EDITORIAL

Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19?

Irene Telias, MD; Bhushan H. Katira, MD; Laurent Brochard, MD

A substantial proportion of patients with coronavirus disease 19 (COVID-19) develop severe respiratory failure and require mechanical ventilation, most often fulfilling criteria for acute respiratory distress syndrome (ARDS).[1] The characteristics of these patients are heterogeneous, consistent with what is known about ARDS.[1,2] Inflammatory edema leads to varying degrees of lung collapse resulting in ventilation perfusion ratio ($\dot{V}/\dot{Q}$) mismatching, including a significant shunt fraction. Additionally, lung microthrombi are suspected and result in different levels of dead space and inefficient ventilation.[3] In sedated patients, gravitational forces lead to lung atelectasis occurs in the dependent lung regions, and the remaining aerated lung available for gas exchange becomes small. Insufficient hypoxic vasoconstriction, another feature of ARDS that contributes to $\dot{V}/\dot{Q}$ mismatch, is suggested by the finding of hypoxemia with relatively preserved compliance in some patients.[4]

Related articles

Vigorous breathing efforts among patients with moderate and severe ARDS during spontaneous or assisted invasive or noninvasive ventilation (NIV) can worsen lung injury and result in patient self-inflicted lung injury (P-SILI).[5] Strong respiratory efforts lead to large negative swings in pleural pressure generating excessive lung stress and strain and to increased lung edema due to negative transalveolar pressure. Because of atelectasis in the dependent regions, the force generated by diaphragmatic contractions remains predominantly localized in regions close to the muscular portion of the diaphragm and generates a pressure gradient inside the lung, with displacement of gas from nondependent to dependent areas. This phenomenon, called *pendelluft*, increases regional lung stress and strain even in the absence of large tidal volumes.[6]

Strong breathing efforts are controlled by the output of the respiratory centers, the respiratory drive, primarily regulated by the chemoreflex control system.[7] The combination of a high metabolic rate (eg, sepsis, fever) and inefficient ventilation increases respiratory drive. Additionally, lung injury, through J receptors in the lung, and systemic or brainstem inflammation stimulate the respiratory drive. A dissociation between what the brain expects and what the ventilatory system can achieve results in dyspnea that further stimulates the respiratory drive. Excessive drive can then overcome lung-protective reflexes, such as Hering-Breuer inflation reflex, and worsen lung injury.

In the context of worsening oxygenation and increased work of breathing, invasive mechanical ventilation with sedation, paralysis, and positive end-expiratory pressure to control breathing effort ensures lung protective ventilation (ie, low tidal volume) minimizing P-SILI.[5] However, potential adverse consequences are well known including immobilization, disuse diaphragmatic atrophy, associated infections, sleep disturbances, and possibly neurocognitive dysfunction. Helmet NIV and high-flow nasal cannula–delivered oxygen were suggested to be clinically more effective than NIV delivered via facemask and regular oxygen in early hypoxemic respiratory failure.[8] However, monitoring tidal volume and breathing effort in these patients is challenging with the potential risk of direct harm and delayed intubation, as shown during NIV. During the COVID-19 pandemic, high burden of intensive care unit workload and concern for possible ventilator shortage further prompted clinicians to pursue alternative strategies to avoid intubation.

In this issue of *JAMA*, 2 small case series describe the use of the prone position in awake patients with COVID-19 during spontaneous and assisted breathing outside the ICU. The studies have limitations but illustrate interesting points. Elharrar et al[9] reported a single-center before-after study that included 24 patients with acute hypoxemic respiratory failure and infiltrates on chest computed tomographic scans. Prone positioning was started without changing the system for oxygen supply or fraction of inspired oxygen (F_{IO_2}). Four patients did not tolerate the prone position for more than an hour (requiring later intubation); 6 of 15 patients who tolerated prone position showed a mean (SD) increase in Pa_{O_2} of more than 20% from baseline (74 [16] to 95 [28] mm Hg; P = .006) but 3 patients returned to baseline Pa_{O_2} after supination.

Sartini et al[10] performed a 1-day cross-sectional before-after study that included 15 awake patients with mild and moderate ARDS. The estimated mean (SD) Pa_{O_2}:F_{IO_2} was 157 (43). Patients received NIV with sessions of prone positioning after poor response to continuous positive airway pressure (CPAP) of 10 cm H_2O. On the day of the study, the patients had a median of 2 sessions (interquartile range [IQR], 1-3) of prone positioning for 3 hours (IQR, 1-6 hours). Compared with before receiving NIV, oxygenation and respiratory rate improved during NIV while prone (estimated Pa_{O_2}:FiO_2, 100 [IQR, 60-112] to 122 [IQR, 118-122] and respiratory rate 28 breaths/min [IQR, 27-30] to 24 [21-25] breaths/min), and remained improved 1 hour after NIV session in prone position in most patients (12 of 15). At 14 days, 1 patient was intubated and another died.

Several conclusions can be drawn cautiously from these case series, although the findings cannot be generalized

without confirmation in larger trials. Many but not all patients with hypoxemic respiratory failure tolerate the prone position while awake, breathing spontaneously or while receiving NIV. Among patients who tolerated a session of prone positioning, improvement in oxygenation and decrease in respiratory rate occurred, suggesting a lower power of breathing (respiratory rate is poorly correlated with respiratory drive but in this context, it is potentially associated with lower power). The effects were transient, and respiratory rates and oxygenation often returned to baseline after supination.

Limitations have been listed by the authors, including the small sample size and lack of control groups. Overall, prone sessions during the studies were short, partly because of limited patient tolerance. Important information for interpretation of the results was missing such as baseline severity of hypoxemia[9] and which NIV interface and settings were used during the prone sessions.[10] It is also unclear if the physiological changes while prone were due to the position, the use of NIV, or a synergistic effect of both. The inclusion of patients who initially worsened after a trial of CPAP may suggest that the prone position improved tolerance of NIV.

The prone position can improve oxygenation and can potentially result in less injurious ventilation. Because of a higher density of pulmonary vessels in the dorsal lung region (independently of gravity), the change of ventilation distribution while prone (ie, relative increase in ventilation in the dorsal nondependent areas) results in improved $\dot{V}/\dot{Q}$ matching and oxygenation.[11] This does not necessarily equate to lung protection and better outcome.[12] While prone, the chest wall compliance decreases when the anterior, more flexible part of the chest is facing the bed, explaining in part a more homogeneous distribution of ventilation and regional lung stress and decreasing the risk of ventilation-induced lung injury and possibly pendelluft.[13] It is possible that the contraction of the muscular diaphragm, which faces the open dorsal lung during pronation exerts a more uniform distribution of stress, whereas the muscular diaphragm exerts a more localized stress when facing the collapsed lung during supination. These mechanisms and the effect of prone positioning on respiratory drive and effort need to be investigated in spontaneously breathing patients. In a crossover study involving 14 infants with bronchiolitis, the prone position with nasal CPAP reduced effort and improved neuromechanical coupling.[14]

Prone position during invasive mechanical ventilation improved oxygenation in large randomized clinical trials (RCTs) of patients with ARDS.[15] However, better oxygenation was not associated with improved survival in trials with short duration of prone positioning. In an RCT that included 466 patients with moderate and severe ARDS (Pao_2:FIO_2 <150), prone positioning for at least 16 hours per day with protective mechanical ventilation reduced 90-day mortality.[16] Previously, small case series showed feasibility and improvement in oxygenation in awake patientsplaced in the prone position during spontaneous or assisted breathing while receiving NIV and oxygen through high-flow nasal cannula.

The prone position during spontaneous and assisted breathing in patients with acute hypoxemic respiratory failure may become a therapeutic intervention in the near future. Tolerance is sometimes a limitation of the technique, the physiological effects are not clarified, and the benefits of very short sessions may be questionable. Can the prone position prevent intubation? This question is essential, but intubation is a medical decision, not a physiological state. Improvement in oxygenation during prone positioning may prevent clinicians from making decisions about intubation solely based on hypoxemia. This is potentially a good outcome, but clinical assessment of work of breathing is essential in this context to avoid delayed intubation with eventually poor outcome. A detailed physiological study is ongoing (NCT03095300) and at least 2 RCTs (NCT04347941, NCT04350723) will address some of these questions. In the meantime, clinicians should closely monitor patients for whom prone positioning is used for tolerance and response and aim to prevent delayed intubation and controlled mechanical ventilation when necessary.

ARTICLE INFORMATION

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Letters

RESEARCH LETTER

Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit

The pandemic of coronavirus disease 2019 (COVID-19), with a large number of patients requiring respiratory support, threatens to overload intensive care units (ICUs). Noninvasive ventilation (NIV) use in general wards may be an alternative for some patients but has seldom been described and is not used worldwide.[1] One study described the feasibility of NIV in the prone position[2]; pronation can recruit dorsal lung regions and drain airway secretions, improving gas exchange and survival in acute respiratory distress syndrome (ARDS).[3] We report respiratory parameters after using this intervention in a case series of patients with COVID-19.

Editorial

Related articles

Methods | On April 2, 2020, in San Raffaele Scientific Institute, Milan, Italy, COVID-19 patients with ARDS were treated either in the ICUs (n = 48) or medical wards (n = 202). Noninvasive ventilation was used for 62 patients with mild to moderate ARDS who had saturation less than 94% on face mask with high-oxygen concentration, applying 10 cm H_2O continuous positive airway pressure and 0.6 fraction of inspired oxygen (FIO_2). In case of poor response to NIV, the intensive care surgeon suggested a trial of NIV in the prone position, which was continued if there was improvement in the first hour of treatment. Noninvasive ventilation cycles were individualized based on a patient's severity of illness, adherence to the treatment, and dyspnea in the periods without NIV.

On April 2, 2020, we performed a cross-sectional survey to identify all patients undergoing the prone position NIV outside the ICU, irrespective of the day they started using this technique. Respiratory parameters were measured at 3 time points: before NIV, during NIV in pronation (60 minutes after start), and 60 minutes after NIV end. We investigated oxygen saturation as measured by pulse oximetry (SpO_2), derived PaO_2:FIO_2,[4] respiratory rate, and patient's comfort using a numerical rating scale (0, totally uncomfortable, to 10, fully comfortable). Follow-up was conducted at 14 days to determine how many patients were discharged, were still treated in the prone position, or were intubated. Continuous measures were compared using Wilcoxon matched pairs signed rank test or *t* test if paired data were normally distributed. Two-sided $P < .05$ defined statistical significance. All analyses were performed with STATA version 16 (STATA Corp). The study was approved by the Ethics Committee of IRCCS San Raffaele Scientific Institute. Written informed consent was obtained.

Table. Baseline Characteristics of 15 Patients With COVID-19 Who Received Noninvasive Ventilation in the Prone Position Outside the ICU

Characteristics	Value
Age, mean (SD), y	59 (6.5)
BMI, mean (SD)	24 (3.4)
Sex, No. (%)	
Women	2 (13.3)
Men	13 (86.6)
Time, median (IQR), d	
From first symptom appearance	15 (12-21)
From hospitalization	9 (7.5-14)
From NIV start	7 (4-10)
From NIV in the prone position start	5 (3-10)
PaO_2:FIO_2 on first MET call[a]	157 (43.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COVID-19, coronavirus disease 2019; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; MET, medical emergency team; NIV, noninvasive ventilation; PaO_2, arterial partial pressure of oxygen.

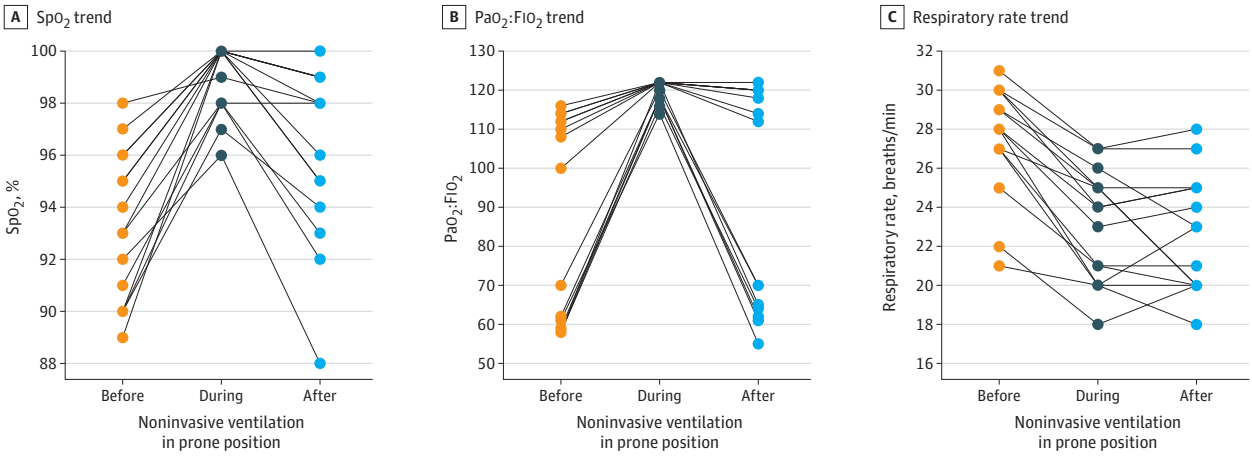
[a] The normal PaO_2:FIO_2 ratio is more than 400 mm Hg; a PaO_2:FIO_2 of less than 300 mm Hg indicates acute respiratory distress syndrome.

Results | Fifteen patients receiving NIV in the prone position outside the ICU on April 2 were identified. Mean (SD) age was 59 years (6 years); 13 were men. Noninvasive ventilation in the prone position started a median of 5 days (interquartile range [IQR], 3-10 days) before April 2 (**Table**) and no patient started NIV in the prone position on April 2. The median number of NIV cycles in the prone position on April 2 was 2 (IQR, 1-3 cycles) for a total duration of 3 hours (IQR, 1-6 hours). Compared with baseline, all patients had a reduction in respiratory rate during and after pronation ($P < .001$ for both) (**Figure**); all patients had an improvement in SpO_2 and PaO_2:FIO_2 during pronation ($P < .001$ for both); 12 patients (80%) had an improvement in SpO_2 and PaO_2:FIO_2 after pronation; 2 (13.3%) had the same value; and 1 (6.7%) had worsened. Compared with baseline, 11 patients (73.3%) had an improvement in comfort during pronation and 4 (26.7%) had the same value; 13 patients (86.7%) had an improvement in comfort after pronation and 2 (13.3%) had the same value. At the 14-day follow-up, 9 patients were discharged home, 1 improved and stopped pronation, 3 continued pronation, 1 patient was intubated and admitted to ICU, and 1 patient died.

Discussion | Providing NIV in the prone position to patients with COVID-19 and ARDS on the general wards in 1 hospital in Italy was feasible. The respiratory rate was lower and the oxygenation was higher during and after pronation than they were at baseline. Whether intubation was avoided or delayed remains to be determined.

Limitations include the small number of patients, short duration of NIV in the prone position, and lack of a control group. Comparisons of NIV in the prone position with oxygen by face

Figure. Respiratory Parameters in the Individual Patients Before, During, and After Noninvasive Ventilation in the Prone Position



The graphs represent trends of respiratory parameters in the individual patient at the 3 time points. Before pronation: immediately before initiating noninvasive ventilation (NIV) while the patient was still in the supine position. During pronation: after 1 hour of receiving NIV treatment while the patient was in the prone position. After pronation: 1 hour after NIV treatment stopped when the patient was in the supine position. A, Peripheral oxygen saturation (Spo_2), $P < .001$ between before and during pronation, $P < .004$ between before and after pronation. B, Arterial partial pressure of oxygen (Pao_2) to inspired oxygen fraction (Fio_2), $P < .001$ between before and during pronation, $P < .004$ between before and after pronation. C, Respiratory rate $P < .001$ between before and during pronation, $P < .001$ between before and after pronation.

mask or NIV in the standard position are needed. Importantly, selection bias is possible. Patients were not included if NIV failed while in the prone position or were treated and either died or recovered before April 2. Therefore, patients in the study may not be representative of all patients treated with NIV in the prone position.

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Letters

RESEARCH LETTER

Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure

Patients with coronavirus disease 2019 (COVID-19) are at risk for acute respiratory distress syndrome.[1] In intubated patients with severe acute respiratory distress syndrome, early and prolonged (at least 12 hours daily) prone positioning (PP) improves oxygenation and decreases mortality.[2,3] Because intensive care units (ICUs) are overloaded with patients with COVID-19, awake PP may be useful to improve oxygenation and prevent ICU transfers.[4] The objective of the study was to evaluate the feasibility, efficacy, and tolerance of PP in awake patients with COVID-19 hospitalized outside the ICU.

Editorial

Related articles

Methods | This prospective, single-center, before-after study was conducted among awake, nonintubated, spontaneously breathing patients with COVID-19 and hypoxemic acute respiratory failure requiring oxygen supplementation. The patients were admitted to Aix-en-Provence Hospital (France) from March 27 to April 8, 2020.

All consecutive patients with confirmed COVID-19 were screened and considered eligible if they (1) required oxygen supplementation and (2) had chest computed tomography findings suggestive of COVID-19 with posterior lesions. The main exclusion criteria were acute respiratory failure requiring intubation and impaired consciousness. The same oxygen

Table. Characteristics of Patients and Main Results

Characteristic	Total (N = 24)[a]	PP subgroups <1 h (n = 4)	1-<3 h (n = 5)	≥3 h (n = 15)
Baseline characteristics				
Age, mean (SD), y	66.1 (10.2)	63.8 (7.8)	61 (7.9)	68.4 (11.1)
Sex, No. (%)				
Women	8 (33)	2 (50)	1 (20)	5 (33)
Men	16 (67)	2 (50)	4 (80)	10 (67)
BMI >30, No. (%)	5 (23)	1 (50)	1 (20)	3 (20)
High blood pressure, No. (%)	6 (26)	1 (25)	2 (50)	3 (20)
SOFA score, mean (SD)	2.8 (0.9)	3.5 (0.7)	2.8 (0.8)	2.7 (1)
Oxygen supplementation, No. (%)				
<4 L/min	16 (67)	2 (50)	3 (60)	11 (73)
≥4 L/min or HFNC	8 (33)	2 (50)	2 (40)	4 (27)
Respiratory rate, mean (SD), breaths/min	18 (2.7)	18.3 (4)	20 (3.6)	17.3 (1.8)
Gas exchange and VAS scores before PP				
Pao_2, mean (SD), mm Hg	72.8 (14.2)	79.7 (11.7)	66.4 (8.9)	73.6 (15.9)
$Paco_2$, mean (SD), mm Hg	34.1 (5.3)	39.7 (4.6)	32.4 (3.9)	33.5 (5.4)
VAS, median (IQR)[b]				
Dyspnea	3 (2-5)	3 (1-3)	5 (3-7)	2 (1-5)
Discomfort	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)
Gas exchange and VAS scores during PP[c]				
Pao_2, mean (SD), mm Hg	91 (27.3)		73 (12.1)	94.9 (28.3)
$Paco_2$, mean (SD), mm Hg	32.8 (4.5)		32 (3)	33 (4.8)
VAS, median (IQR)[b]				
Dyspnea	2 (1-4.5)		7 (2-8)	2 (1-4)
Discomfort	4 (1-5.5)		2 (2-4)	4 (1-6)
Gas exchange and VAS scores after resupination[c]				
Pao_2, mean (SD), mm Hg	77.6 (11.5)		77 (2)	77.8 (13)
$Paco_2$, mean (SD), mm Hg	32.3 (5.1)		28.7 (5.9)	33.3 (4.7)
VAS, median (IQR)[b]				
Dyspnea	2.5 (1-5)		5 (4-7)	2 (1-4)
Discomfort	0 (0-1)		0 (0-1)	0 (0-1)

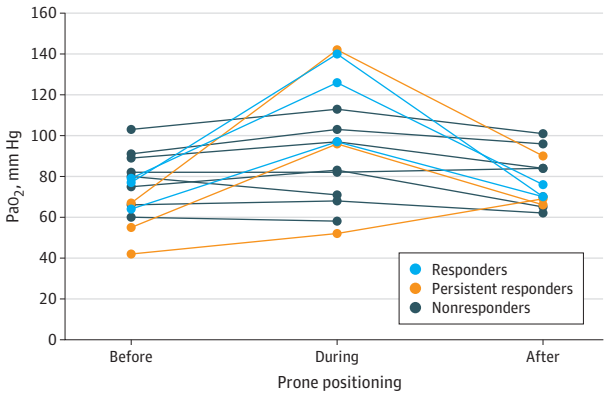
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HFNC, high-flow nasal cannula; IQR, interquartile range; $Paco_2$, partial pressure of arterial carbon dioxide; Pao_2, partial pressure of arterial oxygen; PP, prone positioning; SOFA, Sequential Organ Failure Assessment (score range, 0-24); VAS, visual analog scale.

[a] Missing data: SOFA score for 2 patients, high blood pressure profile for 1, BMI for 2, respiratory rate for 8, before-PP VAS scores for 1, arterial blood gases before PP for 2, and $Paco_2$ for 1. VAS scores were missing during PP for 5 and after resupination for 7. During PP, arterial blood gases were missing for 7 patients and after resupination for 9. The 4 patients unable to sustain PP ≥1 were excluded from evaluations after baseline.

[b] The VAS was a 10-cm line anchored with no breathlessness or discomfort at 0 cm and maximum possible breathlessness or discomfort at 10 cm; 1 cm represents minimum clinically significant difference.

[c] During PP: 1 to 2 hours after patients were placed in PP. After resupination: 6 to 12 hours after resupination.

Figure. Individual Partial Pressure of Arterial Oxygen (Pao_2) Variation for Patients Who Sustained Prone Positioning (PP) for at Least 3 Hours



During PP indicates the 1 to 2 hours after proning and after PP indicates the 6 to 12 hours after resupination. Responders to PP = Pao_2 increase ≥20% between before and during PP. Persistent responders to PP = Pao_2 increase ≥20% between before PP and after resupination. All the persistent responders are also responders. One patient among the 15 refused arterial blood gases during PP and after resupination. For 2 patients, arterial blood gases after resupination were missing.

supply (device and fraction of inspired oxygen) was maintained during the study. Arterial blood gases were performed just before PP, during PP, and 6 to 12 hours after resupination.

The main outcome was the proportion of responders (partial pressure of arterial oxygen [Pao_2] increase ≥20% between before and during PP). Secondary outcomes included Pao_2 and partial pressure of arterial carbon dioxide ($Paco_2$) variation (difference in Pao_2 or $Paco_2$ between before and during PP or after resupination), feasibility (proportion of patients sustaining PP ≥1 hour and ≥3 hours), and proportion of persistent responders (Pao_2 increase ≥20% between before PP and after resupination). Tolerance was monitored with 10-cm visual analog scales for dyspnea and discomfort, anchored with no breathlessness or discomfort at 0 cm and maximum possible breathlessness or discomfort at 10 cm. Adverse events were monitored.

Patients were followed up for 10 days until April 18, 2020. Institutional review board approval was obtained. Written informed consent from patients was required.

Variations of Pao_2 were compared using a Wilcoxon signed-rank test for patients tolerating PP for 3 hours or more with a $P < .01$ (2-sided) to adjust for test multiplicity. Analyses were conducted using Stata version 14.0 (StataCorp).

Results | A total of 88 patients with COVID-19 were admitted during the period. Sixty-three patients did not meet inclusion criteria. Among the 25 eligible, 24 agreed to participate; of those, 4 (17%) did not tolerate PP for more than 1 hour, 5 (21%) tolerated it for 1 to 3 hours, and 15 (63%) tolerated it for more than 3 hours. Characteristics of the patients and main results are displayed in the **Table**. The median time from admission to first PP was 1 day (interquartile range, 0-1.5). Neither sedation nor anxiolytics were used.

Six patients were responders to PP, representing 25% (95% CI, 12%-45%) of the 24 patients included and representing 40% (6/15) (95% CI, 20%-64%) of the patients who sustained PP for 3 hours or more. Three patients were persistent responders. Among patients who sustained PP for 3 hours or more, Pao_2 increased from a mean (SD) of 73.6 (15.9) mm Hg before PP to 94.9 (28.3) mm Hg during PP (difference, 21.3 mm Hg [95% CI, 6.3-36.3]; $P = .006$) (**Figure**). No significant difference was found between Pao_2 before PP and Pao_2 after resupination ($P = .53$). None of the included patients experienced major complications. Back pain was reported by 10 patients (42%) during PP. At the end of a 10-day follow-up period, 5 patients required invasive mechanical ventilation. Four of them did not sustain PP for 1 hour or more and required intubation within 72 hours.

Discussion | In this study of patients with COVID-19 and hypoxemic respiratory failure managed outside the ICU, 63% were able to tolerate PP for more than 3 hours. However, oxygenation increased during PP in only 25% and was not sustained in half of those after resupination. These results are consistent with findings from previous small studies of PP in nonintubated patients.[5,6] A trial of PP may be a mechanism to select patients who will do well or it may be useful in a subset.

The study had several limitations. The sample was small, a single episode of PP was evaluated, the follow-up was short, clinical outcomes were not assessed, and causality of the observed changes cannot be inferred.

Further studies to identify optimal PP regimens and patients with COVID-19 in whom it may be beneficial are warranted.

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