BJA

British Journal of Anaesthesia, 126 (1): 48–55 (2021)

doi: 10.1016/j.bja.2020.09.042
Advance Access Publication Date: 10 October 2020
COVID-19 and the anaesthetist: a Special Series

Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study

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Abstract

Background: The role of repeated prone positioning in intubated subjects with acute respiratory distress syndrome caused by COVID-19 remains unclear.
Methods: We conducted a retrospective observational cohort study of critically ill intubated patients with COVID-19 who were placed in the prone position between March 18, 2020 and March 31, 2020. Exclusion criteria were pregnancy, reintubation, and previous prone positioning at a referring hospital. Patients were followed up until hospital discharge. The primary outcome was oxygenation assessed by partial pressure of oxygen/fraction of inspired oxygen ratio (Pao_2/Fio_2) ratio. A positive response to proning was defined as an increase in Pao_2/Fio_2 ratio ≥20%. Treatment failure of prone positioning was defined as death or requirement for extracorporeal membrane oxygenation (ECMO).
Results: Forty-two subjects (29 males; age: 59 [52–69] yr) were eligible for analysis. Nine subjects were placed in the prone position only once, with 25 requiring prone positioning on three or more occasions. A total of 31/42 (74%) subjects survived to discharge, with five requiring ECMO; 11/42 (26%) subjects died. After the first prone positioning session, Pao_2/Fio_2 (mean (standard deviation)) ratio increased from 17.9 kPa (7.2) to 28.2 kPa (12.2) ($P<0.01$). After the initial prone positioning session, subjects who were discharged from hospital were more likely to have an improvement in Pao_2/Fio_2 ratio ≥20%, compared with those requiring ECMO or who died.
Conclusion: Patients with COVID-19 acute respiratory distress syndrome frequently responded to initial prone positioning with improved oxygenation. Subsequent prone positioning in subjects discharged from hospital was associated with greater improvements in oxygenation.

Keywords: acute respiratory distress syndrome (ARDS); COVID-19; mechanical ventilation; oxygenation; prone positioning

Editor's key points

- The role of repeated episodes of prone positioning in intubated subjects with ARDS secondary to COVID-19 remains unclear.
- The authors report an observational cohort single-centre study of intubated COVID-19 subjects.
- The primary outcome was Pao_2/Fio_2 ratio after initial proning.
- After the initial proning session, improved oxygenation was more likely in subjects who survived to discharge after repeated prone positioning.

Received: 11 July 2020; **Accepted:** 14 September 2020

Coronavirus disease-19 (COVID-19) is a global pandemic that has affected more than 200 countries and territories worldwide, resulting in more than 1.1 million deaths.[1]

COVID-19 causes acute respiratory distress syndrome (ARDS) in approximately 20% of hospitalised subjects with COVID-19.[2,3] ARDS has a high mortality rate (35–46%), particularly in subjects with a greater degree of lung injury.[4] As of May 15, 2020, 57% of the 4855 UK hospitalised subjects with COVID-19 who required advanced respiratory support died.[5] Management of respiratory failure in COVID-19 patients is largely supportive. One treatment recommended by the Surviving Sepsis Campaign (SSC) COVID-19 subcommittee is prone positioning.[6] Before the COVID-19 pandemic, studies have shown that early prone positioning can improve the ratio of partial pressure of oxygen to the fraction of inspired oxygen (Pa_{O_2}/Fi_{O_2} ratio) and reduce 28-day and 90-day mortality in severe ARDS.[7–9] Although initial prone positioning improves oxygenation in both non-intubated[10–14] and intubated[15–17] patients with COVID-19, the physiological response to repeated prone positioning and its association with length of stay and mortality for COVID-19 has not been reported.

To prepare for the COVID-19 pandemic, we developed a treatment guideline and standardised approach to initiate prone positioning based on our previous research[18] and input from an interdisciplinary team of respiratory therapists, nurses, and physicians. The aim of this study was to investigate the effect of prone positioning for patients with COVID-19 ARDS that required invasive mechanical ventilation.

Methods

Study design

This retrospective observational cohort study was approved by the Institutional Review Board in Rush University Medical Center (approval No. 20041301-IRB01; approved 4/17/2020).

Inclusion criteria

Adult subjects admitted to any of the adult ICUs at our facility with laboratory-confirmed COVID-19 infection requiring invasive mechanical ventilation with prone positioning between March 18, 2020 and March 31, 2020 were included in this study. COVID-19 was confirmed by a positive result on a reverse-transcriptase—polymerase-chain-reaction assay of a specimen collected on a nasopharyngeal swab.

Exclusion criteria

Individuals were excluded if they were: (1) pregnant; (2) intubated and placed in the prone position at least once at an outside hospital; (3) reintubated and placed in the prone position on their second intubation during hospitalisation.

Prone positioning protocol

A checklist with an accompanying education video was created to assure consistent prone positioning (Supplementary material).[19] Considering the volume of subjects that required prone positioning, a multidisciplinary team led by a respiratory therapist was ultimately established to complete all prone and supine sessions. The team was trained using a volunteer to simulate a patient who was intubated.[18,19] A treatment guideline was established (Supplementary material), based on the PROSEVA study[7] and consensus among physician, nursing, and respiratory care leadership at our institution. Intubated subjects diagnosed with ARDS were placed in the prone position by the team when a patient had a Pa_{O_2}/Fi_{O_2} ratio of <20 kPa with PEEP set ≥10 cm H_2O and $Fi_{O_2} \geq 0.6$. Prone positioning was maintained for at least 16 h, except if cardiopulmonary resuscitation was needed. Prone positioning was terminated when Pa_{O_2}/Fi_{O_2} ratio remained >20 kPa in the supine position or if extracorporeal membrane oxygenation (ECMO) or palliative care was needed. Lung protective ventilation (tidal volume targeted at 6 ml kg^{-1} of predicted body weight, plateau pressure ≤30 cm H_2O, and ARDS network high-PEEP low-Fi_{O_2} tables)[20] were utilised for all subjects. ECMO was considered if oxygenation could not be maintained under lung protective ventilation with prone positioning, paralysis, and inhaled pulmonary vasodilators.

Data collection

Subject characteristics including age, sex, race, laboratory results, microbiology findings, and diagnosis were collected. COVID-19 related risk factors including age, pre-existing pulmonary disease, chronic kidney disease, diabetes, hypertension, cardiovascular disease, and immunosuppression were also recorded. Pre- and post-prone positioning changes in vital signs, arterial blood gases, ventilator settings, respiratory mechanics (plateau pressure and respiratory system static compliance) and ventilatory ratio (calculated as: [minute volume (mL/min) × Pa_{CO_2} (mm Hg)]/[predicted body weight × 100 (mL/min) × 37.5 (mmHg)]) for the first three prone positioning sessions (if applicable) for each individual were recorded. Laboratory tests included creatine kinase myocardial band, lactate dehydrogenase, C-reactive protein, D-dimer, troponin, ferritin, and absolute lymphocyte within 24–48 h of pre- and post-prone positioning for the first prone positioning session. Use of sedatives and paralytics was also recorded pre and post the first prone positioning session. Patient outcomes, including mechanical ventilation duration, successful extubation, escalation of care to ECMO, survival, and length of stay in ICU and hospital were collected. Each patient was followed until hospital discharge.

Primary outcome

The primary outcome was oxygenation, assessed by Pa_{O_2}/Fi_{O_2} ratio, before and after the initial prone positioning manoeuvre. A positive response was defined a priori as an increase in Pa_{O_2}/Fi_{O_2} ratio ≥20%.

Secondary outcomes

We assessed the following secondary outcomes:

1. Serial Pa_{O_2}/Fi_{O_2} ratios were assessed after repeated prone positioning, compared between subjects discharged to home or long-term care facility *versus* those who died or required ECMO.
2. Haemodynamic (heart rate, arterial blood pressure) and ventilatory parameters (tidal volume, ventilatory frequency, PEEP, plateau pressure and ventilatory ratio) after repeated prone positioning.

Table 1 Overall patient characteristic information and comparisons between groups of treatment success and treatment failure. BMI, body mass index; CK-MB, creatine kinase myocardial band; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; Cst, static compliance; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; PBW, predicted body weight; LDH, lactate dehydrogenase; Pao_2, partial pressure of oxygen; PEEP, positive end expiratory pressure; Pplat, plateau pressure; SOFA, sequential organ failure assessment; Vt, tidal volume.

	Overall	Treatment success	Treatment failure	P
	N=42	N=26	N=16	
Age, yr	58.5 (51.8–69.3)	57.0 (49.8–65.8)	61.5 (52.3–72.0)	0.27
Gender, male, n (%)	29 (69)	16 (61.5)	13 (81.3)	0.09
Ethnicity, n (%)				0.80
African American	16 (38)	11 (42.3)	5 (31.3)	
Hispanic/Latino	16 (38)	10 (38.5)	6 (37.5)	
Caucasian	4 (9.5)	2 (7.7)	2 (12.5)	
Asian	3 (7)	1 (3.8)	2 (12.5)	
Other	3 (7)	2 (7.7)	1 (6.3)	
Height, cm	171.6 (10.7)	170.1 (164.5–176.5)	170.1 (165.7–180.2)	0.19
Weight, kg (SD)	100.6 (19.4)	103.9 (20.0)	95.2 (17.7)	0.16
PBW, kg (SD)	66.0 (10.9)	64.5 (11.8)	68.5 (9.1)	0.25
BMI, kg m^{-2} (SD)	34.2 (7.5)	35.8 (7.9)	31.6 (6.2)	0.08
BMI ≥35 kg m^{-2} (%)	14 (33.3)	11 (42.3)	3 (18.8)	0.18
COVID-19 epidemiological risk factors				
Age ≥55 yr, n (%)	26 (61.9)	14 (53.8)	12 (75.0)	0.21
Hypertension, n (%)	25 (59.5)	15 (57.7)	10 (62.5)	1.0
Diabetes mellitus with A1C >7.6%, n (%)	15 (35.7)	10 (38.5)	5 (31.3)	0.75
Cardiovascular disease, n (%)	13 (31)	7 (26.9)	6 (37.5)	0.51
Pre-existing pulmonary disease, n (%)	9 (21.4)	5 (19.2)	4 (25.0)	0.71
COPD, n (%)	3 (7.1)	2 (7.7)	1 (6.3)	1.0
Asthma, n (%)	5 (11.9)	4 (15.4)	1 (6.3)	0.63
Immunosuppression, n (%)	4 (9.5)	4 (15.4)	0	0.28
Chronic kidney disease, n (%)	4 (9.5)	3 (11.5)	1 (6.3)	1.0
Intubated and transferred from outside hospital, n (%)	16 (38.1)	8 (30.8)	8 (50.0)	0.33
From intubation to 1st prone, h	25.7 (8.9–55.1)	23.5 (8.0–50.9)	42.0 (19.9–94.0)	0.20
Duration for the 1st prone, h	16.1 (16–17)	16.2 (16.0–17.0)	16.0 (15.7–16.6)	0.41
Ventilator settings and respiratory mechanics before the 1st prone positioning				
Vt, ml kg^{-1} of PBW (n=39)	6.0 (5.9–6.4)	6.0 (5.9–6.5)	5.9 (5.1–6.3)	0.21
PEEP, cm H_2O	15 (13.5–16)	14 (12–16)	16 (14–18)	0.38
Pplat, cm H_2O (SD) (n=39)	27.7 (4.0)	27.1 (3.8)	28.8 (4.3)	0.20
Cst, ml cm H_2O^{-1} (SD) (n=39)	33.7 (11.1)	34.3 (11.6)	32.7 (10.6)	0.67
Laboratory tests				
D-dimer, ng ml^{-1} (n=18)	5.0 (0.75–10.46)	1.60 (0.65–7.71)	8.81 (2.18–14.19)	0.22
CK-MB, U L^{-1} (n=30)	232 (134.5–560)	209.0 (129.0–585.5)	255.0 (130.5–672.0)	0.85
CRP, mg L^{-1} (SD) (n=37)	220.0 (107.4)	203.3 (107.8)	247.2 (104.8)	0.23
LDH, U L^{-1} (n=29)	574 (449–705)	528.5 (389.0– 632.8)	670.0 (559.5–844.0)	0.13
Troponin, ng ml^{-1} (n=35)	0.05 (0.02–0.15)	0.04 (0.02–0.14)	0.07 (0.02–0.25)	0.35
Ferritin, μg L^{-1} (SD) (n=36)	1842 (1153.7)	1753.4 (1226.6)	1998.6 (1040.5)	0.55
Absolute lymphocyte, $\times 10^9$ (n=38)	0.94 (0.60–1.51)	0.97 (0.73–1.63)	0.89 (0.46–1.35)	0.87
pH (SD) (n=36)	7.30 (0.08)	7.30 (0.09)	7.31 (0.06)	0.85
HCO_3, mmol l^{-1} (SD) (n=36)	25.1 (4.7)	24.4 (4.0)	26.6 (6.0)	0.33
$Paco_2$, kPa (n=36)	7.2 (5.7–7.9)	6.4 (5.5–8.2)	7.2 (5.7–7.6)	0.56
Pao_2/Fio_2, kPa (SD) (n=36)	17.9 (7.2)	18.7 (7.6)	16.4 (6.6)	0.44
SOFA score (SD)	6.8 (2.5)	6.4 (2.2)	7.4 (3.0)	0.23
Pao_2/Fio_2 improvement at the first three prone positions, kPa				
1st prone (n=36)	7.3 (2.1–16.7)	7.3 (3.5–17.9)	3.1 (1.3–16.5)	0.56
2nd prone (n=27)	4.0 (−0.2–18.1)	10.7 (3.7–19.0)	1.4 (−1.6–3.4)	<0.01
3rd prone (n=20)	6.3 (−0.4–16.0)	10.2 (5.2–18.3)	0.5 (−1.4–2.9)	0.03
Pao_2/Fio_2 improvement at the first three prone positions, %				
1st prone (n=36)	48.2 (15.8–110.3)	63.8 (19.3–108.9)	41.3 (9.5–113.8)	0.73
2nd prone (n=27)	18.3 (−0.6–102.7)	54.4 (14.0–127.7)	7.6 (−15.6–7.9)	<0.01
3rd prone (n=20)	36.7 (−1.5–95.4)	50.8 (22.2–102.9)	3.2 (−12.3–27.3)	0.04
Ventilatory ratio changes at the first three prone positions				
1st prone (n=33)	0.17 (0.06–0.36)	0.12 (−0.11–0.33)	0.35 (−0.01–0.93)	0.13
2nd prone (n=22)	0.03 (−0.11–0.26)	0.08 (−0.19–0.28)	0 (−0.10–0.22)	0.63
3rd prone (n=17)	0.08 (−0.20–0.26)	−0.04 (−0.20–0.20)	0.23 (−0.17–0.30)	0.48
Number of prone positioning sessions during intubation	3.0 (2.0–6.0)	3.0 (1.75–6.25)	3.50 (2.0–4.75)	0.80
Antivirus medication use, n (%)				
Remdesivir	1 (2.4)	1 (3.8)	0	1.0
Tocilizumab	18 (42.9)	12 (46.2)	6 (37.6)	0.75

Continued

Table 1 Continued

	Overall	Treatment success	Treatment failure	P
	N=42	N=26	N=16	
Hydroxychloroquine	40 (95.2)	25 (96.2)	15 (93.8)	1.0
Azithromycin	37 (88.1)	23 (88.5)	14 (87.5)	1.0
Corticosteroids use, n (%)				
Dexamethasone	6 (14.3)	3 (11.5)	3 (18.8)	0.66
Prednisone	2 (4.8)	1 (3.8)	1 (6.3)	1.0
Hydrocortisone	19 (45.2)	12 (46.2)	7 (43.8)	1.0
Methylprednisolone	8 (19.0)	5 (19.2)	3 (19.8)	1.0
Bronchoscopy, n (%)	13 (31.0)	10 (38.5)	3 (18.8)	0.30
For diagnosis	3	3 (11.5)	0	0.42
For secretion management	8	6 (23.1)	2 (12.5)	
Other	2	1 (3.9)	1 (6.3)	

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (inter-quartile range), depending on the normality of distribution; the Kolmogorov–Smirnov test was used to test normality of distribution for continuous variables. Continuous variables were compared pre- and post-prone positioning by the paired *t*-test or Wilcoxon signed rank test for the same prone positioning session. The changes in oxygenation after the first three prone positioning sessions was compared by repeated measures analysis of variance or the Friedman test. Comparisons between two groups (treatment success *vs* failure) were analysed by an independent *t*-test or the Mann–Whitney test. Differences in categorical variables were assessed using the χ^2 or Fisher's exact test. Binary stepwise logistic regression was performed to assess the impact of a number of factors on the likelihood of treatment failure. Data analysis was conducted with SPSS statistical software (SPSS 26.0: SPSS; Chicago, IL, USA) and a *P*-value of <0.05 was considered to be statistically significant.

Results

Subject characteristics

Between March 18, 2020 and March 31, 2020, 50 subjects with laboratory-confirmed COVID-19 were intubated and admitted to intensive care. Eight subjects were excluded for not meeting the criteria for prone positioning (n=6), being placed in the prone position after reintubation (n=1), or being intubated and placed in the prone position at an outside hospital for >24 h (n=1). Of the 42 subjects eligible for analysis (Table 1), 26 were intubated at our institution because of refractory hypoxaemia; 16 subjects were intubated elsewhere before transfer to our institution. Individuals underwent three (two to six) prone positioning manoeuvres for 16.1 (16–17) h, with 25 subjects requiring prone positioning on at least three occasions. No major complications, including pneumothorax, were observed. A total of 31/42 (74%) subjects survived to discharge (Fig 1) requiring intensive care for 21.5 (14.8–31.5) days. Five subjects were placed on ECMO. Eleven subjects died, nine of whom died within 28 days of ICU admission.

Primary outcome: oxygenation after initial prone positioning

The Pao_2/Fio_2 ratio improved from 17.9 (7.2) to 28.2 (12.2) kPa within 81 (61–119) minutes of prone positioning in 36 subjects who had complete arterial blood gas data (P<0.01). The Pao_2/Fio_2 ratio improved ≥20% in 26/36 (72%) subjects. After being returned to the supine position, improvements in Pao_2/Fio_2 ratio persisted (Table 2).

Secondary outcomes

Serial Pao_2/Fio_2 ratios after repeated prone positioning sessions

Twenty-five subjects were placed in prone positioning three or more times. Similar changes in arterial blood gases were observed for the first three prone positioning sessions, although the reduction in Fio_2 was more pronounced after the first prone positioning session than subsequent sessions (Table 3).

Respiratory mechanics

Tidal volume, PEEP, plateau pressure (Table 2), and respiratory system static compliance (Fig 2) were similar throughout repeated prone positioning manoeuvres. Both set and measured ventilatory frequencies were increased after prone positioning (P<0.01). The ventilatory ratio also improved after prone positioning (Tables 2 and 3).

Haemodynamic and laboratory parameters

Vasopressor requirements did not alter after prone positioning, although the propofol dose decreased after the first prone positioning session (Supplementary Table S1). Laboratory test results were similar throughout (Supplementary Table S2).

Oxygenation after prone positioning and outcome

After the initial prone positioning session, subjects who were discharged from hospital were more likely to have an improvement in Pao_2/Fio_2 ratio ≥20% compared with those requiring ECMO or who died after both the second (11/16 vs 2/11, P=0.01) and third (9/12 vs 2/8, P=0.07) prone positioning sessions, respectively. In the second prone positioning session, the Pao_2/Fio_2 improvement was higher in the treatment success group than in the treatment failure group (10.7 [3.7–19.0] vs 1.4 [−1.6–3.4] kPa, P<0.01). This was also observed during the third prone positioning session (10.2 [5.2–18.3] vs 0.5 [−1.4–2.9] kPa, P=0.03); Table 1). In the logistic regression analysis, Pao_2/Fio_2 ratio incremental change in the second

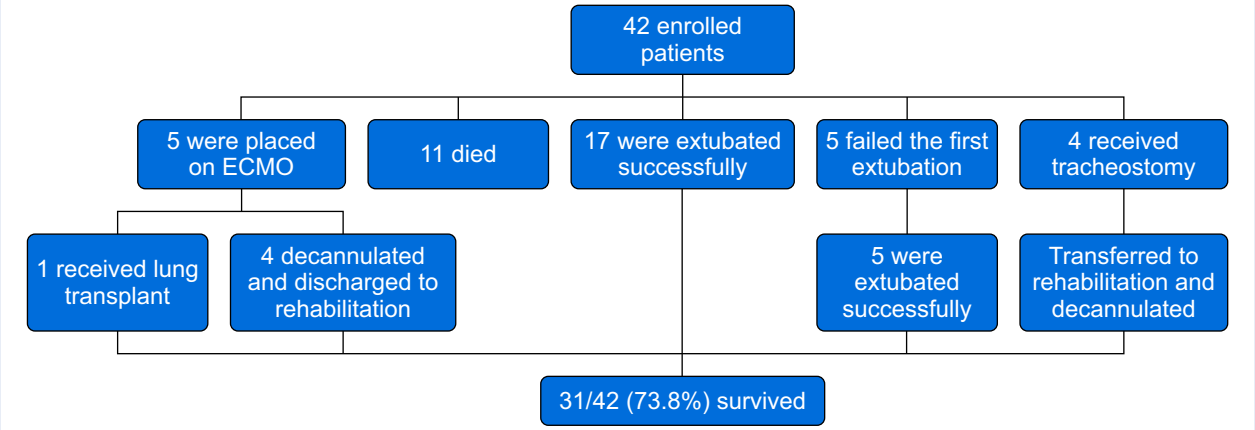

Fig 1. Clinical outcomes. ECMO, extracorporeal membrane oxygenation.

Table 2 Vital signs, respiratory mechanics, and arterial blood gases at phases of pre- *vs* post-prone positioning and pre- *vs* post-supine positioning for the first prone positioning session. The significance level is 0.05. Significance values have been adjusted by the Bonferroni correction for multiple tests. *Compared with pre-prone (w/in 1 h) $P<0.05$. †Compared with post-prone (w/in 2 h) $P<0.05$. DBP, diastolic blood pressure; Fio_2, fraction of inspired oxygen; HR, heart rate; Pao_2, partial pressure of oxygen; $Paco_2$, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; SBP, systolic blood pressure; Spo_2, saturation of pulse oximetry; VF, ventilatory frequency.

	Pre-prone (w/ in 1 h)	Post-prone (w/in 2 h)	Post-prone (4 h after)	Pre-supine (0.5–2 h before)	Post-supine (0.5 –2 h after)	N	P
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)		
HR, bpm	82.0 (76.0 –94.0)	85.0 (77.0 –103.5)	87.0 (76.0 –100)	83.0 (72.0–92.0)	80.0 (67.0–88.5)†	41	<0.01
SpO_2, %	96.0 (93.0 –99.0)	97.5 (95–99)	97. 0 (95.0 –99.0)	98.0 (96.0–99.0)	96.5 (94.0–99.0)	41	0.21
SBP, mm Hg	113.0 (102.0, 131.0)	119.0 (106.0, 129.0)	117.0 (107.0, 130.0)	121.0 (103.0, 130.0)	116.0 (98.0, 132.0)	39	0.94
DBP, mm Hg	60.0 (55.0, 65.0)	59.0 (54.0, 68.0)	59.0 (54.0, 67.0)	63.0 (55.0, 69.0)	59.0 (53.0, 65.0)	39	0.68
Tidal volume set, ml kg^{-1}	6.0 (5.85 –6.39)	6.0 (5.84 –6.18)	6.0 (5.91 –6.33)	6.02 (5.91–6.27)	6.0 (5.91–6.27)	36	0.34
VF set, bpm	20.0 (16.0 –25.0)	22.0 (16.0– 28.0)	24.0 (18.0 –28.0)*	25.0 (22.0–30.0)	25.0 (22.0–29.0)	41	<0.01
VF measure, bpm	22.0 (17.0 –27.0)	24.0 (16.5 –28.5)	24.0 (20.0 –28.0)*	26.0 (22.0–30.0) *,†	26.0 (22.0–29.0)*	41	<0.01
PEEP set, cm H_2O	16.0 (13.0 –16.0)	16.0 (14.0 –16.0)	14.0 (14.0 –16.0)	14.0 (13.0–16.0)	14.0 (14.0–16.0)	41	0.13
Plateau pressure, cm H_2O	27.5 (26.0 –30.0)	28.0 (24.0 –30.0)	27.0 (24.0 –30.0)	26.50 (25.0–29.0)	27.0 (23.0–30.0)	28	0.62
Respiratory system static compliance, ml cm H_2O^{-1}	29.2 (23.3 –35.5)	29.2 (24.0 –36.2)	29.6 (25.5 –35.0)	27.7 (26.5–33.0)	29.3 (25.7–37.3)	27	0.38
Fio_2	0.80 (0.60 –1.0)	0.60 (0.50 –0.70)	0.55 (0.40 –0.70) *	0.50 (0.40–0.60)*,†	0.50 (0.45–0.60)*	40	<0.01
Pao_2/Fio_2, kPa	17.5 (11.6 –19.2)	27.7 (19.5 –35.7)*			26.1 (17.9–33.1)*	32	<0.01
Pao_2, kPa	11.8 (9.3 –14.2)	14.5 (10.2 –20.4)*			13.5 (10.3–17.3)	32	<0.01
pH	7.31 (7.23 –7.36)	7.31 (7.24 –7.36)			7.33 (7.30–7.37)	32	0.13
$Paco_2$, kPa	7.2 (5.7–7.9)	6.8 (6.0–7.7)			6.3 (5.5–6.8)	32	0.29
HCO_3^-, mmol L^{-1}	26.0 (21.8 –27.2)	24.5 (21.80 –7.6)			23.2 (20.7–27.0)*	32	0.01
Ventilatory ratio	1.79 (1.42 –2.37)	1.97 (1.61 –2.76)			1.82 (1.64–2.24)	32	0.03

Table 3 The pre- and post-prone positioning changes of vital signs, ventilator settings and arterial blood gases during the first three prone positioning sessions. DBP, diastolic blood pressure; F_{IO_2}, fraction of inspired oxygen; HR, heart rate;P_{AO_2}, partial pressure of oxygen; P_{ACO_2}, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; SBP, systolic blood pressure; S_{PO_2}, saturation of pulse oximetry; VF, ventilatory frequency.

	N	Pre and post changes in 1st prone position	Pre and post changes in 2nd prone position	Pre and post changes in 3rd prone position	P
Vital signs					
HR, beats min^{-1}	25	1.0 (−3.0–12.0)	0 (−3.0–4.0)	2.0 (−4.0–8.0)	0.04
VF, bpm	25	0 (0–3.5)	0 (0–1.0)	0 (0–0)	0.24
SBP, mm Hg	25	3.0 (−8.5, 20.5)	4.0 (−9.0, 18.0)	9.0 (−4.5, 16.5)	0.96
DBP, mm Hg	25	1.0 (−4.5, 10.5)	0 (−4.5, 7.5)	3.0 (0, 9.5)	0.42
SpO_2, %	25	1.0 (−0.5–4.0)	2.0 (0–5.0)	1.0 (0–3.0)	0.15
Ventilator settings and respiratory mechanics					
Tidal volume, ml kg^{-1}	20	0 (0–0)	0 (−0.4–0)	0 (0–0)	0.85
PEEP, cm H_2O	25	0 (0–0)	0 (0–0)	0 (0–0)	0.55
F_{IO_2}	24	−0.15 (−0.4–0)	0 (−0.10–0)	0 (−0.08–0.08)	<0.01
Plateau pressure, cm H_2O	18	0 (−1.0–1.0)	0 (−0.25–3.0)	0 (−0.25–1.0)	0.82
Respiratory system static compliance, ml cm H_2O^{-1}	17	0 (−4.7–3.7)	−1.6 (−5.7–1.4)	0 (−2.2–2.8)	0.90
Ventilatory ratio	13	0.27 (0.03–0.41)	0 (−0.12–0.27)	−0.04 (−0.23–0.18)	0.06
Arterial blood gases					
P_{AO_2}/F_{IO_2} change	17	7.8 (2.5–17.9)	7.5 (1.9–18.5)	4.0 (−0.7–15.2)	0.66
P_{AO_2}/F_{IO_2} change, %	17	71.9 (16.5–142.9)	36.4 (9.5–126.4)	15.9 (−2.9–88.7)	0.59
P_{AO_2}, kPa	17	2.0 (−0.9–8.8)	4.4 (−0.7–10.7)	2.4 (−0.5–6.8)	0.94
pH	17	−0.02 (−0.04–0.05)	−0.01 (−0.05–0.02)	0.01 (−0.03–0.03)	0.87
P_{ACO_2}, kPa	17	0.3 (−0.8–1.0)	0.3 (−0.2–0.7)	−0.1 (−0.5–0.4)	0.65
HCO_3^-, mmol L^{-1}	17	−0.6 (−1.4–0.8)	0 (−0.9–0.9)	0.1 (−0.4–0.9)	0.29

prone positioning session was associated with treatment success (odds ratio, 1.03; 95% confidence interval, 1.0–1.05; P=0.03).

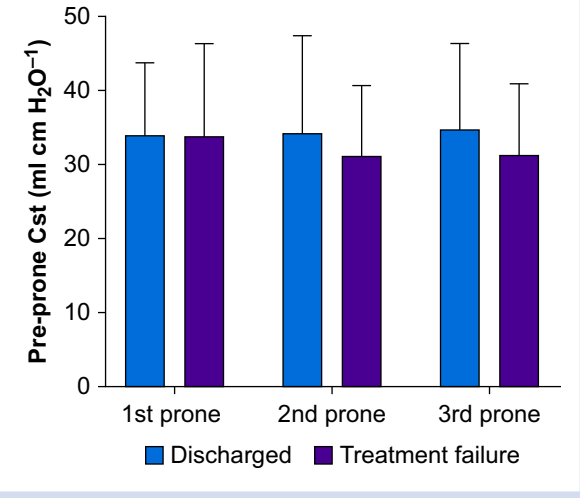

Fig 2. Respiratory system compliance and prone positioning. Using the change in P_{AO_2}/F_{IO_2} ratio pre- and post-prone positioning ≥20% as the response criteria, 26 subjects met the criteria in the first prone positioning session (n=36) whereas 13 and 11 subjects responded in the second (n=27) and third (n=20) prone positioning sessions, respectively. Responders' respiratory system compliance before each prone positioning in the three sessions was similar to non-responders. Cst, compliance of respiratory system.

Discussion

We found that in COVID-19 subjects placed in prone positioning, oxygenation improved and better oxygenation responses were associated with overall better outcomes. This is the first report, to our knowledge, on changes in P_{AO_2}/F_{IO_2} ratio after repeated prone positioning sessions and the associated outcomes of those changes. Although high mortality from severe COVID-19 has been reported,[5,21–23] our 28-day ICU mortality was 21.4%, which is similar to the PROSEVA study. In PROSEVA, 62.4% of subjects had ARDS as a result of pneumonia,[7] whereas all of our subjects had virus-induced ARDS. The pre-prone positioning P_{AO_2}/F_{IO_2} ratio in our study was higher than that in the PROSEVA study, possibly because of the higher level of PEEP we utilised. If the five subjects we placed on ECMO were grouped with those who died, to simulate the incidence of ECMO utilisation in Italy during the pandemic (1%),[24] our mortality rate (38.1%, 16/42) is still lower than reported mortality for intubated COVID-19 subjects with severe ARDS.[5,21–23]

Similar to the findings from other studies,[11–13,15–17] P_{AO_2}/F_{IO_2} ratio improved after the first prone positioning session in our study, but we did not find differences in improvement of P_{AO_2}/F_{IO_2} ratio between treatment success and failure groups, as also reported by Meenen and colleagues.[25] Nevertheless, our study also showed that survivors responded to prone positioning on the second and third prone positioning cycles, in contrast to little or no response in those who ended up being placed on ECMO or those who died. Our findings suggest that the oxygenation response to prone positioning, after each cycle, may be helpful in guiding decisions regarding facility transfer or earlier escalation to ECMO.

COVID-19 ARDS has been proposed to be an atypical form of ARDS in terms of recruitability.[26] Gattinoni and colleagues[27] indicated that intubated COVID-19 subjects whose

respiratory system compliance was high (50.2 [14.3] ml cm H_2O^{-1}) had lower recruitability, which was consistent with two other European reports.[17,27] In our study, however, the respiratory system compliance was lower (median: 29.2 ml cm H_2O^{-1}) than that reported by Gattinoni and colleagues,[17,27,28] but similar to four other studies.[15,16,22,29] Additionally, in subjects who responded to prone positioning (defined as Pao_2/Fio_2 ratio improvement of ≥20%), we found no difference in pre-prone positioning respiratory system compliance when compared with non-respondents during the first three prone positioning sessions. The same result was found between the treatment success and treatment failure groups. It should be noted that body mass index (BMI) was ~1.3 times larger in our study compared with BMI in the European ARDS population reported by Guérin and colleagues[8] and others.[28] This might explain the low compliance found in our subjects. A trend of higher BMI was seen in the treatment success group, which may reflect the obesity survival paradox described in pneumonia.[30] Future studies are needed to validate this finding in subjects with COVID-19.

We used ventilatory ratio to evaluate dead space.[29,31] The pre-prone positioning ventilatory ratio in our subjects was higher than in the subjects in a preceding study which used similar volume settings.[15] This might be explained by the higher acuity of subjects in our study, as evidenced by the need for higher PEEP, higher plateau pressures, lower compliance, and lower Pao_2/Fio_2 ratio before initial prone positioning. After prone positioning, the ventilatory ratios were increased within 1 h. This might be explained by alveolar over-distension caused by the same (pre-prone positioning) PEEP being applied during post-prone positioning. PEEP was reduced around 4 h after prone positioning in our study, as a result of the improvement of oxygenation. It was also maintained at that level after supine positioning, and interestingly, ventilatory ratios returned to pre-prone positioning levels. This finding suggests that close monitoring of changes in dead space and timely reduction in PEEP during prone positioning is needed, which might help to avoid alveolar over-distension.

A limitation of this single-centre study was that we did not transport subjects for a CT scan to investigate pulmonary morphology that might explain why some subjects did not respond to being placed in the prone position. Second, we used ventilatory ratio as a surrogate assessment of dead space.[29] Future studies are needed to understand if ventilatory ratio is an acceptable way to approximate dead space in subjects with COVID-19.[28] Lastly, some data were missing as a result of the immediate need for prone positioning and increased staff workload.

In summary, prone positioning improved oxygenation for patients with COVID-19 ARDS who required invasive mechanical ventilation. Serial assessment of the Pao_2/Fio_2 ratio may help guide decisions for earlier escalation of treatment, including ECMO.

Authors' contributions

Conceived the study: JL, TW
Designed the study: JL
Validated the data: JL, AAA, RK, AEA
Analysed the data: JL
Interpreted the data: JL, TW, FC, JBS, RK, SS, SHM
Drafted the manuscript: JL, TW
Revised and approved the manuscript: TW, FC, RK, SS, SHM, AAA, RK, AEA
Substantially revised and approved the manuscript: JL, JBS

Declarations of interest

JBS discloses a relationship with Ventec Life Systems and Teleflex. JL discloses research support from Fisher & Paykel Healthcare and Rice Foundation outside the submitted work. All other authors declare that they have no conflicts of interest.

Acknowledgements

We thank all the respiratory therapists in the Respiratory Care Department in Rush University Medical Centre for their dedicated and diligent work during the COVID-19 pandemic. We also thank Sharon Foley, Guoqiang Jing, and Rongshou Zheng for consultancy in data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.09.042.

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Handling editor: Gareth Ackland