OBSERVATIONAL STUDY

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

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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/m^2 (27–35 kg/m^2), and 50 patients (41%) were female. The ratio of Pa_{O_2} to F_{IO_2} improved with prone positioning in 90% of patients. Prone positioning was associated with a significant increase in the ratio of Pa_{O_2} to F_{IO_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 Pa_{O_2} to F_{IO_2}, respiratory system compliance, positive end-expiratory pressure, and body mass index did not correlate with absolute change in the ratio of Pa_{O_2} to F_{IO_2} with prone positioning. However, patients with ratio of Pa_{O_2} to F_{IO_2} less than 150 experienced a greater relative improvement in oxygenation with prone positioning than patients with ratio of Pa_{O_2} to F_{IO_2} greater than or equal to 150 (median percent change in ratio of Pa_{O_2} to F_{IO_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 Pa_{O_2} to F_{IO_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 Pa_{O_2} to F_{IO_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

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of supine respiratory system compliance, positive end-expiratory pressure, or body mass index. There was a greater relative benefit among patients with more severe disease. Prone positioning confers an additive benefit in oxygenation among patients treated with inhaled nitric oxide.

KEY WORDS: acute respiratory distress syndrome; coronavirus disease 2019; critical care; physiology, respiratory

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 $Pa{O_2}$ to $F{IO_2}$ [$Pa{O_2}$:$F{IO_2}$] 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 ARDS severity and patient characteristics. We hypothesized that PP results in a more homogenous distribution of ventilation—recruiting dependent lung and decreasing overdistention of non-dependent lung—yielding improved respiratory system compliance (C_{RS}) and decreased dead space ventilation (dead-space-to-tidal-volume ratio [Vd/Vt]) 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 $Pa{O_2}$:$F{IO_2}$ 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 $Pa{O_2}$:$F{IO_2}$ 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/$F{IO_2}$ 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 episode 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 expenditure and the rearranged Weir equation for CO_2 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 (interquartile 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 samples. 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 managed with mechanical ventilation and PP. Median age was 60 years (51–71 yr), and median body mass index (BMI) was 31.5 kg/m^2 (27–35 kg/m^2). Fifty patients (41%) were female. Median hospital day of intubation was 1 (1–2), and median time between intubation and PP was 37 hours (15–80 hr). Pre-PP Pao_2:Fio_2 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 mechanics were collected retrospectively at four time points: immediately after intubation (post-intubation), immediately prior to PP, while supine (pre-PP), immediately 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 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 Pao_2:Fio_2 (from median 149 [123–170] to median 226 [169–268], $p < 0.001$) but no change in Vd/Vt, VR, or C_{RS}. Of 122 patients, 110 (90%) experienced an increase in Pao_2:Fio_2 with PP. There was no correlation among pre-PP Pao_2:Fio_2 (assessed immediately prior to PP and after optimization of PEEP according to institutional protocols), C_{RS}, PEEP, or BMI with pre-PP to post-PP change in Pao_2:Fio_2 (p [correlation], 0.181, 0.393, 0.164, and 0.842, respectively). Notably, patients receiving high PEEP (greater than or equal to 14 cm H_2O) 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/m^2 experienced similar benefits to patients with lower BMI. **Figure S1** (http://links.lww.com/CCX/A680) depicts the association between BMI subgroup and Pao_2:Fio_2, PEEP, VR, Vd/Vt, and C_{RS} before and after PP. Examination of BMI subgroups demonstrated significant improvement in oxygenation with PP even among patients with BMI greater than 40 kg/m^2. Furthermore, pre- to post-PP change in VR, Vd/Vt, C_{RS}, 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 Pao_2:Fio_2 was less than 150 among 62 patients and greater than or equal to 150 among 60 patients. The change in Pao_2:Fio_2 when assessed relative to pre-PP Pao_2:Fio_2 was greater in patients with pre-PP Pao_2:Fio_2 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 significant differences between pre-PP to post-PP change in C_{RS}, Vd/Vt, or VR between patients with Pao_2:Fio_2 less than 150 and those with Pao_2:Fio_2 greater than or equal to 150 (**Fig. 3**).

Pre-PP to post-PP change in Pao_2:Fio_2 did not correlate with change in C_{RS} (p [correlation], 0.972). However, increasing pre-PP to post-PP Pao_2:Fio_2 correlated with decreasing Vd/Vt (Spearman r, –0.290; p [correlation], 0.001) and VR (Spearman r, –0.265;

TABLE 1.
Ventilator Settings, Respiratory Mechanics, and Gas Exchange in Patients With Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Before and After Initiation of Prone Positioning

	Supine		Prone			
***n* = 122**	**Post-intubation**	**Pre-PP**	**Post-PP**	**16-hr Post-PP**	***P* (Pre-PP/Post-PP)**	***P* (Pre-PP/16-hr Post-PP)**
Ventilator settings, median (IQR)						
FIO_2	1.0 (0.7–1.0)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.6)	0.193	**<0.0001**
Tidal volume, mL/kg predicted body weight	6.3 (5.6–6.7)	6.0 (5.5–6.5)	6.0 (5.5–6.4)	6.0 (5.5–6.4)	0.305	0.362
Positive end-expiratory pressure, cm H_2O	10 (8–12)	12 (10–14)	12 (10–15)	12 (10–14)	0.080	0.121
Respiratory mechanics, median (IQR)						
Plateau pressure, cm H_2O	22 (20–25)	23 (21–26)	24 (22–26)	23 (21–25)	0.305	0.362
Driving pressure, cm H_2O	11 (9–12)	11 (9–12)	11 (9–12)	10 (9–12)	0.788	0.401
Respiratory system compliance, mL/cm H_2O	33 (27–40)	31 (27–39)	33 (27–38)	33 (28–38)	0.721	0.411
Gas exchange, median (IQR)						
Ratio of PaO_2 to FIO_2	156 (109–203)	149 (123–170)	226 (169–268)	235 (186–285)	**<0.0001**	**<0.0001**
Dead space ratio	0.51 (0.42–0.58)	0.55 (0.50–0.63)	0.55 (0.49–0.62)	0.55 (0.49–0.64)	0.149	0.973
Ventilatory ratio	1.29 (1.13–1.49)	1.47 (1.23–1.74)	1.42 (1.20–1.72)	1.44 (1.22–1.77)	0.538	0.493

16-hr post-PP = nearest available to 16 hr after PP, while prone, IQR = interquartile range, Post-PP = immediately after PP, PP = prone positioning, Pre-PP = immediately prior to PP, while supine, VR = ventilatory ratio.
Boldface values indicate $p < 0.05$.

p [correlation], 0.003; **Fig. S3**, http://links.lww.com/CCX/A682).

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 PaO_2:FIO_2 (136 [77–168] to 170 [138–213], $p = 0.003$) and decreases in 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 PaO_2:FIO_2 with iNO. Median improvement in PaO_2:FIO_2 with iNO was 31.6% (19.4–42.6%), with nine patients improving by over 20%. Subsequent PP while receiving iNO increased PaO_2:FIO_2 (145 [122–183] to 205 [150–232], $p = 0.017$) but did not affect C_{RS} (29 mL/cm H_2O [25–40 mL/cm H_2O] to 33 mL/cm H_2O [27–38 mL/cm H_2O], $p = 0.613$), 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 PaO_2: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

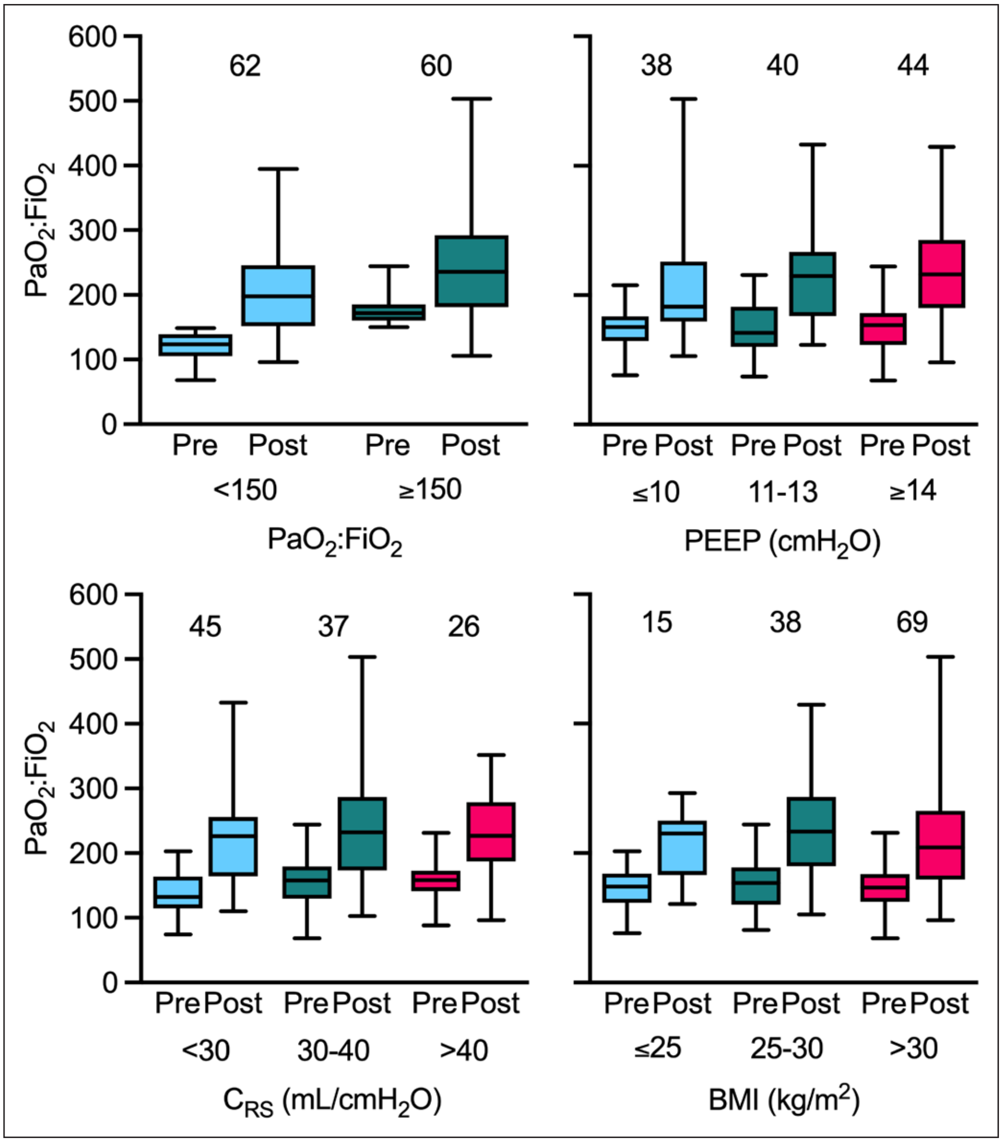

Figure 1. Associations between ratio of Pao_2 to Fio_2 (Pao_2:Fio_2), respiratory system compliance, positive end-expiratory pressure, and body mass index and change in Pao_2:Fio_2 with prone positioning. There were no significant differences in change in Pao_2:Fio_2 with prone positioning (PP) by pre-PP Pao_2:Fio_2, positive end-expiratory pressure (PEEP), respiratory system compliance (C_{RS}), or body mass index (BMI) subgroup. Pao_2:Fio_2, PEEP, and C_{RS} were measured immediately prior to prone positioning, in the supine position (designated "Pre"). "Post" indicates Pao_2:Fio_2 immediately after transition to the prone 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.

mild disease, but the majority of patients experienced an improvement in oxygenation. PP was neither associated with a change in global C_{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_{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_2:Fio_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_2:Fio_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_2:Fio_2 less than 150 (62 patients) and Pao_2:Fio_2 greater than or equal to 150 (60 patients). Most of these 60 patients with Pao_2:Fio_2 greater than or equal to 150 had moderate ARDS; only seven had Pao_2:Fio_2 greater than 200 at the time of PP. The application of PP to patients with ARDS and Pao_2:Fio_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).

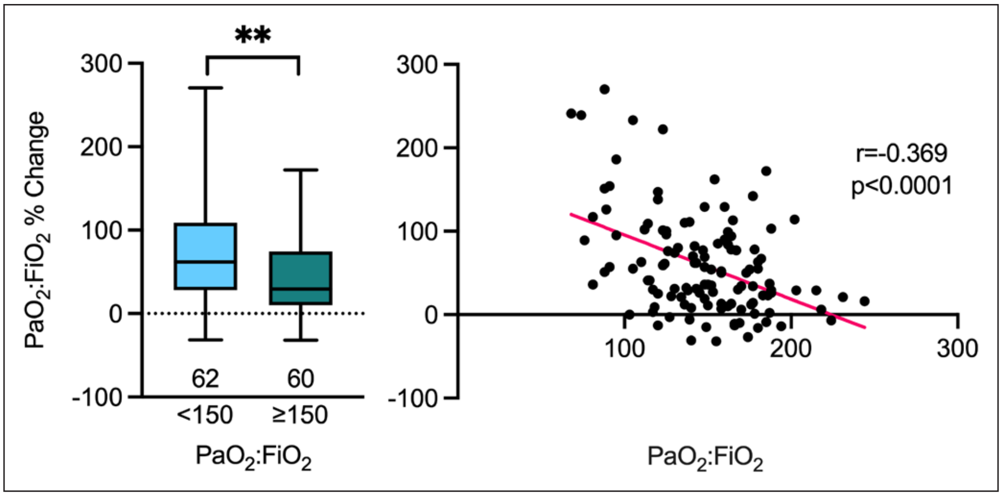

Figure 2. Association between ratio of Pao_2 to Fio_2 (Pao_2:Fio_2) and relative change in Pao_2:Fio_2 with prone positioning. Pao_2:Fio_2 was measured immediately prior to prone positioning, in the supine position. Pao_2:Fio_2 percent change represents the postprone minus preprone Pao_2:Fio_2 (Δ Pao_2:Fio_2) difference relative to pre-prone Pao_2:Fio_2. *Boxes* depict the median with interquartile range, and *whiskers* indicate minimum and maximum values. $^{*}p \le 0.05$, $^{**}p \le 0.01$, $^{***}p = 0.001$. *Numbers below box plots* represent the number of patients included in each subgroup. *Regression line* corresponds to Spearman rank correlation coefficient, *r*, also shown.

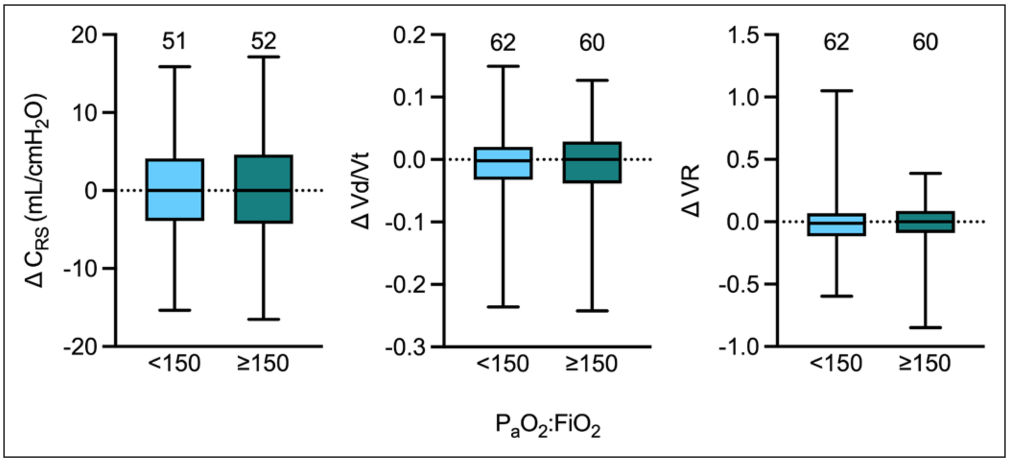

Figure 3. Association between ratio of Pao_2 to Fio_2 (Pao_2:Fio_2) subgroup and changes in respiratory system compliance, dead space ventilation, and ventilatory ratio with prone positioning. Pao_2:Fio_2 was measured immediately prior to prone positioning, in the supine position. *Boxes* depict the 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. Δ C_{RS} = postprone respiratory system compliance minus preprone respiratory system compliance, Δ Vd/Vt = postprone dead space ratio minus preprone dead space ratio, ΔVR, postprone ventilatory ratio minus preprone ventilatory ratio.

Although ARDS severity as reflected by oxygenation deficit did not predict absolute change in oxygenation with PP (Fig. 1), the group of patients with Pao_2:Fio_2 less than 150 experienced over twice the percent change in Pao_2:Fio_2 that the group of patients with Pao_2: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 Pao_2: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

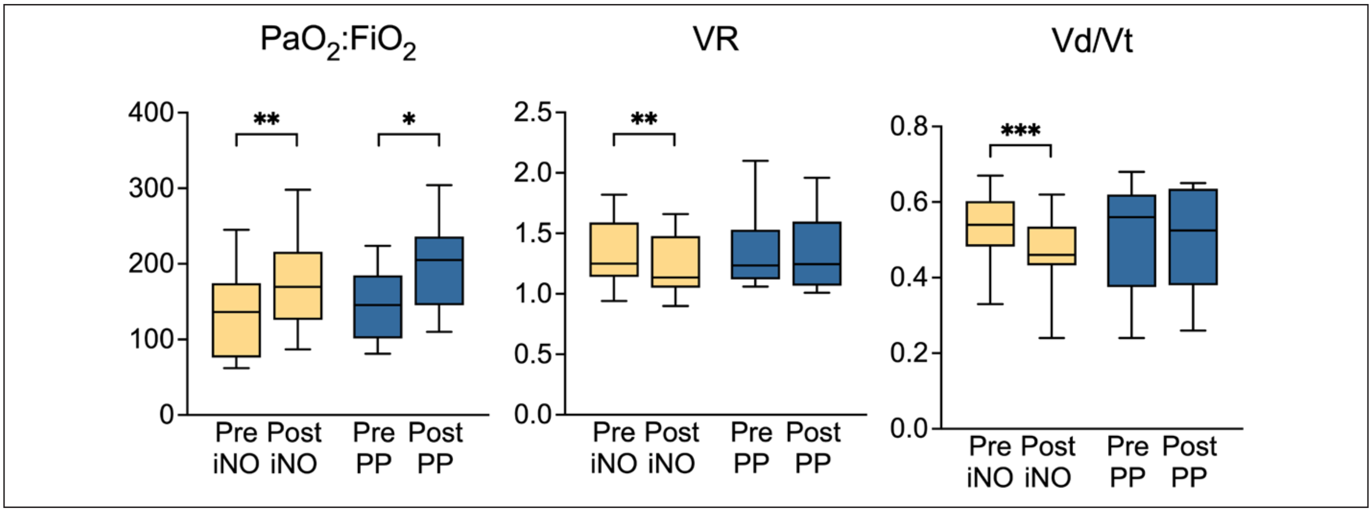

Figure 4. Ratio of Pao_2 to Fio_2 (Pao_2:Fio_2), ventilatory ratio, and estimated dead space ratio before and after initiation of inhaled nitric oxide (iNO) in the supine position and subsequently before and after prone positioning while receiving inhaled nitric oxide in a subset of 12 patients. *Boxes* depict the median with interquartile range, and *whiskers* indicate minimum and maximum values. $^{*}p \le 0.05$, $^{**}p \le 0.01$, and $^{***}p = 0.001$. post-iNO = immediately after initiation of iNO, in the supine position, post-PP = immediately after prone positioning, pre-iNO = immediately prior to initiation of iNO, in the supine position, pre-PP = immediately prior to prone positioning, in the supine position, Vd/Vt = dead space ratio, VR = 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 Pao_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 Pao_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 Pao_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 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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