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Inhaled nitric oxide for a severe respiratory syncytial virus infection in an infant with bronchopulmonary dysplasia

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Abstract. *Objective:* To report the first case of ARDS in children treated with nitric oxide (NO) inhalation.
Methods: A 13-months infant presented with BPD and severe hypoxemia related to RSV infection and ARDS. Inhaled NO was delivered in the ventilatory circuit of a continuous flow ventilator (Babylog 8000, Dräger) in a concentration of 20–80 ppm for 7 days. NO and NO_2 were continuously monitored (Polyton Draeger). Respiratory mechanics were evaluated by using the method of passive inflation by the ventilator.
Results: NO inhalation improved oxygenation ($tcSaO_2$) and reduced respiratory system resistance without affecting arterial pressure. NO_2 level remained below 5 ppm, and methaemoglobin level below 1%. The child survived without neurologic sequela.
Conclusions: Two mechanisms to explain oxygenation improvement can be suggested: *selective* improvement in perfusion of ventilated regions and bronchodilation.

Key words: Acute respiratory distress syndrome – Respiratory syncytial virus infection – Bronchopulmonary dysplasia – Nitric oxide – Child

Respiratory syncytial virus (RSV) causes lower respiratory tract infections (bronchiolitis and/or pneumonia) that are more often severe in children with bronchopulmonary dysplasia (BPD) [1, 2]. Profound respiratory failure related to RSV infection has been treated with aerosolized ribavirin [3], and extra corporeal membrane oxygenation [4]. Recently, adult respiratory distress syndrome (ARDS) has been treated with inhaled nitric oxide (NO) [5], but to our knowledge, this therapy of ARDS has not been reported in children. We report here a child with severe BPD who presented with acute respiratory failure related to RSV infection. Despite aggressive therapy (controlled ventilation and aerosolized ribavirin), he did not improve, and it was decided to try inhaled NO.

Case report

A male infant born at 30 weeks of gestational age presented during the neonatal period a hyaline membrane disease complicated by a super infection due to *Staphylococcus epidermidis.* He was treated, in the neonatal intensive care unit, with exogenous surfactant (one dose of curosurf, Chiesi Farmaceutici-Italy), controlled ventilation (66 days), and antibiotics. BPD subsequently developed, and he was discharged at 4 months of age with nasal oxygen (FIO_2:0.25) and cisapride (gastrooesophageal reflux diagnosed by pH probe). He was readmitted at 5 months of age for acute respiratory distress requiring 3 weeks of controlled ventilation, and he was discharged with nasal oxygen (FIO_2:0.40). Fifteen days later, he was admitted to our paediatric intensive care unit with a septicaemia due to *Escherichia coli,* and a bronchitis requiring controlled ventilation and antibiotics. During the following weeks, several episodes of oxygen desaturation and hypercapnia were observed, and a tracheostomy was performed; he was then treated with nocturnal controlled ventilation and daytime oxygen. Echocardiography and Doppler did not show pulmonary hypertension. At 13 months of age his condition deteriorated with bronchospasm and oxygen desaturation (capillary blood gas was pH 7.31 units, PCO_2 83 mmHg). RSV antigen was detected in tracheal secretion by direct fluorescent antibody (Clonatec-Biosoft, France). Treatment included intravenous salbutamol and aminophylline, controlled ventilation (pressure preset Servoventilator Siemens 900 C, Elema-Sweden). Three days later a chest radiograph was consistent with an ARDS, and tracheal aspiration remained positive for RSV antigen. Aerosolized ribavirin (aerosol generator SPAG 2. ICN Pharmaceuticals. Inc., Costa Mesa, USA) was delivered for 4 days, salbutamol was stopped, and sedation (midazolam, fentanyl, pancuronium) was started. Despite this treatment, his condition did not improve; with aggressive controlled ventilation (Table 1) $tcSaO_2$ was between 50 and 60%, and capillary blood gas was pH 7.34 units, PCO_2 106 mmHg. Echocardiography and Doppler did not show pulmonary hypertension. The probability of survival being poor, we decided to try inhaled NO, with the aim of improving oxygenation and avoiding multiple organ failure. Informed consent was obtained from parents. Inhaled NO, started at 30 ppm, was delivered in the ventilator inspiratory circuit, between the Y-piece and humidifier (continuous flow ventilator Babylog 8000, Dräger, Lübeck-Germany, inspiratory flow 15 l/mim) from a tank of nitrogen with a NO concentration of 900 ppm (CFPO, Meudon-France). NO and NO_2 concentrations were continuously monitored near the Y-piece in the expiratory part of the circuit (Polytron, Dräger). Ventilator settings, blood gases, and arterial pressures, recorded immediately before and during NO inhalation, are shown in Table 1. After NO was breathed for 3 min, $tcSaO_2$ increased from 60–75%. Respiratory mechanics measurements were performed using the passive inflation method as described previously [6]. Respiratory system resistance values (including resistance of the endotracheal tube no. 3.5) expressed in cm H_2O/l/sec. were as follows: 215 just before NO, 140 after 5 min; 126 after 15 min; and 103 after 30 min. Respiratory system compliance values expressed in ml/cm H_2O were as follows: 1.70 just before NO, 2.11 after 5 min, 1.75 after 15 min, and 2.54 after 30 min. After 2 h of inhaled NO at 30 ppm, $tcSaO_2$ decreased to 60%; NO concentration was increased to 80 ppm, and $tcSaO_2$ increased to 74%. After 3 h of inhaled NO (1 h at 80 ppm), PEEP was reduced from 10–6 cm H_2O; crepitations were noted and

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Table 1. Respiratory and haemodynamic variables before and during nitric oxide inhalation

	Before NO	Delay after NO [and concentration of NO (ppm)]													
		3 mn [30]	1 h [30]	2 h [30]	2 h 30 [80]	3 h [80]	6 h [80]	12 h [80]	15 h [0]	24 h [80]	2 d [80]	3 d [60]	4 d [40]	5 d [20]	7 d [0]
Ventilator settings															
PIP (cm H_2O)	40	36	37	36	37	34	39	39	39	39	39	35	30	28	30
PEEP (cm H_2O)	10	10	10	10	10	6	12	12	12	11	11	10	10	10	9
FIO_2 (%)*	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Blood gases															
pH (units)	7.40	7.39	7.41	nd	nd	7.19	7.33	7.31	7.26	7.47	7.44	7.38	7.30	7.30	7.46
PCO_2 (mmHg)	84	88	66	nd	nd	156	102	98	123	85	63	84	110	140	71
$tcSaO_2$ (%)	60	75	75	60	74	60	76	78	59	73	82	76	77	79	79
Arterial pressures															
SAP (mmHg)	106	126	120	125	120	113	116	118	119	93	95	120	112	105	110
MAP (mmHg)	81	88	80	89	99	74	91	92	81	71	85	85	64	81	80

PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; *, FIO_2 delivered by the ventilator; $tcSaO_2$, transcutaneous oxygen saturation (mean value of at least 3 measurements during the period); SAP and MAP, systolic and mean arterial pressures; nd, not determined

pulmonary infiltrates worsened, suggesting pulmonary oedema, and leading to increase PEEP to 12 cm H_2O. After 15 h of NO inhalation, the tank was empty, and NO concentration fell to zero ppm; $tcSaO_2$ decreased to 59%, and rapidly increased to 80% with a new tank, while ventilator settings were not modified. After 3 days of inhaled NO at 80 ppm, NO concentration was progressively decreased to zero (by steps of 20 ppm, between day 3 and day 7), without change in $tcSaO_2$. At this time, resumption of inhaled NO at 80 ppm did not increase $tcSaO_2$ (not shown in Table 1). During NO inhalation, NO_2 level remained below 5 ppm (maximum level: 1.7 ppm), and methaemoglobin (measured at 4 h intervals) below 1%. Then, his condition progressively improved; 20 days after inhaled NO withdrawal, daytime controlled ventilation could be stopped with oxygen (1 l/min into the tracheostomy tube) $tcSaO_2$ was 100%, and capillary blood gas was pH 7.44 units PCO_2 52 mmHg. Three months after this RSV infection, his condition was the same as that before ARDS and remained stable with oral aminophylline, salbutamol, and cisapride. There were no neurologic sequela, and EEG was normal.

Discussion

Our child, who had typical features of ARDS, was treated with NO in a concentration of 20–80 ppm for 7 days; arterial oxygenation improved while systemic haemodynamics were not affected. NO_2 and methaemoglobin remained at low levels. The high NO concentrations, chosen because hypoxaemia was profound, can be criticised, since the effect of lower NO concentrations was not determined. The pulmonary oedema observed after 3 h of inhaled NO, is difficult to explain by these high NO concentrations, as NO_2 levels, which may explain toxicity [7], were low (0.4 ppm) when it occurred. Rossaint et al. have reported the successful use of NO in 10 adults with ARDS. In 7, NO was inhaled at 5–20 ppm for 3–53 days [5]. NO reverses hypoxic pulmonary vasoconstriction [8]. In patients with ARDS, inhaled NO reduces intrapulmonary shunting by selectively improving the perfusion of ventilated regions [5]. This is probably the main mechanism of action in our child. Another mechanism of action of NO can be suggested; inhaled NO reverses bronchoconstriction in anaesthetised guinea pigs [9]. Respiratory system resistance was elevated in our child, and the decrease observed with inhaled NO, suggests that bronchodilation participated in the oxygenation improvement. This potentially important mechanism of action needs further investigations.

In our child with ARDS and severe hypoxemia, related to RSV infection, inhaled NO was probably beneficial by significantly increasing O_2 saturation. Collaborative studies are needed to confirm this efficacy, to exclude potential toxicity when used for several days, and to determine the exact mechanisms of action in this disease.

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References

1. La via WV, Marks MI, Stutman HR (1992) Respiratory syncytial virus puzzle: clinical features, pathophysiology, treatment, and prevention. J Pediatr 121:503–510
2. Groothuis JR, Gutierrez KM, Lauer BA (1988) Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 82:199–203
3. Smith DW, Frankel LR, Mathers LH et al (1991) A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 325:24–29
4. Steinhorn RH, Green TP (1990) Use of extracorporeal membrane oxygenation in the treatment of respiratory syncytial virus bronchiolitis: the national experience, 1983 to 1988. J Pediatr 116:338–342
5. Rossaint R, Falke KJ, Lopez F et al (1993) Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399–405
6. Storme L, Riou Y, Leclerc F et al (1992) Comparison of respiratory mechanics measurements during volume and pressure controlled ventilation in neonates. Intensive Care Med 18 [Suppl 2]:P337
7. Frostell C, Fratacci MD, Wain JC et al (1991) Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047
8. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT et al (1991) Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 338:1173–1174
9. Dupuy PM, Shore SA, Drazen JM et al (1992) Bronchodilator action of inhaled nitric oxide in guinea pigs. J Clin Invest 90:421–428