RESPIRATORY CARE Paper in Press. Published on June 14, 2022 as DOI: 10.4187/respcare.09783

# Decline in Ventilatory Ratio as a Predictor of Mortality in Adults With ARDS Receiving Prone Positioning

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**BACKGROUND: Prone positioning reduces mortality in patients with moderate/severe ARDS. It remains unclear which physiological parameters could guide clinicians to assess which patients are likely to benefit from prone position. This study aimed to determine the association between relative changes in physiological parameters at 24 h of prone positioning and ICU mortality in adult subjects with ARDS. METHODS: We conducted a cohort study using the VENTILA database, including adults with ARDS receiving prone positioning. We used multivariable logistic regression to assess the association between relative changes in physiological parameters ($P_{aO_2}/F_{IO_2}$, dynamic driving pressure, $P_{aCO_2}$, and ventilatory ratio defined as [minute ventilation [mL/min] × $P_{aCO_2}$ [mm Hg]]/[predicted body weight × 100 [mL/min] × 37.5 [mm Hg] with ICU mortality) (primary outcome). We report adjusted odds ratios with 95% CI as measures of association. RESULTS: We included 156 subjects of which 82 (53%) died in the ICU. A relative decline in the ventilatory ratio at 24 h was associated with lower ICU mortality (odds ratio 0.80 [95% CI 0.66–0.97], every 10% decrease). Relative changes in $P_{aO_2}/F_{IO_2}$ (odds ratio 0.89 [95% CI 0.77–1.03], every 25% increase), $P_{aCO_2}$ (odds ratio 0.97 [95% CI 0.82–1.16], every 10% decrease), and dynamic driving pressure (odds ratio 0.98 [95% CI 0.89–1.07], every 10% decrease) were not associated with ICU mortality. CONCLUSIONS: In subjects with ARDS receiving prone positioning, a relative decline in the ventilatory ratio at 24 h was associated with lower ICU mortality.** *Key words: ARDS; prone position; ventilatory ratio; respiratory dead space*. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

## Introduction

Prone positioning is an effective adjuvant treatment for adult patients with moderate-to-severe ARDS.[1] The mechanisms underlying its benefit are related to the optimization of ventilation-perfusion matching, lung recruitment, and reducing the risk of ventilator-induced lung injury by rendering a more homogenous distribution of tidal volume and regional stress and strain.[2-6] Several randomized clinical trials and meta-analyses have shown consistent benefits in both surrogate physiological parameters and clinical outcomes, including mortality.[1,7-12]

Although average treatment effects point toward a mortality benefit associated with prone positioning in patients with moderate-to-severe ARDS, there is still a subset of patients who die despite receiving the intervention.[1] Importantly, it remains unclear which dynamic physiological parameters are associated with improved survival and could help guide clinicians to identify patients who are more likely to benefit from prone positioning.[13] Although improvement in oxygenation after prone positioning has been well documented,[14] this has not consistently translated into a subsequent lower risk of death.[15,16] Conversely, a reduction in the partial pressure of $P_{aCO_2}$ has been associated with improved mortality.[17] In a physiological study that classified subjects into responders and nonresponders according to changes in $P_{aO_2}$ and $P_{aCO_2}$, an improvement in respiratory mechanics after prone position was more prominent in $P_{aCO_2}$ responders rather than $P_{aO_2}$ responders.[18] More recently, a post hoc analysis of an observational study demonstrated changes in respiratory system driving pressure ($\Delta P_{RS}$) after prone positioning were significantly associated with mortality, whereas changes in oxygenation (as measured by $P_{aO_2}/F_{IO_2}$) or dead-space fraction ($V_D/V_T$) were not. However, changes in $\Delta P_{RS}$ after the first proning session had poor discrimination for predicting mortality.[19] The prognostic role of changes in gas exchange and lung mechanics' parameters remains unclear.

Identifying which relative changes in respiratory physiological parameters after prone positioning are associated with patient important outcomes has relevant physiological and clinical implications. For instance, it may assist clinicians in the decision-making process of whether to continue prone positioning or to consider consultation with centers that perform advanced therapies such as extracorporeal life support (ECLS).[20,21] Furthermore, it could potentially shed light into which of the many potential mechanisms of benefit associated with prone positioning plays a higher role in patients' outcomes. In the present study, we sought to determine the association between changes in physiological parameters at 24 h of prone positioning and subjects' outcomes (mortality and liberation from invasive ventilation) in adult subjects with ARDS.

## QUICK LOOK

### Current knowledge

Prone positioning is associated with reduced mortality in patients with moderate-to-severe ARDS. The ventilatory ratio is an index of impaired efficiency of ventilation that correlates positively with pulmonary dead space and is associated with increased risk of mortality in patients with ARDS.

### What this paper contributes to our knowledge

In subjects with ARDS receiving prone positioning, a relative decline in the ventilatory ratio at 24 h was associated with lower ICU mortality and a shorter time to liberation from mechanical ventilation within 28 d. Ventilatory ratio is a simple tool that could potentially aid clinicians when assessing response to prone position in patients with moderate-to-severe ARDS.

## Methods

### Study Design and Population

We performed a retrospective cohort study using data from the VENTILA Group, a prospective cohort study that includes adult subjects with ARDS receiving invasive mechanical ventilation in 349 ICUs from 23 different countries from 2010–2016.[22] For the purpose of the main analysis, only subjects receiving prone positioning at any time during the first 7 d of ventilation were included (Figure E1, see related supplementary materials at http://www.rc.rcjournal.com).

We included adult subjects (> 17 y old) receiving invasive mechanical ventilation for at least 12 h and a diagnosis of ARDS based on the Berlin definition.[23] The VENTILA Group cohort collects information daily on a prespecified schedule between 08:00–10:00 AM. Therefore, the main exposures of this study were relative changes at 24 h of prone positioning. Patients who died or were started on ECLS within 24 h of prone positioning were excluded from the analysis.

### Measurements

We included subjects demographics (age and sex), reason for mechanical ventilation (ARDS vs not), organ dysfunction (Simplified Acute Physiology Score II [SAPS II][24] and presence of shock), timing of prone positioning relative to initiation of mechanical ventilation, gas exchange parameters ($P_{aO_2}/F_{IO_2}$, $P_{aCO_2}$, ventilatory ratio), and respiratory mechanics (PEEP, plateau pressure, peak airway pressure, and dynamic driving pressure defined as peak airway pressure −PEEP). Ventilatory ratio was defined as (minute ventilation [mL/min] × $P_{aCO_2}$ [mm Hg]/[predicted body weight × 100 [mL/min] × 37.5 [mm Hg]).[25-27]

Relative changes at 24 h were estimated for the following 4 parameters: $P_{aO_2}/F_{IO_2}$, dynamic driving pressure, $P_{aCO_2}$, and ventilatory ratio (online data supplement, see related supplementary materials at http://www.rc.rcjournal.com). First, we

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Dr Ferreyro is supported by a Vanier Canada Graduate Scholarship. Dr Fan discloses relationships with ALung Technologies, Baxter, Boehringer-Ingelheim, Fresenius Medical Care, and MC3 Cardiopulmonary. The remaining authors have disclosed no conflicts of interest.

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Supplementary material related to this paper is available at http://rc.rcjournal.com.

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DOI: 10.4187/respcare.09783

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calculated the change in the first 24 h as Δ value = value day 2 − value day 1. Second, we calculated the relative change as follows: Δ value/value day 1. These parameters were chosen based on physiologic rationale and previous literature, as they can be affected by prone positioning.[2,4]

### Outcomes

The primary outcome of this study was ICU mortality. The secondary outcome was the time to liberation from mechanical ventilation that accounted for the competing risk of death before liberation from invasive ventilation.

### Statistical Analysis

We summarized subjects' baseline characteristics using descriptive statistics. We used bivariate analysis to compare characteristics of subjects who died with those who survived the ICU admission. Continuous variables were compared using Student *t* test or Wilcoxon test as appropriate. Categorical variables were compared using the Fisher exact test.

For the primary outcome, we assessed the association between relative changes at 24 h in oxygenation, $P_{aCO_2}$, dynamic driving pressure, and ventilatory ratio with ICU mortality. We used multivariable logistic regression models to evaluate the association between the relative change of each physiological variable (main exposure) and ICU mortality as the dependent variable. Models were adjusted by age, sex, SAPS II, and presence of shock. Baseline $P_{aO_2}/F_{IO_2}$ and dynamic driving pressure were only included in the models assessing the effect of relative changes in $P_{aCO_2}$ and ventilatory ratio. We report adjusted odds ratios and corresponding 95% CI as measures of association.

For the secondary outcome, we assessed the association between relative changes in physiological parameters at 24 h and time to liberation from mechanical ventilation within 28 d using a proportional hazard model that accounted for the competing risk of death using the Fine-Gray approach.[28,29] These models were adjusted for the same variables as in the primary analysis. We report sub-distribution hazard ratios (sHRs) and corresponding 95% CI as measures of association.

All analyses were performed using SAS University Edition (SAS Institute, Cary, North Carolina), and we considered a *P* value < .05 for statistical significance. Additional details are provided in the online data supplement.

### Sensitivity Analyses

We performed several sensitivity analyses of the primary outcome to assess the robustness of our findings. First, we performed multiple imputation to account for missing data (see Table E2 for further details on missing data patterns; see related supplementary materials at http://www.rc.rcjournal.com). Second, we restricted our analysis to subjects with $P_{aO_2}/F_{IO_2}$ < 150 and to those who received prone positioning within 48 h of invasive ventilation. Finally, we generated a propensity score–matched cohort of subjects that did not receive prone positioning to assess whether the observed association of ventilatory ratio changes and mortality was also applicable to subjects in supine position. Initially, we refitted our primary analysis for ventilatory ratio in the population of subjects in supine position. Furthermore, we assessed the interaction between relative changes in ventilatory ratio and subject position (supine vs proned) for the association with ICU mortality in a cohort that included both proned and propensity score–matched supine subjects. Additional details are provided in the online data supplement.

## Results

During the study period, 1,124 patients with ARDS were included in the registry of which 163 (15%) were placed in prone position at any time during the first 7 d of mechanical ventilation. Seven additional patients were excluded as 4 died, 2 were started on ECLS within 24 h of prone positioning, and one had inconsistent data (Figure E1). Finally, 156 subjects were analyzed.

### Study Population

The main characteristics of these subjects are described in Table 1. Briefly, the mean (SD) age was 56 (17) y, and 53 (34%) were female. ARDS was the primary reason for invasive mechanical ventilation in 68 (44%) subjects, and 99 (63.5%) subjects were placed in prone position within 48 h of ARDS. Time to prone positioning for the overall cohort is described in Figure E2 (see related supplementary materials at http://www.rc.rcjournal.com. Subjects were pronated for a mean (SD) of 13.5 (6.0) h on day 1, and the median (interquartile range [IQR]) $P_{aO_2}/F_{IO_2}$ on day 1 was 113 (85–152).

During follow-up, 82 subjects (53%) died in the ICU. When compared to ICU survivors, nonsurvivors were significantly older (mean age [SD] 59 [17] y vs 52 [15] y, *P* = .006), had greater severity of illness (mean [SD] SAPS II score 56 [18] vs 44 [18], *P* = .001), and a significantly higher prevalence of shock at baseline (70% vs 51%, *P* = .02). At ICU admission, nonsurvivors had lower $P_{aO_2}/F_{IO_2}$ (median [IQR] 100 [78–142] vs 127 [97–175], *P* = .005) and a higher ventilatory ratio (median [IQR] 2.3 [1.9–3.0] vs 2.1 [1.7–2.5], *P* = .03).

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Table 1. Baseline Characteristics of Subjects With ARDS Receiving Prone Positioning

| | Overall Study Population ($N$ = 156) | Status at ICU Discharge | | |
|---|---|---|---|---|
| | | Dead ($n$ = 82) | Alive ($n$ = 74) | $P$* |
| Demographics | | | | |
| Age, y | 55.8 (17.0) | 59.1 (17.0) | 51.9 (15.0) | .006 |
| Female | 53 (34) | 29 (35) | 24 (32) | .70 |
| Body mass index, kg/m$^2$ | 26 (23–31) | 25 (23–30) | 26 (22–31) | .48 |
| Reason for Invasive Ventilation† | | | | |
| ARDS as the primary reason for invasive ventilation | 68 (44) | 33 (40) | 35 (47) | .38 |
| ARDS during the course of invasive ventilation | 88 (56) | 49 (60) | 39 (53) | |
| Severity of Disease | | | | |
| SAPS II | 50.2 (19.0) | 55.5 (18.0) | 44.4 (18.0) | .001 |
| Shock | 95 (61) | 57 (70) | 38 (51) | .02 |
| Timing of Prone Positioning | | | | |
| Prone positioning at 48 h of ARDS | 99.0 (63.5) | 53.0 (64.6) | 46.0 (62.2) | .87 |
| Hours prone day 1 | 13.7 (5.9) | 13.5 (5.8) | 13.8 (6.1) | .79 |
| Respiratory Variables at Baseline | | | | |
| $P_{aO_2}/F_{IO_2}$ | 113 (85–152) | 100 (78–142) | 127 (97–175) | .005 |
| $P_{CO_2}$, mm Hg | 48 (42–59) | 50 (44–59) | 46 (40–57) | .17 |
| Ventilatory ratio | 2.2 (1.8–2.7) | 2.3 (1.9–3.0) | 2.1 (1.7–2.5) | .03 |
| Frequency, breaths/min | 25.0 (5.5) | 25.1 (5.7) | 24.6 (5.4) | .57 |
| Tidal volume, mL/kg | 6.7 (5.8–7.9) | 6.9 (5.8–8.2) | 6.6 (5.9–7.6) | .36 |
| Minute ventilation, L/min | 10.7 (8.6–12.6) | 10.8 (8.8–12.6) | 10.5 (8.6–12.4) | .66 |
| PEEP, cm $H_2O$ | 12.2 (4.3) | 12.1 (4.6) | 12.2 (3.9) | .88 |
| Plateau pressure, cm $H_2O$ | 26.3 (4.8) | 27.1 (4.9) | 25.4 (4.6) | .08 |
| Peak pressure, cm $H_2O$ | 32.0 (7.4) | 32.1 (7.0) | 31.9 (7.8) | .88 |
| Driving pressure, cm $H_2O$ | 14.1 (5.6) | 14.7 (5.9) | 13.4 (5.2) | .23 |
| Dynamic driving pressure, cm $H_2O$ | 19.8 (8.9) | 20.1 (8.6) | 19.5 (9.2) | .68 |
| Ventilatory Mode at Baseline | | | | |
| Assisted control | 146.0 (95.4) | 80.0 (98.8) | 66.0 (91.7) | .05 |
| Pressure support | 7.0 (4.6) | 1.0 (1.2) | 6.0 (8.3) | |
| Adjunctive Therapies at Baseline | | | | |
| Neuromuscular blockers | 102 (65) | 51 (62) | 51 (69) | .37 |
| Steroids | 81 (52) | 48 (59) | 33 (45) | .08 |
| Fluid balance on first day | 1.02 (2.37) | 1.56 (2.52) | 0.42 (2.05) | .005 |

Data are presented as $n$ (%), median (interquartile range), and mean (SD).
* $P$ values refer to the comparison between subjects who were dead versus alive at ICU discharge.
Data on ventilatory ratio and minute volume ventilation were available for 151/156 subjects. Data on breathing frequency rate were available on 152/156 subjects. Data on plateau pressure and driving pressure vwere available on 110/156 subjects. Data on peak pressure and dynamic driving pressure were available on 141/156 subjects. Data on fluid balance on the first day were available on 138/156 subjects. Data on ventilatory mode were available in 153/156 subjects.
† Reason for invasive mechanical ventilation composes 2 groups of subjects, those who were started on invasive mechanical ventilation due to ARDS and those who developed ARDS during the course of invasive mechanical ventilation. For the latter, the main reasons included pneumonia, sepsis, postoperative respiratory failure, neurologic diseases, and trauma.
SAPS II = Simplified Acute Physiology Score II

## Relative Physiological Changes at Twenty-Four Hour and ICU Mortality

Relative changes on respiratory physiological parameters associated with ICU mortality are outlined in Figure 1 and Table E1 (see related supplementary materials at http://www.rc.rcjournal.com). The primary analyses were evaluated in subjects with complete data (117 of 156 total subjects). Among the 4 physiological parameters evaluated, only a relative change in the ventilatory ratio was significantly associated with a reduction in ICU mortality. Subjects that died in the ICU had a median (IQR) relative increase in the ventilatory ratio of 3% (–12 to 17%), whereas subjects that survived the ICU had a median decrease of 7% (–22 to 5%, $P$ = .02). (Table E1). After multivariable adjustment, we observed that every 10% decrease in the ventilatory ratio after 24 h of prone positioning was associated with a 20% decrease in the odds of mortality (odds ratio 0.80 [95% CI 0.66–0.97]). In contrast, relative changes in $P_{aO_2}/F_{IO_2}$ (for every 25% increase: odds

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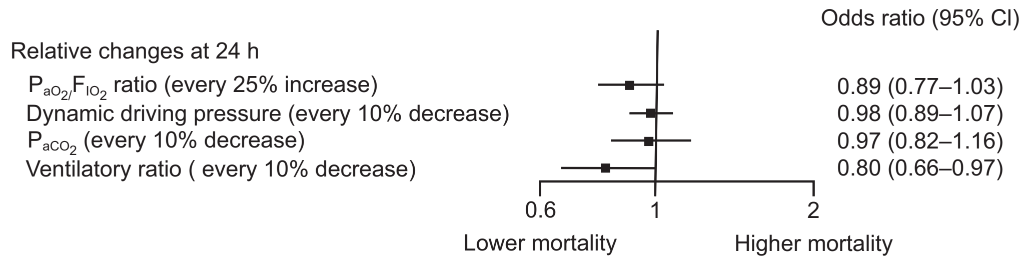


Fig. 1. Relative changes on respiratory physiologic parameters and mortality. The figure shows results of 4 different multivariable logistic regression models. Each model includes the key exposure represented in the figure and the following potential confounders: age, sex, Simplified Acute Physiology Score II, presence of shock, $P_{aO_2}/F_{IO_2}$ at baseline, and dynamic driving pressure at baseline. Models where the exposure are relative changes in dynamic driving pressure and $P_{aO_2}/F_{IO_2}$ do not include these respective variables at baseline.

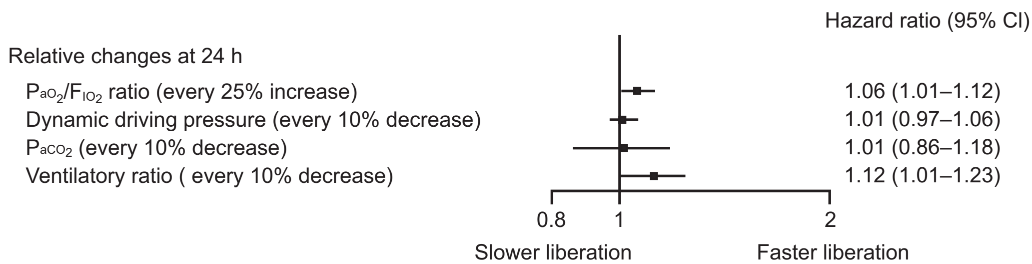


Fig. 2. Relative changes on respiratory physiologic parameters and time to liberation from mechanical ventilation. The figure shows results of 4 different proportional-hazards regression models that account for the competing event of death before liberation from mechanical ventilation. Each model includes the key exposure represented in the figure and the following potential confounders: age, sex, Simplified Acute Physiology Score II, presence of shock, $P_{aO_2}/F_{IO_2}$ at baseline, and dynamic driving pressure at baseline. Models where the exposure are relative changes in dynamic driving pressure and $P_{aO_2}/F_{IO_2}$ do not include these respective variables at baseline.

ratio 0.89 [95% CI 0.77–1.03]), $P_{aCO_2}$ (for every 10% decrease: odds ratio 0.97 [95% CI 0.82–1.16]), and dynamic driving pressure (for every 10% decrease: odds ratio 0.98 [95% CI 0.89–1.07]) were not significantly associated with ICU mortality.

### Relative Physiological Changes at Twenty-Four Hour and Time to Liberation From Invasive Mechanical Ventilation

Relative changes on respiratory physiological parameters associated with time to liberation from mechanical ventilation are depicted in Figure 2. A 10% decrease in the ventilatory ratio (sHR 1.12 [95% CI 1.01–1.23]) and 25% increase in $P_{aO_2}/F_{IO_2}$ (sHR 1.06 [95% CI 1.01–1.12]) were significantly associated with a shorter time to liberation from mechanical ventilation within 28 d. However, relative changes in $P_{aCO_2}$ (sHR 1.01 [95% CI 0.86–1.18]) and dynamic driving pressure (sHR 1.01 [95% CI 0.97–1.06]) were not significantly associated with time to liberation from mechanical ventilation.

### Sensitivity Analyses

The results of the sensitivity analyses are detailed in the online data supplement (Tables E3-4, see related supplementary materials at http://www.rc.rcjournal.com). Briefly, the results of our primary analysis remained robust when repeated with multiple imputation for missing data and restricting our cohort to subjects with moderate-to-severe ARDS and pronated in the first 48 h of ARDS diagnosis. Furthermore, changes in ventilatory ratio were not significantly associated with mortality in a propensity score-matched cohort of subjects in the supine position. The median (IQR) relative change in ventilatory ratio was 0% (−20 to 20%) and −3% (−18 to 10%) in the supine and proned cohort, respectively. We observed an interaction between changes in ventilatory ratio and prone positioning for ICU mortality (*P* for interaction = .067) (Fig. 3 and Table E4).

## Discussion

Our study evaluated the association between relative changes on respiratory physiological parameters at 24 h of

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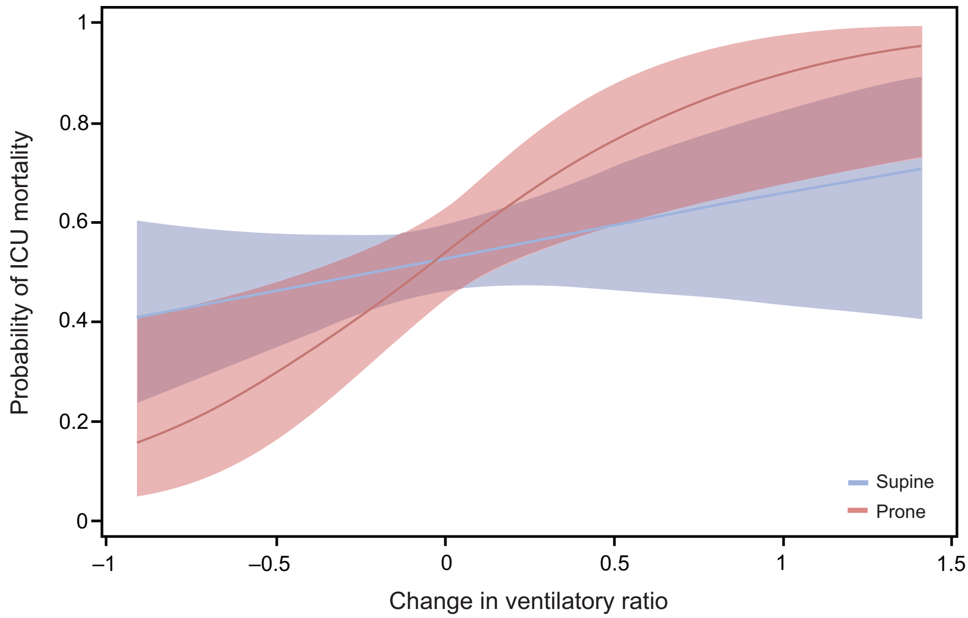


Fig. 3. Association between the change in ventilatory ratio and mortality in subjects with ARDS in supine versus prone position. The figure represents the results of the association between relative changes in ventilatory ratio and the probability of ICU mortality in the study cohort including proned and propensity score–matched supine patients. The plot represents a post-estimation effect fit plot. As depicted in the figure, there is an interaction between changes in ventilatory ratio and subjects' position in its association with ICU mortality. Changes in ventilatory ratio of zero or less imply an improvement within 24 hours, whereas a change in ventilatory ratio of zero or more implies no change or worsening.

prone position and outcomes in adult subjects with moderate-to-severe ARDS who received invasive mechanical ventilation. We observed that a relative decrease in ventilatory ratio at 24 h was significantly associated with lower ICU mortality and a shorter time to liberation from mechanical ventilation. Furthermore, a relative improvement in $P_{aO_2}/F_{IO_2}$ was also associated with a shorter time to liberation from mechanical ventilation but not with lower ICU mortality.

Identifying which patients are most likely to have an improvement in mortality from prone position is a daily challenge for clinicians treating adults with ARDS. Understanding how long to continue with prone positioning before escalating to other interventions, such as ECLS, is important given the time-sensitive nature of candidacy for ECLS and the potential need for a window of clinical stability for interhospital transfer to receive ECLS that may be required. Changes in oxygenation are frequently used as a marker of response in routine practice; however, current data suggest that this response is not consistently associated with improvement in important clinical outcomes.[15] Similarly, we did not observe an association between improvement in oxygenation and decreased ICU mortality in our study, although it was associated with a shorter duration of mechanical ventilation. This finding suggests that perhaps this is still a relevant parameter to monitor the severity of lung injury, but it might not be the primary one to assess response to prone positioning.

To the best of our knowledge, no previous research has focused on the role of changes in the ventilatory ratio during prone positioning as a prognostic marker for clinical outcomes. Ventilatory ratio is an index of impaired efficiency of ventilation that correlates positively with pulmonary dead space ($V_D/V_T$), being both parameters independently associated with increased risk of mortality in ARDS.[25-27,30] Prone positioning has been shown to result in a significant reduction of alveolar dead space, posing the ventilatory ratio as an available bedside tool to monitor patients' response.[18,19] Van Meenen et al[19] reported a reduction in alveolar dead space after prone positioning. However, this was not different in survivors and nonsurvivors, which could obey to the small sample assessed. Interestingly, Gattinoni et al showed an association of the ratio between minute ventilation and $P_{aCO_2}$ with mortality in subjects placed in the prone position.[17] Given that the ventilatory ratio integrates both the $P_{aCO_2}$ and the minute ventilation, our findings are consistent with those from Gattinoni and colleagues and highlight the role of measures beyond oxygenation to guide clinical response to prone positioning. Indeed, a reduction in ventilatory ratio after prone positioning suggests that more effective $P_{aCO_2}$ clearance can be achieved without the need of increasing, or even decreasing, the intensity of ventilation.

A logical question that could arise from our findings is whether an improvement in ventilatory ratio could serve as

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a prognostic tool in a broader population of patients with moderate-to-severe ARDS (ie, in the supine position) or whether this association is specific to individuals receiving prone positioning. Interestingly, our post hoc sensitivity analysis was not able to confirm that a relative change in ventilatory ratio translated into a similar clinical benefit in a propensity score-matched cohort of subjects in the supine position. This finding highlights whether relative changes in ventilatory ratio exhibit higher prognostic yield in subjects receiving prone positioning. Moreover, there was evidence of effect modification of ventilatory ratio on outcome by body position (ie, supine vs prone), as evidenced by the observed interaction. Perhaps, in supine patients, ventilatory ratio can be decreased at the cost of increasing ventilation intensity (driving pressure, breathing frequency, and subsequent mechanical power), resulting in no net benefit in patient outcome. Conversely, it might be possible that during prone positioning the decrease in ventilatory ratio responds to the change in position itself and not to an increment in the intensity of ventilation. These hypotheses require confirmation in future studies.

The association between different ventilatory parameters and improved survival in subjects with ARDS has been studied over time.[31,32] Several recent studies have established a strong association between driving pressure and survival.[33,34] There is conflicting evidence regarding the association of prone position−induced changes in driving pressure and survival. Van Meenen et al[19] reported that the changes in driving pressure induced by the first session of prone position have poor prognostic capabilities. Conversely, a retrospective analysis of subjects with severe ARDS done by Modrykamien and Daoud showed that plateau pressure and driving pressure were associated with ICU mortality.[35] Similarly, an increase in dynamic driving pressure was associated with 60-d mortality in subjects with ARDS due to influenza pneumonia receiving prone position.[36] In our study, a relative improvement in dynamic driving pressure after prone positioning was not associated with ICU mortality or shorter time of mechanical ventilation.

Our study has important limitations. First, data were collected once daily, and temporal correlation between prone positioning and physiologic measurements was not standardized. Furthermore, clinicians might argue that 24 hours might be a prolonged time window to decide whether a patient has a beneficial response to prone positioning. Indeed, our findings highlight the need for future prospective studies to assess the prognostic value of changes in ventilatory ratio with serial longitudinal measurements, including before and after prone positioning. Second, given the relatively small sample size, our study may have been underpowered to detect other associations, such as changes in oxygenation and mortality. However, the lack of association between changes in oxygenation and mortality is consistent with previous studies.[15,18] Third, the presence of missing data on variables such as ventilatory ratio restricted our analytic cohort and could potentially introduce selection bias. However, our overall results were robust when considering a sensitivity analysis using multiple imputation.

Finally, this study was not designed to assess causal association between changes in physiological parameters and outcomes. Thus, we cannot conclude that clinicians can intervene based on ventilatory ratio to modify patient's trajectories. However, even if changes in ventilatory ratio have only a predictive role, this novel information may prove useful for clinicians as a measure of response with translation into improved survival.

## Conclusions

Our study demonstrates that a decline in the ventilatory ratio at 24 hours of prone positioning was significantly associated with a lower ICU mortality and a shorter time to liberation from mechanical ventilation within 28 days. Furthermore, a relative increase in $P_{aO_2}/F_{IO_2}$ was associated with a shorter time to liberation from mechanical ventilation within 28 days. Given that ventilatory ratio is a parameter easily and readily available at the bedside, the results of this study offer a simple tool that could potentially help clinicians to assess the response to prone position in patients with moderate-to-severe ARDS. Before applying our results to guide clinical management, prospective studies should replicate our findings.

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RESPIRATORY CARE Paper in Press. Published on June 14, 2022 as DOI: 10.4187/respcare.09783



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