

ARDS: Who Needs to be Pronated?

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Abstract

Acute Distress Respiratory Syndrome (ARDS) is defined as a severe respiratory failure characterized by marked hypoxemia, bilateral infiltrates on the chest X-ray and the absence of signs of cardiogenic pulmonary edema. ARDS treatment remains primarily supportive and the use of mechanical ventilation with positive and expiratory pressure is required to maintain adequate gas exchange. Lung-protective mechanical ventilation strategy decreases mortality and increases ventilator free days. Prone positioning is considered a rescue therapy despite it improves gas exchange through resolution of dorsal atelectases with lung recruitment, better distribution of pulmonary perfusion and reduction of lung stress and strain. Nevertheless, several randomized controlled trials failed to demonstrate a reduction in mortality in pronated ARDS patients. Recent meta-analysis instead demonstrated a significant reduction of mortality in patients with most severe ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio < 200) ventilated in prone position. These data were confirmed by the results of the PROSEVA study, published in June 2013 that reports a 16% reduction of mortality rate. The results of several meta-analysis and this large clinical trial suggest that prone positioning is a useful strategy that saves lives in more severely ill ARDS patients, when applied earlier and for at least 16 hours/day.

Keywords: ARDS; ALI; Prone position; Lung-protective mechanical ventilation

Review

Acute Distress Respiratory Syndrome (ARDS) is characterized, according to the American-European Consensus Conference criteria, by severe respiratory failure, marked hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 200) and bilateral pulmonary infiltrates on the chest X-ray due to a permeability pulmonary edema with no signs of cardiogenic pulmonary edema [1]. A recent definition of ARDS considers not only these routine criteria, but also the timing, the physiological derangements and three different degrees of ARDS (mild, moderate and severe) [1]. ARDS mortality rate remains high [1,2], from 31% to 65% and is related to the severity of the lung injury, the number of failed non-pulmonary organs and patient co-morbidities [1-4]. The 80% of deaths are due to Multiple-Organ Failure (MOF), while the remaining 20% is related to refractory persistent hypoxemia [1].

An etiological therapy is not available and the impairment of gas exchange requires mechanical ventilation. ARDS treatment is primarily supportive and the use of mechanical ventilation with Positive End Expiratory Pressure (PEEP) is required to maintain adequate gas exchange [1]. Ventilation itself might though worsen the underlying lung injury [2]. The reduction of lung compliance and the decreased respiratory compliance in patients with ARDS accelerates the development of high alveolar pressures during mechanical ventilation with consequent onset of parenchymal damage that worsens a severely compromised situation [1].

In ARDS patients lung-protective mechanical ventilation strategy with lower tidal volumes (6-8 mL/kg of predicted body weight), FiO_2 and PEEP titrated to predefined table and end-inspiratory plateau pressure of the respiratory system (P_{plat}) ≤ 30 cm H_2O is recommended to reduce ventilation-induced lung injury (VILI). This ventilation strategy decreases mortality and increases ventilator free-days [1].

Prone positioning was suggested to improve oxygenation and reduce VILI for the first time in 1976 [1], today however its use is still controversial since it is often considered as a rescue therapy [1] and is not widely accepted. Prone position improves gas exchange through the resolution of dorsal atelectases with lung recruitment, a better distribution of pulmonary perfusion and reduction of lung stress and strain [1]. This leads to a decrease in ventilation-perfusion mismatch and improvement of ventilation-perfusion relation [1].

The tidal volume seems to be distributed more homogeneously in the prone position, with possible reduction of VILI and optimal recruitment at a given PEEP [5].

In the supine position transpulmonary pressure (the alveolar pressure minus the pleural pressure) is greater in non dependent areas and lower in dependent areas. This factor, in addition to the weight of the overlying edematous lungs, causes the collapse of the dependent areas. The prone position subverts this situation and allows the recruitment of the alveoli of the dependent areas increasing the transpulmonary pressure and surpassing the pressure for alveolar closure [6]. The transpulmonary pressure decreases in ventral areas (that becomes dependent during prone position) but continues to remain above the alveolar closure pressure so that most of the alveoli in this area remain open [1].

Drainage of bronchial secretions is increased during prone positioning [1], the migration of the diaphragm towards the head is more uniform with a lower propensity to atelectasis [1] and a smaller volume of lung is compressed by the heart [1]. The thoracic shape is similar to a triangle in supine position, allowing the formation of more extensive atelectasis than in prone position, when the thoracic shape is similar to a rectangular [5]. During prone positioning chest-wall compliance is decreased but the improvement of lung compliance due to alveolar recruitment in dependent areas is generally greater than the decrease in compliance of the thoracic cage [6].

Nevertheless, several Randomized Controlled Trials (RCTs) failed to demonstrate a reduction in mortality in prone positioning group [1,2].

Prone position studies on the whole Acute Lung Injury (ALI) and

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ARDS population do not show an improvement of overall survival, although a significant reduction of the mortality rate (about 10%) was observed in the most hypoxemic patients ($\text{PaO}_2/\text{FiO}_2$ ratio < 100 and with Simplified Acute Physiology Score II ≥ 50) [1-4,7].

This significant mortality reduction in the subgroup of most severe patients ventilated in prone position was further confirmed by recent meta-analysis of Sud et al. [8] and Gattinoni et al. [9]. Charron et al. [10] report a 13-year experience of ARDS management combining a low stretch ventilation (plateau pressure < 28 cm H₂O, PEEP 5-7 cm H₂O and controlled hypercapnia) in the prone position in patients with most severe ARDS, demonstrating the routine feasibility of this maneuver and high survival rate. They emphasize the importance of the duration (18 h/day) and timing (24-48 h after intubation) of prone positioning [1]. Also Sud et al. [8] reported a reduction of mortality when prone positioning was maintained longer than 14 hours [9]. Patients respond better in the early stages of ARDS because there is a larger proportion of atelectasia than later, when increases the amount of fibrosis [1](Table 1).

Unfortunately there is a lack of standardization in clinical trials of prone positioning in patients with ARDS: prone position duration, severity of hypoxemia, strategy of ventilation, associated treatments, criteria of enrollment differ significantly among these studies. Abroug F et al. [11] in a recent updated meta-analysis on seven RCTs, including a total of 1,675 adult patients, showed different effects of prone positioning on mortality among the earlier and the most recent clinical trials; earlier studies included patients with different degrees of ARDS illness while most recent trials included only patients with $\text{PaO}_2/\text{FiO}_2$ ratio < 200. A significant reduction in ICU mortality rate was demonstrated only in patients with severe lung injury [1]. Prone positioning seems to be efficient in severe forms of ALI (ARDS) because these patients have a higher percentage of recruitable lung, a greater amount of lung edema and a small portion of aerated lung areas [1]. Another important

difference between older and most recent trials is the duration of the prone treatment, a pivotal determinant for survival benefit. In the most recent studies, prone duration is longer than in older studies [1]. In June 2013, the results of the PROSEVA group study have been published. This was a multicenter, prospective, randomized, controlled trial conducted in 26 ICUs in France and 1 in Spain in patients with severe ARDS treated with prone-positioning sessions of at least 16 hours (mean duration per session of prone positioning was 17 ± 3 hours). The 28-day mortality was 16% in the prone group, versus 32, 8% in the supine group. They also found lower 90-day mortality in patients treated with prone positioning (23, 6% in prone group versus 41% in the supine group) [1]. In this study the most severe ARDS patients selection was achieved not only on the basis of an impaired oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio < 150) but also evaluating PEEP values (> 5 cmH₂O) and FiO_2 concentration (at least 0,6). Patients were enrolled in the study after a period of 12-24 hours mandatory in order to confirm the ARDS diagnosis by using its criteria. The long prone-positioning sessions (>16 hours) should be emphasized and we believe that plays a key role in the increased survival rate showed by Guerin et al. [12]. Mortality reduction in earlier (within 48 hours) and continuously (≥ 20 hours/day, with short periods of supine positioning) pronated patients was previously demonstrated in other RCTs, but the small sample sizes of these studies preclude the statistical significance of these results [1,2]. The study of Guerin et al. included a total of 466 patients, 237 in the prone group and 229 in the supine group, granting a strong statistical significance to the obtained results [13]. Taccone et al. [14] also reached a target of 20 hours/day of prone positioning in the Prone-Supine II Study, not obtaining significant benefit in overall survival [15] (Table 2).

Prone positioning remains a delicate maneuver that requires a systematic approach and a period of training [6]. The technical aspects of prone positioning are not simple and a trained team is required [13]. This technique usually causes minor complications, while severe

Authors	Year	28-day Mortality Prone Supine	P Value	N° Patients Prone Supine	Hours/day in Prone position
Gattinoni L et al.* [17]	2001	21% 25%	0.65	152 152	7 h
Guerin C et al. [12]	2004	32% 32%	0.77	413 378	8 h
Voggenreiter et al. [18]	2005	23.8% 84%	0.27	21 19	11 h
Manchebo et al. ** [19]	2006	43% 58%	0.12	76 60	17 h
Fernandez R et al.# [12]	2008	38% 53%	0.36	21 19	≥ 20 h
Taccone P et al. [13]	2009	31% 32.8%	0.72	168 174	20 h
Guerin C et al. [12]	2013	16% 32.8%	< 0.001	240 234	16 h

* 10-day mortality; ** ICU mortality; # 60-day mortality

Table 1: RCTs comparing prone vs. supine position in ARDS patients

Authors	Year	Population (Prone-Supine)	P Value Overall pts	P Value Subgroup Severely ill patients	n° of RCTs
Tiruvoipati R et al. [14]	2008	1271 (662-609)	0.91	-	5
Alsaghir AH et al. [20]	2008	1271 (662-609)	0.92	0.006*	5
Kopterides P et al. [21]	2009	1271 (662-609)	0.97	0.001*	4
Fessler HE et al. [22]	2010	466 (241-255)	0.41	0.006*	3
Sud S et al. [8]	2010	1786 (919-867)	0.54	0.01**	10
Gattinoni et al. [9]	2010	1573 (764-809)	0.66	0.03**	4
Abroug F et al. [11]	2011	1675 (862-813)	0.39	0.048**	7

*p value in subgroup of patients with SAPS II > 50; **p value in subgroup of patients with P7F < 100

Table 2: Main recent meta-analysis comparing prone vs. supine position in ARDS patients.

complications are rare. Adverse effects described are pressure ulcers, facial edema, removal of vascular catheters, main-bronchus intubation, inadvertent extubation [15,1].

Endotracheal tube displacement and pressure sores due to skin compression are the most common complications [10]. The Prone-Supine II Study shows a high incidence of adverse events such as displacement of vascular lines, transient episodes of hypoxemia or arterial hypotension, arrhythmias, desynchronization with the mechanical respirator and the need for increased sedation [15]. However, the meta-analysis of Abroug et al. [11] did not find a statistically significant increase in major airway complications of prone positioning [16]. Prone position may require deep sedation and muscle blockage during changes of position from prone to supine and vice versa [6]. The study of Guerin et al. [12] did not find differences in the incidence of complications between prone and supine groups [12].

In conclusion, prone positioning is today a determinant factor and a useful strategy that should be applied to the most severe ARDS patients ($\text{PaO}_2/\text{FiO}_2$ ratio < 150) in order to save lives always considering its risks. It's probably time to include this therapeutic maneuver in a routinary ICU protocol for these patients' treatment. Severely ill ARDS patients benefit from prone positioning applied early and correctly for at least 16 hours reducing the mortality rate. We believe that its use should be encouraged.

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