CASE REPORT

Inhalation of nitric oxide - dependence: case report

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Abstract

Objective: to describe hemodynamic response with rebound of pulmonary hypertension after withdrawal of inhaled nitric oxide in a pediatric patient with acute respiratory distress syndrome.

Methods: case report of a child with acute respiratory distress syndrome and pulmonary hypertension. The patient was examined using Doppler echocardiography. Inhalation of nitric oxide was administered for 21 days.

Results: we observed a decrease in pulmonary artery pressure from 52 mmHg to 44 mmHg after initial nitric oxide dosage. After withdrawal of nitric oxide inhalation, an increase in pulmonary artery pressure was observed (55 mmHg); consequently, it was necessary to reinstitute nitric oxide inhalation for improvement of pulmonary artery pressure (34 mmHg). A new attempt at withdrawing nitric oxide inhalation was carried out after continued use of nitric oxide (20 days); we observed worsening of clinical status and increase in pulmonary artery pressure. Consequently, nitric oxide inhalation was reinstituted. The patient died on the 24th day of treatment at the Intensive Care Unit due to multiple organ dysfunction.

Conclusion: rebounding of pulmonary hypertension after withdrawal of nitric oxide inhalation is a complication that may cause important clinical consequences for patients submitted to prolonged treatment with nitric oxide. This case report illustrates these consequences.


Introduction

Inhaled nitric oxide (NO) has been used in assisting treatment of pediatric acute respiratory distress syndrome (ARDS) with increase in pulmonary vascular resistance. Inhaled NO is used as a selective pulmonary vasodilator in numerous clinical situations.1 Assessment of pediatric patient response to vasodilators is rarely carried out with direct measurement of pulmonary artery pressure (PAP). In this sense, pulmonary artery catheter (Swan-Ganz) is scarcely used in patients with acute respiratory distress. Doppler echocardiography has been used progressively for bedside assessment of PAP.2,3

This is a case report of administering NO inhalation with unexpected results. Initial response was assessed and maintained with continuing of NO inhalation. We observed a rebound-type phenomenon after interruption of inhaled NO therapy.
Case report

A 6-year old female patient was admitted to the Intensive Care Unit in September 1997 in the immediate postoperative period, after being submitted to intra-abdominal debridement.

The patient had a history of abdominal omphalocele at birth, with surgery (silo reduction) and mechanical ventilation for 3 weeks. She was dismissed from the hospital at 1 month of age. At 3 1/2 years of age, the patient was resubmitted to surgery due to acute abdomen with obstructive symptoms as a consequence of bridles. The patient remained without other complications until reaching the present clinical status, at which point she presented recurrence of vomiting, abdominal pain, fever, and abdominal distention. She was admitted to our hospital for clinical and laboratory examinations. After the diagnosis of obstructive intestinal clinical status, the patient was submitted to exploratory laparotomy.

The patient was admitted to the Intensive Care Unit presenting slight dehydration, and was given 0.9% physiological saline solution intravenously. After approximately 4 hours, she presented successive vomiting episodes, followed by sudden respiratory distress with inspiratory and expiratory stridor. We started intravenous administration of corticoid. Chest X-ray indicated bilateral enlargement of bronchial tree with heterogeneous infiltration at right apex and left base. The patient presented progressive worsening of respiratory distress and decrease in arterial oxygen saturation. Subsequently, the patient was intubated and submitted to mechanical ventilation. X-rays indicated aggravation of pulmonary infiltrate. The patient developed arterial hypotension. We introduced dopamine in association with metronidazole into the patient’s antibiotic therapy (ceftadizime, amicacin, vancomycin, cotrimoxazole, amphotericin B). The following exams were carried out: urea 87 mg/dl; creatinine 1.2 mg/dl; total protein 4.0 mg/dl; albumin 2.6 mg/dl; Na+ 117 mEq/l; K+ 4.4 mEq/l. The patient also presented leukopenia/lymphopenia and platelet deficiency. We prescribed 0.9% intravenous saline solution and 20% albumin, and, also, an increase in the restitution of sodium. Subsequently, we observed that the patient presented digestive bleeding, and we decided to introduce omeprazol and interrupt the use of corticoid. The patient was given red blood cell and platelet concentrates. Collection of cerebrospinal fluid was carried out due to clinical status suggestive of convulsion (cerebrospinal fluid was normal on examination). Patient presented fever after the 2nd day at the Intensive Care Unit, which persisted throughout the evolution of clinical status. Clinical improvement was observed, allowing a reduction of FiO2 to 40% and of dopamine. On the 5th day at the Intensive Care Unit, however, the patient presented significant worsening of clinical status, at which point mechanical ventilation parameters had to be increased: FiO2 100%; breathing frequency 40 bpm; peak inspiratory pressure 40 cm H2O; positive end-expiratory pressure 9 cm H2O.

Chest X-ray indicated ARDS or acute pulmonary edema. Due to the increasing difficulty in managing ventilation parameters, we started monitoring respiratory mechanics with the assessment of pressure-volume and flow-volume curves. According to data yielded by the monitoring, we replaced the intratracheal cannula due to a significant leakage, and adjusted the mechanical ventilation parameters (FiO2 80%; breathing frequency 24 breaths/min; peak inspiratory pressure 38 cm H2O; positive end-expiratory pressure 12 cm H2O). At this point, we also started therapy with NO inhalation. Nitric oxide was administered with continuous afferent flow and digital monitoring of NO and nitrogen dioxide (NO2). NO therapy, at first, was administered at 5 ppm. Examination of PAP was carried out with Doppler echocardiography.

The first echocardiography, 10 hours after administering NO, indicated an estimated mean PAP of 52 mmHg. Next, NO dosage was increased to 12 ppm. The patient presented noticeable improvement in lung compliance and gas exchange, causing reduction of mechanical ventilation parameters (FiO2 60%; breathing frequency 24 breaths/min; peak inspiratory pressure 32 cm H2O; positive end-expiratory pressure 8 cm H2O). A second echocardiography was carried out after 30 hours of NO inhalation, at which point FiO2 had already been decreased to 50%. The estimated mean PAP was of 44 mmHg. Patient presented improvement, at chest X-ray, of pulmonary infiltration; however, there was also indication of a perihilar infiltration. We observed an increase in systemic arterial pressure and started administering nifedipine, and, later on, associate diuretic and captopril. The patient remained with normal diuresis and renal function. FiO2 was decreased to 45%, and inhaled NO, to 10 ppm. On the 11th day of hospital admission (6th day of NO inhalation), due to the improvement in clinical status, we stopped the use of dopamine and reduced inhaled NO to 5 ppm. Later, with the estimated mean PAP at 44 mmHg, NO inhalation was withdrawn. After 15 minutes, PAP had not changed. However, 2 hours after withdrawal of NO inhalation, the patient indicated decrease in blood saturation and aggravation of respiratory distress. NO inhalation was reinstated at up to 26 ppm, and mechanical ventilation parameters were increased. Dopamine was reintroduced, and continuous infusion of prostaglandin E1 was initiated. Six hours after reinstituting NO inhalation, mean PAP was of 55 mmHg. These procedures allowed improvement of respiratory status. Chest X-ray was confirmed indicating diffuse alveolar-interstitial infiltration. Antibiotic therapy was modified to vancomycin, cotrimoxazole, amicacin, and amphotericin B. The patient fasted throughout her stay at the hospital, and demonstrated bile secretion by stomach catheter. She was given parenteral feeding since the 8th day after hospital admission. Two days after reinstituting NO inhalation, mean PAP was of 34 mmHg. The administration of prostaglandin E1 was terminated after 48 hours; only inhalation of NO was maintained.
On the 14th day, we decided to carry out pulse therapy with methylprednisolone, in an attempt to lessen the inflammatory process. Patient presented improvement with gradual reduction of mechanical ventilation parameters. On the 18th day, FiO2 was at 40%, and NO inhalation, at 10 ppm. Mean PAP was of 33 mmHg. NO inhalation was decreased to 5 ppm, and dopamine administration was terminated. Examination 30 minutes after a decrease in inhaled NO levels indicated no status changes. The patient indicated moderate, stable clinical status, but required mechanical ventilation up to the 20th day - at which point we considered withdrawing NO inhalation. Mean PAP before withdrawal of NO inhalation was of 37 mmHg, and, after withdrawal, it increased to 54 mmHg. We reinstituted NO inhalation at 5 ppm. On the 20th day, the patient presented worsening of clinical status again, with increased condensation at lung bases. FiO2 and positive end-inspiratory pressures were gradually increased. The patient did not present improvement when moved from supine to prone position, or when inhaled NO was increased (up to 26 ppm). Doppler echocardiography indicated increase mean PAP to 57 mmHg. The administration of prostaglandin E1 was reinstituted without significant positive results. The patient status continued to deteriorate, resulting in death on the 24th day of hospital stay.

Figure 1 describes the relationship between inhaled NO and PAP during hospital stay. It is possible to observe that at both attempts of withdrawing NO inhalation there was a significant increase in PAP. Increase in NO inhalation levels caused a decrease in PAP at the first attempt of withdrawing NO inhalation; at the second attempt, however, PAP remained high even after an increase in NO inhalation levels. At that stage, however, the patient was already presenting multiple organ dysfunction.

![Figure 1](https://example.com/figure1.png)

**Figure 1** - Evolution of pulmonary artery pressure in relation to hospitalization time; rebound of pulmonary hypertension is evident at both attempts of weaning from nitric oxide

**Discussion**

At first, NO was considered only an environmental polluting agent. Currently, however, it is also known as a substance that actively participates in important bioregulating functions. There are two systems that synthesize NO in the organism (Ca++-dependent and non-Ca++-dependent). NO is produced from L-arginine and oxygen, having the enzyme NO-synthase as a catalyst. Since 1987, it is known that the endothelium-derived relaxing factor is the NO itself. The nitric oxide diffuses into smooth muscle cells in the vascular wall and binds to guanylate cyclase, which stimulates conversion of guanosine 5’-triphosphate into 3’, 5’-cyclic monophosphate. The latter is responsible for relaxing vascular musculature (vasodilation). Vasodilation, in turn, is very brief: it has a half-life of 3-5 seconds. NO is 4 to 5 times more diffusible than carbon monoxide. The NO that diffuses into the blood vessel lumen is avidly bound by hemoglobin, and does not cause important systemic vasodilation. Exogenous NO has the same vascular effect of carbon monoxide, and the vasodilation effect is restricted to the vasculature of the lung, since NO is rapidly deactivated once it reaches the bloodstream. This characteristic makes NO an important vasodilator in relation to other drugs, such as nitroprusside and prostaglandin E1, which offer the disadvantage of being also systemic vasodilators.

ARDS is characterized by mismatch of ventilation/perfusion and by increase in pulmonary vascular resistance. Increase in vascular resistance is a result in part of vascular endothelial lesion compromising the production of NO. Inhaled NO may reach the more ventilated areas of the lung, promoting reduction of local pulmonary resistance and consequent improvement in gas exchange. Administering of NO should be carried out according to clinical data and to the monitoring of PAP. Usually, concentration of NO inhalation varies from 1 to 20 ppm. Toxic effects have been described in administering NO. The most serious problems are related to the formation of NO2 and methemoglobin. An additional problem related to the presence of rebound has also been described in literature. Patients being submitted to gradual removal of NO inhalation due to significant improvement of oxygenation may present an increase in pulmonary vascular resistance. This results in need for increasing FiO2 and reinstituting inhalation of NO. The literature describes an incidence of rebound in 10% of cases. The rebound phenomenon is still not well understood. It is possible that endogenous NO production is inhibited by the presence of exogenous NO, similarly to the case of other vasodilators, such as PGI2. The rebound effect has also been described in rapid withdrawal of NO. In some cases, increase in PAP may be reduced with an increase in FiO2.

Our case report illustrates difficulties that may be found in the use of inhaled NO. Nitric oxide inhalation, however, is still an important therapy for the treatment of acute respiratory failure associated with pulmonary hypertension.
References


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