Prone Position in Acute Respiratory Distress Syndrome

Rationale, Indications, and Limits

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In the prone position, computed tomography scan densities redistribute from dorsal to ventral as the dorsal region tends to reexpand while the ventral zone tends to collapse. Although gravitational influence is similar in both positions, dorsal recruitment usually prevails over ventral derecruitment, because of the need for the lung and its confining chest wall to conform to the same volume. The final result of proning is that the overall lung inflation is more homogeneous from dorsal to ventral than in the supine position, with more homogeneously distributed stress and strain. As the distribution of perfusion remains nearly constant in both postures, proning usually improves oxygenation. Animal experiments clearly show that prone positioning delays or prevents ventilation-induced lung injury, likely due in large part to more homogeneously distributed stress and strain. Over the last 15 years, five major trials have been conducted to compare the prone and supine positions in acute respiratory distress syndrome, regarding survival advantage. The sequence of trials enrolled patients who were progressively more hypoxemic; exposure to the prone position was extended from 8 to 17 hours/day, and lung-protective ventilation was more rigorously applied. Single-patient and meta-analyses drawing from the four major trials showed significant survival benefit in patients with $Pa_{O_2}/F_{I_{O_2}}$ lower than 100. The latest PROSEVA (Proning Severe ARDS Patients) trial confirmed these benefits in a formal randomized study. The bulk of data indicates that in severe acute respiratory distress syndrome, carefully performed prone positioning offers an absolute survival advantage of 10–17%, making this intervention highly recommended in this specific population subset.

Keywords: prone positioning; acute respiratory distress syndrome; mechanical ventilation; respiratory failure; ventilator-induced lung injury

The first report on prone positioning in patients with acute respiratory distress syndrome (ARDS) appeared in 1976 (1) and described striking improvement of oxygenation when patients were turned from the supine to the prone position. Over the subsequent four decades prone positioning has been studied from different perspectives: physiological, experimental, and clinical. Available data on prone positioning now justify an integrated description of its pathophysiology, clinical aspects, and place in the treatment of patients with ARDS. In this review we discuss the most relevant physiologic aspects of prone positioning, its putative mechanisms for altering gas exchange, and its contribution toward making mechanical ventilation less hazardous. Last, we summarize and discuss the clinical studies on which we base our clinical recommendations on why, when, and how to apply prone positioning to patients with ARDS.

PATHOPHYSIOLOGY

Respiratory Mechanics in Prone Position

Chest wall. During mechanical ventilation in the supine position, the pleural pressure (Ppl), which drives the chest wall, lifts up the ventral chest wall (driving pressure = Ppl – $P_{atmospheric}$), moves caudally to the diaphragm (driving pressure = Ppl – $P_{abdomen}$), and has little effect on the dorsal chest wall, which lies in contact with the firm supporting surface. In the prone position, the dorsal chest wall lifts up, the diaphragm shifts similarly to supine, and the ventral chest wall, now in contact with the firm surface of the bed, is impeded from expanding. Because the dorsal chest wall is less compliant than the ventral chest wall, the overall effect of prone positioning is to decrease overall chest wall compliance (2). In adults (3), as opposed to children (4), the use of pelvic and thoracic supports does not usually alter chest wall compliance.

Normal lung. In the supine position, there is a decrease in alveolar size from sternum to vertebra at end expiration, which may be quantified as a progressive increase in computed tomographic (CT) density (2). This nonuniformity is due both to gravitational forces and to the need for the lung and the chest wall to adapt their original shapes to occupy the same volume. The mandate for shape matching (modeling the original shape of the lung as a cone, and the chest wall as a cylinder [5]) generates greater distension in the ventral lung regions (*see* Figure 1). In the prone position, the gravitational forces compress the ventral region (6, 7), but this effect is damped by regional expansion due to shape matching. Therefore, although the gravity and shape differences both act in the same direction in the supine position (i.e., greater expansion of the nondependent regions and lesser expansion of the dependent parenchyma), they oppose one another in the prone position (*see* Figure 1). In addition, other factors, such as the heart weight (8) (which compresses primarily the left lower lobe) and the abdominal pressure (which increases from ventral to dorsal regions), contribute to differences in density distribution throughout the lung parenchyma. The final result is a steeper decrease in alveolar size when supine than when prone, that is, alveolar inflation, expressed as a gas-to-tissue ratio, is more uniform in the prone position (*see* Figure 1), with more homogeneous distribution of stress and strain. As lung inflation and ventilation are more even

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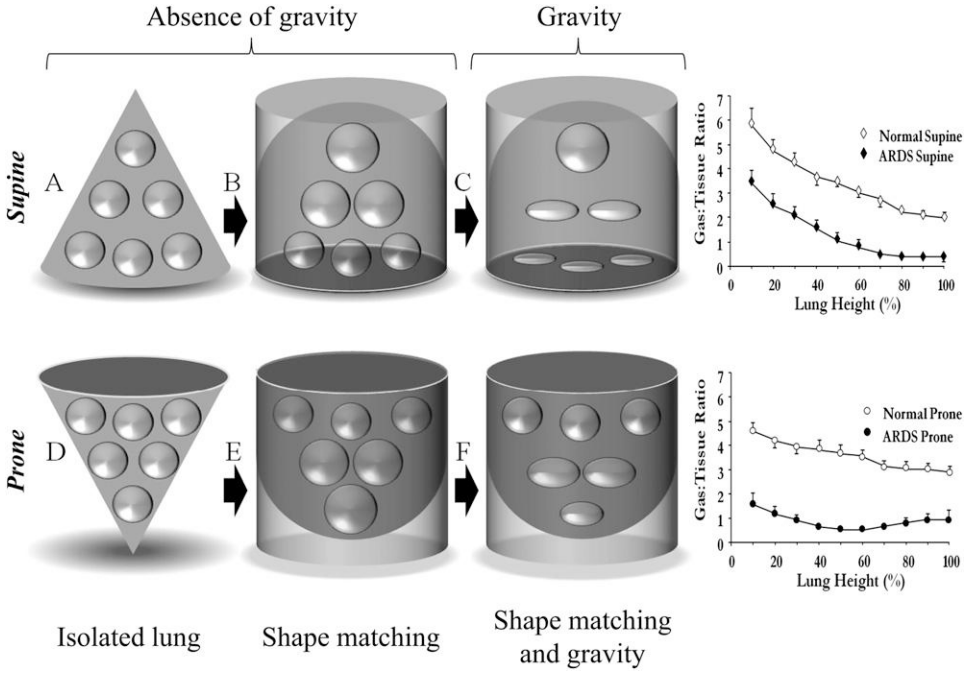

Figure 1. A model showing the relative and combined effects of shape matching of the lung to the chest wall and of gravity on the distribution of alveolar size (inflation) along the vertical axis. *Top, supine position*: (*A*) Original shape of the isolated lung (cone). In the absence of gravity, all pulmonary units (spheres) are equally inflated. (*B*) In the absence of gravity, the cone, attempting to adapt its shape to the confining chest wall (cylinder), must expand its upper regions more than the lower regions. Therefore the upper pulmonary units increase their size (and experience greater strain). (*C*) With the application of gravitational force the chest wall–confined pulmonary units at a given level are compressed by the weight of the units of the levels above. The composite effect is reflected in the scale of the upper panel, in which we show the decrease in the gas-to-tissue ratio from sternum to vertebra in normal subjects (n = 7) and in patients with acute respiratory distress syndrome (n = 10), rearranged from Reference 6. *Bottom, prone position*: (*D*) Original shape of the isolated lung in the prone position. In the absence of gravity all pulmonary units are equally inflated. (*E*) Shape matching in the absence of gravity leads to expansion of the ventral pulmonary units, which, unlike when supine, are now in the dependent position. (*F*) Applying gravitational forces decreases the size of the pulmonary units that bear the weight of the units above. Note that in the supine position shape matching and gravity act in the same direction, jointly expanding the ventral regions, whereas in the prone position, they act in opposing directions. The final effect is to "damp" the gravitational forces by shape matching, allowing more homogeneous inflation of the pulmonary units from sternum to vertebra, as reflected by a shift along the scale of gas-to-tissue ratios.

in the prone than in the supine position, whereas perfusion is similar in both conditions, the ventilation–perfusion ratios are more homogeneously distributed in the prone position (9).

ARDS lung. During ARDS, the primary alteration of this schema owes to increased lung mass (10), which may develop a superimposed pressure four to five times greater than normal and collapse the most dependent lung regions (compression atelectasis) (2). The contributions of shape matching, heart weight, and abdominal pressure (11) to lung collapse are overshadowed by the increase in superimposed pressure, which remains its primary cause. When patients are shifted into the prone position, chest wall compliance decreases (12) and lung density redistributes from dorsal to ventral (6) as a consequence of recruitment in dorsal lung regions and collapse of ventral ones (*see* Figure 2). The decrease in chest wall compliance, per se, would result in an increase in plateau pressure during volume control ventilation or a decrease in tidal volume during pressure control ventilation. These effects, however, may be offset if dorsal recruitment prevails over ventral derecruitment, leading to increased lung compliance. Because the lung mass is anatomically greater in dorsal regions (nondependent when prone) than in ventral regions (dependent when prone), the increased aeration and recruitment of the dorsal regions tend to exceed the decreased aeration and derecruitment of the ventral regions (6, 13).

Gas Exchange in Prone Position

Oxygenation. The Pa_{O_2} improvement, observed without exception in all clinical (14) and experimental (15, 16) studies dealing with the prone position, may be due either to recruitment and aeration of perfused and previously degassed lung regions or to diversion of blood flow from gasless regions to aerated ones. The redistribution of blood flow seems unlikely as the primary mechanism. In fact, the bulk of available data, obtained in experimental animals with microspheres (17) and by positron emission tomography (18), suggests that blood flow distribution does not change substantially in the conversion from the supine to prone position. The fact that nitric oxide inhalation adds to the positional Pa_{O_2} increase (19–22) suggests indirectly that blood flow is not redirected by prone positioning per se. Therefore, the most probable mechanism of oxygenation improvement is that the recruitment of perfused tissue in dorsal regions exceeds ventral derecruitment. To improve oxygenation it is sufficient that the recruited regions remain inflated; such zones, however, are not necessarily well ventilated. Therefore, the responses of oxygenation and CO_2 clearance to proning may present different patterns (23).

CO_2 clearance. In ARDS, impaired CO_2 clearance reflects structural changes of the lung parenchyma, such as alveolar wall destruction, microthrombosis, cysts, blebs, and edema (24), and strongly predicts outcome (25, 26). Dead space and Pa_{CO_2} do not necessarily change when patients are transitioned from supine to prone. However, by dividing patients with ARDS into two groups according to the median change in Pa_{CO_2} after the first pronation, we found that those who decreased Pa_{CO_2} in the prone position with unchanged minute ventilation experienced greater lung recruitment (23) and better outcomes (27) than those who increased their Pa_{CO_2}. This benefit occurred independently of oxygenation response.

Proning may improve CO_2 clearance if repositioning causes dorsal recruitment to prevail over ventral derecruitment, and/or if hyperinflation that occurs in ventral regions when supine decreases to improve compliance (13, 28). In the first case, the increase in CO_2 clearance owes to an increased number of open and ventilated alveoli; in the second case, reduced overdistention allows better ventilation of previously hyperinflated units. Both mechanisms lead to a decrease in regional stress and strain and may explain why improved CO_2 clearance, and not oxygenation, relates to outcome.

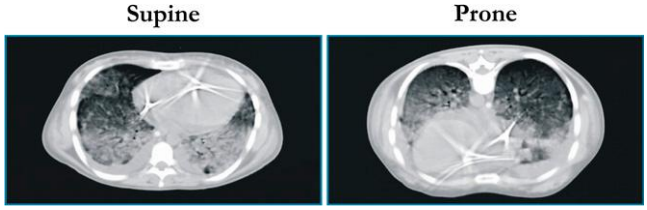

Figure 2. A representative computed tomography scan of a patient with acute respiratory distress syndrome in the supine position (*left*) and prone position (*right*). Prone positioning redistributes opacities from dorsal to ventral zones. End-expiratory images were taken with the patient sedated and paralyzed immediately before and after assuming the prone position, at identical end-expiratory pressures.

PRONE POSITIONING AND VENTILATOR-INDUCED LUNG INJURY

Experimental Evidence for Proning Effect

Experimental studies provide convincing evidence that prone positioning influences the generation and evolution of ventilator-induced lung injury (VILI). VILI arises from repeated application of high mechanical forces that either tear fragile tissue directly or initiate signaling that culminates in inflammatory change (29, 30). Interfacial zones at the junction of open and closed tissues, which are prevalent in gravitationally dependent zones (31), are subjected to amplified tensions, to surfactant-depleting tidal cycles of airspace opening and closure, and to shearing forces higher that those experienced among lung units that remain continuously open (32). Characteristics of the alveolar environment, notably vascular pressures, surface tension, abnormal pH, and oxygen concentration, either influence the amplitude of mechanical stresses applied to the alveolar capillary membrane, or condition its inflammatory response. Last, airway biofluids and secretions may directly inhibit surfactant viability or production, impede the ease of airspace opening, or predispose to lung infection (33, 34). Regional mechanics, vascular filling, and airway drainage are each affected by prone positioning.

Regional Mechanics

The prone position may alter absolute lung volume as well as its distribution. Reports from various investigators conflict regarding the impact of proning on FRC (35). Inconsistencies relate potentially to differences in the preexisting recruitability of the lung, respiratory muscle activity, flexibility and shape of the chest wall (36, 37), nature of the supporting surface (38), and presence of abdominal hypertension (39). It is generally conceded, however, that any increment in FRC that occurs after turning neither fully explains the proning-related improvements in oxygenation nor the reduced propensity to VILI. The regional distribution of transpulmonary forces across the lung appear to be of greater importance (6, 17, 40).

From the viewpoint of airspace mechanics, the more even distribution of transpulmonary pressure that results from prone positioning helps establish and sustain recruitment in response to positive end-expiratory pressure (PEEP) (41–43). An experimental study using quantitative CT in patients with ARDS strongly suggests that prone positioning may add to the efficiency of PEEP by improving recruitment while diminishing alveolar hyperinflation (12). Evening the distribution of transpulmonary forces promotes uniformity of ventilation–perfusion matching ratios in acutely injured lungs (44). Resolving disparities of regional alveolar distension may also help prevent inappropriate redirection of blood flow from inflated to collapsed tissues in response to rising PEEP and mean airway pressure. Prone positioning relieves cardiac compression of the supporting lung and may improve lymphatic drainage as the heart moves inferiorly toward the sternum (8), helping to explain why prone positioning improves the gas-exchanging efficiency and gradual resolution of hydrostatic edema An experimental study using quantitative CT in patients with ARDS strongly suggests that prone positioning may add to the efficiency of PEEP by improving recruitment while diminishing alveolar hyperinflation (13).

Distribution of VILI

VILI favors gravitationally dependent areas, whatever the postural orientation (8). For example, the dorsal regions are predisposed to injury in the supine position (being dependent) but are relatively spared when prone (being nondependent). By reducing the number of interfaces between open and closed units, as well as by moderating transpulmonary forces, the excursions of mechanical tension on well-vascularized dorsal tissues (effective driving pressures) are lessened. Hemorrhagic pulmonary edema and inflammation that result in healthy lungs from adverse ventilation is differentially affected by positioning (45, 46). In both healthy canine lungs and those preinjured by infused oleic acid, proning may reduce dorsal hemorrhage, edema, and inflammation otherwise incurred during supine ventilation whereas nondependent zones are relatively spared (45, 46). Prone positioning could delay injury onset, rather than attenuate the eventual extent of injury (47), but the issue of whether reduced severity or slower development predominates as the primary effect of prone positioning remains unsettled.

Nonmechanical Cofactors of VILI

In addition to reducing regional transpulmonary force disparities, prone positioning confers a secondary benefit simply by improving the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen ($Pa_{O_2}/F_{I_{O_2}}$ ratio), thereby reducing the need for iatrogenic intervention to sustain it. Measures normally taken to improve oxygenation or increase ventilation when supine may encourage VILI; improved oxygenation and ventilation efficiency by prone positioning may allow reduction of $F_{I_{O_2}}$ (48), infused fluid volume, and mean airway pressure (49), thereby lowering the risk of injury to mechanically stressed membranes and/or right ventricular loading (50).

Apart from effects on the airspaces, gravitational forces influence regional vascular pressures, airway drainage, and efficiency of the lymphatic sump. Dependent vasculature is exposed to greater hydrostatic forces than is nondependent vasculature. These dependent regions are also at risk for collecting biofluids, which may inhibit surfactant, directly injure alveolar epithelial surfaces, or predispose to infection (51, 52). Prone positioning encourages transfer of secretions from dorsal lung toward the airway opening. Cross-compartmental translocation of instilled albumen and bacteria has been demonstrated in animal experiments (53–55). In that work dependent positioning of the previously unaffected lung predisposed to generalization of pathologic change, as did high tidal volumes and low levels of PEEP.

Fluids entering the central airway also tend to drain to gravity-dependent regions. Ladoire and colleagues (56) demonstrated in the setting of lobar pneumonia that prone positioning mitigates the tendency toward bacterial contamination of the unaffected lung. These observations complement those of Drakulovic and colleagues, Li Bassi and colleagues, and Li Bassi and Torres, who reported that the propensity for pneumonia to occur in patients with ARDS can be attenuated by prone positioning (57–59). Taken together, the experimental

database indicates that prone positioning exerts a lung-protective influence by improving the mechanical, vascular, and secretion drainage environments.

CLINICAL EVIDENCE

The Major Trials

Parallel to studies that refined our knowledge of the pathophysiology of prone positioning, five large randomized clinical trials, conducted over a period of 15 years, investigated its possible benefit on ARDS outcome. New information gleaned from each trial of prone positioning, interpreted against a rapidly evolving understanding of lung injury causation, influenced the design of the subsequent trials. Notably, over these years, the rationale supporting the possible benefit of prone positioning shifted from oxygenation improvement to lung protection. The main characteristics of the five trials are summarized in Table 1. In the first trial (60), patients were enrolled with Pa_{O_2}/FI_{O_2} lower than 300 mm Hg, the prone position was limited to 6 hours/day, the approach to mechanical ventilation was not controlled, and no overall survival advantage was found. At that time in 1996, when the study was conceived, the information provided by the ARDS Network (ARDSNet) trial regarding the benefits of low tidal volume ventilation and the understanding that improved oxygenation may not directly relate to outcome (61) were not available. Moreover, the concepts of biotrauma and atelectrauma were still in their infancy (62). Despite these limitations, when the subset of patients within the most severe Pa_{O_2}/FI_{O_2} quartile (lower than 88 mm Hg) was isolated, those subjects allocated to the prone position experienced a relative reduction of mortality of 51% compared with quartile-matched supine subjects (absolute reduction of 24%). The first trial of Guérin and colleagues (63), which was performed between 1998 and 2002, experienced the same limitations (and results) of our first trial: the average Pa_{O_2}/FI_{O_2} at enrollment was 152 mm Hg, the exposure to prone positioning was 8 hours/day, mechanical ventilation was uncontrolled, and no outcome advantage was demonstrated.

The trial from Mancebo and colleagues (64), although performed approximately at the same time of the Guérin-led French study, was the first to introduce both longer daily duration of prone positioning and to exert some control over mechanical ventilation. Moreover, their enrollment criteria led to a selection of patients more hypoxemic than in the previous trials (Table 1). The mortality outcome at intensive care unit discharge favored prone positioning over supine positioning (43% vs. 58%, respectively, representing a 15% absolute and 25.8% relative risk reduction). These figures, however, did not reach statistical significance, because of insufficient enrollment and premature termination of the trial. In the subsequent study by Taccone and colleagues (65), we applied a protocol similar to the trial conducted by Mancebo and colleagues. The prone position was sustained for 18 hours/day, and although protective mechanical ventilation was strongly recommended (tidal volume lower than 8 ml/kg ideal body weight), it was not mandatory. In this study we randomized patients in stratified fashion, according to the criterion of Pa_{O_2}/FI_{O_2} higher or lower than 100 mm Hg. No significant advantages for mortality risk were found in the whole population (47% prone; 52.3% supine). Even in the group with Pa_{O_2}/FI_{O_2} lower than 100 mm Hg at entry, the absolute and relative mortality risk reductions of 10.5 and 16.6%, respectively, were still not statistically

TABLE 1. SUMMARY OF THE MAJOR TRIALS PERFORMED ON PRONE POSITIONING

	Gattinoni *et al.* (60)	Guérin *et al.* (63)	Mancebo *et al.* (64)	Taccone *et al.* (65)	Guérin *et al.* (PROSEVA) (68)
Study characteristics					
Patients, n	304	802	142	344	474
Study period, yr	1996–1999	1998–2002	1998–2002	2004–2008	2008–2011
Enrollment rate, patients/month/unit	0.28	0.24	0.24	0.26	0.43
Trial ended early	Yes (slow enrollment)	No	Yes (slow enrollment)	No	No
Enrollment					
Enrollment criteria	ALI/ARDS with PEEP $\geq$ 5 cm H_2O	Hypoxemic acute respiratory failure (413 patients with ALI/ARDS)	ARDS with four-quadrant infiltrates on CXR	ARDS with PEEP $\geq$ 5 cm H_2O	Severe ARDS, i.e., $Pa_{O_2}/FI_{O_2} < 150$ with PEEP $\geq$ 5 cm H_2O and $FI_{O_2} \geq 0.6$
Average Pa_{O_2}/FI_{O_2} at enrollment	127	152	105	113	100
Average PEEP at enrollment, cm H_2O	10	8	7	10	10
Average enrollment SAPS II	40	46	41	41	46
Time after meeting enrollment criteria	Not prespecified	>12–24 h*	<48 h	<72 h	>12–24 h*
Treatment					
Planned duration of prone positioning, average	6 h/d for 10 d	$\geq$8 h/d until weaning criteria	20 h/d until weaning criteria	20 h/d until weaning criteria	$\geq$16 h/d until enrollment criteria not met
Actual duration of prone positioning, average	7 h for 5 d	9 h for 4 d	17 h for 10 d	18 h for 8 d	17 h for 4 d
Protective mechanical ventilation	No	No	Yes ($V_T \leq$ 10 ml/kg of PBW or ABW)	Yes ($V_T \leq$ 8 ml/kg of PBW)	Yes (V_T = 6 ml/kg of PBW)
Crossover (supine to prone group)	12/152 (7.9%)	81/378 (21.4%)	5/60 (8.3%)	20/174 (11.5%)	17/229 (7.4%)
Outcome					
Last follow-up	6 mo	90 d	Hospital discharge	6 mo	90 d
Mortality, prone vs. supine	62.5% vs. 58.6%	43.3% vs. 42.2%	50.0% vs. 60.0%	47.0% vs. 52.3%	23.6% vs. 41.0%
P value	0.50	0.74	0.22	0.33	<0.001

Definition of abbreviations: ABW = actual body weight; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; CXR = chest X-ray; FI_{O_2} = fraction of inspired oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PROSEVA = Proning Severe ARDS Patients; SAPS = Simplified Acute Physiology Score; V_T = tidal volume.

*A period of 12–24 hours supine was mandated by the protocol for stabilization, after which prone positioning was instituted within 1 hour.

significant. A meta-analysis of the prone patients from published major trials suggested a significant survival benefit for patients with a Pa_{O_2}/FI_{O_2} lower than 140 mm Hg at entry (66). In addition, a single-patient analysis (67) of the first four major trials (60, 63–65), which was limited to those with Pa_{O_2}/FI_{O_2} below 100 at entry, showed a significant absolute risk reduction of 10.5% and a relative reduction of 15.3% (*see* Figure 3B).

In the latest prospective study on prone positioning (Proning Severe ARDS Patients, PROSEVA) (68), Guérin and colleagues included only patients with ARDS with Pa_{O_2}/FI_{O_2} lower than 150 mm Hg, and their average Pa_{O_2}/FI_{O_2} at enrollment averaged 100 mm Hg—lower than in the prior studies. The daily time spent in the prone position was 17 hours and proning was imposed for approximately 4 days. Mechanical ventilation was strictly controlled according to a framework of lung protection: tidal volume, 6 ml/kg; and PEEP selected according to the Pa_{O_2}/FI_{O_2}/PEEP table of the ARDSNet (61). Interestingly, in other work we have found that selecting PEEP according to the Pa_{O_2}/FI_{O_2}/PEEP table, a tactic based on oxygenation rather than on conventional measures of mechanics, is the best approach to selecting lower PEEP in patients with lower recruitability and higher PEEP in patients with higher recruitability (69). In addition, intensive care units participating in the PROSEVA trial were experienced in the routine use of the prone position. The results of PROSEVA were impressive (*see* Figure 3A), with an absolute mortality risk reduction of 17% and a relative risk reduction of 50%.

In considering all five major trials on prone positioning with regard to the design features that evolved over time, three main trends appear evident. First, the patients enrolled had progressively more severe disease, at least as assessed by Pa_{O_2}/FI_{O_2} level. Second, the daily duration of prone positioning was increased from 7–9 hours to 17–18 hours. Third, lung-protective strategies were applied more strictly. Indeed, in their PROSEVA trial, Guérin and colleagues (68) employed protective PEEP selection and muscle relaxation in early phases (70). Therefore, over the years progressive refinements led, first, to suggest benefit in the patients with more severe disease; second, to recognize by meta-analysis that in the patients with the most severe disease prone positioning reduced mortality risk; and finally, to prove by formal randomized clinical trial that prone position linked to strict application of a lung-protective strategy by an experienced team significantly improved survival.

Indications for Prone Positioning

Short-term positioning. Observational and experimental investigations into the short-term use of prone positioning have been limited in number (71). However, there is no doubt that prone positioning may be useful as a rescue maneuver for severe hypoxemia when carefully conducted and protocolized, a feature that parallels the experience of large trials testing the use of higher and lower PEEP (Lung Open Ventilation Study [72] and Expiratory Pressure Study [73]). Beyond this indication, short-term prone positioning improves airway drainage and appears effective in facilitating the reversal of atelectasis that proves refractory to maneuvers conducted in the supine position (74). Benefit is particularly likely to occur in left lower lobe atelectasis, as prone positioning unloads the heart's weight from the dorsal lung (75). The effectiveness of prone positioning in these contexts may be easily documented by improvement of gas exchange, the appearance of crackles in the region of interest, and by echography (76). Apart from facial edema and skin breakdown at unpadded pressure points, possible complications of short-term prone positioning include accidental extubation and catheter displacement. Therefore, great attention and a skilled team are required even when short-term prone positioning is applied. The technique for safe proning has been fully described elsewhere (77).

Long-term positioning. It is now well established that prone positioning is indicated for patients with "severe ARDS." Expert consensus regarding the definition of "severe" ARDS, however, has been reached only recently and formalized in the Berlin definition of ARDS (78), after the major trials on prone position were completed. In clinical practice the severity of the syndrome has been graded according to Pa_{O_2}/FI_{O_2} ratio level. However, for a given lung pathological status, Pa_{O_2}/FI_{O_2} may vary according to the level of PEEP and the FI_{O_2} in use, as well as on comorbidities, cointerventions, and the effectiveness of innate compensatory mechanisms (79). Despite this variability, available data indicate that the use of long-term prone positioning in severe ARDS (characterized by $Pa_{O_2}/FI_{O_2} < 100$ mm Hg according to the Berlin criteria) can be highly recommended, whereas its use is discouraged in mild ARDS (Pa_{O_2}/FI_{O_2} ranging between 300 and 200 mm Hg) as existing data clearly indicate that it does not provide any survival advantage over that higher range (67). In moderate ARDS the pattern of response is less clear; however, we believe that the results of previous meta-analyses (66), the pooled analysis of the major trials before PROSEVA (67), and the PROSEVA trial (68) suggest that prone positioning should be strongly considered in patients with moderate ARDS in whom applied Pa_{O_2}/FI_{O_2} is lower than 150 mm Hg when assessed at a PEEP equal to or greater than 5 cm H_2O and an FI_{O_2} equal to or greater than 0.6. Introducing a standard assessment of Pa_{O_2}/FI_{O_2}

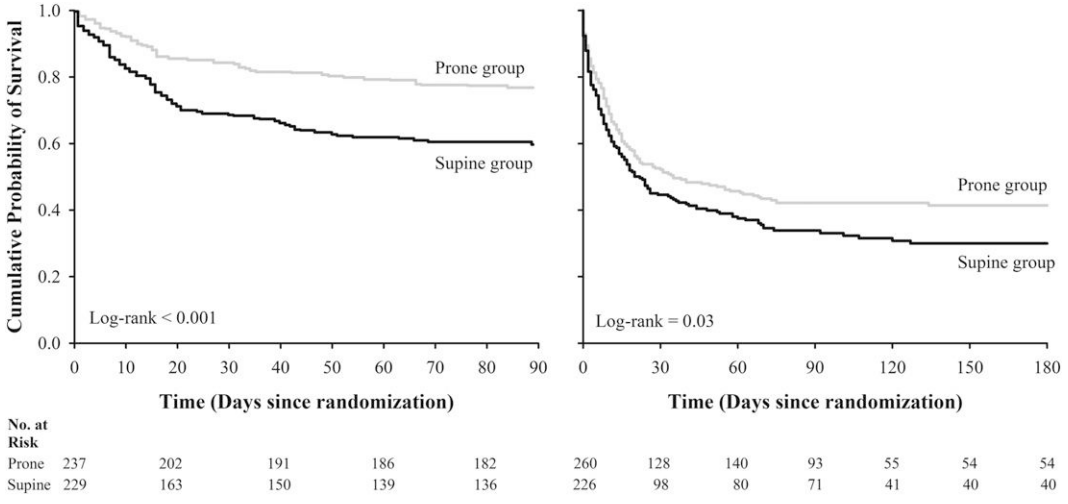

Figure 3. The survival curve obtained in the PROSEVA (Proning Severe ARDS Patients) trial by Guérin and colleagues (*left*) and the survival curve obtained by pooling all the patients enrolled in the four preceding trials with Pa_{O_2}/FI_{O_2} values lower than 100 mm Hg (*right*). FI_{O_2} = fraction of inspired oxygen.

after 24 hours, as implemented by Guérin and colleagues and suggested by Villar and colleagues (80), may help to further refine our indications. In prior work we found that the Pa_{O_2}/FI_{O_2} measured on 5 cm H_2O PEEP reflects the amount of edema detected by CT scan (10), a correlate of recruitability. Despite the acknowledged need for further refinements in the indications for repositioning, a Pa_{O_2}/FI_{O_2} lower than 150 mm Hg measured on at least 5 cm H_2O PEEP currently appears a reasonable threshold for applying prone positioning in ARDS.

Although prone positioning may effectively increase oxygenation several days after disease onset (60), data relative to outcome have been gathered in the early phase of ARDS (*see* Table 1), a phase during which all conditions that favor proning effectiveness are maximally represented, that is, edema, reversible collapse, and absence of structural lung alterations. In this early stage of the syndrome the advantages provided by the prone position for decreasing the risk of ventilator-induced lung injury are likely to exceed those of late-stage ARDS, a phase during which damage has already been inflicted. Because the putative benefits of prone positioning relate to decreased harm from mechanical ventilation, the longer the daily time spent in the prone position the less the lung damage should be, as suggested by the latest trials. Although the criteria for terminating prone positioning were quantitatively different among the various trials, the common denominator was to suspend it arbitrarily after a few days or empirically when oxygenation in the supine position during the daily prone interruptions stabilized at a value greater than a fixed threshold. As these criteria are observations that are plausibly linked to changes of recruitability, we think that this is a reasonable approach to this problem.

Contraindications and Complications

Only a few absolute contraindications to prone positioning exist, such as spinal instability and unmonitored increased intracranial pressure. For other relative contraindications (e.g., open abdominal wounds, multiple trauma with unstabilized fractures, pregnancy, severe hemodynamic instability, and high dependency on airway and vascular access), the risks related to the procedure should be balanced against the possibility of foregoing the application of a potentially life-saving treatment. Some complications, fully described in the major trials, such as transient desaturation, transient hypotension, accidental extubation, and catheter displacement, relate to the mechanics of the proning maneuver itself. Another series of complications, such as pressure ulcers, vomiting, and need for increased sedation, are associated with the duration of staying prone. Particularly harmful is the compression of nerves and retinal vessels, seriously adverse events that may be prevented by skilled nursing. The incidence of these problems decreases with experience gained by a team routinely using this intervention or with the use of special devices and beds that facilitate the mechanics of safe proning.

CONCLUSIONS

In conclusion, prone positioning improves oxygenation by optimizing lung recruitment and ventilation–perfusion matching. Beyond its value in improving gas exchange, prone positioning helps protect against VILI by distributing stress and strain more homogeneously through the lung parenchyma. These beneficial effects appear to confer a survival advantage in patients with severe forms of ARDS, in which the preconditions for prone positioning to work are fully expressed. Its long-term use is not indicated for mild/moderate ARDS, with Pa_{O_2}/FI_{O_2} greater than 150 mm Hg, as it may expose the patient to unnecessary risk of complications in the absence of proven benefits. Prone positioning does not require special equipment but should be performed only by specifically trained personnel and undertaken with great care to minimize the risk of any potential life-threatening complications.

Author disclosures are available with the text of this document at www.atsjournals.org.

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