Effects of Prone Position on Inflammatory Markers in Patients with ARDS Due to Community-acquired Pneumonia

Ming-Cheng Chan,1,2 Jeng-Yuan Hsu,1 Hsiu-Hwa Liu,3 Yao-Ling Lee,4 Su-Chen Pong,2 Li-Yin Chang,2 Benjamin Ing-Tiau Kuo,5 Chieh-Liang Wu6-7*

Background/Purpose: Acute respiratory distress syndrome (ARDS) is a serious disorder of intensive care unit patients. We evaluated the safety of continuous prone position ventilation (PRONE) and its effects on oxygenation and plasma cytokine concentrations in patients with ARDS caused by severe community-acquired pneumonia (CAP).

Methods: This was a prospective observational clinical study conducted in a respiratory intensive care unit of a 1200-bed medical center in central Taiwan. Twenty-two patients with severe CAP and ARDS were included. They were treated by traditional supine ventilation (SUPINE, n = 11) or PRONE (n = 11) if they met the criteria for ARDS. Patients in the PRONE group were ventilated in prone position continuously for at least 72 hours. Plasma cytokines were collected and analyzed at baseline, 24 hours and 72 hours after enrolment. Serial PaO2/FiO2 and complications were evaluated.

Results: Complications associated with PRONE were minor and self-limited. PRONE had higher PaO2/FiO2 ratio than SUPINE did at 48 hours after enrolment. The levels of plasma IL-6 concentration declined significantly with time in the PRONE group (p = 0.011). The levels of plasma IL-6 concentration at enrolment, 24 hours and 72 hours after enrolment also predicted the 14th day mortality of all patients.

Conclusion: PRONE was a safe and effective maneuver for improving oxygenation in patients with severe CAP and ARDS. PRONE also influenced IL-6 expression in patients with severe CAP. [J Formos Med Assoc 2007;106(9):708–716]

Key Words: adult respiratory distress syndrome, ARDS, CAP, community-acquired pneumonia, continuous prone position ventilation

Acute respiratory distress syndrome (ARDS) is a serious disorder of intensive care unit patients. The morbidity and mortality rates associated with ARDS are considerable, with significant impact on public health.1 Among the diverse etiologies of ARDS, pneumonia is the most common one.2 Pro-inflammatory and anti-inflammatory cytokines are important mediators in host response to infection. Puren et al demonstrated the expression pattern of cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6 and IL-10, in patients with community-acquired pneumonia.
Ventilatory support is generally required for managing these patients and the avoidance of ventilator-induced lung injury is an important issue. In an animal model, mechanical ventilation strategy affected the release of cytokines into the systemic circulation. Furthermore, the increase in systemic cytokine concentration may lead to the development of multiple system organ failure.

A protective ventilator setting strategy, which consists of low tidal volume (VT) and high positive end-expiratory pressure (PEEP), has been proven to reduce overall mortality. Low VT ventilation is associated with a more rapid attenuation of the inflammatory response. Gattinoni et al reported that prone position ventilation did not influence the overall outcome, but the 10-day mortality was improved in patients with lower PaO₂/FiO₂. Furthermore, prone position placement may lower the incidence of ventilator-associated pneumonia. However, adverse events of prone position ventilation are also a concern while applying this maneuver. The longer duration seemed to be associated with more complications, but several studies indicated that 12 or even 18 hours of prone position ventilation was a safe procedure and allowed for a continuous improvement in oxygenation throughout the entire session.

Prone position ventilation and PEEP have additive effects in improving oxygenation in patients with diffuse infiltrates. It can also attenuate ventilation-associated lung injury by recruiting the atelectatic lungs. We expected that prone position ventilation could influence cytokine expression. Thus, we conducted a prospective observational study to verify this hypothesis and assessed the oxygen responses and prone position ventilation-related complications.

Materials and Methods

Patients

This was a prospective observational clinical study that was conducted from September 2002 to December 2003 at Taichung Veterans General Hospital (TCVGH), a 1200-bed medical center in central Taiwan. The protocol and procedure for obtaining informed consent were reviewed and approved by the ethics committee/institutional review board of TCVGH. Patients with acute respiratory failure caused by severe CAP were enrolled in the study. CAP was defined as fever plus cough with purulent sputum production, and infiltrates over chest X-ray within 72 hours of admission. The patients must not have been admitted 14 days before this admission. All of them met the criteria for ARDS as defined by the American–European Consensus Conference. The onset of ARDS had to be within 72 hours before enrolment.

We performed Gram’s stain and culture of tracheal aspirate, urine pneumococcal and Legionella antigen test, and serology test for Chlamydia, Legionella and Mycoplasma for pathogen diagnosis. Patients were assigned to either the continuous prone position ventilation (PRONE) or traditional supine ventilation (SUPINE) group according to the in-charge physician’s decision. The following demographic, clinical and laboratory data were recorded: age, sex, comorbidities, survival rate, daily blood analysis and chest X-ray. Acute Physiology and Chronic Health Evaluation (APACHE) II score and lung injury score (LIS) were also calculated.

The definition of comorbidities was as follows: chronic lung diseases including chronic obstructive lung disease and interstitial lung disease; cardiovascular diseases including coronary artery disease, cardiomyopathy and valvular heart disease; chronic liver diseases including chronic hepatitis B, C and liver cirrhosis; chronic renal disease defined as plasma creatinine > 1.5 mg/dL for more than 6 months. Facial swelling was determined by direct observation of whether or not the lips or face were edematous. Nipple, knee and iliac swelling were defined as the presence of pitting edema over those areas. We used nasogastric pump infusion to improve feeding if the residual amount of nasogastric suction before feeding was more than half of that fed 2 hours ago.

Patients were excluded if they had one of the following: home oxygen use needed, pulmonary tuberculosis, malignancy under chemotherapy, AIDS, organ transplant or autoimmune disease.
under immunosuppressant therapy, bone fracture and spine instability.

**Treatment protocol and PRONE**

According to our ARDS treatment protocol, all patients had Swan-Ganz catheter placement and arterial line for hemodynamic monitoring (including cardiac index, pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary arterial pressure) and blood sampling. All of them received continuous oxygen saturation monitoring by pulse oximeter. The choice of antibiotics was based on the guidelines of the American Thoracic Society for CAP and clinical condition as diagnosed by the in-charge physician. During the study period, all patients were sedated with a continuous infusion of midazolam and received neuromuscular blockade with atracurium besylate.

Patients were placed in prone position according to a step-by-step protocol by two nursing staff, one respiratory therapist and a physician. One nurse kept all the tubes and catheters from being dislodged during the procedure. Patients were placed on a silicone pad (Action Products Inc., Maryland, USA), and dependent parts, including the hip and face, were on a silicone cushion. Patients were kept prone continuously for at least 72 hours and faced right or left alternately every 2 hours to avoid pressure sore formation. A nasogastric tube was inserted and a pump was used for continuous slow feeding. The sputum was suctioned with a closed system suction tube (PHASCO Inc., Taiwan). All patients were intubated and underwent mechanical ventilation with volume control mode in both groups. The protective strategy of low tidal volume was then applied. The tidal volume was around 6–8 mL/kg of ideal body weight. PEEP was adjusted to achieve better oxygenation. The allowable combinations of PEEP (H2O) and FiO2 at enrolment were: 5–8/0.6 or less, 10–12/0.7, 12–14/0.8, 14–16/0.9 and 16–18/1.0. The FiO2 was adjusted to keep SpO2 above 90%. After oxygenation was improved and clinical condition stabilized, FiO2 was tapered gradually. PEEP was lowered gradually when FiO2 was less than 60%. Patients were turned to the supine position when SpO2 > 90% with FiO2 < 60% for more than 24 hours after 72 hours of PRONE.

**Cytokine measurement**

Levels of cytokines were determined by commercial ELISAs in accordance with manufacturer instructions. ELISA kits for detection of TNF-α, IL-6, IL-10 and IL-1β were obtained from BioSource International Inc. (Camarillo, CA, USA). The measuring ranges for cytokines were 0–62.5 pg/mL for TNF-α and IL-1β, 0–500 pg/mL for IL-6, and 0–125 pg/mL for IL-10.

**Statistical analysis**

Demographic data including age, LIS score, APACHE II score, PEEP and Vt are expressed as mean ± standard deviation. Plasma cytokine concentrations are expressed as mean ± standard error. Mann–Whitney test was used to compare the clinical variables, PaO2/FiO2 ratio and FiO2 at different time points between the groups, and the plasma cytokine concentration between patients in the 14-day survival and mortality groups. Serial plasma cytokine levels were examined by one-way ANOVA and post hoc analysis was performed by Scheffe’s test. Analysis was performed with SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) for Windows. The significance level was set at p = 0.05.

**Results**

**Patients**

Eleven patients received PRONE and the others were placed in supine position after enrolment. The demographic data are listed in Table 1. There was no difference in comorbidities, including diabetes, cardiovascular, liver, renal and cerebrovascular diseases, between the two groups. In addition, there was no difference in LIS, APACHE II score and the ventilator setting of PEEP and Vt between the two groups at enrolment. The 14-day survival rate was 81.8% in the PRONE group and 72.7% in the SUPINE group. The 28-day combined survival rate was 63.6% for the two groups. The mortality rates were similar in both groups.
Complications of PRONE

The PRONE group had more position-related complications, such as vomiting, tissue swelling and pressure sores (Table 2). Nine patients in the PRONE group had facial swelling but only one did in the SUPINE group \( (p < 0.05) \). Two patients had vomiting in the PRONE group but none did in the SUPINE group. Eight patients in the PRONE group needed nasogastric pump infusion to improve feeding but only two in the SUPINE group did \( (p < 0.05) \). No patients in either group had dislodgment of the endotracheal tube, Swan-Ganz catheter, arterial line or venous access. There was only one episode of pneumothorax in the SUPINE group. Facial swelling soon resolved after the patient was turned back to the supine position. The pressure sores did not lead to major sequelae. The hemodynamic profile (including cardiac index, pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary arterial pressure)
pressure) was not significantly different between the SUPINE and PRONE groups at baseline, and 24 hours and 72 hours after enrolment.

**Improvement in oxygenation**

There was no difference in the PaO$_2$/FiO$_2$ ratio between the two groups at enrolment. The PaO$_2$/FiO$_2$ ratio increased steadily in the PRONE group (one-way ANOVA, $p = 0.002$), but not in the SUPINE group ($p = 0.064$). In a *post hoc* analysis, we found that the difference was between baseline and 48 hours in the PRONE group ($p = 0.002$) (Figure 1). The FiO$_2$ was lowered more rapidly in the PRONE group, but did not reach statistical significance (Figure 2). There was no statistically significant difference in PaCO$_2$ between the two groups (Figure 3).

**Change of cytokine expression with PRONE**

The average plasma cytokine concentrations, including IL-10, IL-6 and TNF-α, at baseline, 24 hours and 72 hours after enrolment are shown in Table 3. Plasma IL-1β was measured, but most of the results were below the detection threshold. We found that plasma IL-6 concentration declined steadily in the PRONE group (one-way ANOVA, $p = 0.011$). A *post hoc* analysis found that the difference was between baseline and 72 hours in the PRONE group.

**Correlation of cytokine expression with disease severity and outcome**

We compared the cytokine expression between survivors and non-survivors at 14 days after enrolment (Table 4). Those who survived 14 days after admission had lower plasma IL-6 concentrations than those of the non-survivors at baseline.

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### Table 2. Complications associated with continuous prone position ventilation*

<table>
<thead>
<tr>
<th></th>
<th>PRONE ($n=11$)</th>
<th>SUPINE ($n=11$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial swelling</td>
<td>9 (81.8)</td>
<td>1 (9.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Eye swelling</td>
<td>5 (45.4)</td>
<td>3 (27.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Nipple swelling</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Knee swelling</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Iliac swelling</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure sores</td>
<td>2 (18.2)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (18.2)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Nasogastric pump infusion</td>
<td>8 (72.7)</td>
<td>2 (18.2)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Data are presented as n (%). NS = not significant.
24 hours and 72 hours after enrolment ($p=0.007$, 0.011 and 0.049, respectively). But plasma IL-6 concentration was not correlated with APACHE II score at admission.

**Discussion**

This is the first report to examine the safety and oxygenation response of prone position ventilation...
for more than 24 hours and assess the cytokine expression between PRONE and SUPINE groups. We found that the best oxygenation improvement was at 48 hours after PRONE. We also found that plasma IL-6 concentration, as a marker of systemic inflammation, declined steadily in the PRONE group. These results might suggest a close relationship between systemic inflammation and prone position ventilation.

Refractory hypoxemia is a devastating and dangerous condition in the management of ARDS. Although 6 or 8 hours of prone position ventilation improves PaO2/FiO2 ratio, some patients may experience desaturation when they are turned back to the supine position. We found that there was a continuous increment of PaO2/FiO2 ratio after applying our PRONE protocol continuously for at least 48 hours. There were more increments in the PaO2/FiO2 ratio in the PRONE group than in the SUPINE group, and the difference reached statistical significance at 48 hours after enrolment. The PRONE patients benefited from improvement in oxygenation by a rapid decline of FiO2. The PaO2/FiO2 ratio was not different between PRONE and SUPINE groups at 72 hours after enrolment. The reason may be newly developed atelectasis in the PRONE group after continued prolonged prone position ventilation. Another possible explanation is that PRONE and high PEEP recruited the lungs more rapidly than high PEEP alone. However, after 72 hours, most of the atelectatic lungs were recruited by high PEEP alone. Furthermore, no patient experienced desaturation after turning to the supine position. Although longer duration of prone positioning had the advantage of oxygenation, the complications of PRONE were still a concern. In order to minimize cutaneous ulcerations, we put a silicone pad under the dependent part of the body. Most of the complications related to prone positioning were minor and most subsided spontaneously in 1–2 days after turning patients to the supine position. In this study, none of the PRONE patients experienced a severe adverse event while changing position. With the application of our protocol, the complications associated with changing position can thus be minimized.

In addition, the nursing staff workload can be reduced because a patient’s position does not have to be changed so often. Therefore, early application of PRONE for at least 48 hours in patients with severe CAP and ARDS should be a safe and effective maneuver for improving oxygenation.

Cytokines are important mediators of infection and inflammation. The etiology of ARDS encompasses a heterogeneous group of diseases. In order to minimize the heterogeneity, we measured the plasma cytokine concentration of patients with a single disease entity, severe CAP with ARDS. Most of the plasma IL-1β concentrations were below the detection threshold. In pneumonia, the lung is the site of the initial inflammatory response to the pathogens and the cytokine expression in pneumonia is compartmentalized in the lungs. IL-1β concentration in bronchoalveolar lavage fluid is a marker of bacterial burden in pneumonia, but the systemic concentration is low or even undetectable. We suggest that IL-1β, as an early response cytokine of inflammation, is compartmentalized in the lung.

Comparison with baseline level, plasma IL-6 concentration declined steadily in the PRONE group. This result demonstrated that PRONE could influence plasma cytokine concentration. The conventional mechanical ventilation setting can induce a cytokine response that may be attenuated by a protective strategy to minimize overdistension of the “good” lung and cyclic opening and collapsing the atelectatic part. Cytokine expression, both in bronchoalveolar lavage fluid and plasma, is exaggerated with ventilator-induced lung injury. With a protective ventilator strategy, the plasma IL-6 concentration was lower in comparison with the conventional setting. Furthermore, in animal models, the injurious ventilator setting can increase cytokine production in the lung parenchyma and affect the release of cytokines into the systemic circulation, and prone position ventilation could attenuate the histologic change in oleic acid-induced acute lung injury. In acute lung injury, the non-dependent part is continuously open to ventilation and the dependent part is atelectatic and consolidated. Prone position ventilation can
not only improve oxygenation, but also, as a means of recruitment maneuver, attenuate ventilation-induced lung injury by increasing the homogeneity of transpulmonary pressure distribution.\textsuperscript{14} It could also delay the progression of ventilation-induced lung injury.\textsuperscript{25} Therefore, it was one of the reasons why PRONE could influence plasma IL-6 concentration over time. Another possible mechanism responsive to the change in cytokine expression might be rapid lowering of FiO\textsubscript{2} in the PRONE group. Hyperoxia may lead to the development of acute lung injury, and increased IL-6 level is associated with exposure to high oxygen concentration.\textsuperscript{26} With exposure to a lower concentration of oxygen in the PRONE group, the plasma IL-6 concentration was also lower than that in the SUPINE group.

We also found that patients who survived 14 days after admission had lower plasma concentrations of IL-6 than those of non-survivors. Plasma IL-6 concentration is associated with disease severity of CAP.\textsuperscript{20} The APACHE II score was lower in those who survived to 14 days after admission (22.24 ± 4.55 vs. 30.6 ± 9.56, respectively; \( p = 0.031 \)), but was not related to plasma IL-6 concentration.

The present study was limited by the relatively low number of patients that were included. However, we did our best to ensure the similarity of patients' characteristics, not only in the diagnosis but also in the severity with nearly the same disease course. During the study, we found that PRONE was a safe and effective maneuver to improve oxygenation up to at least 48 hours. Most of the complications were minor and self-limited. PRONE, as a recruitment maneuver, can influence plasma cytokine expression in PRONE patients. In addition, plasma IL-6 concentration was correlated to outcome in patients with severe CAP and ARDS. However, the interplay of these cytokines is complex. Further study is necessary to consolidate our hypothesis.

Acknowledgments

We thank Ms. Shiang-Liang King and Tsai-Yun Lee for data processing and statistical assistance.

References


