Additive Effect of Nitric Oxide Inhalation on the Oxygenation Benefit of the Prone Position in the Adult Respiratory Distress Syndrome


Background: The response to inhaled nitric oxide and prone positioning was investigated in 47 patients with adult respiratory distress syndrome to test the hypothesis that inhalation of nitric oxide when in the prone position would result in additive improvement in oxygenation.

Methods: The authors prospectively studied patients of both genders who were 15 to 75 yr old and had adult respiratory distress syndrome confirmed by computed tomography (lung injury score, 3.1 ± 1).

Results: Compared with baseline values in the supine position (T1), inhalation of 10 ppm nitric oxide for 1 h (T2) decreased the mean pulmonary artery pressure from 33 ± 9 mmHg to 28 ± 6 mmHg (P < 0.05; T2 vs. T1) and increased the ratio of the partial pressure of oxygen in arterial blood (P_{A,O_2}) to inspired oxygen concentration (F_{I,O_2}) from 115 (median first quartile [Q1] 97, median third quartile [Q3] 137) to 148 (Q1 132, Q3 196) (P < 0.05; T2 vs. T1). Cessation of nitric oxide brought the values back to baseline (T3). Two hours of prone positioning (T4) significantly increased the P_{A,O_2}/F_{I,O_2} ratio (T4 vs. T3). However, after an additional hour of nitric oxide inhalation in the prone position (T5), a significant decrease of the venous admixture (from 33 ± 6% to 25 ± 6%; P < 0.05) and an increase of the P_{A,O_2}/F_{I,O_2} ratio (from 165 [Q1 129, Q3 216] to 199 [Q1 178, Q3 316] [P < 0.05; T5 vs. T4]) were observed.

Conclusions: In patients with isolated severe adult respiratory distress syndrome, inhalation of nitric oxide in the prone position significantly improved oxygenation compared with nitric oxide inhalation in the supine position or in the prone position without nitric oxide. The combination of the prone position with nitric oxide inhalation in the treatment of severe adult respiratory distress syndrome should be considered. (Key words: ARDS treatment algorithm; body positioning; pulmonary hypertension; right ventricular ejection fraction.)

Despite recent progress, the overall mortality rate for adult respiratory distress syndrome (ARDS) remains disturbingly high at approximately 50%. No therapy that specifically reduces or prevents the severe inflammatory reaction of acute lung injury has been introduced into clinical practice. The mainstay of therapy to maintain sufficient arterial oxygenation is mechanical positive-pressure ventilation. There is considerable evidence that the use of high peak-airway pressures 2 and high inspired oxygen concentrations (F_{I,O_2}) 3 perpetuates and exacerbates acute lung injury and may contribute to the continued poor outcome of patients with ARDS. Approaches to the therapy of ARDS therefore focus on means to limit peak-airway pressures and F_{I,O_2}. These include pressure-limited ventilation modes with inverse-ratio ventilation, 5 permissive hypercapnia, 6,7 and dehydration. 8

Two other interventions in ARDS that have received considerable attention include the prone position and inhaled nitric oxide. The beneficial effects of the prone position on arterial oxygenation in acute lung injury have been known for many years, 9 but new reports of its dramatic effect on oxygenation continue to appear. 10 The mechanism has been considered to be enhanced matching of perfusion to ventilation when dependent, atelectatic lung zones are moved to the dorsal position. 11 but recent evidence suggests that the situation may be considerably more complex. 12 Nitric oxide, a potent

*Assistant Professor and Intensive Care Unit Director, University of Vienna.
†Anesthesiology Resident, University of Vienna.
‡Research Assistant, Department of Medical Computer Sciences, University of Vienna.
§Associate Professor, Department of Anesthesiology, College of Physicians and Surgeons, Columbia University.

Received from the Department of Anesthesiology and General Intensive Care and the Department of Medical Computer Sciences, University of Vienna, Vienna, Austria, and the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York. Submitted for publication January 6, 1998. Accepted for publication July 27, 1998. Supported in part by Messer Griesheim, Gumpoldskirchen, Austria. Presented in part at the 1994 annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 17, 1994.

Address reprint requests to Dr. Germann, Department of Anesthesiology and General Intensive Care, Währinger Gürtel 18—20, A-1090 Vienna, Austria. Address electronic mail to peter.germann@univie.ac.at

Anesthesiology, V 89, No 6, Dec 1998
endothelial-derived vasodilator, has unique actions when inhaled as a gas by patients with ARDS. Because it is directed to the best-ventilated lung areas, the resultant vasodilation may decrease the ventilation-perfusion mismatch and intrapulmonary shunt and improve oxygenation. Nitric oxide avidly binds to hemoglobin and is thereby inactivated. Thus, its vasodilator activity is confined to the pulmonary circulation, decreasing elevated pulmonary vascular resistance without systemic hypotension, with beneficial effects on right ventricular ejection fraction. With the exception of mild methemoglobinemia, clinically important side effects have not been reported when nitric oxide is administered in concentrations less than 50 ppm.

Therefore, we designed a study to determine whether nitric oxide inhalation could further enhance the beneficial effects of prone positioning on gas exchange and pulmonary hemodynamics in patients with isolated, severe ARDS.

Materials and Methods

The study protocol was approved by our institutional ethical committee, and written informed consent was obtained from each patient’s next of kin. We prospectively studied 47 patients (30 male, 17 female) who were 37 ± 16 yr old (mean ± SD). Patients were enrolled in the study if they had a diagnosis of new onset of severe ARDS (according to the European American Consensus Conference criteria) confirmed by computed tomography of the lung that revealed patchy and lobar infiltrates, a pulmonary artery occlusion pressure less than 18 mmHg, a Murray lung injury score15 more than 2.5, and in whom ARDS was the cause of primary organ failure. During a 2 yr period, 47 patients fulfilled the entrance criteria. The mean lung injury score was 3.1 ± 1, the APACHE II score was 17 ± 6, and the mean total intensive care unit duration of stay was 28 ± 19 days. The cause of ARDS was intrapulmonary in 33 cases (16 lung contusion, 11 pneumonia, 3 aspiration, 2 bronchial-olitis obliterans obstructive pneumonia, and 1 near drowning) and extrapulmonary in 14 cases (7 poly-trauma, 3 pancreatitis, 2 massive transfusion, and 2 sepsis).

All patients required mechanical ventilation (Evita 2; Dräger, Lübeck, Germany) in a pressure-controlled mode. The ventilatory settings were respiratory rate, 18 ± 4 breaths/min; tidal volume, 8.1 ± 1.5 ml/kg; inspiration: expiration ratio, 1.1 ± 0.7; peak inspiratory pressure, ≤ 35 cm water; positive end-expiratory pressure, 10 to 15 cm water; and FIO₂, 0.75 to 0.95 to attain an arterial oxygen saturation rate ≥ 90%. These settings were not altered for the duration of the study. All patients were deeply sedated with midazolam and sufentanil, and muscle relaxation was provided with vecuronium. Patients were monitored continuously by electrocardiography, peripheral oxygen saturation (SpO₂; CareVue 9000; Hewlett-Packard, Böblingen, Germany) and indwelling peripheral arterial catheter. A 7.5-French fiberoptic pulmonary artery catheter (REF-Sat; Baxter, Irvine, CA) was placed via the internal jugular vein.

Cardiogenic (dobutamine) or vasoactive (dopamine, norepinephrine) drugs (or both) were used during the initial phase of stabilization to maintain mean arterial pressure more than 70 mmHg and cardiac index more than 3.5 l·min⁻¹·m⁻², and dosages were not changed during the study itself. Directly measured hemodynamic indices included heart rate, mean arterial pressure, mean pulmonary artery pressure, and pulmonary artery occlusion pressure. Cardiac output was measured by the thermodilution technique and expressed as the mean of four injections of 10 ml saline at 5°C. Right ventricular ejection fraction was derived from the REF-Sat catheter. Systemic and pulmonary vascular resistance indices were calculated according to standard formulas. Arterial (Patm) and mixed venous (PvO₂) oxygen tensions were measured using standard blood gas electrodes (AVL 995-Hb; AVL, Graz, Austria), and the total hemoglobin concentration, hemoglobin oxygen saturation, and methemoglobin levels were measured using spectrophotometry (AVL 912; AVL). The ratio of the partial pressure of arterial oxygen (Pao₂) and the FiO₂ was used as a parameter for arterial oxygenation because the admixture of nitric oxide/N₂ gas decreases the actual FiO₂. FiO₂ was kept constant with the aid of an oxygen analyzer (Oxydig 16; Draeger, Lübeck, Germany) placed immediately proximal to the patient’s endotracheal tube. Hemodynamic variables (pulmonary and systemic vascular resistance indices, right ventricular ejection fraction, cardiac index) and the venous admixture were calculated using a cardiac output computer (Explorer; Baxter) and a pressure monitoring kit (Baxter) according to standard formulas.

Delivery and analysis of nitric oxide was provided by a newly developed system (Pulmonox; Messer-Griesheim, Gumpoldskirchen, Austria). The device electronically controls the flow of nitric oxide to decrease the concentration from 900 ppm in the tank to the concentration desired at the airway. It adapts to
the gas flow of the mechanical ventilator to ensure nitric oxide delivery during the inspiratory phase of the respiratory cycle. Continuous analysis of the concentration in parts per million of nitric oxide and nitric oxide degradation products was performed using the chemiluminescence detection method (ECO Physics, D"{u}nten, Switzerland). Gas samples were withdrawn a short distance proximal to the patient’s endotracheal tube, ensuring that a length of 50 cm was maintained between nitric oxide instillation and withdrawal of gas for analysis.

Figure 1 summarizes the study design. Measurements and calculations were performed with the patient in the supine position 6 h after initial stabilization (T1), after 1 h inhalation of 10 ppm nitric oxide in the supine position (T2), after 1 h with nitric oxide off in the supine position (T3), after 2 h in the prone position (T4), and after 1 h inhalation of 10 ppm nitric oxide in the prone position (T5). A patient was defined as a responder if the PaO$_2$/FiO$_2$ increased by 20% from baseline.

Statistical Analysis

Values are expressed as the mean ± SD. In the case of the PaO$_2$/FiO$_2$ ratio, the first median quartile (Q1) and the third median quartile (Q3) are used for description because of the skewed distribution of the ratio. Treatment effects are reported as the mean of the values in the respective groups. Analysis of variance (randomized block design)$^{17}$ was used to assess the independent effect of nitric oxide inhalation and positioning (supine or prone) on oxygenation and pulmonary hemodynamics. Because of the skewed distribution, log-transformed values of the PaO$_2$/FiO$_2$ ratio are used for analysis. A P value < 0.05 was considered significant.

Results

Of 47 patients, 4 died of multiple-organ failure while in the intensive care unit.

Table 1 shows the measurements made during the study. The inhalation of 10 ppm nitric oxide in the supine position induced a significant change in several parameters compared with control (T2 vs T1): the venous admixture decreased by 16%, the PaO$_2$/FiO$_2$ ratio increased by 37%, the mean pulmonary artery pressure decreased by 15%, the pulmonary vascular resistance index decreased by 16%, and the right ventricular ejection fraction increased by 20%. After termination of nitric oxide inhalation, all these parameters returned toward baseline values (T3 vs T1). Prone positioning (T4 vs T3) caused a significant 35% increase in the PaO$_2$/FiO$_2$ ratio. However, mean pulmonary artery pressure, pulmonary vascular resistance, right ventricular ejection fraction, and venous admixture did not change significantly. The inhalation of 10 ppm nitric oxide in the prone position yielded significant changes in several parameters compared with the prone position without nitric oxide inhalation (T5 vs T4). Venous admixture decreased by 21%, mean pulmonary artery pressure decreased by 16%, pulmonary vascular resistance index decreased by 15%, and right ventricular ejection fraction increased by 19%. In addition, the PaO$_2$/FiO$_2$ ratio increased by 40% compared with that achieved by the prone position alone. Systemic hemodynamic indices (heart rate, mean arterial pressure, cardiac index, and systemic vascular resistance index) did not change at any of the study time points. Methemoglobin levels were measured before the end of the procedure and never exceeded 0.8%.

As a first step, we performed within-group analyses of variance, which are tests of the overall therapeutic effect of nitric oxide inhalation. We found a significant effect of nitric oxide on the PaO$_2$/FiO$_2$ ratio, independent of body positioning. As a second step, we tested for an interaction between nitric oxide and positioning. No statistical significance was found related to this interaction. We interpreted these results to indicate that nitric oxide effect is independent of supine or prone positioning, and that the significant difference in the PaO$_2$/FiO$_2$ ratio at T5 vs T4 represents an additive effect of nitric oxide and positioning (table 2).

Discussion

Gattinoni et al.$^{18}$ were the first to observe that lung density on computed tomographic images in supine patients with acute respiratory failure is frequently maxi-
Table 1. Systemic and Pulmonary Hemodynamics and Oxygenation

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
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<tbody>
<tr>
<td>HR</td>
<td>105 ± 18</td>
<td>102 ± 16</td>
<td>100 ± 17</td>
<td>103 ± 14</td>
<td>101 ± 17</td>
</tr>
<tr>
<td>MAP</td>
<td>72 ± 11</td>
<td>75 ± 12</td>
<td>76 ± 10</td>
<td>82 ± 9</td>
<td>84 ± 11</td>
</tr>
<tr>
<td>CI</td>
<td>3.9 ± 0.8</td>
<td>4.3 ± 1.3</td>
<td>4.0 ± 1.2</td>
<td>4.1 ± 1.0</td>
<td>4.3 ± 1.2</td>
</tr>
<tr>
<td>SVRI</td>
<td>1,281 ± 215</td>
<td>1,328 ± 264</td>
<td>1,343 ± 378</td>
<td>1,399 ± 386</td>
<td>1,473 ± 401</td>
</tr>
<tr>
<td>REF</td>
<td>35 ± 9</td>
<td>42 ± 10*</td>
<td>35 ± 8</td>
<td>37 ± 8</td>
<td>44 ± 6*§</td>
</tr>
<tr>
<td>MPAP</td>
<td>33 ± 9</td>
<td>28 ± 6*</td>
<td>31 ± 7</td>
<td>32 ± 9</td>
<td>27 ± 7*§</td>
</tr>
<tr>
<td>PVRI</td>
<td>370 ± 105</td>
<td>309 ± 70*</td>
<td>366 ± 84</td>
<td>349 ± 128</td>
<td>298 ± 70*§</td>
</tr>
<tr>
<td>Qs/Qt</td>
<td>37 ± 6</td>
<td>31 ± 6*</td>
<td>35 ± 6</td>
<td>33 ± 6*</td>
<td>25 ± 6*§</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>115 (97,137)</td>
<td>148 (132,192)*</td>
<td>119 (105,146)</td>
<td>165 (129,216)*</td>
<td>199 (178,316)*; t§</td>
</tr>
<tr>
<td>PaCO2</td>
<td>40 ± 4</td>
<td>39 ± 5</td>
<td>41 ± 5</td>
<td>43 ± 6</td>
<td>43 ± 5</td>
</tr>
</tbody>
</table>

Values are mean ± SD except for PaO2/FIO2; median (quartiles: Q1, Q3); n = 47.

T1 = after 6 h supine; T2 = after 1 h supine + 10 ppm nitric oxide; T3 = after 1 h supine without nitric oxide; T4 = after 2 h prone; T5 = after 1 h prone + 10 ppm nitric oxide; HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); CI = cardiac index (L·min⁻¹·m⁻²); SVRI = systemic vascular resistance index (dyne·s·cm⁻⁵·m²); REF = right ejection fraction (%); MPAP = mean pulmonary arterial pressure (mmHg); PVRI = pulmonary vascular resistance index (dyne·s·cm⁻⁵·m²); Qs/Qt = venous admixture (%); PaO2/FIO2 = ratio of arterial oxygen tension to inspired oxygen fraction.

* P < 0.05 versus T1.
† P < 0.05 versus T2.
‡ P < 0.05 versus T3.
§ P < 0.05 versus T4.

The inhalation of nitric oxide in ARDS appears to exert its beneficial effects on oxygenation because it is preferentially delivered to areas of better ventilation. There it induces pulmonary vasodilation, enhances ventilation-perfusion matching, and decreases the magnitude of the intrapulmonary shunt. It is rapidly inactivated by hemoglobin, so that its actions are confined to the pulmonary circulation, where it decreases the elevated mean pulmonary artery pressure and right ventricular afterload. These actions may also decrease elevated microvascular filtration pressure and thereby curb accumulation of extravascular lung water. We hypothesized that when used together these two therapies would have an additive effect, by combining the benefit of redistribution of previously atelectatic areas (prone position) with enhancement of ventilation-perfusion matching (nitric oxide). Responders to inhaled nitric oxide are recognized within minutes of its application. Therefore, we designed the study to allow more than enough time.

Table 2. Comparison of NO/Supine (T2 vs. T1) and NO/Prone (T5 vs. T4)

<table>
<thead>
<tr>
<th></th>
<th>T2 vs. T1</th>
<th>T5 vs. T4</th>
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<tbody>
<tr>
<td>PaO2/FIO2</td>
<td>44 ± 24</td>
<td>69 ± 34</td>
</tr>
<tr>
<td>PVRI</td>
<td>−61 ± 48</td>
<td>−51 ± 69</td>
</tr>
</tbody>
</table>

Values are mean of Δ ± SD; n = 47.

PaO2/FIO2 = ratio of arterial oxygen tension to inspired oxygen fraction; PVRI = pulmonary vascular resistance index (dyne·s·cm⁻⁵·m²).
ADDITIVE EFFECT OF NO TO OXYGENATION IN PRONE POSITION

(1 h after nitric oxide exposure—cessation, 2 h after prone positioning) for stabilization at each setting.

Administration of 10 ppm nitric oxide to our patients in the supine position induced a significant improvement in oxygenation and pulmonary hemodynamics (Table 1). The prone position by itself provided a similar improvement in oxygenation, although pulmonary hemodynamics were relatively unaffected. When nitric oxide was inhaled in the prone position, a further significant improvement in oxygenation followed, with a 21% decrease in venous admixture and a significant increase in the PaO\textsubscript{2}:FiO\textsubscript{2} ratio (Table 2). In addition the beneficial effects of nitric oxide on pulmonary vascular resistance and mean pulmonary artery pressure were realized. We suggested that the observed improvement in oxygenation and pulmonary hemodynamics from T3 (supine, nitric oxide off) to T5 (prone, with nitric oxide inhalation) represents a clinical scenario in which the benefit of prone positioning is enhanced by the addition of inhaled nitric oxide.

The notion of combining two or more interventions in ARDS is not new and certainly reflects current clinical practice. One such approach is to combine inhaled nitric oxide with a vasoconstrictor. Almitrine bimesylate, a selective pulmonary arterial vasoconstrictor, has been shown to have an additive effect with inhaled nitric oxide on arterial oxygenation in ARDS.24

Jolliet et al.19 found that combining nitric oxide, prone positioning, and almitrine bimesylate improved oxygenation in a small group of patients. Approximately 60% of our patients responded to prone positioning, compared with 85% of patients in our study. Their lower response rate may be explained by the finding that, in their group of 12 patients, 8 died and most patients were in a state of severe immunosuppression (e.g., they had received bone marrow transplants or had Pneumocystis carinii pneumonia). Chatte et al.25 in a series of 32 consecutive patients, observed a positive response to prone positioning (PaO\textsubscript{2}:FiO\textsubscript{2} ratio increased by > 20) in 78% of their patients. This is comparable to the response rate in our population, although we used a threshold of a 20% increase in the PaO\textsubscript{2}:FiO\textsubscript{2} ratio as an index of response.

Our study shows that in patients with severe isolated ARDS the combination of nitric oxide inhalation with the prone position offers a greater improvement in oxygenation than either treatment used alone. Nitric oxide also provides a favorable effect on pulmonary hemodynamics, which is not accomplished by using the prone position alone. Improved oxygenation can allow a decrease in high FiO\textsubscript{2} and airway pressures, thus potentially reducing the risk of oxygen toxicity and barotrauma. Pulmonary vasodilation induced by nitric oxide facilitates permissive hypercapnia by minimizing its effect on pulmonary vascular resistance. Furthermore, the combination of the prone position with inhaled nitric oxide could help to decrease the necessary dose of nitric oxide, with its potential for the accumulation of toxic proinflammatory degradation products, such as nitrogen dioxide.26-28

The major limitation of this study lies in its relatively short duration, therefore long-term conclusions about outcomes cannot be drawn. Indeed, there is no conclusive evidence that either inhaled nitric oxide or the prone position decrease the morbidity and mortality rates associated with ARDS. Although the prone position appears to be a relatively simple intervention, it necessitates skilled nursing and vigilance to prevent "disconnects" or pressure injury. Nonetheless, Albert29 suggests that “complications severe enough to raise concerns about employing [it] occur infrequently." A second limitation is that the effect of the time course of the disease could not be tested. Although disease progression or improvement is unlikely to have been a factor during the relatively short time course of this study and is supported by the finding that there were no significant differences in parameters between T1 (supine control) and T3 (supine, 2 h later), it cannot be completely discounted.

Statistical analysis of our data revealed a significant effect of nitric oxide on the PaO\textsubscript{2}:FiO\textsubscript{2} ratio, independent of body placement in the supine or prone position. This suggests that the significant increase in PaO\textsubscript{2}:FiO\textsubscript{2} from T4 (prone position without nitric oxide inhalation) to T5 (prone position with nitric oxide inhalation) represents an additive effect of nitric oxide on the enhancement of oxygenation by the prone position in patients with ARDS.

In patients with severe ARDS, clinicians should consider combining nitric oxide inhalation with the prone position, even if an improvement in oxygenation has already been achieved by using one of these measures used alone. Our data further emphasize the notion that it is unlikely that a single treatment modality will cost-effectively alter outcome in ARDS. Rather, it appears to be prudent for us to develop coherent treatment algorithms for ARDS in which different interventions are added in a methodical and rational sequence. Future investigations of the management of severe ARDS should evaluate such combined treatment algorithms and monotherapy.

Anesthesiology, V 89, No 6, Dec 1998
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