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

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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 (Pa_{O_2}) to inspired oxygen concentration (FI_{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 Pa_{O_2}:FI_{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 Pa_{O_2}:FI_{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%.[1] 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 (FI_{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 FI_{O_2}.[4] 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

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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.[13] 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.[14] 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 score[15] 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 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 bronchiolitis obliterans obstructive pneumonia, and 1 near drowning) and extrapulmonary in 14 cases (7 polytrauma, 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 $F_{I_{O_2}}$, 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 (Sp_{O_2}; 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.

Cardiotonic (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 $l \cdot min^{-1} \cdot m^{-2}$, 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 (Pa_{O_2}) and mixed venous (Pv_{O_2}) 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 (Pa_{O_2}) and the $F_{I_{O_2}}$ was used as a parameter for arterial oxygenation because the admixture of nitric oxide/N_2 gas decreases the actual $F_{I_{O_2}}$. $F_{I_{O_2}}$ was kept constant with the aid of an oxygen analyzer (Oxydig^R, 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).[16] 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

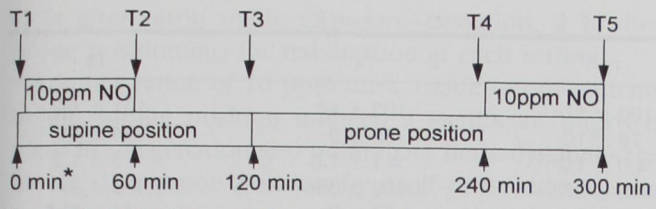

Fig. 1. Study design and time course. T1: supine position, 6 h after initial stabilization. T2: supine position, after 1 h of inhalation of 10 ppm nitric oxide. T3: supine position, after 1 h with nitric oxide turned off. T4: after 2 h in the prone position. T5: prone position, after 1 h of inhalation of 10 ppm nitric oxide. NO = nitric oxide.

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 chemoluminescence detection method (ECO Physics, Dürnten, 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 Pa_{O_2}:FI_{O_2} increased by 20% from baseline.

Statistical Analysis

Values are expressed as the mean ± SD. In the case of the Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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

	T1	T2	T3	T4	T5
HR	105 ± 18	102 ± 16	100 ± 17	103 ± 14	101 ± 17
MAP	72 ± 11	75 ± 12	76 ± 10	82 ± 9	84 ± 11
CI	3.9 ± 0.8	4.3 ± 1.3	4.0 ± 1.2	4.1 ± 1.0	4.3 ± 1.2
SVRI	1,281 ± 215	1,328 ± 264	1,343 ± 378	1,399 ± 366	1,473 ± 401
REF	35 ± 9	42 ± 10*	35 ± 8	37 ± 8	44 ± 6*,§
MPAP	33 ± 9	28 ± 6*	31 ± 7	32 ± 9	27 ± 7*,§
PVRI	370 ± 105	309 ± 70*	366 ± 84	349 ± 128	298 ± 70*,§
Qs/Qt	37 ± 6	31 ± 6*	35 ± 6	33 ± 6*	25 ± 6*,†,§
Pa_{O_2}/FI_{O_2}	115 (97,137)	148 (132,192)*	119 (105,146)	165 (129,216)*,‡	199 (178,316)*,†,§
Pa_{CO_2}	40 ± 4	39 ± 5	41 ± 5	43 ± 6	43 ± 5

Values are mean ± SD except for Pa_{O_2}/FI_{O_2}: 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 ($L \cdot min^{-1} \cdot m^{-2}$); SVRI = systemic vascular resistance index ($dyne \cdot s \cdot cm^{-5} \cdot m^2$); REF = right ejection fraction (%); MPAP = mean pulmonary arterial pressure (mmHg); PVRI = pulmonary vascular resistance index ($dyne \cdot s \cdot cm^{-5} \cdot m^2$); Qs/Qt = venous admixture (%); Pa_{O_2}/FI_{O_2} = 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.

mal in the dorsal (*i.e.*, dependent) zone. When patients were turned from the supine to the prone position, the lung density ultimately redistributed from the dorsal to the ventral component. This suggested that the improvement in oxygenation in ARDS observed with assumption of the prone position results from decompression of dependent lung regions previously compressed by overlying lung structures, which then improves ventilation–perfusion matching. However, a beneficial effect is not observed in all cases,[11] and it has been speculated that the true benefit of the prone position is that it creates a transpulmonary pressure sufficient to exceed the airway opening pressure in dorsal lung regions.[12] In ARDS, the prone position induces redistribution of lung density, regardless of whether patients respond with improvement arterial oxygenation.[11,18] Thus, it remains speculative whether the beneficial effect on arterial oxygenation results from redistribution of blood flow to nonatelectatic lung regions, recruitment of previously atelectatic lung areas, or more efficient bronchial drainage.[18]

Regardless of its mechanism, it appears to be appropriate to turn patients who have ARDS to the prone position and observe their responses. If improvement in oxygenation does occur—and in most cases it will within 30 min of the time when the prone position is assumed[19]—it allows a decrease in high levels of FI_{O_2}, airway pressure, or both. As also described by Friedrich *et al.*,[20] most of the improvement in oxygenation occurs within the first hour after the patient is turned to the prone position.

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.[13] 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[21] and right ventricular afterload.[14] These actions may also decrease elevated microvascular filtration pressure[22] and thereby curb accumulation of extravascular lung water.[23] 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)

	T2 *vs.* T1	T5 *vs.* T4
Pa_{O_2}/FI_{O_2}	44 ± 24	69 ± 34
PVRI	−61 ± 48	−51 ± 69

Values are mean of Δ ± SD; n = 47.

Pa_{O_2}/FI_{O_2} = ratio of arterial oxygen tension to inspired oxygen fraction; PVRI = pulmonary vascular resistance index ($dyne \cdot s \cdot cm^{-5} \cdot m^2$).

(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 Pa_{O_2}:FI_{O_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 bismesylate, 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 bismesylate 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 (Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 FI_{O_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, Albert[29] 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 Pa_{O_2}:FI_{O_2} ratio, independent of body placement in the supine or prone position. This suggests that the significant increase in Pa_{O_2}:FI_{O_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.

References

1. Suchyta MR, Clemmer TP, Orme JFJ, Morris AH, Elliott CG: Increased survival of ARDS patients with severe hypoxemia (ECMO criteria). Chest 1991; 99:951–5

2. Kolobow T, Moretti MP, Fumagelli R, Mascheroni D, Prato P, Chen V, Joris M: Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. Am Rev Respir Dis 1987; 135:312–15

3. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 1967; 276:368–74

4. Rossaint R, Lewandowski K, Pappert D, Slama K, Falke K: Die Therapie des ARDS. Anaesthesist 1994; 43:298–308

5. Gurevitch MJ, Van-Dyke J, Young ES, Jackson K: Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome. Treatment with inverse ratio ventilation. Chest 1986; 89:211–13

6. Hickling KG, Henderson SJ, Jackson R: Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intens Care Med 1990; 16:372–7

7. Pesenti A: Target blood gases during ARDS ventilatory management. Intensive Care Med 1990; 16:349–51

8. Petty TL: Acute respiratory distress syndrome (ARDS). Dis Month 1990; 36:1–58

9. Bryan AC: Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis 1974; 110:143–4

10. Mure M, Martling CR, Lindahl SGE: Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. Crit Care Med 1997; 25:1539–44

11. Langer M, Mascheroni D, Marcolin R, Gattinoni L: The prone position in ARDS patients. A clinical study. Chest 1988; 94:103–7

12. Lamm WJE, Graham MM, Albert RK: Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 1994; 150:184–93

13. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM: Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993; 328:399–405

14. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM: Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 1991; 83:2038–47

15. Murray JF, Mathey MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720–3

16. Krebs C, Escuyer M, Urak G, Zimpfer M, Germann P: Technological basis for NO application and environmental security. Acta Anaesth Scand 1996; 40(Suppl 109):84–7

17. Kirk RE: Experimental Design-Procedures for the Behavioral Sciences. Belmont, CA, Brooks/Cole Publishing Company, 1982

18. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D: Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. ANESTHESIOLOGY 1991; 74:15–23

19. Jolliet P, Bulpa P, Ritz M, Ricou B, Lopez J, Chevrolet JC: Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in acute respiratory distress syndrome. Crit Care Med 1997; 25:786–94

20. Friedrich P, Krafft P, Hochleuthner H, Mauritz W: The effects of long-term prone positioning in patients with trauma-induced adult respiratory distress syndrome. Anesth Analg 1996; 83:1206–11

21. Frostell CG, Blomquist H, Hedenstierna G, Lundberg J, Zapol WM: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. ANESTHESIOLOGY 1993; 78:427–35

22. Brigham KL, Woolverton WC, Blake LH, Staub LH: Increased sheep lung vascular permeability caused by pseudomonas bacteremia. J Clin Invest 1974; 54:792–804

23. Erdmann AJ 3d, Vaughan TR Jr, Brigham KL, Woolverton WC, Staub NC: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ Res 1975; 37:271–84

24. Wysocki M, Delclaux C, Roupie E, Langeron O, Liu N, Herman B, Lemaire F, Brochard L: Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. Crit Care Med 1994; 20:254–9

25. Chatte G, Sab JM, Dubois JM, Sirodot M, Gaussorgues P, Robert D: Prone position in mechanically ventilated patients with severe acute respiratory failure. Am J Respir Crit Care Med 1997; 155:473–8

26. Oda H, Nogami H, Kusumoto S: Long-term exposure to nitric oxide in mice. J Jpn Soc Air Pollut 1976; 11:150–60

27. Moncada S, Palmer RM, Higgs EA: Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991; 43:109–42

28. Hugod C: Effect of exposure to 43 ppm nitric oxide and 3.6 ppm nitrogen dioxide on rabbit lung. Int Arch Occup Environ Health 1979; 42:159–67

29. Albert RK: The prone position in acute respiratory distress syndrome: where we are, and where do we go from here [Editorial]. Crit Care Med 1997; 25:1453–4