Australian Critical Care xxx (xxxx) xxx

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Research paper

Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome

Madeline Coxwell Matthewman, MBBS, BSc (Hons) [a,*], Fumitaka Yanase, MD, PhD [a,b], Rahul Costa-Pinto, MBBS [a], Daryl Jones, PhD, MBBS [a], Dharshi Karalapillai, MBBS [a], Lucy Modra, MBBS [a], Sam Radford, MBBS [a], Ida-Fong Ukor, MBBS [a], Stephen Warrillow, MBBS, PhD [a], Rinaldo Bellomo, MD, PhD, MBBS. [a,b,c,d]

[a] *Department of Intensive Care, Austin Hospital, Melbourne, Australia;* [b] *Australian and New Zealand Intensive Care Research Centre, Monash University School of Public Health and Preventive Medicine, Melbourne, Australia;* [c] *Department of Critical Care, Department of Medicine and Radiology, University of Melbourne, Melbourne, Australia;* [d] *Data Analytics Research and Evaluation Centre, Austin Hospital, Melbourne, Australia*

ARTICLE INFORMATION

Article history:
Received 13 June 2022
Received in revised form
10 March 2023
Accepted 25 March 2023

Keywords:
COVID-19
ARDS
Cardiac output
Haemodynamic
Prone position
Supine position
Oxygen delivery

ABSTRACT

Background: Prone positioning improves oxygenation in patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19. However, its haemodynamic effects are poorly understood.
Objectives: The objective of this study was to investigate the acute haemodynamic changes associated with prone position in mechanically ventilated patients with COVID-19 ARDS. The primary objective was to describe changes in cardiac index with prone position. The secondary objectives were to describe changes in mean arterial pressure, FiO_2, PaO_2/FiO_2 ratio, and oxygen delivery (DO_2) with prone position.
Methods: We performed this cohort-embedded study in an Australian intensive care unit, between September and November 2021. We included adult patients with severe COVID-19 ARDS, requiring mechanical ventilation and prone positioning for respiratory failure. We placed patients in the prone position for 16 h per session. Using pulse contour technology, we collected haemodynamic data every 5 min for 2 h in the supine position and for 2 h in the prone position consecutively.
Results: We studied 18 patients. Cardiac index, stroke volume index, and mean arterial pressure increased significantly in the prone position compared to supine position. The mean cardiac index was higher in the prone group than in the supine group by 0.44 L/min/m2 (95% confidence interval, 0.24 to 0.63) ($P < 0.001$). FiO_2 requirement decreased significantly in the prone position ($P < 0.001$), with a significant increase in PaO_2/FiO_2 ratio ($P < 0.001$). DO_2 also increased significantly in the prone position, from a median DO_2 of 597 mls O_2/min (interquartile range, 504 to 931) in the supine position to 743 mls O_2/min (interquartile range, 604 to 1075) in the prone position ($P < 0.001$).
Conclusion: Prone position increased the cardiac index, mean arterial pressure, and DO_2 in invasively ventilated patients with COVID-19 ARDS. These changes may contribute to improved tissue oxygenation and improved outcomes observed in trials of prone positioning.

1. Introduction

In the first 2 years of the COVID-19 pandemic, more than 500 million cases and 6.1 million deaths were reported worldwide.[1] COVID-19 causes acute respiratory distress syndrome (ARDS) in approximately 20% of unvaccinated hospitalised patients.[2] Prone positioning in patients with ARDS has been shown to improve oxygenation and decrease mortality.[3] Similarly, in mechanically ventilated patients with COVID-19 ARDS, prone positioning improves oxygenation[4,5] and may decrease mortality.[6,7] These findings have made prone positioning common in COVID-19–associated ARDS.

Despite the above observations, the haemodynamic effect of prone position in ARDS remains controversial, with some studies reporting that cardiac index increased significantly with prone positioning,[8–13] whereas others found no difference.[14–23] Only three small studies have assessed the haemodynamic effect of

* Corresponding author at: Department of Intensive Care, Austin Hospital, 145 Studley Rd, Heidelberg, Victoria, 3084, Australia. Tel.: +61 3 9496 5992; fax: +61 3 9496 3932
E-mail address: madeline.matthewman@austin.org.au (M. Coxwell Matthewman).

https://doi.org/10.1016/j.aucc.2023.03.006

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006

prone position in ventilated COVID-19 patients.[24–26] Importantly, all of these studies were of limited power because they measured haemodynamic data at only a few, discrete time points during prone positioning. This results in potentially high risks of both type I and type II errors.

We therefore studied the haemodynamic changes associated with the prone position in invasively ventilated patients with COVID-19 ARDS, recording haemodynamic data every 5 min for 4 h using pulse contour technology. The primary outcome of our study was to describe changes in cardiac index in the prone position compared to the supine position. The secondary outcomes were mean arterial pressure, oxygen delivery (DO_2), fraction of inspired oxygen, and ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F) in the prone position compared to the supine position.

2. Methods

2.1. Setting

This single-centre, cohort-embedded study was performed in the intensive care unit (ICU) of an Australian tertiary teaching hospital, between September, 21, 2021, and November, 15, 2021. This study period corresponded to a peak of the COVID-19 Delta variant in our region. Based on the principles of the National Statement on Ethical Conduct in Research,[27] ethics committee approval was obtained and the need for consent waived by the Austin Health Office for Research (HREC project number: Audit/22/Austin/22).

2.2. Patient selection

Adult subjects (≥18 y) admitted to our ICU with polymerase chain reaction–confirmed SARS-CoV-2 infection requiring intubation and mechanical ventilation in prone position were included using a convenience sample based on the availability of pulse contour cardiac output monitors (FloTrac®, Edwards Lifesciences, Irvine, CA). Patients with atrial fibrillation and/or aortic valve or mitral valve diseases expected to impair arterial waveform analysis were excluded.[28]

2.3. Prone positioning protocol

A dedicated multidisciplinary team led by a respiratory physiotherapist completed the prone and supine sessions.[29] Intubated patients diagnosed with COVID-19 ARDS were placed in the prone position if the P/F ratio was less than 150 mm Hg, with positive end-expiratory pressure set at 10 cm H_2O or higher. Each prone position episode was maintained for at least 16 h. Patients were placed in the prone position with pillows under the thorax and pelvis, leaving the abdomen free to move. Patients were nursed either face-down with a dedicated foam-prone pillow or in the "swimmer's position" with the head turned to one side on a polyvinyl chloride mosaic air cushion. In the supine position, patients were placed on their back with the head of the bed elevated by 30°. This is considered a standard of care in our ICU to reduce the incidence of ventilator-associated pneumonia.[30]

Mechanical ventilation was applied in a volume-controlled mode with a lung-protective ventilation protocol including tidal volume of 6 mL/kg or less of ideal body weight, airway plateau pressure less than 30 cm H_2O, target driving pressure less than 15 cm H_2O, and positive end-expiratory pressure between 8 and 15 cm H_2O titrated to optimal respiratory compliance or oxygen saturations. FiO_2 was titrated to a target SpO_2 90–94%, whilst other ventilator settings remained the same during the measurement period. Patients were sedated with propofol and fentanyl by continuous intravenous infusion, with the addition of midazolam if needed. Cisatracurium was administered to achieve paralysis if required.

2.4. Haemodynamic monitoring

All patients received invasive blood pressure monitoring through a radial arterial line, which was connected to the FlowTrac/HemoSphere system (software version 2.0; Edwards Lifesciences). The FloTrac system analyses the arterial pressure waveform, providing advanced haemodynamic parameters that update every 20 s including stroke volume, cardiac output (CO), mean arterial pressure (MAP), stroke volume variation, and systemic vascular resistance (SVR).

FloTrac has some advantages over other methods of haemodynamic monitoring. FloTrac is minimally invasive and can be connected to a radial arterial line, inserted as a standard of care in our unit. FloTrac has a lower risk of complications compared to pulmonary artery catheters (PAC).[31] Additionally, different from the FloTrac, proning patients with a PAC requires considerable care to ensure displacement does not occur, a risk deemed too high to be acceptable in our study. Echocardiography can be performed in prone patients, but it requires technically trained staff and can only provide intermittent data.

Regarding accuracy and precision of FloTrac compared to other CO-monitoring devices, it is first important to note that FloTrac has undergone modifications to its algorithms since 2005, which makes prior comparisons less accurate. Lamia et al.[32] compared five commercially available CO-monitoring devices, including PAC and the current version of FloTrac. The authors highlighted that given the intrinsic error of PAC-derived CO values, PAC may not be an acceptable reference measure to compare other devices that estimate CO. They found that all five devices reported similar mean CO values, and the Pearson's product moment analysis demonstrated that all the devices displayed a tight linear correlation to changes in CO. The mean CO bias between PAC and FloTrac was −0.4 L/min, with limits of agreement (1.96 standard deviation; ±95% confidence interval [CI]) of ±2.27, giving a percentage error of 40%. From regression analyses, PAC CO values were significantly correlated with FloTrac CO ($y = 0.43x + 3.57$, $r = 0.46$, $p = 0.05$). FloTrac CO values were also significantly correlated with LiDCO™ (Irvine, USA) CO values ($y = 0.47x + 3.39$, $r = 0.76$, $p = 0.0004$) and with PiCCO CO values ($y = 0.30x + 4.41$, $r = 0.49$, $p = 0.04$). Additionally, it was found that the directional changes between any two paired CO measurements showed a significant and very tight correlation between all devices, in particular PAC CO vs FloTrac CO which had an $r = 0.73$, $p = 0.0258$.

Comparing echocardiography-derived CO measurements with FloTrac in critically unwell patients, excluding patients with atrial fibrillation and aortic stenosis, found a small bias of 0.02 L/min and a percentage error of 29.5%.[33] Finally, the use of the same measurement technique in the same patient comparing two periods minimised the impact of any technology-induced bias or accuracy concerns. For these reasons, FloTrac was used in this study.

2.5. Data collection

We recorded patient demographic data and COVID-19–specific risk factors from the electronic health record. Use of sedatives, muscle relaxants, vasoactive medications, and inhaled nitric oxide immediately prior to the first prone positioning session were also obtained.

Preprone position ventilator settings were recorded. Arterial blood gas results were obtained approximately 6 h before prone positioning and at 6, 12, and 18 h from the start of prone position.

Advanced haemodynamic data from the FloTrac/HemoSphere system were recorded every 5 min for 4 h: the first 2 h while in the supine position and the next 2 h after moving to the prone position.

Patient outcomes including mechanical ventilation duration, length of stay in ICU and hospital, survival, and escalation of care to extracorporeal membrane oxygenation were collected, with each patient followed up until hospital discharge.

2.6. Outcomes

The primary outcome was cardiac index before and after being placed in the prone position. Secondary outcomes were MAP, DO_2, FiO_2, and P/F ratio before and after prone positioning.

2.7. Study size

Whilst there is no consensus definition of a minimally clinically important difference in CO, we chose a change >10% in keeping with previous work in intensive care patients.[34] Given the paired nature of the data and the statistical impact of mixed-effect modelling, we estimated that 15 patients with 12 measurements per hour for 2 h, a measurement to subsequent measurement correlation >95% and a standard deviation <20% of the mean of all measurements would have a >80% power to identify a >10% difference in the cardiac index at an alpha of 0.05. We studied 18 patients to compensate for potential data loss.

2.8. Equations

DO_2 and systemic vascular resistance were calculated using Equation S1 and Equation S2, respectively, available in the Electronic Supplementary Material.

2.9. Statistical analysis

R version 4.0.3 (R Foundation, Vienna, Austria) was used for analysis. Patient characteristics are shown as median (interquartile range [IQR]) or count (percentage). A mixed-effects model was applied to assess haemodynamic changes before prone positioning and after prone positioning, accounting for repeat measurement within individuals and treating time as a continuous variable. We used mixed-effects modelling to account for each patient's random intercept. To compare the difference of P/F ratio between baseline and each time point, we used a mixed-effects model, accounting for repeated measurements and treating time as a continuous variable. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Subject characteristics

During the 8-week inclusion period, we admitted 71 consecutive patients with polymerase chain reaction–confirmed COVID-19. Sixty-one patients required mechanical ventilation, and of these, 31 patients were treated in the prone position and 18 received FloTrac monitoring in the supine and prone positions (eFig. 1).

Amongst the 18 included patients, the median age was 54 y (IQR, 49–63) and 10 (55%) patients were male. No patients had ischaemic heart disease or heart failure at baseline, and no patients were on steroids or immunosuppressive drugs prior to hospital admission. Additional baseline characteristics are summarised in Table 1. Five patients (27%) were admitted after transfer from another ICU. Fourteen patients (77%) were placed in the prone position on at least three occasions. Five patients (27%) required noradrenaline, and five patients (27%) were treated with low-dose milrinone infusion (0.125 µcg/kg/min) at the time of the first prone session, with no change in milrinone dose over the 4-h supine to prone period. Cisatracurium was used in 14 (77%) patients.

Table 1
Patient characteristics and baseline clinical data for patients with COVID-19 ARDS.

	Overall
Number	18
Age, y (median [IQR])	55 [50–64]
Weight, kg (median [IQR])	89 [74–121]
Height, cm (median [IQR])	170 [159–170]
Gender, male, n (%)	10 (56)
Diabetes, n (%)	5 (28)
Hypertension, n (%)	5 (28)
Asthma, n (%)	2 (11)
COPD, n (%)	1 (6)
Vaccination status, n (%)	
One vaccine	3 (17)
Two vaccines	1 (6)
None	14 (78)
Duration of COVID-19 symptoms before first prone, d (median, IQR)	14 [9–15]
Baseline ABG before first prone	
pH before prone (median [IQR])	7.38 [7.35–7.41]
CO_2 before prone, mm Hg (median [IQR])	47 [42–54]
HCO_3 before prone, mmol/L (median [IQR])	28 [24–31]
Ventilator settings before first prone	
Mode, SIMV, n (%)	17 (94)[a]
TV, mL (median [IQR])	400 [367–450]
TV, mL/kg IBW (median [IQR])	6.7 [6.1–7.2]
PEEP, cmH_2O (median [IQR])	14 [12–15]
Respiratory rate, breaths per min (median [IQR])	20 [18–22]
Total number of prone sessions during ICU stay, n (median [IQR])	5 [3–6]
Treatment at enrolment (first prone)	
Dexamethasone treatment, n (%)	18 (100)
NMBA use, n (%)	14 (78)
Remdesivir, n (%)	3 (17)
Tocilizumab, n (%)	3 (17)
Baricitinib, n (%)	2 (11.1)
Noradrenaline dose, µcg/kg/min (median [IQR])	0 [0–0.75]
Milrinone dose, µcg/kg/min (median [IQR])	0 [0–0.04]
Propofol dose, mg/hr (median [IQR])	200 [200–247]
Midazolam dose, mg/hr (median [IQR])	5 [1–10]
Fentanyl dose, µcg/hr (median [IQR])	150 [112–200]
Morphine dose, mg/hr (median [IQR])	0 [0-0]
iNO use, n (%)	3 (17)

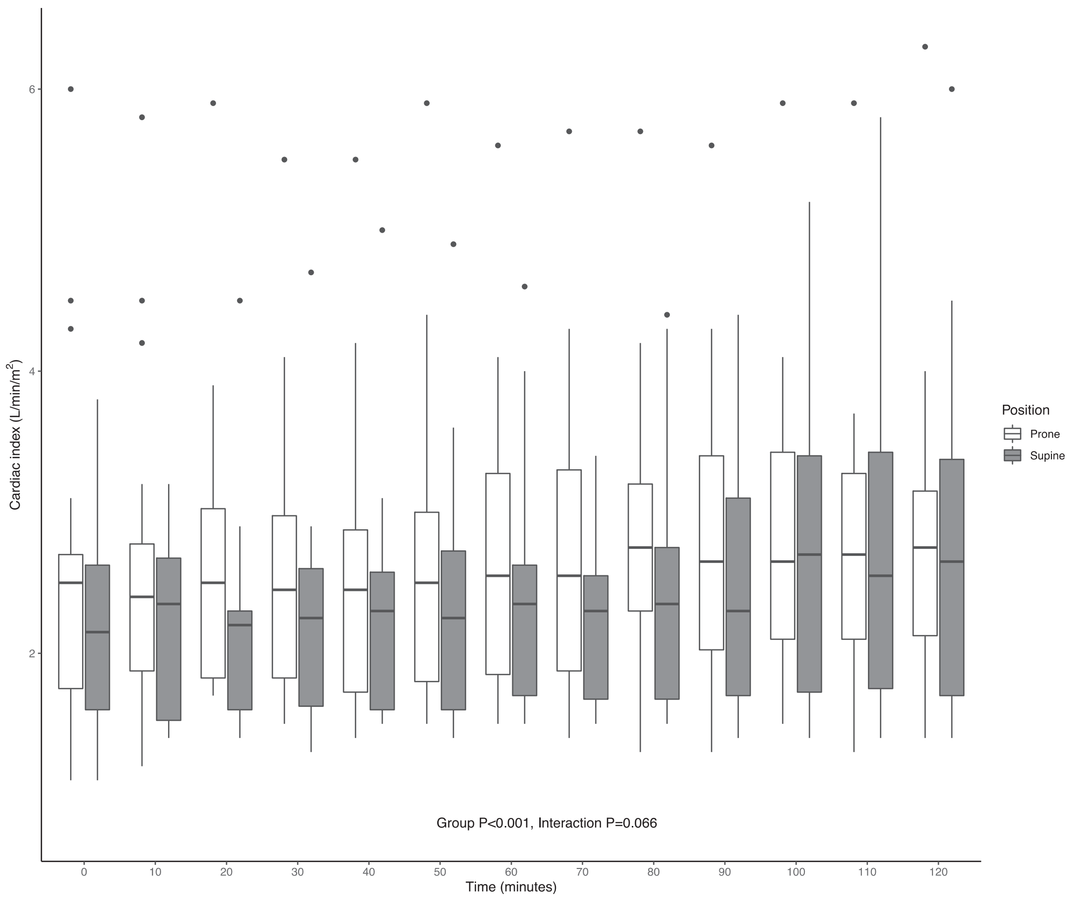
ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; HCO_3, bicarbonate; IBW, ideal body weight; iNO, inhaled nitric oxide; IQR, interquartile range; MV, mechanical ventilation; NMBA, neuromuscular blocking agents; PEEP, positive end-expiratory pressure; TV, tidal volume.
[a] One patient on pressure support (PS) mode.

Table 2
Clinical outcomes for patients with COVID-19 ARDS.

	Overall
Number	18
VV ECMO, n (%)	0 (0)
VA ECMO, n (%)	0 (0)
Alive at discharge from ICU, n (%)	13 (72.2)
Alive at discharge from hospital, n (%)	13 (72.2)
Admission to intubation, h (median [IQR])	5 [−2-(60)]
Admission to prone analysis, h (median [IQR])	98 [33–161]
Intubation to end of MV, d (median [IQR])	18 [13–36][a]
Admission to ICU discharge, d (median [IQR])	16 [11–26][a]
Admission to hospital discharge, d (median [IQR])	23 [13–43][a]

ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; VV ECMO, venovenous extracorporeal membrane oxygenation; VA ECMO, venoarterial extracorporeal membrane oxygenation.
[a] For the 13 patients who survived to hospital discharge.

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006



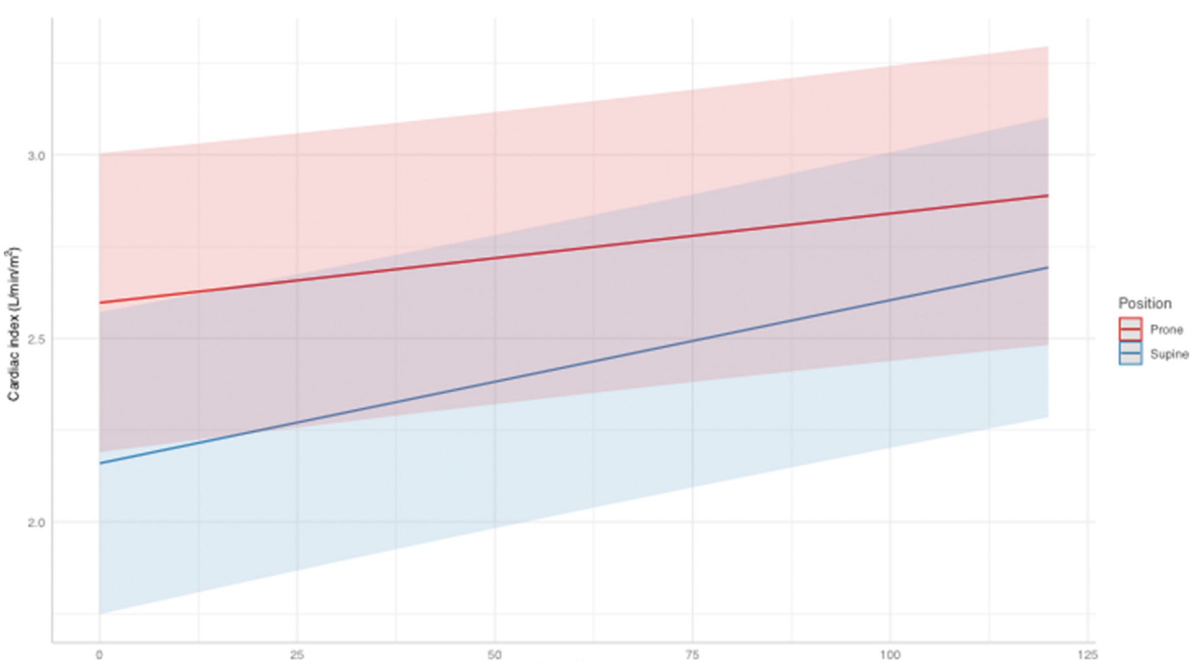


Fig. 1. (A) Time course of the cardiac index in supine versus prone position. Box plot comparing the cardiac index (CI) in the prone position (white box plots) to CI in the supine position (grey box plots). Ten-minutely CI is displayed for 2 h in the supine position, followed by 2 h in the prone position. CI was significantly higher in the prone position than in the supine position (group effect) ($P < 0.001$). The group-by-time interaction effect was not significant ($P = 0.066$), meaning the difference in CI between supine and prone positions did not change with time. (B) Graph of the estimated marginal means and 95% confidence intervals (shaded regions) of the cardiac index in the supine and prone positions.

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006

3.2. Clinical outcomes

Thirteen (72%) patients survived to discharge, requiring intensive care for a median of 16 days (IQR, 11–26). The time to cessation of mechanical ventilation was a median of 18 days (IQR, 12 to 35), with four patients weaning off the ventilator on the respiratory ward. Median length of hospital stay was 23 days (IQR, 13 to 43). Clinical outcome data are summarised in Table 2.

3.3. Primary outcome: cardiac index after prone positioning and other haemodynamic variables

The cardiac index was significantly higher in the prone position than in the supine position (group effect, $P < 0.001$) (Fig. 1A and B). Mean CI was higher in the prone group by 0.44 L/min/m^2 (95% CI, 0.24–0.63). The median CI value in the prone position was 2.6 L/min/m^2 (IQR, 1.9 to 3.3) compared with 2.3 L/min/m^2 (IQR, 1.6 to 2.8) in the supine position. The group-by-time interaction effect was not significant ($P = 0.066$), indicating that the difference in CI between supine and prone positions did not change with time. Given that the group effect comparing CI in supine and prone positions was significant, this indicates that CI was higher in the prone position than in the supine position but that the difference in CI between prone and supine positions remained stable and did not change significantly with time.

The MAP was also significantly higher in the prone position than in the supine position as shown by the significant group effect ($P < 0.001$) (Fig. 2). The median MAP in the prone position was 83 mm Hg (IQR, 77–89) compared to 77 mm Hg (IQR, 73–85) in the supine position.

The median heart rate was faster at 80 beats per min (IQR, 67–89) in the prone position vs 74 beats per minute (IQR, 66–87) in the supine position (group effect $P < 0.001$). Fig. 3 shows that the stroke volume index was significantly higher in the prone position than in the supine position (group effect, $P < 0.001$), with a median stroke volume index of 29 mL/min/m^2 (IQR, 27–38) in the supine position to 33 mL/min/m^2 (IQR, 27–39) in the prone position.

The systemic vascular resistance index (SVRI) was similar, with a median SVRI of 2217 dyn/s/cm^{-5}/m^2 (IQR, 1829–2949) in the prone position vs. 2400 dyn/s/cm^{-5}/m^2 (IQR, 1928–3153) in the supine position (group effect, $P = 0.79$).

3.4. Secondary outcomes: FiO_2, PF ratio, and DO_2 after prone position

FiO_2 requirement decreased significantly with prone positioning (eFig. 2), with a significant increase in P/F ratio (eFig. 3). Median FiO_2 requirement in the supine position was 55% (IQR, 50–63), which decreased to an FiO_2 of 35% (IQR, 30 to 40) after 12–18 h of prone position ($P < 0.001$). Median P/F ratio increased from 120 mm Hg (IQR, 115–170) in the supine position to 220 mm Hg (IQR, 195–244) after 12–18 h of prone position ($P < 0.001$). DO_2 increased significantly in the prone position (Fig. 4), with a median DO_2 of 597 ml O_2/min (IQR, 504 to 931) in the supine position

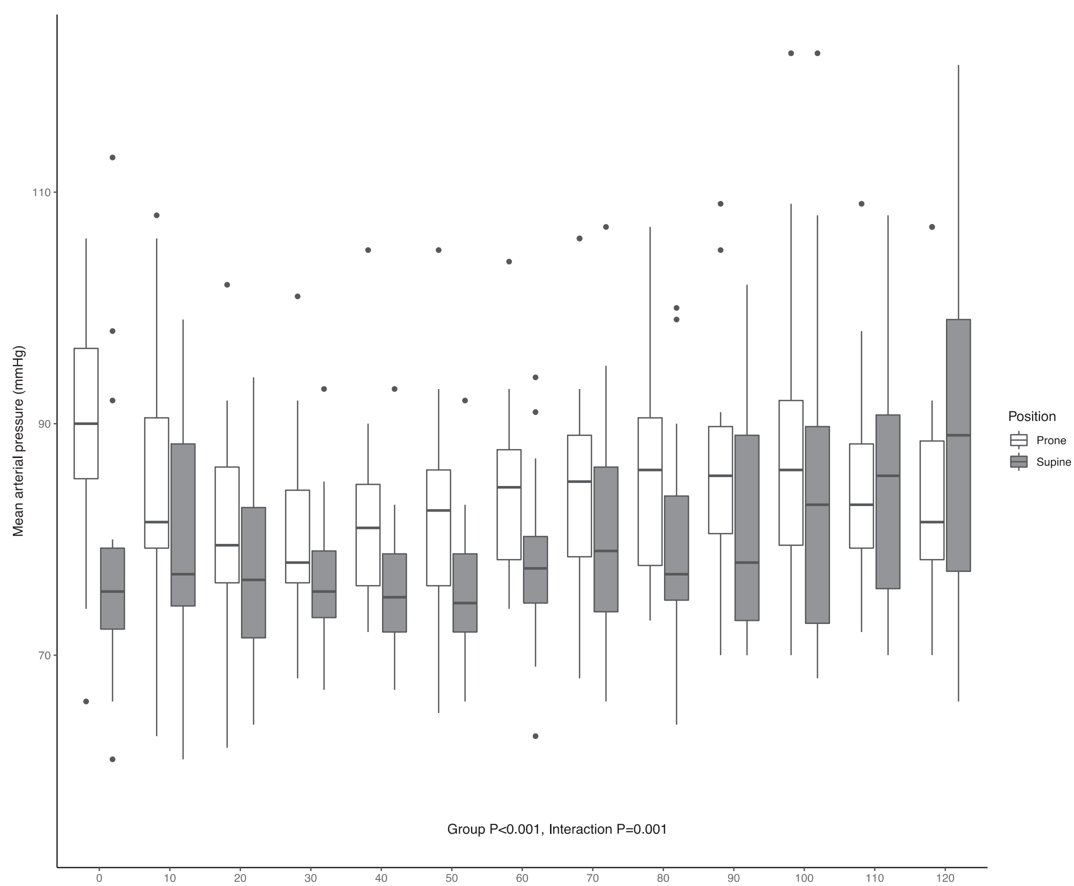


Fig. 2. Time course of mean arterial pressure in supine versus prone position. Box plot comparing mean arterial pressure (MAP) in the prone position (white box plots) to MAP in the supine position (grey box plots). Ten-minutely MAP data are displayed for 2 h in the supine position and then 2 h in the prone position. MAP was significantly higher in the prone position than in the supine position (group effect) ($P < 0.001$), and the group-by-time interaction effect was also significant (interaction) ($P = 0.001$), meaning the difference in MAP between the prone and supine positions changed with time.

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006

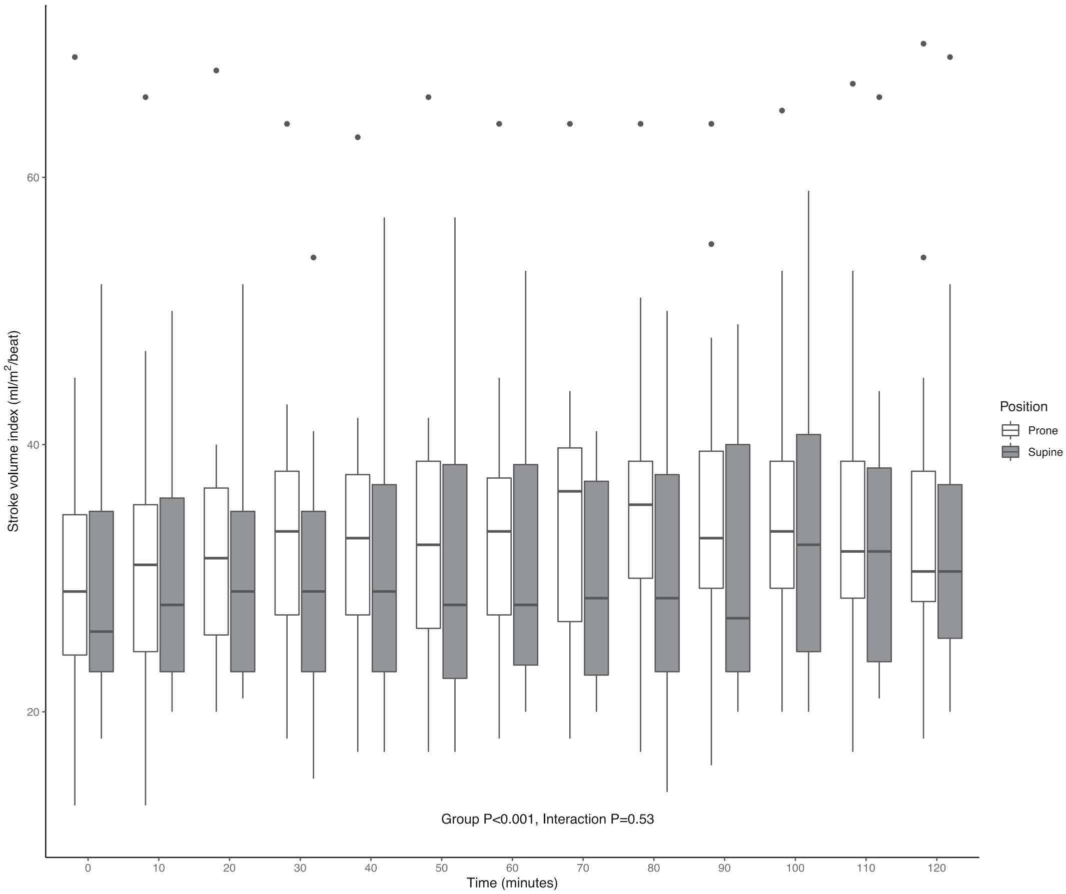


Fig. 3. Time course of stroke volume index in supine versus prone position. Box plot comparing the stroke volume index (SVI) in the prone position (white box plots) to the SVI in supine position (grey box plots). The SVI was significantly higher in the prone position than in the supine position (group effect) ($P < 0.001$). The group-by-time interaction effect was not significant ($P = 0.53$), meaning the difference in SVI between supine and prone positions did not change with time.

increasing to 743 ml O_2/min (IQR, 604 to 1075) in the prone position (group effect $P < 0.001$).

4. Discussion

4.1. Key findings

We found that, in invasively ventilated patients with COVID-19 ARDS, cardiac index, stroke volume index, and mean arterial pressure significantly increased with prone positioning. Moreover, FiO_2 requirement decreased with a significant increase in P/F ratio. Finally, because of the changes in CO and oxygenation, DO_2 increased significantly with prone positioning.

4.2. CO and prone position

In our study, we found that CI was significantly higher in the prone position than in the supine position, with a mean CI increase of 0.44 L/min/m^2 (95% CI, 0.24 to 0.63) (group effect, $P < 0.001$). Given that DO_2 is dependent on both arterial oxygen content, which is low in severe COVID-19 ARDS, and CO, even a small increase in the cardiac index is likely to lead to meaningful improvements in DO_2. Indeed, combined with the increase in arterial oxygen content observed with prone positioning, we found DO_2 increased from a median of 597 mL O_2/min in the supine position to 743 mL O_2/min in the prone position (group effect $P < 0.001$). We believe such change to be clinically relevant.

The prone position may improve CO through several mechanisms. First, it may lead to a reduction in right ventricular afterload.[11,35] This is because an increase in arterial oxygenation with prone positioning may decrease hypoxic pulmonary vasoconstriction and pulmonary vascular resistance.[35] Prone positioning may also increase central blood volume leading to the recruitment of collapsed pulmonary small vessels, further reducing pulmonary vascular resistance.[36]

Second, the prone position may increase preload. In this regard, some investigators have previously found that prone positioning only improved CO in those ARDS patients who were preload responsive, as demonstrated by the use of a positive passive leg raise test.[11] One proposed mechanism for such increased preload is that moving from the semirecumbent supine position into the prone position mobilises venous blood from the abdominal compartment and increases venous return.[37]

4.3. Relationship with previous findings

Our findings of increased CO with prone positioning in patients with COVID-19 ARDS are in contrast with those of Dell'Anna et al.[25] However, these investigators measured the effects of prone positioning in only six patients, using only a single CO measurement. Another small study found no change in cardiac index in the prone position in eight out of nine patients with COVID-19 using three-dimensional transthoracic echocardiography but only measured the cardiac index once.[26]

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006

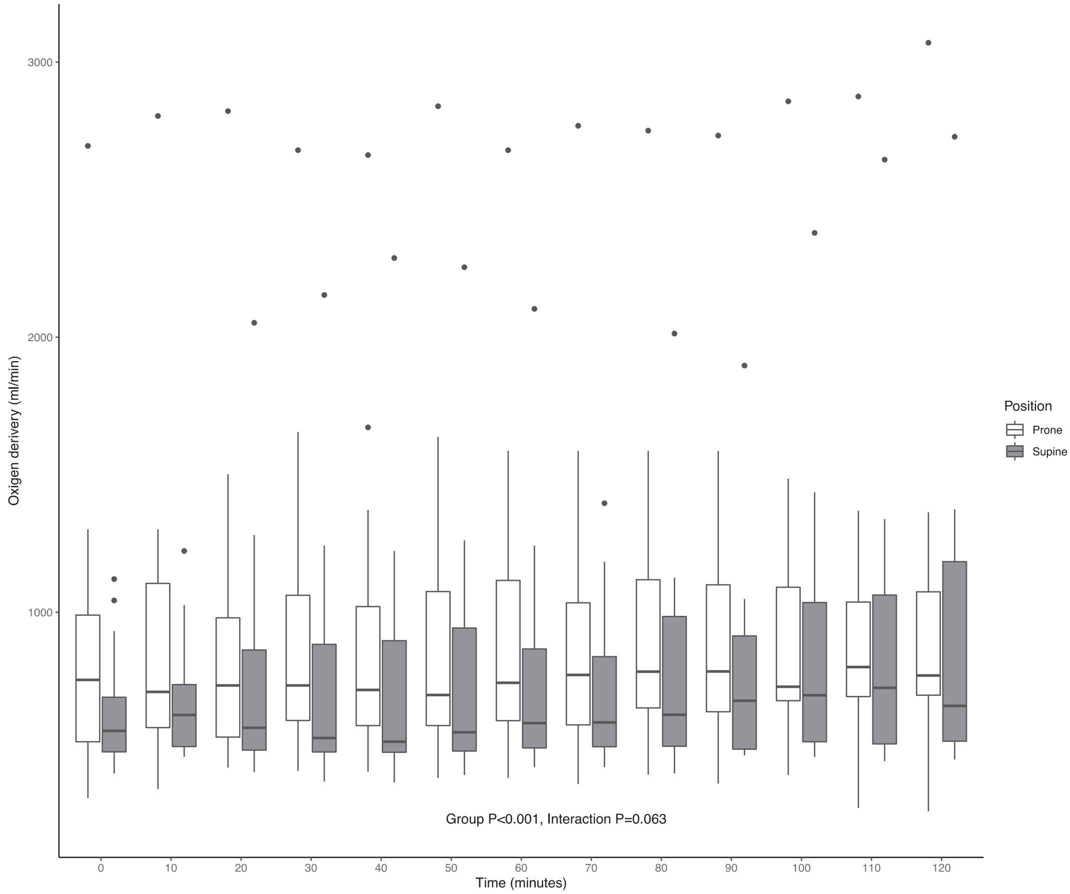


Fig. 4. Oxygen delivery in prone and in supine positions. Box plot comparing oxygen delivery (DO_2) in the prone position (white box plots) to the DO_2 in the supine position (grey box plots) every 10 min for 2 h in the supine position and for 2 h during the prone position. DO_2 was significantly higher in the prone position than in the supine position (group effect) ($P < 0.001$). The group-by-time interaction effect was not significant ($P = 0.063$), meaning the difference in DO_2 between the supine and the prone positions did not change with time.

A larger study using transpulmonary thermodilution reported that in COVID-19 ARDS patients, median CO was 5.9 L/min (IQR, 5.1 to 7.5) in the supine position and 6.2 L/min (IQR, 5.1 to 8.1) in the prone position.[24] However, the study compared haemodynamics in COVID-19 ARDS versus non-COVID-19 ARDS patients, no test of statistical significance was provided comparing prone and supine values, and CO was measured only twice.

In non-COVID ARDS patients, some studies found a significant increase in CI with the prone position,[8–13,38] whereas others found no difference.[14–23] The largest study of non-COVID ARDS patients found a highly heterogenous response in the cardiac index to prone positioning.[38] However, cardiac index measurements were only at a few specific time points, thus failing to provide a near-continuous assessment and decreasing the statistical power. In contrast, our study collected advanced haemodynamic data every 5 min during supine and prone positioning for a total of 4 h.

Another study found that cardiac index increased during the prone position only in patients with acute cor pulmonale.[35] There is substantial evidence that right ventricular dysfunction occurs in a high proportion of patients hospitalised with COVID-19[39,40] and that right ventricular dysfunction may be observed in up to 70% of mechanically ventilated COVID-19 patients.[41] Moreover, in a recent large multicentre study, acute cor pulmonale was noted in over 17% of echocardiograms performed on ICU patients with severe COVID-19 and was associated with a significant increase in hospital mortality.[40] In our study, prone positioning was associated with a significantly improved oxygenation as demonstrated by the increase in P/F ratio. Improvement in oxygenation may have led to the observed increase in CI and MAP by reducing hypoxic pulmonary vasoconstriction and therefore right ventricular afterload.

We found improvement in P/F ratio with prone positioning, which is consistent with findings of several other studies.[4,5,7] Multiple potential mechanisms may account for improved oxygenation in the prone position. They include improved global alveolar recruitment, decreased shunting in the dorsal regions, and decreased dead space ventilation in ventral regions.[42] Moreover, prone positioning may decrease the dependent lung mass, thereby reducing hyperperfusion of atelectatic units and reducing V/Q mismatch.[43]

4.4. Implications of study findings

Using continuous CO monitoring, we found prone positioning was associated with an increased CO and mean arterial pressure and improved systemic oxygen levels and DO_2. This indicates that prone positioning may improve DO_2 not only through its pulmonary effects but also by increasing CO. Assuming unchanged oxygen extraction, an increased CO and its related increase in DO_2 will increase mixed venous oxygen saturation. Even in the presence of an unchanged shunt fraction, such an increase in mixed venous oxygen saturation will contribute to improved systemic oxygen levels.

In addition to improved oxygenation, the beneficial haemodynamic changes seen with prone positioning may in themselves contribute to the reduction in mortality observed in clinical trials.[3,4]

Please cite this article as: Coxwell Matthewman M et al., Haemodynamic changes during prone versus supine position in patients with COVID-19 acute respiratory distress syndrome, Australian Critical Care, https://doi.org/10.1016/j.aucc.2023.03.006

4.5. Potential barriers to using prone positioning

Given the proven benefits of prone positioning in ARDS,[3] it is important to address the barriers to its use. Perceived barriers to prone positioning include lack of knowledge of patient eligibility and optimal timing, lack of training in prone positioning processes, inadequate staffing, lack of leadership, and poor interdisciplinary communication.[44] Strategies to address such barriers include interprofessional educational programs, written clinical protocols, and prone positioning teams led by local experts.[44] In our ICU, a simulation using a mannequin was used to train multidisciplinary staff members in prone positioning; each prone positioning session was led by a local expert, and a clinical protocol was developed where prone positioning was considered in all patients with a P/F ratio less than 150 mmHg.

4.6. Strengths and limitations

To our knowledge, this is the largest report of the haemodynamic changes associated with prone positioning in mechanically ventilated patients with COVID-19 ARDS. Moreover, this study included detailed haemodynamic data, which were collected almost continuously during prone positioning and were then compared with identical data from the same patients during supine positioning. Finally, we obtained complete data on all included patients and no imputation was required.

Limitations of this study include the relatively small sample size, although it is larger than that of most physiological studies on this topic.[24–26] It was also not possible to include every ventilated patient with COVID-19 placed in the prone position, due to insufficient FloTrac device availability. However, more than half of eligible patients were included. It is possible that the FloTrac device may be less reliable than other methods to measure CO.[45] However, the FloTrac is less invasive, allows essentially continuous data collection, and has been shown to perform similarly to other CO-measuring technologies.[32] Finally, and more importantly, our investigation makes no assumption about the accuracy of FloTrac; it simply compares changes in its measurement in two different patient positions and shows a change with prone positioning.

5. Conclusion

In summary, in this study we found that prone positioning improved cardiac index, stroke volume, MAP, systemic oxygenation, P/F ratio, and DO_2 in patients with COVID-19 ARDS. These changes in CO identify another mechanism by which prone positioning can improve systemic oxygenation in COVID-19 ARDS and further support its application in this condition.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Madeline Coxwell Matthewman: Conceptualisation, Methodology, Formal Analysis, Investigation, Resources, Writing - Original Draft, Review & Editing. **Fumitaka Yanase:** Conceptualisation, Methodology, Formal Analysis, Investigation, Resources, Writing - Original Draft, Review and Editing, Visualisation. **Rahul Costa-Pinto:** Investigation, Resources, Writing - Review & Editing. **Daryl Jones:** Investigation, Resources, Writing - Review and Editing. **Dharshi Karalapillai:** Investigation, Resources, Writing - Review and Editing. **Lucy Modra:** Investigation, Resources, Writing - Review and Editing. **Sam Radford:** Investigation, Resources, Writing - Review and Editing. **Ida-Fong Ukor:** Investigation, Resources, Writing - Review and Editing. **Stephen Warrillow:** Investigation, Resources, Writing - Review and Editing. **Rinaldo Bellomo:** Conceptualisation, Methodology, Investigation, Resources, Writing - Original Draft, Review and Editing, Supervision.

Conflict of interest

All the authors declare that they do not have any conflicts of interest.

Acknowledgements

We thank all the nurses, doctors, and physiotherapists at Austin Hospital for the help and support provided to the investigators of this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2023.03.006.

References

[1] World Health Organisation. WHO coronavirus disease dashboard [Internet] [cited 2022 Mar 1]. who.int; 2022. p. 1. Available from: https://covid19.who.int/.
[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA, J Am Med Assoc 2020;323(13):1239–42.
[3] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68.
[4] Weiss TT, Cerda F, Scott JB, Kaur R, Sungurlu S, Mirza SH, et al. Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study. Br J Anaesth 2021;126(1):48–55.
[5] Carsetti A, Paciarini AD, Marini B, Pantanetti S, Adrario E, Donati A. Prolonged prone position ventilation for SARS-CoV-2 patients is feasible and effective. Crit Care 2020;24:1–3.
[6] Mathews KS, Soh H, Shaefi S, Wang W, Bose S, Coca S, et al. Prone positioning and survival in mechanically ventilated patients with coronavirus disease 2019-related respiratory failure. Crit Care Med 2021;49(7):1026–37.
[7] Behesht Aeen F, Pakzad R, Goudarzi Rad M, Abdi F, Zaheri F, Mirzadeh N. Effect of prone position on respiratory parameters, intubation and death rate in COVID-19 patients: systematic review and meta-analysis. Sci Rep 2021;11(1): 1–16.
[8] Lai C, Adda I, Teboul JL, Persichini R, Gavelli F, Guérin L, et al. Effects of prone positioning on venous return in patients with acute respiratory distress syndrome. Crit Care Med 2021:781–9.
[9] Brücken U, Grensemann J, Wappler F, Sakka SG. Influence of prone positioning on the measurement of transpulmonary thermodilution-derived variables in critically ill patients. Acta Anaesthesiol Scand 2011;55(9):1061–7.
[10] Hering R, Vorwerk R, Wrigge H, Zinserling J, Schröder S, Von Spiegel T, et al. Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. Intensive Care Med 2002;28(1):53–8.
[11] Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013;188(12):1428–33.
[12] Voggenreiter G, Neudeck F, Aufmkolk M, Fassbinder J, Hirche H, Obertacke U, et al. Intermittent prone positioning in the treatment of severe and moderate posttraumatic lung injury. Crit Care Med 1999;27(11):2375–82.
[13] Hering R, Wrigge H, Vorwerk R, Brensing KA, Schrö Der, Md S, et al. The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. Crit Care Trauma 2001;92. 1226–1131.
[14] Matejovic M, Rokyta R, Radermacher P, Krouzecky A, Sramek V, Novak I. Effect of prone position on hepato-splanchnic hemodynamics in acute lung injury. Intensive Care Med 2002;28(12):1750–5.
[15] Rialp G, Betbesé AJ, Pérez-Márquez M, Mancebo J. Short-term effects of inhaled nitric oxide and prone position in pulmonary and extrapulmonary acute respiratory distress syndrome. Am J Respir Crit Care Med 2001 Jul 15;164(2):243–9.

[16] McAuley D, Giles S, Fichter H, Perkins G, Gao F. What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome? Intensive Care Med 2002;28(4):414–8.
[17] Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. Crit Care Med 1998;26(12):1977–85.
[18] Blanch L, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. Intensive Care Med 1997;23(10):1033–9.
[19] Xu Y, Deng X, Han Y, Zhou L, He W, Chen S, et al. A multicenter retrospective review of prone position ventilation (PPV) in treatment of severe human H7N9 Avian flu. PLoS One 2015 Aug 28;10(8):e0136520.
[20] Chiumello D, Cressoni M, Racagni M, Landi L, Li Bassi G, Polli F, et al. Effects of thoraco-pelvic supports during prone position in patients with acute lung injury/acute respiratory distress syndrome: a physiological study. Crit Care 2006;10(3):R87.
[21] Saran S, Gurjar M, Azim A, Mishra P, Ghosh PS, Baronia AK, et al. Transesophageal Doppler assessment of acute hemodynamic changes due to prone positioning in acute respiratory distress syndrome patients. Shock 2019;52(4):e39–44.
[22] Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. Eur Respir J 2005;25(3):534–44.
[23] Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 1998;157(2):387–93.
[24] Asar S, Acicbe Ö, Sabaz MS, Tontu F, Canan E, Cukurova Z, et al. Comparison of respiratory and hemodynamic parameters of COVID-19 and non-COVID-19 ARDS patients. Indian J Crit Care Med 2021;25(6):703–7.
[25] Dell'Anna AM, Carelli S, Cicetti M, Stella C, Bongiovanni F, Natalini D, et al. Hemodynamic response to positive end-expiratory pressure and prone position in COVID-19 ARDS. Respir Physiol Neurobiol 2022;29:103844.
[26] Evrard B, Goudelin M, Fedou AL, Vignon P. Hemodynamic response to prone ventilation in COVID-19 patients assessed with 3D transesophageal echocardiography. Intensive Care Med 2020;46(11):2099–101.
[27] Australian Government: National Health and Medical Research Council. Conduct in human research national statement on ethical conduct in human research, vol. 2007; 2018. p. 104.
[28] Mclean AS, Huang SJ, Kot M, Rajamani A, Hoyling L. Comparison of CO measurements in critically ill patients: Flotrac/Vigileo vs transthoracic Doppler echocardiography. Anaesth Intensive Care 2011;39(4):590–8.
[29] Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: recommendations to guide clinical practice. Pneumon 2020;33(1):32–5.
[30] Pozuelo-Carrascosa DP, Cobo-Cuenca AI, Carmona-Torres JM, Laredo-Aguilera JA, Santacruz-Salas E, Fernandez-Rodriguez R. Body position for preventing ventilator-associated pneumonia for critically ill patients: a systematic review and network meta-analysis. J Intensive Care 2022;10(1):1–14.
[31] Evans DC, Doraiswamy VA, Prosciak MP, Silviera M, Seamon MJ, Rodriguez Funes V, et al. Complications associated with pulmonary artery catheters: a comprehensive clinical review. Scand J Surg 2009;98(4):199–208.
[32] Lamia B, Kim HK, Severyn DA, Pinsky MR. Cross-comparisons of trending accuracies of continuous cardiac-output measurements: pulse contour analysis, bioreactance, and pulmonary-artery catheter. J Clin Monit Comput 2018;32(1):33–43.
[33] Mclean AS, Huang SJ, Kot M, Rajamani A, Hoyling L. Comparison of CO measurements in critically ill patients: Flotrac/Vigileo vs transthoracic Doppler echocardiography. Anaesth Intensive Care 2011;39(4):590–8.
[34] Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. Crit Care Med 2016;44(5):880–91.
[35] Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest 2007;132(5):1440–6.
[36] Fougères E, Teboul JL, Richard C, Osman D, Chemla D, Monnet X. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. Crit Care Med 2010;38(3):802–7.
[37] Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 2016;42(12):1935–47.
[38] Ruste M, Bitker L, Yonis H, Riad Z, Louf-Durier A, Lissonde F, et al. Hemodynamic effects of extended prone position sessions in ARDS. Ann Intensive Care 2018;8(1):120.
[39] Bonnemain J, Ltaief Z, Liaudet L. The right ventricle in COVID-19 patients. Eur Heart J 2021;42(6):559–60.
[40] Huang S, Vignon P, Mekontso-Dessap A, Tran S, Prat G, Chew M, et al. Echocardiography findings in COVID-19 patients admitted to intensive care units: a multi-national observational study (the ECHO-COVID study). Intensive Care Med 2022;48(6):667–78.
[41] Kim J, Volodarskiy A, Sultana R, Pollie MP, Yum B, Nambiar L, et al. Prognostic utility of right ventricular remodeling over conventional risk stratification in patients with COVID-19. J Am Coll Cardiol 2020;76(17):1965–77.
[42] Fossali T, Pavlovsky B, Ottolina D, Colombo R, Basile MC, Castelli A, 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(5):723–32.
[43] Gattinoni L, Camporota L, Marini JJ. Prone position and COVID-19: mechanisms and effects. Crit Care Med 2022;50(5):873–5.
[44] Klaiman T, Silvestri JA, Srinivasan T, Szymanski S, Tran T, Oredeko F, et al. Improving prone positioning for severe acute respiratory distress syndrome during the COVID-19 pandemic. An implementation-mapping approach. Ann Am Thorac Soc 2021;18(2):300–7.
[45] Kaufmann T, Clement RP, Hiemstra B, Vos JJ, Scheeren TWL, Keus F, et al. Disagreement in CO measurements between fourth-generation FloTrac and critical care ultrasonography in patients with circulatory shock: a prospective observational study. J Intensive Care 2019;7(1):1–8.