Successful Repair of a Severe Left Congenital Diaphragmatic Hernia during Continuous Inhalation of Nitric Oxide

Christine Lévêque, M.D.,* Jamil Hamza, M.D.,† Alain E. Berg, M.D.,* François Barbotin-Larrieu, M.D.,* Gérard Laguenie, M.D.,* Françoise Goutall-Flaud, M.D.,* Christian Couturier, M.D.,* Jean-François Egu, M.D.,* Rochdi Mekouar, M.D.,‡ Claude Saint-Maurice, M.D.§

CONGENITAL diaphragmatic defects commonly are associated with pulmonary vasoconstriction and persistent pulmonary hypertension of the newborn (PPHN).1 These complications carry a high postoperative mortality rate. The pulmonary vasodilators given intravenously in association with hyperventilation and profound sedation2 frequently are unable to increase arterial oxygen tension (PaO₂) consistently and may lead to systemic hypotension, thus resulting in an increase of the right-to-left shunting.3,4

Inhaled nitric oxide reduces the pulmonary vascular resistances in adults as well as in neonates.5-7 It is inactivated rapidly because it binds to hemoglobin in blood, resulting in a lack of systemic vasodilator effect.8 It has shown efficacy at a concentration of as little as 6 ppm.9

We report the effects of a continuous inhalation of nitric oxide during the perioperative period in a premature neonate with a severe left congenital diaphragmatic hernia (CDH) and congenital heart disease.

Case Report

The patient was a 1.8-kg male infant born in the 35th week of an uncomplicated pregnancy. The diagnosis of left CDH was made in the 19th week of gestation by a routine ultrasonographic examination. He was delivered vaginally with an Apgar score of 8 at 1 min of life. The trachea was intubated immediately, and the baby was referred to our institution in the 3rd h of life. He was admitted to the surgical neonatal intensive care unit for preoperative assessment and stabilization.

His lungs were ventilated mechanically during transport with a respiratory rate of 76 breaths per min, an inspired oxygen fraction (FiO₂) of 1.0, a peak inspiratory pressure of 20 cm H₂O, and a positive end-expiratory pressure of +4 cm H₂O. On arrival, his postductal arterial blood gases were as follows: pH, 7.57; arterial carbon dioxide tension, 21 mmHg; PaO₂, 76 mmHg; arterial oxygen percent saturation, 96%; and D(A-a)O₂ (alveolo-arterial oxygen tension difference), 616; there was no evidence of right-to-left shunting across the ductus arteriosus, as the postductal arterial oxygen saturation (SpO₂) was 97%. The chest x-ray showed a large left CDH that involved the stomach. It was impossible to alter the parameters of artificial ventilation even after the administration of a synthetic surfactant (Surfactex Neonatal, Wellcome Lab., London, UK).

In the patient’s 15th h of life, his cardiorespiratory condition started to deteriorate. An echocardiographic examination revealed a large ventricular septal defect with evidence of a mild bidirectional shunting and an increased isosystolic pulmonary arterial pressure. Post-ductal arterial blood gases were as follows: pH, 7.36; arterial carbon dioxide tension, 34 mmHg; PaO₂, 81 mmHg; arterial oxygen percent saturation, 95%; and D(A-a)O₂, 598.

Hyperventilation with a respiratory rate of 240 breaths per min, a FiO₂ of 1.0, a peak inspiratory pressure of 28 cm H₂O, a positive end-expiratory pressure of +6 cm H₂O, associated with a profound sedation (with allfentanil and midazolam), did not improve the oxygenation. After an intravascular volume expansion with 4% serum albumin, an infusion of epoprostenol (1.3 ng·kg⁻¹·min⁻¹) was attempted but failed to increase the PaO₂. Moreover, it caused systemic hypotension and was stopped rapidly. An infusion of dobutamine (5 μg·kg⁻¹·min⁻¹) was necessary to restore adequate systemic blood pressure and urinary output. At the 20th h of life, the patient’s post-ductal arterial blood gases were as follows: pH, 7.40; arterial carbon dioxide tension, 31 mmHg; PaO₂, 52 mmHg; arterial oxygen percent saturation, 80%; and D(A-a)O₂, 630. Post ductal SpO₂ then was 95%, showing evidence of right-to-left shunting.

After informed consent was obtained from the infant’s family, we introduced nitric oxide with progressively increasing concentrations (10 ppm/h) up to 60 ppm. We used a nitric oxide gas (CFPO, Paris- La Défense, France) containing 450 ppm nitric oxide with less than

* Staff Anesthesiologist, Department of Anesthesiology and Surgical Intensive Care.
† Assistant Professor, Department of Anesthesiology and Surgical Intensive Care.
‡ Surgeon, Department of Pediatric Surgery.
§ Professor, Department of Anesthesiology and Surgical Intensive Care.

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Address reprint requests to Dr. Lévêque: Département d’Anesthésie-Réanimation, Hôpital Saint-Vincent-de-Paul, 74, avenue Denfert-Rochereau, 75014 Paris, France.


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0.005% contamination by other oxides of nitrogen. Nitric oxide was delivered into the inspiratory limb of the breathing circuit of a Servo 900C ventilator (Siemens Elema, Stockholm, Sweden). We continuously measured the concentrations of nitric oxide at the tip of a double-lumen endotracheal tube of 3 mm of internal diameter (Hi-Lo Jet, Mallinckrodt, Athlone, Ireland), by means of a chemiluminescence device (NOX 2000, Seres, Aix on Provence, France), with a precision of 0.01 ppm. The exhaled gases, as well as those discharged from the chemiluminescence device, were scavenged. Nitric oxide did not seem effective initially; a small improvement of the peripheral oxygenation occurred at 60 ppm in the 30th h of life. Postdural arterial blood gases showed a pH of 7.40, an arterial carbon dioxide tension of 29 mmHg, a PaO₂ of 68 mmHg, and an arterial oxygen percent saturation of 93%. The association of nitric oxide with a continuous intravenous infusion of PGE1 (Alprostadil); Prostine VR Upjohn, Paris-La Défense, France; 0.02 µg·kg⁻¹·min⁻¹) caused a transient systemic hypotension, followed by a rapid and sustained improvement of the hemodynamics. Postdural PaO₂ increased up to 94 mmHg but with a marked dependence on nitric oxide as it decreased to 67 mmHg within 3 min after the nitric oxide was discontinued.

The cardiorespiratory condition remained stable for 3 h, thus allowing a decrease of inhaled nitric oxide concentration from 60 ppm to 40 ppm. The surgical repair of the CDH was done in the patient’s 34th h of life during continuous inhalation of nitric oxide (40 ppm) using the same delivery system. The infusions of PGE1 (0.02 µg·kg⁻¹·min⁻¹) and dobutamine (5 µg·kg⁻¹·min⁻¹) were continued throughout the operation. Anesthesia was maintained with fentanyl (20 µg·kg⁻¹) and vecuronium bromide (100 µg·kg⁻¹). The diaphragmatic defect consisted of a large posterolateral hernia with a pouch; a primary closure was performed easily. The arterial blood pressure, heart rate, and pre- and postdural hemoglobin oxygen saturations remained stable during anesthesia and surgery; however, we observed a transient tachycardia when the herniated viscera were moved from the thorax to the abdomen.

The continuous inhalation of nitric oxide was maintained during the postoperative period with decreasing concentrations from 40 ppm to 15 ppm on the 4th postoperative day. PaO₂ simultaneously could be have been reduced progressively from 1.0 to 0.5. The baby, however, remained markedly dependent on nitric oxide; even after short interruptions of nitric oxide inhalation, a dramatic deterioration of the systemic oxygenation occurred in less than 3 min, with postdural SpO₂ and PaO₂ decreasing to half their initial values. When we reintroduced nitric oxide at the same concentration, PaO₂ and SpO₂ recovered in 3–5 min.

On the 10th postoperative day, surgery was necessary because of a small bowel obstruction; this procedure also was done with a continuous inhalation of nitric oxide at a concentration of 4 ppm and an FIO₂ of 0.7. The nitric oxide requirements increased to 12 ppm postoperatively and returned to 4 ppm on the next day.

Nitric oxide was stopped after a total of 15 days of treatment, with a transient increase of FIO₂ (0.4 to 0.5) to maintain a constant oxygenation. The concentration of methemoglobin measured on the 8th day was 0.7%. The nitrous oxide concentrations reached a maximum value of 0.6 ppm at a nitric oxide concentration of 60 ppm and were less than 0.3 ppm throughout the treatment. At 5 weeks of life, the infant underwent a bilateral hemicorpphalry under general anesthesia. His recovery was uneventful, and his trachea was extubated 2 days later. At 3 months of life, he underwent the surgical repair of his ventricular septal defect under extracorporeal circulation. Again, anesthesia and recovery were uneventful, and the trachea was extubated 5 days later. At 5 months of life, he underwent a Nissen procedure with a gastrostomy because of a severe gastroesophageal reflux. Recovery again was uneventful. He was discharged home in his 7th month of life with no respiratory support and physiotherapy twice a week. A chest x-ray showed no abnormalities except those associated with the surgical repair of the CDH. He will be scheduled in a few months for a complete assessment of respiratory function and pulmonary circulation, including ventilation/perfusion scintigraphy.

**Discussion**

To our knowledge, this is the first report of surgical repair of CDH during continuous inhalation of nitric oxide.

Our case met several criteria for severity: early prenatal diagnosis at 18 weeks’ gestation, a large defect with an intrathoracic stomach, and a postdural PaO₂ of lower than 100 mmHg. In these severe cases, delayed operation and preoperative stabilization, rather than emergency surgical repair, can improve survival. The aim of this preoperative stabilization is to reduce PPHN to improve gas exchange. This stabilization can be obtained by various combinations of treatments, including hyperventilation, pulmonary vasodilators, extracorporeal membrane oxygenation therapy, and, more recently, high-frequency oscillation. Clear criteria regarding how long surgery should be delayed are not yet well defined. The stabilization period has been reported to last from a few hours up to 20 days. Therefore, we decided to attempt preoperative stabilization in our patient.

As previously suggested by most of the authors in the literature, we first tried hyperventilation with an FIO₂ of 1 in combination with profound intravenous sedation brought about with opioids and neuromuscular relaxants. Despite maximal hyperventilation (respiratory rate, 240 breaths per min; peak inspiratory pressure, 25 cm H₂O; mean airway pressure, 14 cm H₂O), we were unable to maintain an arterial carbon dioxide tension of less than 30 mmHg and a pH greater than 7.40. Some authors have proposed the use of high-frequency oscillation in these cases in which maximal hyperventilation fails to provide adequate alkaeemia. Unfortunately, this technique was not yet available in our intensive care unit when we performed this procedure. As arterial oxygenation was still unsatisfactory despite an FIO₂ of 1, and the alveolo-arterial oxygen tension difference remained approximately 600 for more than 12 h, we considered the use of venousous extracorporeal membrane oxygenation ther-
apy.\textsuperscript{12,17–21} Veno-venous extracorporeal membrane oxygenation therapy could not be offered to our patient, however, because of coexisting contraindications (a birth weight < 2,000 g, an intraventricular septal defect, and a best postdural Pao\textsubscript{2} < 100 mmHg).\textsuperscript{15,19–22} Despite recent controversies regarding their use, vasodilators were administered. Epoprostenol was chosen because it was considered to be more effective and to induce less systemic hypotension than tolazoline.\textsuperscript{4} There was no improvement in oxygenation, however, and dobutamine was required for the treatment of the subsequent hemodynamic instability.

The administration of nitric oxide then was considered. Nitric oxide gas recently has been identified as an endothelium-derived relaxing factor.\textsuperscript{23} It seems to be a selective arterial pulmonary vasodilator, as it is inactivated rapidly in blood because it binds to hemoglobin, thus resulting in a lack of systemic vasodilator effect.\textsuperscript{7} It has shown efficacy in decreasing pulmonary vascular resistances in animals\textsuperscript{7,24,25} as well as in humans.\textsuperscript{26} According to the results of animal studies,\textsuperscript{27,28} nitric oxide might play a role in transitional circulation at birth. Roberts \textit{et al.}\textsuperscript{6} and Kinsella \textit{et al.}\textsuperscript{9} reported successful treatment of PPHN using nitric oxide without the development of any systemic hypotension.

Concentrations of nitric oxide greater than 60 ppm were not used in this case, because there was a sustained improvement of postdural Pao\textsubscript{2} and Spo\textsubscript{2} after intravenous infusion of PGE1 was begun. It also could be related to the preemptive administration of the exogenous surfactant, which has shown efficacy in an animal model of a CDH when administered just before the initiation of nitric oxide inhalation,\textsuperscript{29} but this improvement was seen 30 h after the administration of a single dose of exogenous surfactant in our patient. Some authors have reported the improvement of oxygenation and outcome in patients with PPHN (one of them with a CDH) with low doses of inhaled nitric oxide (6–20 ppm).\textsuperscript{8,30} By giving a patient 10–20 ppm of inhaled nitric oxide, Frostell \textit{et al.}\textsuperscript{31} reversed a nearly fatal case of pulmonary hypertension that followed surgical repair of a CDH. Roberts \textit{et al.}\textsuperscript{32} and Zayck \textit{et al.}\textsuperscript{33} however, suggest that higher levels of nitric oxide may produce further reduction in pulmonary vascular resistances in newborn animals. In addition, Roberts \textit{et al.}\textsuperscript{34} found that inhalation of up to 80 ppm NO led to progressive reductions in pulmonary vascular resistances in infants and children with pulmonary hypertension and congenital heart lesions, such as that seen in our patient. In addition, Roberts \textit{et al.}\textsuperscript{6} found that some infants with PPHN did not have elevation of postdural Pao\textsubscript{2} until 80 ppm NO was inhaled. These latter studies support our observation that higher concentrations of nitric oxide may be required to improve clinical conditions in some patients.

Because of our patient's dependence on nitric oxide, a long-term administration of up to 15 days was necessary. Roberts \textit{et al.}\textsuperscript{6} reported a duration of nitric oxide therapy of up to 23 days in a neonate with PPHN. This dependence also was noted by Frostell \textit{et al.}\textsuperscript{31} in their report of a patient with CDH treated with 10–20 ppm inhaled NO for 40 h postoperatively: 5 ppm NO were administered for an additional 12 h because of evidence of the recurrence of pulmonary hypertension shortly after the first attempt at nitric oxide discontinuation. Despite this long-term administration, nitrous oxide concentration remained less than 4% of the concentrations of inhaled nitric oxide (less than 0.3 ppm\textsuperscript{25}). These low values could be related to a high ventilatory rate that reduces the contact time between nitric oxide and inspired oxygen.\textsuperscript{35} Here, Frostell \textit{et al.}\textsuperscript{31} found a maximal concentration of 0.9 ppm NO\textsubscript{2}. Methemoglobin measured on the 8th day of nitric oxide therapy was found to be 0.7%; this value is less than those reported by Frostell \textit{et al.}\textsuperscript{31} Roberts \textit{et al.},\textsuperscript{6} and Kinsella \textit{et al.},\textsuperscript{9} although the erythrocyte activity of methemoglobin reductase is impaired in neonates.\textsuperscript{36} This low value could be related to the routine use of ascorbic acid for parenteral nutrition in our neonatal intensive care unit.\textsuperscript{37}

In summary, we believe that nitric oxide was useful in this neonate, because it improved arterial oxygenation without causing any systemic hypotension, thus allowing surgical repair of the left CDH after a short period of stabilization. Despite several initial criteria suggesting a poor outcome, this neonate survived without apparent signs of respiratory failure. We believe that nitric oxide might play a role in preoperative stabilization of patients with severe CDH.

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Acute Hyperosmolar Coma Complicating Anesthesia for Hydatid Disease Surgery

Mladen Rakic, M.D., * Brijana Vegan, M.D., † Juraj Sprung M.D., Ph.D., ‡ Mihovil Biocic, M.D., §
George M. Barnas, Ph.D., ‖ Denis L. Bourke, M.D. ‖

HYDATID disease is a zoonotic infection caused by cystodes of the genus Echinococcus. The definitive hosts are dogs, wolves, jackals, and coyotes; intermediate hosts are sheep, cattle, and deer. Intermediate hosts and humans enter the disease cycle via contact with the feces of an infected canine or other definitive host. In the intermediate host, the ingested Echinococcus embryo bores its way through the small bowel mucosa and reaches the liver through the portal circulation. Most of the embryos are trapped in the liver where they form cysts; however, some may pass through the liver and form cysts in other organs, particularly the lungs, and less frequently the brain, kidneys, heart, and bones. The cyst cavity is filled with a highly antigenic fluid and small secondary cysts that develop from the germinal layer. The latter produce multiple protoscolices by asexual budding. In intermediate hosts and humans, protoscolices released from a cyst, as a result of spontaneous rupture or surgical manipulation, can differentiate by vesication and form secondary hydatid cysts within the host.1,2 Surgical intervention is the primary treatment for hydatid disease. During surgery, the cysts must be handled carefully to prevent spillage of the antigenic fluid and viable protoscolices that can cause anaphylaxis or peritoneal echinococcosis.3 To minimize these complications during surgical manipulation, the area around the cyst usually is packed with pads saturated with 20% saline or 0.5% silver nitrate.4 Additionally, the protoscolices can be killed by irrigation of the cyst cavity with hypertonic saline, silver nitrate, formalin, or cetrimide before resection.5 We present a case of hyperosmolar coma that developed during the surgical removal of a liver hydatid cyst. During surgery, 20% saline solution was used for irrigation and on packing sponges.

Case Report

A 13-yr-old boy (38 kg) was admitted to the hospital with flu-like symptoms and acute pain in the left upper abdomen. Hepatomegaly was noted on palpation. The chest radiogram showed a well-circumscribed infiltrate in the inferior lobe of the right lung, consistent with cyst formation. Ultrasonic scanning of the abdomen revealed a cystic defect in the left lobe of the liver, with internal echoes typical of an Echinococcus cyst.4 Computed tomography confirmed the cystic nature of both defects. The lung cyst was 6 cm in diameter. The liver cyst, 12 cm in diameter, occupied the entire left lobe of the liver. Both cysts had homogeneous contents, a thick capsule, and minimal

* Attending Anesthesiologist, General Hospital.
† Resident Anesthesiologist, General Hospital.
‡ Assistant Professor of Anesthesiology, University of Maryland.
§ Attending Surgeon, General Hospital.
‖ Associate Professor of Anesthesiology, University of Maryland.

Received from the Departments of Anesthesia and Surgery, General Hospital, Split, Croatia,* and the Department of Anesthesiology, Veterans Administration Medical Center, and the University of Maryland, Baltimore, Maryland. Accepted for publication January 21, 1994.

Address reprint requests to Dr. Sprung: Veterans Administration Medical Center, 10 North Greene Street, Baltimore, Maryland 21201-1566.


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