




Tolerability and safety of awake prone positioning COVID-19 patients with severe hypoxemic respiratory failure

Tolérabilité et sécurité de la position ventrale éveillée chez des patients atteints de la COVID-19 et d'insuffisance respiratoire hypoxémique grave

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Received: 1 June 2020 / Revised: 14 July 2020 / Accepted: 29 July 2020 / Published online: 14 August 2020
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Abstract

Purpose Prone positioning of non-intubated patients with coronavirus disease (COVID-19) and hypoxemic respiratory failure may prevent intubation and improve outcomes. Nevertheless, there are limited data on its feasibility, safety, and physiologic effects. The objective of our study was to assess the tolerability and safety of awake prone positioning in COVID-19 patients with hypoxemic respiratory failure.

Methods This historical cohort study was performed across four hospitals in Calgary, Canada. Included patients had suspected COVID-19 and hypoxic respiratory failure requiring intensive care unit (ICU) consultation, and underwent awake prone positioning. The duration, frequency, tolerability, and adverse events from prone positioning were recorded. Respiratory parameters were assessed before, during, and after prone positioning. The primary outcome was the tolerability and safety of prone positioning.

Results Seventeen patients ($n = 12$ ICU, $n = 5$ hospital ward) were included between April and May 2020. The median (range) number of prone positioning days was 1 (1–7) and the median number of sessions was 2 (1–6) per

day. The duration of prone positioning was 75 (30–480) min, and the peripheral oxygen saturation was 91% (84–95) supine and 98% (92–100) prone. Limitations to prone position duration were pain/general discomfort (47%) and delirium (6%); 47% of patients had no limitations. Seven patients (41%) required intubation and two patients (12%) died.

Conclusions In a small sample, prone positioning non-intubated COVID-19 patients with severe hypoxemia was safe; however, many patients did not tolerate prolonged durations. Although patients had improved oxygenation and respiratory rate in the prone position, many still required intubation. Future studies are required to determine methods to improve the tolerability of awake prone positioning and whether there is an impact on clinical outcomes.

Résumé

Objectif Le positionnement ventral des patients non intubés atteints de coronavirus (COVID-19) et d'insuffisance respiratoire hypoxémique pourrait éviter de devoir les intuber et améliorer leurs pronostics. Nous ne disposons toutefois que de peu de données concernant la faisabilité, la sécurité et les effets physiologiques d'un tel positionnement. L'objectif de notre étude était d'évaluer la tolérabilité et la sécurité du positionnement ventral éveillée chez des patients atteints de la COVID-19 et d'insuffisance respiratoire hypoxémique.

Méthode Cette étude de cohorte historique a été réalisée dans 4 hôpitaux de Calgary, au Canada. Les patients inclus avaient une suspicion de COVID-19, souffraient d'insuffisance respiratoire hypoxémique nécessitant une consultation à l'unité de soins intensifs (USI), et ont été positionnés sur le ventre éveillés. La durée, la fréquence, la

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tolérabilité et les événements indésirables liés au positionnement ventral ont été enregistrés. Les paramètres respiratoires étaient évalués avant, pendant et après le positionnement ventral. Les critères d'évaluation principaux étaient la tolérabilité et la sécurité du positionnement ventral.

Résultats Dix-sept patients ($n = 12$ USI, $n = 5$ à l'étage) ont été inclus entre avril et mai 2020. Le nombre médian de jours de positionnement ventral était de 1 (fourchette 1-7) et de 2 sessions (fourchette 1-6) par jour. La durée médiane du positionnement ventral était de 75 min (fourchette, 30-480). La saturation en oxygène périphérique médiane en position dorsale était de 91 % (fourchette, 84-95) et de 98 % (fourchette 92-100) en position ventrale. Les obstacles à une durée prolongée de la position ventrale étaient la douleur / l'inconfort général (47%) et le delirium (6%). Au total, 47 % des patients n'ont fait état d'aucun obstacle. Sept patients (41 %) ont nécessité une intubation, et deux patients (12 %) sont décédés.

Conclusion Dans un petit échantillon, le positionnement ventral de patients non intubés atteints de COVID-19 et d'hypoxémie grave était sécuritaire, mais plusieurs patients n'ont pas toléré cette position pour une durée prolongée. Bien que l'oxygénation et la fréquence respiratoire des patients étaient améliorées en position ventrale, bon nombre ont tout de même nécessité une intubation. Des études futures sont nécessaires afin de déterminer quelles méthodes amélioreraient la tolérabilité du positionnement ventral éveillé et si cette position a un impact sur les devenir cliniques.

Keywords COVID-19 · prone positioning · hypoxemic respiratory failure · case series · intubation

Coronavirus disease (COVID-19) is associated with acute hypoxemic respiratory failure. A proportion of these patients will progress to acute respiratory distress syndrome (ARDS) and require invasive mechanical ventilation.¹ Prone positioning improves oxygenation and mortality in moderate-to-severe ARDS patients receiving mechanical ventilation.² Recent studies suggest prone positioning non-intubated COVID-19 patients may improve oxygenation, reduce work of breathing, and possibly prevent intubation.³⁻⁵ Several questions remain about the feasibility of awake prone positioning, including its tolerability and safety in patients with severe hypoxemia.⁶⁻⁸ We describe the use of prone positioning in a cohort of non-intubated COVID-19 patients with severe hypoxemia and report patients' tolerance of the prone position (duration and frequency), reasons for

discontinuation, adverse events, and physiologic as well as clinical outcomes.

Methods

This study was conducted at four hospitals in Calgary, Canada (1 April to 25 May 2020). The Conjoint Health Research Ethics Board institutional research ethics board approved this study and waived the need for consent. We reviewed consecutive non-intubated patients with: 1) COVID-19 (suspected or confirmed) who had had an intensive care unit (ICU) consult or admission and 2) severe hypoxemia (defined as a new requirement for ≥ 5 L·min⁻¹ oxygen to maintain a peripheral oxygen saturation $\geq 90\%$, which corresponds to a peripheral oxygen saturation: fraction of inspired oxygen (SpO₂:F_IO₂) ratio of ≤ 250), and 3) were prone positioned at least once. Prone positioning frequency and duration were applied at the ICU clinician's discretion without a standardized protocol; however, in general, patients were encouraged to stay in the prone position as long as tolerated. As a standard policy, the use of high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) were discouraged for COVID-19 patients because of infection control concerns. Patients on the ward had vital signs monitored with oxygen saturation probes and non-invasive blood pressure cuffs at intervals determined by the most responsible physician. Patients admitted to the ICU were placed on continuous cardiac monitoring with continuous oxygen saturation monitoring at a minimum. Invasive arterial lines for continuous blood pressure monitoring were placed at the discretion of the ICU physician.

Data were abstracted retrospectively from electronic medical records (*Sunrise Clinical Manager* and *eCritical Metavision*). Respiratory variables collected included peripheral oxygen saturation (SpO₂), nasal cannula oxygen flow rate, and respiratory rate. The SpO₂:F_IO₂ ratio of inspired oxygen ratio was calculated as previously described.^{9,10} Respiratory variables were collected in the supine position 10–20 min after prone positioning and one to two hours after resupination. The duration, total number, sleep position, patient reason for supinating, and adverse events (intravenous catheter dislodgement, vomiting, aspiration, pressure ulcers, oxygen cannula removal, or hemodynamic decompensation) of all prone positioning sessions were reviewed. The primary clinical outcome was the duration of tolerability and safety of awake prone positioning. Other clinical outcomes included ICU and hospital mortality. All outcomes were followed up until hospital discharge or censored on 25 May 2020. Data are represented as medians (range) and frequencies. This study was reported following the STROBE guidelines.¹¹

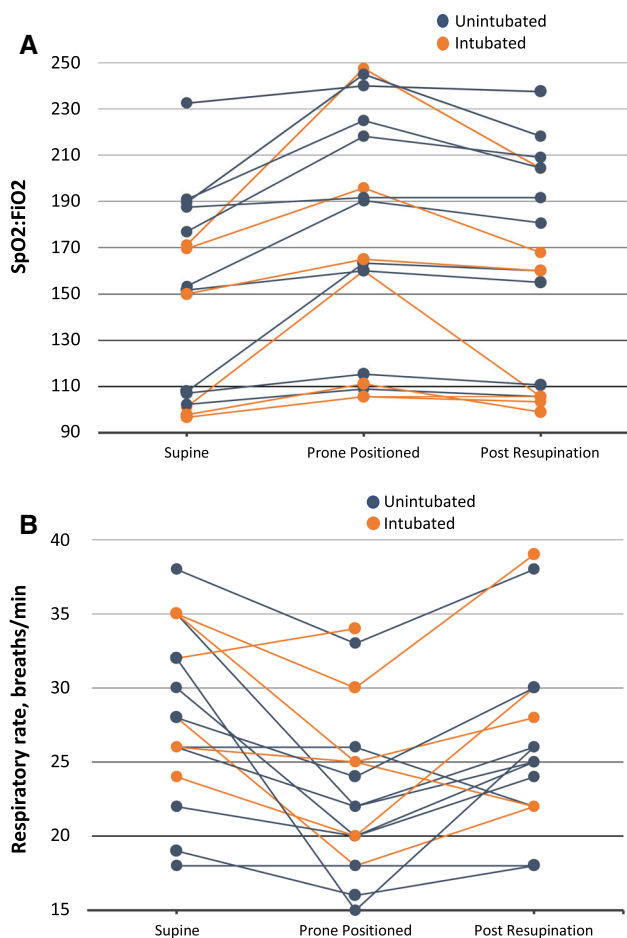


Figure 1 Individual patient data of peripheral oxygen saturation: fraction of inspired oxygen ($\text{SpO}_2:\text{FiO}_2$) ratio and respiratory rate during supine, prone, resupinated positions. The three assessments occurred: 1) immediately before prone positioning (supine), 2) 10–20 min after prone positioning (prone positioned), and 3) one to two hours after resupinating (post respiration). A) $\text{SpO}_2:\text{FiO}_2$ is the oxygen saturation to the fraction of inspired oxygen ratio plotted over assessment periods. B) The respiratory rate ($n = 16$) plotted over assessment periods. Non-intubated patients were treated with nasal cannula only, with the exception of one patient who was treated with high-flow nasal cannula, and were not intubated during hospital admission. Intubated patients were endotracheal intubated at a time point after the trial of prone positioning.

Results

Seventeen non-intubated COVID-19 patients (presumed positive, $n = 4$) underwent prone positioning (medical ward $n = 5$, ICU $n = 12$) during the study period. All 17 patients accepted full resuscitation (including cardiopulmonary resuscitation, intubation, and invasive mechanical ventilation) based on their predetermined goals of care. The five patients not admitted to ICU were felt by the ICU consultant to be safely managed on the hospital ward. Prone positioning was initiated a median of 6 (3–15) days after COVID-19 symptom onset and 2 (0–6) days after

hospitalization. The median number of daily prone positioning sessions was 2 (1–6) with a duration of 75 (30–480) min for the first session. Six patients (35%) were in the prone position for ≤ 60 min; two patients (12%) had single prone sessions > 12 hr. Most patients were prone positioned for 1 (1–7) day with one patient prone positioned for seven consecutive days (Table 1). Four patients (24%) slept in the prone position at least once. Patients were stratified based on their ability to prone position < 75 min or ≥ 75 min during their first prone positioning session. Patients in the < 75 min group were prone positioned for 45 (30–70) min. Patients in the ≥ 75 min group were prone positioned for 120 (75–480) min. Patient characteristics and outcomes for this stratified analysis are presented in Table 1.

Limitations to patients maintaining the prone positioning were related to back or shoulder pain (12%), general discomfort (35%), and delirium (6%). Eight patients (47%) had no tolerability problems. Nine patients (53%) were able to continue an oral diet between prone positioning and the rest were kept *nil per os*. No patients required an enteral feeding tube. No adverse events, including worsening dyspnea, intravenous catheter dislodgement, aspiration, pressure ulcers, oxygen cannula removal, or hemodynamic decompensation were observed. Of the five patients who initiated prone positioning on the ward, three (60%) required transfer to the ICU, but none needed a medical emergency team.

Oxygen was delivered via nasal cannula in 16 patients and HFNC in one. When prone positioned, all patients showed improvements in oxygenation [SpO_2 supine 91% (84–95) vs prone 98% (92–100)], and respiratory rate [supine 28 (18–38) breaths·min⁻¹ vs prone 22 (15–33) breaths·min⁻¹] (Figure 1). The median difference between prone and supine positioning in $\text{SpO}_2:\text{FiO}_2$ was 15 (4–76). After resupination, the median (range) $\text{SpO}_2:\text{FiO}_2$ ratio was mildly improved compared with baseline (pre-prone positioning) [7 (-2 to 52)] (Figure 1). There was no observed difference in the severity of hypoxemia or response to prone position for patients who were intubated compared with those who were not (Figure 1).

Seven patients (41%) required intubation and invasive mechanical ventilation. The median (range) duration of symptoms to prone positioning was similar for those patients intubated for those patients not intubated [6 (3–8) days vs 6 (3–15) days, respectively]. The duration from the first prone position session to intubation was 2 (1–7) days. No patients were intubated within 30 min of resupination, but five patients (29%) were intubated within one hour of resupination. All intubations were semi-controlled, with no emergent intubations required. Of the five patients who were prone positioned on the ward, three were admitted to ICU (60%). Two of these five ward patients (40%) were

Table 1 Patient characteristics, prone positioning details, and outcomes

Characteristics	All patients (n = 17)	Prone duration < 75min (n = 8)	Prone duration ≥ 75 min (n = 9)
Baseline characteristics			
Age, yr	53 (34–81)	54 (34–81)	53 (43–60)
Sex, n (%)			
Women	5 (29)	0 (0)	5 (56)
Men	12 (71)	8 (100)	4 (44)
Body mass index > 35, n (%)	3 (18)	2 (25)	1 (11)
HTN, n (%)	9 (53)	5	4
Coronary artery disease	3 (18)	2	1
Obstructive sleep apnea	3 (18)	2	1
Chest x-ray*, n (%)			
Bilateral lower lobe airspace disease	4 (25)	2 (25)	2 (25)
Bilateral lower and upper lobe airspace disease	12 (75)	6 (75)	6 (75)
Respiratory variables			
Supine position			
SpO ₂	91 (84–95)	91 (87–95)	91 (84–95)
Oxygen flow rate†, L·min ⁻¹	10 (5–15)	9 (7–15)**	10 (5–15)
Respiratory rate‡, breaths·min ⁻¹	28 (18–38)	30 (24–38)**	26 (18–35)
SpO ₂ :F _i O ₂ ratio	152 (97–233)	138 (97–198)	152 (97–233)
Prone position			
SpO ₂	98 (92–100)	98 (94–100)	96 (92–99)
Oxygen flow rate†, L·min ⁻¹	9 (5–15)	7 (5–15)**	10 (5–15)
Respiratory rate‡, breaths·min ⁻¹	22 (15–33)	20 (15–33)**	24 (16–32)
SpO ₂ :F _i O ₂ ratio,	165 (106–248)	155 (106–248)	165 (106–240)
Tolerability and safety			
Duration of first prone positioning session, min	75 (30–480)	45 (30–70)	120 (75–480)
Prone position ≤ 60 min, n (%)	6 (35)	6 (75)	0 (0)
Number of daily of prone positioning sessions	2 (1–6)	1 (1–2)	2 (1–7)
NPO due to prone positioning sessions, n (%)	8 (47)	4 (50)	4 (44)
Prone positioning-related adverse events§, n (%)	0 (0)	0 (0)	0 (0)
Hospital location of first prone positioning			
Medical ward, n (%)	5 (29)	2 (25)	3 (33)
Intensive care unit, n (%)	12 (71)	6 (75)	6 (67)
Reason for discontinuation of prone positioning session			
Musculoskeletal pain, n (%)	2 (12)	1 (13)	1 (11)
Mental status, n (%)	1 (6)	1 (13)	0
General discomfort, n (%)	6 (35)	5 (62)	1 (11)
No tolerance issues, n (%)	8 (47)	1 (13)	7 (78)
Patient outcomes			
Invasive mechanical ventilation, n (%)	7 (41)	4 (50)	4 (44)
Endotracheal intubation complications			
Oxygen desaturation, SpO ₂ < 70%, n (%)	1 (14)	0 (0)	1 (11)
Hypotension during, SBP < 90 mmHg, n (%)	0 (0)	0 (0)	0 (0)
In-hospital death, n (%)	2 (12)	2 (20)	0 (0)
Hospital length of stay	13 (4–28)	21 (6–28)	12 (4–16)

All values are reported as median (range) unless specified otherwise. Abbreviations: FiO₂, fraction of inspired oxygen; NPO = *nil per os*; SBP = systolic blood pressure; SpO₂ = oxygen saturation. * n = 16, one patient did not have a chest x-ray completed; † n = 16, excludes patient on high-flow nasal cannula; ‡ n = 16; § Adverse event: intravenous catheter dislodgement, vomiting, aspiration, pressure ulcers, oxygen cannula removal or hemodynamic decompensation; || n = 13, four patients remain in hospital; ** n = 7.

Table 2 Comparison of respiratory parameters by location of first prone position session ($n = 17$)

Characteristics	ICU ($n = 12$)	Ward ($n = 5$)
Age, yr	54 (34–76)	53 (49–81)
Sex, n (%)		
Women	3 (25)	2 (40)
Men	9 (75)	3 (60)
Duration of first prone positioning, min	75 (30–480)	75 (45–240)
Supine position		
SpO ₂	91 (87–95)	90 (84–95)
Oxygen flow rate, L·min ⁻¹	13* (7–15)	7 (5–9)
Respiratory rate, breaths·min ⁻¹	30 [†] (19–38)	24 (18–35)
SpO ₂ :F _I O ₂ ratio	108 (97–190)	188 (170–233)
Prone position		
SpO ₂ , %	98 (95–100)	96 (92–99)
Oxygen flow rate, L·min ⁻¹	10* (5–15)	6 (5–7)
Respiratory rate, breaths·min ⁻¹	24 [†] (15–33)	20 (18–25)
SpO ₂ :F _I O ₂ ratio	160 (106–245)	225 (192–248)
Intubation rate, n (%)	5 (42)	2 (40)

All values are reported as median (range) unless specified otherwise. F_IO₂ = fraction of inspired oxygen; ICU = intensive care unit; SpO₂ = oxygen saturation.

* $n = 11$, excludes patient on high-flow nasal cannula; [†] $n = 11$.

intubated in the ICU (Table 2). Baseline and prone positioning respiratory rates and oxygen requirements were higher in patients prone positioned in the ICU (Table 2). Two patients died (12%) in the ICU following a course of invasive mechanical ventilation. Four patients remain admitted to a medical ward.

Discussion

We describe 17 non-intubated COVID-19 patients with severe hypoxemia for whom awake prone positioning was attempted. Although no significant adverse events related to prone positioning were observed, several patients did not tolerate long durations of prone positioning (median duration 75 min), or prone positioning for more than one session. Seven patients required intubation and invasive mechanical ventilation despite all patients improving their respiratory rate and oxygenation while in the prone position.

This study presents one of the first descriptions of awake prone positioning for COVID-19 patients with severe acute hypoxemic respiratory failure. Previous studies describing the use of prone positioning for non-intubated COVID-19 patients included patients with less severe hypoxemia.⁷ One recent study included patients with a similar degree of hypoxemia, but they received NIV in addition to prone positioning.⁶ In that report, it is difficult to distinguish if

the physiologic effects observed are secondary to the prone positioning or the NIV. The strategy of NIV and prone positioning had a lower probability of requiring intubation (one of 15 patients, 7%) compared with the rate of intubation in the patients in our cohort (seven of 17 patients, 41%). Future studies will need to delineate if there is a role for awake prone positioning patients with acute severe hypoxemic respiratory failure who are not receiving positive pressure ventilation.

The allure of using awake prone positioning is to potentially mitigate the need for mechanical ventilation (either NIV or invasive ventilation) for patients at the highest risk of needing intubation. We demonstrate that awake prone positioning hypoxemic unintubated COVID-19 patients is feasible. Nevertheless, a significant number of patients may not tolerate prolonged courses of awake prone positioning or more than one session. This is despite all patients having an improvement in oxygenation and respiratory rate while in the prone position. In this cohort, 35% of patients had prone positioning durations less than 60 min and the most common reasons for intolerance were musculoskeletal pain or general discomfort. Recently published cohorts have limited descriptions of the duration, frequency, and protocols used for prone positioning.^{6–8} Moreover, the reduction in respiratory rate (a marker for work of breathing) was not sustained after resupination. A previous meta-analysis showed for invasively mechanically ventilated patients with

moderate-to-severe ARDS that longer durations of prone positioning (> 12 hr) were required before the patients had a significant survival benefit.¹² Given this observation, the clinical benefits of short prone positioning durations may be limited.

This study is also one of the first to systematically describe adverse events, in particular those complications that are known to be associated with prone positioning invasively ventilated patients. In this cohort, we did not observe any iatrogenic removal of lines or tubes associated with the act of prone positioning. Nor did we observe any pressure ulcers, aspiration events, or hemodynamic instability. Previous studies make no mention of the presence or absence of these important events.⁸ Moreover, five of our 17 (29%) of our patients were successfully and safely prone positioned (21 sessions) on a hospital ward with no additional monitoring. This highlights the potential for this therapy to be used safely on the hospital ward, particularly during a pandemic when ICU resources and ventilators may be strained. Nevertheless, the small sample size in this study precludes any strong conclusions regarding safety or the frequency of less common adverse events. Indeed, for potential serious adverse events that were not observed in this cohort of 17 patients, the upper limit of the 95% confidence interval for each adverse event frequency could be as high as 17.6%.¹³ Almost half the patients (47%) were kept fasting as a result of prone positioning and the need for potential intubation. Although not an adverse event, fasting patients for extended periods of time may be associated with malnutrition and delayed recovery.¹⁴ Future large randomized-controlled trials (e.g., NCT04350723 and NCT04402879) are required to determine if any potential clinical benefits outweigh the risks of these adverse events. The observations in this case series can help inform prone positioning protocol design for trials and guidelines.

This study must be interpreted within the context of its limitations. These include the small number of patients, selection bias by the providers who were choosing to prone position patients, and lack of a control group for comparison of outcomes. Also, a standardized prone positioning protocol was not used, which may have led to variability in clinicians' approaches to duration and frequency of prone positioning. Only one patient received HFNC during a prone positioning session. All others in this cohort received oxygen by nasal prongs, face mask, or non-rebreather masks while undergoing prone positioning. Therefore, the results of this study should not be extrapolated to those undergoing prone positioning with HFNC or NIV, which could improve tolerability and physiologic effectiveness.^{5,6}

In summary, awake prone positioning is a promising therapy for acute hypoxemic respiratory failure due to COVID-19. Nevertheless, there remain many questions about its clinical benefit, dosing, potential risks, and adverse events associated with prone positioning non-intubated patients. Strategies to increase the duration and tolerability of the prone position will likely be required before it can have a significant impact on patient outcomes. Randomized-controlled trials are needed to determine the efficacy of prone positioning on intubation avoidance, safety, and mortality.

Author contributions All authors were involved in study design, data collection, data analysis, and the writing and revision of the manuscript.

Disclosures None.

Funding statement None.

Editorial responsibility This submission was handled by Dr. Philip M. Jones, Associate Editor, *Canadian Journal of Anesthesia*.

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