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The Combined Therapy of Inhaled Nitric Oxide and Prone Positioning Has an Additive Effect on Gas Exchange and Oxygen Transport in Patients with Acute Respiratory Distress Syndrome

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급성호흡곤란증후군 환자에서 복와위(prone position)와 산화질소흡입(nitric oxide inhalation) 병용 치료의 효과

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고윤석, 임채만, 이기만, 진재용, 심태선, 이상도, 김우성, 김동순, 김원동

연구 배경 :

급성호흡곤란증후군(ARDS) 환자의 폐 산소화를 개선시키기 위한 보조적 치료법인 복와위 자세에서의 인공환기는 대상 환자의 약 61%에서, 흡입 산화질소 투여는 60-80%에서 효과가 있는 것으로 보고되어 있다. 산소화 호전의 주된 기전은 복와위시는 이환이 심한 등쪽 폐의 환기 호전에 의한 단락 감소이며, 산화질소 투여 시는 이환 부위로부터 정상 폐포로의 폐 혈류의 재분포에 의한 단락 감소인 것으로 알려져 있다. 그러므로 복와위와 산화질소의 병용 치료 시 산소화 개선에 상승 효과를 기대할 수 있으나 이에 관한 임상 연구는 없었다. 이에 저자들은 ARDS환자에서 두 치료의 병합이 가스 교환 및 혈류 역학에 미치는 영향을 관찰하였다.

방 법 :

ARDS 환자 12명(연령 56±12세, 남:여=9:3)을 대상으로 양와위에서 호흡 및 혈류역학적 지표를 측정 후 복와위로 전환하였다. 복와위 30분과 2시간에 동일 지표들을 측정 후 산화질소를 투여하고(5-10 ppm), 이후 30분, 2시간 및 산화질소 투여 중단 후 10분에 각각 동일 지표들을 재 측정하였다.

결 과 :

가스 교환 지표: 복와위에서 산화질소 병용 치료시, 양와위 및 복와위에서보다 PaO₂/FiO₂가 증가되었고(각각 p < 0.01) 폐동맥혈 산소분압차(AaDO₂)는 감소하였다(각각 p < 0.005).

호흡 역학적 지표: 폐 탄성, 호흡기계 탄성, 기도 저항 및 흡기말 기도압은 치료 방법에 따른 차이가 없었다.

혈류 역학적 지표 : 복와위에서 산화질소 병용 치료시, 양와위 및 복와위에서보다 심 박출량 및 조직산소전달량(DO₂)이 증가되었으며(각 P < 0.05), 폐혈관 저항, 평균 폐동맥압 및 폐동맥쇄기압은 감소되었다(각 P < 0.05).

결 론 :

급성호흡곤란증후군 환자에서 복와위 및 산화질소 흡입의 병용 치료는 복와위 단독 치료에 비해 폐산소화 호전에 상승 작용이 있으며, 조직으로의 산소 전달량도 증가시키므로 급성호흡곤란증후군 환자의 보조적인 치료법으로써 유용할 것으로 사료되었다. (Tuberculosis and Respiratory Diseases 1998, 45 : 1223-1235)

Key words : ARDS, Nitric oxide, Prone, Oxygenation, Combined therapy.

Introduction

ARDS is characterized by refractory hypoxemia to the usual oxygen therapy due to intra-pulmonary shunting, increased dead space ventilation and pulmonary hypertension resulting in sustained decreases in tissue oxygen delivery leading to multiple organ failure. Conventional supportive therapy to correct hypoxemia consists of oxygen supplementation and positive pressure ventilation with moderate to high positive end-expiratory pressure (PEEP) aimed at recruitment of functional gas exchange areas that have collapsed due to closing of airways and alveoli. However, the increment of PEEP can enhance peripheral organ dysfunction by depressing cardiocirculatory performance and borderline systemic tissue oxygenation. Therefore, various therapeutic modalities to improve gas exchange with protection from ventilator induced lung damage have been pursued. Among these, there has been intense clinical interest in the application of inhaled nitric oxide (NO) therapy and position change from supine to prone because of their potential efficacy on gas exchange and low cost related to the application in patients with ARDS. Although prone positioning and NO inha-

lation have been reported to improve ventilation/perfusion(V/Q) matching, some patients with ARDS still fail to respond to prone positioning¹⁻⁴⁾ or NO inhalation^{5,6)}. In addition, there seems to be no hemodynamic improvement with prone positioning alone in patients with acute lung injury^{7,8)}.

We can expect that the combination of inhaled nitric oxide and prone positioning may have an additive effect on oxygenation in patients with ARDS, because each intervention has a different mechanism to improve arterial oxygenation. In addition, the combined therapy of nitric oxide inhalation and prone positioning could increase tissue oxygen transport because of the effect of nitric oxide on hemodynamics^{9,10)}. The aim of this study was to evaluate the combined effect of inhaled nitric oxide and prone positioning on oxygenation in patients with ARDS.

Methods

Patients Selection and Characteristics

From March 1997 to August 1997, we studied 12 consecutive patients without a history of previous lung disease who met the diagnostic crite-

ria for ARDS as defined by the American-European Consensus Conference⁽¹⁾ on ARDS. Their clinical characteristics at the time of the study and outcome are shown in Table 1. This study was approved by the Institutional Review Boards and informed consent was obtained from each patients next of kin. The severity of illness was described as acute physiology and chronic health evaluation III (APACHE III) score⁽²⁾. The ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) was used as an index of arterial oxygenation. During the study, all patients were intubated, sedated, paralyzed and mechanically ventilated in the volume controlled pressure limited mode with 8 ml per kg of body weight of tidal volume and 35 cm H_2O of plateau pressure limit. Positive end-expiratory pressure (PEEP) was increased up to 15

cm H_2O depending on arterial oxygenation starting from 5 cm H_2O without trying to find an inflection point in the lung. Except one patient who had an intractable hypotension, ranges of applied PEEP level for all patients were from 10 cm H_2O to 15 cm H_2O (table 1). The tidal volumes, FiO_2 , and PEEP were kept constant during the period of study. Vasoactive drugs were given as necessary before the study, but neither the drugs nor the doses were changed during the investigation.

Measurements

A peripheral arterial catheter and pulmonary arterial catheter (Baxter Healthcare, Irvine, CA., USA) were inserted in the patients for clinical monitoring. Heart rate was determined by

Table 1. Clinical characteristics of the patients

Patient No.	Age(yr)/Sex	$\text{PaO}_2/\text{FiO}_2^*$	Cause of ARDS	APACHE III Score	PEEP	Survival
1	71/M	155	Pneumonia	90	14	Yes
2	61/F	159	Pneumonia/Sepsis	101	15	Yes
3	66/M	76	Sepsis	102	13	Yes
4	80/M	187	Aspiration pneumonia	102	12	No
5	68/M	159	Sepsis	86	4	No
6	55/M	103	Sepsis	90	12	Yes
7	35/F	158	Pneumonia/Sepsis	45	10	Yes
8	63/M	63	Aspiration pneumonia	95	11	Yes
9	59/F	76	Aspiration pneumonia	61	10	Yes
10	64/M	163	Sepsis	94	10	No
11	50/M	118	Malaria	123	10	Yes
12	75/M	117	Pneumonia	89	10	No

* $\text{PaO}_2/\text{FiO}_2$ at the base-line value, PEEP ; Positive End Expiratory Pressure (cm H_2O), ARDS ; acute respiratory distress syndrome, APACHE ; Acute physiology and chronic health evaluation.

electrocardiograph. Systemic arterial pressure, mean pulmonary arterial pressure (MPAP) and pulmonary artery occlusion pressure (PAOP) were measured with the transducers. Cardiac output (CO) was measured using the thermodilution method (Edwards Cardiac Output Computer COM-2, Baxter Healthcare, Irvine, CA., USA), and given as mean value of the three measurements. Pulmonary vascular resistance (PVR), stroke volume (SV), alveolar-arterial oxygen difference (AaDO₂) and oxygen delivery (DO₂) were calculated using standard formulas¹³. For monitoring of lung compliance, esophageal balloon pressure sensors were inserted. The sensor was connected to the pulmonary mechanics monitor (Bicore CP-100 ; Allied Health Care Products ; Riverside, CA, USA). Dynamic and static compliance of the total respiratory system were calculated by dividing total volume by pressure amplitude determined at the peak inspiratory, end-inspiratory plateau and end-expiratory zero-flow phase.

Protocol

Gas exchange, respiratory mechanics and hemo-

dynamic data were collected with the patients lying supine at first (baseline). Following the baseline measurements, the patients were then turned to prone position and the measurements were made after 30 minutes (prone 30 min) and 120 minutes (prone 120 min) respectively. After measuring the blood gas, hemodynamic and respiratory mechanics in prone positioning, nitric oxide was delivered from a tank of nitrogen with a nitric oxide concentration of 400 or 800 parts per million (ppm) to the high pressure air port of a Servo Ventilator 900C or 300 (Siemens-Elema AB, Solna, Sweden) or Puritan Bennett 7200 ae Ventilator (Nellcor Puritan Bennett, CA, USA). NO was blended with medical air using a high pressure blender before delivery to the ventilator¹⁴. The arterial blood gas and hemodynamic measurements were repeated consecutively at 30 minutes (prone+NO 30 min) and 120 minutes (prone+NO 120 min) after NO inhalation (Fig. 1). Inhaled nitric oxide and nitric dioxide concentration were continuously monitored at the distal tip of endotracheal tube by electrochemical analysis (TMX-100, Taiyo Toyo Sanso CO., Osaka, Japan). Inspired oxygen concentration was also continuously monitored.

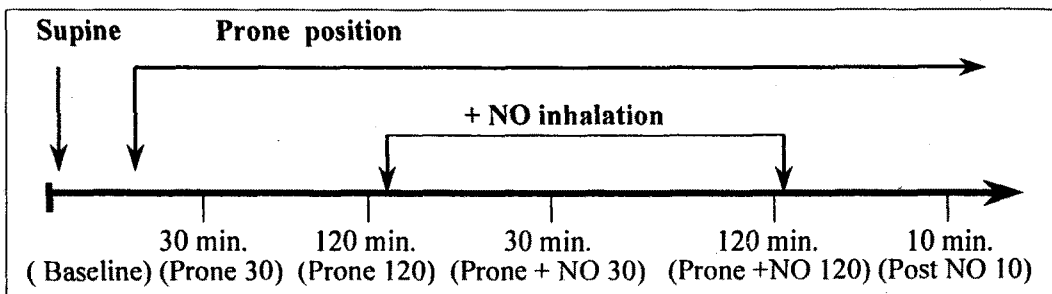


Fig. 1. Protocol outline. The blood gases, hemodynamics and respiratory mechanic measurements were performed at the time shown in figure.

Prone positioning and nitric oxide (NO) inhalation are indicated by above line.

Table 2. Individual change in PaO₂/FiO₂ during the study

Patient	Supine baseline	Prone 30 min	Prone 120 min	Prone+No 30 min	Prone+NO 120 min	Post NO 10 min
1	155	104	167	189	190	174
2	159	239	239	236	298	226
3	76	114	105	160	145	108
4	187	199	231	255	236	213
5	159	357	230	320	369	226
6	103	254	218	267	322	254
7	158	152	98	105	96	103
8	63	93	108	300	345	405
9	76	147	211	334	289	302
10	163	283	180	254	237	231
11	110	97	107	114	129	106
12	117	105	129	133	121	109

Arterial oxygenation was improved after the combination of prone positioning and NO inhalation in patient 1 and 11. All values are PaO₂/FiO₂

Administered concentration of nitric oxide was 5 to 10 ppm. To determine the effect of withdrawal of NO, the measurements were repeated at 10 minute (post NO 10 min) after the discontinuation of NO administration. The responders were remained under combined treatment of prone positioning and NO inhalation until their FiO₂ reduced to 40%. If PaO₂/FiO₂ increased more than 20 mm Hg after prone positioning compared to supine position, the patient was considered a responder to prone positioning. The same criteria were applied to nitric oxide during nitric oxide inhalation in comparison with prone 120 min measurements.

Statistical analysis

All data were expressed as means ± SD. Statistical analysis were performed, with software

(SPSS 7.5 for windows, SPSS Inc ; Chicago, USA). The Wilcoxon test for paired samples was used to compare values obtained during treatment. Differences between the responders and the non-responders were evaluated by unpaired t-test. A p value < 0.05 was assumed to indicate significance.

Results

Response to Prone Positioning and Additional NO Inhalation

There were no complications related to prone positioning and NO inhalation during the study. Eight patients (66.6%) responded to prone positioning and two more patients (83.3%) responded to the addition of NO inhalation including the eight patients who responded to

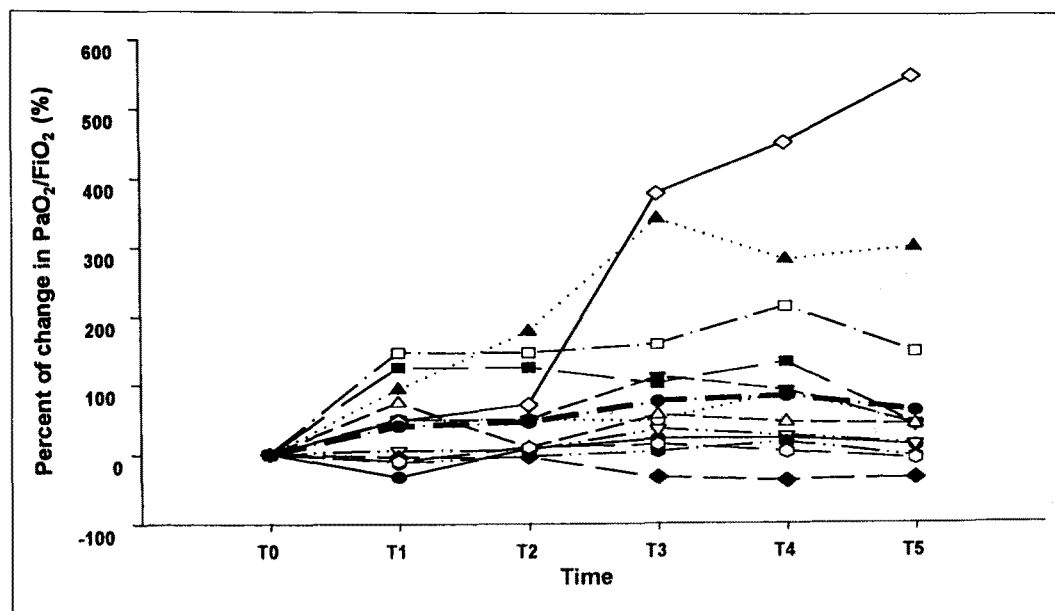


Fig. 2. Individual change in $\text{PaO}_2/\text{FiO}_2$ during the study period.

Eight patients (66.6%) responded to prone positioning and two more patients (83.3%) responded to addition of NO inhalation T0 : supine position ; T1 : prone 30 min ; T2 : prone 120 min ; T3 : Prone+NO 30 min ; T4 : Prone+NO 120 min ; T5 : Post-NO 10 min. Values are expressed as the percent of change compared with T0. Each line represents one patient. Bold dashed line represents the mean value of percent change in $\text{PaO}_2/\text{FiO}_2$ in all patients compared with T0.

Table 3. Gas exchange of the patients during the study

Patient	Supine Baseline	Prone 30 min	Prone 120 min	Prone+No 30 min	Prone+NO 120 min	Post NO 10 min
$\text{PaO}_2/\text{FiO}_2$	127 ± 41	179 ± 87*	169 ± 57*	222 ± 80**	231 ± 94**	213 ± 113
AaDO ₂ (mmHg)	377 ± 150	327 ± 149	256 ± 137*	191 ± 109**	184 ± 109**	202 ± 112
PaCO_2 (mmHg)	40.8 ± 9.7	38.7 ± 9.1	40.0 ± 8.2	38.5 ± 8.7	38.3 ± 8.1	37.0 ± 10.2
pH	7.38 ± 0.07	7.40 ± 0.09	7.40 ± 0.08	7.39 ± 0.06	7.41 ± 0.08	7.42 ± 0.09
HCO_2 (mEq/L)	24.1 ± 6.0	24.9 ± 4.9	25.3 ± 5.3	25.3 ± 5.3	25.4 ± 4.8	24.9 ± 5.5

$\text{PaO}_2/\text{FiO}_2$ and AaDO₂ are significantly different ($p^* < 0.05$) comparing the supine positioning with the prone positioning at 120 min. The values are also significantly different ($p^{**} < 0.05$) compared to those of the prone positioning at 120 min. Values are mean ± SD.

* $P < 0.05$ compared with the base-line value ; ** $p < 0.05$ compared with the prone 120 min. The wilcoxon test for paired samples was used to compare values obtained during treatment.

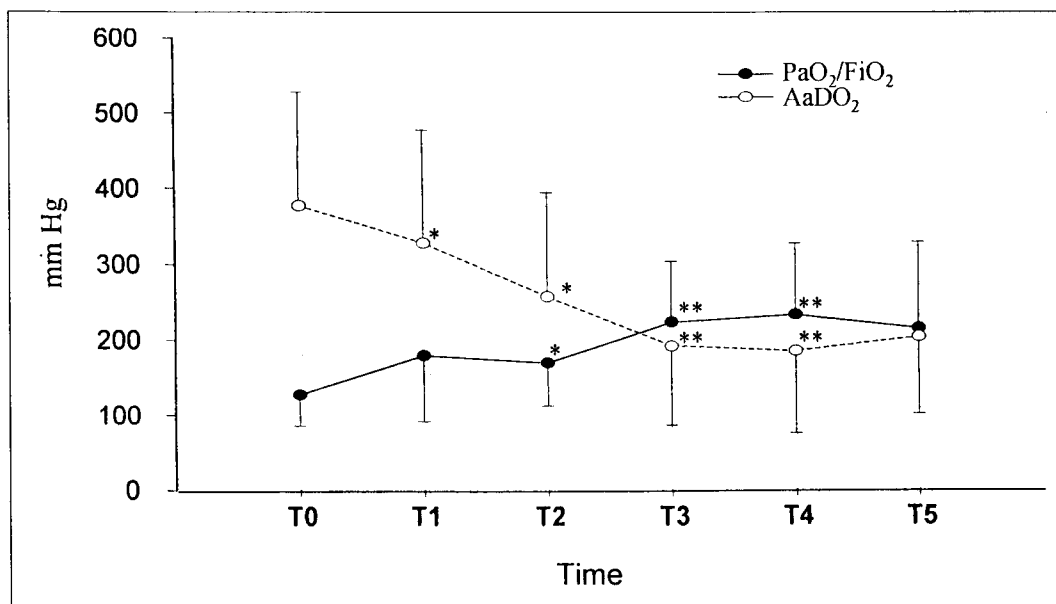


Fig. 3. Serial changes of gas exchange.

T0 : supine ; T1 : prone 30 min ; T2 : prone 120 min ; T3 : prone+NO 30 min ; T4 : prone+NO 120 min ; T5 : Post-NO 10 min, *P<0.05 compared with the base-line value, **<0.05 compared with the prone 120 min.

prone positioning (Table 2, Fig. 2). At baseline, none of the parameters was significantly different between responders and non-responders in prone positioning or addition of NO inhalation.

Gas exchange

The prone positioning increased PaO₂/FiO₂ ratio and decreased AaDO₂ compared to supine baseline (Table 3). The addition of nitric oxide inhalation to prone positioning further increased PaO₂/FiO₂ ratio and decreased AaDO₂ compared to prone 120 min. But PaCO₂, pH and HCO₃ were not changed by prone positioning or NO inhalation (Table 3). Ten minutes after discontinuation of nitric oxide inhalation, PaO₂/FiO₂ ratio decreased and AaDO₂ rose, but the results

did not reach statistical significance (P=0.099).

Hemodynamics and Oxygen Delivery

Hemodynamic parameters were not changed significantly during prone positioning only (Table 4). Following the addition of NO inhalation to prone positioning, both MPAP and PAOP decreased compared with prone 120 min (P<0.05). PVR showed a decreasing tendency during the combined therapy of prone positioning and NO inhalation compared to supine position. Cardiac output, stroke volume and oxygen delivery increased after the combined therapy of prone positioning and NO inhalation compared to prone 120 min (P<0.05) (Table 4).

Table 4. Hemodynamic values and oxygen delivery

Patient	Supine baseline	Prone 30 min	Prone 120 min	Prone+No 30 min	Prone+NO 120 min	Post NO 10 min
MAP (mmHg)	96.6±9.6	92.1±21.0	97.8±17.4	90.8±14.2	99.7±7.2	105.6±27.5
MPAP (mmHg)	25.9±4.8	263.±4.9	26.8±4.1	23.9±6.0*	22.9±6.3**	23.3±4.5
PAOP (mmHg)	15.2±2.4	16.5±2.2	15.4±1.3	14.0±3.8	12.8±3.4**	11.3±3.9
PVR (dyne · sec/cm ⁵)	242±141	224±132	210±116	178±118	172±115	198±63
CO (L/min)	3.93±1.54	3.83±1.43	4.22±1.69	4.81±1.79	4.84±1.73**	4.59±1.52
SV (mL/beat)	33.9±15.5	32.7±15.0	33.3±14.3	38.9±15.6	39.3±13.0**	39.0±12.9
DO ₂ (mL/min)	599±217	593±201	619±205	719±236	720±204**	674±171

MPAP is significantly decreased ($p^{**}<0.05$) at 30 min and 120 min of combined therapy with prone positioning and NO inhalation compared with prone 120 min. Cardiac output, stroke volume and oxygen delivery are significantly increased ($p^{**}<0.05$) at 120 min of combined therapy with prone positioning and NO inhalation compared with prone 120 min. Value are mean±S.D.,; $**p<0.05$ compared with the prone 120 min.

The Wilcoxon test for paired samples was used to compare values obtained during treatment.

MAP, mean systemic artery pressure ; MPAP, mean pulmonary artery pressure ; PAOP, pulmonary artery occlusion pressure ; PVR, pulmonary vascular resistance ; CO, cardiac output ; SV, stroke volume ; DO₂, oxygen delivery.

Respiratory Mechanics

During the study, dynamic compliance and static compliance of the total respiratory system were not changed substantially. Lung compliance was also not changed during prone positioning (Table 5).

Discussion

Our data showed that the combination of prone positioning and low dose NO inhalation resulted in better arterial oxygenation and systemic oxygen transport than did prone positioning alone in twelve mostly sepsis-induced ARDS patients. These results were expected because the main factor influencing oxygenation is different between two modalities; ventilation redistribution

in the prone positioning^{1,15} and the decrease in shunt in the NO inhalation^{5,10}. Since the non-homogeneous distribution of interstitial edema has been recognized in ARDS¹⁶, prone positioning has been advocated to improve overall ventilation/perfusion (V/Q) matching in clinical investigations^{1-4,17}. But, the effect on systemic oxygenation was found to be 50-78% of all patients undergoing position change from supine to prone¹⁻⁴. In addition, there seems to be no hemodynamic improvement with prone positioning alone in patients with acute lung injury^{6,7}. Inhaled NO improves blood flow selectively to ventilated alveoli, resulting in improvement of gas exchange. NO also has some positive effect on hemodynamics⁹. Because the result of the studies showed that beneficial effect on oxygenation was lower than 5 ppm of inhaled NO and the

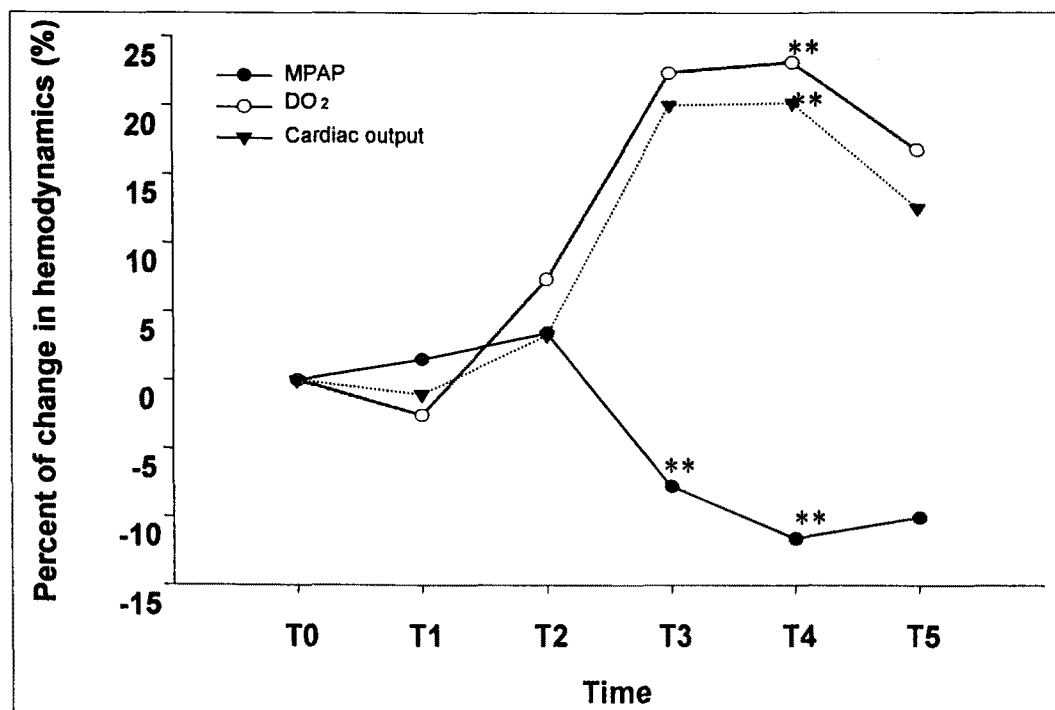


Fig. 4. Serial changes of hemodynamics and oxygen delivery.
 T0 : supine ; T1 : prone 30 min ; T2 : prone 120 min T3 : prone+NO 30 min ; T4 : prone+NO 120 min ; T5 : post-NO 10 min
 ** p<0.05 compared with the prone 120 min.

Table 5. The values of respiratory mechanics

Patient (mL/cm H ₂ O)	Supine baseline	Prone 30 min	Prone 120 min	Prone+NO 30 min	Prone+NO 120 min
Lung compliance	30.8 ± 15.4	27.9 ± 11.5	27.9 ± 10.1		
Dynamic compliance*	21.9 ± 4.8	22.1 ± 7.9	24.8 ± 9.0	25.1 ± 9.5	25.2 ± 8.8
Static compliance*	30.4 ± 12.7	32.0 ± 11.0	33.0 ± 10.1	33.4 ± 14.5	35.3 ± 14.4

There are no significant changes of respiratory mechanics during the study. Lung compliance was not measured at the combined therapy of prone positioning and NO inhalation. The wilcoxon test for paired samples was used to compare values obtained during treatment. Value are mean ± SD. ; *Dynamic and static compliance of total respiratory system.

maximum effect was about 10 ppm in patients with ARDS^{6,18}), we initiated and maintained inhaled NO therapy at a dose between 5 and 10 ppm. In our study protocol, NO inhalation was

begun after 2 hours of prone positioning to observe any additional gain in oxygenation with NO because oxygenation improvement has been observed immediately after prone positioning

and no further significant improvement was demonstrated between 30 and 120 min in ARDS¹⁾

After recruitment of collapsed alveoli by prone positioning for 2 hours, the addition of NO inhalation might be improved V/Q match further in our ARDS patients. It could be speculated by the previous data that NO-induced improvement in arterial oxygenation and pulmonary vascular effects was positively influenced by the degree of PEEP-induced alveolar recruitment^{19, 20)}. In fact, all eight patients who responded to prone positioning also responded to the addition of NO inhalation in this study. In addition, two patients among the non-responders to prone positioning responded to the addition of NO inhalation.

One important aspect observed in our study is the possible role of NO in the improvement of CO. Although inhaled NO decreases pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) without affecting systemic blood pressure¹⁰⁾, the effect of NO on CO remains unclear. The results of the present investigation indicate that NO seems to exert beneficial effects on left ventricular performance and systemic oxygen delivery when it is combined with prone positioning in ARDS. This finding is in accordance with Krafft's data, demonstrating that responders to NO inhalation showed an increase in the right ventricular ejection fraction (RVEF) accompanied by higher cardiac index and DO₂ compared with non-responder in septic ARDS⁹⁾. An explanation for the increase in CO in the association of NO inhalation with prone positioning is not readily apparent in this study. Possible RVEF improvement induced by the decrease in PAP might lead to the improvement of

left ventricular performance when considering the interventricular interaction²¹⁾, although we can not provide a definite answer to this possible mechanism since RVEF was not measured in the patients in our study. In cases with severe acute right heart failure, inhalation of NO was reported to increase cardiac output in a dose-dependent manner in the patients with ARDS²²⁾, while other investigation demonstrated that an increase in RVEF by NO inhalation was not necessarily associated with a rise in cardiac index²²⁾. However, due to the protocol of our study, we are unable to verify that observed improvement in oxygen transport with the combination of two modalities is caused by NO alone. Recently, combined therapy including prone positioning, NO inhalation, and almitrine bismesylate injection were reported in severe ARDS patients⁴⁾. An association of NO inhalation with intravenous almitrine has been shown to improve oxygenation significantly in ARDS^{4, 24, 25)}.

The mortality rate of patients was 33%. However, the small sample size and the limitation of study protocol did not enable us to make precise estimates of survival benefits of the combination therapy in the ARDS patients.

In summary, combined therapy with NO inhalation and prone positioning may have a great advantage in terms of tissue oxygenation in patients with ARDS according to our data. In addition, a combination of NO inhalation and prone positioning would be acceptable as a rescue therapy in patients with severe ARDS without serious complications related to the application.

Summary

Background and Objective : Although prone positioning has been reported to improve gas exchange, prone positioning alone does not seem to be sufficient to increase systemic oxygen transport in an acute lung injury. The objective of this study was to investigate whether the combined therapy of low dose nitric oxide (NO) inhalation and prone positioning has an additive effect on the oxygenation and hemodynamics in patients with severe ARDS.

Patients and Methods : Twelve patients with ARDS were included. Prone positioning alone, later combined with nitric oxide inhalation (5~10 ppm) from the supine position (baseline) were performed with serial measurement of gas exchange, respiratory mechanics and hemodynamic at sequential time points. The patient was regarded as a responder to prone positioning if an increase in $\text{PaO}_2/\text{FiO}_2$ of more than 20 mm Hg at 30 min or 120 min intervals after prone positioning was observed compared to that of the baseline. The same criterion was applied during nitric oxide inhalation.

Results : Eight patients (66.5%) responded to prone positioning and ten patients (83.3%) including the eight just mentioned responded to the addition of NO inhalation. The AaDO_2 level also decreased promptly with the combination of prone positioning and NO inhalation compared to that of prone positioning alone (191 ± 109 mm Hg vs. 256 ± 137 mm Hg, $P < 0.05$). Hemodynamic parameters and lung compliance did not change significantly during prone positioning only. Following the addition of NO inhalation to prone positioning, the mean pulmonary artery

pressure and pulmonary artery occlusion pressure decreased and cardiac output, stroke volume and oxygen delivery increased ($P < 0.05$) compared to those of prone 120 min.

Conclusion : These findings indicate that NO inhalation would provide additional improvement in oxygenation and oxygen transport to mechanically ventilated patients with ARDS who are in a prone position.

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