

## Early View

Original research article

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# Physiological effects and subjective tolerability of prone positioning in COVID-19 and healthy hypoxic challenge

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## Take home message

Awake prone positioning in patients with COVID-19 causes a small increase in SpO<sub>2</sub> within 10 minutes of proning but is associated with increased subjective discomfort, with challenges in the identification of hospital patients suitable for the procedure.

## **Abstract**

### **Background**

Prone positioning has a beneficial role in COVID-19 patients receiving ventilation but lacks evidence in awake non-ventilated patients, with most studies being retrospective, lacking control populations and information on subjective tolerability.

### **Methods**

We conducted a prospective, single-centre study of prone positioning in awake non-ventilated patients with COVID-19 and non-COVID-19 pneumonia. The primary outcome was change in peripheral oxygenation in prone versus supine position. Secondary outcomes assessed effects on end-tidal CO<sub>2</sub>, respiratory rate, heart rate, and subjective symptoms. We also recruited healthy volunteers to undergo proning during hypoxic challenge.

### **Results**

238 hospitalised patients with pneumonia were screened; 55 were eligible with 25 COVID-19 patients and 3 non-COVID-19 patients agreeing to undergo proning – the latter insufficient for further analysis. 10 healthy control volunteers underwent hypoxic challenge. Patients with COVID-19 had a median age of 64 years (interquartile range [IQR] 53 – 75). Proning led to an increase in SpO<sub>2</sub> compared to supine position (difference +1.62%;  $P = 0.003$ ) and occurred within 10 minutes of proning. There were no effects on end-tidal CO<sub>2</sub>, respiratory rate, or heart rate. There was an increase in subjective discomfort ( $P = 0.003$ ), with no difference in breathlessness. Among healthy controls undergoing hypoxic challenge, proning did not lead to a change in SpO<sub>2</sub> or subjective symptom scores.

### **Conclusion**

Identification of suitable patients with COVID-19 requiring oxygen supplementation from general ward environments for awake proning is challenging. Prone positioning leads to a small increase in SpO<sub>2</sub> within 10 minutes of proning though is associated with increased discomfort.

## Introduction

The COVID-19 pandemic has caused significant global morbidity and mortality. Whilst most individuals have mild infection, a significant proportion develop hypoxia and some progress to respiratory failure. Supplemental oxygen remains the mainstay of treatment for COVID-19 patients and the delivery of adequate oxygen capacity has become a critical issue during times of peak infection [1]. There remains a need for evidence of non-pharmacological interventions, particularly in resource-poor settings.

Prone positioning is considered standard care in patients with severe acute respiratory distress syndrome (ARDS) by increasing the  $\text{PaO}_2/\text{FiO}_2$  (PF) ratio and reducing mortality [2]. Physiologically, proning is thought to reduce atelectasis of dorsal lung regions, improve ventilation-perfusion mismatch, and reduce compression from the abdominal cavity and the mediastinum. Mortality benefit from proning has also been linked with a decreased risk of ventilator-induced lung injury [3].

In the setting of patients with non-COVID-19-related respiratory failure receiving non-invasive ventilation, a few small retrospective case studies suggest potential beneficial effects of awake prone positioning, with improved oxygenation and a reduced rate of intubation [4] [5] [6]. In awake patients with COVID-19 pneumonia, studies have shown a beneficial effect of proning on oxygenation [7]. However, most studies are limited by their retrospective nature, include minimal time-points for physiological assessment, lack data on the tolerability of the procedure and are focused on patients receiving ventilatory support (non-invasive ventilation, continuous positive airway pressure and high-flow nasal oxygen) [8] [9]. Despite this proning has been recommended by guidelines in conscious COVID-19 patients requiring supplemental oxygen only [10].

Therefore, our study aimed firstly to determine the proportion of hypoxic patients with pneumonia eligible for proning; secondly to assess the physiological effects of proning on this milder group of awake patients with pneumonia requiring only supplemental oxygen without ventilatory support (representing the majority of hospitalised patients with COVID-19); and thirdly to assess the tolerability of proning by assessing the subjective experience of those who underwent the procedure.

## Methods

### Study design and participants

We conducted a prospective study to comprehensively investigate the detailed physiological effects and subjective tolerability of proning in awake, spontaneously breathing, non-ventilated hypoxaemic patients with and without COVID-19 pneumonia, who were recruited from a general hospital ward environment. We also recruited healthy volunteer controls to undergo proning during hypoxic challenge. The rationale for this latter group was to specifically test the hypothesis that parenchymal consolidation (rather than hypoxia alone) was required to observe the effects of proning on physiological parameters. Furthermore, this group acted as a control comparator group to assess the impact of proning on the subjective tolerability of the procedure.

This single centre study was conducted at Cambridge University Hospitals NHS Foundation Trust, UK, a large acute medicine hospital in the East of England. This study was funded by support from the Addenbrooke's Charitable Trust and received favourable Ethics Committee opinion from the Health Research Authority Southwest – Cornwall & Plymouth Research Ethics Committee (20/SW/0097) and registered with ClinicalTrials.gov (NCT04589936). All participants provided written consent.

Patients were recruited from general medical wards from 03<sup>rd</sup> September 2020 to 23<sup>rd</sup> February 2021. Inclusion criteria were predominantly based on the United Kingdom Intensive Care Society (ICS) guidance for prone positioning of the conscious COVID-19 patient [10], including patients with:  $\text{FiO}_2 \geq 0.24$  requiring basic respiratory support (supplemental oxygen via face mask or nasal cannula) to achieve their clinical target  $\text{SpO}_2$  (e.g.  $\text{SpO}_2$  92-96%); confirmed COVID-19 (by nasal swab PCR test) or non-COVID pneumonia with confirmed radiological changes; able to provide informed consent, communicate and cooperate with the procedure; could rotate and adjust position independently and had no anticipated airway issues. The exclusion criteria included those with signs of respiratory distress; haemodynamic instability; unstable spinal injury or recent abdominal surgery; pregnancy; morbid obesity; neurological issues; facial injury; gastrointestinal issues such as vomiting and any other clinical reason which may preclude entry in the opinion of the investigator.

Inclusion criteria for healthy volunteers in the hypoxic challenge sub-study were those without respiratory illness, able to cooperate with the procedure and could rotate and adjust position independently.

Electronic health records were used to collect data on demographics, anthropometrics, baseline arterial blood gas measurement if taken on admission, white cell count (WCC) and C-reactive protein (CRP) taken at a time closest to proning, COVID-19 nasal swab PCR test status, radiographic severity score from chest X-ray [11], concomitant medications for COVID-19, co-morbidities, and smoking status.

## **Procedures**

Participants were asked to proceed through a cycle of position changes: starting in the supine position for approximately 15 minutes, followed by lateral position on either side for 15 minutes, then prone position aiming for at least 30 minutes, ending with resupination. Prompts were provided by a member of the investigator team to ensure participants change position at the appropriate time. Proning was discontinued if participants were unable to tolerate the position, or due to any other clinical concerns.

Hypoxic challenge is a safe and tolerable procedure used to assess the suitability of adults with respiratory disease for flying at altitude [12]. We wished to assess the effects of proning in healthy volunteers without lung parenchymal disease undergoing hypoxic challenge. This involved delivery of 100% nitrogen through a 40% Venturi mask, which mixed with room air within the mask resulting in a  $\text{FiO}_2$  of 15%. Hypoxic challenge would be stopped if  $\text{SpO}_2$  fell below 85% or if participants could not tolerate the procedure.

All participants (COVID-19 pneumonia, non-COVID-19 pneumonia, and healthy individuals) were fitted with a Masimo monitoring device (Irvine, USA) that enabled continuous monitoring of  $\text{SpO}_2$ , end-tidal  $\text{CO}_2$ , heart rate and respiratory rate.

A questionnaire with a modified visual analogue scale (VAS) and free-form questions was designed to evaluate the participant's experience during the procedure [13]. After 10-15 minutes in each position, the participant was asked to rate their subjective breathlessness and discomfort, with each question displayed on a 0-10 VAS. Higher rates signified increased

breathlessness and discomfort. VAS scores at all positions were compared with score at the initial supine position for each participant. Free-form questions included how the participant felt in each position, investigators' observation of the participant, factors that may facilitate or impede the ability to lie in the position, and changes felt during the position.

### **Study outcomes**

The primary outcome of the study was the change in peripheral oxygenation saturation with a fixed fraction of inspired oxygen ( $\text{FiO}_2$ ) in the prone position versus supine position.

The secondary outcomes included assessment of the effects of prone position versus supine or lateral position on other physiological parameters including end-tidal  $\text{CO}_2$ , respiratory rate, and heart rate. The subjective experience of participants undergoing prone positioning was assessed using VAS of the degree of breathlessness and discomfort in each position compared with the VAS at the initial supine position, and free text question responses were also collated.

### **Statistical analysis**

An estimation of sample size required to determine the effect of proning was calculated using a Wilcoxon signed-rank test, estimating an effect size of change in  $\text{PaO}_2$  of 6.6 mmHg based on published data [14]. Although  $\text{SpO}_2$  rather than  $\text{PaO}_2$  was used for this study, similar changes in outcome measures can be anticipated. A sample size of 28 for COVID-19 and non-COVID-19 pneumonia participants was deemed suitable, with a two-sided significance level of 0.05, power of 0.8, allowing for a 10% drop-out rate. The hypoxic challenge study was not formally powered but aimed to recruit 10 volunteers as a pragmatic number of control participants.

A linear mixed effect regression was used to model the effect of position on the various outcome variables as it allows for correlation between the repeated measures across individuals. Position was included as a fixed effect and the interaction between the individual and their position was included as a random effect.

A further linear mixed effect model was produced as part of a post-hoc sensitivity analysis. The SpO<sub>2</sub> in each position was measured every 2 seconds, and for each individual, summarised to a single value (median) and used as the outcome measurement. A multiple regression model was created to analyse which variables influence the magnitude of the SpO<sub>2</sub> change associated with proning.

In order to provide insight into whether a longer duration of proning might improve SpO<sub>2</sub>, the median SpO<sub>2</sub> in the last 60 seconds of the prone position was compared to the median SpO<sub>2</sub> for the entire prone position using a paired two sample t-test.

The visual analogue scale (VAS) data was analysed using Friedman test with Dunn's multiple comparison.

Analysis and figures were produced using R and the following packages: *tidyverse*, *lmerTest*, and *tableone*, and GraphPad Prism 9.1.0 for Windows (San Diego, CA, USA).

## Results

### *Screening*

Electronic health records of 390 patients admitted for a respiratory illness were screened (**Figure 1**). 238 patients were hospitalized for pneumonia: 191 due to COVID-19 and 47 without COVID-19 pneumonia. 142 (74.3%) COVID-19 patients and 41 (87.2%) non-COVID-19 pneumonia patients had one or more exclusion criteria, with the main reason being psychiatric or cognitive issues (25.4% of COVID-19 patients and 29.3% of non-COVID-19 patients).

49 COVID-19 patients and 6 non-COVID-19 pneumonia patients were approached, of which the study procedure was performed on 25 COVID-19 patients and 3 non-COVID-19 pneumonia patients. The main reason for COVID-19 patients declining to participate in the trial was due to anxiety about proning (22.7%) or feeling too tired or breathless to even attempt the procedure (18.2%). Eleven healthy volunteers were recruited to undergo hypoxic challenge and body positioning changes, of which ten participants were analysed. Continuous monitoring data from one COVID-19 participant and one healthy volunteer were



lost due to technical issues. Non-COVID pneumonia cases were not analysed due to insufficient numbers.

#### *COVID-19 cohort*

The detailed characteristics of the study population are shown in **Table 1**. Participants with COVID-19 had a median (IQR) age of 64 (53 - 75) years. Eighteen (72%) participants were male, and the median BMI was 28.5 (25.7 - 31.4) kg/m<sup>2</sup>. Ten (40%) were ex-smokers and one (4%) a current smoker at the time of the study. Common comorbidities included hypertension (32%), asthma (20%), type II diabetes mellitus (16%) and ischaemic heart disease (12%). Median FiO<sub>2</sub> at proning was 0.32 (0.28-0.36). Baseline blood gases showed a median PaO<sub>2</sub> of 8.00 (7.83-9.03) kPa and PaCO<sub>2</sub> of 4.50 (3.98-4.60) kPa. Participants had a median WCC of 7.9 (6.0-11.1) x10<sup>9</sup>/L and median CRP of 77 (44-141) mg/L. Participants were admitted to hospital a median of 9 (3 - 11) days after symptom onset and were prone a median of 2 (1 - 3) days after admission. The median radiographic severity score was 5 (4-7). All patients were treated with dexamethasone, 10 (40%) were treated with dexamethasone without additional COVID-19 therapy and 15 (60%) trialled various additional therapeutic regimens. Regarding clinical outcomes, one patient (4%) required intubation, one patient (4%) required non-invasive ventilation, one patient (4%) died, 24 patients (96%) were discharged and median time from proning to discharge was 7 days (IQR 4-10.5 days).

#### *Effect of position on SpO<sub>2</sub>*

Patients were instructed to remain in the prone position for at least 30 minutes if possible. 16/25 patients were able to prone for at least 30 minutes with a range of 10 – 60 minutes. The median SpO<sub>2</sub> in the prone position was significantly higher than the initial supine position (94.74% prone [standard error 0.38], 93.12% supine [0.53], difference +1.62%; *P* = 0.003, **Figure 2A, Supplementary Table 1**). SpO<sub>2</sub> in lateral and resupination positions did not differ from initial supination. A post-hoc sensitivity analysis was also performed using a single median SpO<sub>2</sub> (as opposed to using multiple raw data points) for each position in each

individual (**Supplementary Table 2**), which did not differ from the results of the full mixed effect model.

Improvement in SpO<sub>2</sub> occurred within 10 minutes of proning and was sustained for the duration of the proning position (**Figure 2C**). The SpO<sub>2</sub> at the end of the proning position (median of the last 60 seconds) was not significantly different from the median prone SpO<sub>2</sub> (95% vs 95%;  $p = 0.93$ ).

The majority of participants showed an improvement in oxygenation in the prone position which was not maintained upon resupination (**Supplementary figures 1 and 2**). There was no change to these results when considering only those ( $n = 16$ ) who were in the prone position for at least 30 minutes (**Supplementary Table 3**). There was no effect of body position on respiratory rate, end-tidal CO<sub>2</sub> nor heart rate in COVID-19 participants or healthy volunteers (**Supplementary figures 3 and 4, Supplementary tables 4 and 5**).

#### *Healthy volunteers*

For healthy volunteers, the median age was 35 (22.5 - 44) years. Two (20%) participants were male, the median BMI was 23.9 (22.8 - 25.9), and only 1 (10%) participant was an ex-smoker. There was no significant difference in SpO<sub>2</sub> between positions (**Figure 2B and Supplementary Table 6**), and SpO<sub>2</sub> remained constant over 30 minutes in the prone position (**Figure 2D**).

#### *Predictors of SpO<sub>2</sub> improvement*

We produced a linear model to assess whether selected clinical variables are able to predict the magnitude of the SpO<sub>2</sub> change from the supine to prone position. We found that a lower baseline SpO<sub>2</sub> was predictive of a greater improvement in SpO<sub>2</sub> with proning ( $P = 0.003$ ). Older patients had a smaller improvement with proning ( $P = 0.013$ ). Other variables (BMI, radiographic severity score, and FiO<sub>2</sub> at time of proning) had no significant predictive effect on the size of SpO<sub>2</sub> improvement upon proning (**Supplementary Table 7**).

### *Tolerability and subjective experience of prone positioning*

COVID-19 patients experienced a significant increase in discomfort in both lateral (median score 3 [IQR 1.5 – 4.5,  $P = 0.035$ ]) and prone (median score 4 [IQR 2.5-5.0,  $P = 0.003$ ]) positions, compared with initial supine position (median score 2 [IQR 1-3]) (**Figure 3A, C**). There was no significant difference in the degree of reported breathlessness in any position. Healthy volunteers undergoing hypoxic challenge did not experience a significant increase in subjective breathlessness or discomfort (**Figure 3B, D**).

Qualitative data on participant and investigator observations of proning and the factors that helped or hindered tolerability are shown in **Supplementary Table 8**. 15/25 participants reported some discomfort including discomfort in arms, neck and shoulders and becoming hot. For some, it became more comfortable over time as they settled into it. 8/25 participants found the position comfortable. Some found the use of additional support such as pillows helpful.

## **Discussion**

In this prospective, single-centre study of 25 awake non-ventilated COVID-19 patients on supplementary oxygen recruited from general medical wards, we found that a brief period of proning resulted in a small but significant increase in oxygenation of 1.6% compared to supine position. However, this was associated with worse subjective tolerability with increased discomfort in this position. We did not find any significant effect of proning on end-tidal CO<sub>2</sub>, respiratory rate, heart rate or a subjective sensation of breathlessness.

Our population included patients with a median age of 64 years, a male prevalence of 72% and common comorbidities including hypertension and diabetes. This is broadly in line with the demographic features common to patients presenting with COVID-19 in the UK [15]. Therefore, although this was a single-centre study, the findings are likely to have reasonable generalisability across medical ward environments in UK hospitals. An important observation, however, is that about three-quarters of COVID-19 patients screened requiring oxygenation, met the study's exclusion criteria and in a significant proportion (25%), this was due to the presence of cognitive or psychiatric issues (such as dementia), which would

have made it difficult to reliably perform the intervention. Furthermore, of 49 suitable patients who were approached, 22 declined due to pre-existing anxiety or experience of discomfort with proning or were too tired to attempt the procedure. Of the 25 patients who were suitable to undertake proning, only 64% were able to do so for a duration of at least 30 minutes. These findings therefore highlight the significant challenges of identifying and performing proning in unwell and often older-age patients with COVID-19 in general medical ward environments, despite formal guidelines that recommend widespread use of the procedure.

Virtually all studies of proning in COVID-19 have relied on very few time-points for collection of physiological data. In contrast, our study included the use of continuous physiological monitoring of multiple parameters simultaneously, permitting greater insights into the exact physiological changes during and after proning. For example, by collecting more than 50,000 data points for SpO<sub>2</sub>, we demonstrated that increases in oxygen saturation typically occur within the first 10 minutes of proning. Therefore, this may be a useful clinical guide to help identify those patients who are most likely to benefit from more extended durations of proning. Indeed, at the start of the COVID-19 pandemic, rapidly delivered pragmatic guidance on the use of proning in awake patients was published [10]. The recommendation was to trial 15 minutes of proning and to only continue if the patient was physiologically stable and found the procedure tolerable. The data from our study support this trial duration to assess suitability of the procedure for patients.

We collated detailed subjective symptomatic data on the tolerability of the procedure in different positions, finding that the lateral and prone positions were associated with greater discomfort, even after exclusion of a large proportion of patients due to tolerability related factors. The qualitative data suggested variability in patients' experience of proning, with the majority of people finding it uncomfortable, experiencing discomfort in the arms, neck and shoulders, as well as feeling hot. In certain individuals, breathing did become easier with increased time in the prone position, and they may benefit from a longer duration of proning. The implications for practice to help make patients more comfortable include the use of pillows for the head, neck and limbs, raising the arms forward in bed, ensuring no devices or wires are in the way and to try adjusting the angle of the bed.

Physiologically, prone positioning is thought to reduce dorsal atelectasis and compression on the lungs from the abdominal cavity, and improve ventilation-perfusion mismatch [16]. Therefore, the benefits of awake proning in respiratory failure may extend to aetiologies beyond COVID-19. In this study, we attempted to investigate the effect of awake proning on non-COVID-19 pneumonia patients. However, cases of COVID-19 pneumonia far exceeded non-COVID-19 pneumonia cases at our hospital, and we were unable to recruit sufficient numbers of non-COVID-19 patients. This was consistent with a decline in the prevalence of and mortality due to influenza and non-COVID-19 pneumonia across the UK in recent months, which for example was half the 5-year average in the month of December 2020 [17]. Nonetheless, we recruited a healthy control population with no pre-existing respiratory symptoms or clinical evidence of lung parenchymal disease and subjected them to hypoxic challenge, to mimic the conditions seen with pneumonia. Whilst the relatively small sample size precludes definite conclusions, the lack of improvement in SpO<sub>2</sub> after proning, suggests that parenchymal consolidation is required to see the full benefits of proning.

We focused on comprehensively understanding the physiological and subjective effects of a relatively brief (less than one hour) period of proning and as such do not have data on longer durations of proning. Due to the shorter duration of proning and the lack of randomisation, it was not appropriate to determine the impact of proning on clinical outcomes such as ICU admission; randomised trials to assess this are ongoing (NCT04402879; NCT04383613).

A further limitation of the study was that it was single-centre and although we used ICS guidance criteria for inclusion of appropriate patients, enrolment of centres with younger age groups and from less-well-resourced settings would provide greater generalisability.

In summary, we provide evidence that prone positioning of hospital ward-based non-ventilated awake COVID-19 patients requiring supplemental oxygenation leads to a small but significant increase in SpO<sub>2</sub>, with an improvement seen within 10 minutes of proning. Careful selection of appropriate patients and monitoring of subjective symptoms as well as physiological parameters at the early stages of the procedure are required to optimise the identification of patients who are most likely to benefit.

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## **Author contributions**

*Conception and design of work:* AJ, HL, DW, IG, FE, MF, JF

*Acquisition of data:* AJ, FC, SM, RS, RA, HP, HL, JC, DC, KF, CG, RM, SM, VN, TO, CO, LR, MS, AW, AY, CZ, MF

*Analysis or interpretation of data:* AJ, FC, SM, RS, RA, HP, HL, FE, MF, JF

*Drafting and/or revising the article:* AJ, FC, SM, RS, RA, HP, DW, IG, FE, MF, JF

All authors have reviewed the manuscript and approved it for submission.

## **Competing Interests**

All authors declare no conflict of interest

## **Support statement**

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## References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; 324: 782-793.
2. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2013; 368: 2159–2168.
3. Guérin C. Prone ventilation in acute respiratory distress syndrome. *European Respiratory Review* 2014; 23(132): 249–257.
4. Valter C, Christensen AM, Tollund C, Schønemann NK. Response to the prone position in spontaneously breathing patients with hypoxemic respiratory failure. *Acta Anaesthesiologica Scandinavica* 2003; 47(4): 416–418.
5. Feltracco P, Serra E, Barbieri S, Milevoj M, Michieletto E, Carollo C, Rea F, Zanusi G, Boetto R, Ori C. Noninvasive high-frequency percussive ventilation in the prone position after lung transplantation. *Transplantation Proceedings* 2012; 44(7): 2016-2021.
6. Scaravilli V, Grasselli G, Castagna L, Zanella A, Isgrò S, Lucchini A, Patroniti N, Bellani G, Pesenti A. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. *Journal of Critical Care* 2015; 30(6): 1390–1394.
7. Prud'homme E, Trigui Y, Elharrar X, Gaune M, Loundou A, Lehingue S, Boyer A, Lefebvre L, Dols A-M, Chanez P, Papazian L, Forel JM. Effect of Prone Positioning on the Respiratory Support of Nonintubated Patients With Coronavirus Disease 2019 and Acute Hypoxemic Respiratory Failure. *Chest* 2021; S0012-3692(21)00125-2
8. Solverson K, Weatherald J, Parhar KKS. Tolerability and safety of awake prone positioning COVID-19 patients with severe hypoxemic respiratory failure. *Canadian Journal of Anesthesia* 2021; 68(1): 64–70
9. Johnson SA, Horton DJ, Fuller MJ, Yee J, Aliyev N, Boltax JP, Chambers JH, Lanspa MJ. Patient-Directed Prone Positioning in Awake Patients with COVID-19 Requiring Hospitalization (PAPR). *Annals of the American Thoracic Society* 2021; Epub ahead of print
10. Bamford P, Bentley A, Dean J, Whitmore D, Wilson -Baig N. Intensive Care Society Guidance for Prone Positioning of the Conscious COVID Patient 2020.
11. Galloway JB, Norton S, Barker RD, Brookes A, Carey I, Clarke BD, Jina R, Reid C, Russell MD, Snee R, Sugarman L, Williams S, Yates M, Teo J, Shah AM, Cantle F. A clinical risk score to identify patients with COVID-19 at high risk of critical care

admission or death: An observational cohort study. *Journal of Infection* 2020; 81(2): 282–288.

12. Mestry N, Thirumaran M, Tuggey JM, Macdonald W, Elliott MW. Hypoxic challenge flight assessments in patients with severe chest wall deformity or neuromuscular disease at risk for nocturnal hypoventilation. *Thorax* 2009; 64(6): 532–534.
13. Ambrosino N, Scano G. Dyspnoea and its measurement. *Breathe* 2004; 1: 100–107.
14. Elharrar X, Trigui Y, Dols AM, Touchon F, Martinez S, Prud'Homme E, Papazian L. Use of Prone Positioning in Nonintubated Patients with COVID-19 and Hypoxemic Acute Respiratory Failure. *JAMA* 2020; 323(22): 2336–2338.
15. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJM, Baillie JK, Semple MG. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. *The BMJ* 2020; 369: m1985.
16. Koeckerling D, Barker J, Mudalige NL, Oyefeso O, Pan D, Pareek M, Thompson JP, Andre Ng G. Awake prone positioning in COVID-19. *Thorax* 2020; 75(10): 833–834.
17. England and Wales - Office for National Statistics [Internet]. Monthly mortality analysis; 2020 [cited 2021 May 24]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/monthlymortalityanalysisenglandandwales/december2020>.



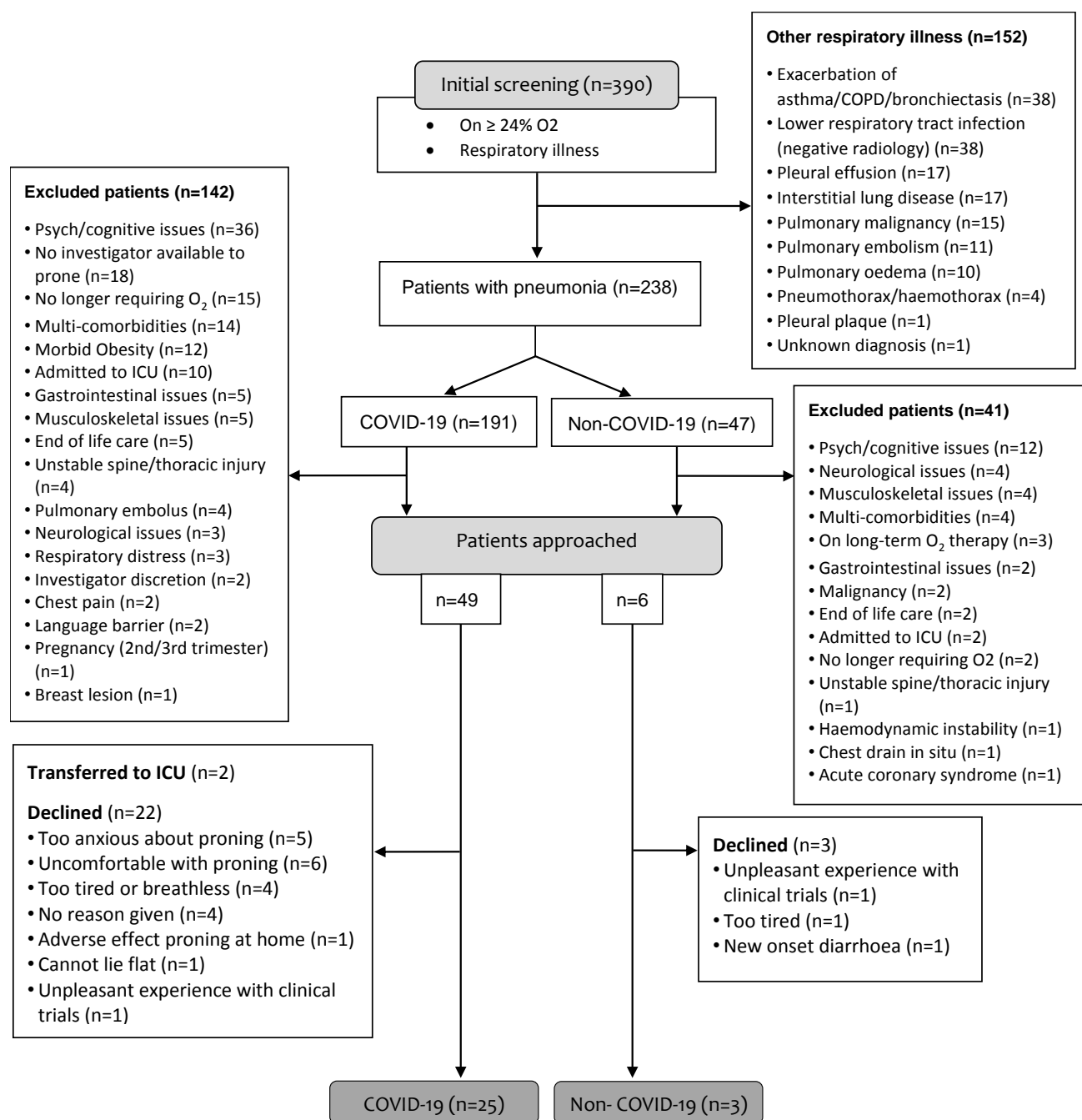
## Figure Legends

**Figure 1** Summary flowchart of study recruitment

**Table 1** Baseline demographic and clinical characteristics of patients with COVID-19 and healthy volunteers

**Figure 2** Change in SpO<sub>2</sub> in different body positions in COVID-19 pneumonia and healthy hypoxic challenge

**Figure 3** Visual analogue scales (VAS) for subjective breathlessness and discomfort in COVID-19 patients and healthy volunteers



**Figure 1** Summary flowchart of study recruitment

**Table 1** Baseline demographic and clinical characteristics of patients with COVID-19 and healthy volunteers

	Patients with COVID-19 (n = 25)	Healthy volunteers (n = 10)
<b>Baseline demographics</b>		
<b>Age (years)</b>	64.0 (53.0 – 75.0)	35.0 (22.5 – 44.0)
<b>Sex</b>		
Female	7 (28.0%)	8 (80.0%)
Male	18 (72.0%)	2 (20.0%)
<b>BMI (kg/m<sup>2</sup>)</b>	28.50 (25.70 – 31.40)	23.86 (22.77 – 25.89)
<b>Smoking history</b>		
Current smoker	1 (4.0%)	0
Ex-smoker	9 (36.0%)	1 (10.0%)
<b>Patients with COVID-19 (n = 25)</b>		
<b>Baseline clinical variables</b>		
<b>FiO<sub>2</sub> at proning</b>	0.32 (0.28 – 0.36)	
<b>ABG</b>	n = 10	
pH	7.43 (7.40 – 7.47)	
PaO <sub>2</sub> (kPa)	8.00 (7.83 – 9.03)	
PaCO <sub>2</sub> (kPa)	4.50 (3.98 – 4.60)	
Lactate (mmol/L)	1.70 (1.50 – 2.10)	
FiO <sub>2</sub>	0.28 (0.22 – 0.33)	
<b>Inflammatory markers</b>	n = 25	
WCC (10 <sup>9</sup> /L)	7.90 (6.00 – 11.10)	
CRP (mg/L)	77.00 (40.00 – 141.00)	
<b>COVID-19 status</b>		
SARS-CoV-2 PCR positive	n = 25	
Symptom onset to admission (days)	9.0 (3.0 – 11.0)	
Admission to prone (days)	2.0 (1.0 – 3.0)	
Radiographic severity score	5 (4 – 7)	
<b>COVID-19 therapeutic regimen</b>		
Dexamethasone only	10 (40.0%)	
Dexamethasone + Baricitinib	2 (8.0%)	
Dexamethasone + Dapagliflozin + Ambrisentan	3 (12.0%)	
Dexamethasone + EDP1815	1 (4.0%)	
Dexamethasone + Ravulizumab	2 (8.0%)	
Dexamethasone + Remdesivir	4 (16.0%)	
Dexamethasone + Tocilizumab	1 (4.0%)	
<b>Comorbidities</b>		
<b>Respiratory</b>		
Asthma	5 (20.0%)	
COPD	2 (8.0%)	
Interstitial lung disease	1 (4.0%)	
Pulmonary Tuberculosis	1 (4.0%)	

**Cardiovascular**

Atrial fibrillation	2 (8.0%)
Dilated cardiomyopathy	1 (4.0%)
Hypercholesterolaemia	1 (4.0%)
Hypertension	8 (32.0%)
Ischaemic heart disease	3 (12.0%)
Peripheral vascular disease	1 (4.0%)

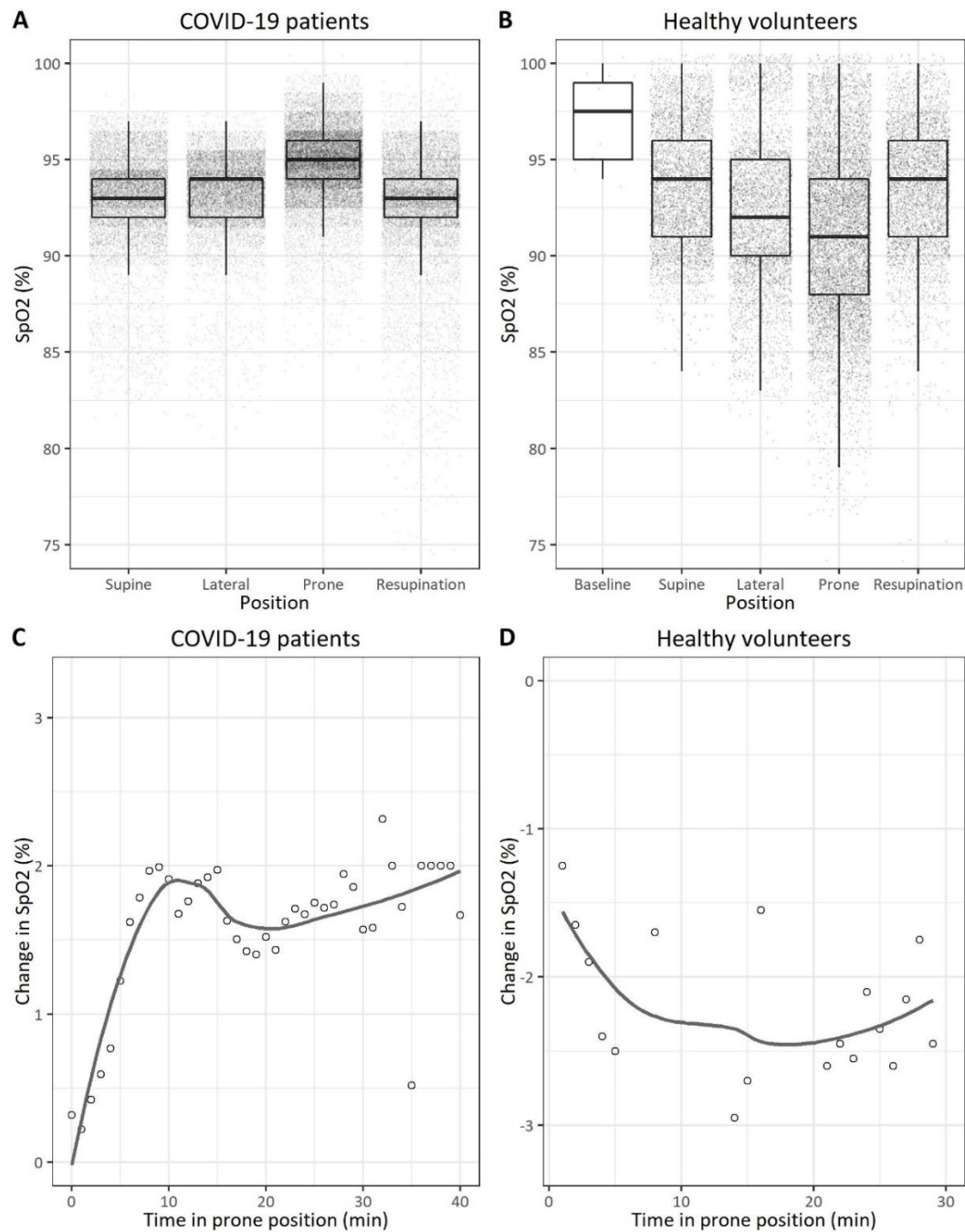
**Other significant**

Connective tissue disease	2 (8.0%)
Chronic kidney disease	2 (8.0%)
Haematological malignancy	1 (4.0%)
Hypothyroidism	2 (8.0%)
Osteoarthritis	2 (8.0%)
Polymyalgia rheumatica	2 (8.0%)
Raynaud's disease	1 (4.0%)
Rheumatoid arthritis	1 (4.0%)
Type II diabetes mellitus	4 (16.0%)

**Outcomes**

Death	1 (4.0%)
Intubation and ventilation	1 (4.0%)
Non-invasive ventilation	1 (4.0%)
Discharge	24 (96%)
Time from proning to discharge (days)	7 (4 - 10.5)

Data are n (%) or median (IQR), BMI = body-mass-index, FiO<sub>2</sub> = fractional concentration of oxygen in inspired air at point of proning. ABG = arterial blood gas. PaO<sub>2</sub> = arterial partial pressure of oxygen. PaCO<sub>2</sub> = arterial partial pressure of carbon dioxide. WCC = white cell count. CRP = C-reactive protein. SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2. Radiographic severity score = semi-quantitative score indicating extent of radiographic changes with a maximum score of 8. COPD = chronic obstructive pulmonary disease. NA = not applicable.



**Figure 2 Change in SpO<sub>2</sub> in different body positions in COVID-19 pneumonia and healthy hypoxic challenge.** Boxplots showing SpO<sub>2</sub> measured in (A) COVID-19 patients (n=24, one dataset unavailable due to technical loss) and (B) healthy volunteers (n=10) in different body positions. Boxes represent 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile. The lower and upper whiskers extend to 1.5 times the interquartile range from the 25<sup>th</sup> and 75<sup>th</sup> percentile, respectively. The overlaid dot plots show each SpO<sub>2</sub> value that was measured (every 2 seconds). Dot plot and LOESS smooth curve showing the absolute change in SpO<sub>2</sub> (percentage points) over time in prone position for (C) COVID-19 patients and (D) healthy volunteers. The SpO<sub>2</sub> at each timepoint in prone position was corrected for every individual's baseline SpO<sub>2</sub> (in supine position) – each dot represents the mean corrected SpO<sub>2</sub> in all individuals for every minute in prone position.



# Physiological effects and subjective tolerability of prone positioning in COVID-19 pneumonia and healthy hypoxic challenge

## Supplementary materials

**Supplementary Table 1** Change in SpO<sub>2</sub> (all values) in different positions compared to baseline supine position in COVID-19 cohort

**Supplementary Table 2** Change in SpO<sub>2</sub> (median value in each position for every individual) in different positions compared to baseline supine position in COVID-19 cohort

**Supplementary Table 3** Change in SpO<sub>2</sub> (all values) in different positions compared to baseline supine position in participants from the COVID-19 cohort who were in the prone position for at least 30 minutes.

**Supplementary Table 4** Change in respiratory rate in different positions compared to baseline supine position in COVID-19 cohort

**Supplementary Table 5** Change in heart rate in different positions compared to baseline supine position in COVID-19 cohort

**Supplementary Table 6** Change in SpO<sub>2</sub> in different positions compared to baseline supine position in hypoxic challenge cohort

**Supplementary Table 7** Effect of selected clinical variables on SpO<sub>2</sub> in prone and supine positions in COVID-19 cohort

**Supplementary Table 8** Patient reports and investigator observations of experience and factors that helped or hindered tolerability of prone position

**Supplementary Figure 1** Dot plot and LOESS smooth curve of SpO<sub>2</sub> change across time at individual level

**Supplementary Figure 2** Dot plot of mean SpO<sub>2</sub> in supine, prone and resupination position at individual level

**Supplementary Figure 3** Effect of body position on respiratory rate

**Supplementary Figure 4** Effect of body position on heart rate

Position	Estimate	Standard Error	p value
Supine	93.12	0.377	-
Lateral	+0.358	0.533	0.505
Prone	+1.62	0.533	0.0030
Resupination	-0.335	0.533	0.531

**Supplementary Table 1 Change in SpO<sub>2</sub> (all values) in different positions compared to baseline supine position in COVID-19 cohort.** This shows the effect of the four positions on the SpO<sub>2</sub> estimate compared to initial supine. All SpO<sub>2</sub> values recorded during the study are included in the model (n = 50719). *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.

Position	Estimate	Standard Error	p value
Supine	93.17	0.355	-
Lateral	+0.500	0.295	0.0943
Prone	+1.88	0.295	1.64x10 <sup>-8</sup>
Resupination	-0.292	0.295	0.3259

**Supplementary Table 2 Change in SpO<sub>2</sub> (median value in each position for every individual) in different positions compared to baseline supine position in COVID-19 cohort.** This shows the effect of the four positions on the SpO<sub>2</sub> estimate compared to initial supine. A single SpO<sub>2</sub> (median) in each position for every individual was taken as the outcome variable, resulting in 96 SpO<sub>2</sub> values included in the model. *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.



Position	Estimate	Standard Error	p value
Supine	93.51	0.381	-
Lateral	+0.045	0.539	0.933
Prone	+1.45	0.539	0.0096
Resupination	-0.358	0.539	0.510

**Supplementary Table 3 Change in SpO<sub>2</sub> (all values) in different positions compared to baseline supine position in participants from the COVID-19 cohort who were in the prone position for at least 30 minutes (n = 16).** This shows the effect of the four positions on the SpO<sub>2</sub> estimate compared to initial supine. All SpO<sub>2</sub> values recorded during the study are included in the model (n = 32061). *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.

Position	Estimate	Standard Error	p value
Supine	20.613	1.069	-
Lateral	+1.222	1.511	0.421
Prone	-1.2341	1.511	0.416
Resupination	+0.5147	1.511	0.734

**Supplementary Table 4 Change in respiratory rate in different positions compared to baseline supine position in COVID-19 cohort.** This shows the effect of the four positions on the respiratory rate estimate compared to initial supine. All respiratory rate values recorded during the study are included in the model (n = 42264). *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.

Position	Estimate	Standard Error	p value
Supine	79.149	2.287	-
Lateral	+0.148	3.234	0.964
Prone	+1.910	3.234	0.556
Resupination	+1.373	3.234	0.672

**Supplementary Table 5 Change in heart rate in different positions compared to baseline supine position in COVID-19 cohort.** This shows the effect of the four positions on the heart rate estimate compared to initial supine. All heart rate values recorded during the study are included in the model (n = 50718). *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.

Position	Estimate	Standard Error	p value
Supine	93.694	0.907	-
Lateral	-1.530	1.282	0.240
Prone	-2.467	1.282	0.0615
Resupination	-0.128	1.283	0.921

**Supplementary Table 6 Change in SpO<sub>2</sub> in different positions compared to baseline supine position in hypoxic challenge cohort.** This shows the effect of the four positions on the SpO<sub>2</sub> estimate compared to initial supine. *P*-values are calculated using two tailed t-tests and Satterthwaite's method to estimate the degrees of freedom.

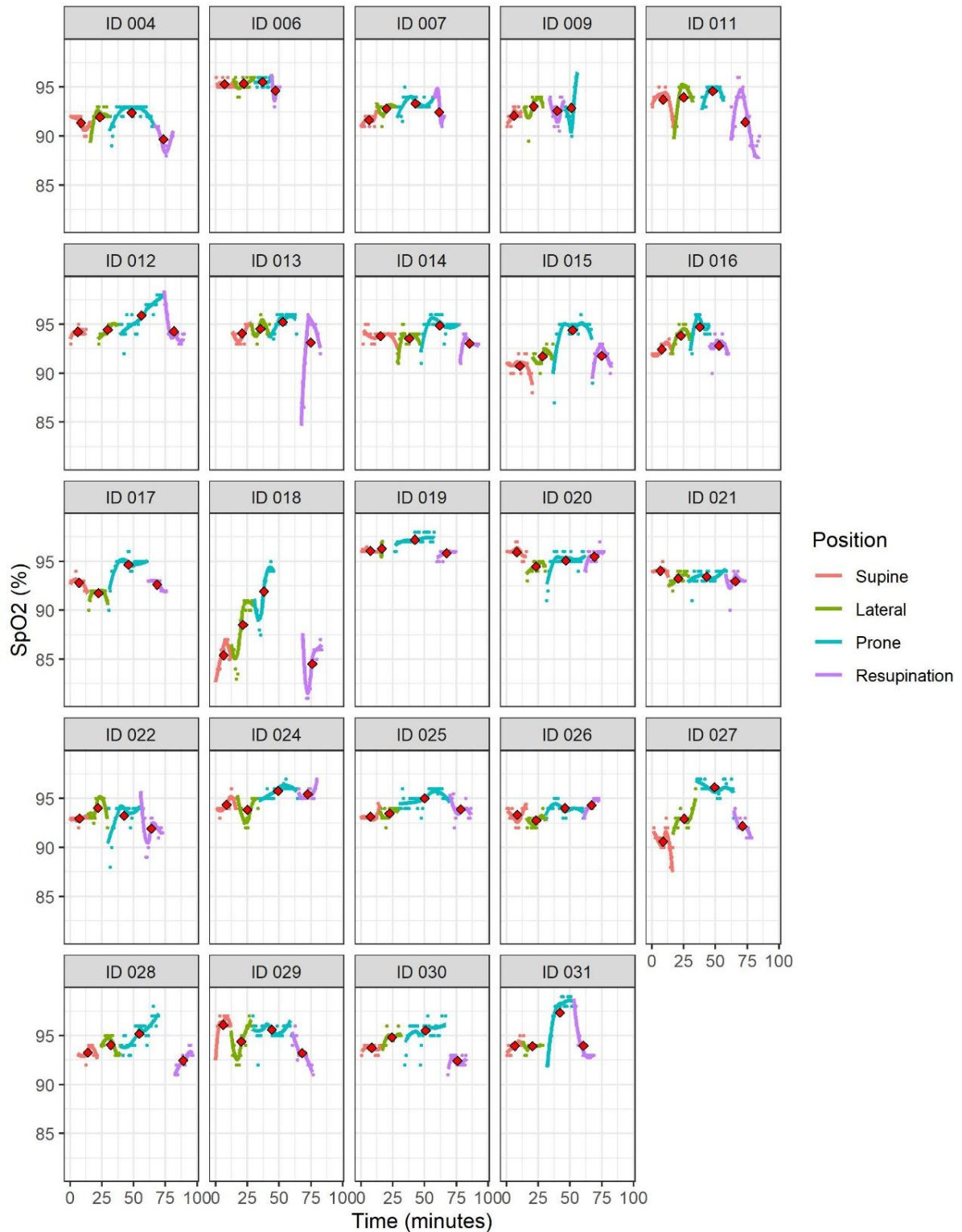
Term	Estimate	Standard error	p value
Age	-0.030	0.009	0.013
BMI	-0.067	0.044	0.156
Radiographic severity score	0.036	0.078	0.653
FiO <sub>2</sub>	4.182	2.714	0.149
Duration in prone position	0.014	0.017	0.436
Baseline SpO <sub>2</sub>	-0.228	0.061	0.003

**Supplementary Table 7 Effect of selected clinical variables on the magnitude of SpO<sub>2</sub> change between prone and supine positions in COVID-19 cohort** using linear modelling. *P*-values are calculated using two tailed t-tests.

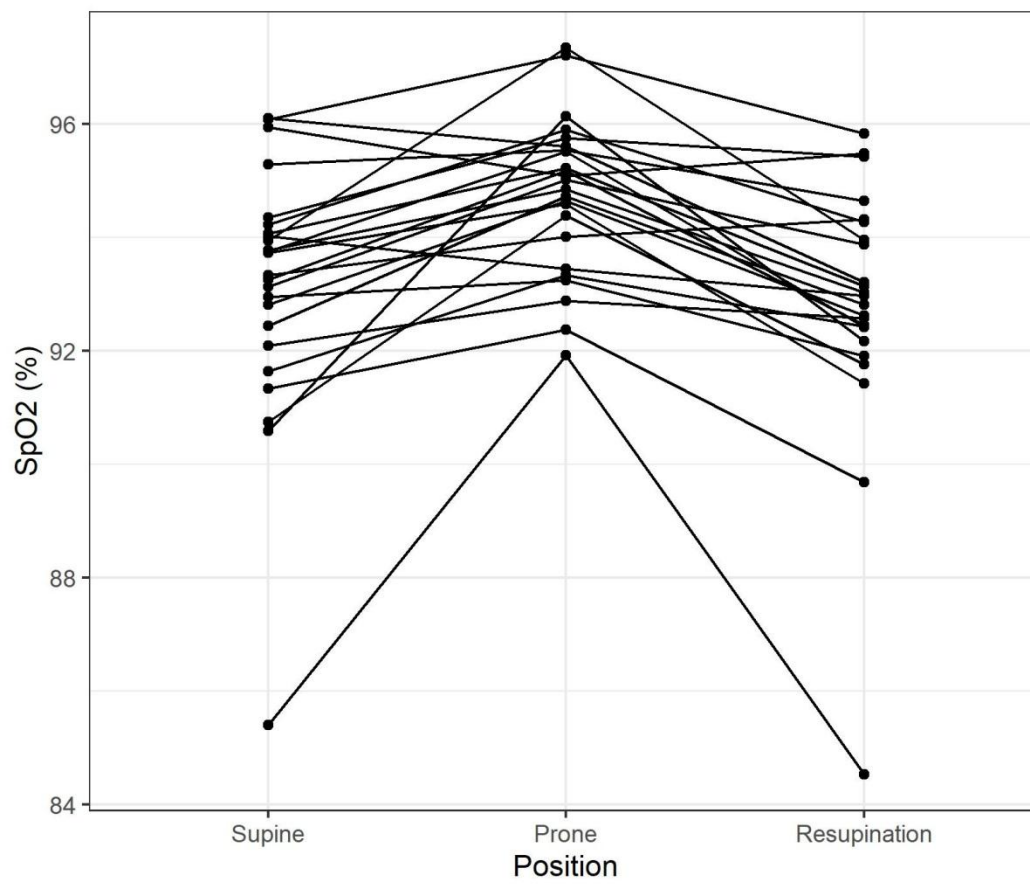
**Supplementary Table 8: Patient reports and investigator observations of experience and factors that helped or hindered tolerability of prone position**

	POSITIVE		NEGATIVE	
	Patient experience report	Investigator observation	Patient experience report	Investigator observation
<b>Comfort</b>	Eight patients found the position comfortable [14, 15, 18, 20, 21, 22, 28, 29]. For two of these it was less comfortable than supine and lateral but became easier over time [18, 20]. For one, it took effort to get into position but became more relaxing with time [14]. For five of these [14, 18, 20, 21, 29] plus one other [12] the position became easier over time. One noted it was how they were at home [28].	Four patients were calm and comfortable [14, 18, 19, 24]. For two it was a natural sleeping position [11,15].	Five said it was uncomfortable, not a position of choice [7, 9, 27, 30, 31] though one said they would do it if they had to [7]. For three of these [9, 27, 30] plus five others [10, 11, 16, 22, 26] it became more uncomfortable over time with patient [27] reporting discomfort in arms and neck and patient [9] burning energy holding themselves up. Patients [10] and [11] had shoulder pain. One became hot and uncomfortable on the face over time [26]. Patient [22] reported slightly more murmur and strain in heart. Patient [16] had to discontinue due to discomfort even though their breathing improved.	Four had difficulty moving into the position, moving was difficult and effortful [6, 19, 31, 28]. One was heavy and unable to support his own weight [31]. Three were unable to maintain the position [7, 9, 29]. Two had neck pain [6, 7]. One patient was less settled than previous position (Lateral) and needed to readjust position frequently at the beginning of proning[10]. One patient with high discomfort and breathlessness scores, couldn't get fully flat (arms raised to level of pillow made it appear upper body a bit raised from bed) [30].
<b>Breathing</b>	Three patients said it felt easier to breathe [12, 17, 19], for one because pressure on lungs was removed [19]. For three their breathing improved over time [12, 20, 29].	Patient [19]'s breathing improved.	Three found it more difficult to breathe [13, 24, 26]. One felt they had to work slightly harder [26] and another that breathing was difficult due to trying to lift own weight when breathing in [24]. For one there was no difference to breathing [10].	
<b>Throat/coughing</b>	One hadn't been coughing in this position [16].		One could not lie fully prone; the position made him cough [4]. For one it was harder to clear throat than when lateral [14]. One person got hotter, had a sore dry throat [13] and another's throat became sore over time [22].	
<b>Devices</b>			Three reported face hot and stuffy, nasal cannula digging in or not comfortable with mask on [10, 11, 16]. For one the devices became more uncomfortable over time [11].	
<b>Other</b>	One noted it was better for their heel [26].		One person needed to go to the toilet [13]. One said that they might struggle to go to the toilet [28]. Three reported that lying on their back was easier [13, 18, 19].	In one patient the position pressed on the bladder [13].

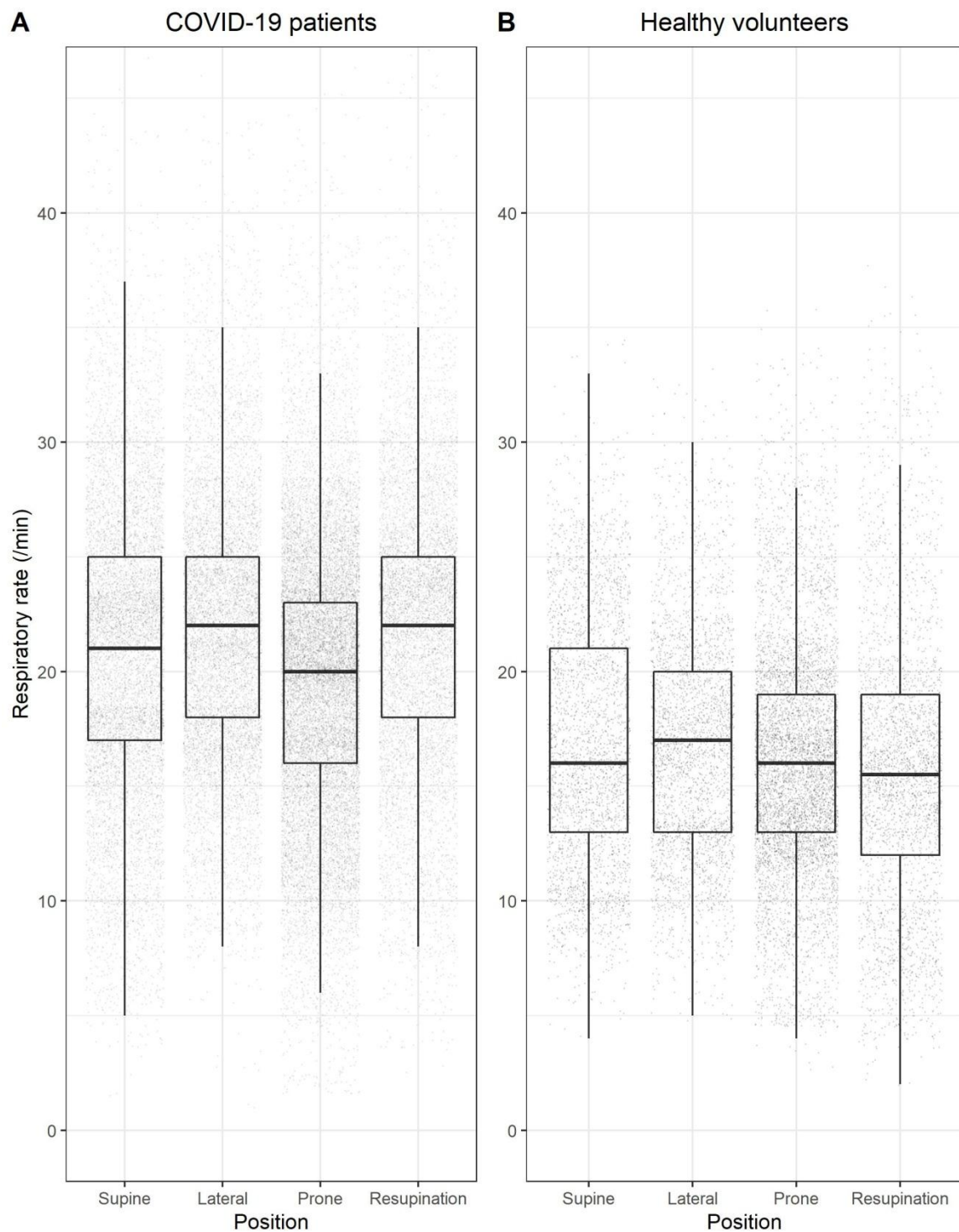
	HELPED TOLERABILITY		HINDERED TOLERABILITY	
	Patient report	Investigator observation	Patient report	Investigator observation
<b>Pillows for support</b>	Pillows in the right places, e.g. to help neck [16, 26]. A doughnut pillow [10] or 'toilet seat' could help [9].	Pillows helped seven patients to be more comfortable: arms on pillow beside head [12], arms raised on pillow [29], arms under pillow [28], flat bed with pillow under face [10] and under head [17], head turned to left and pillow under right side of head [22], under chest and forehead [9].	Lack of support for head and shoulders. One reported neck pulling [7] and lack of design for the head - need shoulders supported so head is looking down and free [9]. Pillows on the face were uncomfortable [31].	
<b>Body position</b>	Raising arms or having them by the side [14, 24]. Raising arms takes pressure off the body weight pressing on chest [14].	One patient became comfortable after lifting arm above head while in a slight prone/left lateral position [24].	What to do with arms [26], hand being stuck under body [31]. 90kg, has whole body weight pushing down, almost as if need to do a press up to get up [28].	
<b>Devices</b>			Devices made it uncomfortable for five patients [4, 10, 11, 21, 26]: CO2 probe [4], nasal cannula [10, 11], tubes [21, 26].	Seven patients had problems with equipment and probes getting in the way [9,11,14,29] or falling out [12,19,24].
<b>Bed</b>	Flat bed [18]. Raising bed 15-20 degrees [24].	Incline of the bed was helpful at 10 degrees for one patient [19]. Two needed a flat bed [10, 20].		
<b>Other</b>	More comfortable with gown half off (as neck of gown was digging into neck) [14].	Patient talked less in this position which may have helped breathlessness [16].	Had just eaten [28]. Difficult to move bedding, had to kick blankets off [28].	In one patient talking raised the respiratory rate [7].
<b>Summary</b>	<p>17 patient-reported problems [4, 7, 9, 10, 11, 13, 14, 16, 18, 19, 20, 24, 26, 27, 28, 30, 31]. Investigators noted 15 patients who had problems [6, 7, 9, 10, 11, 12, 13, 14, 19, 24, 27, 28, 29, 30, 31].</p> <p>15/25 patients reported some discomfort including discomfort in arms, neck and shoulders and becoming hot. For some it became more comfortable over time as they settled into it. 8/25 said they found the position comfortable. Some found it easier to breathe and some found it more difficult, some were more prone to coughing.</p> <p>Implications for practice to help make patients more comfortable:</p> <ul style="list-style-type: none"> <li>• Support with pillows for the head, neck and limbs could be helpful and a 'doughnut' pillow to avoid neck strain could help.</li> <li>• Raising the arms could help.</li> <li>• Devices getting in the way were a source of discomfort.</li> <li>• The angle of the bed was important for some and the preferred angle varied between individuals.</li> </ul>			



**Supplemental Figure 1 Dot plot and LOESS smooth curve of SpO<sub>2</sub> change across time at individual level.** Colours indicate the position (supine, lateral, prone, resupination). The red diamond represents the mean SpO<sub>2</sub> for each position. The thirty SpO<sub>2</sub> readings within each minute are averaged and plotted. Subject 009 became tired in the lateral position and therefore needed to resupinate before attempting the prone position.

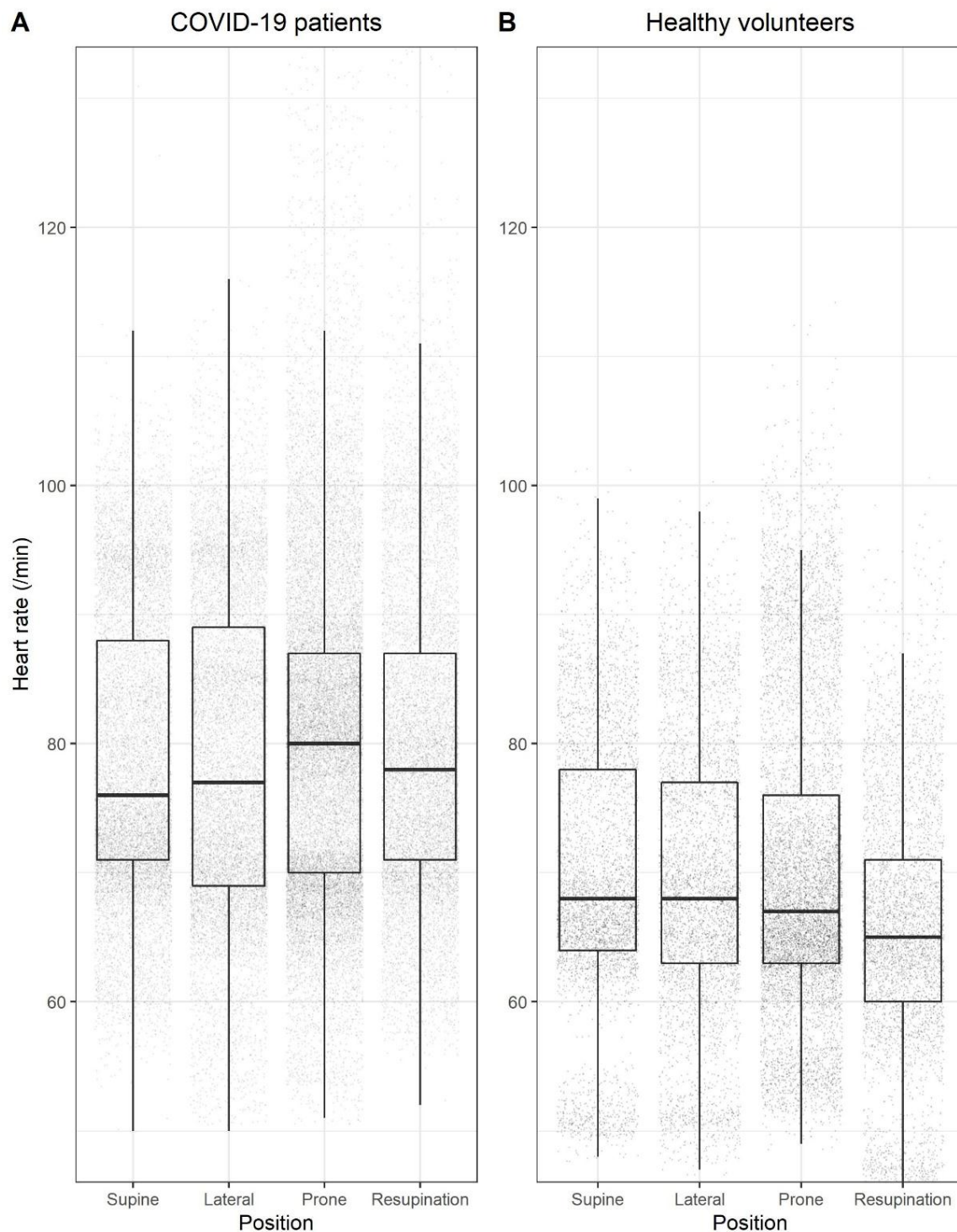


**Supplementary Figure 2 Dot plot of mean SpO<sub>2</sub> in supine, prone and resupination position at individual level.** Lines connect values from the same individual.



**Supplementary Figure 3 Effect of body position on respiratory rate.** Boxplots showing the respiratory rate measured in COVID-19 patients (A) and healthy volunteers (B) in the different positions. Boxes represent 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile. The lower and upper whiskers extend to 1.5 times the interquartile range from the 25<sup>th</sup> and 75<sup>th</sup> percentile respectively. The overlaid dot plots show each respiratory rate that was recorded every 2 seconds.





**Supplementary Figure 4 Effect of body position on heart rate.** Boxplots showing the heart rate measured in COVID-19 patients (A) and healthy volunteers (B) in different positions. Boxes represent 25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile. The lower and upper whiskers extend to 1.5 times the interquartile range from the 25<sup>th</sup> and 75<sup>th</sup> percentile, respectively. The overlaid dot plots show each heart rate that was recorded every 2 seconds.