Inhaled nitric oxide induced methemoglobinemia on extracorporeal circulatory support: Black versus red

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ABSTRACT

Administration of inhaled nitric oxide after left ventricular assist device implantation decreases pulmonary vascular resistance and right ventricular afterload. However, inhaled nitric oxide is not innocent and serious adverse effects may occur. In this article, we report a case of severe methemoglobinemia caused by inhaled nitric oxide administration after left ventricular assist device implantation. We stabilized the patient’s hemodynamic status with veno-arterial-venous extracorporeal membrane oxygenation support and inhaled nitric oxide treatment. Nevertheless, severe methemoglobinemia was detected with discolorization of the tubing lines of the extracorporeal membrane oxygenation circuit in association with hypoxia. The methemoglobin levels up to 19.9% were accompanied by hypoxemia and fatal arrhythmias. Methemoglobinemia was successfully treated by exchange blood transfusion.

Keywords: Extracorporeal membrane oxygenation; heart failure; mechanical support; methemoglobinemia; nitric oxide.

Öz


Anahtar sözü: Ekstrakorporeal membran oksijenasyonu; kalp yetmezliği; mekanik destek; methemoglobinemi; nitrik oksit.

Methemoglobinemia is a condition where ferrous (Fe⁺2) irons of heme are oxidized to the ferric cation state. The oxygen transport requires reversible oxygen bound to ferrous hemoglobin. However, methemoglobin cannot bind oxygen and carbon dioxide. Thus, methemoglobinemia causes markedly reduced oxygen delivery to the tissues and removal of carbon dioxide from the tissues.

Methemoglobin recycles back to hemoglobin (Fe⁺2) by the cytochrome b5 reductase enzyme found in erythrocytes for intracellular steady state.

Medications commonly used at the intensive care units that may cause methemoglobinemia are direct oxidants (nitrites, nitrates, nitric oxide) and indirect oxidants (sulphonamides, sulfones, lidocaine, benzocaine, prilocaine, phenacetin, nitrobenzenes and dapsone). Delayed diagnosis should be avoided for this potentially lethal condition.

In this article, we describe a case of acquired methemoglobinemia caused by inhaled nitric oxide (iNO) in a patient who presented with low arterial partial pressure of oxygen (paO₂) and oxygen saturation...
(SaO₂) even though he was on veno-arterial-venous extracorporeal membrane oxygenation (VAV-ECMO) and ventilatory support.

CASE REPORT

A 55-year-old male patient with ischemic cardiomyopathy and pulmonary hypertension was admitted to our department with decompensated heart failure. After urgent evaluation in cardiac intensive care unit, he was intubated and ventilated with 100% fraction of inspired oxygen. Despite high dose inotropic therapy and vasopressors, sufficient oxygenation and perfusion could not be achieved. Percutaneous femoral-femoral-jugular VAV-ECMO support was initiated. Chest radiography revealed pulmonary edema. Transthoracic echocardiography (TTE) revealed depressed left ventricle and right ventricle with a tricuspid annular plane systolic excursion of 12 mm. Systolic pulmonary artery pressure (sPAP) was 60 mmHg and left ventricular ejection fraction was 10%. A written informed consent was obtained from the patient.

The patient underwent HeartMate III device (St. Jude Medical, Inc., St Paul, Minn, USA) implantation for left ventricular failure and temporary right heart support continued with VAV-ECMO. Following the procedure, low dose milrinone and iNO were administered for high pulmonary vascular resistance and sPAP during surgery. Low flow VAV-ECMO support (1.5 L/min) was also required because of right ventricular failure while weaning from cardiopulmonary bypass. Inhaled nitric oxide was administered using a ventilator with a rate of 20 ppm and the rate was checked from the screen hourly.

Although hemodynamic parameters of the patient were stable, radial arterial blood gas revealed PaO₂ of 55 and SaO₂ of 78 while receiving 100% oxygen by VAV-ECMO and ventilation support. He appeared cyanotic and was in acute distress with dyspnea and tachycardia; heart rate: 125 beats/min, respiratory rate: 33 breaths/min, blood pressure: 74/68 mmHg. His postoperative chest X-ray was normal. His postoperative TTE revealed normally positioned LVAD cannula, and sPAP of 55 mmHg without any valvular pathology. After one hour of follow-up, we realized that arterial and venous circuits of ECMO appeared approximately in the same color “like chocolate” although oxygenator values of ECMO were in normal range proven with blood gas samples taken from ECMO circuits. At that time, methemoglobin was 19.9% and oxyhemoglobin was 66.9% in radial arterial blood gas analysis.

Cessation of iNO treatment was followed by ascorbic acid (100 mg) administration intravenously. However, this treatment did not increase PaO₂ and SaO₂ levels, so we decided to use exchange blood transfusion with the suggestion of hematology due to delayed onset of action of ascorbic acid and presence of new onset ventricular arrhythmias. The patient recovered from this acute event after exchange transfusion in two hours and bridged to cardiac transplantation successfully nine days later.

DISCUSSION

This case highlights the challenges involved when patients develop persistent hypoxia, cyanosis and arrhythmias unresponsive to ventilatory support and VAV-ECMO. To our knowledge, the reported case is the first adult case with acquired methemoglobinemia on VAV-ECMO and ventilatory support for right ventricular failure following continuous-flow LVAD implantation.

Normal methemoglobin fraction in the body is less than 1-2%. Discoloration of the skin and cyanosis can be detected at early stages (3-20%) and blood appears chocolate-brown or dark blue color. At conversion levels above 20% patients experience fatigue, weakness, dyspnea, confusion, nausea, vomiting, tachypnea and arrhythmias. Methemoglobin conversion levels above 60%, central nervous system depression may result in coma and death.

The major advantage of iNO over intravenously infused vasodilators, such as prostacyclin and milrinone, is that it directly reduces the pulmonary vascular resistance without causing adverse systemic effects. The main disadvantages with this drug are that it may be associated with methemoglobinemia and elevated nitrogen dioxide levels. Hence, most of the studies recommend 20 ppm as the initial iNO dose and doses above this level are not recommended.[4] Another difficulty about maintaining the iNO treatment is to set up the dosage from a monitor, since, if there is a calibration error in the machine, it may cause a fatal result by overdosing.

Recognition and early diagnosis of this condition are essential. Cyanosis, low arterial PaO₂, and SaO₂ unresponsive to oxygen therapy are the initial signs. For a definitive diagnosis, methemoglobin fraction should be measured by a co-oximeter which is also commonly found in blood gas machines. As in our patient, if patient has VAV-ECMO support and circuits of arterial and venous lines are in the same color -almost black or dark chocolate- and blood gas samples taken from oxygenator are in normal range,
clinicians should be suspicious of methemoglobinemia (Figure 1).

Treatment options for methemoglobinemia are oxygen, administration of methylene blue and discontinuation of the offending drug or chemical. Methylene blue of 1%, 1-2 mg/kg intravenously for over five minutes can be administered to resolve methemoglobinemia. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Ascorbic acid can be used 100 mg twice daily for an adult patient, but in urgent cases, reversibility is slower than methylene blue. Exchange transfusion is a less commonly preferred treatment option, hence it is mostly used for patients with severe life-threatening complications such as fatal arrhythmias.\(^5\)

In this condition, exchange blood transfusion may be the first line therapy to achieve a rapid response. The complications and sequelae of methemoglobinemia can be averted effectively if the condition is diagnosed in a timely manner.

In conclusion, methemoglobinemia should be considered in patients with refractory hypoxemia and discolorization of the tubing lines on extracorporeal membrane oxygenation support. Careful monitoring of nitric oxide and methemoglobin levels is mandatory in patients receiving inhaled nitric oxide, even in those with veno-arterial-venous extracorporeal membrane oxygenation support.

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### REFERENCES


Figure 1. (a) Representative photos of color of venous and arterial lines of veno-arterial-venous extracorporeal membrane oxygenation in a patient with methemoglobinemia (19.9%). Please note that arterial line is dark blue and venous line is black. (b) Representative photos of color of venous and arterial lines of extracorporeal membrane oxygenation after exchange blood transfusion. Please note that arterial line is red and venous line is blue.