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Treatment of ARDS With Prone Positioning

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Journal

CHEST Journal, 151(1)

ISSN

0012-3692

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Publication Date

2017

DOI

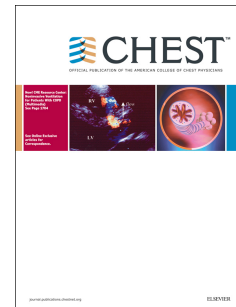
10.1016/j.chest.2016.06.032

Peer reviewed

# Accepted Manuscript

Treatment of Acute Respiratory Distress Syndrome with Prone Positioning

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PII: S0012-3692(16)52643-9

DOI: [10.1016/j.chest.2016.06.032](https://doi.org/10.1016/j.chest.2016.06.032)

Reference: CHEST 545

To appear in: *CHEST*

Received Date: 1 March 2016

Revised Date: 11 June 2016

Accepted Date: 29 June 2016

Please cite this article as: Scholten EL, Beitler JR, Prisk GK, Malhotra A, Treatment of Acute Respiratory Distress Syndrome with Prone Positioning, *CHEST* (2016), doi: 10.1016/j.chest.2016.06.032.

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WORD COUNT = 2776 (Word count not inclusive of title page, abstract, figures, or citations.)

ABSTRACT WORD COUNT= 147

**Title:** *Treatment of Acute Respiratory Distress Syndrome with Prone Positioning*

**Short Running Title:** *Prone Positioning in ARDS*

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**Conflicts of interest: None of the authors listed above have any relevant conflicts of interests (as defined below) to disclose.**

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**Funding Information:** Not applicable

**Notation of prior abstract publication/presentation:** Not applicable

**Abbreviation list (in order of appearance):**

1. ARDS - acute respiratory distress syndrome
2. PRSOEVA trial - Proning Severe ARDS Patients trial
3. PEEP - positive end-expiratory pressure
4.  $\text{PaO}_2/\text{FiO}_2$  - ratio of arterial oxygen tension to the fraction of inspired oxygen
5. CT – computed tomographic
6. VILI - ventilator-induced lung injury
7.  $V_t$  – tidal volume
8. RR – risk ratio
9. AECC – American-European Consensus Conference (definition of ARDS)

**Abstract**

Prone positioning was first proposed in the 1970s as a method to improve gas exchange in the acute respiratory distress syndrome (ARDS). Subsequent observations of dramatic improvement in oxygenation with simple patient rotation motivated the next several decades of research. This work elucidated the physiology mechanisms underlying changes in gas exchange and respiratory mechanics with prone ventilation. However, translating physiological improvements into a clinical benefit has proven challenging; several contemporary trials showed no major clinical benefits with proning. By optimizing patient selection and treatment protocols, the most recent Proning Severe ARDS Patients (PROSEVA) trial demonstrated a significant mortality benefit with prone ventilation. This trial, and subsequent meta-analyses, support the role of prone positioning as an effective therapy to reduce mortality in severe ARDS, particularly when applied early with other lung-protective strategies. This review discusses the physiological principles, clinical evidence, and practical application of prone ventilation in ARDS.

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Approximately 170,000 cases of ARDS occur annually in the United States, with mortality rates of 25-40%.<sup>1</sup> Treating ARDS consumes 5% of all hospital ventilator-days, which incurs great costs (an average of \$115,000 per hospital stay).<sup>2,3</sup> As early as the 1960s, when the knowledge-base for ARDS consisted of descriptive case-series, the need for effective therapies was readily apparent.<sup>4</sup> Early investigators noted the reduced pulmonary compliance and increased atelectasis that characterize the disease, and suggested applying positive end-expiratory pressure (PEEP) to improve oxygenation.<sup>4</sup> To reduce further atelectasis in injured lungs, Bryan proposed prone positioning, theorizing that proning would reduce pleural pressure gradients and restore aeration to dorsal lung segments.<sup>5</sup> Clinical case series supported this concept, documenting significant improvement in oxygenation with proning.<sup>6</sup> Subsequent studies

suggested that prone positioning improves oxygenation in most patients (70-80%) with ARDS, increasing the average ratio of arterial oxygen tension to the fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) by +35 mmHg.<sup>7-14</sup> Prone positioning was thus established as a rescue strategy for severe hypoxemia, and early research focused on establishing the mechanism of improved gas exchange.<sup>12,15,16</sup>

### **Prone Positioning and Gas Exchange**

While supine, the weight of the ventral lungs, heart, and abdominal viscera increase dorsal pleural pressure. This compression reduces transpulmonary pressure (airway opening pressure – pleural pressure) in the dorsal lung regions.<sup>17,18</sup> Increased mass of the edematous ARDS lung further increases the ventral-dorsal pleural pressure gradient and reduces regional ventilation of dependent dorsal regions.<sup>19,20</sup> The ventral heart is estimated to contribute an additional ~3-5 cm H<sub>2</sub>O of pressure to the underlying lung tissue, with experimental studies showing improved ventilation of these infra-cardiac lung regions when prone.<sup>18,21</sup> In addition to the weight of the heart, intra-abdominal pressure is preferentially transmitted through the (often paralyzed and relaxed) diaphragm, further compressing dorsal regions. While the above factors tend to collapse dependent dorsal regions, the gravitational gradient in vascular pressures preferentially perfuses these regions, yielding a region of low ventilation and high perfusion, manifesting clinically as hypoxemia.

Prone positioning reduces the pleural pressure gradient from non-dependent to dependent regions in part via gravitational effects and conformational shape-matching of the lung to the chest cavity. As a result, lung aeration and strain distribution are more homogeneous.<sup>15,22-24</sup> Figure 1 illustrates the gravitational and geometric factors contributing to more uniform pulmonary aeration when prone.<sup>25,26</sup> When supine, both gravity and the chest wall compress the dependent lung segments, causing major inequalities in

aeration along a ventral/dorsal axis (see Fig 1. column III). In contrast, when prone, the geometry favors a more equitable aeration distribution.

Multiple physiological studies support the theory that proning promotes more homogeneous aeration of the ARDS lung. Geometric modeling of computed tomographic (CT) data demonstrated the asymmetry of lung shape leads to a greater gravitationally-induced pleural pressure gradient in the supine posture compared to prone positioning.<sup>27</sup> Additional CT, nuclear, and inert-gas experiments have measured aeration and ventilation, and demonstrated improved homogeneity when prone.<sup>15,26,28,29</sup> Finally, while the model in Figure 1 neglects abdominal factors, animal models of both volume overload and intra-abdominal hypertension have shown more evenly distributed trans-diaphragmatic forces and improved parenchymal homogeneity in the prone position.<sup>23,30-32</sup>

Unlike its effects on dorsal lung aeration, proning does not have a major impact on regional distribution of pulmonary blood flow. In both the supine and prone positions, pulmonary blood flow is directed dorsally in normal and injured lungs (Figure 2).<sup>32-34</sup> Thus, regional perfusion distribution is dictated in large part by non-gravitational factors (lung/heart geometry, airspace compression of vessels, reduction in the ventral region's hypoxic vasoconstriction, etc.).<sup>34</sup> With perfusion patterns relatively constant, and a marked improvement in ventilatory homogeneity upon proning, the shunt fraction would be expected to fall substantially upon proning. Many animal and human studies confirm this hypothesis; on average, proning injured lungs reduces the relative shunt fraction by ~30%.<sup>12,15,16,32,35</sup> Thus, in most patients, decreased shunting when prone leads to clinically significant improvements in oxygenation.

### **Lung Protection**

Adequate oxygenation is necessary for organ function, but many interventions in acute lung injury that raise arterial oxygen tension do not confer a survival advantage (e.g. high tidal volume ventilation, oxygen toxicity).<sup>36,37</sup> Proning generally improves oxygenation, but its ability to attenuate mechanical lung injury may be the more important mechanism of clinical benefit. Indeed, while all major clinical trials of prone positioning in ARDS significantly improved oxygenation, the only trial to reduce mortality significantly was also the only trial to reduce ventilator-days.<sup>9</sup> Furthermore, in this trial (PROSEVA), changes in gas-exchange did not explain the observed mortality benefit.<sup>38</sup>

How could proning reduce VILI, ventilator-days, and death? Comparing the supine and prone aeration (gas:tissue ratio) curves in Figure 1 column III suggests a mechanism. First, note how proning improves dependent aeration, effectively recruiting parenchyma (white arrows). Second, the non-dependent lung regions show dramatic reduction in hyperinflation with proning (black arrows). The net effect is more homogenous lung aeration, which reduces regional shear strain, leading to less VILI.<sup>15,23,24</sup>

Proning and high PEEP ventilation may have complementary benefits. In ARDS, increased PEEP is known to prevent alveolar derecruitment, but may deleteriously promote over-distension of previously well-ventilated alveoli.<sup>39,40</sup> Proning may help mitigate these deleterious effects of PEEP.<sup>41</sup> Adding prone positioning to high-PEEP ventilation: 1) further increases lung aeration while 2) simultaneously *reducing* regional hyperinflation and 3) decreasing small airway opening/closing events during the respiratory cycle.<sup>42</sup> These observations suggest proning may decrease barotrauma and atelectrauma, and thereby protect against ventilator-induced lung injury (VILI).<sup>29</sup> In support of this theory, rat, dog, and sheep models have shown improved histological VILI scores when comparing prone to supine ventilation.<sup>43-47</sup> More recently, in experimental injured rodents, proning reduced expression of cellular signaling pathways known to correlate with the development of VILI, especially in ventral regions that are at risk



of hyperinflation while supine.<sup>43,48</sup> Intriguingly, pharmacologically inhibiting these same pathways protects experimental animals from lung injury, thus identifying molecular mechanisms underlying VILI.<sup>43</sup> In humans, histological data are unavailable, but both serum and bronchoalveolar lavage inflammatory markers are reduced by prone positioning, which may reflect less VILI.<sup>49,50</sup>

Although studies of respiratory mechanics after proning have reached variable conclusions, their results suggest the importance of recruiting the lung to achieve clinical benefit. When proned, chest wall compliance typically falls initially, then increases gradually over time.<sup>35</sup> Those proned patients who achieve greater drops in chest wall compliance have more pronounced improvement in oxygenation ( $r=0.62$ ), potentially due to improved dorsal recruitment.<sup>35</sup> Furthermore, recruitment maneuvers (sustained high pressure inflations) were found to be highly effective in improving oxygenation when applied to proned patients.<sup>51</sup>

Finally, independent of mechanical effects, infectious complications may also be reduced by proning. In pigs, a tracheal position relatively anterior to the lung parenchyma markedly decreased VAP incidence.<sup>52</sup> While prone, gravity can assist secretion drainage along the general dorsal-lungs to ventral-trachea drainage vector. This enhanced drainage may explain observations that proning 1) improves secretion clearance 2) causes opacities to migrate ventrally on imaging while improving overall aeration 3) may decrease rates of ventilator-associated pneumonia.<sup>8,26,29,53</sup>

### **Extra-Pulmonary Organ Systems**

In addition to its lung-protective effects, proning impacts cardiac and abdominal pressures. In general, total cardiac output is unchanged when proning ARDS patients. However, while prone, the right atrium moves ventrally, such that venous return now is aided by gravity. Thus, preload responsive patients may

augment their cardiac output with proning.<sup>54</sup> Additionally, right ventricular afterload typically falls, likely due to relief of hypoxic pulmonary vasoconstriction.<sup>54</sup> This effect may be most clinically relevant in severe ARDS populations, as proning reduces the RV dilation and septal dysfunction that accompanies this disease.<sup>55</sup> To measure these hemodynamic changes accurately, pressure transducers need to be carefully re-leveled to reflect the right atrium's more ventral position while prone.<sup>56</sup>

Proning also affects the chest-abdominal interactions. Obesity worsens dependent dorsal atelectasis, and prone ventilation improves oxygenation during routine surgery in obese patient and obese animal models without lung injury.<sup>30,57</sup> However, in obese humans with ARDS, proning may worsen intra-abdominal hypertension, and lead to subsequent renal and hepatic dysfunction.<sup>58-61</sup> Thus, it is reasonable to monitor intra-abdominal pressure while proning, and consider using an air-mattress or a suspended abdomen if abdominal pressures become excessive.<sup>59,61</sup> Finally, studies have reported increased vomiting and decreased tolerance of high-volume enteral feeds while prone.<sup>11,62</sup> To facilitate gastric emptying, some centers closely monitor gastric residuals, adjust pharmacotherapy, and position the bed in reverse Trendelenburg while prone.<sup>63</sup>

### **Clinical trials**

While the physiological effects of prone positioning are well described, clinical trials have yielded mixed results regarding the clinical benefit. Table 1 reviews five major randomized trials of prone ventilation in adults.<sup>7-11,64</sup> Note the significant mortality benefit of proning in the PROSEVA trial, with no mortality benefit in the previous trials. What accounts for these discrepant findings?

The 2013 PROSEVA trial design benefited from recognition of the limitations of the first studies, including: a limited sample size, significant treatment cross-over, unstandardized ventilator

management with high-tidal volumes, the inclusion of patients without or with only mild ARDS, a small “dose” of time spent prone, arbitrary criteria for cessation of proning, and enrollment of patients late in their disease course. Trial designs evolved further over time. Mancebo’s 2006 trial had potential advantages over previously published trials: patients had more severe lung injury, were enrolled early in their course, and received higher doses of proning compared to earlier trials.<sup>7</sup> Unfortunately, slow enrollment led to early study termination with just 142 patients. The authors reported a non-significant trend towards improved survival with proning, and post-hoc analysis demonstrated considerable benefit for severely ill patients. Next, in 2009, Taccone et al. used a similar design to Mancebo, and reached enrollment goals.<sup>11</sup> Again, no significant decrease in mortality was noted with proning, although this trial too likely was underpowered and showed a trend towards improved survival with proning.

Many possible explanations can account for the discrepant findings of Taccone and PROSEVA. As Table 1 illustrates, compared to Taccone, PROSEVA had increased power, enrolled a highly selected population of severe ARDS, had less supine/prone cross-over, more neuromuscular blockade, and, perhaps most importantly, a lower administered tidal volume ( $V_t$ ). One recent meta-analysis divided proning trials into those with high ( $>8$  mL/Kg) or low ( $<8$  mL/Kg) tidal volume ventilation. Only in the low tidal volume ventilation cohort was proning shown to decrease mortality (risk ratio of death at 60-days, proning with low  $V_t$  RR 0.66, 95% CI 0.50-0.86;  $p = 0.002$ ; proning with high  $V_t$  RR 1.00, 95% CI 0.88-1.13;  $p = 0.949$ ).<sup>65</sup> These findings suggest the benefits of proning are realized only in the background of protective low tidal volume ventilation.

Taccone did describe more frequent complications with proning compared to PROSEVA (which reported no significant increase in any complications). For Taccone, loss of vascular access, airway obstruction, extubation, and increased vasopressor requirement all occurred more frequently in the prone arm.<sup>11</sup> All

centers in the PROSEVA trial had used prone positioning in daily practice for more than five years, minimizing risk associated with an implementation learning curve. The longer duration and more frequent proning maneuvers performed in Taccone's trial may have increased risks. Alternatively, inter-trial adjudication of subjective events may have differed. These complications, while important to note, do not seem harmful enough to account for the magnitude of the mortality difference between these two trials.

Of note, the supine (control) group in PROSEVA may have had slightly higher acuity of illness than the prone group. Relative to the prone group, the supine group had higher mean sequential organ failure assessment (SOFA) scores and more frequent vasopressor use. However, this high-acuity supine group still had excellent clinical outcomes, and their mortality was identical to the supine group in Taccone's "healthier" population. This finding argues against baseline differences in study arms as a mechanism to explain the different trial conclusions. The excellent control group survival in PROSEVA was likely due to strict adherence to evidence-based therapy for ARDS, namely an achieved tidal volume of 6.1 cc/kg and liberal use of neuromuscular blockers (87% of all patients).<sup>9,11</sup>

In summary, clinical trial evidence suggests that to achieve improved survival with proning, one needs: patients with severe ARDS treated early in their course; a long duration of prone positioning (>16 hours/day); physiologically driven criteria for cessation of daily proning (e.g. minimal ventilator requirements); the concurrent use of lung-protective therapies for ARDS; and experienced staff able to minimize procedural risks. The interested readers may review other trials of prone positioning.<sup>49,50,66-71</sup> These studies were not discussed in this review as they were smaller (5 studies had <40 patients), in unique populations (pediatrics, trauma), and had various design issues that limit their generalizability.

### Practical Considerations

With this evidence base, prone positioning moves from a salvage therapy for refractory hypoxemia to an up-front lung-protective strategy intended to improve survival in severe ARDS. Indeed, proning has never been proven to afford a survival benefit when employed as a late rescue therapy for refractory hypoxemia. However, a contemporary prospective observational study (the 2016 LUNG-SAFE study) found that only 16.3% of severe ARDS patients were treated with prone ventilation.<sup>72</sup> Among other factors, perceived logistical difficulties may contribute to poor implementation; interested clinicians are referred to an excellent pragmatic overview (including a pre-turn checklist) as well as an online video that models successful techniques.<sup>9,73</sup> Generally, after prophylactic oxygenation with 100% FiO<sub>2</sub>, proning can be safely performed with 3-4 staff members, with one member dedicated solely to the endotracheal tube (ETT) management. Immediately post-maneuver, there often is an increase in secretion mobilization that requires suctioning. Once prone, staff should especially focus on preventing pressure ulcers and managing endotracheal obstruction, for which the prone patient is at increased risk.

74

As far as when to revert to supine-only therapy, in PROSEVA, proning was continued for at least 16 hours/day until sustained oxygenation improvement was achieved, defined as PaO<sub>2</sub>/FiO<sub>2</sub> ≥ 150 mmHg with PEEP ≤ 10 cmH<sub>2</sub>O and FiO<sub>2</sub> ≤ 60% for at least 4 hours after repositioning supine.<sup>63</sup> While this protocol is informative, the optimum duration of proning is unknown, and supinating prematurely might lead to derecruitment and potentially even VILI.<sup>9</sup> We recommend continuing proning for least 16 hours per day and ceasing proning when clinical variables (such as PaO<sub>2</sub>/FiO<sub>2</sub>, lung recruitability, ventilatory efficiency, static compliance, resolution of underlying non-pulmonary processes) show clear sustained improvement. Further research may help identify the optimal criteria to cease prone ventilation. Relatively strong contraindications to proning are: severe facial or neck trauma, pelvic/spinal instability,

elevated intra-cranial pressure (as turning the head compresses the internal jugular vein), hemothysis, and frequent cardiac arrhythmias or high-probability of requiring CPR (Table 2).<sup>73</sup> Experienced centers have published case reports of success proning in extreme circumstances, including third trimester pregnancy, patients on venovenous ECMO, and with invasive intracranial pressure monitoring.<sup>47,75-77</sup>

### **Next Steps**

Future studies of proning will need to emulate the extended-duration and low tidal volume approach of PROSEVA. Several clinical questions remain regarding the optimal approach to proning and concomitant lung-protective therapies. 1) What is the optimal approach to PEEP management in prone positioning, and is proning effective in patients receiving a high-PEEP strategy or might these therapies even be synergistic? 2) Does effective proning necessitate neuromuscular blockade for several days, and does this intervention contribute to critical illness neuromyopathy and associated functional impairment in survivors? 3) Is proning most effective in only a subset of patients with ARDS, and how can we further clarify the population who may have a survival (rather than just an oxygenation) benefit? 4) What is the learning curve and associated risk to patients if inexperienced centers newly adopt prone positioning?

In conclusion, proning was first recognized for its ability to improve oxygenation and historically used as salvage therapy for refractory hypoxemia. A recent multicenter trial and subsequent meta-analyses have made a compelling case that proning select patients with severe ARDS early in their course improves survival. This survival benefit is likely mediated by reduced VILI, as regional differences in lung aeration, compliance, and shear strain are minimized. In contrast to historical views, early improvement in gas exchange with proning does not reliably predict improved survival. Prone ventilation may be underutilized in clinical practice: in the LUNG-SAFE trial, only 16.4% of severe ARDS patients were

proned.<sup>72</sup> If proning is pursued, it should be done early, with experienced staff to avoid logistical complications, and at extended durations ( $\geq 16$  hours/day). For patients who fall outside these relatively narrow criteria, the clinician must balance the appealing physiological rationale behind proning against the equivocal evidence base for patients with less-severe lung injury, late-stage ARDS, or non-ARDS conditions.<sup>78</sup>

### **Acknowledgments**

All of the authors reviewed the literature and provided contributed important intellectual content to this review.

	<b>Table 1. Major trials of prone ventilation in ARDS</b>				
	<b>Gattinoni</b>	<b>Guérin</b>	<b>Mancebo</b>	<b>Taccone</b>	<b>Guérin (PROSEVA)</b>
	2001, NEJM	2004, JAMA	2006, Am J Respir Crit Care	2009, JAMA	2013, NEJM
Prone group mortality	50.7% (ICU mortality)	32.4% (28-day)	43% (ICU mortality)	31% (28-day)	<b>16% (28-day)</b>
Control group mortality	48% (ICU mortality)	31.5 % (28-day)	58% (ICU mortality)	32.8% (28-day)	<b>32.8% (28-day)</b>
RR of mortality (prone/control)	1.05 ( $p=0.65$ )	1.02 ( $p=0.77$ )	0.74 ( $p=0.12$ )	0.97 ( $p=0.72$ )	<b>0.48 (<math>p&lt;0.001</math>)</b>
Patients (n)	304	<b>802</b>	142	342	466
Targeted disease	ALI <sup>‡</sup> & ARDS <sup>‡</sup>	Respiratory failure with PaO <sub>2</sub> /FiO <sub>2</sub> <300	ARDS <sup>‡</sup>	ARDS <sup>‡</sup>	<b>ARDS<sup>‡</sup> with PaO<sub>2</sub>/FiO<sub>2</sub>&lt;150</b>
PaO <sub>2</sub> /FiO <sub>2</sub> at enrollment	128	153	139	113	<b>100</b>
Enrollment early in disease course?	No	No	Yes, <2 days of intubation	Yes, <3 days	<b>Yes, &lt;1.5 days</b>
SAPS II	40	<b>46</b>	43	41	<b>46</b>
V <sub>t</sub> delivered	10.3 ml/kg	7.9 ml/kg	8.5 ml/kg	8 ml/kg	<b>6.1 ml/kg</b>
Patients paralyzed	Not reported	21%	45%	Not reported	<b>87%</b>
Mean increase in PaO <sub>2</sub> /FiO <sub>2</sub> upon proning	19 mmHg	18 mmHg	32 mmHg <sup>†</sup>	44 mmHg	<b>59 mmHg</b>
Average time prone	7 hr/day	8 hr/day	17 hr/day	<b>18 hr/day</b>	17 hr/day
Average days prone	<b>10 days</b>	4 days	<b>10 days</b>	8.4 days	4 days
Significant reduction in ventilator days? <sup>*</sup>	No	No	No	No	<b>Yes</b>
Difficulty enrolling?	<b>Yes</b>	No	<b>Yes</b>	No	No
Cross-over (supine to prone)	8%	<b>21%</b>	8%	12%	7%

## Table Legend:

Bolded text indicates the most extreme value across all 5 trials. <sup>†</sup>This value was estimated based on graphical data presented in the text. <sup>\*</sup>Not all trials reported ventilator days or ICU length of stay, absence of reporting was taken to imply no significant difference. <sup>‡</sup>ALI and ARDS were defined according to the AECC definition of ARDS.<sup>64</sup> Abbreviations: ARDS = acute respiratory distress



syndrome, RR = relative risk, ALI= acute lung injury, AEEC= American-European consensus conference,  $\text{PaO}_2/\text{FiO}_2$  = ratio of arterial oxygen tension to the fraction of inspired oxygen, SAPS II = simplified acute physiology score II,  $V_t$  = tidal volume.

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**Table 2. Summary Recommendations for Prone Ventilation**

<p><b><u>Who to prone?</u></b></p> <ul style="list-style-type: none"> <li>• Severe ARDS (<math>\text{PaO}_2/\text{FiO}_2 &lt; 150</math>)</li> <li>• Early in the course (ideally within 48 hours).</li> <li>• Best outcomes reported when proning is used in combination with BOTH low-tidal volume ventilation (6 cc/kg) and with neuromuscular blockade</li> </ul>	<p><b><u>Who not to prone?</u></b></p> <ul style="list-style-type: none"> <li>• Facial/neck trauma or spinal instability</li> <li>• Recent sternotomy or large ventral surface burn</li> <li>• Elevated intracranial pressure</li> <li>• Massive hemoptysis</li> <li>• Patients at high risk of requiring CPR or defibrillation</li> </ul>
<p><b><u>How to prone?</u></b></p> <ul style="list-style-type: none"> <li>• Requires 3-5 people, close attention to ETT and central lines. A demonstration video and checklist are available<sup>9,73</sup></li> <li>• Preparation: Pre-oxygenate, empty stomach, suction ETT/oral cavity, remove EKG leads and reattach to back, re-zero hemodynamic transducers</li> <li>• Support and frequently reposition pressure points: face, shoulder, anterior pelvis</li> </ul>	<p><b><u>Potential complications:</u></b></p> <ul style="list-style-type: none"> <li>• Temporary increase in oral and tracheal secretions occluding airway</li> <li>• ETT migration or kinking</li> <li>• Vascular catheter kinking</li> <li>• Elevated intra-abdominal pressures</li> <li>• Increased gastric residuals</li> <li>• Facial pressure ulcers, facial edema, lip trauma from ETT, brachial plexus injury (arm extension)</li> </ul>
<p><b><u>How long to prone each day?</u></b></p> <ul style="list-style-type: none"> <li>• Successful trials use at least 16 hours of proning per day.</li> <li>• Long-proning sessions likely avoid derecruitment.</li> </ul>	<p><b><u>When to stop?</u></b></p> <ul style="list-style-type: none"> <li>• In PROSEVA, proning was stopped when <math>\text{PaO}_2/\text{FiO}_2</math> remained <math>&gt;150</math> four hours after supinating (with PEEP <math>&lt;10</math> and <math>\text{FiO}_2 &lt; 0.6</math>).</li> <li>• Optimal strategy is unclear: consider continuing proning until clear improvement in gas exchange, mechanics, and overall clinical course.</li> </ul>

## REFERENCES

1. Chambers J, Manley L, Nolen JE, Pruitt K, Weaver T, Maple D. American Lung Association: Lung Disease Data. New York, NY: American Lung Association; 2008.
2. Esteban A, Ferguson ND, Meade MO, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177(2):170–177.
3. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;174(5):538–544.
4. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute Respiratory Distress in Adults. *Lancet* 1967;290(7511):319–323.
5. Bryan AC. Comments of a devil's advocate. *Am Rev Respir Dis* 1974;110(62):143–144.
6. Piehl M, Brown R. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976;4(1):13–14.
7. Mancebo J, Fernández R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173(11):1233–1239.
8. Guerin C, Gaillard Sa, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292(19):2379–2387.
9. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368(23):2159–2168.
10. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345(8):568–573.
11. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302(18):1977–1984.
12. Pappert D, Rossaint R, Slama K, Gruning T, Falke KJ. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. *Chest* 1994;106(5):1511–1516.
13. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis* 1977;115(4):559–566.
14. Mure M, Martling CR, Lindahl SG. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. *Crit Care Med* 1997;25(9):1539–1544.
15. Lamm WJE, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994;150(1):184–193.
16. Blanch L, Mancebo J, Perez M, et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997;23(10):1033–1039.
17. Lai-Fook SJ, Rodarte JR. Pleural pressure distribution and its relationship to lung volume and interstitial pressure. *J Appl Physiol* 1991;70(3):967–978.

18. Malbouisson L, Busch C, Puybasset L, Lu Q, Cluzel P, Rouby J-J. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;161(4):2–4.
19. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149(1):8–13.
20. Puybasset L, Cluzel P, Chao N, Slutsky AS, Coriat P, Rouby J-J. A computed tomography scan assessment of regional lung volume in acute lung injury. *Am J Respir Crit Care Med* 1998;158(5):1644–1655.
21. Wiener CM, McKenna WJ, Myers MJ, Lavender JP, Hughes JM. Left lower lobe ventilation is reduced in patients with cardiomegaly in the supine but not the prone position. *Am Rev Respir Dis* 1990;141(1):150–155.
22. Henderson AC, Sa RC, Theilmann RJ, Buxton RB, Prisk GK, Hopkins SR. The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung. *J Appl Physiol* 2013;115(3):313–24.
23. Mutoh T, Guest RJ, Lamm WJ, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. *Am Rev Respir Dis* 1992;146(2):300–306.
24. Hubmayr RD, Walters BJ, Chevalier PA, Rodarte JR, Olson LE. Topographical distribution of regional lung volume in anesthetized dogs. *J Appl Physiol* 1983;54(4):1048–1056.
25. Gattinoni L, Taccone P, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome: rationale, indications, and limits. *Am J Respir Crit Care Med* 2013;188(11):1286–1293.
26. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991;74(15):15–23.
27. Tawhai MH, Nash MP, Lin C-L, Hoffman E a. Supine and prone differences in regional lung density and pleural pressure gradients in the human lung with constant shape. *J Appl Physiol* 2009;107:912–920.
28. Mure M, Domino KB, Lindahl SG, Hlastala MP, Altemeier W a, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. *J Appl Physiol* 2000;88(3):1076–1083.
29. Galiatsou E, Kostanti E, Svarna E, et al. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006;174(2):187–197.
30. Mure M, Glenny R, Domino K, Hlastala M. Pulmonary gas exchange in pigs improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998;2(6):1785–1790.
31. Mutoh T, Lamm WJ, Embree LJ, Hildebrandt J, Albert RK. Volume infusion produces abdominal distension, lung compression, and chest wall stiffening in pigs. *J Appl Physiol* 1992;72(2):575–582.
32. Richter T, Bellani G, Harris RS, et al. Effect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. *Am J Respir Crit Care Med* 2005;172(4):480–487.
33. Prisk GK, Yamada K, Henderson AC, et al. Pulmonary perfusion in the prone and supine postures in the normal human lung. *J Appl Physiol* 2007;103(3):883–894.

34. Glenny RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol* 1991;71(2):620–629.
35. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998;157(2):387–393.
36. Brower RG, Matthay M, Morris A, Schoenfeld DA, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New Engl J Med* 2000;342(18):1301–1308.
37. Deneke SM, Fanburg BL. Normobaric oxygen toxicity of the lung. *N Engl J Med* 1980;303(2):76–86.
38. Albert RK, Keniston A, Baboi L, Ayzac L, Guerin C. Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189(4):494–496.
39. Gattinoni L, Mascheroni D, Torresin A, et al. Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. *Intensive Care Med* 1986;12(3):137–142.
40. Mercat A, Richard JM, Vielle B. Positive end-expiratory pressure setting in adults with acute lung injury. *JAMA* 2013;299(6):646–655.
41. Beitler JR, Guérin C, Ayzac L, et al. PEEP titration during prone positioning for acute respiratory distress syndrome. *Crit Care* 2015;19:436.
42. Cornejo RA, Diaz JC, Tobar EA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013;188(4):440–448.
43. Park MS, He Q, Edwards MG, et al. Mitogen-activated protein kinase phosphatase-1 modulates regional effects of injurious mechanical ventilation in rodent lungs. *Am J Respir Crit Care Med* 2012;186(1):72–81.
44. Nakos G, Batistatou A, Galiatsou E, et al. Lung and “end organ” injury due to mechanical ventilation in animals: comparison between the prone and supine positions. *Crit Care* 2006;10(1):1–9.
45. Valenza F, Guglielmi M, Maffioletti M, et al. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005;33(2):361–367.
46. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft S a, Marini JJ. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit. Care Med.* 1997;25(1):16–27.
47. Broccard A, Shapiro RS, Schmitz L, Adams AB, Nahum A, Marini JJ. Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Crit Care Med* 2000;28(2).
48. Santana MCE, Garcia CSNB, Xisto DG, et al. Prone position prevents regional alveolar hyperinflation and mechanical stress and strain in mild experimental acute lung injury. *Respir Physiol Neurobiol* 2009;167(2):181–188.
49. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community-acquired pneumonia. *J Formos Med Assoc* 2007;106(9):708–716.

50. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005;33(10):2162–2171.
51. Oczenski W, Hörmann C, Keller C, et al. Recruitment maneuvers during prone positioning in patients with acute respiratory distress syndrome. *Crit Care Med* 2005;33(1):54–61.
52. Zanella A, Cressoni M, Epp M, Hoffmann V, Stylianou M, Kolobow T. Effects of tracheal orientation on development of ventilator-associated pneumonia: An experimental study. *Intensive Care Med* 2012;38(4):677–685.
53. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. *Intensive Care Med* 2010;36(4):585–599.
54. Jozwiak M, Teboul J-L, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013;188(12):1428–33.
55. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007;132(5):1440–1446.
56. Magder S. Is all on the level? Hemodynamics during supine versus prone ventilation. *Am J Respir Crit Care Med* 2013;188(12):1390–1391.
57. Pelosi P, Croci M, Calappi E, et al. Prone positioning improves pulmonary function in obese patients during general anesthesia. *Anesth Analg* 1996;83(3):578–83.
58. Weig T, Janitzka S, Zoller M, et al. Influence of abdominal obesity on multiorgan dysfunction and mortality in acute respiratory distress syndrome patients treated with prone positioning. *J Crit Care* 2014;29(4):557–561.
59. Kirkpatrick AW, Pelosi P, Waele JJ De, et al. Clinical review: intra-abdominal hypertension: does it influence the physiology of prone ventilation? *Crit Care* 2010;14(4):232.
60. Hering R, Vorwerk R, Wrigge H, et al. Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. *Intensive Care Med* 2002;28(1):53–58.
61. Michelet P, Roch A, Gainnier M, Sainty J-M, Auffray J-P, Papazian L. Influence of support on intra-abdominal pressure, hepatic kinetics of indocyanine green and extravascular lung water during prone positioning in patients with ARDS: a randomized crossover study. *Crit Care* 2005;9(3):R251–R257.
62. Reignier J, Thenoz-Jost N, Fiancette M, et al. Early enteral nutrition in mechanically ventilated patients in the prone position. *Crit Care Med* 2004;32(1):94–99.
63. Guérin C. Prone ventilation in acute respiratory distress syndrome. *Eur Respir Rev* 2014;23(132):249–57.
64. Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149(3):818–824.
65. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory

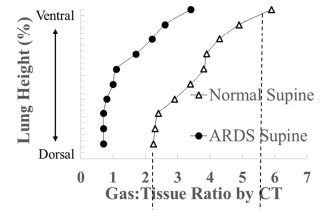
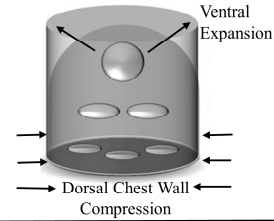
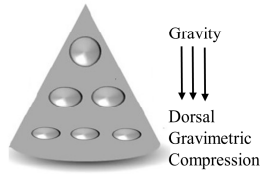
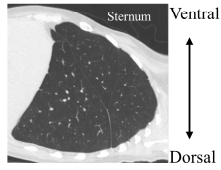
- distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014;40(3):332–341.
66. Fridrich P, Krafft P, Hochleuthner H, Mauritz W. The effects of long-term prone positioning in patients with trauma-induced adult respiratory distress syndrome. *Anesth Analg* 1996;83(6):1206–1211.
  67. Beuret P, Carton M-J, Nourdine K, Kaaki M, Tramoni G, Ducreux J-C. Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study. *Intensive Care Med* 2002;28(5):564–569.
  68. Curley MAQ, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. *JAMA* 2005;294(2):229–237.
  69. Voggenreiter G, Aufmkolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a prospective randomized trial. *J Trauma* 2005;59(2):333–341.
  70. Demory D, Michelet P, Arnal J-M, et al. High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. *Crit Care Med* 2007;35(1):106–111.
  71. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34(8):1487–1491.
  72. Gattinoni L, Haren F Van, Larsson A, Mcauley DF, Ranieri M. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315(8):788–800.
  73. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002;165(10):1359–1363.
  74. Lee JM, Bae W, Lee YJ, Cho Y-J. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014;42(5):1–21.
  75. Samanta S, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy? *Am J Emerg Med* 2014;32(6):687.
  76. Masuda Y, Tatsumi H, Imaizumi H, et al. Effect of prone positioning on cannula function and impaired oxygenation during extracorporeal circulation. *J Artif Organs* 2014;17(1):106–109.
  77. Cornejo R, Romero C, Ugalde D, et al. High-volume hemofiltration and prone ventilation in subarachnoid hemorrhage complicated by severe acute respiratory distress syndrome and refractory septic shock. *Rev Bras Ter Intensiva* 2014;26(2):193–199.
  78. Nakos G, Tsangaris I, Kostanti E, et al. Effect of the prone position on patients with hydrostatic pulmonary edema compared with patients with acute respiratory distress syndrome and pulmonary fibrosis. *Am J Respir Crit Care Med* 2000;161(2):360–368.

**I. Isolated Lung Affected by Gravity (Neglecting the Chest Wall)**

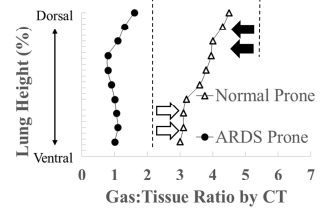
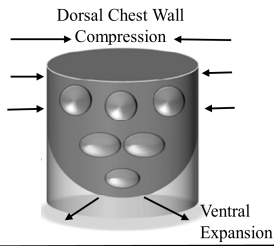
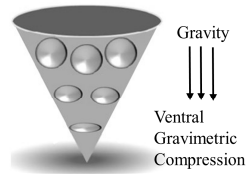
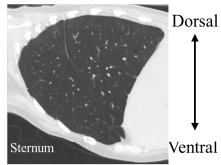
**II. Lung Expansion Constrained by the Chest Wall.**

**III. Proning Homogenizes Pulmonary Aeration**

**Supine Chest**



**Prone Chest**



ACCEPTED MANUSCRIPT



