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Changes in alveolar-arterial oxygen difference and oxygenation index during low-dose nitric oxide inhalation in 15 newborns with severe respiratory insufficiency

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Abstract We evaluated changes in alveolar-arterial oxygen differences (AaDO₂) and oxygenation index (OI) during inhalation of low-dose nitric oxide (INO) in 15 newborns with severe respiratory insufficiency: congenital diaphragmatic hernia (CDH) – 6, asphyxial lung disease – 4, meconium aspiration syndrome (MAS) – 2, respiratory distress syndrome – 2, persistent pulmonary hypertension of newborn – 1. Their mean birth weight was 2522 g (1030–3200 g, SD ± 575), mean gestational age 36 weeks (29–39 weeks, SD ± 3.2), mean initial AaDO₂ = 607 mm Hg (574–628 mm Hg, SD ± 14) and mean initial OI = 32 (6–57, SD ± 12). INO was performed using the Pulmonox system (Messer Griesheim, Austria) at conventional regimens of mechanical ventilation. The initial value of 20 ppm nitric oxide (NO) was decreased 6 h later, first to 15 ppm and then, as quickly as possible, to 3 ppm. The mean inhalation period was 51 h (6–131 h, SD ± 42). The initial values of AaDO₂ and OI decreased significantly within the first 6 h of INO ($P < 0.001$). After

the first 6 h, 4 patients died: 1 with MAS of an extrapulmonary cause and 3 CDH patients because of pulmonary hypoplasia. In the remaining 11 patients the decrease in AaDO₂ and OI during the first 24 h of INO was highly significant ($P < 0.0001$).

Conclusion In a heterogeneous group of 15 newborns with severe respiratory insufficiency, the initial AaDO₂ and OI decreased significantly within the first 6 h of INO.

Key words Nitric oxide · Respiratory insufficiency · Newborn · Pulmonary hypertension · Congenital diaphragmatic hernia

Abbreviations AaDO₂ alveolar-arterial oxygen difference · CDH congenital diaphragmatic hernia · ECMO extracorporeal membrane oxygenation · INO inhalation of nitric oxide · MAS meconium aspiration syndrome · NO nitric oxide · OI oxygenation index · PPHN persistent pulmonary hypertension of the newborn · ppm parts per million in volume

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Introduction

Recent therapeutic options for severe hypoxaemia associated with pulmonary hypertension include mechanical ventilation, administration of vasodilators and long-term extracorporeal lung support. These methods, however,

have some serious disadvantages (decrease in systemic blood pressure, increase in co-existing right-to-left shunt, iatrogenic complications of intensive care therapy, risk of secondary infection) [2, 6, 7, 23]. The latest and very promising therapeutic tool in the treatment of pulmonary hypertension is inhalation of low dose nitric oxide (NO) [14]. NO is a powerful endogenous vasodilator and has

been identified as an endothelium-derived relaxing factor activating soluble guanylyl cyclase. NO is an ideal local transcellular messenger because of its small size, lipophilic nature, and short duration of action. NO inhaled as a gas at low levels dilates selectively the pulmonary circulation. Significant systemic vasodilation does not occur because NO is inactivated by rapidly binding to haemoglobin [14, 27]. Besides smooth muscle relaxation, NO has many diverse physiological functions such as neurotransmission, immunoregulation, inhibition of platelet aggregation and adhesion [3, 13, 27]. Little is known of inhalation of nitric oxide (INO) toxicity which is generally regarded as low because of rapid inactivation of NO in contact with blood. Overdose of 20,000 ppm of NO causes acute pulmonary oedema and methaemoglobinemia. NO might impair energy metabolism or promote inflammation. The formation of hydroxyl radicals might cause oxidative damage to tissue. Its carcinogenic effect on smokers has been suggested. Data are available on DNA changes in *Salmonella* species due to NO [8, 17].

This is the first report of clinical experience with INO in the Czech Republic. The aim of this study was to determine changes in generally accepted ventilatory parameters, i.e., oxygenation index (OI) and alveolar-arterial oxygen difference (AaDO₂) in critically ill newborns with severe respiratory insufficiency during NO inhalation.

Materials and methods

Patients

INO was used in 15 newborns with severe respiratory insufficiency: congenital diaphragmatic hernia (CDH) – 6, asphyxial lung disease – 4, meconium aspiration syndrome (MAS) – 2, respiratory distress syndrome – 2, persistent pulmonary hypertension of newborn – 1. Their mean birth weight was 2522 g (range 1030–3200 g, SD $\pm$ 575), mean gestational age 36 weeks (range 29–39 weeks, SD $\pm$ 3.2), initial mean value of AaDO₂ = 607 mmHg (range 574–628 mmHg, SD $\pm$ 14) and initial mean value of OI = 32 (range 6–57, SD $\pm$ 12). Our criteria for using INO was: (1) newborn patients (28 weeks of gestational age); (2) patients with severe respiratory insufficiency associated with primary or secondary pulmonary hypertension (persistent pulmonary hypertension of the newborn, MAS, CDH, pneumonia, sepsis, asphyxia, respiratory distress syndrome, air-leak syndrome); (3) progressive increase in peak inspiratory pressure > 25 cm H₂O despite positive end expiratory pressure (PEEP) up to 10 cm H₂O with regard to adverse effect of PEEP on circulatory stability; (4) AaDO₂ > 550 mmHg at FiO₂ = 1.0; (5) ultrasonographic evidence of pulmonary hypertension (two-dimensional colour echocardiographic and Doppler examination of blood flow pattern – right-to-left shunt across the ductus arteriosus and foramen ovale during systole (Toshiba SSA 270)); (6) PaCO₂ < 50 mmHg. Our criteria for not using INO included: (1) severe congenital heart diseases; (2) patients with severe intraventricular-periventricular haemorrhage (grade III-IV); (3) patients with irreversible lung injury and fatal chromosomal abnormalities; (4) patients with prolonged metabolic acidosis and severe circulatory failure not reacting to therapy; (5) patients with prolonged bleeding time or coagulopathy; (6) patients treated with surfactant < 4 h prior to INO [9, 15, 18]. Also excluded were patients with chronic lung disease and severe bronchopulmonary dysplasia. INO use was approved by the Ethical Committee, Institute for the Care of Mother and Child, Ministry of Health, Czech Republic.

Nitric oxide inhalation

The system used for INO was the Pulmonox (Messer Griesheim, Austria) at conventional regimens of continuous flow, pressure-limited, time-cycled mechanical ventilation (infant ventilator Bear-Cub BP 2001, USA). Pulmonox is a microprocessor-controlled system for dosing of the Pulmomix (400 ppm NO in nitrogen) to the ventilatory circuit. The system includes a flow meter and continuous chemiluminescence analysis of NO and NO₂. Inspired gas sampled for analysis was drawn proximal to the endotracheal tube. This enabled controlled inhalation of 3–40 ppm of NO [16, 25]. According to our records patients inhaled an initial dose of 20 ppm NO for 6 h. This was decreased to 15 ppm and then to 3 ppm as quickly as possible without decrease in SaO₂ and PaO₂. Patients were weaned from INO at FiO₂ < 0.6 unless interruption of INO caused deterioration of respiratory and circulatory stability. In order to maintain PaO₂ levels after INO weaning, there had to be a temporary increase in FiO₂.

AaDO₂ was evaluated using the equation:

$$\text{AaDO}_2 = 700 \times \text{FiO}_2 - \text{PaCO}_2 / 0.8 - \text{PaO}_2 \text{ [mmHg]}$$

whereby FiO₂ = inspired oxygen fraction

PaCO₂ = partial pressure of carbon dioxide in arterial blood [mmHg]

PaO₂ = partial pressure of oxygen in postductal arterial blood [mmHg]

OI [19] was evaluated using the equation:

$$\text{OI} = \text{MAP} \times \text{FiO}_2 \times 100 / \text{PaO}_2$$

Parameters were assessed before INO, and at 0.5, 6 and 24 h of INO administration, and at the end of inhalation. Results both of the study group and the two other groups (survival and non survival) were presented as the mean $\pm$ standard deviation (SD). Analysis of variance with repeated measures (ANOVA, BMDP Stat. Software Inc., L.A., USA) were used for statistical data.

Results

The mean period of INO was 51 h (range 6–131 h, SD $\pm$ 42). NO₂ concentration never surpassed 0.5 ppm. Initial values for AaDO₂ were 607 $\pm$ 14 mmHg and for OI were 32 $\pm$ 12. Initial values for AaDO₂ and OI decreased significantly in all 15 patients of our study group within the first 6 h of INO (P < 0.001) (Figs. 1, 2).

Of the four deceased patients, one with severe MAS died of circulatory failure in spite of an improvement in ventilatory parameters and a continuous administration of norepinephrine. Three of the four patients who died had CDH. All patients had severe circulatory problems during INO and needed continuous administration of epinephrine, dopamine and dobutamine followed by veno-arterial extracorporeal membrane oxygenation (ECMO). Decrease in AaDO₂ and OI during INO was observed in only one of these patients. Bleeding complications associated with surgical intervention and ECMO were responsible for the death of these patients. Severe pulmonary hypoplasia was confirmed at autopsy (ipsilateral wet lung weight up to 7 g). No significant changes both in AaDO₂ and OI occurred after 6 h of INO in the non-surviving patients. (P = 0.206 and P = 0.151 resp.).

In the 11 surviving patients, the decrease in AaDO₂ and OI was highly significant within the first 24 h of INO

Fig. 1 Changes in AaDO₂ during INO in 15 newborns with severe respiratory insufficiency. (S group of surviving patients ($n = 11$), NS group of nonsurviving patients ($n = 4$), ALL group of all patients ($n = 15$)). Data presented as mean $\pm$ SD. Concentration of NO in inspired gas: 20 ppm for a period 0–6 h; decreasing conc. 15–3 ppm for a 6 h period – END

Fig. 2 Changes in OI during INO in 15 newborns with severe respiratory insufficiency. (S group of surviving patients ($n = 11$), NS group of nonsurviving patients ($n = 4$), ALL group of all patients ($n = 15$)). Data presented as mean $\pm$ SD. Concentration of NO in inspired gas: 20 ppm for a 0–6 h period; decreasing conc. 15–3 ppm for a 6 h period – END

($P < 0.0001$). At present, all patients are breathing spontaneously without problems.

There were no significant differences in the initial values of AaDO₂ and OI in the surviving and non-surviving patients. An interaction was observed between the changes in AaDO₂ within the first 6 h of INO and the rate of survival ($P < 0.05$).

Discussion

According to safety guidelines for the use of NO, the concentration should be kept as low as possible [5, 10, 14]. Even 0.1 ppm was reported to reduce effectively pulmonary arterial pressure and significantly increase PaO₂

in adult respiratory distress syndrome [11]. When using doses up to 20 ppm, methaemoglobin levels should not pose a problem [27]. We used a decreasing concentration of NO suggested by Kinsella et al. [14]. Apparently, most patients require an initial concentration of 20 ppm either for an unfavourable distribution of NO or for a high rate of NO oxidation caused by reactive oxygen species originating from the inflammatory processes in the injured lung [21].

The computer-controlled automatic system Pulmonox (Messer Griesheim, Austria) provides accurate dosing of low concentrations of NO. The dosing is interrupted at an NO concentration surpassing 49.9 ppm. In our opinion, a short-term inhalation of a higher dose does less harm than a sudden interruption of INO. This dependence upon exogenous NO might be caused by a higher rate of degradation of cyclic guanosine monophosphate by phosphodiesterases, a lower endogenous NO production and a further unbalance between vasoconstricting and vasodilating mediators of pulmonary microcirculation. All safety systems should be fitted with a manual device for dosing a defined low concentration of NO independent of microprocessor, analyser and power supply (16, 25).

We examined a heterogeneous group of 15 patients with severe respiratory failure of different origin treated with INO [1, 12, 20, 24, 26]. The most frequent diagnosis was CDH (6 patients) where pulmonary hypoplasia and pulmonary hypertension have generally been accepted as factors limiting survival. All patients had left-sided CDH and respiratory insufficiency developing within the 1st h of delivery (two patients with a prenatally diagnosed CDH). Three patients responded to INO and survived. Three patients died in spite of a temporary improvement in AaDO₂ and OI. All infants had severe circulatory problems during INO, without a decrease in the left ventricular mass, with severe pulmonary hypoplasia confirmed at autopsy. In our opinion, INO supports survival or creates conditions for ECMO therapy, particularly in CDH patients. Because of the small number of patients, this hypothesis needs further investigation (23, 26).

The remaining 9 patients, all with severe acute lung injury of different etiologies, responded to INO, one died of an extrapulmonary cause. All but two patients were mature or nearly mature and met almost all criteria of severe respiratory insufficiency with predictive mortality of above 70% at conventional therapy. Therefore, statistical improvement in AaDO₂ and OI during the first 6 h suggested that the effect of INO on acute lung injury may be beneficial (4). In addition to influencing hypoxic pulmonary vasoconstriction, INO might have an antimicrobial and anti-inflammatory effect on lung tissue. In the presence of an inflammatory process in lung tissue, INO decreases microvascular permeability as a consequence of endothelial cell relaxation and affects negatively adhesion and aggregation of neutrophils and platelets (13, 21). Some centres do not use INO in newborns younger than

33 weeks of gestational because it may provoke intracranial haemorrhage. INO inhibits blood platelet aggregation in the adult, but the mechanism involved remains obscure [22]. Bleeding problems did not occur except in two CDH patients, who had to undergo ECMO and surgery. In our opinion, bleeding was triggered by inadequate heparinisation and low platelet count rather than by INO. On the other hand, its role should not be underestimated. It should always be remembered that INO may potentiate bleeding in premature newborns, surgical patients and patients with haemostatic disorders or with extracorporeal circulation support.

Our results suggest that AaDO₂ and OI values decrease significantly within the first 6 h of INO therapy in new-

borns with acute lung injury. Survival or necessity for ECMO therapy may have been influenced by INO, particularly in CDH patients. This therapy seems to be safe when using a low-dose programme and computer-controlled system with accurate analysis. Sudden interruption of INO should be avoided and the risk for patients with coagulation problems should be considered. All patients are monitored for potentially delayed risk after exposure to INO.

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