Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial

Kharat, Aileen; Dupuis Lozeron, Elise; Cantero, Chloe; Marti, Christophe Alberic; Grosgurin, Olivier; Lolachi, Sanaz; Lador, Frédéric; Plojoux, Jérôme Pierre Olivier; Janssens, Jean-Paul; Gasche-Soccal, Paola Marina Alessandra; Adler, Dan Elie

How to cite

KHARAT, Aileen et al. Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. In: ERJ open research, 2021, vol. 7, n° 1, p. 00692–02020. doi: 10.1183/23120541.00692-2020

This publication URL: https://archive-ouverte.unige.ch/unige:163889

Publication DOI: 10.1183/23120541.00692-2020

ORIGINAL ARTICLE
COVID-19

Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial

Aileen Kharat[1,2], Elise Dupuis-Lozeron[3,4], Chloé Cantero[1], Christophe Marti[3,5], Olivier Grosgurin[5], Sanaz Lolachi[5], Frédéric Lador[1,3], Jérôme Plojoux[1,3], Jean-Paul Janssens[1,3], Paola M. Soccal[1,3] and Dan Adler[1,3]

Affiliations: [1]Division of Lung Diseases, Geneva University Hospitals, Geneva, Switzerland. [2]Montreal University Hospital Center, Montreal, QC, Canada. [3]University of Geneva Medical School, Geneva, Switzerland. [4]Division of Clinical Epidemiology, Geneva University Hospitals, Geneva, Switzerland. [5]Division of Internal Medicine, Geneva University Hospitals, Geneva, Switzerland.

Correspondence: Dan Adler, Division of Lung Diseases, Geneva University Hospitals, 4 Rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland. E-mail: dan.adler@hcuge.ch

ABSTRACT

Rationale and objectives: Prone positioning as a complement to oxygen therapy to treat hypoxaemia in coronavirus disease 2019 (COVID-19) pneumonia in spontaneously breathing patients has been widely adopted, despite a lack of evidence for its benefit. We tested the hypothesis that a simple incentive to self-prone for a maximum of 12 h per day would decrease oxygen needs in patients admitted to the ward for COVID-19 pneumonia on low-flow oxygen therapy.

Methods: 27 patients with confirmed COVID-19 pneumonia admitted to Geneva University Hospitals were included in the study. 10 patients were randomised to self-prone positioning and 17 to usual care.

Measurements and main results: Oxygen needs assessed by oxygen flow on nasal cannula at inclusion were similar between groups. 24 h after starting the intervention, the median (interquartile range (IQR)) oxygen flow was 1.0 (0.1–2.9) L·min^{-1} in the prone position group and 2.0 (0.5–3.0) L·min^{-1} in the control group (p=0.507). Median (IQR) oxygen saturation/fraction of inspired oxygen ratio was 390 (300–432) in the prone position group and 336 (294–422) in the control group (p=0.633). One patient from the intervention group who did not self-prone was transferred to the high-dependency unit. Self-prone positioning was easy to implement. The intervention was well tolerated and only mild side-effects were reported.

Conclusions: Self-prone positioning in patients with COVID-19 pneumonia requiring low-flow oxygen therapy resulted in a clinically meaningful reduction of oxygen flow, but without reaching statistical significance.

@ERSpublications
This randomised controlled trial analysed the effect of self-prone positioning in #COVID 19-associated pneumonia. Prone positioning was easy to implement and oxygen needs were lower in the self-prone group, although not reaching statistical significance. https://bit.ly/2MdFeyX

Cite this article as: Kharat A, Dupuis-Lozeron E, Cantero C, *et al*. Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. *ERJ Open Res* 2021; 7: 00692-2020 [https://doi.org/10.1183/23120541.00692-2020].

Received: 28 Sept 2020 | Accepted after revision: 22 Jan 2021

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated pneumonia is associated with severe hypoxaemic respiratory failure requiring treatment in high-dependency or intensive care units (ICUs) in ∼5–10% of hospitalised patients [1, 2]. Given the rapid increase of cases during the recent pandemic, many high-dependency units and ICUs have been overwhelmed in their capacity to provide care [1, 3]. In addition, several pharmacological agents for the treatment of SARS-CoV-2-associated pneumonia remain of uncertain benefit or have been associated with potentially life-threatening side-effects [4]. In patients hospitalised in a medical ward with a diagnosis of coronavirus disease 2019 (COVID-19) pneumonia, any simple intervention to limit the progression of hypoxaemia and avoid transfers of patients to critical care units for mechanical ventilation may be of benefit for the management of hospital resources.

Lung-protective mechanical ventilation and intermittent prone positioning with neuromuscular blockade are standard care and evidence-based strategies in the management of severe acute respiratory distress syndrome (ARDS) [5–7]. Use of low tidal volume ventilation (4–8 $mL \cdot kg^{-1}$ of predicted weight) targeting a plateau pressure <30 cmH_2O, with high positive end-expiratory pressure and prone mechanical ventilation for 12–16 $h \cdot day^{-1}$ has been integrated into the Surviving Sepsis Campaign guidelines for the management of critically-ill adults with COVID-19 [8]. The rationale behind the prone position is to reduce ventilation/perfusion mismatch and thus hypoxaemia. The prone position decreases the pleural pressure gradient between dependent and nondependent lung regions, which is believed to generate a more homogeneous lung ventilation in ARDS patients [9]. As the prone position does not appear to alter blood flow distribution, a subsequent reduction in shunting might be observed [10].

At present, no published trials have documented the effect of the prone position in awake patients with COVID-19 pneumonia. Case series suggest that the prone position in awake patients treated with high-flow nasal oxygen therapy or noninvasive ventilation is feasible, easier to perform than in heavily sedated, more severely ill patients, and is not associated with major side-effects [11–16]. However, it remains unknown whether prolonged periods of prone position in patients admitted for COVID-19 pneumonia on low-flow oxygen therapy are associated with a persistent improvement in peripheral oxygen saturation (S_{pO_2}) and lower needs of oxygen. We designed this single-centre, cluster randomised controlled trial to test the hypothesis that the prone position is associated with lower needs of oxygen in patients admitted to the medical ward for COVID-19 pneumonia.

Methods

Study design and participants

We conducted a single-centre cluster randomised controlled trial in six medical wards in Geneva University Hospitals (Geneva, Switzerland). As the intervention (incentive to self-prone) was not blinded and delivered by physicians and nurses involved in patient monitoring during the COVID-19 pandemic, a cluster randomised controlled trial design was chosen to minimise contamination between groups (*i.e.* to prevent patients in the control group from receiving the intervention if admitted to the same ward as those in the intervention group). Inclusion criteria were patients aged ⩾18 years admitted to a medical ward for treatment of COVID-19 pneumonia with low-flow oxygen therapy (defined as 1–6 $L \cdot min^{-1}$) through nasal cannulas to obtain a S_{pO_2} level of 90–92%. Exclusion criteria were patients initially treated in the ICU or high-dependency unit and recovering from ARDS; those with oxygen needs >6 $L \cdot min^{-1}$ using a nasal cannula or with >40% inspiratory oxygen fraction (F_{iO_2}) using a Venturi mask to obtain a S_{pO_2} level of 90–92%; pregnant women; terminally ill patients; and those unable to self-prone. Patients were screened by a daily review of admissions to each ward.

Randomisation

The randomisation unit was a medical ward in the division of internal medicine of our hospital with a 15-bed capacity. Six clusters were selected and a computer-generated randomisation scheme was used to assign each medical ward randomly in a 1:1 ratio to either the intervention or usual care. After April 14, 2020, most wards dedicated to the care of COVID-19 pneumonia gradually closed because of effective COVID-19 containment measures and a favourable evolution of the epidemic in our region. Four more patients were individually randomised by the computer-generated programme in the wards which remained open. From 25 April to 29 May 2020, no further eligible patients were admitted to the ward for COVID-19 pneumonia and we decided to close enrolment, despite not having reached the number required by our sample size calculation.

Intervention

We compared an add-on to usual care *versus* usual care alone. Usual care consisted of 1) oxygen titration with nasal cannula according to our institutional recommendations to target S_{pO_2} values between 90% and

94%. Nurses carried out at least six routine rounds per 24 h to monitor oxygen needs and adapt oxygen flow to the prescribed S_{pO_2} target; 2) empirical antibiotics for community-acquired pneumonia; 3) an association of hydroxychloroquine and lopinavir/ritonavir as proposed by our institutional guidelines; and 4) a restrictive fluid strategy. Regarding the intervention, an intern (CC) and a resident (AK) from the division of lung diseases promoted self-proning for 12 h per day as an addition to usual care for 24 h. After an initial demonstration with the study investigators, all patients were given an explanatory brochure with photographs of the prone position and it was suggested that they use their mobile phone "timer" function to alternate their body position every 4 h. Nurses regularly visited patients to encourage them to change their bed position during their rounds. Vital signs were recorded after 24 h and patients answered a brief survey on tolerance and estimated time of prone positioning.

Data collection and study outcomes

Oxygen flow ($L \cdot min^{-1}$), estimated F_{iO_2} (%), S_{pO_2}, respiratory rate and heart rate were retrieved directly from the institutional electronic patient health record. Transfers to critical care units or home discharge were recorded. Time spent in the prone position was self-reported in a diary. S_{pO_2} and other vital signs were recorded at 24 h when the patient was supine at rest for 1 h. S_{pO_2} was recorded after its value had stabilised for $\geqslant$1 min. The pre-specified primary outcome was oxygen needs assessed by nasal cannula oxygen flow at 24 h. Secondary outcomes were the S_{pO_2}/F_{iO_2} ratio (defined as S_{pO_2} percentage divided by the F_{iO_2}) at 24 h [17], respiratory and heart rate at 24 h, patient trajectory (transfer to critical care unit) and potential intervention-related adverse effects as defined by neck pain, position-related discomfort and gastro-oesophageal reflux.

Statistical analyses

Continuous variables were summarised as medians and interquartile ranges (IQR) and categorical variables as numbers and percentages. Differences between groups were assessed using the Mann–Whitney–Wilcoxon test for continuous outcomes.

Sample size estimate

We based our sample size estimation on a preliminary unpublished observation in 20 patients admitted to the respiratory wards for COVID-19 pneumonia on low-flow oxygen therapy. In these patients, prone position for 15 min was associated with an immediate improvement in S_{pO_2}, allowing a decrease in oxygen flow by 1 $L \cdot min^{-1}$ with a standard deviation of 1 $L \cdot min^{-1}$. Flow meters used in our institution for oxygen therapy allow oxygen flow to be read with a precision of 0.5 $L \cdot min^{-1}$. Additionally, we considered that a treatment effect of 1 $L \cdot min^{-1}$ would be clinically relevant for triage strategies in an overwhelmed healthcare system. To show a difference of 1 $L \cdot min^{-1}$ of oxygen flow with a standard deviation of 1 $L \cdot min^{-1}$ in an individually randomised trial with a two-sided significance level of 0.05 and a power of 0.8, enrolment of 32 patients would be needed. To take into account the correlation between patients of the same medical ward, the sample size was multiplied by a design effect of 2.4 corresponding to an intraclass correlation coefficient of 0.1 and a number of patients per ward equal to 15. Therefore, enrolment of 76 patients would have been required.

Analyses were performed with R statistical language [18].

Ethics

The institutional ethics review committee approved the trial (CCER 2020–00705). The study was registered on the Swiss National Clinical Trial portal (SNCTP000003718). All participants provided written informed consent before screening.

Results

Seven medical wards were approached to participate in the trial and six wards were randomised in a 1:1 ratio to the intervention or usual care. From April 6 to April 25, 2020, 54 patients were screened and 27 were enrolled in the trial. Causes for noninclusion were 1) refusal to participate (n=19) and 2) impossibility of self-proning due to morbid obesity, hemiplegia or cervical minerva (n=5); and 3) end-of-life support care (n=3). 10 patients were randomised to self-prone and 17 to usual care (figure 1). Baseline characteristics are described in table 1. Mean±SD age of participants was 58±12 years; 10 (37%) out of 27 were female. Among the participants, 12 (44%) out of 27 had hypertension, five (19%) out of 27 had diabetes, and one patient had chronic kidney disease. Time from first symptoms to inclusion was 10.5±5.1 days.

Estimated self-prone time was 295±216 min in the self-prone group and 7±29 min in the control group (due to a single patient who spent an estimated time of 120 min in the position). At baseline, median (IQR) oxygen flow on a nasal cannula was 2.5 (2.0–3.0) $L \cdot min^{-1}$ in the self-prone group and 2.0 (1.0–

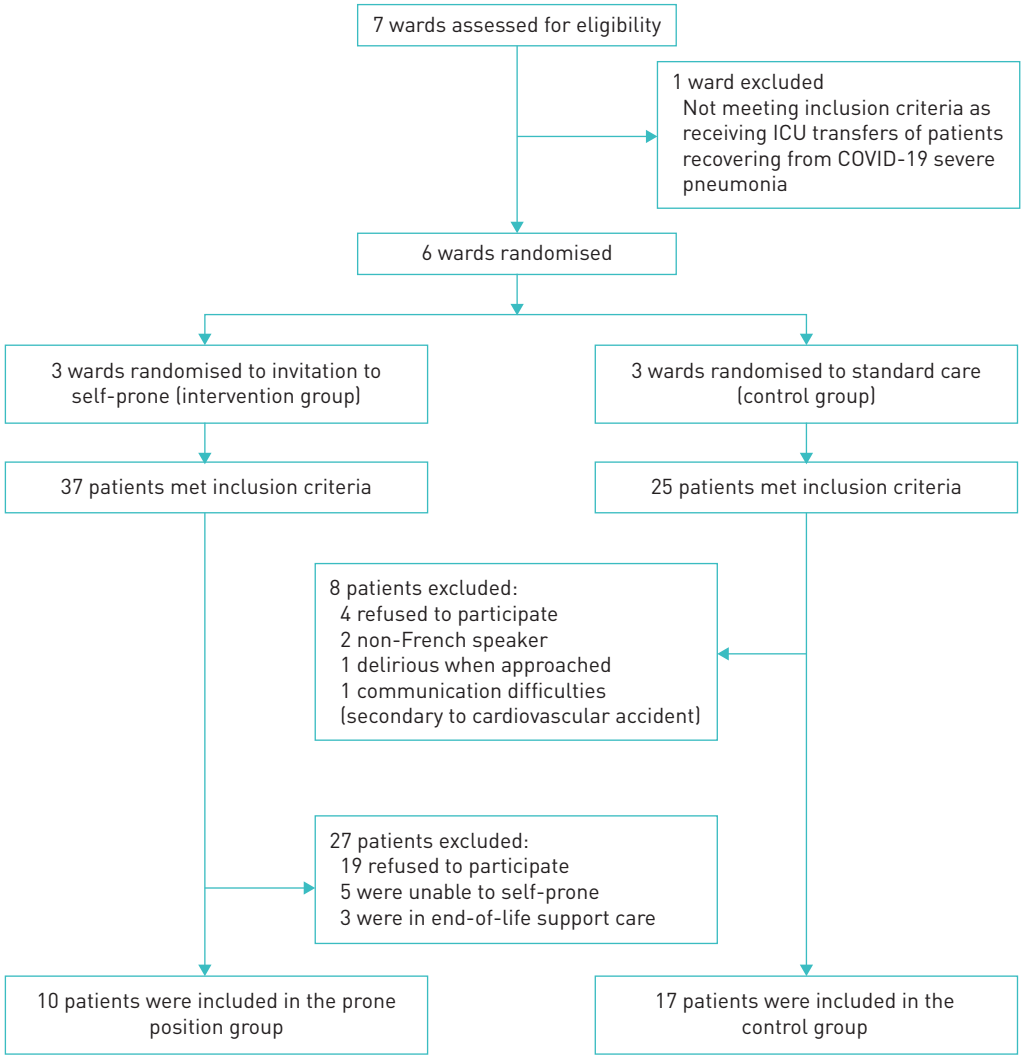

FIGURE 1 Study flowchart. ICU: intensive care unit; COVID-19: coronavirus disease 2019.

TABLE 1 Clinical characteristics of the study population

	Whole population	Self-proning	Usual care
Patients	27	10	17
Male	17 (63)	6 (60)	11 (65)
Age years	58±12	54±14	60±11
Body mass index kg·m^{-2}	28.2±4.7	29.7±5.3	27.3±4.2
Comorbidities			
Hypertension	12 (44)	3 (30)	9 (53)
Diabetes	5 (19)	2 (20)	3 (18)
Chronic kidney disease	1 (4)	0	1 (6)
Self-reported heart disease	0	0	0
COPD	0	0	0
Time onset of symptoms until inclusion days	10.5±5.1	10.6±5.1	10.5±5.3
Treatment received			
Azithromycin	2 (7)	1 (10)	1 (6)
Hydroxychloroquine	19 (70)	6 (60)	13 (77)
Lopinavir/ritonavir	15 (56)	5 (50)	10 (59)

Data are presented as n, n (%) or mean±SD.

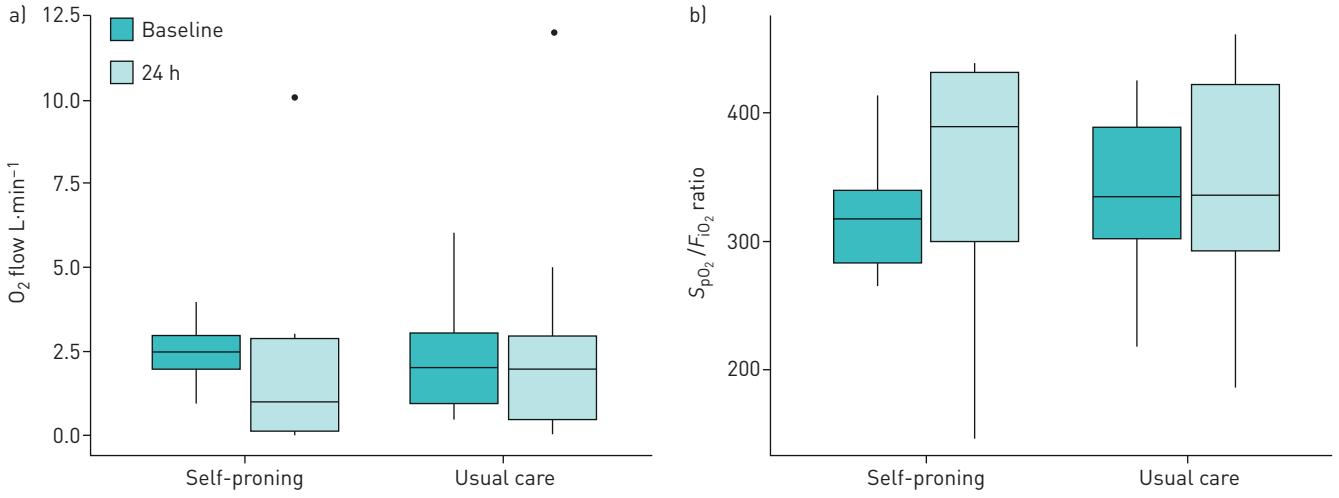

FIGURE 2 a) Oxygen (O_2) flow on nasal cannula in the self-proning group and in the control group; b) peripheral oxygen saturation (S_{pO_2})/inspiratory oxygen fraction (F_{iO_2}) ratio in the self-proning group and in the control group. Data are presented as median, interquartile range and 90th and 10th percentile.

3.0) L·min^{-1} in the control group. At 24 h, median (IQR) oxygen flow was 1 (0.1–2.9) L·min^{-1} in the self-prone position group and 2.0 (0.5–3) L·min^{-1} in the control group (p=0.507). This corresponded to a median (IQR) S_{pO_2}/F_{iO2} ratio of 390 (303–432) in the self-prone group at 24 h compared to 336 (294–423) in the control group (p=0.633) (figure 2). Changes of oxygen flow and S_{pO_2}/F_{iO_2} ratio for individual patients are shown in supplementary figure 1A and B). Main and secondary physiological end-points are presented in table 2. Median respiratory rate decreased with the intervention, whereas no effect was observed for heart rate. One patient randomised to the self-prone position was admitted to the high-dependency unit because of increased oxygen needs *versus* none in the usual care group. This patient was a 45-year-old male with a body mass index of 27.8 kg·m^{-2} without known comorbidities. He had an estimated prone position time of 6 min over 24 h and a reported side-effect of mild discomfort. Five (50%) other patients in the intervention group reported intervention-related adverse events, mainly mild position-related discomfort. No other intervention-related side-effects were reported.

Discussion

In this cluster randomised trial, self-prone positioning in patients admitted for COVID-19 pneumonia requiring low-flow oxygen therapy appeared to be effective in decreasing oxygen needs at 24 h. A clinically meaningful reduction of oxygen flow and an improved S_{pO_2}/F_{iO_2} ratio were observed, although they did not reach statistical significance. With an unprecedented number of ill patients in a small geographical area and the risk of overwhelming local health resources, a reduction of oxygen flow by 1 L·min^{-1} could be of importance to select stable patients for home discharge with an oxygen supply or to prevent unnecessary or premature transfers to intermediate care units.

The intervention consisted of a simple incentive to self-prone for 12 h over a period of 24 h. Invitation to self-prone was easy to implement after an initial demonstration and distribution of an explanatory brochure and resulted in a substantial time spent in this position. The intervention was well tolerated and only mild adverse events were reported. Our results are in line with published case series and expand current knowledge on the prone position in awake patients with hypoxaemic respiratory failure associated with COVID-19 pneumonia [12–16]. Prone positioning is believed to improve hypoxaemia by generating a more homogeneous lung ventilation without altering blood flow distribution [9, 10], as illustrated by data from our trial.

In this unique pandemic situation, health professionals have often been forced to provide immediate medical assistance rather than generating reliable data from randomised trials to inform clinical practice. Awake prone positioning has been widely adopted by physicians around the globe [19] and proposed in conscious COVID-19 patients by the UK Intensive Care Society, but without strong evidence [20]. Such a recommendation may discourage the scientific community to run trials, although most professional bodies emphasise the need for higher quality evidence [21, 22]. Therefore, we specifically focused this randomised trial on a selected population of nonsevere COVID-19 patients with no therapeutic limitations who could all be admitted at any time to the ICU for mechanical ventilation in the event of clinical deterioration. The main explanation for not reaching statistical significance is a small sample size, probably related to the

TABLE 2 Primary and secondary outcomes

	Self-proning	Usual care	Difference between groups (95% CI)
Patients	10	17	
O_2 nasal flow L·min^{-1}			
At baseline	2.5 (2.0–3.0)	2.0 (1·0–3·0)	
At 24 h	1 (0.1–2.9)	2.0 (0.5–3.0)	−1 (−2.75–2)
S_{pO_2}/F_{iO_2} ratio			
At baseline	318 (284–341)	336 (303–388)	
At 24 h	390 (303–432)	336 (294–422)	54 (−91.6–133.0)
Respiratory rate breaths·min^{-1}			
At baseline	22.0 (20.0–25.8)	20.0 (16.0–26.0)	
At 24 h	20.0 (17.3–22.8)	20.0 (18–24.0)	0 (−6.5–3.5)
Heart rate beats·min^{-1}			
At baseline	83 (71–96)	82 (75–89)	
At 24 h	83 (72–89)	80 (70–86)	3 (−13–15)

Data are presented as n or median (interquartile range), unless otherwise stated. The difference between medians of the two randomised groups have been computed with their 95% confidence interval obtained by bootstrap using 1000 replications. O_2: oxygen; S_{pO_2}: peripheral oxygen saturation; F_{iO_2}: inspiratory oxygen fraction.

early interruption of study enrolment. Indeed, a very sharp decrease in COVID-19-related admissions was observed from mid-April 2020 as a result of effective containment measures in Switzerland. The results of this trial are promising, but adequately powered trials are still needed. Our data are in agreement with previous physiological studies and observational reports on prone positioning [11–16, 23].

Our study has some additional limitations. The intervention and assessments of end-points were limited to a 24-h time frame. Therefore, it is not possible to assess medium-term effects on outcomes and follow-up of self-prone positioning. Moreover, according to recent published reports on prone positioning, the effect on oxygenation is transient [14, 15]. As assessment at 24 h was performed in the supine position, the effect of the intervention on oxygen needs could have been minimised, although our data suggest that alternating supine and prone position over 24 h may be associated with lower oxygen needs at 24 h, even in the supine position. Finally, follow-up time in the medical ward was very short and the oxygen needs of patients with acute respiratory failure related to COVID-19 pneumonia should be closely monitored for >24 h, as rapid clinical deterioration is well described in a time window of 7–10 days after the onset of first symptoms [2, 24].

In summary, self-prone positioning in patients with COVID-19 pneumonia requiring low-flow oxygen therapy showed a reduction of oxygen needs in our study, which did not reach statistical significance, probably due to a small sample size and insufficient statistical power. However, the observed reduction of oxygen needs at 24 h is clinically promising without any reported major side-effects. Our findings need to be corroborated by larger randomised trials to confirm the potential beneficial effects of self-prone positioning on oxygen needs. This information would be of particular interest for healthcare systems in low-income countries with a limited access to ICUs.

Acknowledgements: The authors thank all the healthcare workers at the Geneva University Hospitals for their dedicated care of our COVID-19 patients.

This study is registered at https://www.kofam.ch/en/snctp-portal/ with identifier number SNCTP000003718. The individual participant data that underlie the results reported can be shared. The study protocol and statistical analysis plan are also available. Data can be shared with researchers/investigators providing methodologically sound proposals.

Author contributions: A. Kharat and D. Adler designed the study. A. Kharat, C. Cantero, C. Marti, O. Grosgurin, S. Lolachi, F. Lador, J. Plojoux, J-P. Janssens and P.M. Soccal contributed to enrolment and data acquisition. E. Dupuis-Lozeron performed statistical analyses. A. Kharat and D. Adler drafted the first version of the manuscript. All authors assisted with data interpretation, manuscript preparation, and final manuscript review.

Conflict of interest: A. Kharat has nothing to disclose. E. Dupuis-Lozeron has nothing to disclose. C. Cantero has nothing to disclose. C. Marti has nothing to disclose. O. Grosgurin has nothing to disclose. S. Lolachi has nothing to disclose. F. Lador has nothing to disclose. J. Plojoux has nothing to disclose. J-P. Janssens has nothing to disclose. P.M. Soccal has nothing to disclose. D. Adler has nothing to disclose.

References

1 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323: 1239–1242.
2 Yang X, Yu Y, Xu J, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475–481.
3 Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020; 323: 1545–1546.
4 Sanders JM, Monogue ML, Jodlowski TZ, *et al.* Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020; 323: 1824–1836.
5 Fan E, Del Sorbo L, Goligher EC, *et al.* An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 195: 1253–1263.
6 Guérin C, Reignier J, Richard J-C, *et al.* Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368: 2159–2168.
7 Papazian L, Forel J-M, Gacouin A, *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363: 1107–1116.
8 Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. *JAMA* 2020; 323: 1839–1841.
9 Scholten EL, Beitler JR, Prisk GK, *et al.* Treatment of ARDS with prone positioning. *Chest* 2017; 151: 215–224.
10 Glenny RW, Lamm WJ, Albert RK, *et al.* Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol* 1991; 71: 620–629.
11 Pérez-Nieto OR, Guerrero-Gutiérrez MA, Deloya-Tomas E, *et al.* Prone positioning combined with high-flow nasal cannula in severe noninfectious ARDS. *Critical Care* 2020; 24: 114.
12 Ding L, Wang L, Ma W, *et al.* Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care* 2020; 24: 28.
13 Scaravilli V, Grasselli G, Castagna L, *et al.* Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: a retrospective study. *J Crit Care* 2015; 30: 1390–1394.
14 Elharrar X, Trigui Y, Dols A-M, *et al.* Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020; 323: 2336–2338.
15 Sartini C, Tresoldi M, Scarpellini P, *et al.* Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA* 2020; 323: 2338–2340.
16 Coppo A, Bellani G, Winterton D, *et al.* Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. *Lancet Respir Med* 2020; 8: 765–774.
17 Rice TW, Wheeler AP, Bernard GR, *et al.* Comparison of the S_{pO_2}/F_{IO_2} ratio and the P_{aO2}/F_{IO_2} ratio in patients with acute lung injury or ARDS. *Chest* 2007; 132: 410–417.
18 R Core Team. R: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2020. www.R-project.org/
19 Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med* 2020; 27: 375–378.
20 Bamford P, Bentley A, Dean J, *et al.* 2020. ICS Guidance for Prone Positioning of the Conscious COVID Patient 2020. https://icmanaesthesiacovid-19.org/news/ics-guidance-for-prone-positioning-of-the-conscious-covid-patient-2020.
21 Telias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? *JAMA* 2020; 323: 2265–2267.
22 Koeckerling D, Barker J, Mudalige NL, *et al.* Awake prone positioning in COVID-19. *Thorax* 2020; 75: 833–834.
23 Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J* 2002; 20: 1017–1028.
24 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.