



# Predicting Impact of Prone Position on Oxygenation in Mechanically Ventilated Patients with COVID-19

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## Abstract

**Objectives:** Prone positioning is widely used in mechanically ventilated patients with COVID-19; however, the specific clinical scenario in which the individual is most poised to benefit is not fully established. In patients with COVID-19 respiratory failure requiring mechanical ventilation, how effective is prone positioning in improving oxygenation and can that response be predicted?

**Design:** This is a retrospective observational study from two tertiary care centers including consecutive patients mechanically ventilated for COVID-19 from 3/1/2020 – 7/1/2021. The primary outcome is improvement in oxygenation as measured by PaO<sub>2</sub>/FiO<sub>2</sub>. We describe oxygenation before, during and after prone episodes with a focus on identifying patient, respiratory or ventilator variables that predict prone positioning success.

**Setting:** 2 Tertiary Care Academic Hospitals

**Patients:** 125 patients mechanically ventilated for COVID-19 respiratory failure.

**Interventions:** Prone positioning

**Main Results:** One hundred twenty-five patients underwent prone positioning a total of 309 times for a median duration of 23 hours IQR (14 – 49). On average, PaO<sub>2</sub>/FiO<sub>2</sub> improved 19%: from 115 mm Hg (80 – 148) immediately before proning to 137 mm Hg (95 – 197) immediately after returning to the supine position. Prone episodes were more successful if the pre-prone PaO<sub>2</sub>/FiO<sub>2</sub> was lower and if the patient was on inhaled epoprostenol (iEpo). For individuals with severe acute respiratory distress syndrome (ARDS) (PaO<sub>2</sub>/FiO<sub>2</sub> < 100 prior to prone positioning) and on iEpo, the median improvement in PaO<sub>2</sub>/FiO<sub>2</sub> was 27% in both instances.

**Conclusions:** Prone positioning in mechanically ventilated patients with COVID-19 is generally associated with sustained improvements in oxygenation, which is made more likely by the concomitant use of iEpo and is more impactful in those who are more severely hypoxemic prior to prone positioning.

## Keywords

prone positioning, ARDS, COVID-19, oxygenation, mechanical ventilation, paO<sub>2</sub>/fiO<sub>2</sub>

## Background

The COVID-19 pandemic has been marked by countless cases of respiratory failure that have inundated intensive care units (ICUs) worldwide.<sup>1</sup> The severe pneumonia that results from COVID-19 infection requires mechanical ventilation in 10 – 20% of those hospitalized.<sup>2,3</sup> It is apparent that respiratory failure due to COVID-19 is unique in several ways, among them: improved outcomes with immunosuppression,<sup>4-6</sup> increased venous thromboembolism frequency,<sup>7,8</sup> and a protracted course.<sup>9</sup> Additionally, there appears to be a continuum of respiratory physiology, marked by differing lung compliance and imaging findings at various times in the disease course.<sup>10,11</sup> Professional societies recommend managing COVID-19<sup>12,13</sup> similarly to traditional ARDS,<sup>14</sup> including: lung protective ventilation,<sup>15</sup> conservative fluid management,<sup>16</sup> neuromuscular blockade in select cases<sup>17</sup> along with consideration of inhaled

pulmonary vasodilators.<sup>18</sup> Likewise, prone positioning has also been recommended and used based on previously established evidence,<sup>19</sup> with one study demonstrating more frequent use of prone positioning in COVID-ARDS versus non-COVID-ARDS.<sup>20</sup> However, the efficacy of prone positioning in respiratory failure due to COVID-19 remains under active investigation.<sup>21,22</sup>

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In 2013, a landmark study demonstrated that early, repeated, and extensive (~16 hours/day) prone positioning in patients with moderate to severe ARDS results in improved oxygenation, fewer days spent mechanically ventilated, and substantially improved mortality.<sup>19</sup> The practical benefits of prone positioning are numerous: it's not a drug, there is no specific adverse effect or expense, and the timing and frequency are flexible. However, it is resource intensive and time consuming, which is particularly salient in overwhelmed ICUs. Despite that, the use of prone positioning has been widespread during the pandemic<sup>20</sup> – including, notably, an expansion of the practice to non-intubated patients.<sup>23,24</sup> In fact, hospital systems have established teams dedicated to navigating the logistical hurdles of proning patients on multiple organ support therapies.<sup>25</sup>

There are several reports of improved PaO<sub>2</sub>/FiO<sub>2</sub> in COVID-19 respiratory failure immediately after assuming the prone position<sup>21,26,27</sup>, and sustained PaO<sub>2</sub>/FiO<sub>2</sub> improvement with multiple episodes of prone positioning.<sup>22,28</sup> Also, it has been shown that lung recruitment improves with prone positioning in COVID-19, similar to classic ARDS.<sup>26,27,29</sup> However, currently available studies present conflicting data on the value of prone positioning's oxygenation benefit, such that there isn't a clear conclusion about the utility of prone positioning in COVID-19, including the efficacy of prolonged and/or multiple episodes, and who specifically stands to benefit.<sup>10,21</sup>

Anecdotally, our experience is that some patients have marked prone responsiveness (as measured by improved oxygenation) while others do not. Therefore, we seek to describe the physiologic changes (in terms of oxygenation and lung compliance) associated with prone positioning of mechanically ventilated patients with COVID-19. We additionally attempt to determine if there are patient-level variables that predict if an individual will be a “prone responder,” given the importance of efficient resource utilization during the pandemic.

## Methods

This is a retrospective study involving two tertiary care centers in a single health system in Washington, DC: Medstar Georgetown University Hospital and Medstar Washington Hospital Center. All consecutive patients from 3/1/2020 to 7/1/2021 were included if diagnosed with SARS-CoV2, were mechanically ventilated for hypoxemic respiratory failure, and underwent prone positioning. The hospitals share a set of guidelines regarding the general management of patients with COVID-19; however, prone positioning was performed at the treating clinician's discretion. All instances of prone positioning for a particular individual during the hospitalization were included. Patients on extracorporeal membrane oxygenation (ECMO) were excluded.

The primary outcome is the change in oxygenation, as measured by PaO<sub>2</sub>/FiO<sub>2</sub>. We calculated PaO<sub>2</sub>/FiO<sub>2</sub> using the arterial blood gas (ABG) at four separate time points: immediately before and after prone positioning and immediately before and after returning to the supine position, using the ABG closest in proximity to that time. We defined an individual as a “prone responder” if the PaO<sub>2</sub>/FiO<sub>2</sub> improved 10% while prone, and a “sustained responder” if the PaO<sub>2</sub>/FiO<sub>2</sub> improved 10% after returning to the supine position (with reference to the pre-prone value). We felt a 10% improvement was clinically meaningful, and it is a definition that has been used previously.<sup>18,30</sup>

To determine if there were features predictive of responding to the prone position, we recorded patient demographics, severity of illness as measured by the sequential organ failure support (SOFA) score<sup>31</sup>, ventilator parameters (FiO<sub>2</sub>, positive end expiratory pressure [PEEP], tidal volume [Vt], respiratory rate [RR], plateau pressure, driving pressure [plateau pressure – PEEP], static compliance [Vt / driving pressure]), fluid balance, the use of specific therapeutics (iEpo, steroids, neuromuscular blockade, therapeutic anticoagulation), and laboratory data (C-reactive protein, D-dimer, ESR). Neuromuscular blockade was defined as a continuous infusion of cisatracurium or having received vecuronium within 2 hours of prone positioning. Steroid use was defined as the administration of at least 30 mg of methylprednisolone (or equivalent) within 24 hours of prone positioning. Anticoagulation refers to therapeutic dosing of heparin or enoxaparin. Laboratory data values used were most proximate to proning.

Data were obtained directly from the health system's clinical data warehouse and supplemented with direct review of patient records when needed. Summary statistics describe the frequency of each categorical variable and either mean (for normally distributed) or median (for non-normally distributed) of continuous variables. For the purposes of predictive modelling, we considered the prone event (rather than patient) to be the level of interest in regression modelling using a change in PaO<sub>2</sub>/FiO<sub>2</sub> as the outcome variable. Candidate predictor variables had statistically significant univariate associations or were of particular clinical interest; the models were developed in a stepwise fashion with a stopping rule based on minimum

**Table 1.** Patient Characteristics

	Total (n = 125)
<b>Age</b> , mean (SD)	57 ± 13
<b>Male</b> , n (%)	81 (65)
<b>BMI</b> , median (IQR)	31 (28 – 38)
<b>Morbidly obese (BMI &gt;40)</b> , n (%)	24 (19)
<b>Race</b> , n (%)	
African American	65 (52)
White	13 (10)
Other	41 (33)
Unknown	4 (3)
<b>Comorbidities</b> , n (%)	
Hypertension	47 (38)
Diabetes Mellitus	39 (31)
CKD	12 (10)
COPD	25 (20)
CAD	13 (10)
Cancer	12 (10)
Cirrhosis	7 (6)
Organ Transplant	6 (5)
AIDS	4 (3)

Bayesian Information Criterion (BIC). Data extraction and processing were performed in R, and statistical analysis in JMP 16 Pro (Cary, NJ). This project was approved by the Institutional Review Board (IRB) of Georgetown University.

## Results

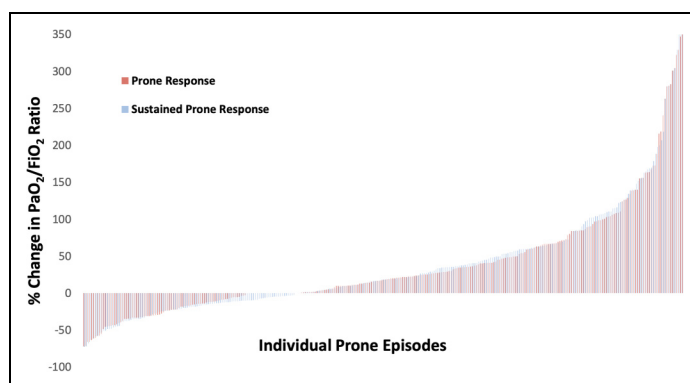
### Patients

During the study period, we identified 125 mechanically ventilated patients with COVID-19 who underwent prone positioning. The mean age was  $57 \pm 13$ , 65% were male, 52% Black, and hypertension, diabetes mellitus and chronic obstructive pulmonary disorder (COPD) were the most represented comorbidities (38%, 31% and 20%, respectively) (Table 1). The timing of the first prone event was variable in reference to the initiation of mechanical ventilation: a median of 16 hours afterwards (interquartile range 6 – 49). The median time spent mechanically ventilated was 14 days (9 – 22), 19 (15%) ultimately received a tracheostomy and 75 (60%) died while hospitalized.

The ventilator mode for most patients while undergoing prone positioning was assist control with volume cycling (AC/VC) (88%), with the remainder being on airway pressure release ventilation (APRV) (9%), or pressure control ventilation (PCV) (3%). At the time of proning, the median  $\text{FiO}_2$  was 70 (60 – 100) and PEEP was 12 cm  $\text{H}_2\text{O}$  (10 – 14) (Table 2).

### Proning

There were 309 prone sessions among the 125 patients, for a median of 2 per patient (IQR [1 – 3], range [1 – 10]) lasting a median duration of 23 hours (14 – 49). For those who underwent prone positioning on multiple occasions, there was a median of 12 hours (5 – 24) between episodes.  $\text{PaO}_2/\text{FiO}_2$  was calculated from the arterial blood gases (ABG) most proximal to the four following time points: before and after proning (T1 and T2) and before and after re-supination (T3 and T4)



**Figure 1.** Graphical representation of the percent change in  $\text{PaO}_2/\text{FiO}_2$  for each prone episode's response (change prior to end of prone episode) and sustained response (change after resuming supine position). The median percent change (IQR) for the prone and sustained prone response was 18% (-6 - 61) and 19% (-11 - 62), respectively.

(Table 2). The median time between ABG measurement and patient position change was 4.4 hours (2.1 – 10.7).

We considered “prone response” as a change in  $\text{PaO}_2/\text{FiO}_2$  from T1 to T3 (that is,  $\text{PaO}_2/\text{FiO}_2$  measurements before and at the end of prone positioning), and “sustained response” as a change in  $\text{PaO}_2/\text{FiO}_2$  from T1 to T4. Using a binary definition of prone or sustained responsiveness as a 10% increase in  $\text{PaO}_2/\text{FiO}_2$ <sup>18</sup>, there were 176 prone responders (57%) and 173 sustained responders (56%) (Figure 1, Table 3). On average, the sustained response was an improvement in  $\text{PaO}_2/\text{FiO}_2$  of 19%: from 115 mm Hg (80 – 148) to 137 mm Hg (95 – 197) (Table 2).

Those that were prone responders were in prone position longer (24 v. 17 hr,  $p < 0.01$ ), had a lower initial  $\text{PaO}_2/\text{FiO}_2$  (105 v. 128,  $p < 0.01$ ) and  $\text{PCO}_2$  (46 v. 49 mm Hg,  $p = 0.01$ ), and were more likely to be on inhaled epoprostenol (iEpo) (35 v. 23%,  $p = 0.02$ ) (Table 3). These relationships were true for sustained responders as well, aside from initial  $\text{PCO}_2$

**Table 2.** Ventilator and Respiratory Parameters during Proning

N = 309	T1	T2	T3	T4
<b>Prone Episode Duration, h</b>	23 (14 – 49)			
<b>I/O from Intubation, mL</b>	1600 (200 – 5000)		2500 (200 – 6500)	
<b>I/O from Admission, mL</b>	1800 (-500 – 6000)		2800 (-300 – 7500)	
<b>PEEP, cm <math>\text{H}_2\text{O}</math></b>	12 (10 – 14)	12 (10 – 14)	12 (10 – 14)	12 (10 – 14)
<b><math>\text{FiO}_2</math></b>	70 (60 – 100)	70 (60 – 100)	60 (50 – 80)	60 (50 – 80)
<b>Tidal Volume, mL</b>	420 (360 – 460)	400 (360 – 450)	400 (360 – 460)	400 (360 – 460)
<b>Respiratory Rate</b>	24 (20 – 28)	24 (20 – 28)	25 (20 – 30)	25 (20 – 30)
<b>Plateau Pressure, cm <math>\text{H}_2\text{O}</math></b>	28 (25 – 30)	28 (25 – 30)	27 (25 – 29)	28 (25 – 30)
<b>Static Compliance, mL/cm <math>\text{H}_2\text{O}</math></b>	26 (22 – 33)	27 (22 – 32)	29 (23 – 33)	26 (21 – 32)
<b>Driving Pressure, cm <math>\text{H}_2\text{O}</math></b>	15 (13 – 19)	15 (12 – 18)	15 (12 – 18)	15 (13 – 19)
<b>pH</b>	7.34 (7.29 – 7.4)	7.35 (7.29 – 7.4)	7.35 (7.29 – 7.4)	7.35 (7.28 – 7.4)
<b><math>\text{PaO}_2</math>, mm Hg</b>	78 (67 – 101)	79 (67 – 101)	83 (70 – 07)	83 (71 – 107)
<b><math>\text{PaCO}_2</math>, mm Hg</b>	47 (41 – 54)	47 (42 – 55)	48 (43 – 55)	48 (42 – 55)
<b><math>\text{PaO}_2/\text{FiO}_2</math>, mm Hg</b>	115 (80 – 148)	114 (86 – 156)	140 (93 – 205)	137 (95 – 197)

\*T1: Supine prior to prone; T2: start of prone; T3: end of prone; T4: after return to supine

**Table 3.** Characteristics of Prone Sessions Based on Responsiveness

N = 309	Initial Prone Responder (n = 176)	Prone Non-responder (n = 133)	P-value	Sustained Responder (n = 173)	Sustained Non-Responder (n = 136)	P-value
<b>SOFA score*</b>	12 (10 – 14)	12 (9 – 14)	0.74	12 (10–14)	12 (9–14)	0.13
<b>Fluid balance / day, mL**</b>	1400 (100 – 5100)	2100 (200 – 4800)	0.42	1400 (200 – 4800)	2400 (300 – 5100)	0.14
<b>Prone Duration, hr</b>	24 (16 – 54)	17 (8 – 32)	<b>&lt;0.01</b>	24 (16 – 60)	18 (12 – 40)	<b>&lt;0.01</b>
<b>Ventilator Days</b>	17 (10 – 22)	18 (11 – 25)	0.57	17 (11 – 22)	18 (9 – 22)	0.75
<b>Respiratory parameters</b>						
	80 (60 – 100)	70 (70 – 100)	<b>0.02</b>	80 (60 – 100)	70 (60 – 90)	<b>&lt;0.01</b>
<b>FiO<sub>2</sub></b>	105 (76 – 139)	128 (92 – 177)	<b>&lt;0.01</b>	100 (72 – 135)	132 (96 – 191)	<b>&lt;0.01</b>
<b>PaO<sub>2</sub> / FiO<sub>2</sub>, mm Hg</b>	185 (121 – 267)	109 (93 – 161)	<b>0.01</b>	166 (120 – 230)	108 (78 – 146)	0.12
Before proning	46 (41 – 53)	49 (43 – 57)		46 (41 – 53)	48 (43 – 55)	
<b>After return to supine</b>						
<b>PaCO<sub>2</sub></b>						
<b>Ventilator parameters</b>						
<b>PEEP, cm H<sub>2</sub>O</b>	12 (10 – 14)	12 (10 – 14)	0.66	12 (10 – 14)	12 (10 – 14)	0.41
<b>Tidal Volume, mL</b>	420 (370 – 460)	40 (360 – 460)	0.67	400 (360 – 460)	420 (360 – 460)	0.94
<b>Respiratory Rate</b>	24 (20 – 28)	24 (20 – 28)	0.63	24 (20 – 28)	24 (20 – 28)	0.91
<b>Plateau Pressure, cm H<sub>2</sub>O</b>	28 (25 – 30)	28 (26 – 30)	0.96	29 (26 – 31)	27 (25 – 30)	0.08
<b>Driving Pressure, cm H<sub>2</sub>O</b>	15 (13 – 19)	16 (12 – 18)	0.45	16 (13 – 19)	15 (12 – 18)	0.32
<b>Static Compliance, mL/cm H<sub>2</sub>O</b>	27 (22 – 35)	25 (21 – 30)	0.18	27 (21 – 32)	26 (22 – 33)	0.89
<b>Therapeutics, n (%)</b>						
<b>Neuromuscular Blockade</b>	94 (53)	74 (56)	0.69	96 (55)	72 (53)	0.65
<b>Anticoagulation</b>	32 (18)	28 (21)	0.53	29 (17)	31 (22)	0.25
<b>Steroids</b>	97 (55)	74 (56)	0.93	97 (56)	74 (54)	0.77
<b>Inhaled Epoprostenol</b>	62 (35)	31 (23)	<b>0.02</b>	65 (38)	28 (21)	<b>&lt;0.01</b>
<b>Laboratory Data</b>						
<b>C-reactive protein, mg/L</b>	163 (88 – 191)	140 (94 – 191)	0.62	165 (93 – 191)	138 (189 – 191)	0.25
<b>D-dimer, mg/L</b>	3.7 (2.4 – 10.1)	3.7 (2.6 – 8.8)	0.67	3.8 (2.3 – 10.6)	3.7 (2.3 – 8.6)	0.96
<b>ESR mm/hr</b>	86 (60 – 86)	86 (72 – 86)	0.32	86 (61 – 86)	86 (71 – 86)	0.21

All continuous variables are presented as medians with interquartile ranges.

Bolded P-values are statistically significant.

\*Sequential Organ Failure Assessment (SOFA) score on day of Proning

\*\*Fluid balance since initiation of mechanical ventilation

(Table 3). We did not find initial ventilator parameters or laboratory data to be associated with proning responsiveness (Table 3). Additionally, there were no observed changes in plateau pressure, static compliance and driving pressure while prone or afterwards (Table 2). There was no difference in total ventilator days between groups (Table 3).

### Predicting Responsiveness

To explore independent predictors of proning success, we made a logistic regression model using 10% improvement in PaO<sub>2</sub>/FiO<sub>2</sub> as the outcome, and a linear one treating PaO<sub>2</sub>/FiO<sub>2</sub> as a continuous outcome. In both cases we focused on “sustained responders” – that is, a comparison of change in PaO<sub>2</sub>/FiO<sub>2</sub> immediately before proning (T1) to after returning to the supine position (T4). We included variables with statistically significant univariate associations along with time between measurements, PEEP, the use of neuromuscular blockade as

additional covariates given the direct relevancy to oxygenation and improvement in PaO<sub>2</sub>/FiO<sub>2</sub> over time. In the logistic model, lower PaO<sub>2</sub>/FiO<sub>2</sub> before proning (adjusted OR 1.15 [95% CI 1.1 – 1.2] p < 0.01 for each 10 mm Hg decrement) and use of iEpo (adjusted OR 1.9 [1.3 – 3.3] p = 0.03) remained the only independent predictors of improved oxygenation. This was true in the linear model as well: PaO<sub>2</sub>/FiO<sub>2</sub> (coefficient 3.4 [2.2 – 4.9] p < 0.01) and iEpo (coefficient 14.3 [7.1 – 19.2] p = 0.01). After multivariate adjustment, prone duration (p = 0.21 when added to the logistic model, p = 0.25 in linear model) was no longer an independent predictor of PaO<sub>2</sub>/FiO<sub>2</sub> improvement.

There were 82 patients with more than one prone episode (including 13 patients with more than 5 episodes, and 2 patients with 10). In these cases, the initial responsiveness, or lack thereof, to prone positioning did not predict a subsequent response to proning. For those whose initial prone episode was successful, subsequent episodes were successful 50% of the time versus 52% of the time for those whose initial episode was unsuccessful.

Given the association of lower  $\text{PaO}_2/\text{FiO}_2$  with prone success, we examined cases of severe ARDS ( $\text{PaO}_2/\text{FiO}_2 < 100$  mmHg at T1). There were 125 such prone episodes (40% of our total sample) of which 65% and 69% had a prone and sustained response (median improvement in  $\text{PaO}_2/\text{FiO}_2$  of 27% and 41%, respectively), compared to 57% and 56% response rate in the total sample (18% and 19% improvement in  $\text{PaO}_2/\text{FiO}_2$ , respectively).

## Discussion

COVID-19 is a novel disease with distinct physiology that, provided a lack of high-quality information, clinicians are managing with interventions proven efficacious for “traditional” ARDS – including prone positioning.<sup>1,12,13</sup> This maneuver improves ventilation-perfusion matching<sup>32</sup>, lowers risk of ventilatory-induced lung injury (VILI)<sup>33</sup>, and improves survival.<sup>19</sup> Extrapolating its use to COVID-associated pneumonia is reasonable: there is often refractory hypoxemia, poor lung compliance, and electrical impedance tomography shows an improvement in ventral dead space and shunt while in the prone position.<sup>21</sup> However, the specific role of prone positioning in COVID-associated respiratory failure is not fully established – in particular, identifying individuals who most stand to benefit.

Over a 15-month period across two tertiary care hospitals in an area heavily afflicted by the pandemic, we identified 125 patients mechanically ventilated for COVID-19 who were placed in the prone position a total of 309 times. In 56% of the cases there was at least a 10% increase in  $\text{PaO}_2/\text{FiO}_2$  after returning to supine position. The mean  $\text{PaO}_2/\text{FiO}_2$  improvement of 19% is more modest than what has been previously described<sup>26–28</sup>; however, similar to prior looks at prone positioning in COVID-19<sup>12–28</sup>, we observed a continued oxygenation benefit after returning to the supine position in the vast majority of those who responded.<sup>22,28</sup> Additionally, there was not an improvement in static lung compliance after prone positioning, which has been observed with prone positioning in COVID-19 elsewhere.<sup>34</sup> After multivariate adjustment, prone success was associated with a lower pre-prone  $\text{PaO}_2/\text{FiO}_2$  (105 mmHg v. 128 mmHg) and receiving iEpo (35% v. 23%).

The mechanistic underpinnings of these findings are not completely clear. Though they may be artifactual due to multiple comparisons, the fact that they remained independent predictors of prone positioning success after adjustment lends credence to the observations. Low  $\text{PaO}_2/\text{FiO}_2$  ratios represent ventilation-perfusion decoupling and greater shunt fraction, which is associated with increased dorsal lung density in the supine position, manifested as dense bilateral infiltrates on imaging.<sup>35</sup> This offers physiologic plausibility of prone positioning’s efficacy in COVID-19, as the positional change in traditional ARDS decreases dorsal lung density, thus providing more even ventilation distribution.<sup>15,21,35</sup> Regarding iEpo, we speculate that improved ventilation in the prone position may lead to better drug distribution. It has been previously described that iEpo itself was more likely to be efficacious in mechanically ventilated patients with COVID-19 who were pronated.<sup>18</sup> Though the average treatment

effect of iEpo is modest<sup>36</sup>, there is wide variability in the individual treatment effect including those who experience marked improvements in  $\text{PaO}_2/\text{FiO}_2$ .<sup>18,37,38</sup> The literature on biomarkers predicting iEpo responsiveness is sparse and inconsistent.<sup>18,38,39</sup> As far as we are aware, augmenting the beneficial physiologic impact of prone positioning with the use of inhaled pulmonary vasodilators has not been previously described.

In contrast to other studies, we focused our analysis on discrete episodes of prone positioning rather than upfront patient features. We did this to generate information that is practical for clinical decision making. Since respiratory failure due to COVID19 is protracted, patient features change over time (eg, oxygenation, ventilator parameters and the use of therapeutics).<sup>40,41</sup> Therefore, prone positioning success is more likely related to clinical variables at the time of prone positioning, rather than on admission to the ICU, initiation of mechanical ventilation, or during a patient’s prior prone instance. Moreover, we recorded the effect of multiple sequential prone episodes along with prone duration in combination with other therapeutic interventions. While prone duration had a favorable univariate association with prone responsiveness, it did not after multivariate adjustment, and should be considered in light of the natural disease course of respiratory failure which is to gradually improve over time, regardless of interventions, in most individuals.

There are several limitations to this study. This is a retrospective observational analysis; therefore, the use of prone positioning was not protocolized. However, it encompasses two tertiary centers over the duration of the pandemic and is one of the largest individual descriptions of proning<sup>19,21,22,41</sup> in mechanically ventilated patients. We do not have a matched cohort that did not receive prone positioning.<sup>34,40,41</sup> We considered this; however, our institutions have a high rate of prone positioning use (50% of mechanically ventilated patients), reserved for the most hypoxemic individuals, limiting accurate identification of “control” patients with sufficiently matched physiologic variables. The 23 hour (IQR 14–49) median prone duration is longer in comparison to prior publications.<sup>21,23,26,27,41,42</sup> This reflects an intentional clinical decision, as in many instances we elected to allow patients to remain in the prone position for extended periods of time if they were improving (with care to prevent anterior soft tissue injury). Lastly, there was a relatively low rate of steroid use; this is because our sample included individuals managed before the results of the RECOVERY trial were available.<sup>43</sup>

## Conclusions

In mechanically ventilated patients with COVID-19, prone positioning was associated with a sustained increase in  $\text{PaO}_2/\text{FiO}_2$  of 19%. Individuals with a lower  $\text{PaO}_2/\text{FiO}_2$  and on inhaled epoprostenol respond more favorably. Notably, lack of benefit with a first prone attempt does not indicate subsequent attempts would not be successful. Further study is needed to determine whether the long-term outcomes of prone positioning in COVID-19 are as beneficial as in traditional ARDS.

## Abbreviations

ABG	arterial blood gas
AC/VC	assist control with volume cycling
APRV	airway pressure release ventilation
ARDS	acute respiratory distress syndrome
COPD	chronic obstructive pulmonary disorder
ECMO	extracorporeal membrane oxygenation
ESR	erythrocyte sedimentation rate
ICU	intensive care unit
IQR	interquartile range
iEpo	inhaled epoprostenol
PCV	pressure control ventilation
PEEP	positive end expiratory pressure
RR	respiratory rate
SOFA	sequential organ failure support
VILI	ventilator induced lung injury
Vt	tidal volume

## Author Contributions

RS, JB, and NC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CWP, CK, JB contributed substantially to data acquisition and analysis. JB and RS contributed significantly to study design, data analysis and interpretation, and writing the manuscript. The authors have no financial disclosures.

## Declaration of Conflicting Interests

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## Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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