Effect of serial awake prone positioning on oxygenation in patients admitted to intensive care with COVID-19

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ABSTRACT

Introduction Awake prone positioning (APP) might benefit patients with COVID-19 by improving oxygenation, but it is unknown whether this improvement can be sustained with serial proning episodes.

Methods We conducted a retrospective review of adults with COVID-19 admitted to one intensive care unit, in those who underwent APP and controls. Patients in both groups had type 1 respiratory failure requiring oxygen (but not initially intubated), confirmed SARS-CoV-2 PCR by nasopharyngeal swab and findings of multifocal ground-glass opacities on imaging. For the APP group, serial SpO_2/FiO_2 measurements were recorded after each proning episode.

Results Of 77 patients admitted, 50 (65%) were excluded because they had already been intubated. Another 7 (9%) had undergone APP prior to admission. Of the remaining 20, 10 underwent APP and 10 were controls. Patients in both groups had similar demographics, subsequent intubation and survival. Of those who underwent APP, SpO_2/FiO_2 was most likely to increase after the first episode (before median: 152, IQR 135–185; after: median 192, IQR 156–234, p=0.04). Half of participants (5) in the APP group were unable to tolerate more than two APP episodes.

Conclusions Most patients with COVID-19 admitted to the intensive care are not suitable for APP. Of those who are, many cannot tolerate more than two episodes. Improvements in SpO_2/FiO_2 secondary to APP are transient and most likely in the first episode. Our findings may explain why other studies have failed to show improvements in mortality from APP despite improvements in oxygenation.

INTRODUCTION

COVID-19 has caused a global pandemic with high morbidity and mortality. Since the start of the second peak (1 September 2020 to 4 December 2020) in the UK, 6388 patients with COVID-19 have been admitted to intensive care units (ICUs), with up to 21.2% requiring invasive mechanical ventilation (IMV), 17.2% needing advanced cardiovascular support and a mortality rate of 28.6% in those with severe disease.[1]

Awake prone positioning (APP) might improve the prognosis of patients with severe COVID-19, with benefits relating to improvements in ventilatory homogeneity and reductions in lung injury through regional hyperinflation.[2] In awake patients with acute respiratory distress syndrome (ARDS), observational evidence suggests that APP may improve PaO_2 and FiO_2.[2–4] However, it remains uncertain whether APP improves clinical outcomes in COVID-19, where the pathophysiology may differ from that of ARDS unrelated to COVID-19.[2 5 6] One prospective cohort study found that a single, 3-hour-long episode of APP led to increases in oxygenation in patients with COVID-19.[7] Despite this, APP has not been associated with reductions in mortality or in the need for invasive ventilation.[8] Crucially, there are no substantial longitudinal data assessing whether repeated episodes of prone positioning can lead to sustained changes in oxygenation.

Due to the fast-moving nature of the pandemic and the relative safety of the intervention, APP has since been advocated by the UK Intensive Care Society (ICS) for suitable patients with COVID-19 who require non-invasive respiratory support, despite no conclusive evidence for its efficacy.[9] In the present study, we outline our experience of APP after introduction of the intervention into our local intensive care unit (ICU). Specifically, we present longitudinal data on how APP affects oxygenation in this cohort.

METHODS

We performed a retrospective review of patients who underwent a standardised APP protocol in the ICU setting of Buckinghamshire NHS Trust, UK, between 26 March and 26 June 2020. Inclusion criteria consisted of

- Age 18 years or over
- Hypoxic respiratory failure (type 1) requiring oxygen
- Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) detected by PCR on nasopharyngeal swab.
- Findings of multifocal ground-glass opacities and/or consolidation on imaging.

We excluded patients who did not have COVID-19, or who were intubated prior to or immediately on arrival to ICU, as well as those who underwent APP on the ward in our analysis. Control patients were those who fit the inclusion criteria, but refused or were physically unable to undergo APP.

APP protocol

All patients were instructed as per the infographic displayed in figure 1. We first examined the patients for any contraindications to APP (morbid obesity,

low Glasgow Coma Scale, delirium pressure sores on dependent areas, pregnancy, severe respiratory distress, systolic blood pressure 90mgHg or below). We then instructed patients to position themselves on their front with their arms either bilaterally abducted to rest in front of them, bilaterally down by their sides, or in a position reminiscent of the 'swimmer's position' used with intubated patients, where one arm is abducted at the shoulder and slightly flexed at the elbow with the other resting by their side. The choice of position was dependent on patient preference and comfort.

We encouraged patients to use pillows under the chest, pelvis and ankles to provide additional comfort and allowed them to maintain the prone position for longer periods. Patients remained in the prone position for as long as possible, before changing position, depending on comfort and oxygen saturations. Between episodes, we encouraged patients to lie in the right or left lateral recumbent position. With every position change, the designated nurse looking after the patient checked oxygen saturations, mask leaks, and for compression of invasive lines.

We aimed to explore whether APP was feasible in the ICU setting and whether ongoing APP was manageable in our patients in addition to improving oxygenation. Our main outcome measure was the SpO_2/FiO_2 ratio, recorded after each APP episode. Secondary outcomes included the admission International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 4C mortality score,[10] length of stay in ICU, escalation to invasive mechanical ventilation (IMV), and 28-day mortality in both awake-proned and control cohorts.

Descriptive statistics were used to characterise the demographics, disease severity and outcomes in both the APP and control group. Continuous variables are all assumed to be distributed non-parametrically due to the low numbers of participants compared, and therefore are displayed as median and interquartile range (IQR); categorical variables are displayed as number and percentage. Fisher's exact test (<5 observations in each cell) or Pearson's χ^2 test (5 or more observations in each cell) were used for nominal data and the Mann-Whitney U test was used for non-parametric data to examine differences between patients and controls. A p value <0.05 was considered statistically significant. Statistical analysis was performed using Stata/IC V.16.1 (StataCorp, USA).

RESULTS

Between 26 March and 26 June 2020, 77 patients were admitted to the ICU with COVID-19. In total, 50 (65%) were excluded because they were already intubated on transferring to the unit. Seven patients (9%) had undergone APP prior to ICU admission. Of the remaining 20 patients, 10 underwent APP, and 10 refused or were unable to prone, thus serving as controls.

Characteristics of both APP patients and controls are shown in table 1. Both groups were similar in age, gender, ethnicity and disease severity as measured by admission SOFA and Apache II scores. Admission ISARIC 4C mortality scores were higher in the control cohort (APP cohort median score: 14, IQR 11–14; control cohort: 19, IQR 15–21, p=0.04). The number of patients requiring non-invasive ventilation and IMV was similar across both cohorts. Among survivors, the length of stay was longer in the awake proned cohort compared with the control cohort (APP group median number of days: 22, IQR 16–41; control: 7, IQR 4–14, p=0.02). Also, 28-day mortality between the APP group and controls was not significantly different (APP group: 1; control: 4, p=0.12).

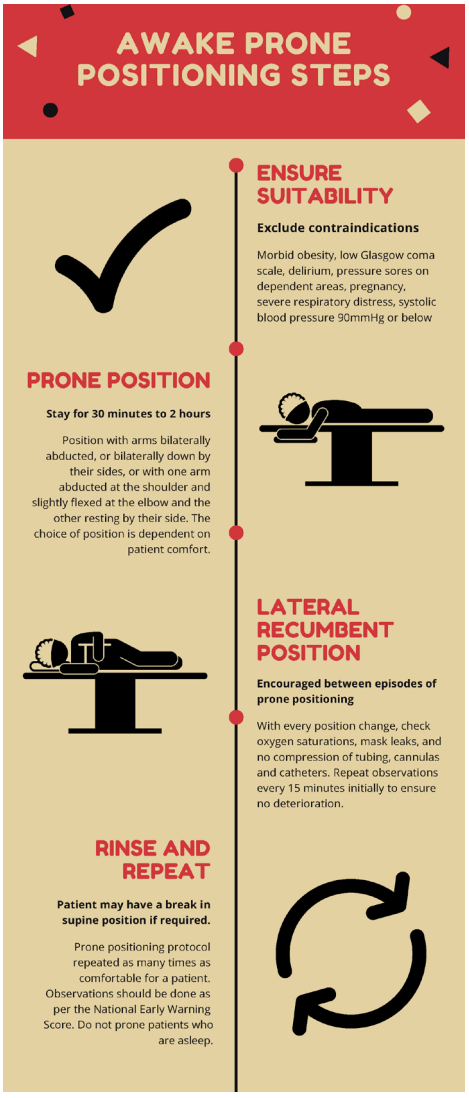

Figure 1 Infographic showing local awake prone positioning protocol.

In the APP group, one patient had evidence of a pulmonary embolism (PE) on CT pulmonary angiogram in addition to severe COVID-19 pneumonia. The median duration of prone positioning was 120 minutes (IQR 76–161); the median number of proning episodes per patient was 4 (IQR 1–7). Table 2 displays the SpO_2/FiO_2 ratios before and after APP, by patient and by episode. When all episodes of APP are taken into account, there was no significant changes to oxygenation. However, SpO_2/FiO_2 ratio was most likely to increase in the first episode of APP (before proning: 152, IQR 135–185; after proning 192, IQR 156–234, p=0.04). Any subsequent changes in SpO_2/FiO_2 ratio were not significant.

Figure 2 displays the trajectory of SpO_2/FiO_2 over time for each patient who underwent APP. Only half (5/10) of participants in this cohort were able to tolerate more than two episodes of APP. For the patient who died, SpO_2/FiO_2 dropped from 240 to 110 after APP. Only one patient had a sustained SpO_2/FiO_2 improvement (from 140 to 210) with several episodes of APP; for the remaining patients, APP only provided transient improvements to oxygenation.

DISCUSSION

The present study found that for the majority of patients in the ICU, APP was not a suitable intervention. This is mainly because

Table 1 Participant characteristics in the study

Variable	Prone (n=10)	Supine (n=10)	P value
Basic demographics			
Male—n (%)	6 (60)	6 (60)	0.99
Age—median (IQR), mean (SD)	59 (55–63), 59 (6)	65 (55–71), 64 (10)	0.21
Caucasian—n (%)	8 (80)	8 (80)	0.53
Asian—n (%)	2 (20)	2 (20)	0.53
Days since COVID-19 onset—median (IQR), mean (SD)	11 (8–13), 12 (8)	6 (3–10), 6 (4)	0.05
Observations and use of NIV on admission			
NIV started on or before ICU admission—n (%)	9 (90)	7 (70)	0.26
Admission SOFA score—median (IQR), mean (SD)	2 (2–3.5), 2.7 (1.6)	2.5 (2–4.5), 3.3 (1.7)	0.35
Admission Apache II—median (IQR), mean (SD)	11 (8–18), 13 (5)	16 (13–20) 16, (4)	0.14
Admission 4C Mortality Score—median (IQR), mean (SD)	**14 (11–14), 13 (3)**	**19 (15–21), 18 (6)**	**0.02**
Requirement of NIV/IMV/ECMO during admission			
Required NIV or IMV—n (%)	10 (100)	8 (80)	0.14
Required IMV—n (%)	6 (60)	5 (50)	0.65
Required ECMO—n (%)	1 (10)	0 (0)	0.31
Outcome			
28-Day mortality—n (%)	1 (10)	4 (40)	0.12
Length of ICU stay in survivor days—n (%), mean (SD)	**22 (16–41), 29 (19)**	**7 (4–14), 9 (7)**	**0.01**

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation.

many were too sick (not physically able to adopt the prone position) or declined to undergo APP due to discomfort. A substantial proportion also required intubation prior or immediately on admission to the unit. For the small number of patients who tolerated APP, the procedure provided only transient improvements in oxygenation that were largest in the first episode and not sustained over time with repeated APP episodes.

Prone positioning is an established evidence-based practice in patients with typical ARDS undergoing IMV. The physiological rationale is to ameliorate ventilation/perfusion mismatching and shunting. Prone positioning is believed to generate more homogenous lung ventilation and strain distribution due to gravitational effects and conformational shape matching of the lung to the chest cavity, thereby enhancing dorsal lung unit recruitment while relatively constant pulmonary perfusion patterns are maintained.[2 11–13]

There is, however, limited evidence for the benefit of applying APP to non-ventilated awake patients. Our study offers the first insights into whether multiple episodes of APP in patients with COVID-19 provide sustained improvements in oxygenation longitudinally. Our findings help to explain results from large cohort studies, which demonstrated that APP did not reduce intubation or mortality rates in patients with COVID-19,[8 14] despite several studies reporting significant improvements in oxygenation parameters following APP.[7 15 16] This disparity is at least somewhat surprising given that a decreasing trajectory of SpO_2/FiO_2 has been associated with an increased risk of mortality in COVID-19.[17] However, findings of improved oxygenation from previous studies are related to a single, isolated episode of APP. A recent systematic review found no existing data that describe the effect of serial prone positioning on oxygenation beyond the initial episode.[18] Two previous studies applied multiple episodes of APP, but do not present longitudinal data.[19 20] Importantly, the median duration of APP in our study was around 2 hours; comparable with early clinical trials investigating APP in patients with COVID-19. Many patients were also unable to undergo more than two episodes of the intervention. This may explain why it is not successful as an intervention in this cohort since in contrast, the maximal benefits of this intervention in intubated patients are achieved when patients are proned for 12–18 hours. Furthermore, there was a slightly higher rate of IMV and extracorporeal membrane oxygenation (ECMO) in our APP cohort compared with controls—highlighting the inadequacy of the duration and frequency of APP in the APP cohort.

Our study observed the most significant improvement in SpO_2/FiO_2 ratios following the first episode of APP; subsequent episodes provided progressively lower improvements in oxygenation. These findings may be explained by pathophysiological differences between typical ARDS and COVID-19-related ARDS. A recent, large observational cohort study demonstrated that while COVID-19-associated lung injury is similar to classical ARDS in many aspects; patients with COVID-19-related ARDS had a 28% higher static lung compliance and ventilatory ratios (a marker for dead space) were significantly increased in those with high D-dimer concentrations.[6] These data indicate that intravascular pathology may play a pivotal role in increasing dead space and causing hypoxaemia in COVID-19-associated lung injury.[6] In relatively compliant lungs with impaired pulmonary perfusion patterns, prone positioning may be used as a rescue manoeuvre to transiently redistribute pulmonary blood

Table 2 Awake prone positioning effect on SpO_2/FiO_2, by patient and by episode

Variable	N	Before proning	After proning	P value
S/F ratio by all episodes—median (IQR), mean (SD)	42	153 (131–188), 159 (43)	158 (150–233), 177 (45)	0.08
S/F ratio by patient—median (IQR), mean (SD)	10	157 (150–187), 164 (34)	193 (155–234), 192 (46)	0.14
S/F ratio by episode:				
Episode 1—median (IQR), mean (SD)	**10**	**153 (135–185), 161 (33)**	**192 (156–234), 197 (50)**	**0.04**
Episode 2—median (IQR), mean (SD)	7	152 (131–173), 155 (44)	158 (153–176), 170 (33)	0.44
Episode 3—median (IQR), mean (SD)	5	153 (152–155), 147 (37)	150 (148–157), 150 (31)	0.92
Episode 4—median (IQR), mean (SD)	5	153 (127–157), 144 (36)	150 (134–160), 162 (46)	0.75
Episode 5—median (IQR), mean (SD)	5	152 (139–153), 156 (56)	163 (157–165), 165 (47)	0.35
Episode 6—median (IQR), mean (SD)	4	195 (143–236), 184 (64)	196 (149–233), 186 (57)	0.78
Episode 7—median (IQR), mean (SD)	3	157 (137–197), 171 (62)	157 (140–197), 173 (59)	0.82
Episode 8—median (IQR), mean (SD)	3	230 (180–235), 174 (58)	233 (187–234), 203 (53)	0.83

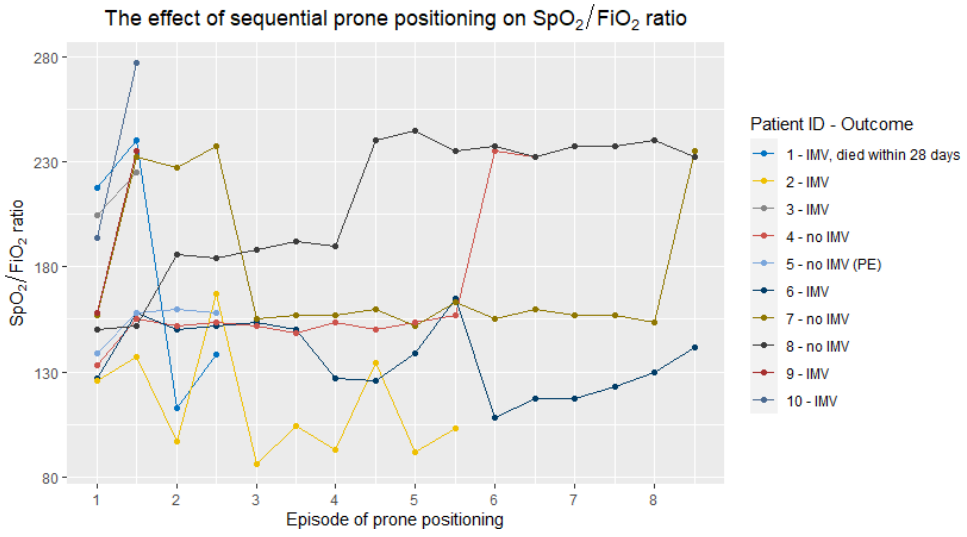

Figure 2 Serial SpO_2/FiO_2 measurements in the awake proned cohort. IMV, invasive mechanical ventilation; PE, pulmonary embolism.

flow, but is unlikely to engender sustained benefits through the recruitment of collapsed lung units.[21]

Our study is also the first to present results of APP in a patient with COVID-19-induced PE, in whom SpO_2/FiO_2 ratios showed little improvement with APP. This finding is in line with the pathophysiological rationale outlined previously and highlights the principle that APP is unlikely to result in substantial benefits where impaired pulmonary perfusion is the main cause for hypoxaemia.

We found that many patients were not able to tolerate more than two episodes of prone positioning. This is comparable with other studies, in which major proportions of participants tolerated few episodes of APP or short durations of a single episode of APP.[3 16 22] Therefore, a more pragmatic and less resource-intensive approach to applying APP in awake patients admitted to critical care is to ask those who can to undergo APP for no more than one or two episodes, or to stop when SpO_2/FiO_2 fails to improve.

Our study had limitations. The sample size is small without a priori sample size calculation, but comparable with previous studies investigating APP in patients with COVID-19. Since APP was not allocated in a randomised way, there may be other characteristics not collected in our study that may be different between those who underwent APP and controls. Multiple univariable p values are reported in our manuscript and therefore any significant differences should be interpreted with caution, given the possibility of a type 1 error. We did not specifically collect reasons for why patients were unable to tolerate APP—whether this would may be due to increased discomfort due to dyspnoea in the prone position, or related to physical circumstances which would impair the ability to prone position effectively, such as weight or the presence of large abdominal pannus. This would be of value to study in future work. Our study included only patients admitted to the ICU—consequently, we did not consider patients on the ward that may have undergone APP with milder or earlier disease. Yet, our main objective was to evaluate whether APP could improve prognosis in those with severe disease; patients who are not admitted to ICU are more likely to survive their acute illness without the requirement for APP or may be too frail to undergo APP.

The majority of patients in our study had been intubated before admission to ICU. Our study was conducted during the first wave of COVID-19 in the UK, where national guidance encouraged those infected to stay at home and to present to hospital only when breathless.[23] Consequently, most patients presented to hospital relatively late—requiring early intubation once admitted. Our findings, therefore, may not be applicable to other countries where patients may present to hospital earlier and a lower threshold for ICU admission exists. Thompson and colleagues found that in a cohort of 24 patients admitted to a step-down unit (prior to ICU admission) in Columbia with severe hypoxaemic respiratory failure due to COVID-19, APP reduced the rate of intubation.[24]

Nevertheless, this study is the first to show that multiple episodes of APP did not lead to sustained benefits in oxygenation for patients with COVID-19, and that the effect size of SpO_2/FiO_2 ratio change may not benefit patients beyond the first few episodes of APP. Our findings help to explain why many other studies failed to have an effect on mortality among patients undergoing APP, despite initial improvements in oxygenation. Future studies, especially ongoing randomised controlled trials,

Main messages

- In this retrospective review of patients admitted to intensive care with COVID-19, we demonstrate that improvements in oxygenation, as measured by SpO_2/FiO_2 after each episode of awake prone positioning, are transient and most likely to occur in the first episode.
- This is the first study to present longitudinal results of oxygenation after awake prone positioning in patients with severe COVID-19; our findings may help to explain why other studies so far have failed to show improvements in mortality from awake prone positioning despite improvements in oxygenation.

Current research question

- What happens to the oxygenation of patients with COVID-19 in the intensive care unit when they undergo serial episodes of awake prone positioning?

investigating APP must present oxygenation data disaggregated by prone positioning episode to confirm this effect. While APP presents a low-cost intervention with minimal potential to cause significant harm to patients, it may not substantially improve clinical outcomes in patients with severe COVID-19, in whom impaired pulmonary perfusion majorly contributes to hypoxaemia. It remains to be determined whether patients with earlier or milder forms of the disease, or those in whom primarily the lung parenchyma are affected, show a more meaningful response.

Twitter Alexander James Baldwin @alex_j_baldwin and Raha West @RahaWest

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Health Research Authority and Health Care Research Wales approved the study protocol (REC reference: 20/HRA/2509). This study was conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice guidelines and the UK Policy for Health and Social Care Research (2017). Data were collected and retained in accordance with the Data Protection Act (2018) and the General Data Protection Regulations (2018). Individual patient consent to participate in the study was not required because patients underwent awake prone positioning as part of the local standard of care and routinely collected data were captured by the direct care team.

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