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Combined Effects of Inhaled Nitric Oxide and a Recruitment Maneuver in Patients with Acute Respiratory Distress Syndrome

Kwang Joo Park[1], Young Joo Lee[2], Yoon Jung Oh[1], Keu Sung Lee[1], Seung Soo Sheen[1], and Sung Chul Hwang[1]

Departments of [1]Pulmonology and [2]Anesthesiology, Ajou University School of Medicine, Suwon, Korea.

Nitric oxide (NO) inhalation therapy has been employed in the management of acute respiratory distress syndrome (ARDS), in order to improve oxygenation. Several factors have been implicated as being responsible for the action of inhaled NO. Alveolar recruitment methods, such as prone positioning and a sufficient positive end expiratory pressure (PEEP), have been identified as having a positive impact on the NO response. A Recruitment maneuver (RM) was introduced for the treatment of ARDS, along with a lung protective strategy. Here, we hypothesized that a RM may further augment the oxygenation of patients treated with NO inhalation. Therefore, the effects of the inhalation of NO, either in combination with a RM, or separately, were evaluated on patients with ARDS for their enhancing action.

23 patients with ARDS were enrolled, and divided into three groups. The patients in group 1 (n=11) were treated with 5 ppm NO via inhalation, followed by a RM, applying a sustained inflation pressure of 30 - 35 cmH_2O for 30 seconds. Group 2 (n=6) received a RM alone, while group 3 (n=3) was treated with NO inhalation alone. The oxygenation and hemodynamic parameters were obtained prior to, and 2, 12, and 24 h after, the respective treatment procedures.

For group 1, the PaO_2/FiO_2 increased from its initial value of 171.8 $\pm$ 67.8 to 203.2 $\pm$ 90.0 2 h after NO inhalation. Further improvement was noted with the continual application of the RM reaching, 215.5 $\pm$ 74.6 (p=0.05) and 254.2 $\pm$ 109.5 ($p<0.05$), after 12 and 24 h, respectively. Initially 7 of the subjects did not respond to NO inhalation, but 3 of these non-responders changed into responders 12 h after the RM. The changes in the PaO_2/FiO_2 from baseline at each time period were greater in group 1 than in the other groups, but with no statistical significance. The hemodynamics of the patients was not significantly altered during the entire study period.

We conclude that the combined application of NO inhalation and a RM could be beneficial and safe for patients with ARDS, showing an enhancing effect in improvement of oxygenation.

Key Words: ARDS (acute respiratory distress syndrome), nitric oxide inhalation, recruitment maneuver, treatment, oxygenation

INTRODUCTION

Inhaled nitric oxide (NO) has been used in the management of acute respiratory distress syndrome (ARDS) for more than a decade. It has been shown to have beneficial effects in improving oxygenation and reversing pulmonary hypertension through selective pulmonary vasodilation. Significant improvement of oxygenation has been demonstrated in two-thirds of ARDS patients.[1,2]

Individual responses to inhaled NO may vary, and while several factors have been proposed, definite predictors of the response have yet to be defined. It has been reported that hemodynamic parameters, such as pulmonary arterial pressure and cardiac output, affect the response to inhaled NO.[3-5] In addition, the presence of septic shock and the delayed use of NO have been shown to decrease the response.[4] The degree of alveolar recruitment can also affect the oxygenation response, since increasing the alveolar aeration can enhance the action of nitric oxide in dilating the pulmonary vessels and diverting blood flow from collapsed units to ventilating alveoli.

Several studies have reported the impact of

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Reprint address: requests to Dr. Kwang Joo Park, Department of Pulmonology, Ajou University School of Medicine, San 5, Wonchon-dong, Paldal-gu, Suwon 442-749, Korea. Tel: 82-31-219-5121, Fax: 82-31-219-5109, E-mail: parkkj@ajou.ac.kr

alveolar recruitment on the response to NO.[6,7] Prone positioning is a well-known method for alveolar recruitment, and has been shown to significantly improve oxygenation responses.[8-10] Likewise, sufficiently increasing the positive end expiratory pressure (PEEP) can also enhance the effect of NO by recruiting alveoli.[3] A recruitment maneuver (RM) has been introduced, and widely applied, as an effective ventilatory method for the improvement of oxygenation by delivering sustained inflation of the lungs, and thereby recruiting collapsed units. Furthermore, a RM can be considered to be more beneficial with regard to the aspects of the lung protective ventilatory strategy compared with other recruiting methods, such as PEEP or prone positioning.[11-13] The beneficial effect of inhaled NO on oxygenation may be enhanced when combined with a RM, which recruits the maximum number of functioning alveoli. However, there have been no previous reports of simultaneously combining the two modes of therapy in ARDS patient populations.

Therefore, the purpose of our study was to evaluate the effect of combining a RM and NO inhalation therapy for the improvement in oxygenation, and to assure the safety of such treatment in patients with ARDS, compared to the individual therapies alone.

MATERIALS AND METHODS

Subjects

We enrolled 23 patients afflicted with ARDS from various origins. They were admitted to the medical and surgical intensive care units during an 8-month period. ARDS was defined according to the criteria recommended by the American European Consensus Conference.[14] The underlying causes of ARDS were as follows: pneumonia (n=9), sepsis (n=8), trauma (n=4), and aspiration (n=2). Patients with underlying chronic obstructive pulmonary disease and cardiac diseases were excluded. Within 24 h of ARDS onset, Acute Physiology and Chronic Health Evaluation III (APACHE III) and lung injury scores (LIS) were obtained. This study included those patients who were given procedures no later than 2 days after the documented onset of ARDS. The protocol was approved by the hospital ethics committee, and a written consent was obtained from the patients' next of kin.

Protocol

The patients were divided into three groups, although randomization was not fully attained. The initial grouping was performed in a random manner, with twice as many patients assigned to group 1, as we were mainly focusing on the effect of the combined therapy of NO inhalation and a RM. Moreover, the physiological data obtained did not appear to be equally distributed among the three groups. The patients in group 1 (n=11) received a RM 2 h following NO inhalation. Those in group 2 (n=6) were given a RM only, while those in group 3 (n=6) received NO inhalation treatment only. For group 1, the hemodynamic and mechanical parameters were measured, and a blood gas analysis was performed prior to, and 2 h after, NO inhalation. These measurements were repeated 2, 12, and 24 h after the RM. The same assessments were carried out prior to, and 2, 12, and 24 h after, NO inhalation therapy in group 2, and the RM in group 3.

Mechanical ventilation

Mechanical ventilation was performed, using Puritan-Bennett 7200ae (Puritan-Bennett, Carlsbad, CA, U.S.A.) and Evita 2 dura (Dräger Werk, Lübeck, Germany), in a volume-controlled mode, with a tidal volume of 6 ml/kg of ideal body weight. The respiratory rate was 20 - 25/min, and the flow rate and inspiratory time were adjusted individually. The baseline PEEP level was set at 8 cmH_2O, but 5 cmH_2O of PEEP was applied to prevent hypotension in three patients who had shown hemodynamic instability. The PEEP was increased, in increments of 2 cmH_2O, according to the oxygenation response, and was maintained for about 15 min at each increment. The static compliance of the respiratory system (Cstat) was determined from the values displayed on the ventilator monitors, and was calculated as:

[Tidal volume/(Plateau pressure - $PEEP_{total}$)].

The previous PEEP level was resumed if the

Cstat decreased, or the blood pressure dropped, by 15%. The applied PEEP ranged from 8 to 15 cmH_2O. The FiO_2 was kept to a minimum as long as the PaO_2 and SaO_2 were maintained above 60 mmHg and 90%, respectively. Patients were in the supine position. Sedation and neuromuscular blockade were achieved by continuous infusion. The mechanical ventilation parameters were kept constant throughout the study period.

Recruitment maneuver

A RM was performed using the continuous positive airway pressure (CPAP) method, administered only after the respiratory, hemodynamic, and blood gas analysis parameters had been stabile for at least 2 hours. The RM was carried out twice a daily, with a sustained inflation pressure of 30 - 35 cmH_2O, applied for 30 seconds. The initial response was determined 2 h after the procedure. If the initial response was negative, the pressure was increased during the next RM session.

Nitric oxide administration

NOdomo (Däager Werk, Lübeck, Germany) was the device used as for administering the NO. The NO was consistently induced, throughout the study to the patients in groups 1 and 3, through the inspiratory limb of the ventilatory tube, at a concentration of 5 ppm. A positive response to the procedure was defined as a difference in the PaO_2/FiO_2 ratio higher than 20 mmHg compared to the baseline value. In some reports, a change in the absolute value of this ratio has been adopted as a positive response,[9,15] although a percent change is now more commonly used. This criterion was considered more reasonable for inter-group comparison due to the relatively wide variability of PaO_2/FiO_2 in this study.

Measurement of hemodynamic and mechanical parameters

The radial artery of each patient was cannulated. A balloon-tipped pulmonary artery flotation catheter (Edwards Lifesciences, Irvine, CA, U.S.A.) was placed in 13 patients (7 patients in group 1), and connected to Vigilance^{TM} (Edwards Lifesciences, Irvine, CA, U.S.A.), which is a continuous cardiac output monitoring system. Using this monitoring device, the arterial blood pressure, central venous pressure, pulmonary arterial pressure, pulmonary arterial occlusion pressure, and cardiac output were serially measured. The Cstat was also serially determined.

Statistical analysis

All the results are expressed as the mean ± SD (unless otherwise specified). The data analysis was performed using the statistical software package SPSS 8 (Statistics Package for Social Sciences, Chicago, IL, U.S.A.). The Mann-Whitney U test was used to compare values between groups, while the Wilcoxon signed rank test was used for the analysis of differences along the time course for the same group in paired samples. Significant differences were considered at $p < 0.05$.

RESULTS

Clinical data

Table 1 shows the general clinical data of the

Table 1. Clinical Data of Patients with Acute Respiratory Distress Syndrome

	No. of patients	Age	PaO_2/FiO_2 (mmHg), initial	APACHE III score	LIS	PEEP (cmH_2O)	Mortality
Group 1 (NO+RM)	11	52 ± 17	140.1 ± 27.1	59 ± 27	3.0 ± 0.5	10.4 ± 1.2	4
Group 2 (RM)	6	50 ± 20	162.2 ± 19.2	52 ± 16	2.3 ± 0.7	11.5 ± 2.0	2
Group 3 (NO)	6	59 ± 13	104.9 ± 14.0	67 ± 14	2.7 ± 0.5	8.2 ± 2.8	4

APACHE III, Acute Physiology and Chronic Health Evaluation III; LIS, lung injury score; PEEP, positive end expiratory pressure; NO, nitric oxide; RM, recruitment maneuver.

patients. All patients received the procedures within a 48 h period following the onset of ARDS, with the duration of mechanical ventilation set at less than 48 h.

Evolution of PaO_2/FiO_2 in each group

For group 1, application of NO alone caused no significant PaO_2/FiO_2 change (171.8 ± 67.8 to 203.2 ± 90.0 at 2 h). The PaO_2/FiO_2 2 h after application of the RM was 207.7 ± 87.5, also showing no significant change. However, 12 h after the RM, the PaO_2/FiO_2 climbed to 215.5 ± 74.6 (p=0.05), and eventually reached the statistically significant level of 254.2 ± 109.5 at 24 h (p< 0.05; Fig. 1). On the other hand, while the patients in group 2 showed a gradual increase in the PaO_2/FiO_2 following the RM, the overall magnitude was less than in group 1. Group 3 showed an initially abrupt increase prior to a steady state being attained (Table 2). The changes in the PaO_2/FiO_2 from the baseline were compared between the three groups at 2, 12, and 24 h following the procedures. For group 1, the changes in the PaO_2/FiO_2 from the baseline gradually increased, and although the magnitudes were greater than in groups 2 and 3, it did not reach statistical significance (Fig. 2).

Number of responders after NO inhalation and RM

Of the 11 patients in group 1, there were 4 responders and 7 non-responders following NO inhalation. 12 h after the RM, 3 out of the 7 non-responders became responders, while 1 of the 4 responders became a non-responder.

Hemodynamic and mechanical changes

The blood pressure, heart rate, central venous pressure, pulmonary arterial pressure, pulmonary

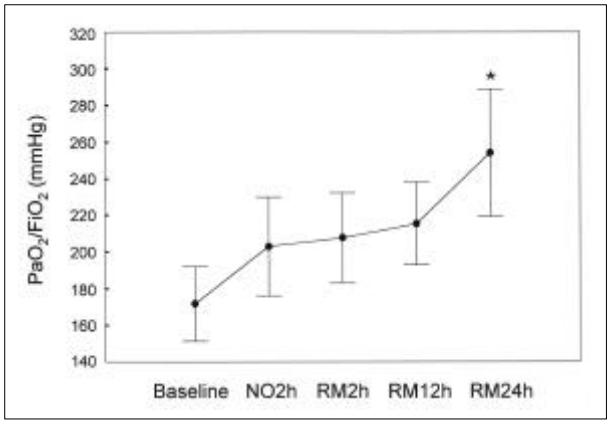

Fig. 1. Serial values of the PaO_2/FiO_2 ratio of ARDS patients that received sequential nitric oxide inhalation and a recruitment maneuver along the time course. Values are expressed as mean ± SEM. (NO2h=2 h after NO inhalation, RM2h=2 h after a RM, RM12h=12 h after a RM, RM24h=24 h after a RM) *p<0.05 vs. baseline.

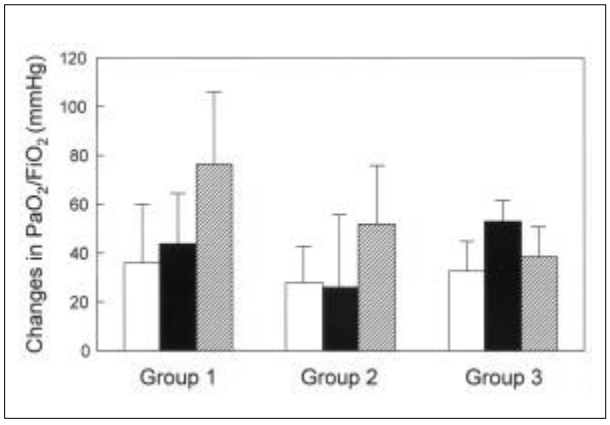

Fig. 2. Changes in the PaO_2/FiO_2 ratio from the baseline values at 2 (blank bar), 12 (solid bar), and 24 h (hatched bar) after the procedures in each group. Values are expressed as mean + SEM.

Table 2. Values of PaO_2/FiO_2 (mmHg) at the Baseline, and 2, 12, and 24 h after the Procedures in Each Group

	Baseline	2 h	12 h	24 h
Group 1	171.8 ± 67.8	207.7 ± 81.5	215.5 ± 74.6	254.2 ± 109.5*
Group 2	196.1 ± 61.9	223.8 ± 79.4	222.2 ± 98.2	247.8 ± 89.1
Group 3	80.0 ± 21.1	108.5 ± 26.2	130.0 ± 48.1	115.5 ± 49.1

*p<0.05 vs. baseline.

Table 3. Serial Hemodynamic and Mechanical Data on Patients in Group 1 along the Time Course

	Baseline	NO 2 h	RM 2 h	RM 12 h	RM 24 h
MBP (mmHg)	77 ± 10	88 ± 17	85 ± 12	84 ± 14	90 ± 14
HR (/min)	108 ± 15	109 ± 12	108 ± 17	110 ± 17	105 ± 20
PVRI (dyn×s×cm^{-5}/m^2)	241 ± 63	259 ± 81	201 ± 67	226 ± 27	234 ± 75
SVRI (dyn×s×cm^{-5}/m^2)	1040 ± 323	1079 ± 227	1002 ± 277	1364 ± 787	1407 ± 540
MPAP (mmHg)	28.6 ± 7.2	31.3 ± 5.3	29.9 ± 5.2	28.0 ± 6.1	27.0 ± 4.5
PAOP (mmHg)	13.6 ± 4.4	14.9 ± 3.4	16.6 ± 4.1	16.3 ± 3.8	14.8 ± 3.0
CI (L/min/m^2)	5.1 ± 1.4	4.8 ± 1.4	5.6 ± 1.7	4.0 ± 1.3	4.7 ± 1.0
Cstat (mL/cmH_2O)	26.4 ± 8.6	27.9 ± 9.7	29.0 ± 9.7	30.9 ± 8.5*	38.9 ± 2.2†

NO 2 h, 2 h after NO inhalation; RM 2 h, 2 h after a RM; RM 12 h, 12 h after a RM, RM 24 h, 24 h after a RM; MBP, mean blood pressure; HR, heart rate; PVRI, pulmonary venous resistance index; SVRI, systemic venous resistance index; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; Cstat, static compliance of the respiratory system.
*$p<0.05$ vs. baseline; $^{\dagger}p<0.01$ vs. baseline.

artery occlusion pressure, and cardiac index were not significantly changed throughout the treatments in all 3 groups (not all data shown). During, and towards the end, of the RM, two patients showed mild cases of transient systolic hypotension, but recovered soon after the RM. In group 1, the Cstat significantly improved at 12 and 24 h following the RM. However, no significant changes were noted in the hemodynamic data (Table 3). Pulmonary shunt fractions (Qs/Qt) were 63 ± 20 and 47 ± 10%, before the procedure and at 12 h after the RM in group 1, respectively, but were accurately assessed in only four cases.

DISCUSSION

This study has demonstrated the individual and combined effects of inhaled NO and a RM in the improvement of oxygenation in ARDS patients. Such results were reasonably expected, as the action of inhaled NO could be enhanced by the recruitment of functioning alveoli. Several methods to recruit alveoli have been tried, such as the application of sufficient PEEP and prone positioning, along with inhaled NO to enhance the oxygenation effects.[3,8,9] Although a RM is widely used in recruiting alveoli, there have been no reports, to our knowledge, on the combined effects of NO and a RM.

The results showed that the combined application of NO and a RM was relatively more effective than as standalone methods, showing a gradual increase, and reaching statistical significance from 12 to 24 h. While absolute changes in the PaO_2/FiO_2 were greater in the group where the NO and a RM were combined, they did not reach statistical significance in the inter-group comparison along the time course. Such result may be partly due to the small population employed and the wide individual variations.

The improvement in the oxygenation via NO inhalation was immediate, while that with the RM was gradual. While the rapid onset of an effect and the achievement of an early steady state via NO inhalation were consistent with previous reports,[1,2] the response to the RM in this study was relatively slower. Lapinsky, et a1[2] reported that in most cases, the maximum improvement in oxygenation was achieved immediately after a RM. Several other studies have also reported that the oxygenation response occurred relatively early, although there was variation between reports, depending on the RM method applied.[13,16,17] While various RM methods have been introduced, the best pressure and duration have yet to be defined.[18] The reversal of atelectasis was attained by applying a sustained pressure of 40 cmH_2O to the patients with general anesthesia-induced atelectasis.[19] Gatinoni, et al.[20] reported that a

plateau pressure of 46 cmH_2O was necessary for adequate recruitment in patients with ARDS. On the other hand, Amato[11] used an inflation pressure of 30 to 35 cmH_2O in clinical trials, while Lapinsky[12] used 30 - 45 cmH_2O. Other clinical studies applied pressure-controlled ventilation to recruit the lungs, with 50 - 60 cmH_2O of peak pressures.[16,21] In previous studies, the sustained inflation was generally for a duration of 15 - 30 s.[11,12,19] The delayed responses in our study may be due, in part, to the application of the relatively low recruiting pressures of between 30 and 35 cmH_2O, over the relatively longer duration of 30 s. Moreover, the recruiting pressure was increased in the subsequent session of RM, according to the previous response, rather than an immediate escalation. A relatively modest pressure was applied, and a slower increase in the pressures adopted. This was done as an ethical safe guard as there are little prior data concerning similar clinical trials at our facility, and also to reflect the lack of experience in Asian ethnic groups using the same settings. Furthermore, the delayed increase in the oxygenation values in this study does not imply the action of a RM is slow. The increase in the PaO_2/FiO_2 occurred immediately in the responders, although the overall change seemed steady. Therefore, another cause of the delayed effect of a RM may be the wide individual variability, rather than the effect per se. Moreover, we cannot entirely exclude the possibility that the patient was already naturally recovering at 24 h.

Another major finding of this study was that a portion of the non-responders to inhaled NO became responders after the additional application of a RM. Several factors have been proposed for determining the response to inhaled NO. Manktelow, et al.[4] reviewed the data of 88 ARDS patients, and an analysis of the patterns of response revealed that patients with septic shock or renal dysfunction were less likely to respond favorably. A course on respiratory failure of less than 7 days tended to be associated with a clinically significant response to NO. Likewise, the degree of ventilation/perfusion matching has been known to affect the response to inhaled NO.[16,21] Putensen, et al.[6] reported that CPAP enhanced the effect of inhaled NO, by improving the ventilation/perfusion matching, using the multiple inert gas elimination technique (MIGET). Johannigman, et al.[3] also obtained similar results by applying adequate PEEP to achieve alveolar recruitment. The prone positioning method is well-known for alveolar recruitment, which reportedly increases the responsiveness to inhaled NO, of both pulmonary and extra-pulmonary origins of ARDS.[8,22] However, another study reported a different response, with the prone positioning and NO only showing a mere additive action, without an interactive relationship.[23] A RM can also boost NO response. It may even be as effective as prone positioning, and more convenient to apply in critical patients. PEEP or CPAP alone may not be the best method for recruiting alveoli, since they can have detrimental physiological effects, such as overdistension of alveoli, larger dead space, and a smaller cardiac output.[24,25] Thus, RM's additional advantages include, protecting the lungs from ventilator-induced lung injury, compared with other recruiting methods.[16]

A RM treatment has been shown to be relatively safe in terms of hemodynamics. However, transient hypotension and bradycardia were noted in some patients, particularly those cases of prolonged sustained inflation.[12] Inhaled NO has been widely known to cause no significant hemodynamic alterations.[1,2] However, RM superimposed on NO inhalation may be assumed to be the cause the exaggerated hemodynamic changes. In particular, hypotension can be anticipated, and is related to the summation of the vasodilatory effect of NO, and the increase in the intrathoracic pressure caused by a RM. In this study, a RM added to NO inhalation did not cause serious adverse hemodynamic effects during the study period. In addition, while the pulmonary vasodilatory effect of NO may be intensified through the recruitment of alveoli, the pulmonary arterial pressure showed no significant change. The effects of NO were too brief to cause systemic hemodynamic impact, regardless of an additional RM. Moreover, the NO doses applied were relatively low, and thus could not cause hypotension, or a significant reversal of the pulmonary hypertension.

There were several limitations to our study. First, the adjustment of PEEP was not based on

the measurement of a lower inflection point; but was based on the empirical escalation according to patients' physiologic variables, such as oxygenation, compliance of the lungs, and cardiac output. Second, the initial oxygenation values showed a relatively wide range of differences between the groups, which were markedly lower in those having received only NO inhalation. In addition, full randomization could not be attained for several reasons. For one, we tried to focus the study on the combined effects of both methods; hence the larger number of patients was allocated to group 1. Moreover, a RM could not be performed on unstable patients whose condition had deteriorated further, thereby causing deviation from the original grouping.

Despite these limitations, this study has to a large extent proven that the combined application of a RM and NO inhalation may be superior to either therapy alone, and is both beneficial and safe for ARDS patients, particularly in those with profound hypoxia. Nevertheless, further studies applying various methods of RM and NO inhalation are recommended to validate our results. Likewise, the exact measurement of the ventilation/perfusion relationship, using quantitative CT scans or MIGET methods, will be required in order to assess the precise effects of combined treatments, and to establish a detailed physiological explanation.

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