Prone Positioning for Patients With COVID-19–Induced Acute Hypoxemic Respiratory Failure: Flipping the Script

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During the COVID-19 pandemic, prone positioning (PP) emerged as a widely used supportive therapy for patients with acute hypoxemic respiratory failure caused by COVID-19 infection. In particular, awake PP (APP)—the placement of non-intubated patients in the prone position—has gained popularity and hence is detailed first herein. This review discusses recent publications on the use of PP for non-intubated and intubated subjects with COVID-19, highlighting the physiological responses, clinical outcomes, influential factors affecting treatment success, and strategies to improve adherence with APP. The use of prolonged PP and the use of PP for patients undergoing extracorporeal membrane oxygenation are also presented. *Key words: prone positioning; awake prone positioning; COVID-19; acute hypoxemic respiratory failure*. [Respir Care 2023;68(10):1449–1464.

Introduction

Prone positioning (PP), which refers to placing a patient face down, was first introduced as "extreme position changes" by Piehl and Brown[1] to improve oxygenation for 5 subjects with ARDS in 1976. Since then, PP has been studied extensively in intubated subjects with ARDS and found to improve oxygenation and reduce mortality.[2] During the COVID-19 pandemic, PP has been widely used as a supportive therapy for patients with acute hypoxemic respiratory failure (AHRF).[3,4] In particular, awake PP (APP), which involves placing non-intubated patients in PP, has become popular due to its ease of implementation and the overwhelming need for avoiding intubation.[5-7] This review will discuss relevant findings from recent publications on the use of PP and APP for patients with COVID-19.

Prone Positioning for Non-Intubated Patients (Awake Prone Positioning)

Prior to the COVID-19 pandemic, APP was reported to improve oxygenation in case series and observational studies with small sample size.[8] At the early stage of pandemic, APP was adopted as a supportive therapy for non-intubated patients with COVID-19–induced AHRF and has emerged as a promising treatment. Numerous studies have been conducted to better understand the physiological mechanisms, effects on clinical outcomes, and factors that influence treatment success of APP in subjects with COVID-19.

Physiological Responses to Awake Prone Positioning

When a patient is placed in PP, there are several physiological responses that can occur, including oxygenation, distribution of ventilation, perfusion distribution, and work of breathing (WOB), as shown in Table 1 and Figure 1.

Oxygenation. In a systematic review of studies on APP use for subjects with COVID-19 during the early stages of the pandemic, Pavlov et al[5] identified 25 publications within 9 months of the outbreak. Of these, 13 observational studies investigated the oxygenation responses to APP, and all reported improved oxygenation after APP.[5] These findings were later confirmed in clinical studies with high-level evidence.[9-14] However, it is important to note that not all subjects had oxygenation improvement after APP, with response rates varying from 50–85%,[15-18] using S_{pO_2}/F_{IO_2} or P_{aO_2}/F_{IO_2} improvement of 20% as a criterion for oxygenation response. Most subjects responded quickly to APP, typically within 30 min.[5] However, Lehingue et al[18] observed variation in oxygenation over time, and the time required to achieve maximum oxygenation improvement under APP remained ill defined. Additionally, the oxygenation response to APP varied with the respiratory support modality. In a small cohort of subjects with non–COVID-19 pneumonia, oxygenation improvement was higher with the combined use of APP and CPAP than with APP and high-flow nasal cannula (HFNC).[19] Similarly, oxygenation improvement to APP was greater with higher CPAP levels (12 cm H_2O vs 6 cm H_2O).[20] The oxygenation response to APP was found to be independent on subject baseline oxygenation level in the supine position[16] or parenchymal abnormalities in baseline computed tomography (CT) scans,[21] but a correlation between the improvement in oxygenation and the reduction in breathing frequency was reported.[18]

Ventilation distribution. In a prospective observational study, Dos Santos Rocha et al[22] used electrical impedance tomography (EIT) to assess changes in lung aeration in 13 intubated and 15 non-intubated subjects with COVID-19 during PP. They found significant improvement in dorsal ventilation after PP in subjects who received invasive ventilation. However, no significant differences in lung aeration were observed in subjects who received 8 cm H_2O CPAP during APP.[22] Liu et al[15] also reported no significant changes in dorsal ventilation after APP in their prospective study with 14 subjects who received HFNC or conventional oxygen therapy. Similarly, Brunelle et al[23] reported no significant differences of lung ventilation inhomogeneity after APP in their randomized crossover trial with 20 subjects, of whom 80% were treated by HFNC. However, in a prospective cohort with 71 subjects with COVID-19 who received HFNC during APP, Ibarra-Estrada et al[24] used lung ultrasound to assess subject responses and found that 51 subjects with treatment success had a significant improvement in dorsal ventilation after APP, whereas no significant changes were observed in the 20 subjects who were eventually intubated and considered treatment failure.

The reduction in dorsal lung ultrasound scores (LUSs) after APP was found to be an independent factor predicting APP treatment success. It is worth noting that subjects in the study by Ibarra-Estrada et al[24] were sicker, reflected by the lower S_{pO_2}/F_{IO_2} ($\sim$100 mm Hg), which may explain the discrepancies in the lung aeration findings in their study[24] and the other 3 studies.[15,22,23] Subjects might have had more collapsed lung in the dorsal zones,[24] which could have been recruited during APP, resulting in improved LUSs. This phenomenon is often observed during PP in intubated patients who typically have collapsed lung in the dorsal zones. Furthermore, the larger sample size and the use of different assessment tools (EIT vs lung ultrasound) might have been attributed to the different findings.

Perfusion variables. In the prospective study using EIT to assess subject responses to APP by Liu et al,[15] regional pulmonary perfusion was evaluated based on the thoracic impedance changes induced by a bolus of hypertonic saline solution. No significant differences in the perfusion in dorsal lung zones were observed after APP. In contrast,

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Table 1. Physiological Responses to Awake Prone Positioning in Non-Intubated Patients With COVID-19 Treated by Different Respiratory Support

Author, y	Design	Breathing Support			PP	Oxygenation				Ventilation and/or Perfusion			Work of Breathing			Breathing Frequency		
		No.	Type	Settings	Duration, h	SP	APP	*P*	Responders, %	SP	APP	*P*	SP	APP	*P*	SP	APP	*P*
Liu et al, 2022	P	14	10 HFNC, 4 NC	47 ± 5 L/min	3.00–5.80	P_{aO_2}/F_{IO_2} 189 ± 81	P_{aO_2}/F_{IO_2} 263 ± 97	< .001	64	$\dot{V}/\dot{Q}$ match 62 ± 11%	$\dot{V}/\dot{Q}$ match 78 ± 9%	< .001	NR	NR	NR	22 ± 5	23 ± 4	.30
Brunelle et al, 2023	RC	20	16 HFNC, 4 NRM	47 ± 7 L/min	2.00	P_{aO_2}/F_{IO_2} 133 ± 44	P_{aO_2}/F_{IO_2} 183 ± 66	.030	NR	GI 74 ± 20 %	GI 72 ± 20%	.85	NR	NR	NR	27 ± 6	22 ± 5	.002
Ibarra-Estrada et al, 2022	P	71	HFNC	40 (40–40) L/min	4.30	S_{pO_2}/F_{IO_2} 103 (91–121)	S_{pO_2}/F_{IO_2} 126 (111–158)	< .001	50	LUS 20 (19–24)	LUS 19 (18–22)	< .001	NR	NR	NR	20 (22–24)	18 (17–21)	< .001
Lehingue et al, 2022	RC	17	HFNC	30 (30–50) L/min	2.00	P_{aO_2}/F_{IO_2} 84 (61–137)	P_{aO_2}/F_{IO_2} 208 (114–226)	< .001	65	NR	NR	NR	WOB 225 (176–332) IE 10.6 (7.4–17.7)	WOB 174 (161–254) IE 9.7 (7.5–13.1)	.049 > .050	26 (21–30)	21 (19–22)	.002
Jacquet-Lagrèze et al, 2023	P	26	22 HFNC, 3 NC, 1 FM	50 (50–58) L/min	1.00–3.00	P_{aO_2}/F_{IO_2} 114 ± 44	N/A	> .050	NR	Cardiac index 2.5 ± 0.6	Cardiac index 3.0 ± 0.8	< .001	NR	NR	NR	NR	NR	NR
Rauseo et al, 2021	P	10	CPAP	6 cm H_2O	0.25	P_{aO_2}/F_{IO_2} 170 ± 20	P_{aO_2}/F_{IO_2} 190 ± 10	> .050	NR	NR	NR	NR	NR	NR	NR	28 ± 2	26 ± 3	NR
				12 cm H_2O	0.25	P_{aO_2}/F_{IO_2} 180 ± 20	P_{aO_2}/F_{IO_2} 220 ± 10	> .050	NR	NR	NR	NR	NR	NR	NR	18 ± 2	17 ± 2	NR
Bianchi et al, 2023	P	12	NIV	PEEP 8 (7–9), PS 8–10 cm H_2O	4.00 (2.90–4.60)	P_{aO_2}/F_{IO_2} 162 (117–227)	P_{aO_2}/F_{IO_2} 284 (226–364)	.030	83	NR	NR	NR	IE 5.8 (4.5–7.0)	IE 3.0 (2.2–5.5)	< .001	19 (16–20)	19 (15–21)	NR
Chiumello et al, 2021	P	40	CPAP	10 (8–10) cm H_2O	3.00	P_{aO_2}/F_{IO_2} 166 (136–224)	P_{aO_2}/F_{IO_2} 314 (232–398)	< .001	85	NR	NR	NR	146 (120–185)	114 (95–151)	< .001	20 (17–24)	17 (15–19)	< .001

PP = prone positioning
SP = supine position
APP = awake prone positioning
P = prospective
HFNC = high-flow nasal cannula
NC = nasal cannula
$\dot{V}/\dot{Q}$ = ventilation/perfusion, breathing frequency in breaths/min
NR = not reported
RC = randomized crossover
NRM = non–rebreather mask
GI = global inhomogeneity
LUS = lung ultrasound score
WOB = work of breathing, cm H_2O* L/min
IE = inspiratory effort, cm H_2O
FM = face mask
N/A = not available
NIV = noninvasive ventilation
PS = pressure support

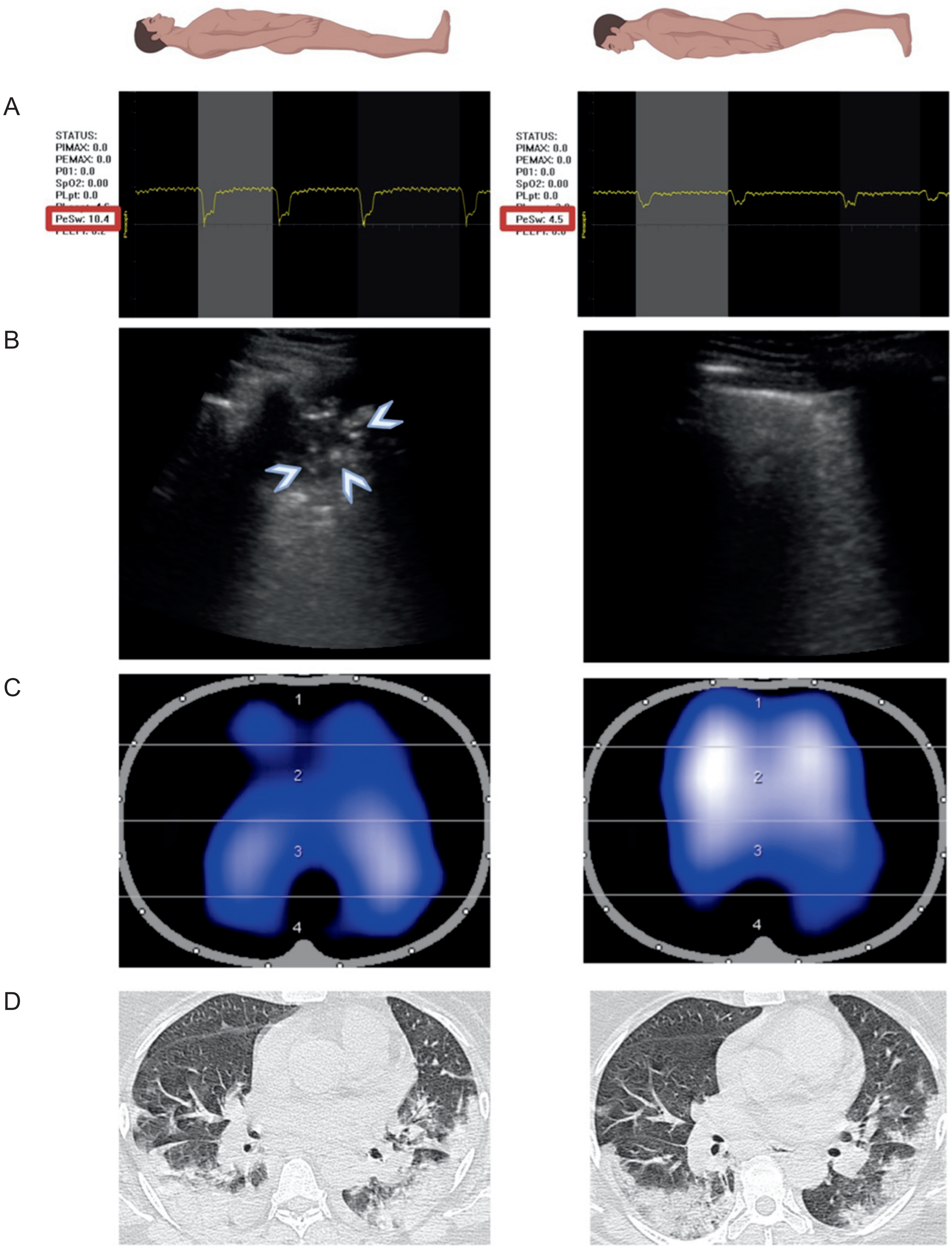

Fig. 1. Physiologic responses to awake prone positioning (APP) as assessed by different bedside clinical tools. (A) Inspiratory effort measured by esophageal pressure swing, which decreased from 10.4 cm H_2O to 4.5 cm H_2O after 30 min of APP. (B) Lung consolidation tissue (arrow heads) disappearance after 1 d of APP as assessed by lung ultrasound. (C) Electrical impedance tomography showing homogenization of lung aeration after APP, especially at ventral lung regions (layers 1 and 2). (D) Computed tomography showing improving of aeration at both lung bases after 3 d of APP. Images are provided by Drs Li and Ibarra-Estrada from their unpublished studies. PeSw = esophageal pressure swing.

Jacquet-Lagrèze et al[25] reported a significant increase in cardiac index, assessed by transthoracic echocardiography, after APP in 26 subjects with COVID-19, of whom 85% received HFNC. This improvement in cardiac index might be attributed to the reduced right-ventricular afterload and increased venous return resulting from the increased abdominal pressure during APP, similar to the effects of PP on hemodynamics for intubated patients.[26] Notably, peripheral perfusion as assessed by capillary refill time was also significantly improved, but half of the included subjects in this study had a low cardiac index and diminished right-ventricular function at baseline,[25] which may limit generalizability of the study's findings to patients with normal cardiac index.

Ventilation/perfusion ($\dot{V}/\dot{Q}$). The aforementioned study by Liu et al[15] reported no significant improvement in ventilation and perfusion after APP in subjects with COVID-19. However, a significant improvement in ventilation/perfusion matching ($\dot{V}/\dot{Q}$) was observed, which explained the significant improvement in oxygenation. Specifically, although there were no significant changes on ventilation or perfusion at dorsal regions, the global dead-space (V_D) fraction significantly decreased (improved perfusion), whereas global intra-pulmonary shunt was not significantly reduced (recruitment).

Work of breathing. Chiumello and colleagues[16] assessed WOB during APP in 40 subjects with COVID-19 ARDS supported by CPAP at average settings of 10 (8–10) cm H_2O and found significant improvement in oxygenation and a reduction in WOB (146 [120–185] cm H_2O vs 114 [95–151] cm H_2O*L/min, $P < .001$), breathing frequency, minute ventilation, and Borg dyspnea scale. However, they did not find any difference in esophageal pressure swing, which reflects inspiratory effort (IE).[16] Likewise, Lehingue et al[18] observed significant improvement in oxygenation and reduction in WOB, breathing frequency, and the physiologic V_D-to-tidal-volume (V_T) ratio during a 2-h APP session using HFNC in 17 subjects with COVID-19, with no significant difference in IE. The failure to reduce IE in both studies may be explained by the lack of inspiratory support in both CPAP and HFNC.

In another study by Bianchi et al,[17] noninvasive ventilation (NIV) with PEEP at 8 (7–9) cm H_2O and pressure support (PS) at 8 (8–10) cm H_2O was used for 12 subjects with COVID-19. Subjects' oxygenation was significantly improved, and compared to spontaneous breathing with oxygen mask, NIV reduced IE; but the difference did not reach statistical significance, whereas the combined use of NIV and APP significantly reduced IE.[17]

Patient self-inflicted lung injury. Menga et al[27] conducted a randomized crossover trial to compare the effects of 1-h phases of helmet PS, CPAP, and HFNC in 15 subjects, of whom 10 had COVID-19 infection. Pendelluft phenomenon, that is, the redistribution of air from the non-dependent to the dependent lung regions at onset of inspiration, was common with noninvasive support, particularly during HFNC, in which 14/15 had pendelluft involvement >10% of V_T. Helmet CPAP significantly reduced pendelluft, and NIV further mitigated it.[27] The authors did not evaluate the effects of the combined use of respiratory support with APP, so it is unknown whether APP would mitigate or exacerbate the pendelluft effect. In a recently published experimental study on intubated animals with spontaneous breathing, PP was found to reduce maldistribution of lung stress and effort-dependent lung injury regardless of the PEEP settings.[28] Clinical studies to validate these findings are sorely needed (NCT05719103).

In all, APP improves oxygenation and reduces WOB for patients with COVID-19–induced AHRF. Oxygenation improvement mainly results from the optimization of lung $\dot{V}/\dot{Q}$.

Impact of Awake Prone Positioning on Patient Outcomes

To date, 25 randomized controlled trials (RCTs) and one quasi-RCT have been registered on ClinicalTrials.gov to compare APP with standard care in subjects with COVID-19, with 21 completed or terminated. Among them, 11 completed RCTs[9-14,29-33] along with 2 additional RCTs[34,35] registered elsewhere have been published. Although numerous systematic reviews and meta-analyses have been conducted on this topic,[5,8,36,37] most of them included both RCTs and observational studies,[4] with few focusing solely on RCTs. Therefore, we will mainly discuss the findings of RCTs[9-14,29-35] and systematic reviews/meta-analyses that focused exclusively on RCTs[36,37] due to the hierarchy of evidence.

Intubation rate. Among the 12 RCTs[9-14,29-32,34,35] and one quasi-RCT,[33] 6 were multi-center studies that primarily assessed intubation rate.[11,29-33] The first systematic review and meta-analysis that exclusively included RCTs comprised 10 trials with 1,985 subjects and found that APP reduced the risk of intubation,[36] particularly in subjects requiring advanced respiratory support, including HFNC, CPAP, and NIV. However, there were no significant differences in intubation risk for subjects receiving conventional oxygen therapy.[36] Subsequently, 2 RCTs[31,35] and one quasi-RCT[33] with large sample sizes were published, but none of them reported significant differences in intubation rate between APP and standard care. Notably, all subjects in one RCT ($n = 502$)[35] and two thirds of the subjects in the quasi-RCT ($n = 501$)[33] used conventional oxygen therapy, whereas > 85% of subjects in the remaining RCT ($n = 400$)[31] received advanced respiratory support. In a subgroup analysis, subjects who received HFNC and APP had a lower intubation rate than those who received HFNC alone (33% vs 49%, hazard ratio [HR] 0.61 [0.42–0.88]),[31] consistent with the findings from the meta-analysis.[36,37]

Mortality. None of the RCTs were designed to investigate the effects of APP on mortality as the primary end point, although it was reported as a secondary outcome in all trials. Interestingly, the pooled analysis from RCTs showed no significant differences in mortality with APP and standard care,[36,37] whereas the pooled results from observational studies showed a lower risk of mortality with APP.[36] This discrepancy is likely due to selection bias and use of historical control groups, highlighting the importance of conducting better-quality studies.[4]

Safety. Regardless of the study types included in the systematic review and meta-analyses, pooled data have consistently shown that APP is a safe treatment with no increased risk of adverse events compared to standard care.[5,36,37] This is likely because conscious patients can adjust their positions for comfort and relieve pressure on their skin.

In summary, APP is safe and effective in avoiding intubation for patients requiring advanced respiratory support, but there is no evidence supporting its role in reducing mortality for patients with COVID-19. But for the non–COVID-19 patients, no data coming from studies with a high level of evidence are available to date.

Influential Factors on the Treatment Success

Initiation timing. Initiating APP within 24 h of HFNC reduced the mortality in a post hoc analysis of an RCT in subjects with COVID-19.[38] The risk of death increased as APP and HFNC initiation was delayed,[38] indicating the importance of timely initiation of APP.

Awake prone positioning duration. In the largest RCT on APP for subjects with COVID-19, Ehrmann et al[29] found that subjects who received APP for at least 8 h/d had a lower intubation rate compared to those who received it for $<$ 8 h/d. In the subgroup of subjects enrolled in Mexico in the meta-trial and who were more adherent to APP than subjects from other countries, this finding was validated, and further analysis revealed that 8 h/d was one of the independent predictors for treatment success.[39] Likewise, in a multi-center prospective study that included 335 subjects with COVID-19 who received APP, Esperatti et al[40] reported the risk of intubation and hospital mortality decreased as the daily APP duration increased.

Concurrent use of respiratory support (conventional oxygen therapy vs HFNC vs CPAP/NIV). The benefits of avoiding intubation are primarily seen in patients requiring advanced respiratory support.[36] The combination of positive airway pressure and APP may be more beneficial than APP alone, but the extent of the additive effect and the role of the respiratory support in the treatment success of APP remain unknown. On the other hand, combining both modalities, especially at high pressure settings, may overdistend the lung and cause lung injury.[41] In fact, subjects who received NIV with APP had a higher intubation rate than those who received NIV alone (58% vs 20%, HR 3.69 [95% CI 1.07–12.70]) in the subgroup analysis of the multi-center RCT that compared APP with standard care.[31] In contrast, in the same study, subjects who received HFNC and APP had a lower intubation rate than those who received HFNC alone.[31]

Strategies to Improve Patient Adherence With Awake Prone Positioning

To improve treatment success, it is crucial to improve patient adherence to APP, and ensuring patient comfort under prone position is the key. Placing pillows under the head, chest, waist, and legs can help relieve the pressure and improve comfort,[6,42] particularly for obese patients, where the pillows under the chest and waist can make the room for their abdomen and reduce the abdominal pressure from compression, reducing breathing difficulty.[6,42] Raising the head of the bed can also help with patient comfort, but the leg of the bed must be put down as a reverse Trendelenburg position to avoid stretching the patient's back,[43] which can cause pain and reduce their tolerance for prone position.

Educating patients on the importance of APP duration for treatment success[44] and distracting patient attention during APP may also improve adherence.[39] Moving patient's bed to face a room window or TV, or allowing them to use a cell phone, can help distract their attention.[42] Additionally, using sedatives such as dexmedetomidine can improve patient tolerance and decrease oxygen demand by reducing anxiety and breathing frequency, leading to better oxygenation.[45] Although dexmedetomidine is considered safe for conscious sedation, close monitoring while using sedatives is highly recommended.

Alternative Positions

For patients who cannot tolerate APP, lateral position may be a helpful alternative that was found to improve oxygenation compared to supine position, although to a lesser extent than APP.[46] To improve patient comfort in lateral position, a group of physiotherapists recommend placing pillows in front or beneath their trunk and between their knees for support.[47] They also suggest using the three-quarter prone position, in which patients lie on their front with pillow support beneath their body and head turned to one side. Additionally, Coppo et al[48] attempted to place 25 subjects with COVID-19 on "Rodin's thinker position," named after the famous sculpture by Auguste Rodin. In this position, patients sit on a chair and rest their chest on a flat and elevated surface, with head resting on the arms, placing the chest in a semi-prone position. They observed a significant improvement in oxygenation using this position.[48] These modified positions can improve oxygenation and patient comfort, although they may not be as effective as APP. It is important to assess each patient's individual needs and preferences to determine which position is most appropriate for them.

Timing for Escalating Care

Delaying intubation can potentially lead to higher mortality; thus, it is crucial to identify when patients should discontinue APP and transition to higher level of respiratory support. In the subgroup analysis of the subjects who received APP and HFNC, subjects who were eventually intubated experienced a cessation of oxygenation responses to APP on the second day of APP,[49] which aligns with findings from a prospective cohort study.[24] This suggests that a lack of oxygenation improvement after APP, particularly on the second day, may indicate the need for escalation of care. However, further studies are needed to investigate the effects of using this criterion to guide the optimal timing for escalation of care.

In summary, APP is safe and effective and can help patients with COVID-19 avoid intubation, especially those who require HFNC. APP improves oxygenation by optimizing the $\dot{V}/\dot{Q}$ matching, although not all patients responded to it, and individual assessments on their responses are necessary. It is important to initiate APP immediately after patients are indicated for HFNC oxygen therapy and to aim for APP duration at least 8 h/d. Patient comfort is crucial for adherence to APP; the use of reverse Trendelenburg position and pillows can help. Patient education and distraction can also improve adherence, and conscious sedatives may be considered if necessary. Alternative positions such as lateral position, three-quarter prone, and Rodin's thinker position can also be used to improve oxygenation. Once the patients stop oxygenation responses to APP, particularly at the second day, escalation of care should be considered.

Prone Positioning for Intubated Patients

Major RCTs have confirmed the improvement in oxygenation with PP in intubated subjects with severe and moderate-to-severe ARDS.[50-53] However, none of these trials had demonstrated the benefits of PP in reducing mortality until 2013, when Guérin et al[2] conducted the PROSEVA trial and reported that PP reduced mortality at 28 d and 90 d with a large effect size. Although the physiological responses to PP had been widely described,[54] it became increasingly recognized at the onset of the COVID-19 pandemic that this disease had different pathophysiological underpinnings compared to classical ARDS.[55] This recognition increased the momentum for enhanced research into the mechanistic effects of PP in patients with COVID-19. In this section, we describe the physiological rationale for using PP in mechanically ventilated patients with AHRF due to COVID-19, clinical considerations, the associated outcomes in recent trials, and future research directions.

Physiological Responses

The short-term response to PP in terms of oxygenation is heterogeneous, but most patients show an increase in P_{aO_2}/F_{IO_2}. The rate of responders, defined as an increase of P_{aO_2}/F_{IO_2} by > 20 mm Hg during PP, has been reported from 9–77%,[3] along with a slight increase in static compliance in the respiratory system by 2 mL/cm H_2O. However, it is important to note that oxygenation response observed during PP does not consistently correlate with patient-centered outcomes. Whereas some patients may experience a favorable oxygenation improvement during PP, this response is not sustained in all cases. In the PROSEVA trial, only those with persistent oxygenation improvement upon re-supination had a significantly reduced mortality.[2] Overall, the response in oxygenation to PP in patients with COVID-19 is similar to that observed in patients with ARDS.[56] Studies have reported that PP improves oxygenation in subjects with non–COVID-19 ARDS by reducing alveolar collapse and homogenizing lung aeration. However, it was unclear whether this mechanism applies to ARDS induced by COVID-19 early in the pandemic; thus, several physiological studies have been conducted to assess it.

Ventilation. CT is the accepted standard to assess lung aeration, as it estimates total lung volume, tissue weight, and gas volume. Based on the density as measured by Hounsfield units (HU), lung compartments can be classified into 4 grades of aeration: non-aerated (> -100 HU), poorly aerated (-100 to -500 HU), normally aerated (-500 to -900 HU), and over-aerated (< -900 HU).[57] EIT is a noninvasive, radiation-free, available-at-the-bedside lung imaging technique that provides real-time information on changes in thoracic impedance during each respiratory cycle and can measure the degree of ventilation.[58] Whereas EIT cannot replace CT, it has some unique features that enable researchers and clinicians to gain important insights into the effects of PP.

Specifically, EIT has provided valuable information on the physiological mechanism underlying oxygenation responses to PP, as well as mechanisms for ventilator-induced lung injury (VILI) related to pendelluft,[59] which may not be captured by CT imaging. However, some disadvantages should be taken into account. For instance, it can only reflect one slice of the lung; and specific characteristics about the collapsed area such as effusion, consolidation, or atelectasis cannot be distinguished. Additionally, it may interfere with pacemakers and other thoracic electrical devices. Moreover, the variability of tidal impedance can be affected by body position and respiratory efforts.[60]

To date, 7 prospective studies[22,59,61-65] on 10−25 intubated subjects with COVID-19 have investigated lung aeration and ventilation during PP, assessed by EIT and/or CT (Table 2). Unlike APP for non-intubated subjects, intubated subjects in most studies were found to have significant increase of lung aeration in dorsal regions and decreased aeration in ventral regions, as shown in Table 2 and Figure 2. The exception was the study by Wang et al, which did not find significant reduction in ventral aeration, probably due to the small sample size ($n = 10$). It should be noted that the degree of recruitment in dorsal regions was consistently reported to be almost twice that of de-recruitment in ventral regions, as demonstrated by Fossali[61] and Rossi.[62] Fossali et al[61] provided compelling evidence of a consistent association between improved aeration, lung recruitment, and enhanced ventilation in the dorsal lung regions. They also revealed that dorsal recruitment outweighed ventral de-recruitment, resulting in an overall increase in lung recruitment. Interestingly, Rossi[62] also assessed the response to PP according to the time elapsed from hospitalization and found that non-responsiveness to PP (defined as an increase in $P_{aO_2}/F_{IO_2} < 20$ mm Hg) increased from 44% in the first week to 67% at 2 weeks and 100% at 3 weeks. This lack of response in later stages could be attributed to a larger amount of consolidated tissue in the sternal lung regions in PP (31% of total tissue mass), which, unlike atelectasis, consists of non-recruitable alveoli units.[62]

Protti et al[63] measured the gas-to-tissue ratios in mechanically ventilated subjects with COVID-19. Higher values indicated excessive air compared to tissue. Interestingly, the baseline gas-to-tissue ratio was close to 1 mL/g in dorsal regions and 3 mL/g in ventral lung. Following PP, both lung zones became closer to 1 mL/g. Their findings demonstrate that besides recruitment of dorsal regions, another important effect of PP is the reduction of over-aerated ventral regions, resulting in more homogeneous aeration throughout the sternovertebral axis.[63] This finding may be explained by the increase in chest wall elastance in PP.

Pierrakos et al[65] assessed the change in ventilation using EIT in 15 subjects with COVID-19 who underwent PP for a median of 19 h. Notably, this is the only study where subjects had spontaneous breathing activity. The authors reported a significant improvement of aeration in dorsal regions and a non-significant decrease in the incidence of pendelluft phenomenon from 46% to 35%.[65]

Ventilation/perfusion match. Despite the mechanisms of alveolar recruitment shown in the aforementioned studies, it should be recognized that the potential for lung recruitment varied widely among individuals. Moreover, early in the pandemic, Diehl et al[66] reported that COVID-19 was characterized by the predominance of endothelial damage and thrombosis. This finding was supported by an observational study published by Mauri et al.[67] They found that subjects with COVID-19 had a higher prevalence of V_D (ventilated but non-perfused lung units) compared to shunt (perfused non-ventilated units). Optimal gas exchange requires ventilation and perfusion to match, so monitoring perfusion is equally important as ventilation in understanding the oxygenation response to PP, and this can be done with EIT.

Two studies found that the improvement in $\dot{V}/\dot{Q}$ matching was primarily due to the increase in alveolar collapse in ventral regions, whereas the perfusion remained unchanged at all regions.[62,63] The closure of these units, which have limited perfusion, led to an overall improvement of $\dot{V}/\dot{Q}$ matching. However, Wang et al found that after 16 h of PP, mean perfusion increased from 36.4% to 46.0% ($P < .010$) in dorsal zones, whereas it decreased from 37.7% to 29.3% ($P = .050$) in ventral zones. Similar patterns were observed in changes of ventilation after PP, with an increase in the aeration of dorsal regions (32.7% vs 49.0%, $P < .005$) and a decrease in ventral regions (50.2% vs 43.5%, $P = .14$), resulting in a significant increase in global matching of $\dot{V}/\dot{Q}$ (52.5% vs 67.4%, $P < .001$). Noteworthy, subjects in this study had more severe lung disease with lower oxygenation and compliance, and they had a larger increase in oxygenation after PP. Therefore, besides the relief in dorsal hydrostatic pressure, the particular response in perfusion could be attributed to a marked reduction in hypoxic pulmonary vasoconstriction and less air compression of the dorsal vessels.[68]

Long-Term Outcomes

Mortality. Given the compelling evidence supporting the beneficial effects of PP on mortality in non–COVID-19 patients, it is reasonable to expect a similar benefit in patients with COVID-19. However, to date, no RCT with mortality as the primary outcome has been conducted in this population. Large observational studies conducted during early pandemic were heterogeneous with respect to the severity of disease, level of support, and mortality.[69] Moreover, earlier large case series reported the utilization of PP in subjects with COVID-19 was as low as 27% in indicated subjects,[70] making it difficult to assess the attributable mortality related to PP.

During the first wave of the pandemic, retrospective studies comparing mortality between intubated subjects exposed and non-exposed to PP yielded conflicting results.[71-74] In a small cohort of 40 subjects from China, Chen et al[72] found an HR of 0.37 (95% CI 0.18–0.76) for death in subjects exposed to PP. Similarly, in a cohort of 335 subjects during the early pandemic surge in New York, Shelhamer et al[71] performed a model with multivariate-adjusted competing risks analysis and found that PP was significantly associated with reduced mortality (HR 0.61 [95% CI 0.46–0.80]). In contrast, in a large cohort of > 1,000 subjects from Italy, Langer et al[73] reported an increased mortality in those who

Table 2. Physiological Responses to Prone Positioning in Intubated Patients With COVID-19 Using Different Assessment Tools in Prospective Studies

Author, y	No.	Assessment Tool	PEEP, cm H_2O	PP Duration at Assessment	P_{aO_2}/F_{IO_2}, mm Hg			$\dot{V}/\dot{Q}$ Match			Main Regional Changes in Ventilation and Perfusion				Compliance, mL/cm H_2O		
					SP	PP	*P*	SP	PP	*P*	Dorsal aeration	Ventral aeration	Dorsal perfusion	Ventral perfusion	SP	PP	*P*
Perier et al, 2020	21	EIT	12	3 h	133 (96–140)	↑ by 64 (41–90)	NR	Shunt 17%	Shunt 6.1%	> .050	↑	↓	↔	↔	44 (38–55)	39 (32–53)	.19
Wang et al, 2022	10	EIT	9	3 h	95 ± 27	161 ± 44	< .001	52.5%	67.4%	< .001	↑	↔	↑	↓	27 ± 11	30 ± 11	< .010
Pierrakos et al, 2022	15	EIT	11	19 (17–21) h	82 (54–115)	↑ by 7.4 (4.0–19.3)	> .050	GI−8%	GI−15%	< .050	↑	↓	NR	NR	45 (30–59)	72 (29–93)	< .050
Fossali et al, 2022	21	CT/EIT	10	30 min	108 ± 41	176 ± 100	.002	DSR 5.1 (2.3–23.4)	DSR 4.3 (0.7–6.8)	.035	↑↑	↓	↔	↔	45 ± 15	45 ± 18	.95
Dos Santos Rocha et al, 2022	15	EIT	10	5 min	120 (110–160)	170 (150–225)	< .001	Shunt 32%	Shunt 29%	< .050	↑	↓	NR	NR	34 ± 14	32 ± 14	> .050
Rossi et al, 2022	25	CT	5	5 min	129 ± 54	144 ± 59	.70	NR	NR	NR	↑↑	↓	NR	NR	35 ± 11*	48 ± 20*	< .001
Protti et al, 2022	15	CT	12	1 h	100 (83–171)	156 (117–300)	< .001	NR	NR	NR	↑	↓↓↓	NR	NR	45 (36–57)	44 (40–56)	.74

*Authors reported elastance instead of compliance.
PP = prone positioning
$\dot{V}/\dot{Q}$ = ventilation/perfusion
SP = supine position
EIT = electrical impedance tomography
GI = global inhomogeneity
NR = not reported
CT = computed tomography
DSR = dead space/shunt ratio

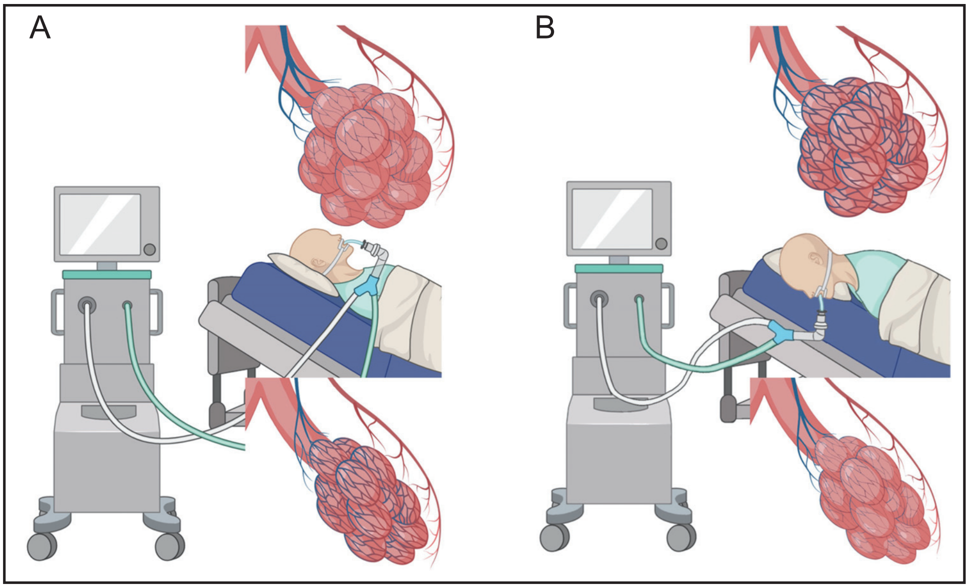

Fig. 2. The effect of prone positioning (PP) in intubated patients. A: Dorsal lung regions with normal perfusion are collapsed (shunt) at supine, whereas ventral regions tend to present overdistention with limited perfusion (functional dead space). B: With PP, matching of ventilation/perfusion improves by inducing collapse of barely perfused ventral regions and recruitment of well-perfused dorsal units.

received PP compared to those who did not (45% vs 33%, $P = .01$). However, a nationwide retrospective study from Sweden with 6,350 subjects showed no significant difference in mortality between those exposed and non-exposed to PP.[74] It is important to note that most of these studies had a selection bias due to their retrospective nature, as subjects who were proned usually had more severe disease. Additionally, data about the criteria for initiation and termination of PP, ventilator settings, duration, and number of proning sessions were unclear.

Although no solid conclusions about mortality can be drawn from these studies,[71-74] the oxygenation response to PP has been identified as an early indicator of reduced mortality in 4 observational studies.[56,73,75,76] In 2 of these studies, responders were defined as those with an increase in P_{aO_2}/F_{IO_2} by $\geq$ 20 mm Hg during PP. Langer et al[73] reported that responders had a lower mortality than non-responders (38% vs 65%, $P = .047$), whereas Camporota et al[56] found no significant reduction in mortality among responders (39% vs 54%, $P = .07$). Interestingly, Weiss et al[76] reported similar oxygenation responses in the first PP session between the subjects who survived and those who eventually received extracorporeal membrane oxygenation (ECMO) or died, but a continuum of oxygenation responses was observed in the subsequent PP sessions among subjects who survived.

Scaramuzzo et al[75] reported a median change of 49% in the P_{aO_2}/F_{IO_2} between pre-PP and 1–3 h after re-supination in the first PP session. Based on this median change, subjects were classified as responders or non-responders. Responders had a lower mortality (33.3% vs 53.7%, $P = .006$) and a higher likelihood of being liberated from mechanical ventilation at 28 d (HR 1.56 [95% CI 1.32–1.83]).[75] These results suggest that oxygenation response to PP could be potentially used for early decision making, such as escalation of care.

The approach of target trial emulation has been proposed to perform effectiveness research when data from RCTs are lacking.[77] This approach involves analyzing patient-level data from reliable observational studies to simulate a randomization procedure and obtain balanced groups for comparison. Mathews et al[78] applied this approach to the STOP-COVID study, a multi-center prospective cohort across the United States, including 2,338 subjects with confirmed COVID-19. They found that early PP within 2 d of ICU admission was associated with a significantly lower HR for mortality (0.84 [95% CI 0.73–0.97]). These results were consistent across multiple sensitivity analyses, supporting the hypothesis that early PP use was more effective than late use of PP in intubated subjects with COVID-19.

Safety. Before the pandemic, the use of PP in patients with severe ARDS was relatively low, with a reported rate of 16%.[79] However, during the first wave of the pandemic, this rate increased dramatically up to 70%,[80] which increased awareness of potential adverse effects (AEs) associated with this procedure. In fact, almost 40% of the literature reporting AEs with PP was published after 2020.[81]

The most common AEs in pooled reports of subjects with ARDS overall were oxygen desaturation (38%), barotrauma (31%), pressure sores (30%), ventilation-associated pneumonia (28%), facial edema (17%), arrhythmias (15%), hypotension (10%), and peripheral nerve injuries (8%).[81] Although no formal comparisons between subjects with and without COVID-19 have been performed, recent observational data focused on COVID-19 show a predominance of pressure sores, which varied between 47–88%. The face was the most affected site, especially at the mouth area, due to contact with the endotracheal tube (ETT).[82-84] Interestingly, the incidence of other AEs decreased, with contemporary studies focusing on subjects with COVID-19 reporting that oxygen desaturation occurred in 5.8–19.0%,[85,86] bronchial secretion retention in 11%, transient hypotension in 9.5–10.0%,[85] ETT dislodgement in 0.4–6.3%,[85,87,88] ETT obstruction in 3.0–13.7%,[86,89] and peripheral nerve injury in 8.2–14.5%.[90,91] This decreasing trend could be attributed to the worldwide increase in experience with the PP procedure during the pandemic, as well as the publication of several recommended mitigation strategies to reduce AEs.[81]

It is worth noting that central venous catheterization can be successfully and safely undertaken during PP when performed by well-trained staff with carefully selected patients.[92] Additionally, in situations where immediate supination is challenging or poses unacceptable risks to the patients, cardiopulmonary resuscitation can also be performed in the PP.[93]

Use of Prolonged Prone Positioning

The usual approach to PP therapy involves 16 h of continuous PP, after which the patient's oxygenation is evaluated upon returning to supine to determine the need for further PP and the interval of the next 16-h PP session. However, due to the overwhelming increase in the work load of health care staff and concerns about contagion exposure during the first wave of the pandemic, there was an increase in research on an alternative approach that involved extending the duration of PP beyond 16 h. This approach had barely been explored before the pandemic.

To date, 5 studies demonstrating feasibility of prolonged prone position have been published (Table 3).[90,94-97] In the study by Douglas et al,[90] subjects were returned to supine only after achieving stable gas exchange, defined by $F_{IO_2} < 0.6$ and PEEP < 10 cm H_2O for at least 4 h. They reported a mortality of 31%, which was similar to that reported in other studies with subjects with ARDS.[2,98] However, they found a high incidence of AEs, including pressure sores, ETT reposition, ETT obstruction requiring emergent bronchoscopy for mucus obstruction, brachial plexus paralysis, and central line–associated bloodstream infections. This high incidence of AEs might be explained by the reduced in-person clinical assessments during the first waves of the pandemic and the high severity of illness.[99] In fact, the Sequential Organ Failure Assessment score at 3 d was inversely associated with the occurrence of dorsal and ventral wounds.[90]

Other 2 observational studies showed a reduction in the rate of AEs, probably due to applications with multi-professional teams and specific training. For instance, in a center with dedicated teams staffed on a 24/7 basis, including attending intensivists, critical care anesthesiologists, surgeons, and

Table 3. Summary of Published Studies Addressing Prolonged Prone Positioning Approach in Patients With COVID-19

Author, y	Study Design	Sample Size	Intervention	Accumulated Duration of PP, h	Baseline Oxygenation P_{aO_2}/F_{IO_2}, mm Hg	Mortality, %	AEs: Pressure Wounds, %	AEs: ETT obstruction, %	AEs: ETT reposition, %	AEs: Hypotension, %	AEs: Others, %
Douglas et al, 2021[90]	Retrospective single-center cohort	61	Prolonged PP	103	99 (73–128)	31.0	70	28.0	64	44.0	Brachial plexus damage 8, CLABSI 5
Parker et al, 2021[94]	Retrospective single-center cohort	12	Prolonged PP	59	130.0 ± 28.4	33.0	0	0	0	0	0
Cornejo et al, 2022[95]	Retrospective multi-center cohort	417	Prolonged PP	96	119 (85–154)	36.2	24 at first session, 36 at 7 d	3.4	NR	NR	Accidental extubation 4.2
Karlis et al, 2023[96]	Prospective single-center cohort	37	Prolonged PP	70	103.0 ± 25.8	20.8	21	NR	NR	NR	NR
		26	Standard PP	42	97.0 ± 27.4	40.0	19	NR	NR	NR	NR
Okin et al, 2023[97]	Retrospective multi-center cohort	157	Prolonged PP	67	138 (106–164)	29.3	30	3.0	4	1.3	NR
		110	Standard PP	47	126 (96–159)	37.7	27	3.0	3	7.3	NR

AE = adverse event
PP = prone positioning
ETT = endotracheal tube
CLABSI = central line–associated bloodstream infection
NR = not reported

experienced nurses, Parker et al[94] placed subjects on prolonged PP for a median duration of 57 h and did not observe any accidental extubations, soft tissue injuries, or other AEs. Similarly, in the largest multi-center observational study on the use of prolonged PP, with most subjects receiving a single session of PP for 3–5 d, Cornejo et al[95] reported a mortality of 36%, with pressure sores being the most common AE and reported as 36% at 7 d. Of note, this Chilean group has long-standing experience with the prolonged PP approach for over a decade,[100] and this protocol was widely adopted in the country early at the first pandemic wave with national experts' guidance, which may explain the lower incidence of AEs.

At the time this manuscript was written, only 2 studies had been published that compared the strategy of prolonged PP with the standard PP of ~16 h (Table 3). In a small prospective study from Greece including 63 subjects, no significant differences in mortality were reported between 2 groups.[96] However, in a retrospective multi-center cohort study with a larger sample size, Okin et al[97] found that subjects who received prolonged PP (median prone duration of 40 h at the first session) had lower 90-d mortality compared to the standard PP group (29.3% vs 37.7%, $P = .02$) and similar incidences of AEs. Interestingly, subjects in the prolonged PP strategy had a lower rate of peri-proning hypotension (1.3% vs 7.3%, $P = .02$). Subjects who received prolonged PP were changed in position fewer times than the standard group (median of 1 time vs 3 times, $P < .001$), which may have reduced the exposure to de-recruitment associated with supination periods that can exacerbate atelectrauma and VILI.[100] However, it should be noted that potential unmeasured confounders are always a possibility in observational studies; therefore, these results need to be confirmed by further RCTs.

Prone Positioning for Patients Receiving Extracorporeal Membrane Oxygenation

A landmark RCT reported no significant difference in mortality from the use of venovenous ECMO (VV-ECMO) in subjects with classic ARDS,[101] and therefore, VV-ECMO is still considered as a rescue therapy after failure to standard ventilatory support. Although observational data suggest a potential of PP to improve outcomes in non–COVID-19 subjects receiving VV-ECMO,[102-104] the literature regarding the effects of this combination in subjects with COVID-19 is scarce.

A recent systematic review and meta-analysis that included 1,836 subjects from 13 studies reported a lower risk of mortality in subjects receiving PP and VV-ECMO compared to VV-ECMO alone.[105] In their subgroup analysis pooling 703 subjects with COVID-19, they also found a significant improvement in survival at day 28 in subjects with PP and VV-ECMO (relative risk 1.32 [95% CI 1.15–1.50]). However, all except one study included in this systematic review and meta-analysis were observational studies; the low/very low certainty of evidence from these observational studies precludes definitive conclusions on this outcome.

Thereafter, 2 other major observational studies were published.[106,107] In a retrospective multi-center cohort including 232 subjects, Zaaqoq et al[106] found that PP during VV-ECMO was associated with a reduced HR for death of 0.31 (95% CI 0.14–0.68). The ECMOSARS Registry was a nationwide prospective cohort including 47 centers in France that aimed to collect all available data of ECMO patients with COVID-19.[107] In their cohort of 517 subjects whose had average P_{aO_2}/F_{IO_2} of 63 mm Hg before cannulation and PEEP at 12 cm H_2O, Massart et al[107] found that subjects who received PP during ECMO had a lower in-hospital mortality (odds ratio 0.49 [95% CI 0.29–0.84]) than those who did not, although this reduction was not significant after propensity-score matching (49.7% vs 60.1%, $P = .09$). Considering clinicians might be less inclined to prone sicker patients, they performed a sensitivity analysis including only subjects who were alive at de-cannulation from ECMO and found that subjects in the PP group had lower hospital mortality (22.4% vs 37.8%, $P = .03$) than the supine group, suggesting that PP should not be withheld for patients while still receiving VV-ECMO.

Overall, these studies suggest a potential survival benefit of PP in certain subgroups of subjects with COVID-19 receiving VV-ECMO, but further RCTs are needed to establish its efficacy.

Future Research Directions

Physiological studies have shown that not all subjects responded to PP and that the mechanism of response varied among responders. Some subjects had oxygenation improvement due to homogenous aeration, whereas others benefited from improved perfusion or optimization of $\dot{V}/\dot{Q}$ matching. Furthermore, patient responses to PP varied between non-intubated and intubated patients. Additionally, the effects of PP on the VILI and self-inflicted lung injury remain largely unknown, especially when the positive pressure is utilized with PP. Given the potential synergistic effects on the stress and strain on the lungs, care assessment of the risks is necessary. With the increasing utilization of imaging technologies like EIT and ultrasound, the mechanism of each individual patient's response to PP can be identified. This information could help to decide the optimal combination of respiratory support modalities and settings for each patient, with the aim of maximizing therapeutic effects and minimizing harms.

Although the World Health Organization has now declared that COVID-19 is not a global health emergency and the number of COVID-19 cases is declining, the utilization of APP is likely to continue. Its use in patients with AHRF remains promising and of great interest, and further studies are needed to evaluate the effects of APP on this patient population, including its impact on the long-term outcomes such as intubation rate. It should be noted that AHRF has numerous causes, including pulmonary and non-pulmonary origins; future studies may need to focus on subjects with homogenous etiology to better evaluate the effectiveness of APP.

Despite the lack of high-quality evidence for the use of PP in intubated patients with COVID-19, current guidelines recommend its routine use (https://www.covid19treatmentguidelines.nih.gov. *Accessed May 20, 2023*), which limits the possibility of conducting new RCTs that include a control group of subjects not being proned. There are still some uncertainties that need to be investigated. One such area is the standardization of protocols for prolonged PP, which could potentially reduce VILI and mortality, as well as the work load for health care staff, especially during the surges of future pandemics.

Another area is the criteria for initiating PP in patients receiving VV-ECMO. Although ongoing RCTs (NCT04139733 and NCT04607551) will address the impact of combined use of PP with VV-ECMO on the duration of VV-ECMO, the optimal timing to initiate PP remains controversial. It is important to note that PP is a time-dependent intervention, even in this specific subgroup of patients receiving VV-ECMO.[108] Thus, we strongly encourage researchers from experienced, high-volume centers to collaborate and develop standardized criteria for the early initiation or continuation of PP after ECMO cannulation, taking into account the potential risks and benefits. By establishing such criteria, there will be an increased likelihood of detecting a significant effect size of the potential benefits of PP in this context.

Summary

This comprehensive review examines the recent evidence surrounding PP for non-intubated and intubated subjects with COVID-19. The review reveals that most subjects experience improved oxygenation following PP, regardless of the respiratory support modalities used. However, the distribution of aeration and perfusion shows varied responses. Nevertheless, PP significantly enhances $\dot{V}/\dot{Q}$ matching. These findings emphasize the importance of personalized respiratory support during PP. The impact of PP on patients with COVID-19 outcomes, including mortality, remains unclear. Moreover, the use of prolonged PP and PP for patients undergoing ECMO shows promise, but further research is needed to establish standardized protocols and assess safety and effectiveness. Overall, this review highlights the potential benefits of PP in COVID-19 management while also identifying areas that require additional investigation.

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