Early Response to Inhaled Nitric Oxide and Its Relationship to Outcome in Children With Severe Hypoxemic Respiratory Failure*

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Objective: To examine whether the early response to inhaled nitric oxide (iNO) is a measure of reversibility of lung injury and patient outcome in children with acute hypoxemic respiratory failure (AHRF).

Design: Retrospective review study.

Setting: Pediatric ICUs.

Patients: Thirty infants and children, aged 1 month to 13 years (median, 7 months) with severe AHRF (mean alveolar arterial oxygen gradient of 568±9.3 mm Hg, PaO₂/fraction of inspired oxygen of 56±2.3, oxygenation index [OI] of 41±3.8, and acute lung injury score of 2.8±0.1). Eighteen patients had ARDS.

Interventions: The magnitude of the early response to iNO was quantified as the percentage change in OI occurring within 60 min of initiating 20 ppm iNO therapy. This response was compared to patient outcome data.

Measurements and results: There was a significant association between early response to iNO and patient outcome (Kendall tau B r=0.43, p<0.02). All six patients who showed <15% improvement in OI died; 4 of the 11 patients (36%) who had a 15 to 30% improvement in OI survived, while 8 of 13 (61%) who had a >30% improvement in OI survived. Overall, 12 patients (40%) survived, 9 with ongoing conventional treatment including iNO, and 3 with extracorporeal support.

Conclusions: In AHRF in children, greater early response to iNO appears to be associated with improved outcome. This may reflect reversibility of pulmonary pathophysiologic condition and serve as a bedside marker of disease stage. (CHEST 1997; 112:752-58)

Key words: acute hypoxemic respiratory failure; acute respiratory distress syndrome; inhaled nitric oxide

Abbreviations: AHRF=acute hypoxemic respiratory failure; ALI=acute lung injury (score); CLD=chronic lung disease; ECMO=extracorporeal membrane oxygenation; FIO₂=fraction of inspired oxygen; HFOV=high-frequency oscillation ventilation; iNO=inhaled nitric oxide; MetHb=methemoglobin; NO=nitric oxide; OI=oxygenation index; Pa(A-a)O₂=alveolar-arterial oxygen gradient; PaO₂/FIO₂=ratio of partial pressure of arterial oxygen to inspired oxygen concentration; PEEP=positive end-expiratory pressure; PH=pulmonary hypertension; PIP=peak inspiratory pressures; SatO₂=arterial saturation; SAP=mean systemic arterial pressure

Acute hypoxemic respiratory failure (AHRF) in the 1990s is still associated with a mortality in excess of 50%.1-5 It is caused by a heterogeneous group of diseases that result in nonhomogeneous disruption of the alveolar-capillary membrane.5-8 In the early phase of the disease process, acute hypoxemia results from ventilation-perfusion mismatching, followed later by fixed structural abnormalities of the alveolar-capillary membrane.

AHRF is, however, a clinical diagnosis and it is not possible, without whole lung histologic study, to determine whether the underlying disease process is reversible. All such patients therefore become the recipients of short-term treatment even to the extent of novel, invasive, and costly therapies such as extracorporeal membrane oxygenation (ECMO). Ideally, these therapies should be offered only to patients in whom the pathologic process is believed to be reversible, which in current practice is determined by the duration of mechanical ventilation.

Recent studies have demonstrated that short-term exposure to inhaled nitric oxide (iNO) is associated
with physiologic improvements in ventilation-perfusion matching and intrapulmonary shunting in both children and adults with AHRF. Neonates with fixed structural changes such as pulmonary hypoplasia and dysplasia appear to have a decreased sensitivity and time course of response to iNO compared to neonates with diseases associated with reversible pulmonary hypertension.15

We hypothesized that the magnitude of response to the introduction of iNO in older infants and children might identify those patients with potentially reversible lung injury, ie, large response may indicate a greater likelihood of lung injury reversibility with less likelihood of pulmonary fibrosis and thus improved survival.

**MATERIALS AND METHODS**

**Patient Population**

Response to iNO was reviewed in 30 consecutive infants and children with severe AHRF who received iNO at our institution between September 1993 and January 1996, at which time we began recruiting such patients for a randomized clinical trial (Table 1). iNO is approved as an investigational drug at our institution.

These patients were given a trial of iNO therapy if oxygenation was deemed inadequate despite optimal mechanical ventilatory support. The ventilator strategy used was one in which peak inspiratory pressures (PIPs) were limited to ≤40 cm H₂O, if possible, in the pressure-controlled mode, while aiming for a pH of >7.25 and arterial saturation (SaO₂) >88%. Positive end-expiratory pressure (PEEP) was used to recruit lung volume and maximize oxygenation. High-frequency oscillation ventilation (HFOV) was used if adequate oxygenation or CO₂ clearance could not be achieved using the above ventilator guidelines. Surfactant was administered when adequate lung volume recruitment could not be achieved with either conventional ventilation or HFOV. Decisions regarding the commencement and withdrawal of iNO therapy, changes in ventilator settings, the order of use of HFOV, iNO, and surfactant as well as the use of neuromuscular blockade were at the discretion of the attending clinical team.

Inotropic agents were used to maintain a mean arterial BP within the expected range for age. Echocardiographic examinations were carried out in 20 patients pre-iNO administration.

**Table 1—Patient Demographics**

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Diagnosis</th>
<th>Days Ventilated</th>
<th>A-a, pre-iNO</th>
<th>OI, pre-iNO</th>
<th>OI, % Δ</th>
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<tbody>
<tr>
<td>Survivor group</td>
<td></td>
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<td>1</td>
<td>Meningococcemia</td>
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<td>2</td>
<td>Adenovirus-RSV-CLD</td>
<td>3</td>
<td>522</td>
<td>16</td>
<td>-46</td>
</tr>
<tr>
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<td>RSV</td>
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<td>490</td>
<td>15</td>
<td>-53</td>
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<tr>
<td>4</td>
<td>Staphylococcus pneumonia, RSV</td>
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<td>587</td>
<td>18</td>
<td>-36</td>
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<tr>
<td>5</td>
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<td>614</td>
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<td>Aspiration pneumonia-febrile convulsion</td>
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<td>7</td>
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<td>3</td>
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<td>RSV-CLD</td>
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<td>455</td>
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<td>605</td>
<td>58</td>
<td>-3</td>
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<tr>
<td>14</td>
<td>RSV-bacterial pneumonia</td>
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<td>574</td>
<td>54</td>
<td>-7</td>
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<tr>
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<tr>
<td>16</td>
<td>ALL-CLD-IVH</td>
<td>44</td>
<td>618</td>
<td>37</td>
<td>30</td>
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<tr>
<td>17</td>
<td>CAM-bacterial pneumonia</td>
<td>50</td>
<td>546</td>
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<td>18</td>
<td>LIP-hypogammaglobulinemia</td>
<td>3</td>
<td>482</td>
<td>38</td>
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</table>

*Pre-iNO=* pre-intravenous oxygenation gradient pre-iNO; ALL=acute lymphocytic leukemia; CAM=cystic adenomatous malformation; IVH=intraventricular hemorrhage; LIP=lymphocytic interstitial pneumonia; OI pre-iNO=oxygenation index pre-iNO; OI % Δ=percentage change in OI within 60 min exposure to iNO; RSV=respiratory syncytial virus; RTA=road traffic accident; SCIDS=severe combined immune deficiency; TOF=tracheoesophageal fistula; Tx=transplant; PFC=Pneumocystis carinii pneumonia; CMV=cytomegalovirus.

1ARDS.
Patients were defined as having pulmonary hypertension (PH) if estimated pulmonary pressures (from the tricuspid regurgitation jet) were greater than half the systemic arterial pressures.

Each patient had a PaO₂ <75 mm Hg despite fraction of inspired oxygen (FIO₂) >0.75, a PEEP=4 cm H₂O, aboeor-arterial oxygen gradient ([P(a-a)O₂] >450 mm Hg, PaO₂/FIO₂ <50, oxygenation index ([OI]=mean airway pressure × FIO₂ × 100/PaO₂) >15, and an acute lung injury (ALI) score >2.0. ARDS was defined according to the criteria from the combined American-European Consensus Conference on ARDS. Impaired oxygenation (PaO₂/FIO₂ <200); bilateral pulmonary infiltrates on frontal radiograph; and absence of clinical or radiographic evidence of elevated left atrial pressure or congestive heart failure. Patients were considered to have chronic lung disease (CLD) if they had been born prematurely, previously ventilated, and oxygen dependent, either in hospital or at home, for >28 days prior to the present hospital admission.

iNO Protocol for AHRF

All patients received a trial dose of iNO of 20 ppm for approximately 60 min. The magnitude of response to iNO was quantified as the percentage change in the OI occurring within this 60-min trial period. Because of a lack of information regarding what constitutes a response to iNO, we stratified the magnitude of response in terms of the percent change in OI into the following: <15% change in OI, 15 to 30% improvement in OI, and >30% improvement in OI.

Patients were continued on a regimen of low-dose iNO (0 to 20 ppm) at the discretion of the attending clinical team. Weaning of the iNO was commenced when an FIO₂ <0.6 and PIP <32 cm H₂O or MAP <20 cm H₂O (HFOV) could be achieved while maintaining SaO₂ >88%. Thereafter, regular reverse dose response weaning was conducted every 12 to 24 h allowing the dose of iNO to be reduced gradually as clinical improvement progressed.

ECMO is used at our institution on the basis of patient-specific goals, rather than according to routine ordering strategies. Patients are generally considered for ECMO if the targeted ventilator values described above (pH >7.25, SaO₂ >88%) could not be achieved with conventional ventilation using PIP <45 cm H₂O, FIO₂ of 1.0 (despite aggressive PEEP), or with HFOV using MAP <30 cm H₂O, FIO₂ of 1.0. ECMO is also considered in patients maintaining targeted ventilator values, but who have significant or worsening barotrauma based on chest radiography or the need for repeated pleural drainage. Patients are excluded from ECMO if they have received high-pressure mechanical ventilation (PIP >35 cm H₂O) for >10 to 14 days or if they have an underlying irreversible disease or evidence of a recent cerebral hemorrhage. Sepsis is not a contraindication for ECMO at our institution. None of the patients in this study received ECMO before the trial of iNO. The iNO therapy was discontinued when patients were placed on ECMO support.

iNO Administration

iNO was delivered via the following ventilators in this study: Babylog 9000 (Dräger; Lübeck, Germany), SLE 2000 (Specialised Laboratory Equipment Ltd; Croydon, England), Servo 900C (Siemens-Elema AB; Solna, Sweden), and the SensoMedics HFOV 3100A (Biltwoven, Netherlands).

Nitric oxide (NO) gas, obtained in a mixture of nitrogen at 1,000 ppm NO (BOC-Special Gases; Surrey, England), was delivered via a calibrated N₂ flow meter (KDG Instruments; Surrey, England) into the inspiratory limb of the infant and HFOV ventilators or into the low-pressure gas inlet of the Servo 900C ventilator. The concentrations of inspired NO and its toxic oxidative product, nitrogen dioxide, were analyzed by either chemiluminescence (model 42; Thermo Environmental Instruments; Franklin, Mass) or electrochemical analysis (Bedfont Scientific; Kent, England; Micro Medical; Kent, England) from samples of circuit gas obtained from a point 25 cm distal to the patient on the infant ventilators as previously described, and 10 cm proximal to the patient on the Servo 900C, and at the proximal end of the endotracheal tube on the HFOV. The analyzers were regularly calibrated at 0 and 10 ppm NO and 0 and 4 ppm nitrogen dioxide.

Physiologic Measurements

The following variables were recorded at baseline, within the first hour of iNO therapy, and regularly thereafter with ongoing iNO treatment: arterial blood gases, arterial saturations (SaO₂), and mean systemic arterial pressure (SAP). SAP was monitored continuously via an indwelling arterial catheter that was connected to high-pressure tubing, fluid-filled transducers, and the component monitoring system (Hewlett-Packard; Boeblingen, Germany). Arterial samples for blood gas analysis were drawn from these indwelling arterial catheters and measured by standard techniques.

The following indexes of oxygenation were derived and recorded at baseline and regularly during ongoing iNO administration: PaO₂/[PaCO₂/0.8]/PaO₂, PaO₂/FIO₂ ratio, and OI.

Statistical Analysis

Data are presented as the mean±SEM. Nonparametric statistical analyses were used because of sample size.

The correlation between response to iNO and patient outcome was assessed using nonparametric rank correlation (Kendall tau B).

The Wilcoxon sign test was used to compare the hemodynamic and arterial blood gas parameters recorded at baseline and during the initial trial of iNO therapy. Differences between the ARDS and non-ARDS groups and between the survivors and nonsurvivors were compared using Fisher’s exact p values. Differences within the three categories of response to iNO were compared using analysis of variance for repeated measures.

Results were considered significant at a p value <0.05.

RESULTS

Patient Population

Thirty patients (16 female and 14 male, aged 1 month to 13.1 years, median 7 months) received a trial dose of iNO for AHRF during the period of study (Table 1). They were receiving high levels of ventilatory support prior to the commencement of iNO therapy: mean FIO₂, 0.97±0.01; MAP, 21±1.5 cm H₂O; PEEP, 8±0.9 cm H₂O; they also had markedly impaired oxygenation: P(A-a)O₂, 568±9.3 mm Hg; PaO₂/FIO₂, 56±2.3; OI, 41±3.8; and ALI score, 2.8±0.1. The mean duration of mechanical ventilation prior to the commencement of iNO was
8.4±2.1 days. Ten patients (33%) were already receiving HFOV and 5 (17%) were receiving surfactant prior to the commencement of iNO. Fifteen patients (50%) required inotropic support with dopamine, dobutamine, and/or epinephrine to optimize systemic hemodynamics. Seven patients had evidence of PH pre-iNO.

Eighteen patients had ARDS. There were no significant differences in age (37.3±11.7 vs 16.2±7.7 months, p=0.18), sex ratio (male:female, 6:12 vs 8:4, p=0.13), days ventilated pre-iNO (6.4±1.2 vs 11.3±5 days, p=0.18), P(A-a)O₂ pre-iNO (573±10.5 vs 562±17.4 mm Hg, p=0.99), OI pre-iNO (43±5.1 vs 38±5.7, p=0.51), the use of HFOV (61% vs 42%, p=0.46), the use of ECMO (17% vs 25%, p=0.66), the administration of surfactant (28% vs 33%, p=0.99), or survival (44% vs 33%, p=0.71) between the ARDS and non-ARDS groups.

Ten patients had respiratory syncytial virus-positive bronchiolitis and six had evidence of underlying CLD. Four patients had immune deficiencies: one following a bone marrow transplant for myelodysplasia, two while receiving chemotherapy (one for Hodgkin’s lymphoma and the other for relapsed acute lymphocytic leukemia), and the fourth was HIV positive.

**Short-term Response to iNO and its Relationship to Patient Outcome**

Overall, exposure to 60 min of 20 ppm iNO was associated with a significant improvement in oxygenation (pre-iNO vs post-iNO): PaO₂, 53±2.2 to 74±4.4 mm Hg, p<0.0001; PaO₂/FIO₂, 56±2.3 to 78±4.8, p<0.0001; and OI, 41±3.8 to 30±3.1, p<0.0001 (Fig 1).

There was a significant association between response to iNO, in terms of percent improvement in OI, and patient outcome (Kendall tau B r=0.43, p<0.02). All six patients who showed <15% improvement in OI died; 4 of the 11 patients (36%) who had a 15 to 30% improvement in OI survived, while 8 of 13 (61%) who had a >30% improvement in OI survived (Table 2 and Fig 2). There were no significant differences in age (p=0.8), P(A-a)O₂ (p=0.69), OI (p=0.54), MAP (p=0.54), PEEP (p=0.8), time ventilated (p=0.09), use of HFOV (p=0.49), surfactant (p=0.98), ECMO (p=0.38), or echocardiographic evidence of PH (p=0.77) prior to the commencement of iNO therapy within these three categories of responders to the trial dose of iNO that could have accounted for which patients were likely to respond to the iNO therapy.

There was no significant association between time ventilated pre-iNO and percent change in OI (r=0.34, p=0.06), nor between baseline PEEP and percent change in OI (r=0.04, p=0.8). There were no significant differences in the percent change in OI between the ARDS vs the non-ARDS group (28±4.6% vs 23±7.4%, p=0.55), between the patients receiving HFOV (n=10) vs conventional ventilation (n=20) pre-iNO (20±7.6% vs 29±4.6%, p=0.32) or between the patients with documented PH (n=7) vs those with estimated PAP/SAP <0.5 who had echocardiographic examinations pre-iNO.

**Figure 1.** OI before and after exposure to iNO in the survivors and nonsurvivors.
Table 2—Relationship Between the Percentage Change in the OI After Exposure to iNO and Patient Outcome

<table>
<thead>
<tr>
<th>Change in OI</th>
<th>Survived, No.</th>
<th>Died, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15%</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>15-30%</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

*No. = number of patients; Kendall tau B r = 0.43, p<0.02.

(n=13) (27±7.6 vs 26±6.3, p=0.94). Echocardiograms were not carried out immediately after commencement of iNO therapy and therefore the short-term effects of iNO on PAF are not available.

Exposure to iNO was not associated with any significant changes in arterial pH (from 7.35±0.03 to 7.36±0.03, p=0.37), PaCO₂ (from 49±3.0 to 49±3.7 mm Hg, p=0.84), or mean SAP (from 60±3.5 to 61±3.4 mm Hg, p=0.31).

Ongoing iNO Therapy

Low-dose iNO (0 to 20 ppm) therapy was continued for between 3 h and 14 days (median, 3 days). During the first 6 h of iNO therapy, the FiO₂ could be weaned from baseline levels in 20 of 25 patients (mean change, −0.11±0.02; range, −0.4 to +0.06, p<0.001) and the MAP reduced in 10 of 23 patients (mean change, −1.3±0.9; range, −13 to +5 cm H₂O, p=0.16).

Changes in ventilator strategy during iNO included administration of surfactant in four patients, changing to HFOV in six patients, and the use of ECMO in six patients. The MetHb levels ranged from 0.2 to 5.5 (median, 1.5%) with ongoing iNO treatment.

Patient Outcome

Overall, 12 patients (40%) survived to discharge from hospital, 9 with ongoing conventional treatment including iNO, and 3 with ECMO support. Among the survivors, the mean time of iNO therapy was 4.3±1.1 days, mean time to extubation was 18.2±2.6 days, and mean time to discharge from hospital was 20±4.1 days. There was no significant association between response to iNO and time to extubation (r=0.08, p=0.8); however, this information was available only in seven patients.

The only baseline index of oxygenation that was significantly different between the survivors and nonsurvivors was the OI (31±5.4 vs 47±4.7, p<0.05), due principally to the differences in the baseline MAP (16±1.7 vs 25±1.8 cm H₂O, p<0.01), since there was no significant difference in baseline FiO₂ (0.98±0.1 vs 0.96±0.2, p=0.9) or PaO₂ (58±3.7 vs 53±3 mm Hg, p=0.72).

There were no significant differences between the survivors and nonsurvivors in age (17.4±7.2 vs 36.5±11.9 months, p=0.35), sex ratio (male:female, 4:8 vs 10:8, p=0.28), days ventilated pre-iNO (6.1±1.8 vs 9.9±3.3 days, p=0.63), baseline P(A-a)O₂ (577±12.6 vs 563±13.3 mm Hg, p=0.61), baseline PaO₂/FiO₂ (57±4 vs 56±2.9, p=0.72), baseline pH (7.36±0.04 vs 7.34±0.03, p=0.47), ARDS vs non-ARDS (66% vs 55%, p=0.71), PH pre-iNO (33% vs 36%, p=0.99), or the use of ECMO support (25% vs 17%, p=0.66).

There was a greater use of surfactant (45%) and HFOV (72%) in the nonsurvivors compared to the survivors (8% and 25%, respectively, p<0.05).

None of the four patients with an underlying immune deficiency survived. The causes of death in the other 14 patients were as follows: 4 died of multisystem organ failure, one despite ECMO support; 3 died of neurologic complications (intracerebral bleeding, hydrocephalus, and myasthenia gravis); 3 died of sepsis (Escherichia coli, Mycoplasma, and staphylococcus septicemia, the latter 2 despite ECMO support); and 4 died who had underlying underlying lung disease with superimposed ALI (2 had CLD following complicated neonatal courses, one had lymphocytic interstitial pneumonitis, and one had cystic adenomatous malformation and pneumonectomy).

Lung histologic study was available only in four patients who died within 3 days of the trial dose of iNO. The postmortem lung histologic findings from case 4 (Table 1), who had a >30% improvement in OI, and case 10, who showed a 15 to 30% improvement in OI, both revealed extensive intra-alveolar hemorrhage and hyaline membrane formation without established interstitial fibrosis. The lung histologic findings from the other two patients, both of whom had a <15% change in OI, showed necrotizing bronchiolitis and extensive alveolar disruption in

FIGURE 2. Acute response to iNO, represented as the percentage change in the OI, in the survivors and nonsurvivors.
one (case 15) and marked lymphoproliferative disease in the other (case 18), the latter from an open lung biopsy carried out the day before the iNO was commenced. Lung histologic study was not available in any of the survivors.

**DISCUSSION**

The results of this study are in keeping with previous reports in the literature showing a short-term improvement in oxygenation and hemodynamics following exposure to iNO, but with there still being a significant mortality (17 to 65%) even among those patients who continue receiving low-dose iNO therapy.9-12,14

The results also show an association between likelihood of survival and magnitude of early response to iNO in terms of improved oxygenation. This supports our hypothesis that a greater early response to iNO would reflect an increased likelihood of lung injury reversibility and thus survival. There was, however, still a high mortality (39%) in those patients with the largest response (>30% improvement in OI), although none of these patients died of acute respiratory failure, but rather of multisystem organ failure, sepsis, underlying immune deficiency, or CLD. This is not surprising when one considers that ARDS is a complex response of the lung to an acute insult with an associated systemic inflammatory response mediated by the host's defense system.19-21

The rationale for using iNO in the treatment of AHRF is based, first, on increasing evidence that the pulmonary endothelium plays a crucial role in the evolution of AHRF.22,23 Injury to the endothelium may result in an inappropriate release of and/or breakdown of endogenous vasodilators, such as endogenous NO, causing ventilation-perfusion mismatch.6 Second, iNO is known to improve ventilation-perfusion matching0,10,14 because of its avid binding to hemoglobin which prevents a spillover effect to nonventilated alveoli. In this sense, iNO would enhance the overall goal of mechanical ventilation by optimizing oxygenation at lower ventilatory pressures and inspired oxygen concentrations. In addition, iNO may potentially dampen the inflammatory response associated with ALI by scavenging toxic radical species such as reactive oxygen species,24 inhibiting xanthine oxidase,25 decreasing neutrophil adhesion,26 and inhibiting platelet aggregation.27

The results of this and other preliminary studies9,10,14 are encouraging in showing that iNO acutely improves oxygenation and, in the short term, allows for a weaning of FiO2 and ventilatory pressures. This, however, has to be interpreted in the light of there not yet being any randomized clinical studies (to our knowledge) demonstrating that iNO improves patient outcome.

This study differs from previous studies in that we sought to review whether the magnitude of the short-term response to iNO might be a useful marker of outcome in AHRF. Other retrospective studies that have attempted to identify positive prognostic indicators of death in ARDS have used parameters such as P(A-a)O2, MAP, and PIP. A P(A-a)O2 in the range of 400 to 470 mm Hg has repeatedly been associated with 80 to 100% mortality in patients treated conventionally without ECMO.1,3,5 The use of PIPs >40 cm H2O and MAPs >23 cm H2O2 has been associated with mortality rates of 81% and 90%, respectively.

In this study, there was no association between increasing baseline P(A-a)O2 and patient outcome. This is not surprising since the P(A-a)O2 does not take into account the mechanical ventilatory pressures being used, which are well known to be major determinants of secondary lung injury. This is further supported by the finding in this study of MAP being the only baseline parameter significantly different in the survivors and nonsurvivors. The worthiness PIP or PEEP as a predictor of outcome in this study could not be assessed because more than half the patients were mechanically ventilated using HFOV. The greater use of HFOV among the nonsurvivors probably reflects our aggressive use of HFOV in patients failing to achieve adequate oxygenation on conventional treatment, rather than the HFOV itself causing an increased mortality.

The advantage of using the early response to iNO as a marker of outcome is that it provides an acute physiologic test of potential ventilation-perfusion mismatch, shunt, and lung injury reversibility in the individual patient. This may be of benefit in selecting specific patients for more invasive and costly therapies such as ECMO; in these patients, there has been an improved reported outcome recently (from 58% pre-1991 to 88% survival after 1991)2; the present selection criteria are diverse and nonspecific.

It was beyond the scope of this study to determine an "ideal" number for the percent change in OI which would definitely reflect potential ventilation-perfusion mismatch, shunt, and lung injury reversibility. Nevertheless, we believe that caution should be exercised in selecting patients for ECMO who have <15% improvement in the OI after exposure to iNO, patients requiring a MAP >50 cm H2O to achieve adequate oxygenation, or patients with an underlying immune deficiency, since all were associated with 100% mortality in the present study, despite the availability of ECMO support. A lack of response to iNO, however, may also reflect an inability to deliver iNO to the alveoli rather than irreversible lung injury. This was not believed to be the case in this study since an aggressive alveoli recruitment strategy was used to
optimize iNO delivery. This is supported by the finding of 100% mortality rate in the nonresponders, even with ECMO support.

Toxicity

We did not experience any untoward effects with MetHb production in the present study that required the discontinuation of the iNO treatment. Although iNO may, as discussed above, be cytoprotective, it is also known to react with superoxide to form peroxynitrite, which is markedly cytotoxic. Studies examining the pro- vs antioxidant effects of iNO are still eagerly awaited.

Conclusion

The clinical role of iNO in AHRF is evolving. This and other preliminary studies showing an acute improvement in oxygenation and hemodynamics with iNO are encouraging. However, not all patients respond to iNO, not all have a sustained response, morbidity and mortality still remain high despite ongoing iNO administration, and the pro- vs antioxidant effects of iNO have yet to be determined. Randomized trials in ARDS patients are therefore urgently required before this promising but unlicensed drug becomes routinely used in the treatment of this potentially lethal disease. The use of iNO as a marker of potential lung injury reversibility is another exciting potential for this selective pulmonary vasodilator.

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