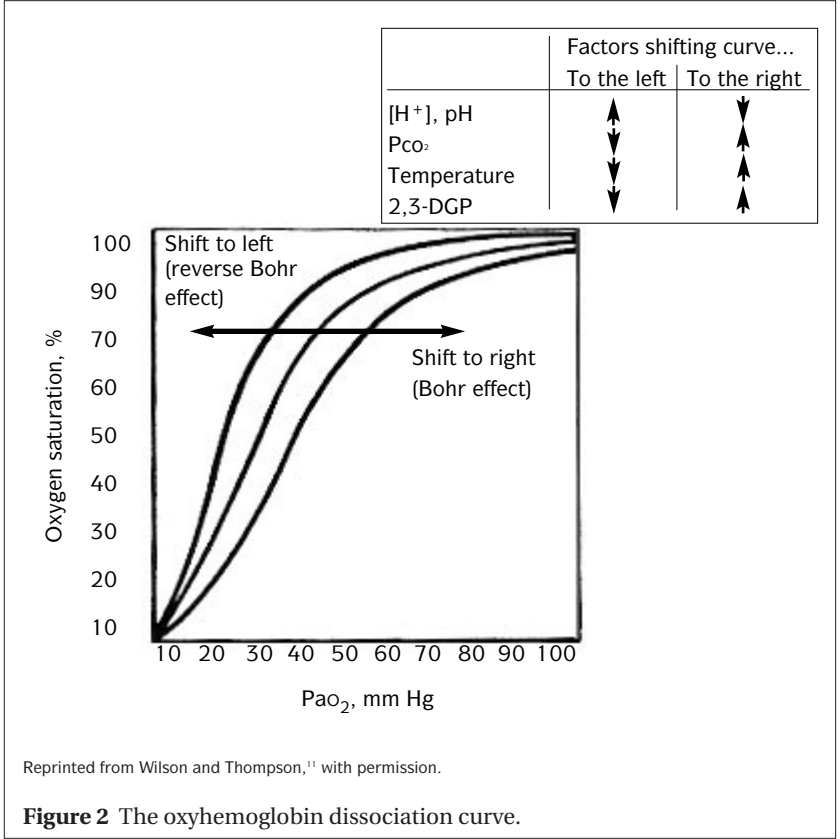
assessment when respiratory status does not explain the cyanosis that a patient has and is refractory to oxygen therapy.<sup>1</sup> Arterial blood is chocolate brown, and the blood gas analysis indicates a Pao<sub>2</sub> that is inappropriately high or normal.<sup>1</sup> Pulse oximetry

is of little value because methemoglobin absorbs both wavelengths of light that are used in pulse oximetry.<sup>6,8</sup> The definitive diagnostic test is multiple wavelength co-oximetry.<sup>4</sup>

Co-oximeters measure the light absorption of blood at numerous ultraviolet wavelengths. Therefore, these machines can determine the amounts of oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin. Pulse oximeters measure ultraviolet absorption at only 2 wavelengths and can therefore only differentiate oxyhemoglobin from deoxyhemoglobin.<sup>5,12,13</sup>

**Table 2** Compounds that may contribute to development of methemoglobinemia

- Amyl nitrite
- Aniline derivatives
- Butyl nitrite
- Bismuth subnitrite
- Dapsone
- Foods contaminated with nitrites or nitrates
- Local anesthetics
  - Lidocaine
  - Benzocaine
  - Prilocaine
- Menthol
- Naphthalene
- Nitroglycerin
- Nitrophenol
- Nitroprusside
- Nitrites
- Nitrates
- Phenacetin
- Phenazopyridine
- Phenols
- Quinones
- Silver nitrate
- Sulfonamides
- Well water contaminated with nitrates



**Table 3** Range of adverse effects of methemoglobin

Level of methemoglobin, proportion of total hemoglobin	Signs and symptoms
0.15-0.20	Clinical cyanosis and chocolate-brown blood evident
> 0.20 to 0.45	Headache, weakness, dizziness
> 0.45	Dyspnea, acidosis, arrhythmias, heart failure, seizures
0.55-0.70	Coma, seizures, arrhythmias, shock
> 0.70	High prevalence of death if untreated

Methemoglobinemia cannot be detected with standard blood gas analysis. In blood gas analysis,  $PO_2$  and pH are measured, and oxygen saturation is calculated on the basis of these values. In patients with methemoglobinemia,  $PaO_2$  determined by using arterial blood gas analysis is falsely elevated, and pulse oximetry measurements are inaccurate.<sup>2,6,7,9</sup> Co-oximetry determines the true amount of oxygen saturation, which is much lower than the calculated oxygen saturation.<sup>6,9</sup>

Pulse oximeters use light at wavelengths of 660 nm (red) and 940 nm (infrared) to generate a ratio of deoxyhemoglobin to oxyhemoglobin.<sup>5,8,10,11</sup> Methemoglobin is detected by both the oxyhemoglobin (940 nm) and the deoxyhemoglobin (660 nm) sensors. At low levels (<0.20), methemoglobin is detected primarily by the deoxyhemoglobin sensor, and a pulse oximeter may indicate a falsely low oxygen saturation. At high levels of methemoglobin (>0.70), detection by the oxyhemoglobin

sensor predominates, and a pulse oximeter may indicate a falsely high oxygen saturation.<sup>5,6</sup> As a further complication, methylene blue is also detected by the deoxyhemoglobin sensor. This situation may lead to falsely low values for oxygen saturation after treatment with methylene blue.<sup>5</sup>

### Treatment

Treatment of methemoglobinemia includes removal of the oxidizing agent and intravenous administration of methylthionine chloride (methylene blue).<sup>1-9</sup> Methylene blue reacts within red blood cells to form leukomethylene blue, which acts as a reducing agent (electron donor) of oxidized hemoglobin, converting the ferric ion ( $Fe^{3+}$ ) back to its oxygen-carrying ferrous ( $Fe^{2+}$ ) state<sup>1-9</sup> (Figure 3). The dose of methylene blue for adults is 1 to 2 mg/kg of a 1% solution administered intravenously during 5 minutes.<sup>1-9</sup>

Importantly, during administration of methylene blue, the

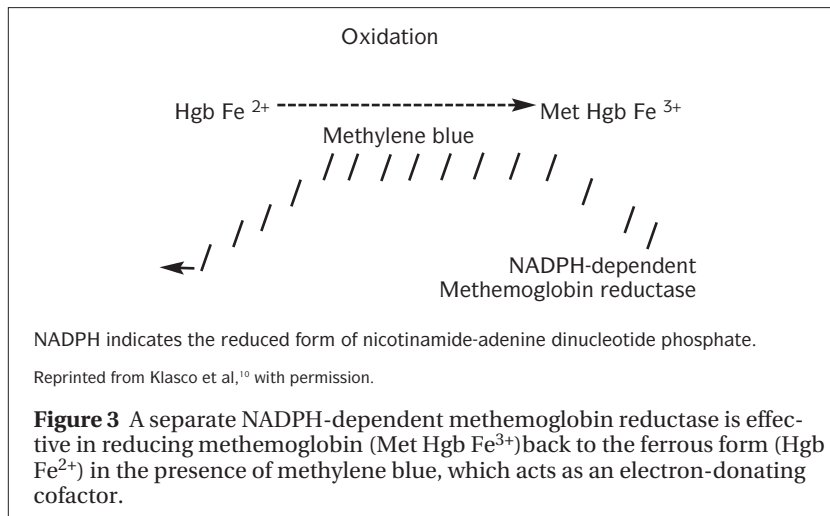
function of pulse oximeters is also affected.<sup>5</sup> Methylene blue has a spectral absorption peak at 668 nm that results in increased absorption of red light, which is interpreted by the oximeter as deoxyhemoglobin, yielding false  $SpO_2$  values. A multiple-wavelength co-oximeter should be used to determine hemoglobin saturation whenever a disparity exists between  $PaO_2$  and  $SpO_2$  and when the response to pharmacological reduction of methemoglobin is being monitored.

Doses of methylene blue should not exceed 7 mg/kg because of its oxidizing properties at high doses. Methylene blue can cause the oxidation of hemoglobin, thereby increasing the formation of methemoglobin and worsening of the methemoglobinemia.<sup>1-3,6</sup>

### Adverse Effects of Methylene Blue

Adverse effects associated with administration of methylene blue include anemia, nausea, vomiting, diarrhea, a burning sensation in the mouth or warmth in the stomach, dyspnea, restlessness, and sweating.<sup>1,2</sup> Urine, feces, saliva, skin, and mucous membranes may be blue.<sup>1,2</sup> Doses greater than 15 mg/kg have actually caused methemoglobinemia.<sup>1</sup> Use of the agent is reserved for patients who have indications of hypoxia and methemoglobin levels greater than 0.30.<sup>1,2,4</sup>

Lack of response to methylene blue suggests the congenital form of methemoglobinemia in which



a deficiency of the intrinsic mechanisms of glucose-6-phosphate dehydrogenase or NADPH (the reduced form of nicotinamide-adenine dinucleotide phosphate) methemoglobin reductase exists. In these patients, or any patient not responding to methylene blue, transfusions of packed red blood cells are necessary to increase the amount of nonionized hemoglobin, thereby allowing increased oxygen binding and transportation.<sup>1,4</sup>

## CONCLUSION

Methemoglobinemia should be considered in patients with cyanosis that is refractory to oxygen administration, especially after administration of topical anesthetics. Acquired methemoglobinemia, although rare, can be fatal, and anyone using chemicals or medications that may lead to the development of methemoglobinemia should be aware of the potential for this

complication. With topical anesthetics used in an ever-increasing number of procedures at the bedside and in outpatient settings, education of staff should include recognition and treatment of this potential life-threatening adverse event. The availability of methylene blue in all areas where these procedures are performed is essential to ensure prompt management of methemoglobinemia. †

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