## Title

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REVIEW ARTICLE

# Prone Positioning in Acute Respiratory Distress Syndrome

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## Introduction

Prone positioning (or "tummy time") has received considerable attention in the lay press because of its role in the prevention and treatment of severe respiratory failure and acute respiratory distress syndrome (ARDS). ARDS has received recent attention as a result of the Covid-19 pandemic,[1–3] and the epidemiology of ARDS has clearly been affected by Covid-19. Even before the pandemic, ARDS was one of the most frequent causes of death, although it was rarely recognized as such.[4] Many patients who succumb to pneumonia or sepsis meet the criteria for ARDS even while the cause of death is generally attributed to the underlying etiology. The Covid-19 pandemic has taken approximately 800,000 U.S. lives, and more than 5 million more globally, predominantly from hypoxemic respiratory failure.[5] Although there was some debate initially, most experts agree that hypoxemic respiratory failure in the setting of Covid-19 is similar to typical ARDS.[6–10] ARDS is defined based on the acute onset of a $PaO_2$:$FIO_2$ (P:F) ratio below 300 mm Hg, in the setting of bilateral infiltrates on chest x-ray and in the absence of congestive heart failure.[11] The Berlin definition also requires invasive mechanical ventilation or positive end-expiratory pressure (PEEP) of 5 cm of $H_2O$ applied via a tight-fitting mask. More recently, given the increased implementation of high-flow oxygen devices, some have suggested for pragmatic reasons that the criteria be expanded to include patients using high-flow oxygen devices with a flow of greater than 30 liters per minute.[12]

Therapeutic strategies in ARDS have focused on optimizing lung mechanics to avoid further injury. Low-tidal-volume mechanical ventilation has been shown in robust randomized controlled trials to have a mortality benefit, with 6 ml per kg of ideal body weight having 30% mortality compared with 12 ml per kg with 40% mortality.[13,14] Prone positioning (lying flat on the stomach) has also been established as a useful strategy in the management of ARDS, based on multiple randomized trials.[15,16] Other therapeutic options for ARDS are more limited and controversial but include extracorporeal membrane oxygenation (ECMO), inhaled vasodilators, conservative fluid strategies, and nontraditional ventilator modes.[17–19] Although evidence for the benefit of prone positioning existed before Covid-19, the scale of the pandemic has meant a drastic expansion of its use.

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## Historical Background of Prone Positioning

From an evolutionary perspective, humans evolved from quadrupeds, which generally function in the prone position. Indeed, animal studies have shown that prone positioning improves matching of ventilation and perfusion particularly in dorsal lung regions.[20] During illness, humans were customarily placed in the supine position to facilitate nursing and other interventions. However, some patients reported improved breathing and gas exchange, leading to the use of prone positioning in the treatment of critically ill patients. In 1977, Douglas et al.[21] reported the benefits of prone positioning in six patients with acute respiratory failure. Gattinoni et al.[22] subsequently reported a randomized trial of prone versus standard of care in the *New England Journal of Medicine* (*NEJM*) in 2001, showing no overall benefit but potential improvements in the subset of patients with the most severe illness. These initial studies helped to lay the groundwork for prone positioning, which is now established as a standard of care for treatment of moderate to severe ARDS.

## Potential Mechanisms of Benefit

A few concepts need to be appreciated in order to understand the potential mechanisms of benefit from prone positioning. First, the lung and chest wall are mechanical structures acting in series. The compliance of the respiratory system (change in volume for a given change in pressure) is a function of the compliance of the lung and the chest wall and thus can be reduced by lung injury, chest wall disease, or both. Second, the pressure that produces a given lung volume change is the transpulmonary pressure, or pressure difference across the lung. Transpulmonary pressure is defined by pressure at the airway opening minus pleural pressure (the pressure at the outside surface of the lung). Transpulmonary pressure is the stress on the lung and is an important predictor of mechanical lung injury.[13,23,24] Third, lung injury is characterized by the flooding or collapse of alveoli. The collapse of alveoli leads to decreased lung compliance. Furthermore, in ARDS, the reduction in the surfactant and subsequent increased surface tension leads to collapsed or flooded alveoli, which receive no ventilation and impair gas exchange. Impaired gas exchange often manifests as shunting (perfusion without ventilation). Finally, increased pressure is required to reopen collapsed or flooded alveoli and restore ventilation. The concept of opening pressure refers to the amount of pressure required to open a collapsed alveolus. Due in part to the activity of the surfactant, the opening pressure is greater than the closing pressure. Therefore, less pressure is typically required to maintain an open alveolus (stay above the closing pressure) than is required to reopen a collapsed alveolus (the opening pressure) (Fig. 1).[25,26] This concept affects the optimal setting of the mechanical ventilator, including administration of PEEP to maintain alveolar patency, and the impact of prone positioning.

A number of mechanisms have been suggested to explain the benefits of prone positioning. First, mechanical stress on the lung is reduced and the distribution of ventilation is thought to be more uniform in the prone position.[27,28] In lung injury, there is an increased ventral to dorsal pleural pressure gradient.[29] In animal studies, prone positioning results in a reduction of the ventral-dorsal pleural pressure gradient[30,31] and decreases transpulmonary pressure, leading to less and more even distribution of mechanical stress on the lung. Ventilation is also more homogeneous, and both the overdistension of ventral units and the collapse of dorsal lung units are reduced.[30,31] Second, prone positioning offers advantageous gravitational and geometric/shape changes of the thorax. In supine patients with ARDS, lung injury and alveolar collapse are frequently prominent in the posterior dependent lung regions such that much of the lung is unable to participate in gas exchange. The remaining aerated lung is often referred to as the "baby lung"[32] because it reflects the only lung units able to participate in gas exchange. In prone positioning, the effects of lung and chest wall shape are advantageous and result in less lung tissue being susceptible to collapse.[33,34] Functional residual capacity is often increased in the prone compared with the supine position.[35] The weight of the heart is also thought to be important. In the supine position, the heart and mediastinum compress the lung, promoting atelectasis; in the prone position, the heart rests on the sternum, relieving compression of the underlying lung. However, the magnitude of the effect is relatively modest.[36] There is also ventral displacement of the diaphragm in the prone position, which may decrease compression of dorsal lung units.[35,37–40] Third, in both the supine and prone positions, perfusion is primarily directed dorsally, while ventilation and atelectasis are more heavily impacted by gravity; thus, dorsal ventilation improves in the prone position (compared with supine), yielding improved ventilation and perfusion matching.[20] However, the relative importance of these possible mechanisms is currently unclear.[41–43]

Prone positioning may also take advantage of lung mechanics by allowing more alveoli to stay open for a given PEEP. Whether in the prone or supine position, a traditional approach to reduce alveolar collapse in ARDS is the application of PEEP. PEEP serves to keep the transpulmonary pressure above the closing pressure throughout

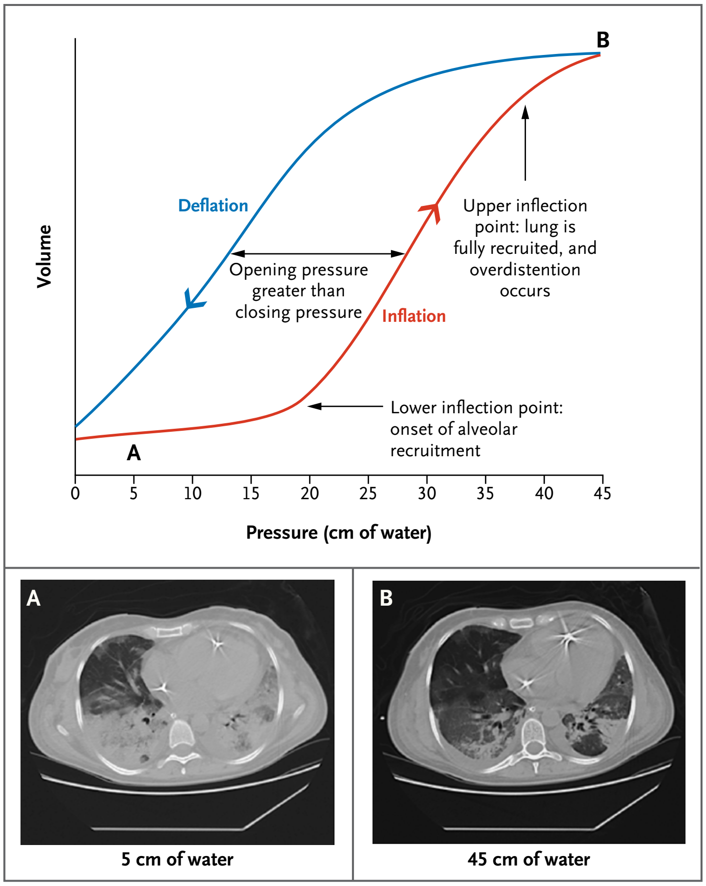


Figure 1. Pressure-Volume Curve and Computed Tomography Images in a Patient with Acute Respiratory Distress Syndrome.

(Top) Diagram of a pressure-volume curve in a patient with acute respiratory distress syndrome. The horizontal line illustrates the opening and closing pressures of the alveoli at a given tidal volume. Note that the opening pressure (to open collapsed alveoli) is greater than the pressure required to keep the alveoli open (i.e., above the closing pressure). The letters A and B correspond to the following computed tomography (CT) images. From *New England Journal of Medicine*, Malhotra A, Drazen JM, High-Frequency Oscillatory Ventilation on Shaky Ground, 368, 863-5. Copyright © 2013 Massachusetts Medical Society. Adapted with permission.[25] (Bottom) CT images of the inspiratory limb (A) and the expiratory limb (B). From *New England Journal of Medicine*, Gattinoni L, Caironi P, Cressoni M, et al. Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome, 354, 1775-86. Copyright © 2006 Massachusetts Medical Society. Adapted with permission.[26]

the respiratory cycle. A challenge when choosing the appropriate magnitude of PEEP is that ventilation, particularly in the supine position, is spatially heterogeneous. In the supine position, the opening and closing pressures in collapsed units may be sufficiently high that the PEEP required to keep a large fraction of a given patient's alveoli open may contribute to overdistension in the ventral lung. As a consequence of the more homogenous distribution of ventilation in the prone position, it may be possible to optimize the ventilation of both dependent and nondependent lung with a PEEP level that does not have other adverse physiological effects.[30] Thus, some patients experience greater recruitment and less overdistension because of prone positioning. As a result of an increased recruitment in the prone position,[38] there is an increase in lung units capable of participating in gas exchange.

As with other interventions in ARDS, improvement in oxygenation does not correlate with mortality benefit. For example, the use of inhaled nitric oxide results in an improvement in oxygenation but without a corresponding reduction in mortality.[44] Of note, data are mixed regarding the prognostic utility of prone improvement in gas exchange to predict mortality.[45–47] Therefore, while improvement in gas exchange is frequently observed when a patient is placed in the prone position, the observed mortality benefit is more likely a function of the mechanical protection on lung mechanics provided by prone positioning. However, further data regarding exact physiological mechanisms underlying leading to a mortality benefit are needed.

Another possible mechanism of benefit of proning includes improved secretion drainage from the posterior dependent lung in some patients. Guérin et al.[48] showed a reduced risk of ventilator-associated pneumonia with the use of prone positioning, ostensibly on this basis. Some have argued that physical movement of patients may reduce stasis in the lung and facilitate secretion clearance as well.[49,50]

## Evidence

The data from randomized trials strongly support the use of prone positioning, particularly in moderate to severe ARDS (P:F ratio of less than 150 mm Hg). In a landmark study published in *NEJM*, Guérin et al.[16] showed a marked relative risk reduction using prone positioning compared with supine positioning for ARDS (absolute mortality of 41% vs. 23.6% favoring prone). This study extended[16] findings from another study by Guérin et al in *JAMA*[48] that failed to show benefit perhaps due to low duration of pronation (8 hours per day) and lack of lung-protective ventilation. Mancebo et al.[51] reported a large, randomized trial of prone positioning, which failed to show statistical significance; however, the trial was stopped prematurely due to a lack of enrollment. Meta-analyses have been performed to synthesize the data from the various randomized trials of prone positioning; and in aggregate, the data do support proning patients with ARDS.[15,52]

Complicating the clarity and/or robustness of trials evaluating prone positioning is the change in approach to mechanical ventilator settings for ARDS over the past 30 years.[53] Lung-protective ventilation has evolved such that earlier studies tended to use higher tidal volumes and lower PEEPs as compared with later studies, given the evolution of evidence that occurred over time. In a meta-analysis, Beitler et al.[15] showed that lung-protective ventilation was the most important effect modifier, such that the beneficial effects of prone positioning were greatest in patients with ARDS who were also given low-tidal-volume mechanical ventilation.[13] Although the study by Guérin et al.[16] was influential, meta-analyses have shown relatively consistent effects across studies that used lung-protective ventilation. Another potential modifier is the duration of pronation (number of hours per day prone). In a prior report by Gattinoni et al.,[22] the patients were placed in the prone position for only 6 hours per day, whereas subsequent studies used up to 18-hour proning or longer. A meta-analysis by Munshi et al.[54] showed that pronation more than 12 hours per day was associated with a reduced risk of mortality.

Also of potential importance in modulating prone response is the use of neuromuscular blockade (paralytics). In another study by Guérin et al.,[55] paralytics were used routinely in patients being placed in the prone position, leading some to speculate that the paralytics may be part of the mechanism of benefit. A study by Papazian et al.[56] did show benefit with 48 hours of a continuous infusion of the paralytic agent, cisatracurium, for 340 patients. However, a subsequent more definitive report by Moss et al.[57] of 1,066 patients in the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial did not support this conclusion. Thus, the observed benefits from prone positioning are unlikely to be mediated by the concomitant use of paralytic medications, although there has not yet been a definitive study evaluating prone positioning with and without paralytics.

## Current Practice Recommendations

Prone positioning is recommended as a management strategy for patients with ARDS who are mechanically ventilated using low-tidal-volume mechanical ventilation. The strongest evidence supports the use of prone positioning when the P:F ratio is less than 150 mm Hg, although this threshold could be debated, given the relative safety of prone positioning. When the prone position is being implemented, 16 to 18 hours per day of this position is recommended, allowing some time in the supine posture for nursing care and helping to avoid the risk of pressure ulcers and facial edema.[58] The potential risks to consider when caring for a patient in the prone position include hemodynamic consequences, if heavy sedation is given concomitantly, the risk of endotracheal tube dislodgement, and/or loss of intravascular access, particularly if being done in inexperienced centers.[59]

With regard to contraindications, prone positioning is not feasible in patients with cervical spine instability or other unstable orthopedic issues (e.g., pelvic fracture, long bone fractures, spinal cord injury, etc.). The use of prone positioning in those with high intracranial pressure is more controversial, but many centers generally avoid it in this context. For hemodynamically unstable patients or those with malignant arrhythmias, proning should be done cautiously, although defibrillation, cardioversion, and even chest compressions can still be performed while prone.[60,61] For patients with morbid obesity, there are recent reports supporting the safety and efficacy of proning, although local experience can vary.[9,62] Video with step-by-step instructions is available through *NEJM* in the article by Guérin et al.[55]

## Areas of Controversy

Regarding areas of controversy, a number exist although we focus on the following three: proning with ECMO, use of proning in nonintubated (PINI) patients, and discontinuation of the prone position.

First, although the data in favor of ECMO are limited to small trials,[63] ECMO has become more common during the Covid pandemic. The use of prone positioning in patients who are undergoing ECMO has been controversial. The ECMO technique requires vascular access, which may be susceptible to dislodgment in the prone position.[64,65] However, some data suggest additional benefits to the prone position in the context of ECMO, given that ECMO supports gas exchange, whereas putting the patient in the prone position may help with mechanical lung protection.[66] Given the potential mechanistic lung-protective benefits in prone positioning, large randomized trials will be needed to draw more definitive conclusions.[67]

Second, in addition to using the prone position in patients who are mechanically ventilated, there is recent interest in using PINI, sometimes referred to as "awake proning."[68] Regarding PINI, a recent report[69] showed benefits in the Covid-19 population. The authors reported a meta-trial that included five different studies from various countries around the world. In aggregate, the data showed a reduction in the need for intubation and mechanical ventilation, with a relative risk of 0.86 (95% confidence interval [CI], 0.75 to 0.98) for combined outcome of treatment failure, a hazard ratio of 0.75 (95% CI, 0.62 to 0.91) for intubation, and a possible mortality benefit of 0.87 (95% CI, 0.68 to 1.11) from the PINI strategy. Although the data are potentially compelling, the majority of the reported benefits were derived from a study from Mexico in which many of the patients were treated outside of an intensive care unit, where practices differed from other standards of care.[70] Nonetheless, the PINI strategy is being increasingly adopted with no major downside apparent from the existing data.

Finally, there is a lack of data regarding when to stop using the prone position in patients who are receiving this therapy. Given the importance of the mechanical benefits of the prone position, its discontinuation should likely not be determined solely based on gas exchange. Guérin et al.[16] used a P:F ratio greater than 150 mm Hg for patients after 4 hours in the supine position while receiving PEEP of less than 10 $cmH_2O$ and a $F_{IO_2}$ of less than 0.6. However, the risk/benefit decision should likely be individualized until further data emerge.

## Conclusions

Prone positioning is a simple, safe, and inexpensive technique to treat patients with respiratory failure or those at risk of developing respiratory failure.[71] The Covid-19 pandemic has highlighted the benefits of good supportive care, which includes the use of prone positioning for many patients.

### Disclosure

Disclosure forms provided by the authors are available with the full text of this article at evidence.nejm.org.


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