Respiratory Physiology of Prone Positioning With and Without Inhaled Nitric Oxide Across the Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Severity Spectrum

IMPORTANCE: Prone positioning improves clinical outcomes in moderate-to-severe acute respiratory distress syndrome and has been widely adopted for the treatment of patients with acute respiratory distress syndrome due to coronavirus disease 2019. Little is known about the effects of prone positioning among patients with less severe acute respiratory distress syndrome, obesity, or those treated with pulmonary vasodilators.

OBJECTIVES: We characterize the change in oxygenation, respiratory system compliance, and dead-space-to-tidal-volume ratio in response to prone positioning in patients with coronavirus disease 2019 acute respiratory distress syndrome with a range of severities. A subset analysis of patients treated with inhaled nitric oxide and subsequent prone positioning explored the influence of pulmonary vasodilation on the physiology of prone positioning.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study of all consecutively admitted adult patients with acute respiratory distress syndrome due to coronavirus disease 2019 treated with mechanical ventilation and prone positioning in the ICUs of an academic hospital between March 11, 2020, and May 1, 2020.

MAIN OUTCOMES AND MEASURES: Respiratory system mechanics and gas exchange during the first episode of prone positioning.

RESULTS: Among 122 patients, median (interquartile range) age was 60 years (51–71 yr), median body mass index was 31.5 kg/m² (27–35 kg/m²), and 50 patients (41%) were female. The ratio of $\text{PaO}_2$ to $\text{FiO}_2$ improved with prone positioning in 90% of patients. Prone positioning was associated with a significant increase in the ratio of $\text{PaO}_2$ to $\text{FiO}_2$ (from median 149 [123–170] to 226 [169–268], $p<0.001$) but no change in dead-space-to-tidal-volume ratio or respiratory system compliance. Supine ratio of $\text{PaO}_2$ to $\text{FiO}_2$, respiratory system compliance, positive end-expiratory pressure, and body mass index did not correlate with absolute change in the ratio of $\text{PaO}_2$ to $\text{FiO}_2$ with prone positioning. However, patients with ratio of $\text{PaO}_2$ to $\text{FiO}_2$ less than 150 experienced a greater relative improvement in oxygenation with prone positioning than patients with ratio of $\text{PaO}_2$ to $\text{FiO}_2$ greater than or equal to 150 (median percent change in ratio of $\text{PaO}_2$ to $\text{FiO}_2$ 62 [29–107] vs 30 [10–70], $p=0.002$). Among 12 patients, inhaled nitric oxide prior to prone positioning was associated with a significant increase in the ratio of $\text{PaO}_2$ to $\text{FiO}_2$ (from median 136 [77–168] to 170 [138–213], $p=0.003$) and decrease in dead-space-to-tidal-volume ratio (0.54 [0.49–0.58] to 0.46 [0.44–0.53], $p=0.001$). Subsequent prone positioning in this subgroup further improved the ratio of $\text{PaO}_2$ to $\text{FiO}_2$ (from 145 [122–183] to 205 [150–232], $p=0.017$) but did not change dead-space-to-tidal-volume ratio.

CONCLUSIONS AND RELEVANCE: Prone positioning improves oxygenation across the acute respiratory distress syndrome severity spectrum, irrespective...
Prone positioning (PP) improves oxygenation and mortality in acute respiratory distress syndrome (ARDS) and has rapidly become a cornerstone of the management of coronavirus disease 2019 (COVID-19) ARDS (1–3). The benefit of PP is established in moderate-to-severe ARDS (ratio of PaO₂ to FiO₂ [PaO₂:Fio₂] less than 150), though PP is increasingly provided to patients with a wider range of disease severity (1, 3, 4). Compared with supine ventilation, PP results in more homogenous ventilation and perfusion, thus improving ventilation/perfusion (V/Q) matching, decreasing shunt, improving arterial oxygenation, and decreasing mortality (1, 5–8). Given the widespread adoption of PP during the COVID-19 pandemic—including among patients with less severe ARDS who may not have met inclusion criteria of prior large, randomized trials of PP—we performed a large single-center analysis of the physiologic response to PP in mild, moderate, and severe COVID-19 ARDS in order to understand the effect of PP on gas exchange and respiratory mechanics across a range of COVID-19 ARDS severity.

We additionally sought to understand the effects of PP when used in combination with inhaled nitric oxide (iNO), a pulmonary vasodilator. The degree to which PP improves V/Q matching via changes in ventilation versus changes in perfusion remains incompletely characterized (9, 10). iNO has been demonstrated to improve oxygenation by better matching of perfusion to ventilation, but its effects when used in combination with PP have been infrequently characterized (11, 12).

**MATERIALS AND METHODS**

**Population and Setting**

We retrospectively studied all adult patients with ARDS due to COVID-19 managed with mechanical ventilation and PP at Massachusetts General Hospital (MGH) between March 11, 2020, and May 1, 2020. Patients were excluded if admitted to an outside hospital ICU prior to transfer to MGH or if PaO₂:Fio₂ was greater than or equal to 300 at any point prior to PP. We excluded patients who were newly initiated on iNO or neuromuscular blockade between the immediately prior to PP, while supine (pre-PP) and immediately after PP (post-PP) data collection time points to ensure that any changes in gas exchange or respiratory mechanics could solely be attributed to PP and not another intervention. Ultimately, our study included 122 patients, 12 of whom were initiated on iNO prior to PP. The study was approved by the MGH institutional review board (protocol number 2015P001650). Informed consent was waived.

Treating physicians determined clinical management, though institutional guidance advised ventilation with Vt less than 6-mL/kg predicted body weight, conservative fluid management, and consideration of PP for PaO₂:Fio₂ less than 150. Institutional guidance advised at least 16-hour prone per session with monitoring for adverse events; ultimately, treating physicians were responsible for the decision to prone and duration of therapy. A multidisciplinary PP team consisting of experienced ICU registered nurses and respiratory therapists was available to assist with PP in COVID-19 surge ICUs and ICUs with less experience with the maneuver. Positive end-expiratory pressure (PEEP) was set at the discretion of the treatment teams though guidance recommended either individualized titration of PEEP by best tidal compliance or use of the ARDS Network low PEEP/Fio₂ table (13, 14). PEEP was optimized in the supine position and assessed again immediately after PP. iNO was provided at a dose of 20–80 parts per million.

**Data Collection and Definitions**

ARDS was defined per the Berlin criteria (15). Data were collected from the electronic medical record, including arterial blood gases and respiratory system mechanics at four time points: 1) immediately after...
intubation, while supine (‘‘post-intubation’’), 2) ‘‘pre-
PP’’, 3) ‘‘post-PP’’, and 4) nearest available to 16 hours
after PP, while prone (‘‘16-hr post-PP’’). The first epi-
sode of PP after intubation was examined. All patients
were managed with volume-controlled ventilation
throughout the observation period. The unadjusted
Harris-Benedict estimate of the resting energy ex-
penditure and the rearranged Weir equation for CO₂
production were used to estimate Vd/Vt (16). The
ventilatory ratio (VR) was calculated as previously
described (17).

Statistical Analysis
Quantitative data are reported as medians (interquar-
tile range). Categorical variables are reported as counts
and percentages. We report all available data without
imputation. We used Spearman correlation coefficient
to assess associations between continuous variables and
the Wilcoxon signed-rank test to compare related sam-
ple. Analyses were performed with GraphPad Prism
Version 9.0 (GraphPad Software, San Diego, CA).

RESULTS

Demographic and Clinical Characteristics
We studied 122 patients with COVID-19 ARDS man-
eged with mechanical ventilation and PP. Median age
was 60 years (51–71 yr), and median body mass index
(BMI) was 31.5 kg/m² (27–35 kg/m²). Fifty patients
(41%) were female. Median hospital day of intuba-
tion was 1 (1–2), and median time between intubation
and PP was 37 hours (15–80 hr). Pre-PP Pao₂/Fio₂ was
less than 100 in 13 patients (10.7%), 100–200 in 102
patients (83.6%), and 200–300 in seven patients (5.7%);
the vast majority of patients had moderate ARDS, with
few patients with severe or mild disease.

Data reflecting gas exchange and pulmonary me-
chanics were collected retrospectively at four time
points: immediately after intubation (post-intubation),
immediately prior to PP, while supine (pre-PP), im-
mediately after PP, while prone (post-PP), and 16-hr post-PP.
The median time between intubation and post-intubation data was 3 hours (1–5 hr). The me-
median time between pre-PP data and the PP maneuver was 2 hours (1–3 hr). The median time between the PP maneuver and post-PP data was 1 hour (1–2 hr). The median time between the PP maneuver and the data closest to the 16-hour time point was 15 hours
(14–18 hr).

Response to Prone Positioning
Table 1 displays patients’ clinical and physiologic parameters. PP was associated with an increase in
Pao₂/Fio₂ (from median 149 [123–170] to median 226
[169–268], p < 0.001) but no change in Vd/Vt, VR, or
Crs. Of 122 patients, 110 (90%) experienced an increase
in Pao₂/Fio₂ with PP. There was no correlation among
pre-PP Pao₂/Fio₂ (assessed immediately prior to PP and
after optimization of PEEP according to institutional
protocols), Crs, PEEP, or BMI with pre-PP to post-PP change in Pao₂/Fio₂ (p [correlation], 0.181, 0.393, 0.164,
and 0.842, respectively). Notably, patients receiving high
PEEP (greater than or equal to 14 cm H₂O) experienced
similar benefits as patients receiving low PEEP (Fig. 1).

Oxygenation similarly improved across the BMI
spectrum; notably, patients with BMI greater than
or equal to 30 kg/m² experienced similar benefits to
patients with lower BMI. Figure S1 (http://links.lww.
com/CCX/A680) depicts the association between BMI
subgroup and Pao₂/Fio₂, PEEP, VR, Vd/Vt, and Crs
before and after PP. Examination of BMI subgroups
demonstrated significant improvement in oxygena-
tion with PP even among patients with BMI greater
than 40 kg/m². Furthermore, pre- to post-PP change in
VR, Vd/Vt, Crs, and PEEP did not differ by BMI class.

Independent of PP, VR significantly correlated with
BMI (Spearman r, 0.290; p [correlation], 0.001 for pre-
PP VR; Fig. S2, http://links.lww.com/CCX/A681).

Pre-PP Pao₂/Fio₂ was less than 150 among 62
patients and greater than or equal to 150 among 60
patients. The change in Pao₂/Fio₂ when assessed rel-
ative to pre-PP Pao₂/Fio₂ was greater in patients with
pre-PP Pao₂/Fio₂ less than 150 compared with those
with greater than or equal to 150 (62% [29–107%] vs
30% [10–70%], p = 0.002) (Fig. 2). There were no sig-
nificant differences between pre-PP to post-PP change
in Crs, Vd/Vt, or VR between patients with Pao₂/Fio₂
less than 150 and those with Pao₂/Fio₂ greater than or
equal to 150 (Fig. 3).

Pre-PP to post-PP change in Pao₂/Fio₂ did not
correlate with change in Crs (p [correlation], 0.972).
However, increasing pre-PP to post-PP Pao₂/Fio₂ cor-
related with decreasing Vd/Vt (Spearman r, −0.290;
p [correlation], 0.001) and VR (Spearman r, −0.265;
Response to Inhaled Nitric Oxide With Subsequent Prone Positioning

Twelve patients were initiated on iNO in the supine position and a median of 16 hours (2–36 hr) later managed with PP while receiving iNO (Fig. 4). Pre-PP initiation of iNO was associated with a significant increase in \(\text{Pao}_2/\text{Fio}_2\) (136 [77–168] to 170 [138–213], \(p = 0.003\)) and decreases in \(\text{Vd/Vt}\) (0.54 [0.49–0.58] to 0.46 [0.44–0.53], \(p = 0.001\)) and VR (1.29 [1.20–1.57] to 1.14 [1.05–1.45], \(p = 0.007\)). Ten patients (83%) experienced an increase in \(\text{Pao}_2/\text{Fio}_2\) with iNO. Median improvement in \(\text{Pao}_2/\text{Fio}_2\) with iNO was 31.6% (19.4–42.6%), with nine patients improving by over 20%. Subsequent PP while receiving iNO increased \(\text{Pao}_2/\text{Fio}_2\) (145 [122–183] to 205 [150–232], \(p = 0.017\)) but did not affect \(C_{rs}\) (29 mL/cm H\(_2\)O [25–40 mL/cm H\(_2\)O] to 33 mL/cm H\(_2\)O [27–38 mL/cm H\(_2\)O], \(p = 0.613\)), \(\text{Vd/Vt}\) (0.56 [0.39–0.62] to 0.52 [0.38–0.62], \(p = 0.467\)), or VR (1.24 [1.16–1.51] to 1.25 [1.08–1.53], \(p = 0.420\)).

DISCUSSION

In this single-center study of COVID-19 ARDS, PP increased \(\text{Pao}_2/\text{Fio}_2\) by a magnitude similar to that observed in past series of patients with pre-COVID-19 ARDS (1). Over 90% of patients experienced an improvement in oxygenation with PP; importantly, the full spectrum of patients with COVID-19 ARDS at our center appeared to benefit from PP. Patients with a more severe baseline oxygenation deficit derived a greater relative benefit from PP than did those with...
mild disease, but the majority of patients experienced an improvement in oxygenation. PP was neither associated with a change in global C\textsubscript{RS} nor a change in dead space ventilation. Our data cannot determine if there were offsetting changes in regional compliance (18). It is also possible that PP improved lung compliance via dorsal alveolar recruitment while reducing chest wall compliance, yielding no overall change in C\textsubscript{RS} (19).

Importantly, we observed similar improvement in oxygenation regardless of BMI or PEEP. PP conferred an additive improvement in oxygenation among patients treated with iNO.

The use of PP has expanded greatly as a result of the COVID-19 pandemic, from among 13.7% of patients in an international observational study of pre-COVID-19 ARDS to over 76% in one recent multicenter study of patients with COVID-19 ARDS (4, 20). PP improves mortality among patients with ARDS and Pao\textsubscript{2}:FiO\textsubscript{2} less than 150 (1). Although most patients in the present cohort had moderate ARDS, this observational study also captures data from patients with COVID-19 ARDS with Pao\textsubscript{2}:FiO\textsubscript{2} greater than or equal to 150 who physicians elected to treat with PP. Patients in our study were nearly equally balanced between those with Pao\textsubscript{2}:FiO\textsubscript{2} less than 150 (62 patients) and Pao\textsubscript{2}:FiO\textsubscript{2} greater than or equal to 150 (60 patients). Most of these 60 patients with Pao\textsubscript{2}:FiO\textsubscript{2} greater than or equal to 150 had moderate ARDS; only seven had Pao\textsubscript{2}:FiO\textsubscript{2} greater than 200 at the time of PP. The application of PP to patients with ARDS and Pao\textsubscript{2}:FiO\textsubscript{2} greater than or equal to 150 at our institution and others throughout the COVID-19 pandemic reflects the paucity of proven therapies for COVID-19 ARDS as well as the safety of PP at institutions with the resources and experience to perform the maneuver (4, 21).
Although ARDS severity as reflected by oxygenation deficit did not predict absolute change in oxygenation with PP (Fig. 1), the group of patients with \( \text{Pao}_2 : \text{FiO}_2 \) less than 150 experienced over twice the percent change in \( \text{Pao}_2 : \text{FiO}_2 \) that the group of patients with \( \text{Pao}_2 : \text{FiO}_2 \) greater than or equal to 150 experienced. However, an improvement in gas exchange does not necessarily indicate a disease-modifying reduction in lung stress or strain, and a post hoc analysis of patients with moderate-to-severe ARDS treated with PP found no significant correlation between improvement in \( \text{Pao}_2 : \text{FiO}_2 \) with PP and mortality (22). Clinical outcomes are outside the scope of the present physiologic study, and further investigation is needed to determine if clinical benefits of PP—beyond an improvement in oxygenation—extend to patients with more mild ARDS (23). Even still, given the safety of PP in well-resourced centers, the associated oxygenation benefit may in some circumstances be sufficient justification for the use of PP among patients with mild-to-moderate ARDS.

A subset of patients treated with iNO while supine demonstrated significant improvements in oxygenation, Vd/Vt, and VR with iNO, consistent with improved perfusion of well-ventilated lung. These findings challenge reports that pulmonary arterial endothelial dysfunction may preclude an oxygenation benefit from iNO in COVID-19 ARDS (24) and are consistent with reports from other centers (11). Among these patients treated with iNO, subsequent PP was associated with a similar magnitude of improvement in oxygenation as observed in the entire cohort of patients treated with PP. These findings support the use of PP in patients treated with iNO and

![Figure 2](image2.png)

**Figure 2.** Association between ratio of \( \text{Pao}_2 \) to \( \text{FiO}_2 \) (\( \text{Pao}_2 : \text{FiO}_2 \)) and relative change in \( \text{Pao}_2 : \text{FiO}_2 \) with prone positioning. \( \text{Pao}_2 : \text{FiO}_2 \) was measured immediately prior to prone positioning, in the supine position. \( \text{Pao}_2 : \text{FiO}_2 \) percent change represents the postprone minus preprone \( \text{Pao}_2 : \text{FiO}_2 \) difference relative to pre-prone \( \text{Pao}_2 : \text{FiO}_2 \). **Boxes** depict the median with interquartile range, and **whiskers** indicate minimum and maximum values. \( *p \leq 0.05, **p \leq 0.01, ***p = 0.001 \). **Numbers below box plots** represent the number of patients included in each subgroup. **Regression line** corresponds to Spearman rank correlation coefficient, \( r \), also shown.

![Figure 3](image3.png)

**Figure 3.** Association between ratio of \( \text{Pao}_2 \) to \( \text{FiO}_2 \) (\( \text{Pao}_2 : \text{FiO}_2 \)) subgroup and changes in respiratory system compliance, dead space ventilation, and ventilatory ratio with prone positioning. \( \text{Pao}_2 : \text{FiO}_2 \) was measured immediately prior to prone positioning, in the supine position. **Boxes** depict the median with interquartile range, and **whiskers** indicate minimum and maximum values. **Numbers above box plots** represent the number of patients included in each subgroup. No between-group differences are statistically significant. \( \Delta \text{Crs} = \) postprone respiratory system compliance minus preprone respiratory system compliance, \( \Delta \text{Vd/Vt} = \) postprone dead space ratio minus preprone dead space ratio, \( \Delta \text{VR} = \) postprone ventilatory ratio minus preprone ventilatory ratio.
emphasize the distinct and complementary physiologic approach of each therapy. The additive improvement in oxygenation with PP in patients who were treated with iNO may reflect a differential effect of gravity and vasomotor tone on perfusion distribution. Taken together, these data suggest redistribution of both ventilation and perfusion with PP, explaining an overall improvement in V/Q matching and oxygenation.

We suspect that offsetting changes in the regional distribution of ventilation with PP are responsible for the net lack of change in $C_{RS}$ and Vd/Vt observed across our cohort. In explaining the variable Paco$_2$ response to PP, other investigators have argued that reduced dead space results from resolution of relative overdistension of some healthy pulmonary units, whereas increased dead space results from reduced venous return due to decreased chest wall compliance (25). Furthermore, any regional derecruitment with PP could lead to overdistension in persistently inflated lung units. We believe the net effect of these changes explains the lack of change in $C_{RS}$ and Vd/Vt in our cohort. On closer analysis, we observed that change in Paco$_2$:Fio$_2$ with PP correlated with change in Vd/Vt and VR. These findings are consistent with studies of pre-COVID-19 ARDS, in which PP has been shown to result in dorsal recruitment and a more homogenous distribution of ventilation (thus reducing overdistension and decreasing Vd/Vt) (7, 26). We speculate that the patients with a more significant improvement in gas exchange are ones who experienced a larger net recruitment. Offsetting changes in regional transpulmonary pressure may have obscured this effect in patients with less significant improvement. In so far as $C_{RS}$, Vd/Vt, and Paco$_2$:Fio$_2$ did not change substantially between the immediate post-PP and 16-hr post-PP time points, our data do not demonstrate additional recruitment over the duration of the first PP session though, as noted, our data are unable to identify offsetting regional changes.

Importantly, we did not observe associations between supine-to-prone Paco$_2$:Fio$_2$ change and parameters with plausible physiologic association, including PEEP. We observed similar improvement in oxygenation with PP despite PEEP level at the time of PP. As an explanation for these findings, we note the more homogenous distribution of ventilation (and thus V/Q) seen in the prone position. It has been reported that in the supine position, the optimal PEEP for dependent and nondependent lung regions is different, limiting the improvement in V/Q matching that may be achieved with PEEP alone (18, 27). However, with PP, optimal levels of regional PEEP are similar. Furthermore, changes in diaphragmatic position in the prone position may result in a more homogenous distribution of pleural pressure (28). We believe our findings are consistent with an improvement in gas exchange.
exchange by PP in addition to any improvement that may be achieved by PEEP titration.

Given the heterogeneity of clinical, physiologic, and biochemical features in ARDS, investigators have endeavored to identify disease subphenotypes with the ultimate goal of personalizing therapy (29, 30). In early studies of COVID-19 ARDS, investigators proposed the existence of “high compliance/low elastance” and “low compliance/high elastance” disease phenotypes and suggested that PP is ineffective in patients with high compliance (31, 32). Our data do not identify a differential response to PP depending on $C_{rs}$ subgroup; improvement in oxygenation with PP was equivalent in high and low compliance subgroups. Within the limits of our study, we do not find evidence of compliance subphenotypes that respond differently to PP.

Similar to other reports, these data emphasize that intensivists should not assume that extremes of PEEP or elevated BMI preclude oxygenation benefit from PP (33). Independent of PP, we observed that VR increased with BMI, likely corresponding to increased atelectasis as well as regional overdistension in obese patients.

This single-institution, observational study has important limitations. The pandemic precluded routine use of resource-intensive techniques to localize and quantify lung ventilation and perfusion, for example, electrical impedance tomography (34). Furthermore, there was infrequent use of CT chest imaging and esophageal balloon manometry. PP was performed at the discretion of treating physicians, which may bias the cohort to include sicker patients or those not responding to conventional therapies. Our cohort may exclude patients who were too unstable to safely undergo PP.

CONCLUSION

This observational clinical study adds necessary detail to our understanding of the physiology of PP in COVID-19 ARDS. We show that PP confers an oxygenation benefit broadly across the spectrum of ARDS severity and without regard to BMI or PEEP prior to PP. We further found that PP resulted in an increase in oxygenation that was additive to that achieved with iNO, as previously reported in pre-COVID-19 ARDS (35). These findings set the stage for future studies to clarify, physiologically, the optimal duration of PP to maximally recruit lung and reduce lung strain. There remains a critical need to determine how to leverage and maintain the benefits of PP.

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