CHEST

Treatment of ARDS With Prone Positioning

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Prone positioning was first proposed in the 1970s as a method to improve gas exchange in ARDS. Subsequent observations of dramatic improvement in oxygenation with simple patient rotation motivated the next several decades of research. This work elucidated the physiological mechanisms underlying changes in gas exchange and respiratory mechanics with prone ventilation. However, translating physiological improvements into a clinical benefit has proved challenging; several contemporary trials showed no major clinical benefits with prone positioning. By optimizing patient selection and treatment protocols, the 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. CHEST 2017; 151(1):215-224

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Approximately 170,000 cases of ARDS occur annually in the United States, with mortality rates of 25% to 40%.[1] Treating ARDS consumes 5% of all hospital ventilator days, which incurs great costs (an average of $115,000 per hospital stay).[2,3] As early as the 1960s, when the knowledge base for ARDS consisted of descriptive case series, the need for effective therapies was readily apparent.[4] 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.[4] To reduce further atelectasis in injured lungs, Bryan proposed prone positioning, theorizing that prone positioning would reduce pleural pressure gradients and restore aeration to dorsal lung segments.[5] Clinical case series supported this concept, documenting significant improvement in oxygenation with prone positioning.[6] Subsequent studies suggested that prone positioning improves oxygenation in most patients with ARDS (70%-80%), increasing the average ratio of Pa_{O_2}/Fi_{O_2} by +35 mm Hg.[7-14] Prone positioning was thus established as a rescue strategy for severe hypoxemia, and early research focused on establishing the mechanism of improved gas exchange.[12,15,16]

Prone Positioning and Gas Exchange

When a person is supine, the weight of the ventral lungs, heart, and abdominal viscera increase dorsal pleural pressure. This compression reduces transpulmonary pressure (airway opening pressure – pleural

ABBREVIATIONS: PEEP = positive end-expiratory pressure; RR = risk ratio; VILI = ventilator-induced lung injury

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pressure) in the dorsal lung regions.[17,18] The increased mass of the edematous ARDS lung further increases the ventral-dorsal pleural pressure gradient and reduces regional ventilation of dependent dorsal regions.[19,20] The ventral heart is estimated to contribute approximately an additional 3 to 5 cm H_2O of pressure to the underlying lung tissue, with experimental studies showing improved ventilation of these infracardiac lung regions in a prone position.[18,21] In addition to the weight of the heart, intraabdominal pressure is preferentially transmitted through the (often paralyzed and relaxed) diaphragm, further compressing dorsal regions. Although these 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.

Placing a person in the prone position reduces the pleural pressure gradient from nondependent to dependent regions, in part through gravitational effects and conformational shape matching of the lung to the chest cavity. As a result, lung aeration and strain distribution are more homogeneous.[15,22-24] Figure 1 illustrates the gravitational and geometric factors contributing to more uniform pulmonary aeration in the prone position.[25,26] When supine, both gravity and the chest wall compress the dependent lung segments, causing major inequalities in aeration along a ventral/dorsal axis (Fig 1, column III). In contrast, when the person is in a prone position, the geometry favors a more equitable aeration distribution.

Multiple physiological studies support the theory that placing a person in the prone position promotes more homogeneous aeration of the lung in ARDS. Geometric modeling of CT data demonstrated that the asymmetry of lung shape leads to a greater gravitationally induced pleural pressure gradient in the supine posture compared with prone positioning.[27] Additional CT, nuclear, and inert gas experiments have measured aeration and ventilation and demonstrated improved homogeneity when the person was placed in a prone position.[15,26,28,29] Finally, although the model in Figure 1 neglects abdominal factors, animal models of both volume overload and intraabdominal hypertension have shown more evenly distributed transdiaphragmatic forces and improved parenchymal homogeneity in the prone position.[23,30-32]

Unlike its effects on dorsal lung aeration, the prone position does not have a major impact on regional

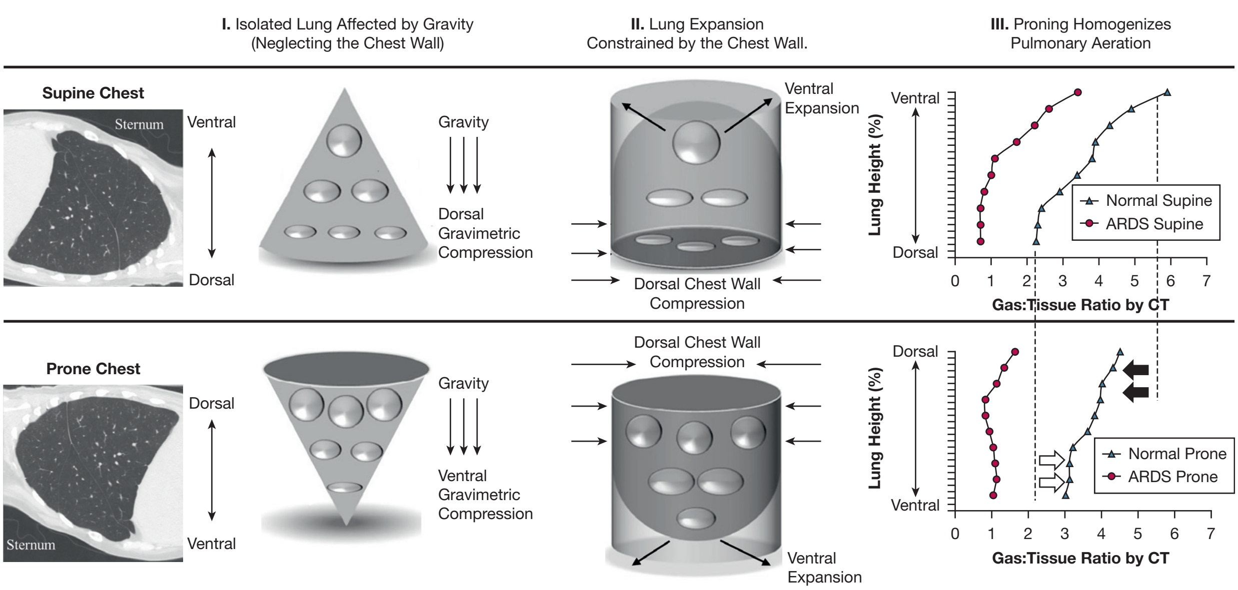

Figure 1 – *Column I shows an isolated lung (cone) and alveolar units (circles) removed from the chest wall. This illustrates how the unhindered lung contains more alveolar units in the dorsal regions than in the ventral regions and how a gravitational pleural pressure gradient leads to compression of dependent segments. When the patient is in a prone position, this results in a smaller fraction of compressed alveolar units than when the patient is supine. Column II illustrates the effects of compressing the native conical shape of the lungs into the rigid chest wall. While the patient is supine, the compressive effects of gravity are magnified by the chest wall, further compressing the dorsal segments while expanding the ventral segments. Conversely, when the patient is prone, the chest wall effects oppose gravimetric effects, leading to more homogeneous aeration. Column III displays experimental data supporting this model. The curves describe how pulmonary aeration (gas to tissue ratio on CT) varies as one moves along the lung's vertical axis in human patients with ARDS. Note the marked asymmetry in aeration (and thus ventilation) along the ventral/dorsal axis when supine and a much more uniform gas to tissue ratio when prone. The white arrows signify recruitment of dependent regions, and the black arrows signify reduced regional hyperinflation in well-aerated lung. (Adapted with permission from Gattinoni et al.[25])*

distribution of pulmonary blood flow. In both the supine and prone positions, pulmonary blood flow is directed dorsally in normal and injured lungs (Fig 2).[32-34] Thus, regional perfusion distribution is dictated in large part by nongravitational factors (lung/heart geometry, airspace compression of vessels, reduction in the ventral region's hypoxic vasoconstriction, and so on).[34] With perfusion patterns relatively constant, and a marked improvement in ventilatory homogeneity in the prone position, the shunt fraction would be expected to fall substantially on placing the person in a prone position. Many animal and human studies confirm this hypothesis; on average, in a prone position, the relative shunt fraction in injured lungs is reduced by about 30%.[12,15,16,32,35] Thus, in most patients, decreased shunting when in the prone position 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 (eg, high tidal volume ventilation, oxygen toxicity).[36,37] The prone position generally improves oxygenation, but its ability to attenuate mechanical lung injury may be the more important mechanism of clinical benefit. Indeed, although 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.[9] Furthermore, in this trial (PROSEVA), changes in gas-exchange did not explain the observed mortality benefit.[38]

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

Prone positioning and high PEEP ventilation may have complementary benefits. In ARDS, increased PEEP is known to prevent alveolar derecruitment but may deleteriously promote overdistention of previously well-ventilated alveoli.[39,40] The prone position may help mitigate these deleterious effects of PEEP.[41] 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.[42] These observations suggest that the prone position may decrease barotrauma and atelectrauma and thereby protect against VILI.[29] In support of this theory, rat, dog, and sheep models have shown improved histologic VILI scores when comparing prone to supine ventilation.[43-47] More recently, in experimental injured rodents, the prone position reduced expression of cellular signaling pathways known to correlate with the development of VILI,

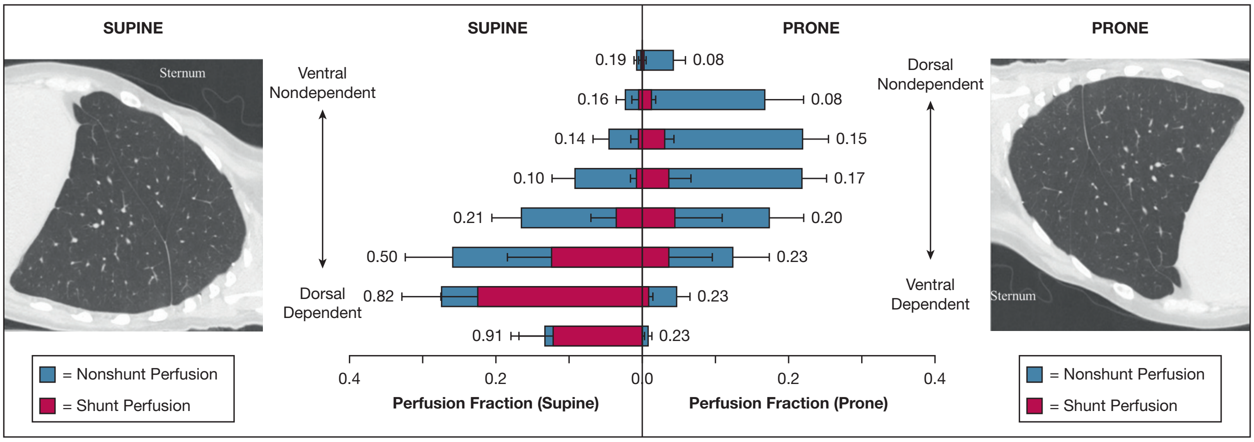

Figure 2 – *In a sheep model, pulmonary perfusion along a lung-height axis is displayed for both the supine (left side of graph) and prone (right side) positions. The total length of each of the eight bars along the x-axis represents the relative perfusion of each of the eight stacked coronal planes. The red shading within each bar represents the fraction of perfusion that is shunt perfusion, whereas the blue coloring is the nonshunt perfusion. The number adjacent to the bar is the precise value of the shunt fraction for that plane. For example, in the supine position, the most dorsal (dependent) plane receives approximately 13% of total perfusion (x-intercept) and of that perfusion, 91% of it is shunt perfusion. Note that prone positioning does not significantly change the distribution of perfusion but it does markedly reduce the total shunt fraction. (Adapted with permission from Richter et al.[32])*

especially in ventral regions that are at risk of hyperinflation while in a supine position.[43,48] Intriguingly, pharmacologically inhibiting these same pathways protects experimental animals from lung injury, thus identifying molecular mechanisms underlying VILI.[43] In humans, histologic data are unavailable, but both serum and bronchoalveolar lavage inflammatory markers are reduced by prone positioning, which may reflect less VILI.[49,50]

Although studies of respiratory mechanics after positioning in the prone position have reached variable conclusions, their results suggest the importance of recruiting the lung to achieve clinical benefit. In the prone position, chest wall compliance typically falls initially and then increases gradually over time.[35] Those patients who have been placed in a prone position and achieve greater drops in chest wall compliance have more pronounced improvement in oxygenation ($r = 0.62$), potentially due to improved dorsal recruitment.[35] Furthermore, recruitment maneuvers (sustained high-pressure inflation) were found to be highly effective in improving oxygenation when applied to patients in the prone position.[51]

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

Extrapulmonary Organ Systems

In addition to its lung-protective effects, a prone position impacts cardiac and abdominal pressures. In general, total cardiac output is unchanged when patients with ARDS are placed in a prone position. However, while prone, the right atrium moves ventrally so that venous return is now aided by gravity. Thus, preload responsive patients may augment their cardiac output by being placed in a prone position.[54] Additionally, right ventricular afterload typically falls, likely due to relief of hypoxic pulmonary vasoconstriction.[54] This effect may be most clinically relevant in populations with severe ARDS, as the prone position reduces the right ventricular dilatation and septal dysfunction that accompanies this disease.[55] To measure these hemodynamic changes accurately, pressure transducers need to be carefully releveled to reflect the right atrium's more ventral position while prone.[56]

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

Clinical Trials

Although 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.[7-11,64] Note the significant mortality benefit of the prone position 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 crossover, unstandardized ventilator management with high tidal volumes, the inclusion of patients with or without only mild ARDS, a small "dose" of time spent in the prone position, arbitrary criteria for cessation of prone positioning, and enrollment of patients late in the disease course. Trial designs evolved further over time. Mancebo et al's[7] 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 prone positioning compared with earlier trials. Unfortunately, slow enrollment led to early study termination with just 142 patients. The authors reported a nonsignificant trend toward improved survival with prone positioning, and post hoc

TABLE 1] Major Trials of Prone Ventilation in ARDS

Variable	Gattinoni et al[10]	Guérin et al[8]	Mancebo et al[7]	Taccone et al[11]	Guérin et al[9] (PROSEVA)
Prone group mortality, %	50.7 (ICU mortality)	32.4 (28 d)	43 (ICU mortality)	31 (28 d)	**16 (28 d)**
Control group mortality, %	48 (ICU mortality)	31.5 (28 d)	58 (ICU mortality)	32.8 (28 d)	**32.8 (28 d)**
RR of mortality (prone/control)	1.05 ($P = .65$)	1.02 ($P = .77$)	0.74 ($P = .12$)	0.97 ($P = .72$)	**0.48 ($P < .001$)**
Patients, No.	304	**802**	142	342	466
Targeted disease	ALI[a] and ARDS[a]	Respiratory failure with $Pa_{O_2}/Fi_{O_2} < 300$ mm Hg	ARDS[a]	ARDS[a]	**ARDS[a] with $Pa_{O_2}/Fi_{O_2} < 150$ mm Hg**
Pa_{O_2}/Fi_{O_2} at enrollment, mm Hg	128	153	139	113	**100**
Enrollment early in disease course?	No	No	Yes, < 2 d of intubation	Yes, < 3 d	**Yes, < 1.5 d**
SAPS II	40	**46**	43	41	**46**
V_T delivered, mL/kg	10.3	7.9	8.5	8	**6.1**
Patients paralyzed, %	Not reported	21	45	Not reported	**87**
Mean increase in Pa_{O_2}/Fi_{O_2} on prone positioning, mm Hg	19	18	32[b]	44	**59**
Average time prone, hr/d	7	8	17	**18**	17
Average days prone	**10**	4	**10**	8.4	4
Significant reduction in ventilator days?[c]	No	No	No	No	**Yes**
Difficulty enrolling?	**Yes**	No	**Yes**	No	No
Crossover (supine to prone), %	8	**21**	8	12	7

Bold text indicates the most extreme value across all five trials. ALI= acute lung injury; PROSEVA = Proning Severe ARDS Patients; RR = relative risk; SAPS II = Simplified Acute Physiology Score II, V_T = tidal volume.
[a]ALI and ARDS were defined according to the American-European Consensus Conference definition of ARDS.[64]
[b]This value was estimated based on graphic data presented in the text.
[c]Not all trials reported ventilator days or ICU length of stay; absence of reporting was taken to imply no significant difference.

analysis demonstrated considerable benefit for severely ill patients. Next, in 2009, Taccone et al[11] used a similar design to Mancebo, and reached enrollment goals. Again, no significant decrease in mortality was noted with prone positioning, although this trial too was likely underpowered and showed a trend toward improved survival with prone positioning.

Many possible explanations can account for the discrepant findings of Taccone et al's[11] study and PROSEVA. As Table 1 illustrates, compared with Taccone et al's study, PROSEVA had increased power, enrolled a highly selected population with severe ARDS, had less supine/prone crossover and more neuromuscular blockade, and, perhaps most importantly, a lower administered tidal volume. One recent meta-analysis divided prone positioning 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 prone positioning shown to decrease mortality (risk ratio [RR] of death at 60 days: prone positioning with low tidal volume: RR, 0.66; 95% CI, 0.50-0.86; $P = .002$; prone positioning with high tidal volume: RR, 1.00; 95% CI, 0.88-1.13; $P = .949$).[65] These findings suggest that the benefits of prone positioning are realized only in the background of protective low tidal volume ventilation.

Taccone et al[11] did describe more frequent complications with prone positioning compared with the PROSEVA trial (which reported no significant increase in any complications). For Taccone et al, loss of vascular access, airway obstruction, extubation, and increased vasopressor requirement all occurred more frequently in the prone positioning arm. All centers in the PROSEVA trial had used prone positioning in daily practice for more than 5 years, minimizing risk associated with an implementation learning curve. The longer duration and more frequent prone positioning maneuvers performed in Taccone et al's trial may have increased risks. Alternatively, intertrial 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 a slightly higher acuteness of illness than that of the prone group. Relative to the prone group, the supine group had higher mean Sequential Organ Failure Assessment scores and more frequent vasopressor use. However, this supine group with highly acute disease still had excellent clinical outcomes, and their mortality was identical to the supine group in Taccone et al's[11] "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).[9,11]

In summary, clinical trial evidence suggests that to achieve improved survival with prone positioning, one needs patients with severe ARDS treated early in their course, a long duration of prone positioning (> 16 h/d), physiologically driven criteria for cessation of daily prone positioning (eg, minimal ventilator requirements), the concurrent use of lung-protective therapies for ARDS, and experienced staff able to minimize procedural risks. Interested readers may review other trials of prone positioning.[49,50,66-71] These studies were not discussed in this review because they were smaller (five studies had < 40 patients), were conducted 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 upfront lung-protective strategy intended to improve survival in severe ARDS. Indeed, prone positioning has never been proved to afford a survival benefit when used as a late rescue therapy for refractory hypoxemia. However, a contemporary prospective observational study (the 2016 Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure [LUNG-SAFE] study) found that only 16.3% of patients with severe ARDS were treated with prone ventilation.[72] Among other factors, perceived logistical difficulties may contribute to poor implementation; interested clinicians are referred to an excellent pragmatic overview (including a preturn checklist) as well as an online video that models successful techniques.[9,73] Generally, after prophylactic preoxygenation, prone positioning can be safely performed with three to four staff members, with one member dedicated solely to endotracheal tube (ETT) management. Immediately after the maneuver, there is often an increase in secretion mobilization that requires suctioning. Once prone positioning is completed, the staff should focus especially 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, prone positioning was continued for at least 16 h/d until sustained oxygenation improvement was achieved, defined as $Pao_2/Fio_2 \geq 150$ mm Hg with PEEP ≤ 10 cm H_2O and $Fio_2 \leq 60\%$ for at least 4 hours after repositioning the patient to a supine position.[63] Although this protocol is informative, the optimal duration of prone positioning is unknown, and supinating prematurely might lead to derecruitment and potentially even VILI.[9] We recommend continuing prone positioning for least 16 hours per day and ceasing prone positioning when clinical variables (such as Pao_2/Fio_2, lung recruitability, ventilatory efficiency, static compliance, resolution of underlying nonpulmonary processes) show clear sustained improvement. Further research may help identify the optimal criteria for ceasing prone ventilation. Relatively strong contraindications to prone positioning are severe facial or neck trauma, pelvic/spinal instability, elevated intracranial pressure (as turning the head compresses the internal jugular vein), hemoptysis, and frequent cardiac arrhythmias or a high probability of the patient requiring cardiopulmonary resuscitation (Table 2).[73] Experienced centers have published case reports of successful prone positioning in extreme circumstances, including third-trimester pregnancy, patients receiving venovenous extracorporeal membrane oxygenation, and invasive intracranial pressure monitoring.[47,75-77]

Next Steps

Future studies of prone positioning will need to emulate the extended-duration and low tidal volume approach of PROSEVA. Several clinical questions remain regarding the optimal approach to prone positioning and concomitant lung-protective therapies: (1) What is the optimal approach to PEEP management in prone positioning, and is prone positioning effective in patients undergoing a high-PEEP strategy or might these therapies even be synergistic? (2) Does effective prone positioning necessitate neuromuscular blockade for several days, and does this intervention contribute to critical-illness neuromyopathy and associated functional impairment in survivors? (3) Is prone positioning most effective in only a subset of patients with ARDS, and how can we further clarify the population that 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, prone positioning was first recognized for its ability to improve oxygenation and was historically used as salvage therapy for refractory hypoxemia. A recent multicenter trial and subsequent meta-analyses have made a compelling case that prone positioning in selected patients with severe ARDS early in their course improves survival. This survival benefit is likely mediated by reduced VILI, as regional differences in

TABLE 2] Summary Recommendations for Prone Ventilation

Who to place in prone position? Patients with severe ARDS ($Pao_2/Fio_2 < 150$ mm Hg) Early in the course (ideally within 48 h) Best outcomes reported when prone positioning is used in combination with *both* low tidal volume ventilation (6 cc/kg) and neuromuscular blockade	Who not to place in prone position? Patients with facial/neck trauma or spinal instability Patients with recent sternotomy or large ventral surface burn Patients with elevated intracranial pressure Patients with massive hemoptysis Patients at high risk of requiring CPR or defibrillation
How to place patient in prone position? Requires 3-5 people, close attention to endotracheal tube (ETT) and central lines; a demonstration video and checklist are available[9,73] Preparation: preoxygenation, empty stomach, suction ETT/oral cavity, remove ECG leads and reattach to back, repeated zeroing of hemodynamic transducers Support and frequently reposition pressure points: face, shoulder, anterior pelvis	Potential complications Temporary increase in oral and tracheal secretions occluding airway ETT migration or kinking Vascular catheter kinking Elevated intraabdominal pressure Increased gastric residuals Facial pressure ulcers, facial edema, lip trauma from ETT, brachial plexus injury (arm extension)
How long to have patient in prone position each day? Successful trials use at least 16 hours of daily proning Long prone positioning sessions likely avoid derecruitment	When to stop? In PROSEVA, prone positioning was stopped when Pao_2/Fio_2 remained > 150 mm Hg 4 h after supinating (with PEEP < 10 cm H_2O and $Fio_2 < 0.6$) Optimal strategy is unclear: consider continuing prone positioning until clear improvement in gas exchange, mechanics, and overall clinical course.

CPR = cardiopulmonary resuscitation; PEEP = positive end-expiratory pressure. See Table 1 legend for expansion of other abbreviation.

lung aeration, compliance, and shear strain are minimized. In contrast to historical views, early improvement in gas exchange with prone positioning does not reliably predict improved survival. Prone ventilation may be underused in clinical practice: in the LUNG-SAFE trial, only 16.4% of patients with severe ARDS were placed in a prone position.[72] If prone positioning is pursued, it should be done early, with experienced staff to avoid logistical complications, and at extended durations (≥ 16 h/d). For patients who fall outside these relatively narrow criteria, the clinician must balance the appealing physiological rationale behind prone positioning against the equivocal evidence base for patients with less severe lung injury, late-stage ARDS, or non-ARDS conditions.[78]

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