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Clinical Meaning of Early Oxygenation Improvement in Severe Acute Respiratory Distress Syndrome under Prolonged Prone Positioning

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Background/Aims: Ventilating patients with acute respiratory distress syndrome (ARDS) in the prone position has been shown to improve arterial oxygenation, but prolonged prone positioning frequently requires continuous deep sedation, which may be harmful to patients. We evaluated the meaning of early gas exchange in patients with severe ARDS under prolonged (≥ 12 hours) prone positioning.
Methods: We retrospectively studied 96 patients (mean age, 60.1 ± 15.6 years; 75% men) with severe ARDS ($PaO_2/FiO_2 \leq 150$ mmHg) admitted to a medical intensive care unit (MICU). The terms "PaO_2 response" and "$PaCO_2$ response" represented responses that resulted in increases in the PaO_2/FiO_2 ratio of ≥ 20 mmHg and decreases in $PaCO_2$ of ≥ 1 mmHg, respectively, 8 to 12 hours after first placement in the prone position.
Results: The mean duration of prone positioning was 78.5 ± 61.2 hours, and the 28-day mortality rate after MICU admission was 56.3%. No significant difference in clinical characteristics was observed between PaO_2 and $PaCO_2$ responders and non-responders. The PaO_2 responders after prone positioning showed an improved 28-day outcome, compared with non-responders by Kaplan-Meier survival estimates ($p < 0.05$ by the log-rank test), but the $PaCO_2$ responders did not.
Conclusions: Our results suggest that the early oxygenation improvement after prone positioning might be associated with an improved 28-day outcome and may be an indicator to maintain prolonged prone positioning in patients with severe ARDS. **(Korean J Intern Med 2010;25:58-65)**

Keywords: Respiratory distress syndrome, acute; Prone position; PaO_2 response; Mortality

INTRODUCTION

Present treatment of acute respiratory distress syndrome (ARDS) is largely supportive in nature, and unacceptable levels of morbidity and mortality persist [1]. Traditionally, the definition of ARDS includes bilateral infiltrates on simple chest radiographs [2], but computed tomography scanning has highlighted the patchy, heterogeneous nature of the disease. In particular, the dependent lung regions are often severely affected by alveolar flooding, increased surface tension, and collapse [3]. Gravitational effects directing pulmonary blood flow augment perfusion to these regions, thereby worsening shunt fraction [4].

The prone position was reported as early as the mid-1970s to improve oxygenation in patients with hypoxic respiratory failure [5], and many investigators have reported that ventilation of ARDS patients in the prone position improves arterial oxygenation [6-13]. Recently, several studies have suggested that prone positioning, when initiated early and applied for most of the day, may reduce mortality in patients with severe ARDS [14,15]. However, prolonged prone positioning frequently requires

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Table 1. Baseline characteristics of all patients at enrollment

Characteristics	Survivors (n = 42)	Non-survivors (n = 54)	*p* value
Age, yr	60.5 ± 16.6	59.7 ± 15.0	0.815
Male	31 (73.8)	41 (75.9)	0.817
SAPS II score on prone positioning day[a]	40.6 ± 13.0	42.2 ± 14.6	0.333
SAPS II score > 49	9 (21.4)	18 (33.3)	0.254
Cause of ARDS			
Pneumonia	30 (71.4)	40 (74.0)	0.820
Sepsis	5 (11.9)	4 (7.4)	0.498
Aspiration	5 (11.9)	3 (5.6)	0.292
Other causes	2 (4.8)	7 (13.0)	0.291
Organ failure			
Circulatory failure	30 (71.4)	31(57.4)	0.194
Coagulation failure	9 (21.4)	22 (40.7)	0.051
Hepatic failure	4 (9.5)	14 (25.9)	0.063
Renal failure	3 (7.1)	10 (18.5)	0.136
Patients with pre-existing comorbidities before MICU admission	17 (40.4)	30 (55.6)	0.156
Numbers of non-pulmonary organ failure at MICU admission	0.9 ± 0.9	1.0 ± 0.9	0.566
Duration of prone positioning, hr	72.4 ± 64.3	83.3 ± 58.9	0.390
Period from diagnosis (ARDS) to prone positioning, day	2.1 ± 2.3	2.4 ± 3.4	0.656
Patients received inhaled nitric oxide therapy	31 (73.8)	39 (72.2)	1.000
Patients received alveolar recruitment maneuver therapy	7 (16.7)	7 (13.0)	0.772

Data are expressed as mean ± SD for continuous values or number (%) for categorical values.
SAPS, simplified acute physiology score; ARDS, acute respiratory distress syndrome; MICU, medical intensive care unit.
[a] SAPS score is used to assess the severity of illness and can range from 0 to 194, with higher scores indicating a higher risk of death.

Table 2. Ventilator and gas exchange values before prone positioning

Characteristics	Survivors (n = 42)	Non-survivors (n = 54)	*p* value
Ventilatory parameters before prone positioning			
Tidal volume/kg ideal body weight, mL/kg[a]	8.2 ± 2.4	8.3 ± 3.4	0.864
Total minute ventilation, L/min	11.1 ± 3.1	11.7 ± 4.1	0.453
PEEP, cmH_2O	8.4 ± 2.8	9.2 ± 3.4	0.250
Respiratory rate, cycles/min	23.4 ± 3.4	22.6 ± 4.4	0.293
Mean pressure level above PEEP, cmH_2O	18.9 ± 5.3	20.0 ± 6.1	0.423
Minute ventilation/$PaCO_2$, mL/min•mmHg	276 ± 170	273 ± 131	0.928
Gas exchange values before prone position			
Arterial pH, unit	7.34 ± 0.12	7.32 ± 0.11	0.387
$PaCO_2$, mmHg	47.7 ± 15.6	47.7 ± 15.7	0.917
PaO_2/FiO_2, mmHg	90.3 ± 28.6	80.8 ± 27.4	0.106

Data are expressed as mean ± SD.
PEEP, positive end-expiratory pressure.
[a] The predicted body weight was calculated as 50 + 0.91 (height - 152.4 cm) for males and as 45.5 + 0.91 (height - 152.4 cm) for females.

continuous sedation of the patient, which has been reported to adversely affect critically ill patients [16,17]. Thus, if we could predict the effect of prolonged prone positioning in the early stages of the prone position, it may obviate the unnecessarily heavy sedation associated with prone positioning.

There are debatable reports as to whether improvements in gas exchange in response to the prone position are

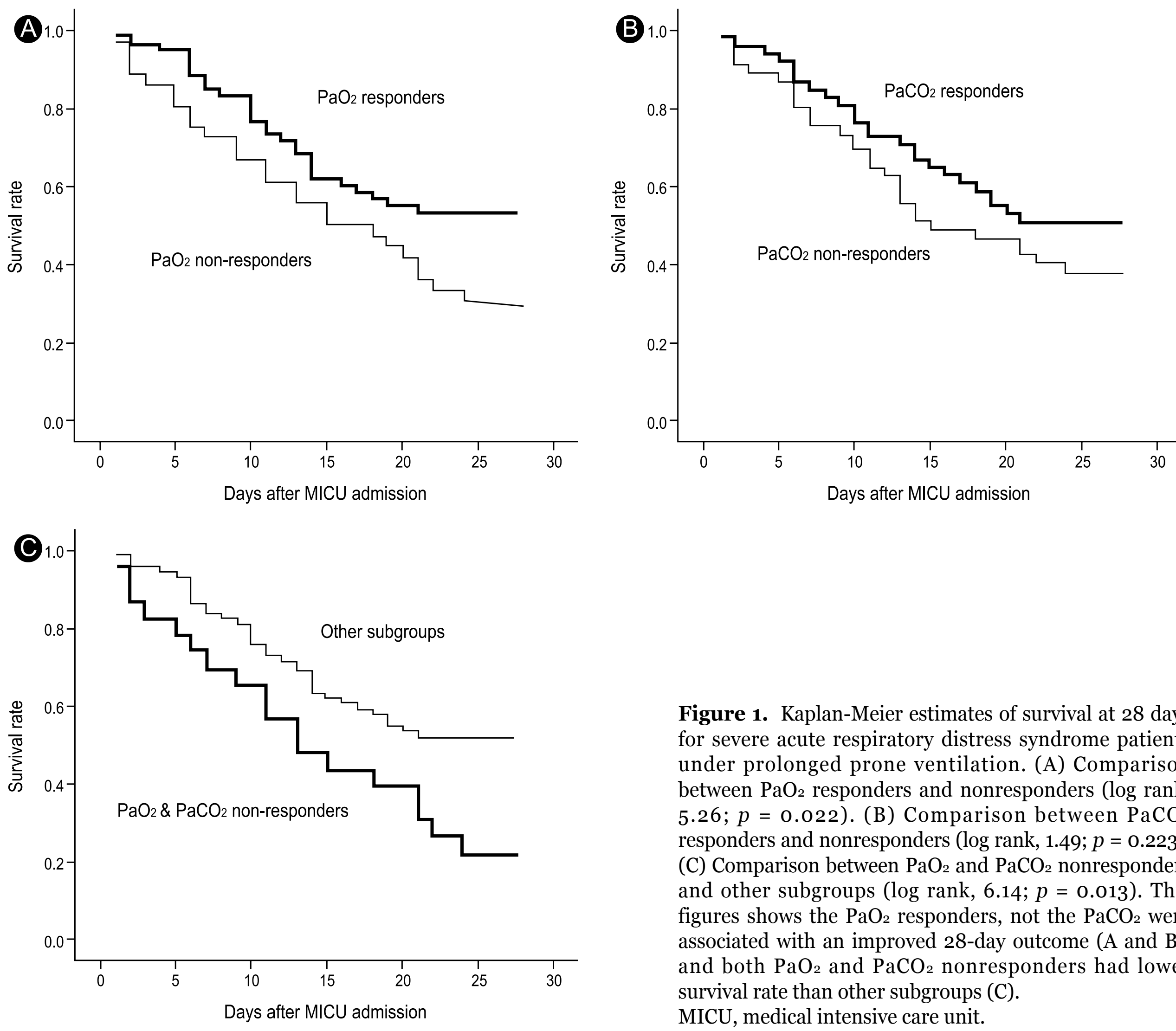

Figure 1. Kaplan-Meier estimates of survival at 28 days for severe acute respiratory distress syndrome patients under prolonged prone ventilation. (A) Comparison between PaO_2 responders and nonresponders (log rank, 5.26; p = 0.022). (B) Comparison between $PaCO_2$ responders and nonresponders (log rank, 1.49; p = 0.223). (C) Comparison between PaO_2 and $PaCO_2$ nonresponders and other subgroups (log rank, 6.14; p = 0.013). This figures shows the PaO_2 responders, not the $PaCO_2$ were associated with an improved 28-day outcome (A and B), and both PaO_2 and $PaCO_2$ nonresponders had lower survival rate than other subgroups (C).
MICU, medical intensive care unit.

actually associated with an enhanced outcome; however, these studies had methodological differences and patients were positioned for only a few hours each day [18,19]. We thus hypothesized that an early gas exchange response to first placement in the prone position might be associated with survival in ARDS patients, as reported previously [18], especially when the time spent prone is prolonged. Moreover, few studies have evaluated patients with severe ARDS who underwent prolonged prone positioning.

Our aim was to evaluate clinical characteristics, gas exchange responses after first placement in the prone position, outcomes, and the clinical meaning of early gas exchange in patients with severe ARDS under conditions of prolonged prone positioning (≥ 12 hours, whether clinical status improved or not) in a university-affiliated tertiary care hospital.

METHODS

Subjects

This study was performed in a 28-bed medical intensive care unit (MICU) at the Asan Medical Center, a tertiary referral academic care hospital in Seoul, Korea (about 2,200 beds). The inclusion period was from January 1, 2000 to July 31, 2006. We conducted a retrospective search of all adult patients (≥ 18 years of age) admitted to the MICU. The inclusion criterion was severe ARDS ($PaO_2/FiO_2 \leq 150$ mmHg with a positive end-expiratory pressure (PEEP) of at least 8 cm H_2O, and bilateral chest radiography showing lung infiltrate without evidence of cardiac failure). We enrolled a total of 96 adult patients who were diagnosed with severe ARDS and who were placed in the prone position for ≥ 12 hours in the MICU until the

Table 3. Clinical characteristics between PaO_2 responders and PaO_2 non-responders

Characteristics	PaO_2 responders (n = 60)	PaO_2 non-responders (n = 36)	*p* value
Age, yr	59.0 ± 17.3	61.8 ± 12.5	0.396
Male	45 (75)	27 (75)	0.999
SAPS II score on prone positioning day [a]	41.8 ± 14.3	42.9 ± 13.4	0.715
Patients with SAPS II > 49	17 (28.3)	10 (27.8)	0.999
Cause of ARDS			
Pneumonia	43 (71.7)	27 (75)	0.815
Sepsis	6 (10)	3 (8.3)	0.999
Aspiration	5 (8.3)	3 (8.3)	0.999
Other causes	6 (10)	3 (8.3)	0.999
Organ failure at admission			
Circulatory failure	40 (66.7)	21 (60)	0.652
Coagulation failure	19 (31.7)	12 (34.3)	0.999
Hepatic failure	9 (15)	9 (25.7)	0.278
Renal failure	9 (15)	4 (6.7)	0.762
Total MICU LOS, day	23.7 ± 20.7	18.3 ± 13.5	0.172
Total hospital LOS, day	40.2 ± 37.4	27.0 ± 21.3	0.056
28-day mortality rate	28 (46.7)	26 (72.2)	0.019
Patients with pre-existing comorbidities before MICU admission	26 (43.3)	21 (58.3)	0.206
Numbers of non-pulmonary organ failure at MICU admission	1.1 ± 0.9	0.8 ± 0.9	0.195
Patients received inhaled nitric oxide therapy	41 (68.3)	29 (80.6)	0.239
Patients received alveolar recruitment maneuver therapy	6 (10)	8 (22.2)	0.136
Duration of prone positioning, hr	71.0 ± 44.7	91.0 ± 80.9	0.121
Period from diagnosis (ARDS) to prone positioning, day	1.9 ± 2.5	2.9 ± 3.5	0.080

Data are expressed as mean ± SD for continuous values or number (%) for categorical values.
SAPS, simplified acute physiology score; ARDS, acute respiratory distress syndrome; MICU, medical intensive care unit; LOS; length of stay.
[a] SAPS is used to assess the severity of illness and can range from 0 to 194, with higher scores indicating a higher risk of death.

patient's position was changed from prone to supine due to improvement ($PaO_2/FiO_2 \geq 150$ or FiO_2 requirement ≤ 0.5 at PEEP of 8 cm H_2O or lower, and an improved chest radiography finding) or deterioration (with no improvement in gas exchange after prone positioning).

Our study protocol regarding medical record review was approved by the Institutional Review Board of the Asan Medical Center. We confirmed that prone positioning was performed after obtaining informed consent from each patient's surrogate, identified through medical records.

Data collection

The following data were gathered from the medical records of each patient: age, gender, causes of ARDS, pre-existing co-morbidities, numbers of non-pulmonary organ failures when diagnosed with ARDS, length of stay in the MICU and in the hospital, and complications attributable to prone positioning. The primary end-point was 28-day mortality. On the day of prone positioning, we calculated the Simplified Acute Physiology Score (SAPS) II as an index of illness severity [20] and recorded biochemical variables indicative of organ failure (renal, hepatic, circulatory, and coagulation failure) as defined by the Acute Respiratory Distress Syndrome Network trial of the US National Heart, Lung, and Blood Institute [21]. Data on adjuvant therapies such as inhaled nitric oxide (NO) and/or alveolar recruitment maneuver (ARM) therapy were also collected [22].

Arterial blood gas exchange variables (PaO_2, $PaCO_2$, pH) and ventilator variables (tidal volume in the pressure-controlled mode, level of pressure support, PEEP, and FiO_2) were collected just before and around 8 hours after first placement in the prone position. If arterial blood gas analysis (ABGA) was not checked at 8 hours after prone positioning, we collected ABGA data until 12 hours after prone positioning. Of these variables, we categorized

Table 4. Ventilatory parameters and gas exchange values after prone positioning[a]

	Survivors (n = 42)	Non-survivors (n = 54)	*p* value
Ventilatory parameters after prone positioning			
Tidal volume/kg ideal body weight, mL/kg[b]	7.9 ± 2.4	7.8 ± 2.0	0.821
Total minute ventilation, L/min	10.6 ± 2.9	11.2 ± 2.3	0.276
PEEP, cmH_2O	9.5 ± 2.7	10.0 ± 2.5	0.311
Respiratory rate, cycles/min	23.6 ± 3.7	23.8 ± 4.6	0.800
Mean pressure level above PEEP, cmH_2O	19.5 ± 5.9	20.3 ± 4.6	0.457
Minute ventilation/$PaCO_2$, mL/min•mmHg	249 ± 122	250 ± 112	0.939
Gas exchange values after prone positioning			
Arterial pH, unit	7.35 ± 0.10	7.30 ± 0.13	0.055
Patients with arterial pH > 7.25	35 (83.3)	40 (74.1)	0.325
$PaCO_2$, mmHg	48.2 ± 13.7	50.6 ± 18.0	0.468
PaO_2/FiO_2, mmHg	149.9 ± 61.8	115.0 ± 49.2	0.003
PaO_2 responders	32 (76.2)	28 (51.9)	0.019
$PaCO_2$ responders	25 (59.5)	26 (48.1)	0.307

Data are expressed as mean ± SD for continuous values or number (%) for categorical values.
PEEP, positive end-expiratory pressure.
[a]Ventilator parameters and arterial blood gas exchange variables were collected just before and around 8 hours after placement in the first prone position.
[b]The predicted body weight was calculated as 50 + 0.91 (height 152.4 cm) for males and as 45.5 + 0.91 (height 152.4 cm) for females.

whether arterial pH was above pH 7.25 in keeping with some experts' recommendation about mechanical ventilation in patients with ARDS [23]. Gas exchange responses to placement in the first prone position were defined as follows: "PaO_2 response" and "$PaCO_2$ response" were defined as an increase in the $PaO_2/FiO_2 \geq 20$ mmHg and as a decrease in $PaCO_2 \geq 1$ mmHg, respectively, after 8 to 12 hours in the prone position [18].

Statistical analysis

Continuous variables are expressed as means ± SD. The Student's *t*-test was used to compare continuous variables, and the chi-square or Fisher's exact tests (for small numbers) were used to compare categorical variables. Patient survival was analyzed using the Kaplan-Meier method, and compared using the log-rank test. Factors with *p* values less than 0.05 or equal by univariate analysis were entered into the model. Statistical analyses were performed using the SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). A two-tailed *p* value less than 0.05 was deemed to indicate statistical significance.

RESULTS

Clinical characteristics of patients

In all enrolled patients (mean age, 60.1 ± 15.6 years; 75% men), the mean duration of prone positioning was 78.5 ± 61.2 hours, the mean period from diagnosis (ARDS) to prone positioning was 2.3 ± 2.9 days, SAPS II score at time of prone positioning was 42.2 ± 13.9, and the lengths of MICU and hospital stays were 21.7 ± 18.5 and 35.2 ± 32.8 days, respectively. Pulmonary ARDS was the most common cause of initial MICU admissions (72.9%). The 28-day mortality rate after MICU admission was 56.3%. All subjects required sedative agents. A neuromuscular blocking agent was administrated to 86 patients (89.6%) during prone positioning, and the total duration of neuromuscular blockade use was 6.2 ± 5.7 days. Complications attributable to prone positioning were skin abrasion (three patients) and unintended extubation (one patient).

No statistically significant difference was found between survivors and nonsurvivors in terms of clinical characteristics, arterial blood gas exchange variables, or ventilator variables just before prone positioning (Tables 1 and 2). When all enrolled patients were stratified by level of illness severity (SAPS II score ≤ 49 vs. > 49 on the day of prone positioning) [13], no significant difference was observed. Of all enrolled subjects, 72.9% and 14.6% patients had received inhaled NO and ARM therapy, respectively, but no outcome difference was associated with the inhaled NO and/or ARM trial (Table 1).

Early gas exchange responses after prone positioning and clinical outcomes

After prone positioning, we found 60 (62.5%) and 51 (53.1%) patients who met our definitions as PaO_2 and $PaCO_2$ responders. For all PaO_2 responders, the mean PaO_2/FiO_2 increase at 8 to 12 hours of prone positioning was 75.4 ± 47.2 mmHg (median, 64.3; range, 20 to 215) and for all $PaCO_2$ responders, the mean $PaCO_2$ change was - 10.6 ± 10.3 mmHg (median, - 7.4; range, - 42 to 1).

We found that the PaO_2 response, but not the $PaCO_2$ response, was associated with an improved 28-day outcome (Tables 3 and 4). The Kaplan-Meier estimate of survival at 28 days showed the same result (Fig. 1A and 1B). When we classified four subgroups from the PaO_2 and $PaCO_2$ data, we identified 38 PaO_2 response and $PaCO_2$ response patients (39.6%), 22 PaO_2 response and $PaCO_2$ non-response cases (22.9%), 13 PaO_2 nonresponse and $PaCO_2$ response subjects (13.5%), and 23 PaO_2 nonresponse and $PaCO_2$ nonresponse patients (24.0%). We found that both PaO_2 and $PaCO_2$ nonresponders had lower survival rates than other subgroups (Fig. 1C).

However, no significant difference in clinical characteristics between PaO_2 and $PaCO_2$ responders and nonresponders was observed (Table 3, data not shown for $PaCO_2$ responders and nonresponders). Furthermore, no difference was found between survivors and nonsurvivors in ventilator parameters or gas exchange values collected just before or around 8 hours after first placement in the prone position (Table 4).

DISCUSSION

To our knowledge, this is the first study to investigate clinical characteristics and outcomes in severe ARDS patients under conditions of prolonged prone positioning in Korea. We found that all PaO_2 responders showed oxygenation improvement soon after prone positioning, and those patients who maintained the oxygenation improvement at 8 to 12 hours after first prone positioning seemed to have better outcomes. Some of our study subjects underwent various adjuvant therapies for improved oxygenation, but no significant difference in the number of patients treated with adjuvant therapies or the duration of therapies was found between PaO_2 responders and non-responders. Thus, our findings indicate that the oxygenation improvement was likely primarily due to prone positioning, not to the adjuvant therapies. We also observed a low rate of complications related to prolonged prone positioning, consistent with previously reported clinical trials [14,15,24]. Our data suggest that using the prone position for prolonged periods of time is both feasible and safe, and this reinforces the idea that a beneficial effect may be expected if prone oxygenation is applied early and continuously, as has been reported in some clinical studies [14,15].

However, these patients with prolonged prone positioning usually require continuous deep sedation using analgesics, sedative agents, and neuromuscular blocking agents, as seen in our study. This continuous deep sedation may be harmful to patients and may be associated with a prolongation of mechanical ventilation, which can increase a patient's likelihood of developing specific complications, including ventilator-associated pneumonia, barotraumas, airway complications (*e.g.*, tracheal stenosis and ulceration), and unanticipated extubation, with resultant arterial oxygenation. It may also be risky because early recognition of brain injury through communication and neurologic examination often is severely limited [16,17,25]. Thus, our results may provide tips to physicians for predicting clinical parameter(s) associated with better outcomes in patients with prolonged prone ventilation.

Our data differ in some aspects from those in a previous report; Gattinoni et al. [18] reported that improved survival at 28 days was significantly associated with decreases in $PaCO_2$, but not with PaO_2 increases, during first session placement in the prone position. In our study, the $PaCO_2$ response to the first prone positioning in ARDS patients with prolonged prone positioning was not associated with survival. Unlike the cases studied by Gattinoni et al. [18], all of our patients had severe ARDS, with much decreased alveolar ventilation and CO_2 elimination. Accordingly, it is possible that our patients had a higher total minute ventilation/$PaCO_2$ ratio (an approximate surrogate for the dead space tidal volume ratio) before prone positioning than did the patients in the study by Gattinoni et al. [18]. Also, many of our patients had pulmonary ARDS with increased stiffness of the thorax and insufficient alveolar ventilation.

Our study has several limitations. First, the study was retrospective in design, and we could not strictly control the various factor that affect the gas exchange response during prone ventilation (especially ventilator parameters). Second, we expected that specific subgroups formed by combining PaO_2 and $PaCO_2$ responders/non-responders to define four subgroups would have differed in outcome, and that those patients who had the most severe form of ARDS (SAPS II score > 49) would benefit from prone positioning; however, we were unable to draw such conclusions, possibly due to the small numbers of enrolled patients. Third, this study was carried out in only one hospital, and it may not represent the general situation.

In summary, we found that improved oxygenation at 8 to 12 hours (PaO_2 response) in patients positioned prone for a long period (≥ 12 hours) was associated with an improved 28-day outcome. Thus, patients with severe ARDS who show initial PaO_2 improvement (more than ≥ 20 mmHg) after prone ventilation seem to be appropriate candidates for prolonged prone ventilation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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