Does prone positioning improve oxygenation and reduce mortality in patients with acute respiratory distress syndrome?

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Acute respiratory distress syndrome (ARDS) is defined as the acute onset of bilateral chest infiltrates with impaired oxygenation that is not explained by cardiac failure or fluid overload (1,2). ARDS is characterized by alterations in pulmonary mechanics, ventilation and perfusion (V/Q) mismatch and severe hypoxemic respiratory failure (3). The most frequently cited precipitating events for ARDS are sepsis, pneumonia, aspiration, trauma, pancreatitis and blood transfusions (2-5). Current estimates of mortality associated with ARDS range from to 22% to 44% (6-8).

With the increased use of computed tomography imaging in the mid-1980s, it became evident that ARDS was characterized by areas of relatively normal lung parenchyma juxtaposed with areas of dense consolidation and atelectasis (9). In supine patients, the dorsal regions of the lung are susceptible to profound lung derecruitment due to increases in parenchymal edema. ARDS patients are at high risk for developing ventilator-associated lung injury (VALI) due to abnormally high localized parenchymal strain due to the regional heterogeneity of lung consolidation and inflammation (10). While the use of low tidal volumes during mechanical ventilation for lung injury has led to improved clinical outcomes, presumably from decreased VALI associated with alveolar distension and trauma (11), it has not improved the severe atelectasis, consolidation, shunt and hypoxia associated with ARDS. More recently, the use of high levels of positive end-expiratory pressure to improve shunt and hypoxia in ARDS has met with mixed results (12). Recognition that the heterogeneous atelectasis and consolidation seen in ARDS is often dorsally distributed led investigators to question whether care for patients with ARDS in the prone – as opposed to the supine – position may lead to improved mortality outcomes. The present clinical review provides an overview of the physiological rationale for, and the clinical evidence related to, prone positioning's effects on oxygenation and mortality in ARDS.

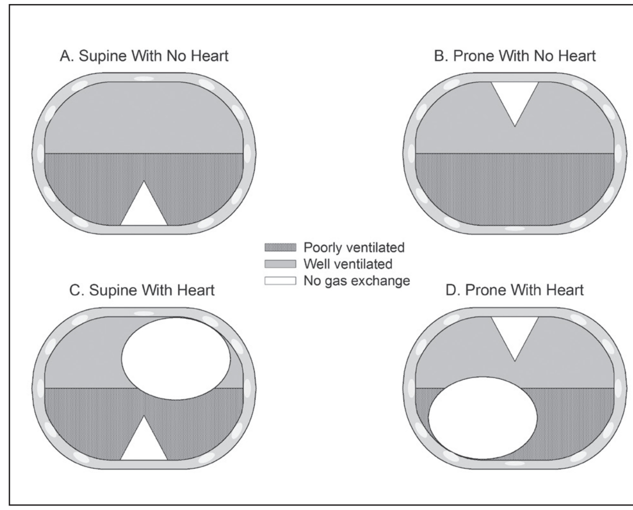

Figure 1) *Schematic representation of changes in the volume of ventilated lung between the supine and prone positions. The vertebral column and associated structures is represented by the white triangle while the heart and associated structures is represented by the white oval. In a chest cavity containing symmetrical lungs, the amount of lung that is well ventilated (where the alveolar pressure exceeds the pleural pressure) roughly equals the amount of lung that is atelectatic and poorly ventilated (where pleural pressure exceeds intra-alveolar pressure) in both supine and prone positions (**A** and **B**). However, when the space occupied by the mediastinum and heart are accounted for, and the effects of the compression of lung tissue subjacent to these structures are considered, there is less ventilated tissue in the supine position (**C**) than in the prone position (**D**). Effects of the transmitted abdominal pressure on the caudal posterior lung are not reflected in this diagram*

ANATOMICAL AND PHYSIOLOGICAL CONSEQUENCES OF PRONE VENTILATION

During prone positioning, ventilation is improved due to changes in pleural pressure (P_{PL}) and the amount of lung atelectasis present. P_{PL} is the sum of all forces acting to compress the alveolus and includes the weight of tissue above the alveolus and the transmitted pressure across the diaphragm from the abdomen. Simplistically, an alveolus will remain open when the intra-alveolar pressure exceeds P_{PL}. When a patient with ARDS is placed prone, the dorsal lung is no longer subject to high P_{PL} and dorsal lung atelectasis decreases. Conversely, the ventral lung units are exposed to a higher P_{PL} and are more likely to collapse. This 'sponge model' was first described by Gattinoni et al (13) and provides a satisfying explanation for the rapid radiographic changes in the distribution of atelectasis apparent with prone positioning in ARDS. If we assume that the lungs are symmetrical, then the amount of lung tissue subject to atelectasis is the same in both the prone and supine positions, and the degree of shunt and hypoxia will not vary between the two positions if blood flow is unchanged (Figures 1A and 1B). However, the lungs are not symmetrical between the two positions due to both the position of the heart (and other ventral intrathoracic structures) and its compression of the subjacent lung parenchyma. Furthermore, in patients who have lost diaphragmatic tone (due to sedation or paralysis), abdominal contents displace the diaphragm caudally, causing compression of the posterior-caudal lung parenchyma (14). All of these factors are reversed in the prone position, creating a situation in which more recruited lung is available in the prone position than in the supine position (Figures 1C and 1D) and the vertical gradient of P_{PL} is decreased. Given that the distribution of pulmonary blood flow is relatively homogenous in ARDS and does not vary significantly between prone and supine positioning, V/Q matching and thus, oxygenation, is improved in the prone compared with the supine position.

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TABLE 1
Selected baseline characteristics, within trial mechanical ventilation parameters and mortality of included trials investigating prone positioning

First author (reference), year	Patients, n		PaO_2/FiO_2 at baseline*, mmHg		Tidal volume during trial*, mL/kg		PEEP during trial*, cmH_2O		Duration of prone*, h	Mortality†, %		P for mortality†
	P	S	P	S	P	S	P	S		P	S	
Gattinoni (29), 2001	152	152	85.7±24.6	88.3±25.9	10.3±2.7	10.3±2.9	9.7±2.9	9.6±3.2	7	21.1	25.0	NS
Guérin (18), 2004	413	378	150±59	155± 59	8.1±2.0	8.1±1.9	7.9± 3.4	7.5± 3.2	8	31.5	32.4	NS
Mancebo (17), 2006	76	60	107±65	126±94	8.3 ±1.7	8.6±1.6	12.4 ±1.9	12.3±2.4	17	43	58	NS
Chan (19), 2007	11	11	111±62	107±81	7.8±1.0	7.6±1.2	13.1±1.5	13.6±2.3	72	36.4	36.4	NS
Fernandez (20), 2008	21	19	113±43	122±40	8.6±2.1	9.2±2.2	11.1±4.1	11.4±3.8	NR	38.0	53.0	NS
Taccone (16), 2009	168	174	113±39‡	–	8.0±1.7	–	10±3	–	18	31	32.8	NS
Guérin (30), 2013	237	229	100±30	100±20	6.1±0.6	6.1±0.6	10±3	10±4	17	16	32.8	<0.001

**All values reported separately for prone (P) and supine (S) groups, and as mean ± SD where data were available. Where separate group values are not shown, values reflect the mean of both P and S groups; †Mortality rates and P values reported for primary outcome measure in each study; ‡Values not reported separately for P and S groups. FiO_2 Fraction of inspired oxygen; NR Not reported; NS Not significant; PaO_2 Partial pressure of oxygen; PEEP Positive end-expiratory pressure*

TABLE 2
Patient- and disease-specific factors that increase the probability of improved oxygenation with initiation of prone ventilation

Empirical	
	>10 mmHg increase in PaO_2 within 30 min of initiation of prone positioning
Pulmonary mechanical	
	Increased intra-abdominal pressure (34)
	Lower chest wall compliance in prone compared with supine position (22)
Disease specific	
	Dependent alveolar collapse and diffuse pulmonary edema (35)
	Extrapulmonary rather than pulmonary cause of ARDS (36)

ARDS Acute respiratory distress syndrome; PaO_2 Partial pressure of oxygen

EFFECT OF PRONE POSITIONING ON OXYGENATION IN ARDS

To date, seven randomized trials investigating the effects of prone positioning on both oxygenation and mortality in adult ARDS have been reported in the peer-reviewed literature (Table 1). While all trials demonstrated improvements in oxygenation with prone positioning, there was no statistical difference in mortality in six of the seven trials (15-20). The oxygenation benefits of prone ventilation were apparent with the first session in most trials, and the difference in oxygenation between the prone and supine groups tended to increase with the number of sessions. Improvements in oxygenation were often preserved after returning to the supine position (suggesting that once alveoli have reopened, they are more likely to stay open) (21,22). In addition to its effects on alveolar recruitment and strain, prone positioning may promote pulmonary secretion drainage in patients. There is evidence that specific disease and patient characteristics may predict which patients are most likely to show improved oxygenation with prone ventilation (Table 2).

EFFECT OF PRONE POSITIONING ON MORTALITY IN ARDS

The improvements in oxygenation apparent in most trials investigating prone positioning were not associated with improvements in mortality, suggesting that oxygenation is not itself the source of improved survival with prone positioning. In fact, previous trials investigating mechanical ventilation have demonstrated a poor association between increases in oxygenation and improved mortality (23). Rather, the prone position decreases regional lung parenchymal heterogeneity and, thereby, decreases the likelihood of extreme tissue strain (24), a precipitant of VALI (10). Decreases in regional tissue strain with prone versus supine positioning have been demonstrated empirically (25), and the use of prone positioning has been associated with less regional lung overdistension, decreased production of inflammatory cytokines and improved lung histology in human and experimental models (26-28). If decreased lung strain (with reductions in the development of VALI) is the source of prone positioning's benefit, it becomes easier to understand why the majority of trials investigating prone positioning have failed to demonstrate a mortality benefit.

For example, most trials investigating prone positioning used tidal volumes that would be considered potentially injurious in ARDS according to current standards. In these trials, the benefit of prone positioning on VALI reduction may have been obscured by the effects of a ventilation strategy that amplified lung strain. In two trials, the duration of prone position sessions was 7 h to 8 h (18,29), potentially providing too brief a respite from exposure to high lung strain to mitigate the risk of VALI. Moreover, the majority of trials occurred during a period when global mortality from ARDS was decreasing and used varying inclusion criteria, which may have led to the trials being statistically underpowered to detect a mortality benefit from prone positioning. Therefore, to demonstrate a benefit of prone positioning, it would be necessary to perform an adequately powered trial using lung protective ventilation in both the control and intervention arms and prone sessions of significant duration. The Proning Severe ARDS Patients (PROSEVA) study randomly assigned 466 patients with ARDS and an average partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of 100 mmHg to either supine or prone positioning, used low tidal volumes in both groups and achieved long periods of prone positioning in the intervention group (Table 1) (30). This trial by Guérin et al (30) demonstrated that prone ventilation resulted in an absolute risk reduction in 28-day mortality of 16.7% (95% CI 9.1% to 24.4%; P<0.001). This mortality benefit persisted at 90 days (absolute risk reduction 17.4% [95% CI 9.1% to 25.5%]; P<0.001). While the PROSEVA trial represents high-quality data on the use of prone positioning in ARDS, several trial features warrant attention. The use of extensive exclusion criteria, the differences in the initial severity of illness and vasopressor use between the supine and the prone group, and the high rate of cardiac arrests in the supine positioning group (31 patients) versus the prone group (16 patients) may limit the external validity of this study.

COMPLICATIONS AND CONTRAINDICATIONS ASSOCIATED WITH PRONE POSITIONING

While patient-specific factors may help select individuals most likely to benefit from prone positioning during mechanical ventilation (Table 2), several potential complications and contraindications exist. Prone positioning may worsen effective chest wall compliance, potentially decreasing delivered tidal volumes or increasing ventilating pressures (31). Complications, such as airway obstruction and endotracheal tube dislodgement, hypotension and arrhythmias, loss of venous access, facial and airway edema, and a greater need for paralysis or sedation, have all been associated with prone positioning with varying frequency (16,32,33). It is unclear whether this increased rate of complications is due to prone positioning per se, or due to a lack of familiarity with the procedure among the surveyed providers. In the PROSEVA trial (whose practitioners were experienced with prone positioning), there was no difference in the rate of most complications between the supine and prone groups, suggesting that it is a safe procedure in the hands of experienced clinicians. Despite prone positioning's potential applicability in ARDS, care must be exercised with its use in patients with hemodynamic instability, facial or ocular injuries, and recent sternotomy or abdominal incisions. Finally, unstable vertebral fractures and significantly increased intracranial pressures are frequently regarded as absolute contraindications to this procedure.

SUMMARY AND RECOMMENDATIONS

Persuasive physiological evidence and clinical trial data support the use of prone position ventilation in selected patients with moderate to severe ARDS (PaO_2/FiO_2 ratios approaching 100 mmHg). For patients to benefit, selection using the criteria used in the PROSEVA trial and Table 2 may be helpful, and the use of long prone positioning sessions (12 h to 18 h per session) begun early in the course of ARDS (within 36 h of diagnosis) may be necessary. Prone positioning benefits oxygenation and improves mortality potentially through the mitigation of abnormal lung tissue strain and VALI. However, it is unclear whether the magnitude of benefit apparent in the PROSEVA trial will be replicated in centres with less expertise or different populations, and further research is warranted in this area.

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