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# Methylene Blue-induced Methemoglobinemia during Cardiopulmonary Bypass? A Case Report and Literature Review

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**Abstract:** The guanylate cyclase (GC) and inducible nitric oxide (iNOS) inhibitor methylene blue (MB) has been used in cardiac surgery patients for the treatment of a variety of conditions. Methylene blue has been successfully used for the prevention and treatment of vasoplegia syndrome (VS) in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Vasoplegia syndrome occurs in up to 10% of cardiac surgery patients and is associated with poor clinical outcomes. Vasoplegia syndrome is described along with the results of studies that have shown benefits of MB in the treatment of VS. These studies include the use of MB prior to CPB, when added to the CPB prime and when given into the CPB circuit during the operation. We report a case of emergency CPB on a 55-year-old male with bacterial endocarditis, scheduled for an AVR/MVR who arrested on arrival to the operating room. Once on CPB the patient developed a profound hypotension despite normal to high pump flows, with low systemic vascular resistance (SVR), which was refractory to vasopressors—consistent with a diagnosis of VS. Unbeknownst to the perfusionist, the patient was treated with MB which was immediately followed by an apparent sudden arterial desaturation, despite oxygenator ventilation with 100% oxygen (O2), and development of severe metabolic acidosis. Troubleshooting the cause of the apparent desaturation and eventual diagnosis of a false indication of arterial oxygen desaturation and methemoglobinemia (MHgb) due to MB injection is described. Methemoglobinemia is explained as well as its presentation and treatment with MB. The importance of intraoperating room communication and knowledge of drug effects are discussed. **Keywords:** methylene blue, methemoglobinemia, vasoplegia syndrome, cardiopulmonary bypass. *JECT. 2008;40: 206–214*

Methylene blue (MB), a water-soluble thiazine dye, has been successfully used for the prevention and treatment of post-cardiac surgery vasopressor refractory hypotension. Methylene blue inhibits inducible NO synthase (iNOS), which is activated in the presence of endotoxin and cytokines, and competes with NO for binding sites of the intracellular enzyme guanylate cyclase (GC). Inhibition of GC prevents an increase in cyclic guanosine 3′,5′ monophosphate (cGMP). Increased levels of cGMP results in relaxation of vascular smooth muscle, hyporeactivity to catecholamines, myocardial depression, and increased vascular permeability (1–3). Cytokines and oxygen radicals are also implicated in the activation of GC, thus resulting in an NO-independent cause of increased cGMP and vascular hyporeactivity (4). Because MB prevents GC activation, it may prevent NO and NO-independent means of increased cGMP. NO also has beneficial effects that are GC independent. This means that GC inhibition by MB may be a more beneficial strategy for the treatment of refractory hypotension than global NO inhibition (3).

Profound hypotension that occurs during or after cardiopulmonary bypass (CPB), which is not a result of hemodilution, has been associated with a systemic inflammatory response to CPB. This profound hypotension, which is often refractory to increasing doses of vasopressors, is frequently referred to as vasoplegia syndrome (VS), norepinephrine refractory hypotension, or vasodilatory shock. Vasoplegia syndrome is often described as a hyperdynamic clinical state characterized by severe hypotension, decreased systemic vascular resistance (SVR), and increased fluid and vasopressor requirements despite a normal to high cardiac output.

The incidence of VS in all patients requiring cardiac surgery with CPB has been reported as high as 10% (5). Argenziano et al. (6) reported an incidence of VS as high as 42% in patients undergoing left ventricular assist device insertion for end-stage heart failure. Vasoplegia syndrome is associated with worse clinical outcomes and mortality rates as high as 28.6% when it persists for >48 hours (7–10). This highlights the importance of an early effective treatment before the development of end-organ failure.

Pre-operative risk factors for post-operative develop-

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ment of VS include low ejection fraction (6), intravenous (IV) heparin, angiotensin-converting enzyme (ACE) inhibitors (10), calcium channel blockers (11), and active endocarditis (12). Vasoplegia syndrome has been associated with higher post-operative morbidity and mortality (8–10) and increased intensive care unit (ICU) and hospital length-of-stay (LOS) (10,13).

A number of case reports have described the effective usage of MB as a treatment for post-CPB VS (14–16). Grayling and Deakin (17) reported the successful use of MB in the CPB prime for a patient with septic endocarditis who presented for cardiac surgery with refractory hypotension. In this case, 2 mg/kg MB was added to the CPB prime in addition to a central venous continuous MB infusion of 1 mg/(kg × h). This resulted in a decreased need for vasopressor support while maintaining a mean arterial blood pressure of 50 mmHg.

In a randomized controlled trial (RCT) of patients on pre-operative ACE inhibitors, Maslow et al. (7) reported significantly higher mean arterial pressure (MAP), significantly decreased phenylephrine use, and significantly reduced lactate levels in a treatment group that received 3 mg/kg MB during CPB versus a control group that received saline.

In another RCT, prophylactic, pre-CPB treatment with MB in patients at high risk for the development of VS resulted in significantly higher SVR, significantly reduced norepinephrine requirements, significantly less crystalloid, colloid, and red blood cell requirements, significantly reduced post-operative VS development, and significantly shorter ICU and hospital LOS (13).

Other reported cardiac surgery–related MB uses include the treatment of protamine reactions (18,19), anaphylaxis (20,21), septic shock (2,22), and hemorrhagic shock (23). MB has also been studied as an inhibitor of $O_2$ radicals and an $O_2$ radical scavenger in ischemia-reperfusion injury. MB inhibits the generation of $O_2$ radicals and superoxides by competing for electrons and shunting electrons away from the area where $O_2$ molecules are usually converted to superoxide radicals (24).

Some adverse effects associated with MB infusion include anaphylaxis (25), hemolysis (26,27), encephalopathy (28), and methemoglobinemia (MHgb) (29,30).

Another treatment option for VS that has been studied is the use of arginine vasopressin. Vasodilatory shock after CPB has been associated with low serum vasopressin concentrations (31). Exogenous vasopressin has been successfully used as an adjunct to treat patients on high doses of catecholamines with VS (31,32). Arginine vasopressin may have adverse side effects, and further studies are needed before its routine use for the treatment or prevention of VS should be widely used.

A case of apparent MB-induced MHgb during CPB is presented.

## CASE REPORT

A 55-year-old, 84-kg man with a history of hypertensive cardiomyopathy and multiple thoraco-lumbar spinal compression fractures was admitted to the emergency room with a complaint of shortness of breath, sweating, and chest pain. Laboratory analysis determined he had a non-ST elevation myocardial infarction and acute renal failure likely secondary to hypoperfusion. During his workup, he was sent for an magnetic resonance image (MRI), where he acutely decompensated and required an increase in his oxygen and non-invasive ventilatory support with bi-level positive airway pressure.

He was admitted to the hospital's cardiology ICU where a decision was made that he likely had subacute bacterial endocarditis as a result of a previous bronchial infection (this was later confirmed). A transthoracic echocardiogram was obtained that showed extensive aortic and mitral vegetations with severe aortic and mitral regurgitation. He was taken to the cardiac catheterization laboratory, where no significant coronary disease was detected. The patient was scheduled for replacement of his mitral and aortic valves the following morning.

During transport to the operating room, the patient developed supraventricular tachycardia, followed by ventricular tachycardia and asystole. Closed chest cardiopulmonary resuscitation (CPR) was begun immediately, and multiple 1-mg doses of epinephrine were administered. The patient's rhythm failed to stabilize, and he remained dependent on CPR for pulsatile flow. The decision was made to open the chest and perform open-chest massage. The chest was prepared with a single prep stick, median sternotomy was performed, a sternal retractor was inserted, and the pericardium was opened. The heart was noted to be motionless. There was a 1-minute lapse in the CPR during conversion from closed-chest to open-chest cardiac massage. The patient was heparinized and emergently cannulated for CPB support.

Once on CPB, the patient became hemodynamically stable. CPB was conducted with a hollow fiber oxygenator (Apex; Sorin Group, Arvada, CO), open venous reservoir (VVR4000i; Sorin Group), an arterial roller pump (Maquet, Hirrlingen, Germany), in-line arterial blood gas monitoring (CDI 500; Terumo Cardiovascular Systems, Ann Arbor, MI), and in-line venous saturation/hematocrit monitoring (CDI 100; Terumo Cardiovascular Systems). A significant metabolic acidosis was treated with multiple 50-mEq boluses of sodium bicarbonate, and 2 units of packed red blood cells were transfused. At this time, a discussion was had between the attending surgeon and the patient's family concerning the potential for end-organ damage, including anoxic brain injury. One option considered was extracorporeal membrane oxygenation (ECMO) support to allow for stabilization and evaluation of any end-organ damage before proceeding with the operation.

It was felt that ECMO support would be complicated because of severe aortic insufficiency. The family decided to proceed with aortic and mitral valve surgery despite the high risk for operative mortality and the possibility of end-organ damage.

After ~30 minutes on CPB, before aortic cross-clamping, the patient developed a profound hypotension with a MAP of 33 mmHg, pump flow of 5.7 LPM (cardiac index = 2.8 LPM/$m^2$), and an SVR of 463 dynes/s/$cm^5$, despite frequent boluses of phenylephrine (0.2–0.8 mg). Around this time, it was noticed that the arterial blood exiting the oxygenator had suddenly turned very dark. The oxygenator was immediately ventilated with 100% oxygen ($O_2$) with no resolution of the problem. The in-line venous saturation ($SVO_2$) had rapidly decreased from 71% to <50%.

Immediate troubleshooting of the oxygenator and oxygenator gas delivery system was begun. Integrity of the gas delivery system was confirmed, and the in-line anesthetic vaporizer was bypassed. The scavenger line that was connected to the oxygenator's gas exhaust port was removed as a possible source of oxygenator gas flow obstruction.

One theory at the time of the incident was that the oxygenator may have suddenly failed, potentially as a result of clots, because the systemic heparinization dose had been given during CPR and may not have been adequately distributed. The only evidence supporting the possibility of clots in the oxygenator was a radial arterial line clotted once on CPB. All activated clotting times were >500 seconds, and the arterial line pressure was normal. No clots were visualized in the CPB circuit.

An attempt was made to wean the patient from CPB while further troubleshooting was conducted. This attempt was not well tolerated because the patient did not have adequate myocardial function to sustain an adequate blood pressure and cardiac output. During this wean from CPB, the oxygenator was ventilated with 100% $O_2$ from an emergency $O_2$ cylinder (thus bypassing the gas delivery system). Once the oxygenator was ventilated from this $O_2$ cylinder, the arterial blood returned to a more normal red arterial color. CPB was re-initiated on the emergency $O_2$ cylinder, and an arterial blood gas (ABG) sample was performed (Gem Premier 3000; Instrumentation Laboratory, Lexington, MA), which showed metabolic acidosis (pH 7.24, base excess [BE] –8.4, lactate 12.9), a $PO_2$ of 373 mmHg, and an arterial oxygen saturation ($SaO_2$) of 100%.

Because the desaturation was corrected when the oxygenator was ventilated with a 100% $O_2$ cylinder, a problem with the gas delivery system (blender, hospital gas supply) was suspected. A new blender was brought to the operating room, and gas delivery to the oxygenator was switched from the $O_2$ cylinder to the new blender. This occurred without incident, and there were no more problems with oxygenation for the remainder of the CPB period. The severe acidosis was treated with 150 mEq sodium bicarbonate. Two units of packed red blood cells were transfused, and hyperoxia was used for 15 minutes to further enhance oxygen delivery. The patient was cooled to 28°C, and the operation proceeded as intended.

The patient aortic and mitral valves were removed, annuli were debrided, and mechanical valves were inserted. The patient was weaned from CPB on an intra-aortic balloon pump and epinephrine, norepinephrine, and vasopressin infusions. His chest had to be left open for adequate cardiac output and blood pressure to be maintained.

The patient was transferred to the cardiac surgery ICU, where he remained on maximal support for 3 days. Neurologically, he never awoke. A computed tomography scan showed a large subdural hematoma and subarachnoid hemorrhage. Neurology was consulted and felt that he showed no brain stem activity and that recovery was unlikely. Given the unlikelihood of any meaningful recovery and the family's wishes to not engage in any more heroic efforts, support was withdrawn, and the patient quickly died.

## DISCUSSION

Post-operative analysis of the apparent desaturation that occurred during CPB was conducted. Analysis of data from the CDI 500 continuous in-line arterial blood gas monitor during the apparent desaturation showed a $PO_2$ of 243 mmHg, with a calculated $SaO_2$ of 100%. The $PO_2$ increased to >400 mmHg on 100% $O_2$. See Table 1 for the inline arterial and venous blood gas and hematocrit/saturation readings immediately before and after MB infusion. At the time of the incident, in the presence of dark arterial blood, this was thought to be erroneous. Retrospectively, it was felt that the apparent desaturation, despite a normal $PO_2$, may have been an indication of MHgb. Further evidence of this possibility was that the hospital biomedical engineering department found that the suspected faulty $O_2$ blender, which was removed from the heart-lung machine, worked as intended.

Further analysis showed that, at nearly the exact moment of the desaturation, a 240-mg bolus (24 mL) of MB was given by the anesthesiologist to treat the patient's profound hypotension. This MB bolus was not communicated with the perfusionist at the time. A discussion was had concerning whether the desaturation was in fact real or just an effect of the MB on the monitors. Interference with pulse oximetry and co-oximetry measurements caused by MB can result in a false presentation of arterial desaturation and MHgb (33,34). In this case, the appearance of dark arterial blood despite a high $PO_2$ on 100% $O_2$ and the apparent profound acidosis that developed made it seem that the patient had in fact desaturated. MB has

**Table 1.** In-line arterial blood gas and venous saturation/hematocrit results.

| | | Arterial | | | | | | Venous | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event | Time | pH | $CO_2$ | $PO_2$ | $HCO_3$ | BE | $SO_2$ | $SO_2$ | HCT | HGB |
| | 8:40 | 7.40 | 36 | 236 | 22 | −2 | 100% | 71% | 23% | 7.8 |
| MB given | 8:41 | 7.37 | 35 | 243 | 21 | −3 | 100% | 50% | 23% | 7.8 |
| | 8:42 | 7.21 | 34 | 370 | 14 | −12 | 100% | —% | 24% | 8.1 |
| Off CPB | 8:43 | | | | | | | | | |
| On CPB CYL | 8:47 | 6.83 | 43 | 234 | 7 | −25 | 99% | —% | 23% | 7.7 |
| | 8:48 | 6.84 | 45 | 315 | 8 | −24 | 99% | 54% | 22% | 7.6 |
| | 8:55 | 7.10 | 41 | 317 | 13 | −15 | 100% | 55% | 24% | 7.9 |
| ABG | 8:55 | 7.23 | 41 | 350 | 17 | −9.6 | 100% | | | |
| BC/PRBC | 9:05 | 7.41 | 38 | 448 | 24 | 0 | 100% | 60% | 24% | 7.8 |

ABG, arterial blood gas; BC/PRBC, 50 mEq sodium bicarbonate/1 unit packed red blood cells; MB, methylene blue; On CPB CYL, on bypass on the emergency $O_2$ cylinder (apparent desaturation resolved); —, ≤50%.

not been reported to interfere with pH measurement. Because of the timing of events, clinical presentation, and lack of a full understanding of MB monitoring effects, MB-induced MHgb was suspected.

The best way to confirm MHgb is by laboratory analysis using co-oximetry (35). Co-oximetry measures the actual amount of the various hemoglobin derivatives, including methemoglobin. During the observed desaturation, an ABG was not drawn. At the time of the incident, the apparent desaturation was obvious, MHgb was not suspected, and waiting for ABG results to confirm the desaturation did not seem necessary (venous and arterial ABGs would have been needed because the CDI $SVO_2$ was below the low limit of the analyzer). Therefore, co-oximetry data during the apparent desaturation were not available to confirm or deny the presence of MHgb. In retrospect, had we trusted that our CDI $PO_2$ reading was accurate, we would have drawn arterial and venous ABGs, calculated the $O_2$ transfer of the oxygenator, and confirmed that the transfer was appropriate. It is possible that the venous blood became so desaturated that, even with appropriate $O_2$ transfer from the oxygenator, the arterial blood appeared cyanotic with no obvious visible increase in oxygenation from venous to arterial blood. This gave the appearance of no $O_2$ transfer and shows the importance of calculating $O_2$ transfer, especially in the presence of very low $O_2$ saturations.

The presence of dark arterial blood despite an elevated $PO_2$, development of severe metabolic acidosis, and the fact that the MB was given at nearly the exact moment of the apparent desaturation, made MB-induced MHgb the suspected cause of the apparent desaturation. Other causes of the desaturation (carboxyhemoglobin, sulfhemoglobin) could be ruled out because of the presentation. The fact that MB is a dye with a low pH (3–4.5) (30) was considered as a potential cause for the change in color of the blood and the acidosis that developed, respectively. Initially, the authors felt that, with the patient's total circulating blood volume of >6000 mL, 24 mL of MB would not have such a dramatic dye effect on the color of the patient's blood. For the same reason, it seemed unlikely that 24 mL of MB would have such a profound effect on the patient's pH and lactate levels.

Methemoglobin forms when the iron atom in hemoglobin (Hgb) loses an electron to an oxidant. Ferrous iron ($Fe^{2+}$) is oxidized into ferric iron ($Fe^{3+}$), which is unable to bind and transport $O_2$. Along with a decreased $O_2$ carrying capacity, methemoglobin results in a leftward shift of the oxygen hemoglobin dissociation curve (OHDC). This increases the affinity of unaltered oxyhemoglobin for $O_2$, resulting in a further reduction in $O_2$ delivery to the tissues (36). The combination of MHgb, leftward shift of the OHDC, and anemia (Hgb 7.8 g/dL) would result in a dramatic decrease in $O_2$ delivery to our patient.

During $O_2$ transport, the ferrous iron molecule shares an electron with $O_2$. Normally when the $O_2$ molecule is released, the shared electron stays with the iron molecule, and it remains in the ferrous state. Occasionally, the shared electron is released with the departing $O_2$ molecule and the iron atom is left in the oxidized, ferric state. This accounts for the normal methemoglobin level of 1% in most individuals.

Methemoglobinemia occurs when >1% of hemoglobin is methemoglobin. Methemoglobinemia often presents as dark, "chocolate brown" blood, despite a normal $PO_2$. Pulse oximetry is unreliable in the presence of MHgb and may have a tendency to read ~85% despite an actual arterial saturation, as measured by co-oximetry, which is much lower (35). In our case, the blood was not an obvious "chocolate brown" in color, which may help with diagnosing a real MHgb.

The cause of MHgb can be hereditary but most commonly is the result of exposure to oxidizing drugs and/or chemicals (Table 2). Methemoglobin levels >15% produce an asymptomatic cyanosis that is unresponsive to supplemental $O_2$. Levels >20% result in the following symptoms: dyspnea, fatigue, nausea, dizziness, headache, and syncope. Death can occur with methemoglobin levels >70% (35). Because of decreased $O_2$ delivery, patients with conditions such as anemia, congestive heart failure, and coro-

**Table 2.** Medications associated with methemoglobinemia.

| | |
|---|---|
| Amyl nitrate | Nitric oxide |
| Benzocaine | Nitroglycerin |
| Cetacaine | Nitroprusside |
| Chloroquine | Phenazopyridine |
| Dapsone | Silver nitrate |
| Lidocaine | Sulfanilamide |
| Methylene blue | Sulfa-containing antibiotics |
| Metoclopramide | |

nary artery disease may be particularly susceptible to bad outcomes from MHgb.

Multiple mechanisms exist to maintain normal methemoglobin levels ≤1%. These mechanisms work by donating an electron to the oxidized iron atom. The most important system under normal circumstances involves nicotinamide adenine dinucleotide (NADH) and the enzyme NADH methemoglobin reductase. Infants are particularly susceptible to oxidizing agents because this enzyme system is not fully functional until ~4 months of age (35). There is also widespread variation in patient responses to oxidant stresses (37).

Another enzyme system responsible for reducing oxidized iron involves nicotinamide adenine dinucleotide phosphate (NADPH). This NADPH system is only responsible for a small percentage of methemoglobin reduction under normal circumstances. However, when combined with MB, the NADPH system becomes the primary means of methemoglobin reduction. MB, an oxidant, in the presence of NADPH and NADPH methemoglobin reductase, is reduced to leukomethylene blue, which reduces methemoglobin to Hgb.

Treatment for MHgb includes removal of the causative agent and, when the MHgb is symptomatic (usually methemoglobin levels >15%), administration of MB 1–2 mg/kg over 5 minutes. If cyanosis remains in 1 hour, a second dose of MB may be given. If MB is ineffective, exchange transfusion or hyperbaric oxygen may be beneficial (36).

Paradoxically, MB has also been reported to cause MHgb in certain cases (29,33). This suggests an equilibrium between the ability of MB to oxidize Hgb to methemoglobin and MB's ability, through enzymatic reduction pathways, to reduce methemoglobin to Hgb. This equilibrium seems to favor the reduction of methemoglobin to Hgb unless large doses of MB are administered (29,34) or if MB is administered too quickly (29). If MB is administered too quickly, a local high concentration of the drug may result in methemoglobin formation.

In an attempt to determine the likelihood of MB-induced MHgb in this particular case, the MB dose that was delivered during CPB was evaluated. This patient weighed 84 kg and received 240 mg of MB (~2.8 mg/kg). Most reports of MB use for profound hypotension use a dose of 1–2 mg/kg; however, cumulative doses of <7 mg/kg are generally considered safe. Further evidence that the apparent methemoglobin formation was not MB dose related is that the patient received a subsequent 240 mg MB dose in the cardiac ICU post-operatively without incident. This dose had a positive effect on MAP and SVR and allowed inotropic support to be dramatically reduced.

The main difference between these doses is that the operating room (OR) dose, which seemed to cause MHgb, was given as a bolus, and the ICU dose was given over 30 minutes. Because the ICU dose was well tolerated, it would be unlikely that the possible MHgb in the OR was caused by an abnormal NADPH methemoglobin reductase system. This suggested that the rate of MB infusion could have been a factor, potentially causing a sudden high concentration of methemoglobin formation that temporarily overwhelmed the patient's normal reducing mechanisms. With no further infusion of the oxidizing agent (MB in this case), it seemed as though it took ~5 minutes for the patient's methemoglobin reducing mechanisms to adequately reduce the methemoglobin back to Hgb, and the arterial blood regained its normal red color.

Hypothermia was considered a potential factor in the patient's possible MHgb development. It was felt that the enzymatic pathways that reduce methemoglobin to Hgb may be slowed by hypothermia, resulting in slower than normal methemoglobin reduction and higher than normal methemoglobin levels. Review of the patient's chart showed the patient was at 36°C at the time of the incident. This ruled out hypothermia as a contributing factor in this case; however, this probably warrants further research.

Another area for future research is if hemodilution and anemia make a patient at increased risk of developing MHgb when given MB. The patient in this case had a Hgb of 7.8 g/dL at the time of the incident. In a case report of MHgb in a lung transplant patient, LeClaire et al. (37) suggested a potentially greater susceptibility for MHgb development in patients with conditions that alter $O_2$ delivery, such as anemia and lung disease.

With recent studies reporting beneficial uses of MB in cardiac surgery patients, including use in the immediate pre-CPB and CPB period, it is increasingly likely that Perfusionists will care for a patient that has been given MB. It is important for Perfusionists to be knowledgeable of medications that will be given before and during CPB, because these medications may have an effect on their conduct of perfusion. This knowledge should include indications, contraindications, drug interactions, dosing, elimination, monitoring effects, patient effects, CPB circuit interactions (i.e., will the drug clog the pores of a hollow fiber oxygenator, is the drug removed or concentrated by ultrafiltration, does the drug interact with tubing coatings?), and adverse drug effects. Studies should be done to determine if the CPB patient is particularly at increased risk of developing MB-induced MHgb because of factors such as hypothermia and hemodilution.

Treatment of drug-induced methemoglobinemia is the only FDA-approved indication for MB use. Contraindications include patients with hypersensitivity to MB, MHgb in cyanide poisoning, and patients with severe renal impairment. MB can exacerbate dapsone-induced hemolytic anemia, but no other drug interactions have been reported (11). Serious adverse effects include cardiac dysrhythmia, hemolytic anemia (in G6PD-deficient patients), malignant hyperthermia, methemoglobinemia, and anaphylaxis. MB should be given with caution in patients with renal impairment and G6PD deficiency. MB is excreted in urine and bile. The dose for MHgb is 1–2 mg/kg IV, usually given as 0.1–0.2 mL/kg of a 1% (10 mg/mL) solution, very slowly over several minutes. MB can also be diluted in NaCl 0.9% (30). A similar dosage is often used for the treatment of VS and the use of a continuous infusion of 0.25–0.5 mg/kg/h (7).

MB effects various monitors commonly used during cardiac surgery. Near infra-red and optic based tests may be erroneous in the presence of MB. MB absorbs light at the same frequency (550–700 nm) as various Hgb derivatives, including methemoglobin. This can result in false elevations of methemoglobin and total Hgb values as measured by co-oximetry (38). MB also interferes with pulse oximeter readings and may falsely decrease $O_2$ saturation readings (34,36,39). The combination of interference with co-oximetry and pulse oximetry values by MB can lead to a false indication of methemoglobinemia. In two reported cases of a false indication of methemoglobinemia, the clinical scenario differed from ours in that the patients did not develop acidosis and the patients' arterial blood was not visibly dark (33).

There is one case report of MB infusion resulting in a dramatic reduction in the bispectral index (40). The authors speculate that this effect may be an artificial reduction, despite the lack of similar reports, but they do not rule out that MB may have a direct neuronal effect or may displace a centrally active drug.

The authors believe that the effect of MB on specific in-line venous and arterial blood gas monitors and cerebral saturation monitors commonly used during CPB has not been sufficiently studied. In a recent publication, Mittnacht et al. (41) reported markedly decreased cerebral oximetry values (INVOS) in all patients given a MB load for vasoplegia. They specifically describe this occurrence in two patients. Both patients were discharged with no obvious sequelae. The authors of the report caution clinicians to be aware of a possible MB, cerebral oximetry affect. The effect of MB on these monitors would be an important area of future research because these monitors are commonly used to guide perfusion practice. MB likely decreases venous saturation measurements that use similar technology as pulse oximeters. To confirm adequate perfusion in the presence of MB, venous blood co-oximetry would be the best way to verify $SVO_2$. See Table 3 for a list of reported and suspected effects of MB on various cardiac surgery–related monitors compared with the presentation of an actual MHgb.

The effects of ultrafiltration also need to be studied. MB has a molecular weight of 373.9 d (30). Molecular weight alone is not enough to determine ultrafiltration rate of a drug, because membrane characteristics also play an important role. The low molecular weight of the drug and the fact that the ultrafiltrate effluent often appears blue or green is evidence that at least some of the drug is removed by ultrafiltration techniques.

The case of MB-induced MHgb during CPB is particularly challenging. Oxygenation of a patient's blood during CPB is complex and is achieved with the use of oxygenators, gas blenders, hospital gas sources, anesthetic vaporizers, scavenger lines, oximeters, and in-line blood gas monitors. All of these components have the potential to fail, and failure of certain components can result in a sudden loss of oxygenation. It is important to quickly distinguish between equipment failure/malfunction and a patient condition that causes the sudden desaturation. In our case, the apparent desaturation coincidentally resolved once the oxygenator was ventilated directly from an $O_2$ tank. This made it appear as though the problem was a gas delivery system malfunction. Had the apparent desaturation not suddenly resolved at this point, our next step would have been to erroneously change out the oxygenator. Had the patient been able to tolerate our attempt to wean from CPB during the apparent desaturation, the inability of the patient to oxygenate while on the ventilator would have been further evidence that something other than CPB equipment malfunction was causing the desaturation. In the case of known MHgb during CPB, weaning from CPB would be the wrong action, because this would require an already compromised heart (coronary artery disease [CAD], valve insufficiency, etc.) to provide a cardiac output with a severely reduced oxygen supply. Remaining on CPB, emergently cooling and aortic cross-clamping and arresting the heart may be appropriate to reduce the metabolic oxygen demand while the MHgb is treated. The fact that the CPB initiation was emergent, with questionable

**Table 3.** Methylene blue effect on cardiac surgery–related monitors compared with methemoglobinemia presentation.

| Monitor | MB Effect | MHgb | References |
|---|---|---|---|
| Pulse oximetry | ↓ | ↓ | 7,11,34,36,39 |
| Inline venous saturation | ↓* | ↓ | 7 |
| Inline CDI 500 pH | ↓* | ↓ | Suspected |
| Bispectral index | ↓* | ? | 40 |
| INVOS cerebral oximetry | ↓* | ↓ | 41 |
| Co-oximetry methemoglobin level | ↑† | ↑ | 38 |

*Not proven.
†Depends on co-oximeter.
MHgb, methemoglobinemia; MB, methylene blue; ?, unknown.

distribution of heparin, likely increased our perception that something must be wrong with the CPB equipment.

Communication of the fact that MB had been given, along with improved knowledge of the various effects of MB, likely would have helped make a more timely and accurate differentiation between a real MHgb or a false presentation of MHgb caused by the effects of MB on the patient's blood and the CPB monitors. This case is a perfect example of the importance of good communication between the various players in cardiac surgery. In the case of a sudden, unexplained desaturation during CPB, it is probably wise to determine whether any drugs had just been given, because many drugs commonly given by anesthesiologists have oxidizing effects and may cause MHgb (Table 2). In the case of MB-induced MHgb, it is important to not just assume an apparent desaturation is an effect of MB on the monitoring devices, because the MB effect on various monitors and a real MHgb present very similarly.

In a more recent case of MB administration on pump, the author noted a similar presentation as the one previously described. This time the MB dose was well communicated, and arterial and venous blood gases with co-oximetry were drawn during the apparent desaturation. Methemoglobin levels and arterial and venous saturations were normal. An acidosis did develop, likely because of the low pH of MB, which was treated with sodium bicarbonate. After the blood discoloration resolved, the CDI 500 continued to show low pH values for ~10 minutes. During this time, two ABGs were drawn to confirm the CDI 500 values. The ABG results showed that the acidosis was in fact resolved (ABG pH = 7.41 versus CDI pH 7.30), the CDI was recalibrated, and no further intervention was needed. It seems that the very low pH of MB has a prolonged effect on the CDI 500 pH sensor. This is also seen between the CDI measured pH and the pH measured by arterial blood gas (Table 1, 8:55) in the first case. As a result, in the presence of MB, blood gasses should likely be used for accurate patient pH measurement. This effect warrants further study.

In the first case, it is the profound acidosis that developed that made it seem as though a real desaturation had occurred. A later literature review on MB showed that it has a very low pH, which could have been a cause for the acidosis. No other reports on MB mention patients developing acidosis after MB infusion. This may be because of the fact that most reports do not involve patients on CPB with continuous blood pH measurement. During MB administration while on CPB, running arterial and venous blood gasses, along with co-oximetry, is likely the best way to accurately measure blood saturations, blood pH, and the presence or absence of methemoglobin.

In light of this more recent case of MB infusion during CPB, and the very similar presentations of the two cases, the authors believe that the suspected MHgb in the first case was in fact a false presentation of arterial desaturation and MHgb.

In another recent case of MB infusion during CPB at the author's institution, the MB was given very slowly. The blood color did not appear to change, and there was no obvious effect on the CDI $SVO_2$. Despite the slow infusion, the CDI pH still gave a significantly lower reading than the pH measured by ABG. This suggests that some of the MB monitor effects may be attenuated by a very slow infusion.

Currently there is very little in the perfusion literature concerning methemoglobinemia and CPB. A previous case of MHgb during CPB was reported in 1985. In this case, the patient was put on CPB with pre-existing hypoxia and cyanosis. Once on CPB, the blood appeared "chocolate brown" with a $PO_2$ of 300 mmHg. MHgb was confirmed by laboratory analysis, and the patient was successfully treated with MB (42). This case is similar to two cases reported in the *Annals of Thoracic Surgery* in 1987 of patients with MHgb that were put on CPB and successfully treated with MB. In both of these cases, the MHgb was the result of IV nitroglycerin infusion (43).

When MHgb is suspected during CPB, arterial blood gases with co-oximetry should be performed. Methemoglobinemia is confirmed by an elevated methemoglobin level and a low measured arterial saturation (despite an adequate $PO_2$), which is lower than a calculated arterial saturation. In the case of actual MHgb during CPB, an attempt should be made to find and remove the causative agent. If the MHgb is severe and not caused by MB, MB should be given (1–2 mg/kg IV) slowly to reverse the MHgb. If MB is the suspected causative agent, no further MB should be given. Hypothermia, hyper-oxygenation, blood transfusion, aortic cross-clamping with hypothermic cardioplegic arrest, and high arterial pump flows may be wise perfusion strategies to decrease oxygen demand and increase oxygen supply until the MHgb is resolved by intrinsic means. The half-life of MHgb is ~1 hour (33). Exchange transfusion is another possible strategy when MB is ineffective.

In the case of "false" MHgb caused by MB infusion, arterial and venous blood gases with co-oximetry should be used to accurately measure arterial and venous oxygen saturations (and confirm that MHgb does not exist) and guide perfusion practice until the MB effect dissipates. Treatment for an acidosis may be necessary because of the low pH of MB. Blood gases should also be used for accurate measurement of blood pH because it seems that MB may interfere with accurate pH measurement of certain in-line blood gas monitors.

MB is potentially an inexpensive treatment option for a variety of cardiac surgery–related conditions. MB alone may not be enough to significantly improve outcomes in

cardiac surgery patients, but its use in combination with other strategies to reduce the systemic inflammatory response to CPB might prove beneficial. Large randomized controlled trials showing improved patient outcomes are needed to verify MB's efficacy before its use becomes more common. As the use of MB in cardiac surgery patients increases, it is important for Perfusionists to be aware of MB uses, adverse events, indications, contraindications, CPB interactions, and monitoring effects.

In light of recent cases of severe anaphylactic reactions being attributed to vials of heparin contaminated with oversulfated chondroitin sulfate, it is noteworthy that this particular case occurred well before any reported cases of contaminated heparin. At the time of this case, reports of deaths in which allergic or hypotensive symptoms potentially related to heparin were extremely rare (44). It is also unlikely that the profound hypotension that occurred in this patient was caused by contaminated heparin because the hypotension did not develop until 30 minutes after the initial heparin bolus, and no hypotension was seen after subsequent heparin boluses during CPB.

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