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Awake proning in COVID-19 pneumonia

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To the Editor,
Prone ventilation has been an important strategy in managing severe Acute Respiratory Distress Syndrome (ARDS) patients on ventilatory support with Po2/Fio2 (P/F) ratio <150 [1,2]. However, awake proning is an emerging concept gaining popularity in COVID-19.
COVID-19 infrequently leads to severe pneumonia and ARDS [3]. The inflammatory edema, pulmonary microthrombi and gravitational lung collapse in a sedated patient of COVID-19 leads to ventilation perfusion (V/Q) mismatch. The insufficient hypoxic vasoconstriction, distorted lung shape and irregular diaphragmatic contraction leading to pendelluft, worsen it further [4]. Proning helps to tackle all these pathophysiologies and improves oxygenation.
Moreover, moderate category of COVID-19 requiring oxygen only is another potential group to benefit from proning. Although still scarse, the published literature in this field is emerging (Table 1). There was observed an improvement in the oxygenation when awake proning was done along with various modalities including nasal prongs, High Flow Nasal Cannula (HFNC) and even Non-Invasive Ventilation (NIV). However, most studies had small sample size, short proning sessions due to intolerance, no control group and unclear benefit.
Gattinoni et al. suggested two type of pneumonia in COVID-19. Type 2 is the typical low compliance pneumonia with bilateral dense infiltrates which should be managed like ARDS and where proning can be used in severe ARDS according to guidelines. Type 1 pneumonia, on the other hand, is a high compliance pneumonia with scanty opacities. In this type of pneumonia, proning may be used as a rescue measure for redistribution of pulmonary blood flow rather than opening up collapsed lung [5]. However, when applied to COVID-19 pneumonia, it has been found that strict H (High elastance) and L (Low elastance) groups are uncommon and the disease manifests as a spectrum with intermediate findings also [6]. Thus, phenotyping COVID-19 does not have enough evidence till date to decide the success of proning.
Even non -COVID studies have suggested the role of awake proning in improving oxygenation in ARDS patients due to infectious, and even non- infectious etiologies and have suggested further large trials (Table 2).
In conclusion, proning in severe ARDS in COVID-19 must be done as per existing guidelines in all patients, even though effect may be variable according to the lung elastance and pathophysiology. Awake proning in non-intubated patients on nasal prongs, NIV and HFNC may help in improving oxygenation. Further studies, especially ongoing randomised controlled trials [7] will help to confirm the role of this therapeutic approach. (Table 3). However, a constant attention is required in awake proning with strict monitoring of vitals to prevent a delayed intubation which may lead to increased morbidity and mortality.

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Table 1 - Studies of awake proning in non COVID-19.

Article	*Patients*	*Intervention*	*Comparison*	*Outcome*	*CAVEAT*
Caputo et al. [8]	50 COVID-19 suspected patients with desaturation (mean so2-80%) without respiratory distress (*the happy hypoxemics*)	Proning: from half hour to two hours in prone, left lateral, right lateral and upright sitting position each in rotation	No control group. Oxygen given to all with nasal cannula or non-rebreather mask	Oxygen therapy had a marginal improvement in saturation (84%). However, 5 minutes of proning raised the mean saturation to 94%. 13 patients (24%) required mechanical ventilation within 24 hours of presentation	No control group. Very small sample size
Elharrar et al. [9]	25 awake, nonintubated, spontaneously breathing COVID-19 patients with hypoxemic acute respiratory and failure requiring oxygen	Proning	Before and after study. No control group. Main outcome was proportion of responders (PaO2 increase ≥20%)	Six (25%) were responders, representing 40% (6/15) of the patients who sustained. Proning for 3 hours or more with an increase in Po2 from 74 to 95 mmHg (>20% increase). Four patients did not tolerate proning and eventually required intubation	Small sample single episode of proning evaluated, clinical outcomes were not assessed, and causality cannot be inferred
Sartini et al. [10]	cross-sectional survey of 15 mild to moderate ARDS patients on prone NIV outside the ICU	Proning	Compared with baseline status of the patients	P/F ratio improved from 100 to 122 and respiratory rate from 28 to 24 after proning and the effect was sustained up to 1 hour of prone NIV	Small number of patients, short duration of NIV in the prone position (3 hours) selection bias as patients were not included if NIV failed
Xu et al. [11]	Retrospective observational study in three hospitals to include ten patients on HFNC	Proning	Follow up of the patient	The median P/F ratio was elevated significantly after Proning	Small sample size despite including three hospitals, no control group
Elkattawy et al. [12]	Case report of a young male (35-year-old) with hypoxia (so2-85) requiring oxygen	Proning for at least 6-8 hours/day	Case report	Clinical improvement. Patient maintained so2 off oxygen	Resolution of illness, drug effect cannot be ruled out

ARDS- Acute Respiratory Distress Syndrome, NIV- Non-invasive Ventilation, ICU- Intensive Care Unit, P/F ratio- Po2/Fio2 ratio, HFNC- High Flow Nasal Cannula.

Table 2 - Studies of awake proning in non-COVID patients.

Article	*Patients*	*Intervention*	*Comparison*	*Outcome*	*CAVEAT*
Pérez-Nieto et al. [13]	Retrospective Case series of 6 severe ARDS patients with a non-infectious etiology (thoracic trauma, lupus pneumonitis, bone marrow transplantation, etc.)	Proning was applied for 2-3 h every 12 h for 2 days	Case series	Clinical improvement with increased P/F ratio	Non-infectious etiologies were included only
Bellone et al. [14]	3 patients affected by acute hypoxemic respiratory failure due to pneumonia	Prone positioning as an additional therapy when HFNC and NIV were ineffective alone	Follow up	improved significantly P/F ratio with a reduced respiratory frequency within three-four days	Small sample size. Study itself admits needs for large scale studies
Ding et al. [15]	20 ARDS patients (10 moderate and 10 severe ARDS)	Proning with NIV/ HFNC. average duration for Proning was 2 h twice daily	Pre and post Analysis	PaO_2/FiO_2 in HFNC+ Proning were significantly higher in the success group than in the failure group (125±41 mmHg vs 119±19 mmHg) All 7 patients with a PaO_2/FiO_2 <100 mmHg on NIV required intubation	Nine patients eventually intubated, nearly 50% failure
Scaravilli et al. [16]	15 non-intubated acute respiratory failure patients (nine of whom were immunocompromised)	Proning in ICU	P/F ratio monitored	Even though P/F ratio remained in severe ARDS category, the improvement was significant on proning (mean value-119 to 165)	Over 5-year study period, only 15 patients

ARDS- Acute respiratory distress syndrome, NIV- Non-Invasive Ventilation, ICU- Intensive Care Unit, P/F ratio- Po2/Fio2 ratio, HFNC- High Flow Nasal Cannula.

Table 3 - Trials underway for awake proning in COVID-19.

Article	*Patients*	*Intervention*	*Comparison*	*Outcome*
NCT04350723 (Awake Prone Position in Hypoxemic Patients With Coronavirus Disease 19 (COVI-PRONE): A Randomized Clinical Trial	350 hypoxemic COVID-19 patients	Awake proning with/without HFNC/NIV	Primary outcome-endotracheal intubation	Estimated study completion date. October 31, 2020
NCT04347941 (Awake Prone Positioning to Reduce Invasive Ventilation in COVID-19 Induced Acute Respiratory failure (APPROVE-CARE)	200 patients with acute respiratory failure due to COVID-19	Intervention patients will remain up to 16 hours per day in Prone Positioning with 45 minutes vs full standard care	Primary outcome-effect of awake prone positioning in reducing requirement for IMV	Estimated study completion date May 11, 2021

NIV- Non-Invasive Ventilation, ICU- Intensive Care Unit, HFNC- High Flow Nasal Cannula, IMV- Invasive Mechanical Ventilation.

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