Awake prone positioning in acute hypoxaemic respiratory failure

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Awake prone positioning of patients with acute hypoxaemic respiratory failure reduces invasive ventilation risk in patients requiring advanced respiratory support, who are managed in higher care environments and who can be prone for several hours https://bit.ly/3ZbLNCp

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Abstract

Awake prone positioning (APP) of patients with acute hypoxaemic respiratory failure gained considerable attention during the early phases of the coronavirus disease 2019 (COVID-19) pandemic. Prior to the pandemic, reports of APP were limited to case series in patients with influenza and in immunocompromised patients, with encouraging results in terms of tolerance and oxygenation improvement. Prone positioning of awake patients with acute hypoxaemic respiratory failure appears to result in many of the same physiological changes improving oxygenation seen in invasively ventilated patients with moderate–severe acute respiratory distress syndrome. A number of randomised controlled studies published on patients with varying severity of COVID-19 have reported apparently contrasting outcomes. However, there is consistent evidence that more hypoxaemic patients requiring advanced respiratory support, who are managed in higher care environments and who can be prone for several hours, benefit most from APP use. We review the physiological basis by which prone positioning results in changes in lung mechanics and gas exchange and summarise the latest evidence base for APP primarily in COVID-19. We examine the key factors that influence the success of APP, the optimal target populations for APP and the key unknowns that will shape future research.

Introduction

Prone positioning (PP) of mechanically ventilated patients with moderate to severe acute respiratory distress syndrome (ARDS) results in an improvement in gas exchange and lung mechanics. As part of a multimodal strategy including neuromuscular blockade, plateau pressure limitation and use of positive-end expiratory pressure, PP has been shown to improve mortality [1]. PP of patients with acute respiratory failure was first described by Piehl and Brown [2] in 1976 in Toronto. Since then, studies have focused mainly on mechanically ventilated patients. PP of nonintubated, awake patients with acute hypoxaemic respiratory failure (AHRF) results in many of the same physiological changes improving oxygenation. Since the coronavirus disease 2019 (COVID-19) pandemic began, interest in its role in the management of AHRF has been increasing. An evidence base is accumulating to guide clinicians on its use and limitations.

The aims of this review are to evaluate the physiologic effects of awake prone positioning (APP), examine the key factors that influence the success of APP, factors impacting PP efficacy including respiratory support, location of care and duration of PP, as well as key unknowns that will shape future research directions regarding APP. Given the current level of evolution of the literature, much of the data examined relates primarily to COVID-19-induced AHRF; although whether APP leads to the same benefit in all patients with AHRF remains to be proven. Although most, but not all, of the evidence base for APP comes from the COVID-19 pandemic, important physiological studies and proof-of-principle case series on its use for AHRF pre-dated the pandemic.

Search strategy

Data for this narrative review were identified by searches of PubMed (https://pubmed.ncbi.nlm.nih.gov) and references from relevant articles using the following search terms: "prone positioning AND acute hypoxemic respiratory failure"; "prone positioning AND physiology"; "awake prone positioning AND acute respiratory failure"; "awake prone positioning AND COVID-19" and "prone positioning AND covid-19". Only articles published in English were considered and no time frame was stipulated in the search criteria. Article references were further reviewed as part of the search strategy.

Physiological effects of PP

Our understanding of the physiological underpinnings for changes in gas exchange related to APP stem from animal studies, healthy volunteers and subjects undergoing invasive mechanical ventilation (IMV) [1, 3–5], although our understanding of changes that occur in awake spontaneously breathing patients is also slowly growing [6, 7].

PP leads to changes in inflation, ventilation and perfusion of the lung and the degree to which these influence gas exchange depends on the disease state of the lung and the patient. In the supine position, dependent dorso-caudal lung regions are compressed, not only by the lungs' weight and the pleural pressure gradient but also by hydrostatic intra-abdominal pressure transmitted through the diaphragm and the weight of the heart [4, 8]. A study on anaesthetised pigs with increased intra-abdominal pressure found that PP further enhanced an increase in arterial oxygenation and decreased the alveolar–arterial oxygen gradient more so than in those without abdominal distension [9]. Compression from abdominal contents results in shortening in the apical to the basal direction and a reduced functional residual capacity (FRC) [10]. In PP, these dorso-ventral lung regions are relieved of the hydrostatic intra-abdominal pressure with FRC increasing from the dorsal to ventral direction. Alveolar inflation from the dorsal to the ventral direction becomes more homogenous compared to the supine position, which alongside homogenous lung perfusion due to a reduced gravitational gradient, results in improved ventilation/perfusion (V'/Q') matching [11–16].

PP increases cardiac output, potentially due to increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction as well as increased systemic venous return related to increased intra-abdominal pressure, resulting in increases in right ventricular pre-load and decreased right ventricular afterload [17–20]. The effect of PP on alveolar dead space is unclear and may include individual variability, with some studies suggesting a reduction [21, 22], while others did not demonstrate any change [23, 24]. The effect on arterial carbon dioxide tension (P_{aCO_2}) is similarly inconsistent with significant individual variation [4, 25]. One proposed mechanism for P_{aCO_2} increases in some patients is that proning can reduce both tidal volume and minute ventilation and, if the alveolar dead space remains constant, this could increase physiological dead space fraction (V_D/V_T) [4]. On the other hand, reductions in P_{aCO_2} in some patients may result from reduced both intrapulmonary and intracardiac (through patent foramen ovale) shunting [4]. In a study of PP in 225 patients with ARDS, P_{aCO_2} responders (defined as patients whose P_{aCO_2} decreased by $\geqslant$1 mmHg) but not arterial oxygen tension (P_{aO_2}) responders (defined as the patients who increased their P_{aO_2}/inspiratory oxygen fraction (F_{IO_2}) by $\geqslant$20 mmHg) had improved survival compared to nonresponders [25]. This suggests the importance of reduced dead space ventilation achieved with PP more so than alveolar ventilation [25].

PP improves diaphragmatic function. In the prone position, the diaphragm is displaced caudally, decreasing compression of the posterior-caudal lung parenchyma. In patients receiving APP, patients with a better outcome demonstrate increased diaphragmatic thickening fraction compared to those who failed to respond to APP [26]. In a study on intubated pigs, PP abolished diaphragmatic contraction induced ventral-to-dorsal negative pleural swing gradients seen in the supine position, reducing the potential for dorsal hyperdistension [27]. The potential for proning to reduce inspiratory effort is further underlined by the finding that proning reduced inspiratory effort and dynamic lung stress in intubated patients allowed to breathe spontaneously, as assessed by oesophageal manometry [28]. Additional mechanisms underlying

the benefit of PP include improvements in compliance and a more homogenous distribution of shear forces with a reduction in ventilator-induced lung injury.

Insights are emerging regarding the physiologic effects of APP. Patients receiving APP with noninvasive ventilation demonstrated a significant reduction in global lung ultrasound score and in the number of consolidated regions, indicating better aeration and less severe consolidation compared to historical controls. APP patients also demonstrated a higher global lung ultrasound reaeration score compared with controls [29]. The improvement in lung ultrasound indices observed in the prone positioned group was driven by greater reaeration in the dorso-lateral lung regions. Many patients in the prone position showed a lung ultrasound reaeration score of ⩾8, consistent with lung recruitment greater than 600 mL. Patients with an increase in carbon dioxide clearance, defined by a reduction in dead space indices, were found to have a greater likelihood of avoiding intubation than those that did not demonstrate such an increase. Similarly, a prospective study of patients with COVID-19 treated with a high-flow nasal cannula (HFNC) demonstrated that APP improved lung aeration predominantly in the dorsal regions [30]. Patients receiving APP who survived without intubation had a more significant reduction in dorsal lung ultrasound score than those who were intubated [30] (figures 1 and 2).

Insights from COVID-19 studies

Prior to the pandemic, reports of APP were limited to case series reporting its use in patients with influenza and immunocompromised patients, with encouraging results in terms of tolerance and oxygenation improvement [31, 32]. Following the onset of the COVID-19 pandemic in January 2020, multiple case reports, series and prospective cohort studies rapidly emerged suggesting a role for the intervention in reducing the need for invasive ventilation [33–35]. From 1 January to November 2021, 1243 studies related to APP have been published, indicating global interest in this strategy. Based on these reports, APP was quickly amalgamated into clinical practice guidelines, even prior to the emergence of clear evidence of its efficacy [36–38].

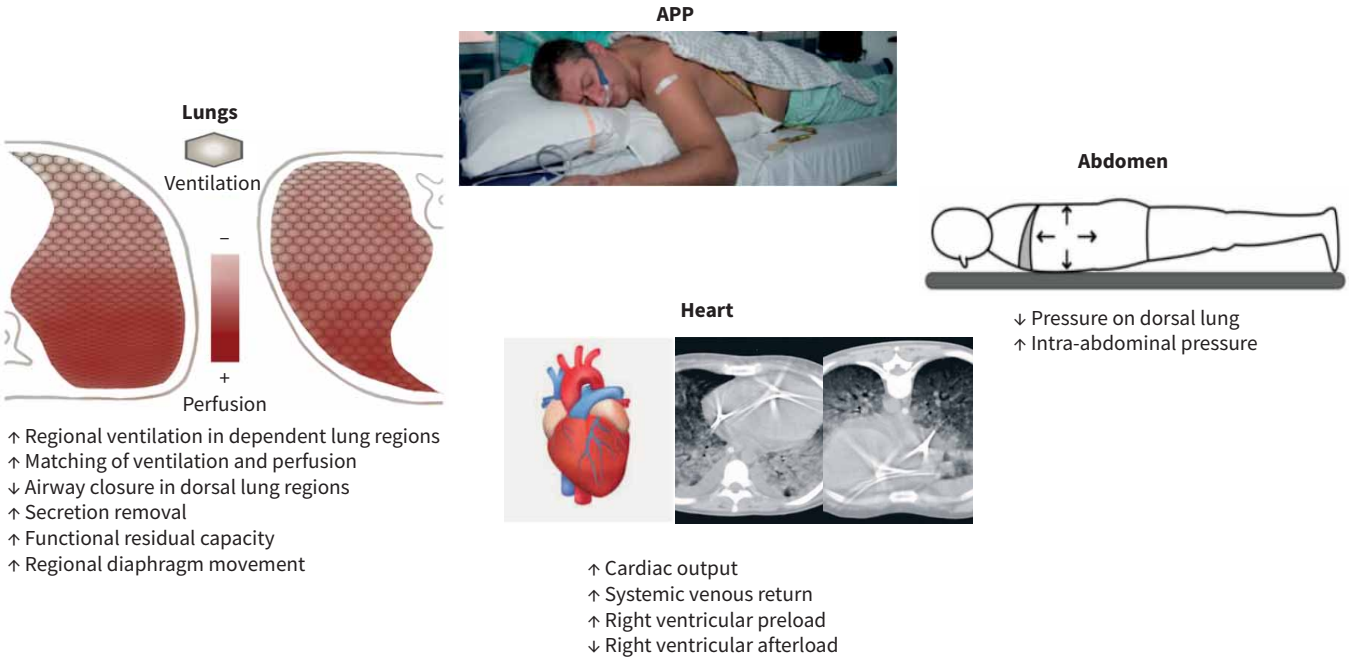

FIGURE 1 Physiological effects of awake prone positioning (APP). When supine, the dependent lung is compressed by the lung weight, the pleural pressure gradient and the weight of the heart. When prone, these dorso-ventral lung regions are relieved of these pressures, with functional residual capacity increasing from the dorsal to ventral direction. Alveolar inflation from the dorsal to the ventral direction becomes more homogenous and ventilation/perfusion ratio matching is improved. Improved diaphragmatic movement and enhanced secretion removal also contribute beneficially. In the cardiovascular system, APP increases cardiac output due to increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction as well as increased systemic venous return related to increased intra-abdominal pressure, resulting in increases in right ventricular pre-load and decreased right ventricular afterload. In the abdomen, APP improves diaphragmatic function, as it moves caudally, reducing pressure on the lung, while a moderate increase in intra-abdominal pressure improves venous return to the heart. Scans reproduced from [81] with permission.

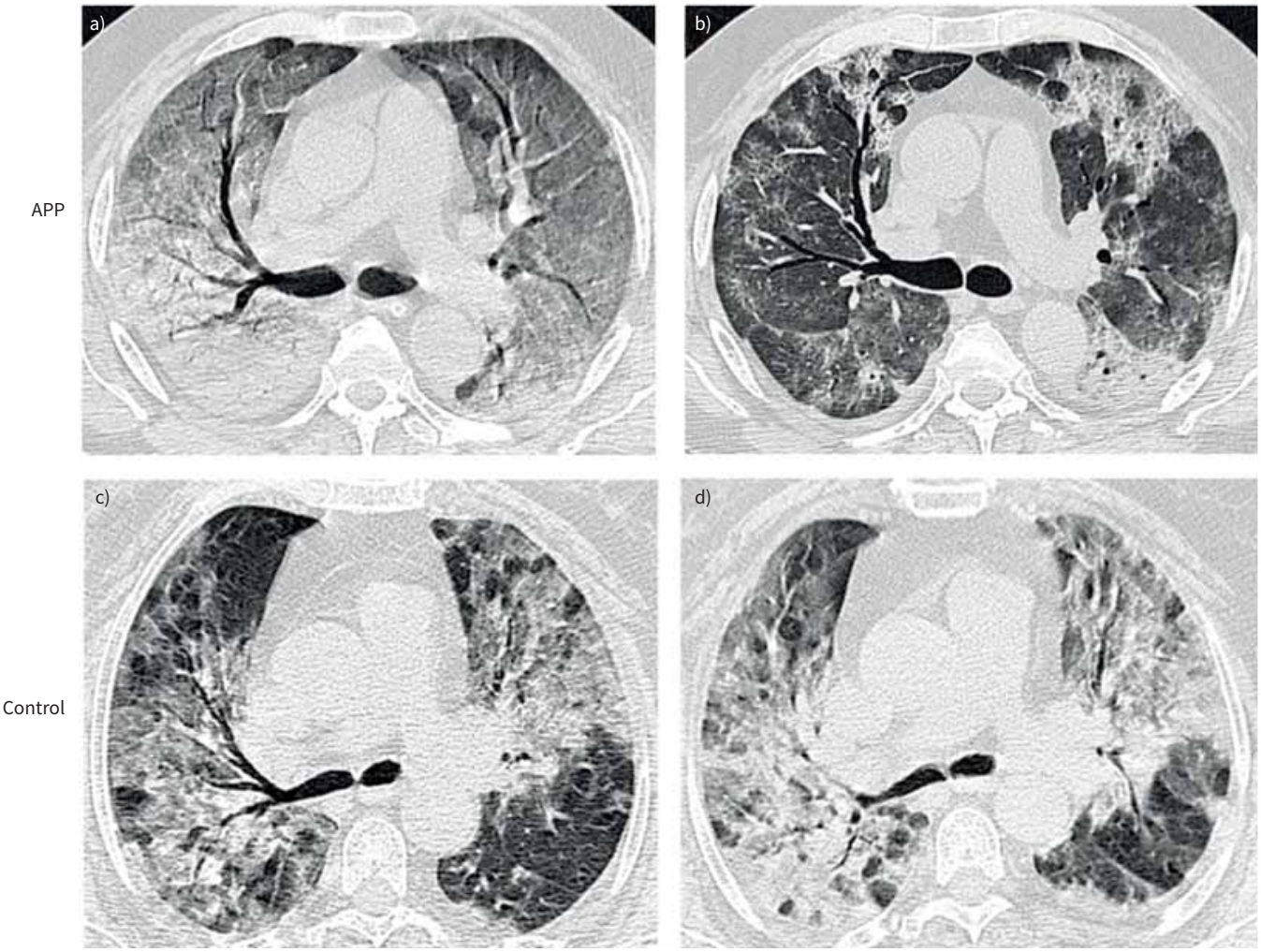

FIGURE 2 Images from two male patients with coronavirus disease 2019 pneumonitis enrolled in the awake prone positioning (APP) trial conducted in Mexico: a) and b) APP group patient; c) and d) control group patient. Both were males in their 50s, admitted 10 days from initial symptoms and thorax computed tomography (CT) was performed at days 1 and 5 after admission. In the proned patient there is a progressive improvement from a) to b) over the 5-day period; in the patient remaining supine, there is a worsening in lung consolidation from c) to d), especially at right lung base, and the second CT was taken right after commencement of invasive ventilation on day 5. Courtesy of Miguel Ibarra-Estrada.

Despite its widespread adoption, there was clear equipoise for clinical trials to determine its role in the management of COVID-19. Concerns regarding its use included the potential for delaying the initiation of IMV, which could potentially increase the risk of patient self-induced lung injury (P-SILI) [26]. Although data from observational studies that reported improved oxygenation with APP led to it being recommended by guidelines [36, 37], none of these studies convincingly demonstrated a reduction in either intubation rate or in mortality risk [39].

It is useful to consider the evolution of clinical trials for PP in mechanically ventilated patients with ARDS, which spanned over 20 years, with earlier trials showing encouraging but not conclusive findings for benefit. These studies differed in the length of time patients were proned, the timing and the homogeneity of its application, as well as the prior degree of experience of the centres with proning [40–42]. The definitive trial, the PROSEVA study, was informed by these prior studies and focused the intervention on a patient group with early established moderate–severe ARDS, used long durations of proning, incorporated additional multimodal approaches to ARDS and was conducted in experienced centres. The PROSEVA study reported a substantial mortality benefit with proning [1], catalysing its incorporation into routine clinical practice.

As of today, in a span of 2 years, 11 randomised controlled trials (RCTs) and one "quasi-randomised" trial have been published on APP [43] (table 1). Among the 12 controlled studies [44–55], five are multi-centre studies with a sample size from 257 to 1126 patients [44–48], with mostly patient-centred primary outcomes, including intubation [46], composite outcomes of intubation or death [44], or of intubation or death or needing F_{IO_2}>0.6 for a minimum of 24 h [45], or respiratory deterioration (an increase in supplemental oxygen requirement) or intensive care unit (ICU) transfer [47], and the World Health Organization (WHO) ordinal outcome scale [48]. None of the studies were powered to compare the differences in mortality. Seven other studies primarily investigated oxygenation improvement [49–52, 54–56]. Of the five large sample size studies [44–48], two only enrolled patients with mild AHRF and treated with conventional oxygen therapy [45, 47], while a large meta-trial confined enrolment to patients with moderate to severe AHRF who received HFNC oxygen therapy [44], while the remaining two studies had mixed patient populations [46, 48].

In the recent meta-analysis implemented by Li *et al.* [43], three large sample size RCTs [44, 45, 47] and six small sample size RCTs [49–52, 55, 56] along with an unpublished RCT (NCT04853979) were included. They reported that APP was associated with a lower risk of intubation, while subgroup analysis showed that this benefit was confined to patients who received advanced respiratory support, such as HFNC oxygen therapy or noninvasive ventilation. No significant differences were observed between APP and standard care in patients treated with conventional oxygen therapy. Additionally, no significant differences in the risk of death, length of hospital stay and adverse events were observed between APP and standard care [43]. Shortly after this meta-analysis was published, two large sample size studies were published [46, 48]. In the quasi-randomised multi-centre study conducted by Qian *et al.* [48], patients were assigned based on medical record number to receive either APP or usual care. Most patients were enrolled from a single centre and most patients were using low-flow oxygen therapy. The median time spent in the prone position was 4.2 h (interquartile range (IQR) 1.8–6.7), which was marginally less than in the meta-trial study (5.0 h (IQR 1.6–8.8)). The authors found using a Bayesian analysis that randomisation to APP appeared to transiently increase the likelihood of harm defined by a transient increase in modified WHO scoring at day 5, although exploratory outcomes such as the need for IMV, length of stay and 28-day mortality did not differ between the two groups. Power calculations for the study were based on the highest level of oxygen support on day 5 post-enrolment [48]. Given the transient nature of oxygen improvement with APP and the meta-trial's finding of a median time of 6.0 (3.0–9.8) days to wean off HFNC [44], APP's potential to improve oxygenation may not have been captured by the study. It was underpowered for more meaningful clinical outcomes of death or IMV and there was imbalance between groups in the number of patients who died without being intubated. Additionally, data on oxygenation response to APP was not recorded. In a subsequent smaller multi-centre RCT of patients with COVID-19 in Canada and Saudi Arabia [46], no significant difference in treatment failure with APP was reported, but this study was also underpowered. Interestingly, in their subgroup analysis, patients treated by HFNC oxygen therapy had a lower intubation rate in the APP group than in standard care group [46]. This result aligns with the findings in the meta-trial [44] and is consistent with the findings of further systematic reviews and meta-analysis since published [57].

Some unique or unusual features of COVID-19 may make APP more likely to be effective and should be considered when extrapolating from these studies to patients with non-COVID ARDS/AHRF. Autopsy and radiological studies of patients with COVID-19 indicated that dilated intra-alveolar capillaries surrounding almost normal alveoli are amenable to redistribution of blood flow that improves oxygenation in COVID-19 [58]. A remarkable phenomenon not isolated to COVID-19 was silent hypoxaemia, which appeared to influence response to APP [59]. In a sub-study of a large meta-trial, intubation occurred in 29 of 117 (25%) patients with silent hypoxaemia and 128 of 313 (41%) patients with dyspnoeic hypoxaemia (risk ratio 0.60, 95% CI 0.43–0.85, p=0.004). Fewer deaths occurred in patients with silent hypoxaemia (23%, 27/113) than in patients with dyspnoeic hypoxaemia (39%, 123/313) (risk ratio 0.58, 95% CI 0.41–0.84, p=0.001).

In all, heterogeneity in patient population and disease severity likely drives differences in APP effects, thus detailed analysis of those subgroups based on disease severity with different respiratory support and treating location, as well as the adherence to APP, are warranted.

Influence of type of respiratory support

The type of respiratory support appears to influence the success rates of APP. Mode of oxygen therapy (conventional oxygen therapy *versus* advanced respiratory support which includes HFNC, continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV)) has been used to differentiate patient severity and response to APP therapy. Early in the pandemic, there was a lack of recruitment of patients

TABLE 1 Summary of randomised controlled trials (RCTs)

Reference, year	Design	Country	Inclusion criteria	Exclusion criteria	Location at inclusion	Intervention	n	BMI, kg·m^{-2}, median (IQR)/mean±SD	Inclusion P/F or S/F median (IQR)/ mean±SD	Target duration of APP	APP duration, h·day^{-1}, median (IQR)/mean±SD	Cross-over, n (%)	Intubation, n (%)	Mortality, n (%)
Taylor *et al.* [56], 2021	Cluster RCT, single centre	USA	Adult, confirmed or suspected COVID-19 pneumonia, S_{pO_2}<93% at room air or requirement of 0_2 ⩾3 L·min^{-1}	Immediate need for IMV, unable to self-turn, spinal instability, facial or pelvic fractures, open chest or abdomen, anticipated difficult airway, altered mental status, signs of respiratory fatigue or end-of-life care	Ward	APP Usual care (room air, nasal cannula, HFNC, NIV)	27 13	29 (26–39) 31 (28–38)	NA NA	As long as possible –	NA NA	17 (63) 3 (23)	0 (0) 0 (0)	0 (0) 0 (0)
Kharat *et al.* [50], 2021	Cluster RCT, single centre	Switzerland	Adult, admission to a medical ward, COVID-19 pneumonia, low-flow oxygen therapy (defined as 1–6 L·min^{-1}) through nasal cannula to obtain a S_{pO_2} level of 90–92%	Patients initially treated in the ICU or high-dependency unit and recovering from ARDS, oxygen needs >6 L·min^{-1} using a nasal cannula or with >40% F_{IO_2} using a Venturi mask to obtain a S_{pO_2} level of 90–92%, pregnancy, terminally ill patients, unable to self-prone	Ward	APP Usual care (nasal cannula)	10 17	29.7±5.3 27.3±4.2	318 (284–341)# 336 (303–388)#	12 h·day^{-1}	4.9±3.6 0.11±0.48 (first 24 h)	NA 1 (5.9)	0 (0) 0 (0)	0 (0) 0 (0)
Gad [55], 2021	RCT, single centre	Egypt	Hospitalised, positive COVID-19 PCR, adult, S_{aO_2} <90% (face mask O_2 5–10 L·min^{-1}), P_{aO_2}/F_{IO_2} <200, respiratory rate >24 breaths·min^{-1}, bilateral lung infiltrates on CT chest, not explained by cardiac failure, ready to cooperate to APP or NIV	Need for immediate IMV, respiratory rate >40 breaths·min^{-1}, use of accessory muscles, systolic pressure <100 mmHg, unable to APP and NIV	ICU	APP Usual care (NRM 10–15 L·min^{-1}) +repeated sessions of NIV	15 15	NA NA	126 (88–164) 111 (97–175)	1–2 h sessions of APP as tolerated	NA NA	NA NA	3 (20) 3 (20)	3 (20) 3 (20)
Jayakumar *et al.* [52], 2021	RCT, multi-centre	India	Adult, COVID-19 infection, admitted to ICU, requiring 0_2 ⩾4 L·min^{-1} or P_{aO_2}/F_{IO_2} between 100 and 300 (if ABG available)	Pregnancy, shock with norepinephrine ⩾0.1 µg·kg^{-1}·min^{-1}, GCS <15, need of immediate IMV, contraindication to APP (severe arrhythmia, spinal instability)	ICU	APP Usual care (nasal cannula, face mask, NRM, HFNC, NIV)	30 30	28.2±5.7 25.8±2.6	201.4±118.8 185.6±126.1	At least 6 h·day^{-1}	NA NA	2 (6.6) 0 (0)	4 (13.3) 4 (13.3)	3 (10) 2 (6.7)
Rosen *et al.* [51], 2021	RCT, multi-centre	Sweden	Adult, positive COVID-19 PCR, hypoxaemic respiratory failure, HFNC or NIV for respiratory support, P_{aO_2}/F_{IO_2} ⩽150 or corresponding S_{pO_2}/F_{IO_2} for more than 1 h	Inability to prone, immediate need for IMV, severe haemodynamic instability; previous intubation for COVID-19 pneumonia, pregnancy, <1 year life expectancy, do-not-intubate order, inability to understand study information	Ward, ICU	APP Usual care (HFNC, NIV)	36 39	28 (25–30) 29 (27–33)	115.5 (86.25–130.5) 115.5 (93.75–129.75)	At least 16 h·day^{-1}	8.5 (5.2–12.2) (first 3 days) 2.6 (0.3–8.1) (first 3 days)	NA NA	12 (33) 13 (33)	6 (17) 3 (8)
Johnson *et al.* [49], 2021	RCT, single centre	USA	Symptoms of COVID-19 combined with either a high clinical suspicion and a pending COVID-19 assay or a positive COVID-19 assay within 10 days	Unable to change position without assistance, pregnancy, incarcerated, admitted to ICU or transfer is imminent, mechanically ventilated, receiving hospice care	ED, ward	APP Usual care (room air, nasal cannula)	15 15	32.9 (27.5–39.4) 29.3 (24.4–32.9)	NA NA	Sessions of 1–2 h every 4 h	NA NA	9 (60) 0	2 (13.3) 1 (6.7)	2 (13.3) 0 (0)

Continued

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TABLE 1 Continued

Reference, year	Design	Country	Inclusion criteria	Exclusion criteria	Location at inclusion	Intervention	n	BMI, kg·m^{-2}, median (IQR)/mean±SD	Inclusion P/F or S/F median (IQR)/ mean±SD	Target duration of APP	APP duration, h·day^{-1}, median (IQR)/mean±SD	Cross-over, n (%)	Intubation, n (%)	Mortality, n (%)
Ehrmann *et al.* [44], 2021	Meta-trial, multi-centre	Mexico, USA, France, Spain, Ireland, Canada	Acute hypoxaemic respiratory failure due to proven (or suspected, pending microbiological confirmation) COVID-19 pneumonia and S_{pO_2}/F_{IO_2} ⩽315	Unable or refused to provide informed consent, haemodynamic instability, BMI >40 kg·m^{-2}, pregnancy, contraindication to APP	ED, ward, intermediate care unit, ICU	APP	564	29.7±4.6	119.3±43.3	As long and as frequently as possible each day	5.0 (1.6–8.8) (first 14 days)	83 (15)	185 (33) (HR 0.75, p=0.004)	117 (21) (HR 0.87, p=0.27)
						Usual care (HFNC)	557	29.7±4.6	117.3±37.2		0 (0–0)	64 (11)	223 (40)	132 (24)
Fralick *et al.* [45], 2022	RCT, multi-centre	Canada, USA	Confirmed or suspected COVID-19, required supplemental oxygen (up to 50% F_{IO_2}), able to prone position independently	Contra-indication to APP (*e.g.* recent abdominal surgery), impractical (*e.g.* dementia, severe delirium), or need of IMV	Ward	APP	126	NA	303 (261–336)#	Four times per day (up to 2 h per session)	2.5 (first 3 days)	NA	6 (4.8)	1 (0.8)
						Usual care (nasal cannula, mask, HFNC)	122	NA	305 (267–339)#		0	NA	5 (4.1)	1 (0.8)
Qian *et al.* [48], 2022	Quasi-RCT, multi-centre	USA	Adult, nonmechanically ventilated, hospitalised, acute hypoxaemic respiratory failure (nasal cannula oxygen, HFNC or NIV to keep S_{aO_2} ⩾89%), positive COVID-19 PCR	Patients receiving IMV at time of review or any time prior within the index hospitalisation	NA	APP	258	32.8±9.1	NA	As often as possible	4.2 (1.8–6.7) (first 5 days)	NA	31 (12)	56/239 (23.4)
						Usual care (nasal cannula, HFNC, NIV)	243	31.1±7.7	NA		0 (0–0.7)	NA	30 (12.3)	47/222 (21.2)
Alhazzani *et al.* [46], 2022	RCT, multi-centre	Canada, Kuwait, Saudi Arabia, USA	Adult, not intubated, suspected or confirmed COVID-19, requirement of at least 40% oxygen (*via* low or high-flow oxygen devices) or NIV, hospitalised in ICU or a monitored acute care unit	IMV within the same hospital admission, contraindications to APP, risk of complications from APP, self-proning prior to enrolment	Monitored acute care unit, ICU	APP	205	29.7±4.7	132 (103–174)#	8–10 h·day^{-1} (2–3 breaks of 1–2 h) as needed	4.8 (1.8–8) (first 4 days)	21 (10.2)	70 (34) (HR 0.81, p=0.20)	46 (22) (HR 0.93, p=0.72)
						Usual care (low flow oxygen, HFNC, NIV)	195	29.5±4.9	136 (110–181)#		0 (0–0)	38 (19)	79 (41)	46 (24)
Rampon *et al.* [47], 2022	RCT, multi-centre	USA, Spain	Hospitalised adults, confirmed/suspected COVID-19, not intubated, with access to a functioning smartphone, >48 h of admission to a medical ward	Requirement of O_2 ⩾6 L·min^{-1}, contraindications to prone positioning (unstable fracture, chest tube, recent facial trauma or surgery), unable to self-prone safely, dementia	ED, ward	APP	159	NA	396 (308–457)#	Up to four 1–2 h sessions daily; nightly for 12 h	NA	109 (68.5)	2 (1.3)	2 (1.3)
						Usual care (room air, nasal cannula, mask, HFNC)	134	NA	402 (311–457)#		NA	41 (30.6)	4 (3)	2 (1.5)

Data are presented as median (interquartile range (IQR)) or mean±SD. ABG: arterial blood gases; APP: awake prone positioning; ARDS: acute respiratory distress syndrome; BMI: body mass index; COVID-19: coronavirus disease 2019; CT: computed tomography; ED: emergency department; F_{IO_2}: inspiratory oxygen fraction; GCS: Glasgow Coma Scale; HFNC: high-flow nasal cannula; HR: hazard ratio; ICU: intensive care unit; IMV: invasive mechanical ventilation; NA: data not available or missing; NIV: noninvasive ventilation; NRM: nonrebreather mask; P_{aO_2}: arterial oxygen tension; P/F: ratio of arterial oxygen pressure to inspired oxygen fraction; S_{aO_2}: arterial oxygen saturation; S/F: ratio of arterial oxygen saturation to inspired oxygen fraction; S_{pO_2}: oxygen saturation measured by pulse oximetry. #: S_{pO_2} to F_{IO_2} ratio.

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requiring advanced respiratory support due to a lack of equipoise by physicians at the planning stage due to the perceived efficacy of the treatment [47]. This skewed the type of study conducted during the initial stages of the pandemic. A systematic meta-analysis using a random effects model on aggregated data from 10 clinical trials demonstrated a significant reduction in the rate of tracheal intubation in patients receiving advanced respiratory support and/or who were receiving ICU care at enrolment [43] (figure 3). In contrast, APP did not reduce the rate of intubation in patients receiving simple low flow supplemental oxygen therapy at enrolment and/or who were in a non-ICU environment at enrolment [43]. Enrolment location or type of respiratory support did not influence risk of intubation as no interaction was found in a meta-analysis which was confirmed by a trial sequential analysis of the studies [43]. The systematic review did not find a reduction in mortality with either type of respiratory support or treatment location. However, optimal information for trial sequential analysis was not reached for ICU patients suggesting further work is required to determine if APP affects mortality when applied to patients in ICU.

Respiratory support through HFNC reduces work of breathing [60], homogenously increases the end-expiratory lung volume in PP [61] and reduces dead space [62] and P_{aCO_2} [63]. Respiratory support with CPAP or NIV reduces dead space only in an open circuit with nasal exhalation ports [64], but not on a double-limb respiratory circuit setup that is usually recommended for COVID-19 patients. High tidal volumes, measurable in NIV, are difficult to avoid in AHRF [64] and are predictive of NIV failure and need for IMV [65]. The increased positive end-expiratory pressure and end-expiratory lung volume could be synergistic with APP and could theoretically reduce the risk of P-SILI [66]. Although P-SILI remains controversial, it has been one of the main arguments against APP, although data from the meta-trial and other studies showing similar durations of ventilation and outcomes in APP patients requiring invasive ventilation provide some reassurance. In addition, data on proned intubated and spontaneously breathing patients suggests a reduction in inspiratory effort that could reduce P-SILI [28]. HFNC may be better tolerated, given the larger face-mask interface along with the tubing required for NIV/CPAP devices. Small studies have demonstrated a reduction in the work of breathing in patients supported with helmet CPAP in the awake prone position [7]. Some studies on APP included mixed respiratory support in their design. To date, there has been no direct comparison of APP supported with different respiratory devices, but in a small prospective cohort where work of breathing was assessed by clinical gestalt, APP was associated with reduced work of breathing regardless of the device [67].

Although APP is mainly considered in unintubated patients, its use in minimally sedated intubated patients has been described on airway pressure release ventilation [68, 69] and post-extubation PP in patients who continued to have severe hypoxaemia that improved in the prone position has been described [70]. The latter requires close monitoring given the loss in muscle mass and power encountered post extubation.

Finally, it needs to be considered that the risk of intubation is lower for patients who are receiving conventional oxygen, likely indicating lower severity of COVID-19 disease but also possibly additional comorbidities that lead to symptoms that may not have been problematic in others [71]. Determining efficacy in this heterogenous patient group based on outcomes such as intubation and death is difficult due to the low event rate in the former and confounders in the latter. In this group of patients, outcome measures such as death and intubation may not be the most appropriate outcome measure and alternatives such as improved comfort, ROX index (ratio of oxygen saturation measured by pulse oximetry (S_{pO_2})/F_{IO_2} to respiratory rate) and discharge may be more clinically meaningful.

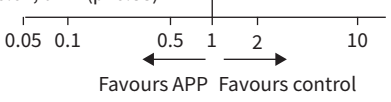
Impact of the location of care

Location of care appears to have an impact on APP effectiveness. A meta-analysis reported a reduction in the need for intubation (but not mortality) among patients requiring higher-level respiratory support and/or an ICU-type setting. In contrast, APP had no benefit in patients requiring less respiratory support and/or not in an ICU-type setting [43]. The ineffectiveness of APP in less sick, ward-managed patients was confirmed by the findings of two recent larger studies [46, 48]. Almost all (96%) of patients in the meta-trial were in intensive or intermediate care units, indicating a disease severity that requires intensive care input [44]. In general, ICU care was reserved for a select group of patients that 1) were deemed potentially recoverable and 2) were in countries with the resources to support them in this environment. Additionally, positive bio-feedback from watching an improvement in oxygen in response to APP available within the intensive care environment may also influence both medical and patients' positive assessment of the therapy that encourages its ongoing use. APP implementation requires patients' cooperation and ongoing support to ensure its efficacy. An outline of APP implementation with HFNC and NIV support is demonstrated in figures 4 and 5.

An important caveat here is that during the pandemic, especially in the early waves, the level of care and support provided in the ICU was extended to other hospital locations to assist with the increase in need.

a)

	APP n/N	Control n/N	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Advanced respiratory support					
EHRMANN *et al.* [44]	185/564	223/557	0.82 (0.70–0.96)	94.4%	94.1%
ROSEN *et al.* [51]	12/36	13/39	1.00 (0.53–1.90)	5.3%	5.6%
HARRIS *et al.* (NCT04853979)	1/5	1/8	1.60 (0.13–20.22)	0.3%	0.4%
Fixed effect model	198/605	237/604	0.83 (0.71–0.97)	100.0%	–
Random effects model			0.83 (0.71–0.97)	–	100.0%
Heterogeneity: I^2=0%, χ^2_2=0.61 (p=0.74)					
Conventional oxygen therapy					
GAD [55]	3/15	3/15	1.00 (0.24–4.18)	16.4%	21.3%
JAYAKUMAR *et al.* [52]	2/27	4/30	0.56 (0.11–2.80)	20.7%	16.7%
JOHNSON *et al.* [49]	2/15	1/15	2.00 (0.20–19.78)	5.5%	8.3%
KHARAT *et al.* [50]	0/10	0/17		0.0%	0.0%
TAYLOR *et al.* [56]	0/27	0/13		0.0%	0.0%
RAMPON *et al.* [47]	2/159	4/134	0.42 (0.08–2.26)	23.7%	15.4%
FRALICK *et al.* [45]	6/126	5/122	1.16 (0.36–3.71)	27.8%	32.4%
HARRIS *et al.* (NCT04853979)	1/26	1/22	0.85 (0.06–12.76)	5.9%	5.9%
Fixed effect model	16/405	18/356	0.86 (0.45–1.64)	100.0%	–
Random effects model			0.87 (0.45–1.69)	–	100.0%
Heterogeneity: I^2=0%, χ^2_5=1.79 (p=0.88)					
Test for subgroup differences (fixed effect): χ^2_1=0.01, df=1 (p=0.92)					
Test for subgroup differences (random effects): χ^2_1=0.02, df=1 (p=0.88)					



b)

	APP n/N	Control n/N	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
ICU					
EHRMANN *et al.* [44]	182/538	219/533	0.82 (0.70–0.96)	96.9%	97.4%
GAD [55]	3/15	3/15	1.00 (0.24–4.18)	1.3%	1.2%
JAYAKUMAR *et al.* [52]	4/30	4/30	1.00 (0.28–3.63)	1.8%	1.4%
Fixed effect model	189/583	226/578	0.83 (0.71–0.97)	100.0%	–
Random effects model			0.83 (0.71–0.97)	–	100.0%
Heterogeneity: I^2=0%, χ^2_3=1.57 (p=0.81)					
Non-ICU					
EHRMANN *et al.* [44]	3/26	4/24	0.69 (0.17–2.78)	25.0%	24.8%
JOHNSON *et al.* [49]	2/15	1/15	2.00 (0.20–19.78)	6.0%	9.1%
KHARAT *et al.* [50]	0/10	0/17		0.0%	0.0%
TAYLOR *et al.* [56]	0/27	0/13		0.0%	0.0%
RAMPON *et al.* [47]	2/159	4/134	0.42 (0.08–2.26)	26.1%	17.0%
FRALICK *et al.* [45]	6/126	5/122	1.16 (0.36–3.71)	30.6%	35.7%
HARRIS *et al.* (NCT04853979)	2/31	2/30	0.97 (0.15–6.44)	12.2%	13.4%
Fixed effect model	15/394	16/355	0.88 (0.45–1.73)	100.0%	–
Random effects model			0.88 (0.44–1.76)	–	100.0%
Heterogeneity: I^2=0%, χ^2_4=1.57 (p=0.81)					
Test for subgroup differences (fixed effect): χ^2_1=0.03, df=1 (p=0.87)					
Test for subgroup differences (random effects): χ^2_1=0.03, df=1 (p=0.86)					

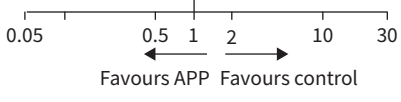


FIGURE 3 Forest plots of randomised controlled trials with a subgroup analysis of intubation based on a) advanced *versus* conventional oxygen respiratory support and b) intensive care unit (ICU) *versus* non-ICU. APP: awake prone positioning. Reproduced and modified from [43] with permission.

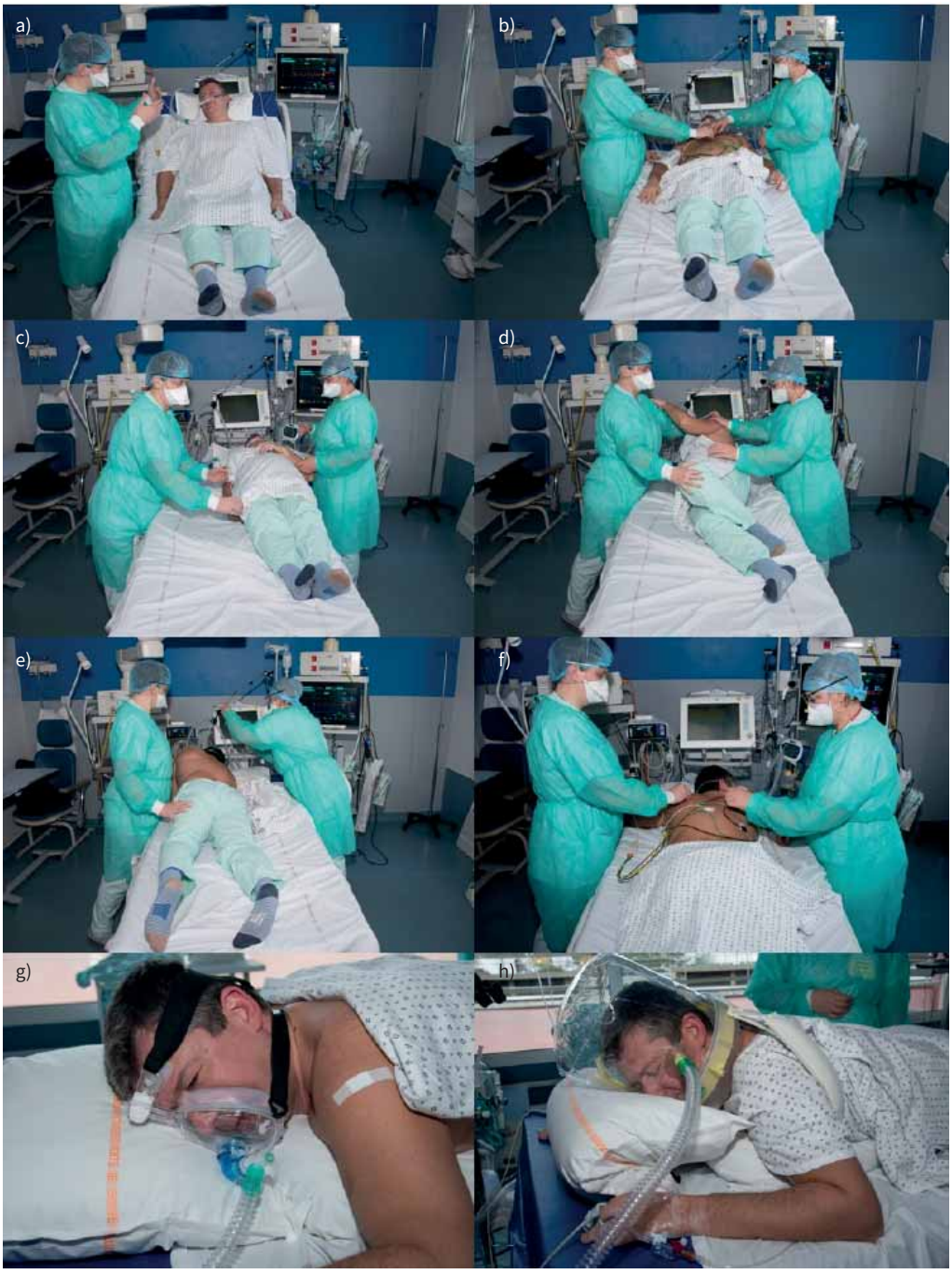


FIGURE 4 Technique for placing patients in awake prone position. a) Explain to the patient the potential benefit of the technique. b) Remove electrodes from the anterior thorax. c) Move the patient horizontally to a side of the bed. d) Slowly place the patient in full lateral position. e) Move the patient to a full prone position. f) Replace the electrodes on the back. g) Awake prone positioning (APP) can be used under high-flow nasal cannula (HFNC) but also under noninvasive ventilation (NIV) with a facial mask. h) APP can be used under HFNC but also under NIV with a helmet.

Sub-ICUs and advanced respiratory wards were suitable for severely hypoxic but otherwise stable patients with COVID-19. These locations likely managed patients that would otherwise have been in the ICU prior to the pandemic. Consequently, the distinction between ward-level care and ICU-level care became less clear. In addition, the location also likely dictated the level of oxygen support available and so it is difficult to discern the impact of degree of respiratory support from location of care. These caveats mean

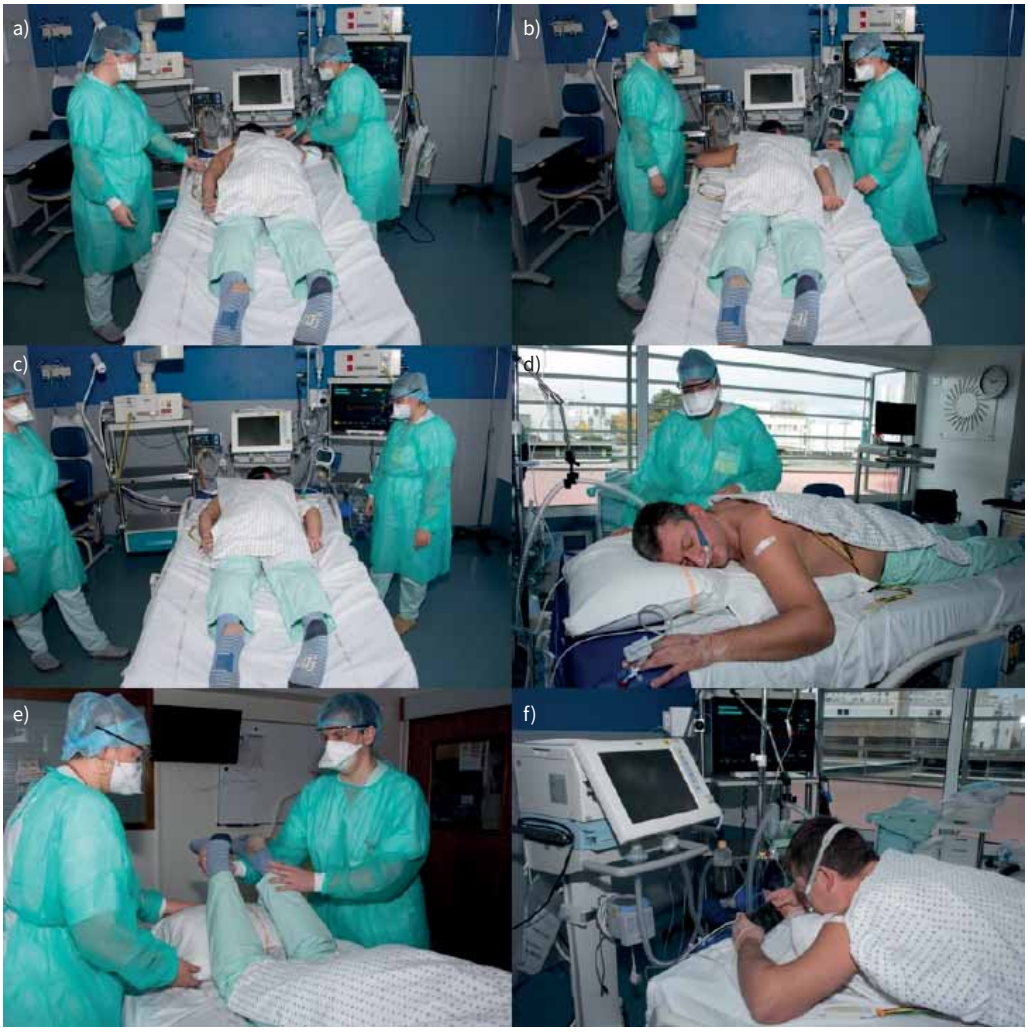


FIGURE 5 Approaches to optimising prone positioning in awake patients receiving advanced respiratory support. a–c) Different positions of the arms can be tried depending on the patient's preferences (swimmer's position). d) and e) Pillows can be placed under the thorax or the legs to improve comfort. f) A smartphone can help to distract/relax the patient.

that one should still consider the use of APP in selected patients at ward level, where resources and facilities permit.

Importance of duration of APP

While no study has been explicitly designed to address the effects of APP duration, data from secondary analyses of studies suggests a dose–response relationship between duration of time spent in APP and the efficacy of APP. In the large RCT from Mexico [59], which was part of the meta-trial [44], IBARRA-ESTRADA *et al.* [59] demonstrated that patients who could maintain APP for ⩾8 h had the least number of intubations and significantly lower mortality. In an observational cohort of 335 patients treated with HFNC, it was found that 56% of patients tolerated 12 h·day^{-1} in APP and those who spent 8 h·day^{-1} had an OR of 0.29 (95% CI 0.15–0.60) for intubation and an OR of 0.37 (95% CI 0.17–0.80) for mortality.

In another study examining physiological responses to proning, the length of PP session on day 1 predicted 50% of the variation in lung ultrasound reaeration and recruitment, with an improvement in P_{aO_2}/F_{IO_2} observed in patients proning for at least 6 h, a reduction in dead space in patients proning for 9 h and a global lung ultrasound reaeration score >8 in patients who proned for >10 h [29]. An important limitation is that objective measures of time spent in APP have been lacking, with studies primarily relying on

nursing records to identify proning times. Further work is needed to determine the optimal time both for each session and when to discontinue this therapy.

APP adherence and tolerance

The adherence of patients to APP, which is generally a function of their ability to tolerate this position, is an important factor in determining its success and one not encountered in invasively ventilated patients [72]. Both patient and systems factors influence the ability of a patient to remain proned while breathing spontaneously, impacting on the technique's feasibility, tolerability and adoption. On the patient side, disease severity and musculoskeletal discomfort will impact the length of time they tolerate APP treatment. Additionally, musculoskeletal discomfort can increase the work of breathing and the patient's body habitus, particularly where insufficient staff are available, may preclude the ability to safely prone the patient [73]. Perhaps unsurprisingly, the duration of APP reported in different studies varies from less than 1 $h \cdot day^{-1}$ [50, 52] to more than 12 $h \cdot day^{-1}$ [59, 74]. As a longer duration of APP is associated with lower requirements for intubation, improving patient adherence to APP is crucial.

Some alternatives to improve the tolerance of APP, including adopting Rodin's position [34] and lateral positioning, have been suggested to enhance tolerability. However, the improved lung recruitment with the latter is not as effective as the full prone position on the stomach [75]. On the providers' side, belief in the usefulness of the treatment, the time available to assist the patient in position change and concern for excessive interaction with the patient as a contagion risk are factors that may impact its application [76]. Healthcare systems issues, such as intensive care capacity, influence adherence to APP, particularly where there are constraints on staff and equipment, as was found during the pandemic [72].

Several studies incorporated efforts to improve adherence (patient tracking logs, smartphone prompts and phone calls) that were unsuccessful in increasing time tolerated in the prone position [45, 47, 49, 56]. A qualitative assessment of the acceptability of proning by Taylor *et al.* [56] noted that adherence to proning was difficult due to the unpredictability and complexity of the working environment. The study reported many protocol violations, with no patients managing the 12–16 h of proning recommended by providers. A small case series of patients with initial mean P_{aO_2}/F_{IO_2} of 121 treated with HFNC showed that implementing a personalised protocol with the active involvement of trained healthcare personnel helped achieve 13 $h \cdot day^{-1}$ on APP for 20 consecutive days [53]. Increasing evidence suggests that a simple suggestion of "self-proning" is not enough to achieve prolonged time on APP [45, 47] as a therapeutic intervention.

Pharmacological interventions may help to improve adherence to APP. Dexmedetomidine has recently shown to be feasible and safe (only five patients presented bradycardia of <40 beats per min) in a single-centre study of 63 COVID-19 patients with moderate to severe hypoxaemia and it appeared to facilitate APP adherence in the study by Taboada *et al.* [74]. Similar to PP in intubated patients, APP should be directly delivered/assisted by the healthcare staff. Self proning, particularly in fragile patients, is a misnomer as it fails to convey the complexity and need for healthcare assistance to harness the potential of this manoeuvre [72].

APP complications and contraindications

An important complication of PP is nerve compression injuries, particularly when the prone position is adopted for longer periods of time. Brachial plexus injuries post prone position for patients undergoing IMV is common and well described in the literature. Fortunately, the incidence of brachial or ulnar injuries with in the awake patient is rare. In a case report, a 61-year-old who practiced nocturnal proning for over 2 weeks noted decreased sensation and dysesthesia in his bilateral ulnar forearms and fourth and fifth digits, which resolved completely after 1.5 months without intervention [77]. The ulnar nerve may be compressed at the elbow in the condylar groove between the olecranon and the medial epicondyle of the humerus. Flexion narrows the cubital groove by tightening the room and causes bulging of its floor. Advice to reduce the incidence of ulnar injury would include reducing elbow flexion of more than 90 degrees.

There are absolute and relative contraindication to APP. Similar to proning of mechanically ventilated patients, absolute contraindications include spinal instability or at risk of spinal instability, unstable fractures (especially facial and pelvic), anterior burns and open wounds, shock, recent tracheal surgery, and raised intracranial pressure [1]. APP is not an alternative to mechanical ventilation and where there are clear indications for intubation and controlled mechanical ventilation it should not be withheld. The evidence base suggests most benefit for preventing need for intubation is in the population requiring advanced respiratory support, which means that careful monitoring of patients is required including oxygen saturation monitoring and blood pressure monitoring. Most studies that examined the effect of APP in

patients requiring advanced respiratory support were carried out in ICU or intermediate care units, which suggests that additional nursing support is needed to safely and effectively carry out the manoeuvre [43].

Key unknowns and future research directions

While much is understood at this point regarding the effectiveness of APP and the patients/situations in which it is most likely to be effective, there are still several important unknowns that should shape future research directions. We need to understand how and to what extent APP is used in current daily practice among COVID-19 patients and the extent (if any) to which it is used in patients with other causes of AHRF. This question may be addressed in a large worldwide-scale 1-day prevalence study that could also investigate barriers to implementation and factors influencing patients' comfort in prone positions.

The potential for APP to modulate the risk of P-SILI is incompletely understood. While evidence exists that APP reduces respiratory efforts and work of breathing, there may be patient types that do not manifest these benefits. Evaluation of the work of breathing in APP under HFNC and other respiratory support modalities in conjunction with respiratory mechanics and lung aeration measurements would give valuable information to explore those questions. Interestingly, in the study by Chiumello *et al.* [7], the work of breathing did not correlate with the ROX index and respiratory rate in the prone position.

Further refining the criteria to identify patients who will benefit most from APP is crucial as it is a labour-intensive process that risks patient stability if they stop responding to the treatment [34]. The role of APP among non-COVID-19 patients, such as patients suffering from other community-acquired pneumonia from either bacterial or viral causes, acute heart failure, and post-anaesthesia, is so far unknown but is currently being explored in an ongoing randomised trial [78]. Differences in the underlying pathophysiology of AHRF from COVID-19, including the presence of silent hypoxaemia and lower incidence of shock [79], may mean it will be less well tolerated as an intervention in non-COVID-19 AHRF. Structural alterations, particularly dilatation of vessels increased areas of shunting typical of COVID-19, may have an optimised response to APP that may not be the case in other causes of AHRF [58]. Additional studies are needed here to fully understand the therapeutic potential of APP in these conditions. The optimal implementation technique of APP is still unknown. Improving the tolerance and comfort of patients deserves investigation with multidisciplinary input from patients, nurses and respiratory therapists [80]. In addition, recommendations focused on low-income countries were generated, given the feasibility and potential benefits of APP in a limited ICU capacity situation. The overall cost of this labour-intensive intervention is primarily unknown [72].

Furthermore, although the evidence base for APP has improved, there are many unanswered questions on the treatment's role, including the optimal patient to undergo, the length of time in the prone position and when to stop this therapy. Some of these questions will be addressed in a planned individual patient meta-analysis of the studies to date. This will influence the design and execution of subsequent studies in APP.

Points for clinical practice

- PP leads to changes in inflation, ventilation and perfusion of the lung and the degree to which these influence gas exchange depends on the disease state of the lung and the patient.
- The type of respiratory support appears to influence the success rates of APP. Meta-analysis of studies has shown that APP reduced the need for invasive ventilation, while subgroup analysis showed that this benefit was confined to patients who received advanced respiratory support, such as HFNC oxygen therapy or NIV.
- The location of clinical care also influences the success rates of APP, with patients receiving care in a critical care location appearing to benefit.
- While no study has been explicitly designed to address the effects of APP duration, data from secondary analyses of studies suggests a dose–response relationship between duration of time spent in APP and its efficacy.

Summary and conclusions

In conclusion, the evidence base for APP has improved, with strong evidence that more hypoxaemic patients requiring advanced respiratory support, who are managed in higher care environments and who can be prone for several hours, benefit most from APP use. However, there remain unanswered questions on the role of this treatment, which will be addressed in a planned individual patient meta-analysis of the studies to date. This will influence the design and execution of subsequent studies in APP.

Provenance: Commissioned article, peer reviewed.

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References

1 Guerin C, Reignier J, Richard JC, *et al.* Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368: 2159–2168.
2 Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976; 4: 13–14.
3 McNicholas B, Cosgrave D, Giacomini C, *et al.* Prone positioning in COVID-19 acute respiratory failure: just do it? *Br J Anaesth* 2020; 125: 440–443.
4 Kallet RH. A comprehensive review of prone position in ARDS. *Respir Care* 2015; 60: 1660–1687.
5 Petersson J, Ax M, Frey J, *et al.* Positive end-expiratory pressure redistributes regional blood flow and ventilation differently in supine and prone humans. *Anesthesiology* 2010; 113: 1361–1369.
6 Liu L, Xie J, Wang C, *et al.* Prone position improves lung ventilation–perfusion matching in non-intubated COVID-19 patients: a prospective physiologic study. *Crit Care* 2022; 26: 193.
7 Chiumello D, Chiodaroli E, Coppola S, *et al.* Awake prone position reduces work of breathing in patients with COVID-19 ARDS supported by CPAP. *Ann Intensive Care* 2021; 11: 179.
8 Hoffman EA. Effect of body orientation on regional lung expansion: a computed tomographic approach. *J Appl Physiol* 1985; 59: 468–480.
9 Mure M, Glenny RW, Domino KB, *et al.* Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998; 157: 1785–1790.
10 Henderson AC, Sá RC, Theilmann RJ, *et al.* The gravitational distribution of ventilation–perfusion ratio is more uniform in prone than supine posture in the normal human lung. *J Appl Physiol* 2013; 115: 313–324.
11 Treppo S, Mijailovich SM, Venegas JG. Contributions of pulmonary perfusion and ventilation to heterogeneity in V'_A/Q' measured by PET. *J Appl Physiol* 1997; 82: 1163–1176.
12 Glazier JB, Hughes JM, Maloney JE, *et al.* Vertical gradient of alveolar size in lungs of dogs frozen intact. *J Appl Physiol* 1967; 23: 694–705.
13 Moreno F, Lyons HA. Effect of body posture on lung volumes. *J Appl Physiol* 1961; 16: 27–29.
14 Rohdin M, Petersson J, Sundblad P, *et al.* Effects of gravity on lung diffusing capacity and cardiac output in prone and supine humans. *J Appl Physiol* 2003; 95: 3–10.

15 Rohdin M, Petersson J, Mure M, *et al.* Distributions of lung ventilation and perfusion in prone and supine humans exposed to hypergravity. *J Appl Physiol* 2004; 97: 675–682.
16 Berg RMG, Hartmann JP, Iepsen UW, *et al.* Therapeutic benefits of proning to improve pulmonary gas exchange in severe respiratory failure: focus on fundamentals of physiology. *Exp Physiol* 2022; 107: 759–770.
17 Amis TC, Jones HA, Hughes JM. Effect of posture on inter-regional distribution of pulmonary perfusion and V_A/Q ratios in man. *Respir Physiol* 1984; 56: 169–182.
18 Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000; 161: 1660–1665.
19 Malbouisson LM, Busch CJ, Puybasset L, *et al.* Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. *Am J Respir Crit Care Med* 2000; 161: 2005–2012.
20 Jozwiak M, Teboul JL, Anguel N, *et al.* Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013; 188: 1428–1433.
21 Perier F, Tuffet S, Maraffi T, *et al.* Effect of positive end-expiratory pressure and proning on ventilation and perfusion in COVID-19 acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020; 202: 1713–1717.
22 Fossali T, Pavlovsky B, Ottolina D, *et al.* Effects of prone position on lung recruitment and ventilation–perfusion matching in patients with COVID-19 acute respiratory distress syndrome: a combined CT scan/electrical impedance tomography study. *Crit Care Med* 2022; 50: 723–732.
23 Sharp T, Al-Faham Z, Brown M, *et al.* Prone position in covid-19: can we tackle rising dead space? *J Intensive Care Soc* 2022; 23: 240–243.
24 Soro M, Garcia-Perez ML, Belda FJ, *et al.* Effects of prone position on alveolar dead space and gas exchange during general anaesthesia in surgery of long duration. *Eur J Anaesthesiol* 2007; 24: 431–437.
25 Gattinoni L, Vagginelli F, Carlesso E, *et al.* Decrease in P_{aCO_2} with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; 31: 2727–2733.
26 Cammarota G, Rossi E, Vitali L, *et al.* Effect of awake prone position on diaphragmatic thickening fraction in patients assisted by noninvasive ventilation for hypoxemic acute respiratory failure related to novel coronavirus disease. *Crit Care* 2021; 25: 305.
27 Yoshida T, Engelberts D, Chen H, *et al.* Prone position minimizes the exacerbation of effort-dependent lung injury: exploring the mechanism in pigs and evaluating injury in rabbits. *Anesthesiology* 2022; 136: 779–791.
28 Yoshida T, Tanaka A, Roldan R, *et al.* Prone position reduces spontaneous inspiratory effort in patients with acute respiratory distress syndrome: a bicenter study. *Am J Respir Crit Care Med* 2021; 203: 1437–1440.
29 Musso G, Taliano C, Molinaro F, *et al.* Early prolonged prone position in noninvasively ventilated patients with SARS-CoV-2-related moderate-to-severe hypoxemic respiratory failure: clinical outcomes and mechanisms for treatment response in the PRO-NIV study. *Crit Care* 2022; 26: 118.
30 Ibarra-Estrada M, Gamero-Rodriguez MJ, Garcia-de-Acilu M, *et al.* Lung ultrasound response to awake prone positioning predicts the need for intubation in patients with COVID-19 induced acute hypoxemic respiratory failure: an observational study. *Crit Care* 2022; 26: 189.
31 Valter C, Christensen AM, Tollund C, *et al.* Response to the prone position in spontaneously breathing patients with hypoxemic respiratory failure. *Acta Anaesthesiol Scand* 2003; 47: 416–418.
32 Scaravilli V, Grasselli G, Castagna L, *et al.* Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: a retrospective study. *J Crit Care* 2015; 30: 1390–1394.
33 Sartini C, Tresoldi M, Scarpellini P, *et al.* Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA* 2020; 323: 2338–2340.
34 Coppo A, Winterton D, Benini A, *et al.* Rodin's thinker: an alternative position in awake patients with COVID-19. *Am J Respir Crit Care Med* 2021; 204: 728–730.
35 Elharrar X, Trigui Y, Dols AM, *et al.* Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020; 323: 2336–2338.
36 Bamford P, Bentley A, Dean J, *et al.* ICS Guidance for Prone Positioning of the Conscious COVID Patient. https://ics.ac.uk/resource/guidance-for-conscious-proning.html Date last updated: 4 December 2020. Date last accessed: 3 April 2023.
37 COVID-19 Protocols: Awake Proning Protocol. https://covidprotocols.org/en/chapters/inpatient-management/#awake-proning-protocol-w144du6d2l4x Date last accessed: 29 March 2023.
38 Munshi L, Fralick M, Fan E. Prone positioning in non-intubated patients with COVID-19: raising the bar. *Lancet Respir Med* 2020; 8: 744–745.
39 Pavlov I, He H, McNicholas B, *et al.* Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19. *Respir Care* 2022; 67: 101–114.
40 Gattinoni L, Tognoni G, Pesenti A, *et al.* Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345: 568–573.
41 Mancebo J, Fernández R, Blanch L, *et al.* A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173: 1233–1239.

42 Taccone P, Pesenti A, Latini R, *et al.* Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009; 302: 1977–1984.
43 Li J, Luo J, Pavlov I, *et al.* Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. *Lancet Respir Med* 2022; 10: 573–583.
44 Ehrmann S, Li J, Ibarra-Estrada M, *et al.* Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021; 9: 1387–1395.
45 Fralick M, Colacci M, Munshi L, *et al.* Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). *BMJ* 2022; 376: e068585.
46 Alhazzani W, Parhar KKS, Weatherald J, *et al.* Effect of awake prone positioning on endotracheal intubation in patients with COVID-19 and acute respiratory failure: a randomized clinical trial. *JAMA* 2022; 327: 2104–2113.
47 Rampon G, Jia S, Agrawal R, *et al.* Smartphone-guided self-prone positioning *vs* usual care in nonintubated hospital ward patients with COVID-19: a pragmatic randomized clinical trial. *Chest* 2022; 162: 782–791.
48 Qian ET, Gatto CL, Amusina O, *et al.* Assessment of awake prone positioning in hospitalized adults with COVID-19: a nonrandomized controlled trial. *JAMA Intern Med* 2022; 182: 612–621.
49 Johnson SA, Horton DJ, Fuller MJ, *et al.* Patient-directed prone positioning in awake patients with COVID-19 requiring hospitalization (PAPR). *Ann Am Thorac Soc* 2021; 18: 1424–1426.
50 Kharat A, Dupuis-Lozeron E, Cantero C, *et al.* Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. *ERJ Open Res* 2021; 7: 00692-2020.
51 Rosen J, von Oelreich E, Fors D, *et al.* Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. *Crit Care* 2021; 25: 209.
52 Jayakumar D, Ramachandran Dnb P, Rabindrarajan Dnb E, *et al.* Standard care *versus* awake prone position in adult nonintubated patients with acute hypoxemic respiratory failure secondary to COVID-19 infection-a multicenter feasibility randomized controlled trial. *J Intensive Care Med* 2021; 36: 918–924.
53 Busico M, Laiz MM, Urrutia JG, *et al.* Strategies to achieve adherence to prone positioning in awake COVID-19 patients with high-flow nasal oxygen. A case series. *Can J Respir Ther* 2022; 58: 151–154.
54 Othman SY, El-Menshawy AM, Mohamed AM. Effects of awake-prone positioning on oxygenation and physiological outcomes in non-intubated patients with COVID-19: a randomized controlled trial. *Nurs Crit Care* 2022; in press [https://doi.org/10.1111/nicc.12833].
55 Gad GS. Awake prone positioning versus non invasive ventilation for COVID-19 patients with acute hypoxemic respiratory failure. *Egypt J Anaesthesia* 2021; 37: 85–90.
56 Taylor SP, Bundy H, Smith WM, *et al.* Awake prone positioning strategy for nonintubated hypoxic patients with COVID-19: a pilot trial with embedded implementation evaluation. *Ann Am Thorac Soc* 2021; 18: 1360–1368.
57 Lee HJ, Kim J, Choi M, *et al.* Efficacy and safety of prone position in COVID-19 patients with respiratory failure: a systematic review and meta-analysis. *Eur J Med Res* 2022; 27: 310.
58 Piciucchi S, Ravaglia C, Vizzuso A, *et al.* Awake prone positioning for COVID-19 acute respiratory failure: imaging and histological background. *Lancet Respir Med* 2022; 10: e14.
59 Ibarra-Estrada M, Li J, Pavlov I, *et al.* Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxemic respiratory failure: analysis of a randomized controlled trial. *Crit Care* 2022; 26: 84.
60 Mauri T, Turrini C, Eronia N, *et al.* Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017; 195: 1207–1215.
61 Riera J, Pérez P, Cortés J, *et al.* Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. *Respir Care* 2013; 58: 589–596.
62 Moller W, Feng S, Domanski U, *et al.* Nasal high flow reduces dead space. *J Appl Physiol* 2017; 122: 191–197.
63 Alnajada AA, Blackwood B, Mobrad A, *et al.* High flow nasal oxygen for acute type two respiratory failure: a systematic review. *F1000Res* 2021; 10: 482.
64 Saatci E, Miller DM, Stell IM, *et al.* Dynamic dead space in face masks used with noninvasive ventilators: a lung model study. *Eur Respir J* 2004; 23: 129–135.
65 Carteaux G, Millan-Guilarte T, De Prost N, *et al.* Failure of noninvasive ventilation for *de novo* acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med* 2016; 44: 282–290.
66 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; 195: 438–442.
67 Fazzini B, Fowler AJ, Zolfaghari P. Effectiveness of prone position in spontaneously breathing patients with COVID-19: a prospective cohort study. *J Intensive Care Soc* 2022; 23: 362–365.
68 Lee SJ, Lee Y, Kong A, *et al.* Airway pressure release ventilation combined with prone positioning in acute respiratory distress syndrome: old tricks new synergy: a case series. *A A Pract* 2020; 14: e01231.
69 Varpula T, Jousela I, Niemi R, *et al.* Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury. *Acta Anaesthesiol Scand* 2003; 47: 516–524.
70 Karpov A, Mitra AR, Crowe S, *et al.* Prone position after liberation from prolonged mechanical ventilation in COVID-19 respiratory failure. *Crit Care Res Pract* 2020; 2020: 6688120.

71 Wang T, Du Z, Zhu F, *et al.* Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet* 2020; 395: e52.

72 Stilma W, Akerman E, Artigas A, *et al.* Awake proning as an adjunctive therapy for refractory hypoxemia in non-intubated patients with COVID-19 acute respiratory failure: guidance from an international group of healthcare workers. *Am J Trop Med Hyg* 2021; 104: 1676–1686.

73 Ali S, Khatri A, Ghouri N, *et al.* Combining non-invasive ventilation with timed position change in the emergency department to improve oxygenation and outcomes in patients with COVID-19: a prospective analysis from a low resource setup. *Pak J Med Sci* 2022; 38: 375–379.

74 Taboada M, Baluja A, Santos LD, *et al.* Effectiveness of dexmedetomidine combined with high flow nasal oxygen and long periods of awake prone positioning in moderate or severe COVID-19 pneumonia. *J Clin Anesth* 2021; 72: 110261.

75 Retucci M, Aliberti S, Ceruti C, *et al.* Prone and lateral positioning in spontaneously breathing patients with COVID-19 pneumonia undergoing noninvasive helmet CPAP treatment. *Chest* 2020; 158: 2431–2435.

76 Nguyen LH, Drew DA, Graham MS, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020; 5: e475–e483.

77 Sayegh MJ, Larsen CG, Pinpin C, *et al.* Ulnar neuropathy after intermittent prone positioning for COVID-19 infection: a preliminary report of 3 cases. *JBJS Case Connect* 2021; 11: e20.00729.

78 Morales-Quinteros L, Schultz MJ, Serpa-Neto A, *et al.* Awake prone positioning in nonintubated spontaneous breathing ICU patients with acute hypoxemic respiratory failure (PRONELIFE) – protocol for a randomized clinical trial. *Trials* 2022; 23: 30.

79 McNicholas BA, Rezoagli E, Simpkin AJ, *et al.* Epidemiology and outcomes of early-onset AKI in COVID-19-related ARDS in comparison with non-COVID-19-related ARDS: insights from two prospective global cohort studies. *Crit Care* 2023; 27: 3.

80 Shikano K, Sakao S, Inaba Y, *et al.* Tolerability of prone positioning in non-intubated patients with hypoxaemia due to COVID-19-related pneumonia. *Respirology* 2022; 27: 370–371.

81 Gattinoni L, Taccone P, Carlesso E, *et al*. Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. *Am J Respir Crit Care Med* 2013; 188: 1286–1293.