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Successful use of inhaled nitric oxide for severe hypoxemia in an infant with acute exacerbation of bronchiolitis due to sepsis

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Introdution

Nitric oxide (NO) has recently been identified as endothelium-derived relaxing factor [1]. The addition of low-dose NO to inspired gas has the potential to selectively improve the perfusion of ventilated regions, thus improving ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching in patients with respiratory failure (RF) [2]. We describe here an infant with chronic lung disease due to severe bronchiolitis, in whom the inhalation of low-dose NO was successfully used to treat life-threatening hypoxemia due to the complication of sepsis.

Case report

An 8-month-old girl weighing 8100 g, who had been receiving mechanical ventilatory support (MVS) for a period of 138 days due to RF caused by severe bronchiolitis, became severely hypoxemic after developing sepsis. She had been prematurely delivered at 37 weeks of gestation with a birth weight of 2560 g, but otherwise she had no particular history of illness before developing bronchiolitis. Various medical therapies had been tried to treat the bronchiolitis, but lung function had worsened progressively. To prevent hypoxemia, MVS had been continued with an inspired oxygen fraction (F_{IO_2}) of 0.4–0.8 and with a positive end-expiratory pressure (PEEP) of 3–7 cmH_2O. Peak airway pressure (PAW) had been maintained at less than 30 cmH_2O to prevent barotrauma. However, arterial oxygenation had deteriorated progressively and the lungs had developed further emphysematous change. The right lung had herniated anterior to the heart and aorta. Thus, the combined use of fentanyl, midazolam, and vecuronium was necessary to prevent hypoxemia during this period of about 40 days.

Further progressive deterioration of oxygenation was observed from about the 135th day after the start of MVS. The patient frequently became hypoxemic despite maximal MVS with an F_{IO_2} of 0.8–1.0. A chest X-ray showed a marked increase in the hyperinflation of the lungs and infiltrates in the lower lung fields. The liver became palpable 7 fingerbreadths below the costal margin. Blood cultures yielded growth of *Staphylococcus cohnii*. Intravenous antimicrobial therapy was changed to the combined administration of imipenem/cilastatin 750 mg daily and tobramycin 35 mg daily. Since the intravenous hyperalimentation line was suspected as a focus of sepsis, the line was removed.

Three days after the start of MVS with an F_{IO_2} of 0.8–1.0, oxygenation worsened further and the patient frequently became hypoxemic even under MVS with an F_{IO_2} of 1.0. The arterial blood gas values under MVS with an F_{IO_2} of 1.0 were pH 7.41, P_{aCO_2} 59 mmHg, P_{aO_2} 48 mmHg, and BE 11 mEq/L. Cyanosis and peripheral coldness became apparent. To prevent hypoxemia, manual ventilation with a Mapleson D system (Z-A, Igarashi-ika, Tokyo, Japan) had to be performed frequently with F_{IO_2} of 1.0 and PAW of 60–70 cmH_2O. WBC and body temperature increased to 20700 cells/min^3 and 39°C. Due to life-threatening deterioration of oxygenation, extracorporeal life support (ECLS) was considered as a life-saving measure. However, ECLS was highly invasive and the patients' parents did not authorize this procedure. Thus, NO inhalation was started after obtaining her parents' written informed consent and institutional approval.

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Pressure-controlled ventilation with F_{IO_2} of 1.0, PEEP of 4 cmH_2O, PAW of 25–30 cmH_2O, and a ventilatory rate of 60 cycles/min was used during NO inhalation. At these settings, minute ventilation was about 5 l/min. The airway pressure was continuously monitored by a CP-100 Pulmonary Monitor (Bicore, Irvine, CA, USA) and was maintained at less than 30 cmH_2O. Peripheral arterial hemoglobin oxygen saturation (Spo_2) was also monitored continuously by pulse oximetry.

NO was obtained from Nihon Sanso (Oyama, Japan), as a mixture of 808 ppm in pure nitrogen. The concentration of nitric dioxide (NO_2) was less than 5 ppm in this stock tank. NO and NO_2 concentrations in the tank were certified using chemiluminescence analyzers by the supplier. NO was administered at a flow rate of 0.1 l/min via a Y-piece into a 10-l/min continuous stream of the fresh gas line. The fresh gas line was connected to the low-pressure gas supply input of a SERVO 900C ventilator (Siemens-Elema, Stockholm, Sweden). The flow rate of NO was regulated by a precise flow meter (RK1200, Kojima, Tokyo, Japan). The calculated concentration of NO of the breathing mixture was 16 ppm. A length of 17 cm of a carbon dioxide soda-lime absorber was incorporated into the inspiratory limb of the ventilator to absorb NO_2 formed [3]. The exhaled gases, as well as those discharging from the ventilator, were scavenged into the outdoors. In this system, a chemiluminescence analysis (Model 42, Thermo Environmental Instruments, Franklin, MA, USA) demonstrated the desired concentration of NO and the presence of NO_2 at less than 0.3 ppm in the inspired gas.

Initially, NO inhalation (16 ppm) was used for a limited time of 30 min to confirm the effects and then was restarted (Table 1). NO inhalation produced immediate improvement, with an increase of Spo_2 from 85% to 90% within a minute, and NO discontinuation worsened oxygenation with a decrease of Spo_2 from 94% to 84% within 5 min. Figure 1 shows the time course of Pao_2/F_{IO_2} during NO inhalation. Arterial blood samplings for both blood gases and methemoglobin analyses were performed every 6–12 h after the start of NO inhalation. Each day, NO was discontinued for a few minutes to confirm whether NO inhalation was required to maintain adequate oxygenation. When the change in Spo_2 was <4% units on discontinuation, inhalation of NO was regarded as nonbeneficial. After the start of NO inhalation, the general condition im-

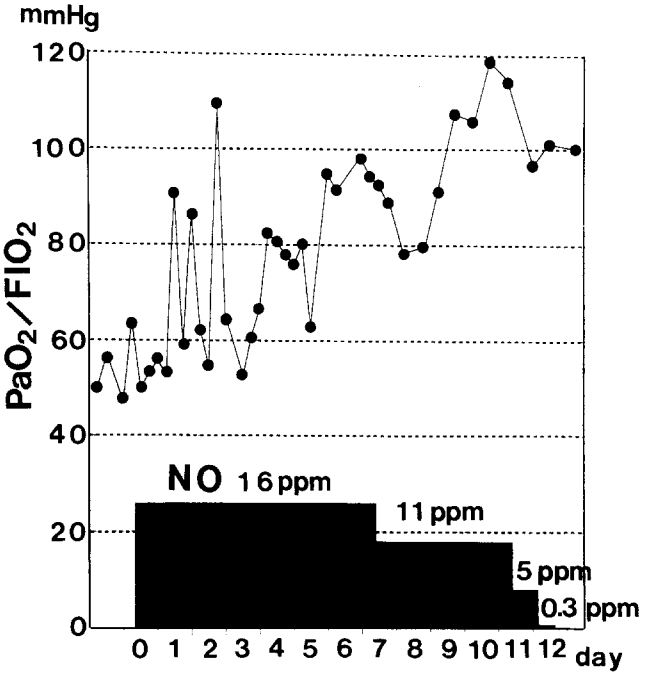

Fig. 1. Changes of Pao_2/F_{IO_2} during inhalation of low-dose nitric oxide over 11 days and 20 h

Table 1. Changes of mean blood pressures (MBP), heart rate (HR), pH and blood gases, oxygen saturation with pulse oximetry (Spo_2), and dynamic pulmonary lung compliance (Cdyn) before, during, and after NO ihhalation

	Before NO	NO (16 ppm) 1 min	NO (16 ppm) 10 min	NO (16 ppm) 20 min	NO (16 ppm) 30 min	5 min after termination of NO
MBP (mmHg)	86	90	94	94	88	82
HR (beats/min)	174	178	180	175	181	171
F_{IO_2}	1.0	1.0	1.0	1.0	1.0	1.0
pH	7.34	–	7.36	7.37	7.36	7.36
Pao_2 (mmHg)	49	–	57	61	64	51
$Paco_2$ (mmHg)	53	–	57	58	61	60
BE (mEq/L)	2.1	–	6.2	7.8	8.3	7.1
Spo_2 (%)	85	90	97	96	94	84
Cdyn (ml/cmH_2O)	3.5	3.3	3.3	3.3	3.3	3.3

F_{IO_2}, inspired oxygen Fraction.

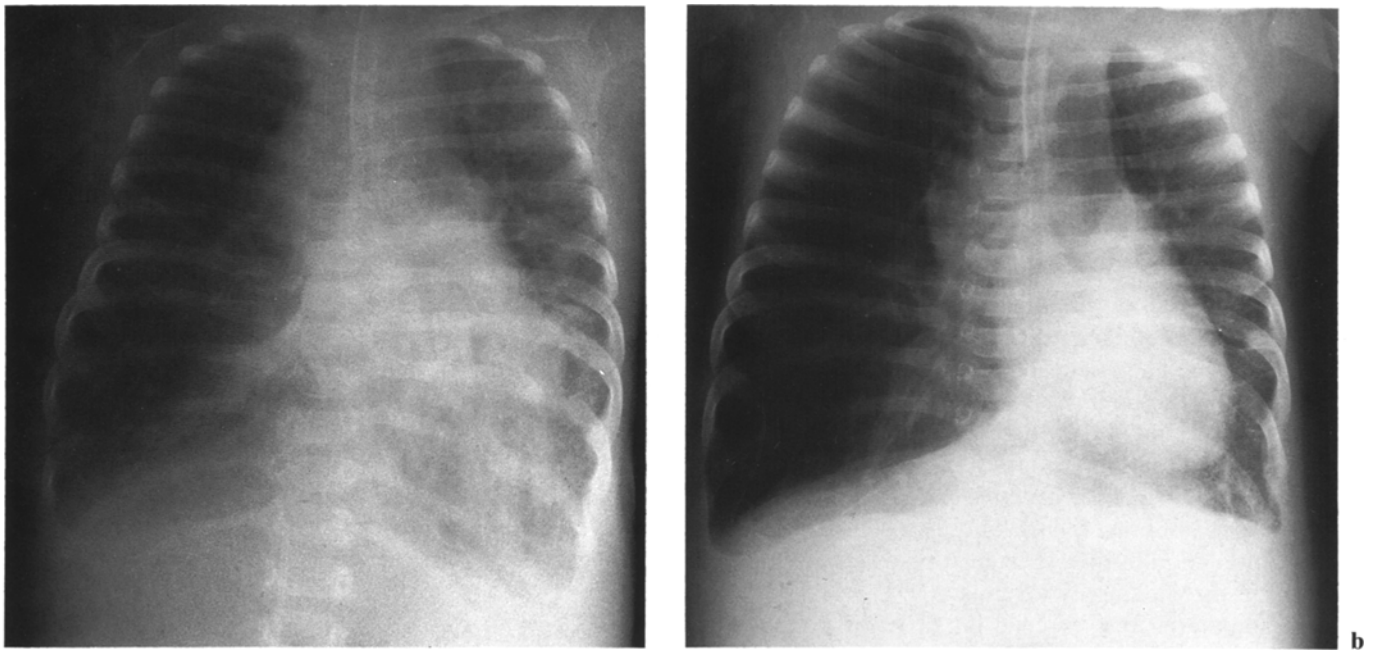

Fig. 2a,b. Chest X-rays before (**a**) and 9 days after (**b**) the start of NO inhalation. **a** Chest X-ray before NO inhalation shows marked increase in the hyperinflation of the lungs and infiltrates in the lower lung fields. **b** Chest X-ray 9 days after NO inhalation shows disappearance of the infiltrates and some improvement of the hyperinflation. The herniated right lung anterior to the heart and aorta, which developed about 1 month after admission, is observed

proved markedly. Cyanosis and peripheral coldness disappeared. The roentgenological infiltrates gradually disappeared and the hyperinflation of the lungs improved partially (Fig. 2A,B). F_{IO_2} could be reduced from 1.0 to 0.6. After a total of 11 days and 20 h of NO administration, NO inhalation was terminated since adequate oxygenation could be obtained with an F_{IO_2} of 0.6. During the period of NO inhalation, methemoglobin levels ranged from 0.1%–0.7%. Blood cultures did not show any growth of bacteria. About 1 month after the termination of NO inhalation, adequate gas exchange was obtained without sedatives and muscle relaxant along with an F_{IO_2} of 0.4–0.6, although the patient still required MVS for the persisting respiratory distress due to bronchiolitis.

Discussion

The most important observation in this case report is that in a severely hypoxemic infant with chronic lung disease due to bronchiolitis, inhalation of low-dose NO produced prompt improvement in oxygenation and maintained adequate oxygenation during an acute exacerbation due to the complication of sepsis.

Bronchiolitis is an acute inflammatory disease of the lower respiratory tract, resulting in obstruction of small airways [4]. Infants born prematurely tend to suffer from a more severe form of the disease and require hospitalization [4]. In about 2%–5% of hospitalized infants, the condition progresses to RF, necessitating MVS [4]. In some of these patients, lung function markedly deteriorates and life-threatening hypoxemia due to $\dot{V}/\dot{Q}$ mismatching often occurs during the evolution of bronchiolitis [4]. In the present case, the complication of sepsis was the cause of severe hypoxemia.

When life-threatening hypoxemia persists despite maximal MVS, life-saving measures are required. Steinhorn and Green [5] reported the usefulness of venoarterial ECLS in hypoxemic infants with bronchiolitis. However, venoarterial ECLS is highly invasive since it requires cannulation and ligation of the carotid artery, which may produce severe brain lesions [4].

NO inhalation is a simple and atraumatic method that has the potential to improve $\dot{V}/\dot{Q}$ mismatching, resulting in increased oxygenation [6]. In this case, NO inhalation produced prompt improvement of oxygenation and maintained adequate oxygenation during a prolonged period of about 12 days without tachyphylaxis. These findings are consistent with those of Rossaint et al. in patients with severe adult respiratory distress syndrome [6].

After the start of NO inhalation, the general condition improved markedly. NO inhalation may reduce the elevated pulmonary artery pressure due to hypoxia [7],

which may in turn improve right-sided cardiac performance. Moreover, although NO inhalation did not show any effect on dynamic pulmonary compliance, the potential bronchodilating actions of NO may have some effect on gas exchange [8].

Finally, the risks and benefits of NO inhalation to treat severe hypoxia associated with bronchiolitis need careful consideration. The main potential dangers of administering NO are methemoglobinemia and spontaneous formation of NO_2 that may induce lung injury [9]. The level of methemoglobinemia in this infant did not exceed 0.7%. The effects of prolonged exposure of low-dose NO_2 (<0.3 ppm) on the diseased lungs of infants are unclear. However, Morrow et al. suggested a slight reduction in pulmonary performance may occur in adults with chronic obstructive pulmonary disease exposed to 0.3 ppm NO_2 [10]. Thus, we consider that NO inhalation should be restricted to use only in patients with life-threatening hypoxemia.

In summary, in a hypoxic infant with bronchiolitis, inhalation of low-dose NO maintained adequate oxygenation during an acute exacerbation due to the complication of sepsis. Although NO inhalation is experimental therapy which should only be contemplated by physicians familiar with its use and limitations, we believe that NO inhalation should be attempted before ECLS in life-threatening situations.

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