Prone positioning in acute respiratory distress syndrome (ARDS): When and how?

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Summary

Acute respiratory distress syndrome (ARDS) is a severe form of respiratory failure. It remains one of the most devastating conditions in the intensive care unit. Mechanical ventilation with positive end-expiratory pressure is a cornerstone therapy for ARDS patients. One adjuvant alternative is to place the patient in a prone position. Since it was first described in 1976, prone positioning has been safely employed to improve oxygenation in many patients with ARDS. Prone positioning may also minimize secondary lung injury induced by mechanical ventilation, although this benefit has not been investigated as extensively, despite its potential. In spite of a strong physiological justification, prone positioning is still not widely accepted as an adjunct therapy in ARDS patients and it is only used regularly in only 10% of ICUs. This may be explained in part by the reluctance to change position, risks and unclear effects on relevant outcomes. In this paper, we review all aspects of prone positioning, from the pathophysiology to the clinical studies of patient outcome, and we also discuss the latest controversies surrounding this treatment.
accepted as an adjunct therapy in ARDS patients and it is only used regularly in only 10% of ICUs [7]. This may be explained in part by the reluctance to change position, risks and unclear effects on relevant outcomes. In this paper, we review all aspects of prone positioning, from the pathophysiology to the clinical studies of patient outcome, and we also discuss the latest controversies surrounding this treatment.

Physiological effects of prone positioning

The gravitational gradient in pleural pressure

Due to the effects of gravity, pleural pressure in the supine position becomes less negative (that is, more positive) throughout the vertical gradient that runs from the ventral zones near the sternum towards the dorsal areas [8,9]. It is important to remember that, in order to maintain the alveoli open, the transpulmonary pressure (the alveolar pressure minus the pleural pressure) must be greater than the alveolar closure pressure. In the supine position, the transpulmonary pressure will be greater in the ventral area (not dependent on the gravitational gradient) and lower in the dorsal area (dependent on the gravitational gradient). To this gradient we must add the weight of the edematous lung, which is characteristic of ARDS. These two factors will cause collapse in the dependent areas.

Several experimental studies have shown that prone positioning lowers these pleural pressure gradients [10,11]. Thus, pleural pressures in the dorsal regions (dependent) now ventral become more negative. The transpulmonary pressure increases and surpasses the pressure for alveolar closure and, as a result, the alveoli are able to open (recruitment). Conversely, pleural pressure in the ventral regions (non-dependent) now dorsal becomes less negative (or more positive). The transpulmonary pressure decreases but continues to remain above the alveolar closure pressure so that most of the alveoli in this area remain open [12] (figure 1).

Effect on motility of the diaphragm

Sedation and muscle paralysis reduce diaphragm tone. In the supine position, the weight of the abdomen causes the posterior part of the diaphragm to migrate towards the head, thus promoting collapse due to atelectasis [13]. In the prone position, this migration secondary to the effect of the abdomen is more uniform and results in a lower propensity to collapse [14].

Effect of compression of the heart

Interaction between the heart and the lungs also influences the distribution of ventilation in supine and prone positions. In the supine position, the mediastinal structures, especially the heart, are supported by the lung, which lies below; in the prone position, however, these structures rest on the sternum. In healthy individuals placed in the supine position, the percentage of lung volume situated below the heart is approximately 40% of the left hemithorax while in prone position it is less than 5% [15,16] (figures 2 and 3). This effect can be more marked in the presence of cardiomegaly or dilatation of the right cavities due to pulmonary hypertension [17].

Effect on the mechanical properties of the chest wall

In the prone position, the overall compliance of the chest wall decreases. The anterior chest wall, which in supine position remains free and elastic, becomes more rigid in the prone position due to contact with the hard surface of the bed even as the posterior chest wall maintains its rigidity due to the vertebrae and the paravertebral musculature. This uniformity helps to homogenize ventilation [18,19].

Effect on lung perfusion

Regional perfusion is always predominantly directed to dorsal rather than ventral lung regions, regardless of patient position (supine or prone). The determinants of this perfusion gradient are not clear but seem to be secondary to the effect of gravity [20].

Effect on drainage of respiratory secretions

Due to the effect of gravity, prone ventilation may promote drainage of bronchial secretions [21].

The results of these physiological effects

Effects of prone position on gas exchange

Oxygenation improves thanks to the confluence of several different physiological effects described above, which can be reduced to two principal effects [19].
The first is related to the increased recruitment that occurs in the dorsal lung versus partial derecruitment experienced by the ventral lung areas.

The second mechanism is associated with the greater normalization of the ventilation-perfusion (V/Q) ratio secondary to a better redistribution of ventilation in the dorsal regions of the lung where perfusion is maintained. However, as we will see later, improved oxygenation by itself does not imply a lower death rate in ARDS patients. While this benefit was the earliest justification for prone positioning, today it seems insufficient. Refractory hypoxemia “per se” only accounts for 20% of deaths in these patients while the remaining 80% may be due to multiple-organ failure [22].

**Effects of prone position on respiratory mechanics**

Various studies have shown an improvement in overall respiratory system compliance (lung plus chest wall) [23–25]. The improvement in lung compliance secondary to recruitment in the dependent areas is generally greater than the decrease in compliance of the thoracic cage that occurs with the change in posture, as we stated previously. However, if the change in position results in only a small or nonexistent change in pulmonary recruitment, the overall compliance of the respiratory system is unchanged [8] or may even decrease.

**Prone position as a lung protection strategy**

Ventilation by itself can aggravate pulmonary lesions caused by ARDS [26]. This ventilator-induced lung injury (VILI) is mainly associated with overdistension of the alveoli, promoted by large tidal volumes and an elevated plateau pressure (defined as the pressure in the alveoli at the end of inspiration), and the repetitive opening and closure of lung units (volutrauma) [27]. In addition, these alveolar lesions can activate or propagate an inflammatory response outside of the lung that could lead to multi-organ failure (biotrauma) [28]. Nowadays, it is accepted that, while improving oxygenation is important, attenuation of VILI is likely one of the primary mechanisms involved in improving survival in this subgroup of patients [29]. Prone positioning could attenuate these reactions by homogenizing ventilation and by reducing lung strain and stress induced by the ventilation [30]. Experimental models have shown that histological lesions in the lung are less severe when animals are ventilated in prone position [6,31]. In humans, a decrease in the inflammatory interleukins in the
lungs of patients ventilated in the prone position has been shown [32].

**Clinical response to prone positioning**

**Responders versus nonresponders**

An increase in PaO₂/FiO₂ of at least 20% (or more than 20 mmHg) as the patient is maneuvered into prone position is usually considered a good response in terms of oxygenation. Using these criteria, 60–80% of patients with ARDS respond favorably [23,25,33–37]. Effects of positioning are, in general, seen after a relatively short delay (less than 1 hour). In a few patients, a late response to prone positioning of up to 4 hours after turning may be observed and for this reason it has been suggested that prone positioning be maintained for a minimum of 4 hours or more to detect late responders [38]. When returned to supine position, some patients maintain improvement in PaO₂, while others do not [38]. The explanation is unclear but improved secretion removal during prone position and the maintenance of recruited dorsal alveoli once in supine position may be some of the reasons that explain a persistent response. It has also been observed that patients who respond favorably to the initial prone positioning trial will probably respond in subsequent occasions. However, a lack of response in the initial attempt is usually predictive of continued nonresponse [34].

**Predictors of a good response**

Some studies have evaluated the effect of pulmonary lesion distribution (as seen on the thoracic CT scan) on the response to prone positioning; however, no differences have been found. The benefits on oxygenation can occur in both lobar and diffuse ARDS [39]. The origin of the ARDS (pulmonary or extrapulmonary) does not appear to influence the response to prone position [40], although ARDS duration does seem to have some relation. Response is more favorable at the beginning of the disease compared to later stages when fibrosis is present [23,36]. The PCO₂ tends to increase when the lung lesions worsen, and an increase in dead space is a prognostic marker for the expected course of ARDS [41]. Thus, a decrease in PCO₂ following pronation in patients with constant minute ventilation has been associated with greater survival [42]. In this case, the decrease in PCO₂ is an indirect sign of recruitment and a decrease in the dead space. It is interesting to note that the PO₂ response has not been shown to impact survival.

**Technique, contraindications and complications**

This is a delicate maneuver requiring a systematic approach and a training period. In addition, it involves an increased workload for the nursing team, who may initially be reticent [43] (see box 1 and see video in Supplementary material). However, no special equipment is necessary and it can be used with a large proportion of ICU patients. Even though there are no absolute contraindications to pronation [44], it does not seem to be indicated for pregnant women or in patients with severe burns, facial lesions, spinal column instability, pelvic fractures, open abdomens, or (perhaps) in those with hemodynamic instability. Head injury could also be a relative contraindication due to compression of the jugular veins. Patients with tracheotomy could present logistical difficulties (box 2). The experience of the team may probably influence which kind of patients are turned prone.

In general, while minor complications may be relatively common, severe complications are quite rare and largely avoidable, though potentially lethal. However, it is important to highlight the fact that published data comes from groups with extensive experience with this technique and, therefore, the risk of severe complications may be greater than reported. The most common complications are pressure sores due to skin compression and facial edema, which is usually more noticeable for the patient’s family. Other complications that may occur are transient episodes of hypoxemia due to desynchronization with the respirator, arterial hypotension and arrhythmias, inadvertent chest tube removal, and loss of venous access.

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**Box 1**

**Recommendations for performing the intervention (see video in the Supplementary material)**

It is recommended that five people assist with the intervention. The expected duration of the intervention is from 10–15 minutes. A physician should be positioned at the headboard of the bed and take charge of the intubation tube. In addition, two people should be positioned on each side of the patient. The intubation tube should be checked to assure proper placement. Consider sedation administration by bolus and muscle relaxants. Place protection plates/shields at the knee level, iliac crests, mamilla/nipples, and face. Depending on the position of the ventilator and the perfusion pumps, decide whether the turn will be rightward or leftward. Remove ECG leads and patches.

Mobilize the patient in two steps. First, perform lateralization and then pronation. This is the trickiest part of the intervention. Reattach ECG leads and patches and verify correct monitoring. Place the patient in the position similar to a swimmer in the crawl position: one arm flexed forward and the other straight along the length of the thorax. The head should be turned towards the straight arm (figure 6). Systematic tracheal aspiration. Bed in anti-Trendelenburg to prevent facial edema. The position of the arms and head should be inverted every 2 hours to avoid eschar (bed sores, pressure sores, etc.).

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Prone positioning can lead to selective intubations and transient obstruction of the endotracheal tube but does not increase the risk of accidental extubation, which occurs in less than 1% of cases. On the other hand, some data suggest that patients treated with prone positioning may have a lower incidence of ventilation-associated pneumonia [45,46]. It is important also to keep in mind that episodes of cardiac arrest during the intervention, caused by inadvertent dislodging of a Swan-Ganz catheter during turning, have been described, although in this case reversal was successful [47].

Prone positioning may require an increase in sedation and muscle relaxants, with up to 25% of cases (depending on the study) requiring an increase in sedation and muscle relaxants during the positional change [48]. In our experience, in most cases, supplemental sedation is only needed occasionally and a single dose of relaxant is sufficient to perform the technique safely. In any case, it is worth pointing out the recent benefit shown by systematic muscle relaxation in patients with severe ARDS [4]. Indeed, early enteral nutrition could be poorly tolerated in these patients [49]. However, a recent study found that larger enteral nutrition volumes could be delivered without increasing vomiting or ventilator-associated pneumonia by employing a strategy that included head elevation in the prone position, increased acceleration of enteral feeding to the target rate, and prophylactic erythromycin administration to enhance gastric motility [50].

Clinical studies and outcomes

Based on the hypothesis that ventilation in prone position is less harmful than in supine position, several studies have tried to demonstrate the benefits of this technique on survival. To date, four large randomized studies have investigated the effects of ventilation in prone position on outcomes in patients with acute respiratory insufficiency. Four studies were performed in adults (table I) and one in children, while a few other small randomized studies [51–53] and several meta-analyses have also been performed.

The first large study to be published was a multicenter Italian study by Gattinoni et al. [54], who randomized 304 patients with ARDS criteria to ventilation in conventional or prone position for a mean of 7 hours per day for approximately 4 days. Despite the positive effect on oxygenation, the authors found no significant benefits in terms of mortality. However, a post-hoc analysis the authors showed that prone positioning presented a reduction in the relative risk of death on the 10th day compared to conventional positioning in the most gravely ill patients (based on severity scores) and in patients with greatest degree of hypoxemia. This tendency disappeared on discharge from the ICU, but leads one to believe that perhaps the dose in prone position was insufficient.

The second study was the multicenter French study by Guerin and al. [55], in which a heterogeneous sample of patients with acute respiratory insufficiency was pronated for 8-hour sessions for approximately 4 days. The main problem with this study is that of the 791 randomized patients, only 31% met the classic criteria for ARDS. The only significant difference observed in that study was a decrease in the incidence of ventilation-associated pneumonia in the pronation group.

The third study was the Spanish multicenter study carried out by Mancebo et al. [47]. In contrast to previous trials, this study introduced new concepts, including early pronation, long daily sessions, and prolonged treatment, which were performed until both groups presented weaning criteria and protective ventilation. A total of 136 patients with severe ARDS were randomized to prone sessions lasting a mean of 17 hours per day for 10 days. The study had to be discontinued early due to insufficient recruitment of patients. Even so, the results showed a strong (though not significant) tendency to reduce ICU deaths (43% in the prone group vs. 58% in the conventional group, P = 0.12), with an absolute reduction in deaths of 15%.

The fourth large and most recent study was once again an Italian study led by Taccone et al. [48]. Based on the findings from their first study [54], and borrowing from the methodology employed by the Spanish study, the authors randomized 342 ARDS patients to undergo 18-hour sessions (daily average) for 8 days. In addition, they stratified the patients into two groups based on disease severity as measured by the degree of hypoxemia (moderate if PaO₂/FiO₂ < 200 mmHg and severe if < 100). The study found no significant differences in mortality at 28 days or overall (31% in the prone group vs. 33% in the standard group, P = 0.72). Nor were any significant differences found in the subgroup of patients with severe disease (P = 0.12). Overall, this study demonstrated that the prone position is a safe and effective strategy for improving oxygenation in critically ill patients with severe ARDS.

Clinical studies and outcomes

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### Table I
Main features of the largest controlled studies in adults

<table>
<thead>
<tr>
<th></th>
<th>Prone-supine I</th>
<th>Guérin et al.</th>
<th>Mancebo et al.</th>
<th>Prone-supine II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (n)</strong></td>
<td>304</td>
<td>791</td>
<td>136</td>
<td>342</td>
</tr>
<tr>
<td><strong>Enrollment criteria</strong></td>
<td>ALI/ARDS with PEEP ≥ 5 cmH₂O</td>
<td>Hypoxemic acute respiratory failure. Only 31% ARDS</td>
<td>ARDS with four-quadrant infiltrate in chest X-ray</td>
<td>ARDS with PEEP ≥ 5 cmH₂O</td>
</tr>
<tr>
<td><strong>Enrollment time after intubation</strong></td>
<td>No criteria</td>
<td>No criteria</td>
<td>&lt; 48 h</td>
<td>&lt; 48 h</td>
</tr>
<tr>
<td><strong>Managing ventilation</strong></td>
<td>American-European Consensus Conference on ARDS</td>
<td>No protocol</td>
<td>Tidal volume ≤ 10 mL/kg PEEP: 10–15 cmH₂O and Plateau ≤ 35 cmH₂O</td>
<td>Tidal volume ≤ 8 mL/kg FiO₂ and PEEP titrated according to a predefined table and Plateau ≤ 30 cmH₂O</td>
</tr>
<tr>
<td><strong>Duration of PP (average)</strong></td>
<td>7 hours for 5 days</td>
<td>9 hours for 4 days</td>
<td>17 hours for 10 days</td>
<td>18 hours for 8 days</td>
</tr>
<tr>
<td><strong>Discontinuation criteria for PP</strong></td>
<td>The same PaO₂/FiO₂ than the enrollment</td>
<td>Improvement PaO₂/FiO₂ ≥ 30% with FiO₂ ≤ 60% and PEEP ≤ 8 cmH₂O</td>
<td>PaO₂ ≥ 100 mmHg with FiO₂ ≤ 45% and PEEP ≤ 8 cmH₂O</td>
<td>FiO₂ ≤ 40% and PEEP ≤ 10 cmH₂O</td>
</tr>
<tr>
<td><strong>Predefined weaning strategy</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Main outcome</strong></td>
<td>10-day mortality</td>
<td>28-day mortality</td>
<td>ICU mortality</td>
<td>28-day mortality</td>
</tr>
<tr>
<td><strong>Mortality at the main outcome (Prone vs. Supine)</strong></td>
<td>21% vs. 25% (RR = 0.84 (0.56–1.27))</td>
<td>32% vs. 32% (P = 0.77)</td>
<td>43% vs. 58% (P = 0.12)</td>
<td>31% vs. 33% (P = 0.72)</td>
</tr>
</tbody>
</table>

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; PP: prone position; VAP: ventilator-associated pneumonia; ICU: intensive care unit; RR: relative risk of death (95% confidence interval).

#### Figure 4
Effect of prone ventilation on mortality in severe and moderate baseline hypoxemic subgroups for a range of PaO₂/FiO₂ threshold values

Error bars indicate width of 95% confidence interval of relative risk in the severe (black squares) and moderate (white squares) baseline hypoxemic subgroups. *: interaction P value < 0.05, indicating that treatment effects differed significantly in subgroups with severe and moderate baseline hypoxemia at the PaO₂/FiO₂ threshold; #: treatment effect P value < 0.05, indicating that prone ventilation significantly decreased mortality in the subgroup with severe baseline hypoxemia defined using the PaO₂/FiO₂ threshold (from reference [46], with permission).
with the worst hypoxemia (38% vs. 46% respectively, \( P = 0.31 \)).

The pediatric study was the multicenter American study by Curley et al. [56]. A total of 102 patients, ranging in age from 2 weeks to 18 years of age and with criteria of acute lung injury, were randomized into two groups. The study was discontinued early due to an intermediate analysis showing a lack of effectiveness. The death rate in pediatric patients with this disease is significantly less than in adults (approximately 25% vs. 50%, respectively). Studies with larger sample sizes are needed to detect differences, which is another reason why studies in this group of pediatric patients are difficult to carry out.

As might be expected, no meta-analyses have shown any overall significant differences in mortality [45,57–60]. It is true that when we analyze the heterogeneous populations included in these studies, we find no impact on survival. However, several clues indicate that only the most severely ill patients may benefit from the technique. From a physiological standpoint, the greater the severity of the pulmonary edema, the more heterogeneous is the ventilation and, consequently, the greater the opportunity to normalize ventilation. From a clinical

**Figure 5**

Decision-tree model for the use or not of prone positioning in ventilating patients with ARDS

The limit given (130 mmHg) is the one previously described [46] but because the PaO2/FiO2 ratio depends on several factors, such as the cardiac output, the FiO2 and the PEEP used [63,64], we propose a range of 100–150 mmHg.

ARDS: Acute Respiratory Distress Syndrome.

\*: maximize PEEP to target Plateau Pressure of 28–30 cmH2O with low tidal volume.

**Figure 6**

Patient in prone position simulating a swimmer in the “crawl” position
standpoint, the study by Mancebo et al. [47] had the most restrictive inclusion criteria (only severely ill patients), yet it is the study that obtained the best results. Thus, when patients with severe hypoxemia are evaluated separately from those with moderate hypoxemia, significant differences are found [46,61,62] (figure 4). This would seem to confirm that only this subgroup of severely ill patients presents the necessary physiological prerequisites for this treatment to work. Based on the data from these studies, we have suggested a decision-tree model (figure 5).

Currently, several studies are underway, including a French study being carried out by the Guerin group (ClinicalTrials.gov identifier: NCT00527813). This new French study is based on disease severity, early intervention, and longer treatment times. (Patient in prone position simulating a swimmer in the “crawl” position is available in figure 6).

Conclusions

Prone positioning allows for an improvement in oxygenation in patients with ARDS. This position permits recruitment in the dorsal regions near the diaphragm and homogenizes ventilation. Complications may occur but life-threatening risks are extremely uncommon and it is an inexpensive intervention. We believe that given the current data, early, prolonged prone position should be used by experienced ICUs to treat the most severe ARDS cases, in which mortality continues to be high. In such cases, mortality can be reduced by 10 to 15%, which we consider to be sufficiently clinically relevant taking into account the risk/benefit ratio. Therefore, given our current understanding, we recommend the use of this technique in this subgroup of patients.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References

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