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Review Article

Prone Position for the Treatment of Acute Respiratory Distress Syndrome: A Review of Current Literature

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ABSTRACT

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have high incidence and mortality rates. Most of the recently introduced treatments have failed to improve the prognosis of patients with ALI or ARDS or to reduce mortality. Several studies have shown improved oxygenation in the prone position during mechanical ventilation in patients with ARDS. However, current evidence strongly suggests that placing ARDS patients in prone position does not improve survival or reduce the duration of mechanical ventilation. Therefore, though in clinical practice this position may improve refractory hypoxemia in patients with ARDS, there is no evidence to support its systematic use.

Evidencias de la posición en decúbito prono para el tratamiento del síndrome de distrés respiratorio agudo: una puesta al día

Palabras clave:
Síndrome de distrés respiratorio agudo
Lesión pulmonar aguda
Ventilación mecánica
Decúbito prono

RESUMEN

La incidencia y la mortalidad de la lesión pulmonar aguda y del síndrome de distrés respiratorio agudo (SDRA) son altas. La mayoría de los nuevos tratamientos no han mejorado el pronóstico de los pacientes con lesión pulmonar aguda/SDRA, de modo que se ha observado una mortalidad similar en los últimos años. Varios estudios han evidenciado un aumento de la oxigenación con el decúbito prono durante la ventilación mecánica en pacientes con SDRA. Actualmente existe una fuerte evidencia de que el decúbito prono en pacientes con SDRA no mejora la supervivencia ni disminuye los días de ventilación mecánica. Por lo tanto, a pesar de que en la práctica clínica puede utilizarse dicha posición para mejorar la hipoxemia refractaria en pacientes con SDRA, no hay evidencia para recomendarla de forma sistemática en estos pacientes.

Introduction

Acute respiratory distress syndrome (ARDS) was described in 1967 by Ashbaugh et al,[1] who presented a series of 12 patients with underlying diseases that all involved acute respiratory failure characterized by severe dyspnea, refractory hypoxemia, and diffuse bilateral alveolar infiltrates. In 1976 Katzenstein et al[2] described the histological change that is characteristic of ARDS, including the initial presence of interstitial and intraalveolar edema, followed by hyalin membranes and reactive type-II pneumocyte hyperplasia in the alveoli and—if the noxious stimulus persists—interstitial fibrosis due to proliferation of fibroblasts. This set of histological changes is called diffuse alveolar damage.

In 1992 the American-European Consensus Conference (AECC) on ARDS agreed on a definition of ARDS,[3] based on 4 clinical essential criteria: *a)* acute onset; *b)* a ratio of PaO_2 to inspired oxygen fraction (FiO_2) of 200 or less; *c)* bilateral chest infiltrates on a chest radiograph; and *d)* pulmonary artery wedge pressure of 18 mm Hg or less, or no evidence of atrial hypertension. The AECC also defined a clinical entity called acute lung injury (ALI), whose diagnostic criteria were identical to those of ARDS, but with a PaO_2/FiO_2 ratio of 300 or less.

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Table 1
Treatments Tested in Acute Respiratory Distress Syndrome

Treatments	Authors, y	Results of Intervention (vs Control); Significance Level
Extracorporeal oxygenation systems	Zapol et al (1979)[11]	90% (92%); NS
Ibuprofen	Bernard et al (1997)[12]	37% (40%); NS
Vasodilators (nitric oxide)	Lundin et al (1999)[13]	40% (44%); NS
Changes in diet	Gadeck et al (1999)[14]	12% (19%); NS
Protective ventilation	ARDS Network (2000)[15]	31% (39.8%); *P*=.007
Ketoconazole	ARDS Network (2000)[16]	35.2% (34.1%); NS
Lisofylline and pentoxifylline	ARDS Network (2002[17]	31.9% (24.7%); NS
Liquid ventilation	Hirschl et al (2002)[18]	42% (36%); NS
High-frequency ventilation	MOAT study (2002)[19]	37% (52%); NS
Intraalveolar surfactant	Spragg et al (2003)[20]	20%, 33% (38%)[a]; NS
Corticosteroids	ARDS Network (2006)[21]	31.9% (31.5%); NS
β_2 agonists	Manocha et al (2006)[22]	50%, 46.9%[b]; NS

Abbreviation: NS, not significant.
[a]Three groups were established: high dose (1 mL/kg), low dose (0.5 mL/kg), and control group.
[b]Two groups were established: high dose (=2.2 mg/24 h) and low dose (<2.2 mg/24 h).

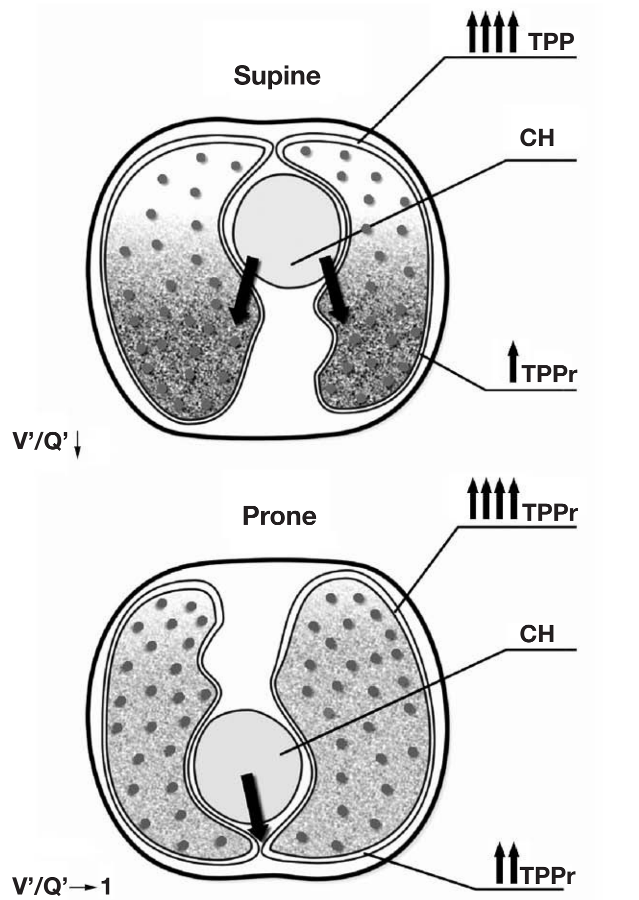

Figure 1. Changes in the distribution of the transpulmonary pressure and perfusion in the prone position. Abbreviations: CH, compression by the heart; TPPr, transpulmonary pressure; V'/Q', ventilation-perfusion matching.

This definition was not validated with regard to the presence of histological changes characteristic of diffuse alveolar damage until a study published 4 years ago[4] reporting that the clinical criteria of the AECC had a sensitivity of 76% and a specificity of 75% for detecting diffuse alveolar damage in patients with risk factors. When patients with a pulmonary risk factor were considered in isolation, these figures fell to 61% and 69%, respectively. However, when patients with an extrapulmonary risk factor were analyzed, sensitivity and specificity rose to 85% and 78%, respectively. At present, until new criteria or better diagnostic tests become available, these criteria are the ones that are used in routine clinical practice and in the selection of patients for inclusion in clinical trials on this disease.

Since the description of ALI and ARDS, many studies have found that these conditions have high incidence rates, ranging between 13.5 and 79 cases per 100 000 inhabitants per year.[5-7] Between 75% and 85% of the cases meet the ARDS criteria of deteriorated oxygenation and account for between 9% and 20% of the patients who require mechanical ventilation in intensive care units.[8,9] Furthermore, this disease has a mortality of 40% to 65%[5-7,9] depending on whether the information comes from randomized clinical trials in which the population is selected or observational studies based on real patient care activities. It is therefore not surprising that in recent years many treatments have been studied with a view to improving the survival of patients with ARDS (Table 1). Most of them have failed to demonstrate reductions in either mortality or the duration of mechanical ventilation. Only the protective ventilation strategy, characterized by a low tidal volume and a limited plateau pressure, has been shown to lead to a clear reduction in mortality in 2 clinical trials.[10,17]

One of the interventions that has roused the greatest expectations since the first study by Douglas et al[23] is the prone position. The real efficacy of this measure will be analyzed below.

Prone Position

In 1976 Douglas and coworkers[23] placed 6 patients with acute respiratory failure in the prone position, bringing about an average increase in PaO_2 of 69 mm Hg (range, 2-178 mm Hg) and reducing the FiO_2 in 4 patients. When the patients returned to the supine position, the PaO_2 maintained an average increase of 35 mm Hg (range, 4-110 mm Hg). Since then many studies have attempted to understand the pathophysiology of this practice and to determine whether it provides clinical benefits to patients with acute respiratory failure due to ARDS.

Why the Prone Position in ARDS?

Prone Positioning Can Improve Oxygenation

The factor that most contributes to the increase in PaO_2 is improved ventilation-perfusion matching. Let us briefly recall that the transpulmonary pressure is the difference between the alveolar pressure and the intrapleural pressure; therefore, the greater the transpulmonary pressure, the greater the expansion of the lung and the more the air that will be inspired. In the supine position the gradient of transpulmonary pressure is greater in the nondependent (sternal) zones than in the dependent (dorsal) zones. The consequence is uneven alveolar filling.

Though ARDS affects the lung in a patchy and apparently diffuse way, it accentuates the difference in the transpulmonary pressure gradient between dependent and nondependent zones. The prone position changes the distribution of this gradient by redistributing infiltrates, reducing the compression of the lungs by the heart, decreasing lung compliance and moving the abdomen towards the head, which leads to more even alveolar ventilation (Figure 1).

Table 2
Studies That Have Analyzed Oxygenation in the Prone Position

Study	No. of Patients	Year	Duration of Pronation, h
Douglas et al[23]	6	1976	NR
Fridrich et al[28]	20	1996	20
Blanch et al[29]	23	1997	
Chatte et al[30]	32	1997	4
Pelosi et al[31]	6	1998	2
Papazian et al[32]	14	1998	6
Voggenreiter et al[33]	22	1999	8
Guérin et al[34]	12	1999	1
Johannigman et al[35]	20	2000	6
Dupont et al[36]	27	2000	4
Johannigman et al[37]	16	2001	1
Gattinoni et al[38]	304	2001	6
Gainnier et al[41]	25	2003	2
Guérin et al[42]	791	2004	8
Vieillard-Baron et al[43]	11	2005	4
Mancebo et al[44]	136	2005	17

Abbreviation: NR, not reported.

Furthermore, perfusion in these patients is greater in the dorsal region in the supine position and does not change significantly in the prone position. Ventilation-perfusion matching therefore improves.[24,25]

Prone Positioning May Improve Respiratory Mechanics

Decreased lung compliance in patients with ARDS is the result of uneven distribution of the transpulmonary pressure, with hyperinflation of nondependent zones and collapse and/or consolidation of dependent ones, accompanied by increased interstitial fluid retention.[24] In patients with ARDS caused by lung disease, in the prone position a decrease in the thoracoabdominal compliance is observed, but the total compliance of the respiratory system remains unchanged.[26] The increase in total compliance after patients are placed in the supine position seems to be associated with an increase in the compliance of the lung itself.

Prone Positioning Can Improve the Effects of Alveolar Recruitment Maneuvers and of Positive End-Expiratory Pressure

The decrease in hyperinflation in the prone position means that the application of positive end-expiratory pressure or alveolar recruitment maneuvers can distribute the pressures more homogeneously, leading to more uniform lung expansion with a minimum redistribution of perfusion.[24]

Prone Positioning Can Reduce the Lung Injury Associated With Mechanical Ventilation

More homogeneous distribution of transpulmonary pressure reduces stress and strain on the lung caused by mechanical ventilation.[27] These factors have been associated with the worsening and acceleration of lung injury.

Studies That Analyze Physiological Effects

The advantage of the prone position considered to provide the greatest benefit to patients with ARDS is improved oxygenation. Many studies have reported such an improvement after patients were placed in the prone position (Table 2). In 1997 Blanch et al[29] reported improved oxygenation in 23 patients with ARDS after they had been placed in the prone position for 60 to 90 minutes, with a mean (SD) increase in the PaO_2/FiO_2 ratio from 78 (37) mm Hg in the supine position to 115 (31) mm Hg in the prone position (P<.001). The patients also showed an improvement in the respiratory mechanics that was reflected by an increase in thoracopulmonary compliance and a decrease in shunt.

The etiology of ARDS also seems to be relevant to achieving a favorable response. Lim et al[43] observed that patients with ARDS of extrapulmonary origin showed an improvement 30 minutes after being placed in the prone position, and the improvement (155 [91] mm Hg) was maintained at 2 hours. On the other hand, patients with ARDS of pulmonary origin showed a significant response after only 2 hours in the prone position (158 [60] mm Hg).

It should be noted that the maintenance of improved oxygenation in these studies was observed in the first few hours after the patients were switched to supine position. Studies analyzing oxygenation over longer periods of days, however, have found that this short-term benefit was lost.

Studies of the effect of alveolar recruitment maneuvers report varying results. In patients with ARDS of pulmonary origin some detected no differences between performing alveolar recruitment maneuvers in the prone and supine positions. However, Pelosi et al[31] did find improved ventilation-perfusion matching in this scenario. In studies of patients with ARDS of extrapulmonary origin, a possible synergistic effect has been observed between alveolar recruitment maneuvers and the prone position.[29,34] In a similar study, Gainnier et al[39] similarly detected an additive effect between the application of PEEP and the prone position, with the consequent improvement in oxygenation when they administered different levels of positive end-expiratory pressure (0, 5, 10, and 15 cm H_2O) in patients with ARDS. The effect was greater in patients with localized infiltrates.

Recently, Mentzelopoulos et al[27] observed that patients with early/severe ARDS show less lung stress and strain in the prone position.[27] These factors are associated with the development of ventilator-induced lung injury. Furthermore, Papazian et al[44] found that concentrations of proinflammatory cytokines (interleukin 8) in alveolar lavage fluid were lower in the prone (vs supine) position in a group of ventilated patients with ARDS.

Of all these possible beneficial effects, only oxygenation has been studied as a secondary measure in clinical trials designed to test the effect of the prone position on patient course[38,40,42]; these trials have confirmed that the prone position improves this parameter (Table 3). The most significant differences were found in the study by Mancebo et al[42] (PaO_2/FiO_2 of 175 [85] in the supine position compared with 218 [85] in the prone position, P<.001). Of the 3 studies, this was the one in which the patients remained in the prone position for more hours per day. However, these differences disappeared by the 7th day of treatment.

Clinical Trials

After the major improvements observed in the physiological parameters in some studies, clinical trials were carried out to analyze the real results in routine clinical practice (mortality, duration of mechanical ventilation and length of stay in the intensive care unit). To date 3 studies have compared the effect on mortality of ventilation in the prone position compared with the supine position.

In the first study, carried out by Gattinoni et al[38] in 2001, a total of 304 patients with ALI/ARDS were randomized to the prone position for 6 hours per day for 10 days or to the supine position. No significant differences were observed in mortality after 10 days (21.1% vs 25%; relative risk [RR]=0.84; 95% confidence interval [CI], 0.56-1.27), on discharge from the intensive care unit (50.7% compared with 48%; RR=1.05; 95% CI, 0.88-1.28), or after 6 months (62.5% compared with 58.6%; RR=1.06; 95% CI, 0.88-1.28). In the analysis of subgroups it was observed that the RR of death on the 10th day was lower for patients with a low PaO_2/FiO_2 ratio, with a high Simplified Acute Physiology Score II (SAPS II), or receiving a high tidal volume

Table 3
Clinical Studies That Have Analyzed the Results of Using the Prone Position

Inclusion Criterion	Gattinoni et al[40] ALI (PaO_2/FiO_2=300)		Guérin et al[42] ARF+PaO_2/FiO_2=300		Mancebo et al[44] ARDS (PaO_2/FiO_2)=200)	
No. of patients	304		791		136	
	PP	SP	PP	SP	PP	SP
	152	152	413	378	76	60
Patients with ARDS	144	142	140	106	76	60
Intervention (prone position)						
Days	10		4		10.1	
Hours per day	7.0		8.0		17	
Mortality in ICU, %	50.7	48.0	32.4	31.5	43	58
Mortality in hospital, %	62.5	58.6	43.3	42.2	62	50
Duration of mechanical ventilation, d	NR	13.7	14.1	NR		

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; FiO_2, inspired oxygen fraction; ICU, intensive care unit; NR, not reported; PP, prone position; SP, supine position.

(>12 mL/kg), but this trend had disappeared by the time of discharge from the intensive care unit. The authors' interpretation of this transient improvement was that it may indicate insufficient duration of prone positioning.

Similar results were obtained in 2004 by Guérin et al,[40] who detected no differences in mortality in 791 patients with acute respiratory failure and PaO_2/FiO_2 of less than 300 at 28 days. Mortality in their series was 32.4% compared with 31.5% in the 2 groups at that time (RR=0.97; 95% CI, 0.79-1.19) and 43.3% compared with 42.2% (RR=0.8; 95% CI, 0.84-1.13; *P*=.74) at 90 days, despite significant differences in favor of the prone position group in the PaO_2/FiO_2 ratio in the first 28 days. In interpreting the results of this study we feel that it should be taken into account that 25% of the pronation group did not remain in this position for the 8 hours per day that had been stipulated in the study design.

In the last study, published in 2006, Mancebo et al[42] randomized 136 patients with ARDS to either the prone position for 20 hours per day from inclusion or the supine position. This is the only one of the 3 studies that included a protocol of mechanical ventilation, sedation, and extubation that was common to both groups. Furthermore, of the 3 studies, it was the one that included the patients with the most recent diagnosis of ARDS (mean time from diagnosis to randomization, 1.25 [1.18] days; range, 0-6 days). Mortality in the intensive care unit showed no significant differences (43% compared with 58%; *P*=.12), despite an absolute decrease of 15% and a relative decrease of 25%, which was maintained on discharge from hospital. It is important to note that in this study it was impossible to reach the sample size of 200 patients targeted in the study design.

As stated above, in these 3 studies a significant improvement in oxygenation was observed not only during the period of pronation, but also subsequently. The question is therefore: Why does an improvement in oxygenation not necessarily lead to a reduction in mortality? Let us remember that hypoxemia itself is the cause of death in "only" 9% to 27% in different series of patients with ARDS,[4,45,46] and that multiorgan failure is the major cause of the remaining deaths.

None of the 3 studies reported differences in the SAPS II at 24 hours, and the development of new organ failure while the patients were in the intensive care unit was only reported by the French and Spanish groups. There are therefore 3 possibilities: *a)* as prone positioning does not play a role in or improve the development of organ failure, it does not reduce mortality; *b)* a higher number of patients is needed to obtain statistically significant differences; and *c)* the definition of ARDS lacks specificity, so many of the patients placed in the prone position could have other underlying diseases.[4]

The Prone-Supine Study Group[47] published a retrospective analysis of 225 patients with ALI/ARDS criteria who were placed in the prone position (152 from the study by Gattinoni et al and 73 from the pilot study). In the multivariate analysis it was observed that the reduction in $PaCO_2$ after pronation was associated with improved survival at 28 days. However, the patients whose oxygenation improved in both the first period of pronation and subsequently showed no differences in mortality.

Comparisons of the results are difficult, however, due to the differences in the populations included in the studies, the time of starting the study, and the period of application of the maneuver.

Of the 3 studies that evaluated results of clinical interest, only those of Gattinoni et al[40] and Guérin et al[42] reported the effect on the period of mechanical ventilation, which showed no difference between the 2 groups.

Complications

Before introducing an intervention of this type in routine clinical practice, one must consider whether the measure is safe for the patient. The possible complications that have been studied are the appearance of pressure ulcers; displacement of endotracheal tubes, thoracotomy tubes, and vascular catheters; accidental extubation; obstruction of endotracheal tubes; increased need for sedation and relaxation; development of ventilator-associated pneumonia; and intolerance of enteral nutrition.

Gattinoni et al[38] were the first to describe complications in a randomized clinical trial, in which they found only an increase in the appearance, or worsening, of pressure ulcers in the pronation group (1.9 [1.3] compared with 2.7 [1.7]; *P*=.004). The ulcers were distributed heterogeneously: 46% were on the pelvis, 21% on the thorax, and 19% on the legs. Guérin et al[40] also observed an increase in the appearance of ulcers, in addition to an increase in the incidence of obstruction and displacement of endotracheal tubes. Mancebo et al[42] reported a high complication rate, but in most cases the complications were not serious for the patient.

With regard to early enteral nutrition, the patients in the prone position showed more episodes of intolerance (82% compared with 49%) and lower volumes of nutrition.[48] Prokinetic agents and nasojejunal tubes are 2 feeding options that must be considered to improve these complication rates.

Clinical Course

To date only 2 studies have reported the frequency of application of prone positioning in routine clinical practice.[49,50] In 1998 our group carried out a study on the use of mechanical ventilation through an observational epidemiologic study in 365 intensive care units in 20 countries,[49] finding that prone positioning was used in 13% of patients with ARDS. It is likely that this practice is a response to the results of studies analyzing mainly its effect on physiologic parameters.

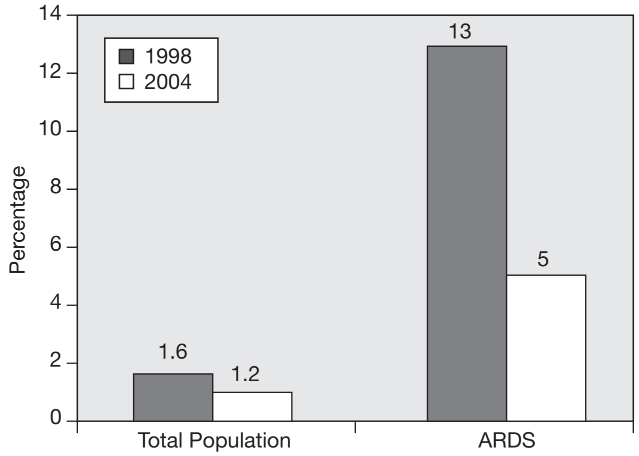

Figure 2. Variation in the use of the prone position between 1998 and 2004 in the total population and in patients with ARDS in the same intensive care units.

In 2004 we repeated the survey using a similar design, enrolling patients from 349 intensive care units in 23 countries.[50] The result was was a 7% decrease in the use of the prone position (Figure 2). In the period between the 2 studies, only 1 clinical trial analyzing the effect on mortality was published and it reported no differences between the prone and supine positions,[38] so the decrease in use would seem to be related to this finding. Two later studies[40,42] showed similar results, so it is unlikely that there will be an increase in the use of pronation procedures.

Conclusions

During the last 20 years many studies have demonstrated improved oxygenation in the prone position in patients with ARDS. There is currently strong evidence that the prone position does not reduce mortality or the period of mechanical ventilation in these patients. Though in routine clinical practice this measure is applied in situations of severe refractory hypoxemia, its systematic use in patients with ARDS is not recommended.

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