Efficacy of Inhaled Nitric Oxide in Children With ARDS*

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Study objective: Data concerning inhaled nitric oxide (iNO) on pediatric ARDS is rare. We investigated the effects of iNO on pediatric ARDS in order to examine the ability to predict a response to iNO, the optimal concentration of iNO, the effects of ≤1 ppm nitric oxide (NO), and the effect of iNO on PaCO₂.

Setting: ICU at Kumamoto (Japan) University Hospital.

Patients and interventions: Seven children with ARDS. The initial responses to 16 ppm NO and the dose-response effects of 0.13 to 16 ppm NO were assessed.

Measurements and results: Sixteen ppm of iNO improved oxygenation in all seven children. The use of iNO significantly increased the ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO₂/FI O₂). A correlation between the NO-induced increase in PaO₂/FI O₂ and the baseline PaO₂/FI O₂ was observed (r=0.93, p<0.01). Dose-response tests showed that the optimal concentration of iNO was ≤4 ppm, improvements in PaO₂/FI O₂ could be observed with concentrations of ≤1 ppm NO, and iNO induced a slight decrease in PaCO₂.

Conclusions: In children with ARDS, iNO frequently improves oxygenation and induces a slight decrease in PaCO₂, with the baseline PaO₂/FI O₂ functioning as a predictor of all NO response. Improvements of PaO₂ and PaCO₂ were observed with concentrations of iNO of ≤1 ppm, a level in which the risk of a toxic reaction in children is minimal. Effects on outcome need verification in larger controlled trials.

Key words: acute respiratory distress syndrome; arterial oxygenation; carbon dioxide elimination; inhaled nitric oxide

Abbreviations: DAP=diastolic arterial pressure; FI O₂=fraction of inspired oxygen; HR=heart rate; iNO=inhaled nitric oxide; MAP=mean arterial pressure; NO=nitric oxide; NO₂=nitric dioxide; (P(A-a))O₂=alveolar-arterial oxygen pressure difference; PaO₂/FI O₂=ratio of arterial oxygen tension to the fraction of inspired oxygen; PaRF=pediatric respiratory failure; SAP=systolic arterial pressure; SpO₂=arterial oxygen saturation measured by pulse oximetry

Acute respiratory distress syndrome (ARDS) is the most severe manifestation of acute lung injury that is characterized by diffuse pulmonary inflammation, increased pulmonary permeability, arterial hypoxemia resistance to oxygen therapy alone, and diffuse radiologic infiltrates.1 Despite recent technical advances in pediatric intensive care, the mortality rate of children with ARDS is very high, ranging from 43 to 62%.2,3

Nitric oxide (NO) is an endogenous-derived relaxing factor of vascular smooth muscle and perhaps bronchial smooth muscle. The addition of NO to inspired gas has been shown to reduce pulmonary arterial pressure without systemic hypotension4 and to improve arterial oxygenation by improving ventilation/perfusion matching in adults with ARDS4 and in children.5

Although a growing number of studies have now been reported regarding the effects of inhaled NO (iNO) on adults with ARDS,6-11 there are only a few studies of iNO concerning pediatric ARDS.5,12,13 Many issues in pediatric ARDS remain to be resolved, including the following: (1) whether iNO can improve arterial oxygenation in children with severe ARDS; (2) whether the response to iNO can be predicted; (3) whether there is an optimal concentration of iNO for arterial oxygenation; (4) whether improvements in arterial oxygenation can be observed using very low concentrations of iNO (≤1 ppm); and (5) whether iNO has any effect on PaCO₂. To examine these issues, we studied the initial responses of children with severe ARDS to 16 ppm of iNO and the dose-response effects of 0.13 to 16 ppm of iNO.

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Materials and Methods

This study was approved by the institutional review board at the Kunnamoto University Hospital. Patients were enrolled after informed consent was obtained from their parents.

Patients

All children with ARDS, as defined by the American-European Consensus Conference,1 who were <18 years old and were admitted to our ICU for respiratory care between June 1993 and July 1996 were considered as potential subjects for this study. Criteria for entry into the study included the following: (1) modified ARDS score for children >3.0;14 (2) ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO2/FIO2) <150; and (3) alveolar-arterial oxygen pressure difference (P(A-a)O2) under an FIO2 = 1.0 >500 mm Hg. Patients were excluded from the study if the deterioration of arterial oxygenation was due to cardiac disease or chronic lung disease.1 At enrollment, as a routine procedure for severe ARDS, all patients were sedated and paralyzed with a continuous IV infusion of fentanyl 1 to 3 μg/kg/h, midazolam 0.1 to 0.25 mg/kg/h, and vecuronium 0.05 to 0.1 mg/kg/h, and lungs were ventilated by pressure control ventilation and positive end-expiratory pressure of 6 to 10 cm H2O using a ventilator (Servo 900C Ventilator; Siemens Elema; Lund, Sweden). Peak airway pressure and expiratory minute ventilation were monitored continuously by a patient data management system (FS-2100; Fukuda Electronics; Tokyo, Japan) connected to the ventilator. Peak airway pressure was limited to <30 cm H2O, permitting hypercarbia if necessary.15 Prone positioning was tried if applicable.16 A trial of iNO was begun when no signs of recovery in arterial oxygenation were observed despite conventional intensive care. Trials of surfactant replacement,17 extracorporeal membrane oxygenation, perfluorocarbon- associated gas exchange, and high-frequency ventilation were not used. Mortality risk before iNO was estimated by the pediatric respiratory failure (PeRF) score.2

Measurements

All patients had an arterial catheter for monitoring arterial pressures and arterial blood gases. A bedside monitor (Stinctress 1281; Siemens Medical Electronics; Danvers, MA) was used to determine systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), heart rate (HR), and rectal body temperature. pH and serial arterial blood gas tensions were measured with a pH/blood gas analyzer (Corning 288; Chiba Corning Diagnostics Co; Medfield, MA). Peripheral arterial oxygen saturation (SpO2) was monitored with a pulse oximeter attached to the bedside monitor. During the study, the actual FIO2 in the inspiratory limb of the ventilator was measured continuously by an on-line oxygen analyzer (TED200; Teledyne Electronic Devices; City of Industry, Calif). Changes in oxygenation were assessed by direct measurements of PaO2 and FIO2. Comparisons were made by indexes for oxygenation: PaO2/FIO2 and P(A-a)O2 (calculated by assuming a barometric pressure of 760 mm Hg and a respiratory quotient of 0.8).

Administration of NO

NO was obtained (Taiyo Sanso Co; Osaka, Japan) as a mixture of approximately 500 ppm of pure nitrogen. The concentration of nitric oxide (NO2) was <4 ppm in this stock tank. NO and NO2 concentrations in the tank were certified by the supplier. To maintain a constant iNO concentration, NO was administered with an NO delivery system of the ventilator (Servo 900C) using the low-pressure inlet15 that premixed NO before entering the ventilator.18 A continuous infusion of air/oxygen at a flow rate of 10 to 30 L/min was supplied to the low-pressure gas input of the ventilator. NO, regulated by a precise flowmeter (BK1200; Kojima; Tokyo, Japan), was added via a Y-piece into the continuous stream to the low-pressure gas input of the ventilator. The concentrations of NO and NO2 in the inspiratory limb were verified by a chemiluminescence analyzer (model 42; Thermo Environmental Instruments; Franklin, MA). The minimum detectable limit of this analyzer was 0.5 parts per billion. Before measurements, the chemiluminescence analyzer was calibrated at 0 and 17.81 ppm of NO. The methemoglobin concentration was measured at least every 8 h (2500 CO-oximeter; Chiba Corning Diagnostics Co).

Protocol

Phase 1: Baseline measurements were made after 1 h of steady-state pressure control ventilation using the following ventilatory settings: FIO2 = 1.0; positive end-expiratory pressure = 6 to 10 cm H2O; inspiratory time = 30 to 50%; respiratory frequency = 20 to 30 breaths/min. Under these ventilatory settings, NO at an inspiratory concentration of 16 ppm was administered. Thirty minutes after NO inhalation, respiratory and hemodynamic measurements were performed. Success was defined as an increase in PaO2/FIO2 to 10 mm Hg above the baseline value, based on the definition by Finer et al.20 If the patient did not meet the criteria for success while receiving 16 ppm of NO, the iNO was discontinued. Patients with a successful response continued to receive 8 ppm of iNO for 2 to 3 h and FIO2 was decreased under a continuous monitoring of SpO2. The concentration of iNO was then maintained at levels of 2 to 8 ppm to minimize the inhalation of NO2.16

Phase 2: The dose response to iNO was evaluated on the following day while the patients were sedated, paralyzed, and treated under the same ventilatory settings as during phase 1. To avoid hypoxemia due to the discontinuation of iNO, the discontinued iNO was tried under the continuous monitoring of SpO2. Thirty minutes after complete discontinuation of iNO, respiratory and hemodynamic parameters were measured, and then NO at concentrations of 0.13, 0.25, 0.5, 1, 2, 4, 8, and 16 ppm were administered in a random order for 20 min.

Based on the dose-response test, iNO was continued at the lowest dose of NO associated with an appropriate improvement in oxygenation. The dose-response test was repeated every 1 to 2 weeks if the patients were sedated, paralyzed, and treated under pressure control ventilation. An attempt to wean NO was made every 24 to 48 h. NO inhalation was discontinued when patients could be treated with an FIO2 <0.6 without NO or muscle relaxant.

Statistical Analysis

All values are expressed as mean ±SE. Statistical analysis for paired data were performed by two-tailed Wilcoxon signed-ranks test. When a linear regression was calculated, the coefficient of correlation was tested using a f distribution (two-tailed). Statistical analysis for the dose-response test was performed using a one-way analysis of variance with repeated measurement. Scheffé’s test was used for internal comparisons. A p value <0.05 was considered significant.

Results

Seven children with severe ARDS, ranging from 2 months to 17 years of age, were studied (Table 1),
including three boys and four girls. The ARDS score was ≥3.0 in each case. Three children had ARDS due to sepsis during therapies for tyrosinemia, acute leukemia, and acute hepatitis. Three had ARDS due to viral pneumonia and one due to a near-drowning. Duration between the time of the diagnosis of ARDS and initiation of NO inhalation ranged from 2 h to 5 days. The mean mortality risk estimated by the PeRF score before iNO was 67±10%.

**Initial Responses to iNO**

Sixteen ppm of iNO produced improvement in arterial oxygenation in all of the seven children (Table 1). The PaO₂/FIO₂ and SpO₂ values significantly increased from 68±10 to 136±37 mm Hg (p<0.02) and from 93±1% to 99±1%, (p<0.05), respectively. There was a significant correlation between the NO-induced increase in the PaO₂/FIO₂ values and the baseline PaO₂/FIO₂ values (r=0.93, p<0.01) (Fig 1). The higher the baseline PaO₂/FIO₂ values, the higher the NO-induced increase in PaO₂/FIO₂ values. The P(A-a)O₂ values significantly decreased from 594±11 to 529±38 mm Hg (p<0.02).

There were no significant changes in pH, PaCO₂, and base excess (pH: 7.39±0.04 vs 7.41±0.04; PaCO₂: 51±5 vs 48±5 mm Hg; base excess: 5±3 vs 6±3 mEq/L). The SAP, MAP, and DAP values slightly increased from 95±10 to 100±10 mm Hg (p<0.05), 67±7 to 72±8 mm Hg (p<0.05), and 52±6 to 56±7 mm Hg (p<0.05), respectively. The HR values were not significantly different following treatments (132±8 vs 131±8 beats/min).

**Dose-Response Test**

Of the seven children with ARDS, the dose-response test was performed in five. The test was not

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**Table 1—Clinical Characteristics of Children With ARDS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Age</td>
<td>2 mo</td>
<td>4 yr</td>
<td>10 yr</td>
<td>16 yr</td>
<td>17 yr</td>
<td>8 mo</td>
<td>1 yr</td>
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<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Tyrosinemia</td>
<td>Measles</td>
<td>Chromosomal anomaly</td>
<td>Ellerpey</td>
<td>Leukemia</td>
<td>Acute hepatitis</td>
<td>Down’s syndrome</td>
</tr>
<tr>
<td>Etiology of ARDS</td>
<td>Sepsis</td>
<td>MRSA</td>
<td>Pneumonia</td>
<td>Measles</td>
<td>Pneumonia</td>
<td>Near-drowning</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Infectious agent</td>
<td>virus</td>
<td>type B</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Septic</td>
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<tr>
<td>PaO₂/FIO₂ before/after NO</td>
<td>3.0</td>
<td>3.0</td>
<td>3.3</td>
<td>3.0</td>
<td>3.3</td>
<td>3.0</td>
<td>3.3</td>
</tr>
<tr>
<td>PaO₂/FIO₂ before/after NO, mm Hg</td>
<td>66/131</td>
<td>51/67</td>
<td>66/153</td>
<td>124/348</td>
<td>66/90</td>
<td>49/78</td>
<td>56/84</td>
</tr>
<tr>
<td>P(A-a)O₂ before/after NO, mm Hg</td>
<td>598/512</td>
<td>624/611</td>
<td>597/509</td>
<td>533/315</td>
<td>603/578</td>
<td>598/582</td>
<td>619/596</td>
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<tr>
<td>Ventilation days before NO</td>
<td>31</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td>13</td>
<td>&lt;1</td>
<td>10</td>
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<tr>
<td>Duration of ARDS before NO, d</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>&lt;1</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Duration of NO inhalation, d</td>
<td>4</td>
<td>3</td>
<td>73</td>
<td>24</td>
<td>10</td>
<td>&lt;1</td>
<td>4</td>
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<tr>
<td>Other organ failure</td>
<td>Liver</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Liver</td>
<td>Kidney</td>
<td>Liver</td>
</tr>
<tr>
<td>Mortality risk by PeRF score before NO</td>
<td>96%</td>
<td>42%</td>
<td>54%</td>
<td>85%</td>
<td>31%</td>
<td>59%</td>
<td>64%</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died</td>
<td>Died</td>
<td>Survived</td>
<td>Survived</td>
<td>Survived</td>
<td>Died</td>
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</tr>
</tbody>
</table>

*MRSA = methicillin-resistant Staphylococcus aureus.

†After 30 min of 16 ppm NO inhalation.
performed in two children (patients 6 and 7) because of deteriorated oxygenation. Of the five children, patients 1 and 2 had only a 3- to 4-day NO inhalation and thus received the dose-response test only once. Patient 3 had a 73-day course of NO inhalation and was tested three times for a dose response while patients 4 and 5 had a 10- to 24-day NO inhalation and were each tested twice. Thus, a total of nine dose-response tests were performed in these five children.

There were statistically significant dose-dependent changes in the mean values of pH (p<0.05), PaO₂/FiO₂ (p<0.0001), P(A-a)O₂ (p<0.0001), and PaCO₂ (p<0.02) when the concentrations of iNO were changed. Figure 2 shows individual and mean changes in PaO₂/FiO₂ and PaCO₂ during the nine dose-response tests. NO induced a significant increase in the mean values of PaO₂/FiO₂ for inspiratory NO concentrations ranging between 0 and 4 ppm and a plateau-like effect was observed at inspiratory NO concentrations ranging between 4 and 16 ppm. The mean PaCO₂ values showed a statistically significant (but clinically insignificant) dose-dependent decrease and the decrease in PaCO₂ was associated with a significant increase in pH. The mean values of NO₂ showed a significant dose-dependent increase (p<0.0001) and 0.14±0.01 ppm of NO₂ were detected for inspiratory NO concentrations of 16 ppm. At levels of ≤4 ppm of inhaled NO using a ventilator (Servo Ventilator 900C), the mean productions of NO₂ in the inspired limb were at ≤0.02±0.01 ppm. The SAP, MAP, DAP, and HR values did not show any significant changes during the tests.

In five of the nine dose-response tests, improvements in oxygenation were observed in response to the very low concentrations of iNO (≤1 ppm). In addition, the magnitudes of PaO₂/FiO₂ responses to iNO tended to improve in subsequent tests in the three children (patients 3, 4, and 5) who received two or three dose-response tests during the course of NO inhalation. All three children survived with

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21828/)
gradual improvement in oxygenation. Individual PaCO₂ values showed obvious decreases for inspiratory NO concentrations ranging between 0 and 2 ppm, specifically in patients 1 and 3 in whom the baseline PaCO₂ values were high. Methemoglobin levels did not rise over 1.5% of total hemoglobin in any of the children during the course of NO inhalation. We did not observe any side effects of iNO therapy, including the formation of high NO₂, increased bleeding time, or hypoxemia due to NO discontinuation. Three patients (patients 1, 6, and 7) died of multisystem organ failure and one (patient 2) died of hypoxemia. The mean mortality rate was 57%.

**Discussion**

The major findings of the present study were that (1) children with severe ARDS had variable responses to iNO, (2) the magnitude of improvement in oxygenation correlated with the baseline PaO₂/FIO₂ ratio, and (3) improvements in arterial oxygenation could be observed with concentrations of iNO of ≤1 ppm.

**Initial Responses to iNO**

From the first report of Rossaint et al⁴ who demonstrated that doses of 18 and 36 ppm of iNO produced significant improvements in arterial oxygenation in adults with ARDS, an increasing number of studies using iNO have been published on adult ARDS.⁵,⁶-¹¹ However, data concerning iNO on pediatric ARDS are rare.⁵,¹²,¹³ Abman et al⁵ showed the effects of 10 and 20 ppm NO on 10 children with ARDS and showed that iNO improved arterial oxygenation. The findings are consistent with those of the present study.

In agreement with the findings of studies on adult ARDS,⁵,¹²-¹³ the magnitude of individual responses in PaO₂ to iNO was quite variable. Associations have been described between presence of septic shock,²¹ severity of sepsis,¹⁰ reversibility of lung injury,¹³ and use of phenylephrine²² and the patient’s initial responsiveness to iNO. We could not determine what factors were predictive of the patient’s initial responsiveness to iNO. However, interestingly, and in contrast to a recent study on adult ARDS,⁸ the magnitude of improvement in oxygenation correlated with the baseline PaO₂/FIO₂ ratio. Patients with severe hypoxemia had a lower NO-induced increase in PaO₂. Our findings are consistent with those of a study by Emil et al²³ who showed that NO was less effective in decreasing pulmonary hypertension in a porcine model with severe hypoxia.

In patients with ARDS, arterial oxygenation depends on the distribution of ventilation perfusion relationships at the alveolar level.⁴ To improve ventilation/perfusion mismatching by iNO in patients with ARDS, iNO must reach the alveolus where gas exchange is performed, and iNO must dilate constricted pulmonary arteries and veins that have smooth muscle. In patients with ARDS, extended consolidation of the alveolar spaces is associated with reduced functional residual capacity.¹⁴ NO may be hindered from reaching the alveolus in patients with severe hypoxemia due to the extended consolidation of the alveolar spaces.

The level of the baseline pulmonary vascular resistance has also been suggested to predict the NO-induced increase in PaO₂.⁸ To measure pulmonary vascular resistance, a pulmonary catheter must be inserted, a procedure that is invasive and difficult in small children. Our observations imply that the application of iNO may be more useful in children whose disease is milder or where there is less remodeling.

Abman et al²⁵ showed significant increases in cardiac output during NO inhalation in a study on pediatric ARDS. We found statistically significant (but clinically insignificant) increases in SAP, MAP, and DAP during NO inhalation. These findings are in contrast to several studies on adult ARDS.⁴,⁸,¹⁰,²⁴,²⁵ Although it is not clear why systemic hemodynamic changes were produced during NO inhalation in children with ARDS, it may be related to the differences of the magnitude of factors participating in pulmonary circulation in adults and children with ARDS. Increased pulmonary artery pressure can arise from functional constriction of lung vessels due to hypoxia and hypercarbia as well as from structural alterations due to thrombosis of the precapillary artery, intimal proliferation, and medial thickening.²⁶ If, in children with ARDS, the functional constriction of lung vessels plays a major role in raising pulmonary artery pressure while the structural alterations do not, this may lead to increased pulmonary vasodilation and decreased afterload of the right ventricle²⁴,²⁵ in response to iNO, resulting in increased cardiac output of the right ventricle. Since iNO does not change systemic vascular resistance,²⁴,²⁵ the increased cardiac output may be associated with increases in systemic arterial pressures.

**Dose-Response Test**

In accordance with previous studies on adult ARDS,⁶,⁷,⁹ the optimum dose of iNO in pediatric patients regarding arterial oxygenation was very low at levels of ≤4 ppm. Improvements in arterial oxygenation were also observed with very low con-
concentrations of iNO of 0.13 ppm, which are similar to those measured in the exhaled air of humans. 

These findings are consistent with those of studies on adult ARDS. 

At levels of ≤4 ppm of iNO using a specific ventilator (Servo Ventilator 900C), the mean productions of NO in the inspired limb were at ≤0.02±0.01 ppm, which is less than the level of 0.05 ppm in the national ambient air quality standard for NO in the United States. NO therapy must frequently be continued for prolonged periods ranging from several hours to several days. When higher concentrations of NO are inhaled, higher concentrations of NO are produced. To minimize NO-induced pulmonary injuries, the maintenance dose of iNO should be kept as low as possible. Based on the dose-response test, patient 3 and 4 had a 72- and 24-day NO inhalation with the maintenance dose of ≤4 ppm. Despite prolonged NO inhalation in both patients, lung functions improved gradually, and the patients were weaned from mechanical ventilation and discharged from the ICU. We did not observe any of the known potential side effects of iNO. 

Finally, in accordance with previous studies on adult ARDS, iNO induced a slight decrease in PaCO2 during the dose-response test. Such a decrease was not observed during the initial response test that was performed in children with severe hypoxemia. The explanation could be that the effect of NO on PaCO2 was likely related to the reopening of pulmonary vessels located in previously nonperfused but ventilated lung regions. Thus, the effect may not be observed in children with severe hypoxemia due to the extended consolidation of the alveolar spaces during the initial response test.

The magnitude of the decrease in PaCO2 was remarkable in children with high baseline PaCO2 values, and this decrease was observed with low concentrations of iNO of ≤1 ppm, concentrations in which the risk of toxic levels of NO in children is minimal. Puybasset et al showed that iNO completely reversed the increase in pulmonary vascular resistance induced by acute permissive hypercapnia. These findings suggest that in a child with ARDS who has hypercapnia because of the desire to prevent lung trauma, the addition of iNO can also reduce the adverse effects of permissive hypercapnia.

In conclusion, this study shows that in children with severe ARDS, iNO improves arterial oxygenation, and the magnitude of improvement in oxygenation is correlated with the baseline PaO2/FIO2 ratio. The optimal concentration of iNO for arterial oxygenation is ≤4 ppm, and improvements in arterial oxygenation can be observed at concentrations of iNO of ≤1 ppm. NO inhalation induces a slight decrease in PaCO2, specifically in children with high baseline PaCO2 values. When a child with ARDS experiences hypoxemia and hypercapnia despite adequate mechanical ventilation, iNO appears to be an option. However, this study has many limitations that should be taken into account when the results are applying both to further research and clinical practice. The sample size is very small. The age range is broad from 2 months to 17 years. The responses to iNO in the infant lungs may differ from those of a full-grown adolescent. In addition, the etiologies of ARDS are widely different. The question of improvement in outcome is unanswered by this study. Further studies are required to verify the potential relevance of iNO in pediatric ARDS.

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