Late Diagnosis of Congenital Methemoglobinemia in an Elderly Patient During Cardiac Surgery

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METHEMOGLOBIN (metHb), resulting from the oxidation of iron in hemoglobin from the ferrous state to ferric state, cannot bind oxygen and thereby leads to a displacement of the hemoglobin dissociation curve to the left. It can, therefore, impair tissue oxygen delivery. Methemoglobinemia, which is characterized by the presence of a higher-than-normal level of metHb, either can be congenital (due to Hb variants or deficiency of enzymes that convert metHb back to Hb) or acquired (caused by drugs or toxins).

During the perioperative period, anesthesiologists should suspect methemoglobinemia when discrepancy is seen between arterial oxygen saturation and arterial partial pressure, with low SpO2 and normal PaO2. Diagnosis of methemoglobinemia requires measurements of metHb using a co-oximeter analyzer.

The authors describe a case of congenital methemoglobinemia in a 78-year-old man, whose diagnosis was made during cardiopulmonary bypass (CPB) for cardiac surgery. Methemoglobinemia was undiagnosed 1 week before, despite the occurrence of low oxygen saturation and generalized seizures during a cervical block for carotid endarterectomy.

CASE REPORT

A 78-year-old man was admitted for carotid endarterectomy prior to a planned aortic valve replacement. He had a history of type-2 diabetes and arterial hypertension. He had an inflammatory pleural effusion with full recovery around 30 years ago. His surgical history included a total hip replacement in 2008, a meniscus surgery in 1970, and a surgery of the right shoulder in 2007. On physical examination, the patient was found to be in good condition without any cyanosis. A systolic murmur was heard. Echocardiography found an estimated aortic valve area of 0.66 cm2, an aortic valve gradient of 48 mmHg, and preserved left ventricular systolic function. Hemoglobin level, hemostasis, and basic metabolic panel were normal. Chest x-ray showed left thickened pleura. Reports of the preoperative pulmonary function tests were normal. No metabolic panel were normal. Chest x-ray did not show any additional parenchyma abnormalities. Physical examination revealed no cyanosis, and no dyspnea was observed during T-tube trial of spontaneous breathing. The patient was extubated 8 hours after the end of surgery, and was discharged 24 hours after his admission in ICU. The last recorded SpO2 was 92% in room air. Local anesthetic-induced systemic toxicity after regional anesthesia was considered as the diagnosis.

Cardiac surgery (aortic valve replacement with a biologic heart valve) was performed 7 days after the carotid endarterectomy. In the operating room, physical examination revealed cyanotic lips and the SpO2 was 92% in room air. General anesthesia was induced with a target-controlled infusion of propofol and remifentanil and a bolus of atracurium. Anesthesia was maintained with remifentanil infusion and target-controlled infusion of propofol, which was adjusted to keep the bispectral index value between 40 and 50. During the procedure, neither preoxygenation before tracheal intubation with pure O2 nor mechanical ventilation with FIO2:1 increased SpO2, despite normal lung auscultation. Recruitment maneuvers were ineffective. A transesophageal echocardiogram was performed, and a contrast bubble study ruled out the possibility of a cardiac right-to-left shunt. The patient remained clinically stable; surgery was continued and CPB was started. Blood in the systemic flow line remained brown and dark. The perfusionist did not find oxygenator failure, low oxygen concentration in the oxygenator gas supply line, or low gas flow to the oxygenator. Dismethemoglobinemia was suspected. ABG measurements were taken immediately using a co-oximeter analyzer. They were pH: 7.40, SaO2: 99%, PaO2: 309 mmHg, hemoglobin:10.5 g/dL, carboxyhemoglobin: 0.1%, and metHb rate: 23.2%. This methemoglobinemia was moderate and well tolerated before and during anesthesia (absence of clinical cyanosis, hemodynamic stability without catecholamine requirement, and absence of hyperlactatemia and metabolic acidosis). No specific treatment was given. MetHb was 17% at the end of surgery after transfusion of 2 units of packed red blood cells. After surgery, the patient was transferred to the postoperative ICU. Physical examination revealed no cyanosis and no dyspnea during a T-tube trial of spontaneous breathing, and the patient was extubated a few hours after the end of surgery. During the postoperative period, several ABG measurements with a co-oximeter analyzer showed metHb around 20%.

The patient denied absorption of any oxidizing substance that could cause methemoglobinemia. Congenital methemoglobinemia was suspected, and a complementary hemoglobin study did not show hemoglobin M mutant. Analysis of mutations in the gene encoding for nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase enzyme then was made and showed a homozygote mutation with a guanine-to-adenine substitution in the codon 61 of exon 3, causing an arginine-to-histidine replacement (DNA sequencing performed in the laboratory of biochemistry and genetics, Henri-Mondor Hospital, AP-HP, Créteil, France). Type-1 congenital methemoglobinemia then was confirmed. The patient recovered rapidly and was discharged from...
the ICU on day 2 and from the hospital on day 13 without any complication.

**DISCUSSION**

Methemoglobinemia is caused by an accumulation of metHb in blood, resulting from oxidation of heme iron from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}). This oxidation induces a spatial conformation change in heme, preventing the oxidized heme site to bind oxygen, and, therefore, is responsible for an increasing affinity of oxygen to other heme sites. Therefore, high levels of metHb may result in low oxygen release to tissues. Normal metHb is maintained under 2% of the total hemoglobin by reducing enzymatic systems, mainly cytochrome b_{5} reductase (ie, metHb reductase), which is an NADH-dependent enzyme that converts metHb to hemoglobin, and, to a lesser extent, NADPH-metHb reductase system.

Methemoglobinemias are acquired or congenital. Congenital methemoglobinemia results from hemoglobin variants or enzymatic deficiencies. In hemoglobin variants (eg, hemoglobin M, autosomal dominant), an amino acid substitution induces resistance to reduction. Recessive congenital enzymatic deficiencies are secondary to genetic mutation of the NADH cytochrome b_{5} reductase gene. Type-I deficiency only concerns the soluble form of the enzyme (contained in red blood cells) and clinical manifestations generally are poor, principally with cyanosis. Often, levels of metHb are between 10% and 40%, rarely reaching 50%. Patients with type-I deficiency have a normal life with no limitation in activity. Type-II deficiency concerns the microsomal and ubiquitous form of the enzyme (which participates in lipid metabolism), which is the major form expressed in other tissues of the organism. Type-II deficiency is associated with cyanosis, serious impaired neurologic development in babyhood, and poor outcome. Diagnosis of congenital methemoglobinemia relies on measurement of the activity of NADH cytochrome b_{5} reductase or investigations for known mutations by molecular biology (about 30 different mutations are known) or both.

Acquired methemoglobinemia is related to the absorption of an oxidant drug. Oxidant drugs include some drugs that may be used in the perioperative period of cardiac surgery as nitrate derivatives or nitric oxide. A few local anesthetics are known to be oxidant agents, so they can induce methemoglobinemia. Methemoglobinemia often is asymptomatic if metHb is less than 15%. Severity of symptoms is proportional to the level of metHb. Cyanosis and dyspnea occur when metHb is around 20%. Neurologic trouble (coma or seizures) and cardiac arrhythmias can occur when metHb is greater than 50%. metHb above 70% increases the risk of death. Patients with anemia or cardiac and pulmonary comorbidities may present clinical symptoms with a lower rate of metHb than healthy people. Treatment of methemoglobinemia is based on clearing of the oxidizing agent, delivery of 100% oxygen, and administration of IV methylene blue (1-2 mg/kg) in case of symptomatic methemoglobinemia or metHb >30%. Methylene blue is reduced to leukomethylene blue by NADPH-metHb reductase, and leukomethylene blue reduces the MetHb in hemoglobin by a chemically nonenzymatic pathway. Use of methylene blue may induce anaphylaxis and disrupts the analysis of SpO_{2} by a traditional pulse oximetry device. At a dose greater than 4 to 5 mg/kg, methylene blue may increase the level of methemoglobinemia due to direct oxidation. Patients with glucose-6-phosphate dehydrogenase deficiency are more likely to develop hemolysis and metHb production with methylene blue. Severe methemoglobinemia with clinically marked symptoms may benefit from transfusion therapy.

Patients with type-I recessive congenital methemoglobinemia generally present with a well-tolerated metHb between 10% and 40%. These patients are very sensitive to oxidant drugs. Preventive treatment is based on elimination of these drugs, which may worsen methemoglobinemia. Curative treatment of the illness includes the use of methylene blue. Antioxidant drugs, such as ascorbic acid or riboflavin (vitamin B2), also have been proposed for the long-term treatment of cyanosis.

Several cases of management of methemoglobinemia during general anesthesia have been described in medical literature, especially with respect to cardiac surgery. However, a lot of them concern toxic-induced methemoglobinemia or supposed and not proven of congenital etiology. This case report emphasizes 2 points.

First, the diagnosis of symptomatic congenital methemoglobinemia was made in a 78-year-old patient with a history of multiple surgical procedures. It underlines the necessity to maintain awareness of methemoglobinemia among anesthesiologists when a discrepancy is found between a low SpO_{2} and normal PaO_{2} or when a true low SpO_{2} is found in asymptomatic patients. Congenital methemoglobinemia is rare and its incidence is unknown. In this case, the diagnosis was made intraoperatively, during CPB, when the arterial line remained brown and dark despite normal gas flow with high oxygen concentration in the oxygenator gas supply line. It should be emphasized that diagnosis of methemoglobinemia requires measurements of metHb using a co-oximeter analyzer or the use of a multiwavelength pulse oximeter. Only a co-oximeter provides measurements of oxygenated hemoglobin, deoxygenated hemoglobin (reduced Hb), carboxyhemoglobin, and metHb as a percentage of the total hemoglobin concentration in the arterial blood sample. SaO_{2} obtained from an ABG analyzer alone is calculated often according to blood pH, PaO_{2}, and temperature, and so it cannot be used to calculate arterial oxygen content in case of methemoglobinemia. Etiologic diagnosis of methemoglobinemia includes investigation for chronic or acute absorption of oxidant toxins or medicines. If it is negative, study for congenital etiologies is indicated.

Second, this case may show that lidocaine increases methemoglobinemia in patients with congenital metHb enzymatic deficiencies. Mepivacaine, bupivacaine, and ropivacaine are not known as hemoglobin oxidant agents, unlike Prilocaine, benzocaine, and benzamidone. They are involved in acquired methemoglobinemia. It seems that lidocaine may increase methemoglobinemia in patients with congenital metHb enzymatic deficiencies, as seen in this patient. In others, cyanosis and hypoxemia after lidocaine administration in patients with congenital methemoglobinemia previously were related more to its respiratory depressant effect than to metHb. In patients with acquired methemoglobinemia induced by local anesthetic agents, MetHb greater than 50% have been reported. Neuhauer et al reported MetHb up to 18% following lidocaine
administration in a case of pediatric craniofacial surgery. In this case, 1 element may support a rise in MetHb level rather than local anesthetic-induced systemic toxicity as initially considered: seizures were not preceded by central nervous system symptoms; delayed time between surgical infiltration of lidocaine and occurrence of seizures (20 min) could fit with tissue absorption but not with accidental arterial or intravenous injection. Unfortunately, blood measurements of local anesthetic and ABG with a co-oximetry analyzer were not taken to confirm the diagnosis.

In summary, the authors report a case of congenital methemoglobinemia in a patient with a history of multiple surgical procedures. This observation underlines the necessity to maintain awareness of methemoglobinemia among anesthetists when a discrepancy is found between a low SpO2 and normal PaO2.

REFERENCES