EDITORIAL

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

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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]

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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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