

# Voluntary Prone Position for Acute Hypoxemic Respiratory Failure in Unintubated Patients

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## ABSTRACT

Severe hypoxemic respiratory failure is frequently managed with invasive mechanical ventilation with or without prone position (PP). We describe 13 cases of nonhypercapnic acute hypoxemic respiratory failure (AHRF) of varied etiology, who were treated successfully in PP without the need for intubation. Noninvasive ventilation (NIV), high-flow oxygen via nasal cannula, supplementary oxygen with venturi face mask, or nasal cannula were used variedly in these patients. Mechanical ventilatory support is offered to patients with AHRF when other methods, such as NIV and oxygen via high-flow nasal cannula, fail. Invasive mechanical ventilation is fraught with complications which could be immediate, ranging from worsening of hypoxemia, worsening hemodynamics, loss of airway, and even death. Late complications could be ventilator-associated pneumonia, biotrauma, tracheal stenosis, etc. Prone position is known to improve oxygenation and outcome in adult respiratory distress syndrome. We postulated that positioning an unintubated patient with AHRF in PP will improve oxygenation and avoid the need for invasive mechanical ventilation and thereby its complications. Here, we describe a series of 13 patients with hypoxemic respiratory of varied etiology, who were successfully treated in the PP without endotracheal intubation. Two patients (15.4%) had mild, nine (69.2%) had moderate, and two (15.4%) had severe hypoxemia. Oxygenation as assessed by PaO<sub>2</sub>/FiO<sub>2</sub> ratio in supine position was 154 ± 52, which improved to 328 ± 65 after PP. Alveolar to arterial (A-a) O<sub>2</sub> gradient improved from a median of 170.5 mm Hg interquartile range (IQR) (127.8, 309.7) in supine position to 49.1 mm Hg IQR (45.0, 56.6) after PP. This improvement in oxygenation took a median of 46 hours, IQR (24, 109). Thus, voluntary PP maneuver improved oxygenation and avoided endotracheal intubation in a select group of patients with hypoxemic respiratory failure. This maneuver may be relevant in the ongoing novel coronavirus disease pandemic by potentially reducing endotracheal intubation and the need for ventilator and therefore better utilization of critical care services.

**Keywords:** Acute hypoxemic respiratory failure, Acute respiratory distress syndrome, Awake, Awake prone, COVID-19, Unintubated, Voluntary prone.

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## INTRODUCTION

Traditionally, early nonhypercapnic acute hypoxemic respiratory failure (AHRF) may be initially managed with noninvasive ventilation (NIV), failing which, invasive ventilation is instituted. Ventilation in prone position (PP) is used in patients with refractory hypoxemia. In patients with moderate to severe acute respiratory distress syndrome (ARDS) (P/F < 150), mechanical ventilation in PP has been shown to improve oxygenation and outcome.<sup>1,2</sup> It is plausible that if patients are able to voluntarily lie in PP with respiratory support in the form of NIV or high-flow nasal cannula (HFNC), they may avoid intubation owing to the favorable effects of PP on the lung. Below is a report of 13 cases of AHRF treated successfully in voluntary PP without endotracheal intubation.

## MATERIALS AND METHODS

### Design

Retrospective case series (from the year 2014 to 2019) of patients with AHRF who were treated with voluntary PP.

### Setting

Nineteen bedded mixed medical surgical intensive care unit (ICU) in a tertiary care teaching hospital manned by full-time intensivists.

### Patients

The patients were with various disease backgrounds and different precipitating causes of AHRF. Apart from lung injury, they did

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not have major organ injury. Some of them had sepsis, but were not in shock. All the patients were admitted in the ICU and closely monitored and preparations were ready for an imminent endotracheal intubation, especially in patients whose hypoxemia was moderate to severe.

### Process

All non-ventilatory strategies to improve oxygenation, namely chest physiotherapy, propped up position, fluid restriction to name

a few, were employed. For the initial 24 to 48 hours, the patients were offered NIV and/or HFNC. If the patient did not improve or tolerate the intervention, they were turned prone. Cooperation of the patient was of utmost importance. Communication was well-established and photographic aids were used for better understanding of the PP. If necessary, small dose infusion preferentially of inj. dexmedetomidine and occasionally inj. midazolam titrated to response was administered for patients who were not comfortable in PP. Relatives were allowed to stay at the bedside if necessary. Access to newspaper, magazines, television, and music was permitted. When able, the patients were ambulated to chair and allowed short walks. Importantly, enteral nutrition was allowed in the form of clear fluids/juices when they were sick and soft solids progressing to normal diet when they improved as tolerated. As patient cooperation was important, the frequency and time spent in PP was determined by the patient. Ventilatory assistance in the PP was determined by the oxygenation status, cooperation, and comfort of the patient. Noninvasive ventilation was continued in some, oxygen via venturi mask, HFNC (from the year 2018), or simple nasal cannula on a case to case basis in others. Inspired oxygen was titrated based on pulse oximeter readings or arterial blood gas analysis if available. Target oxygen saturation was 90–92% in the early stages, and once stability was achieved, target was changed to 88–90%. Arterial blood gases were performed once or twice a day, not necessarily in the PP only. Two patients did not have radiological features conforming to the Berlin definition of ARDS, but for the sake of simplicity, we classified hypoxemia as mild, moderate, and severe for P/F ratios of 200–300, 100–199, and <100, respectively. The time for improvement was defined as time from the initiation of PP to the time P/F ratio improved to and stabilized around 300. This scheme of management resulted in improvement in oxygenation, avoided intubation, and aided in weaning from NIV and subsequent discharge from ICU in all the patients.

### Statistical Analysis

Data with normal distribution are reported as mean  $\pm$  SD and analyzed with paired *t* test. Data which are not normally distributed are reported as median and interquartile range (IQR) and analyzed with Wilcoxon-signed rank test.

### RESULTS

The demographics, diagnosis and etiology of AHRF, pre-prone P/F ratio, and degree of hypoxia are reported in Tables 1 and 2. Clinical features, radiology, and oxygenation parameters of one of the patients are presented in Figures 1 and 2.

There were four men and nine women aged between 22 years and 69 years. Two patients (15.4%) had mild, nine (69.2%) had moderate, and two (15.4%) had severe hypoxemia, lowest P/F being 65.5. Seven (53.9%) patients had P/F < 150 mm Hg, a cutoff value used in PROSEVA trial.<sup>1</sup> Alveolar to arterial oxygen difference (A-a O<sub>2</sub> difference) was also recorded to assess improvements in oxygenation.

The details of oxygenation are represented in Table 3. Prone position improved the P/F ratio from 154.3  $\pm$  52.3 (mean  $\pm$  SD) to 327.8  $\pm$  65.4. The improvement was statistically significant (*p* < 0.0001, with paired *t* test). The A-a oxygen gradient reduced from median of 170.5 with IQR (309.7, 127.8) mm Hg to median of 49.1 IQR (56.6, 45) mm Hg after proning. The improvement in A-a oxygen gradient was also statistically significant (*p* = 0.0015, with

Wilcoxon-signed rank test). Time taken for this improvement was a median of 46 hours, IQR (24, 109). Patients with moderate to severe hypoxemia took longer to improve (Fig. 3).

Below is the clinical profile of one of our patient (Fig. 1) 22-year old man who underwent peripheral blood stem cell transplant for aplastic anaemia was admitted with hypoxic respiratory failure secondary to pneumonia. He did not improve on NIV and was turned prone. There was symptomatic improvement with a marginal improvement in oxygenation in PP. As PP was the best position, he was transferred for HRCT in PP. HRCT demonstrated a left lower lobar consolidation, possible bacterial pneumonia. There was interval worsening of oxygenation in the next 24 hours with an evolving right lower lobe consolidation. He was treated in PP and NIV. He improved over the next 24 hours and was discharged to the ward.

### DISCUSSION

Sedation, muscle relaxants, and positive pressure ventilation with positive end-expiratory pressure (PEEP) worsen the ventilation/perfusion mismatch induced by the assumption of supine position. Assumption of PP negates these effects and there is more uniformity of ventilation and perfusion and V/Q is better matched.<sup>3,4</sup> This pathophysiology of V/Q mismatch and effect of PP is all too well-known and needs no further discussion.

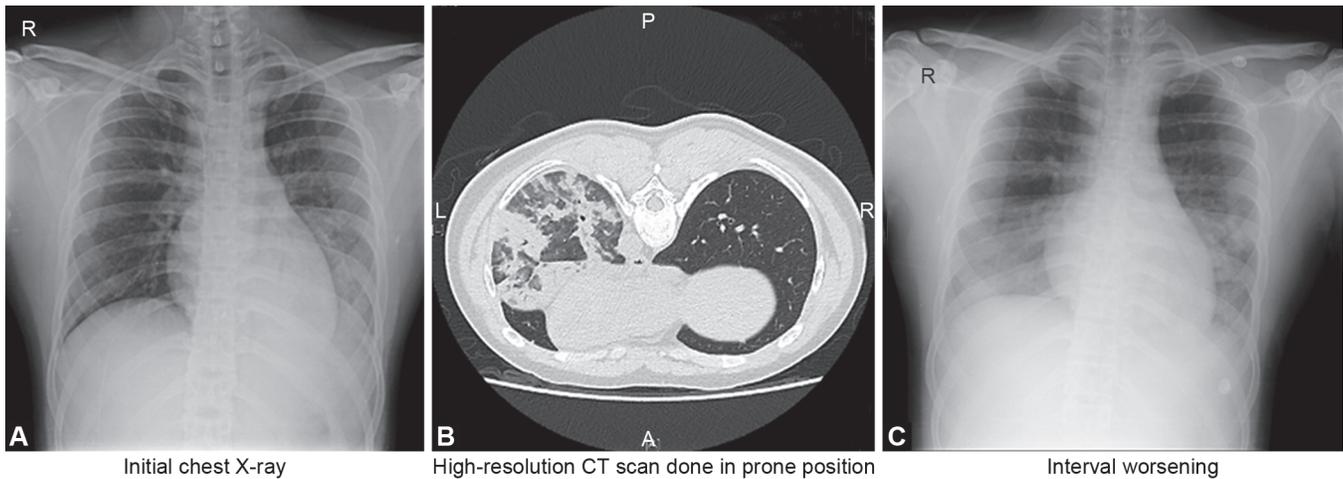
**Table 1:** Patient demography, degree of hypoxia and time for improvement, speciality and precipitating cause

Parameter	N (%)
Gender	
Male	4 (30.8)
Female	9 (69.2)
Age—mean (SD)	40.8 (16.9)
Degree of hypoxia	
Mild (P/F 200–300)	2 (15.4)
Moderate (P/F 100–199)	9 (69.2)
Severe (P/F <100)	2 (15.4)
Time (hours) to improvement—median (IQR)	46 (24, 109)
Time (hours) to improvement—mean (SD)	65.4 (43.7)
Age—mean (SD)	40.8 (16.9)
Specialty	
Hematology and rheumatology (immunocompromised)	8 (61.5)
General medical	1 (7.7)
Surgical/postoperative status	4 (30.8)
Precipitating cause	
Pneumonia	5 (38.5)
Post-extubation respiratory failure (prone ventilation for pneumonia)	1 (7.7)
Post-extubation respiratory failure — postoperative	1 (7.7)
Hypersensitivity pneumonitis	1 (7.7)
TRALI	1 (7.7)
Pleuropulmonary involvement in lymphoma	1 (7.7)
Pulmonary graft vs host disease	1 (7.7)
ARDS secondary to cellulitis leg	1 (7.7)
Dengue fever with pneumonitis	1 (7.7)

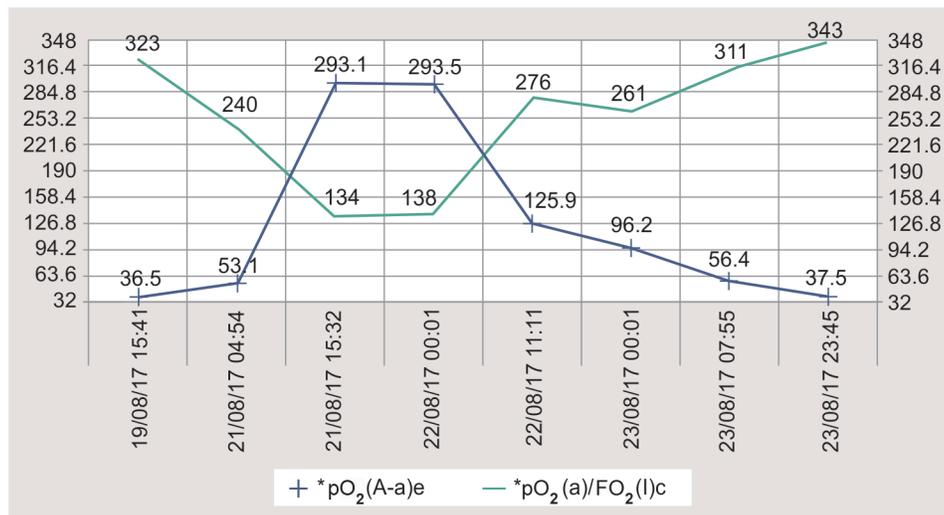
## Voluntary Prone Position

**Table 2:** Patient demographics, diagnosis, pre-prone lowest P/F ratio, and degree of hypoxia

S. no	Age (years)	Sex	Primary diagnosis	Pre-prone P/F ratio	Degree of hypoxia
1	59	F	Burkitt's lymphoma with pleuropulmonary disease	105	Moderate
2	42	M	CNS lymphoma with fungal pneumonia	65.5	Severe
3	34	F	Ruptured ectopic pregnancy, hemorrhagic shock, TRALI	107	Moderate
4	69	M	Cellulitis leg with ARDS	218	Mild
5	29	F	Hodgkin's lymphoma, fungal pneumonia, extubation failure	200	Moderate
6	42	M	Aplastic anemia, bone marrow transplant, pulmonic graft vs host disease	83.9	Severe
7	22	F	Bilateral above knee amputation with extubation failure	217	Mild
8	53	F	Lymphoma, fungal pneumonia	181	Moderate
9	22	M	Aplastic anemia, bone marrow transplant, bacterial pneumonia	134	Moderate
10	20	F	Post-op diagnostic laparoscopy, nosocomial pneumonia	193	Moderate
11	67	F	Rheumatoid arthritis, methotrexate-induced hypersensitivity pneumonitis	188	Moderate
12	43	F	Acute myeloid leukemia, fungal pneumonia	184	Moderate
13	29	F	Dengue fever with ARDS	129	Moderate



**Figs 1A to C:** Clinical picture, progress and images from one of the patients



**Fig. 2:** Graph depicting P/F ratio and A-a oxygen gradient in this patient during the course of the treatment

Though initial studies on prone ventilation in ARDS demonstrated an improvement in oxygenation, they did not demonstrate an improvement in outcome. Guérin et al.<sup>1</sup> demonstrated an improvement in oxygenation and outcome in a cohort of patients with moderate to severe ARDS with P/F ratio of <150.

Noninvasive ventilation has robust evidence in patients with AHRF associated with acute cardiogenic pulmonary edema.<sup>5</sup> In other etiologies of AHRF, such as pneumonia, the evidence for NIV is not strong and even controversial sometimes showing increased mortality, especially if intubation is delayed.<sup>6</sup> However, there is some evidence that interfaces employed in administering NIV may make a difference with helmet being superior to face mask in terms of tolerability and PEEP titration and reduction in the need for endotracheal intubation.<sup>7</sup> Use of helmet NIV also had reduced ICU weakness and did not affect functional independence at hospital discharge and less mortality and more functional independence at 1 year compared to NIV with face mask.<sup>8</sup> Increasingly, self-inflicted lung injury (SILI) is being recognized as a reason for increased mortality when endotracheal intubation is delayed in NIV trial for AHRF.<sup>6</sup> Large tidal volumes generated during NIV has been implicated for SILI.

Oxygen via HFNC is a recent addition to our armamentarium to treat AHRF and there are some data supporting its use in AHRF. Use of HFNC reduces the rate of endotracheal intubation, but had no effect on the outcome.<sup>9</sup> The recent FLORALI study<sup>10</sup> has demonstrated that compared to NIV, though HFNC does not reduce the rate of intubation, its usage has increased the ventilator-free days and reduces mortality at 90 days. However, there is conflicting data also regarding HFNC.<sup>11</sup> The evidence that delay in intubation when NIV is used in AHRF increases mortality necessitates means

to predict failure of NIV and HFNC. The HACOR<sup>12</sup> score and ROX<sup>13,14</sup> index have been used to predict failure of NIV and HFNC, respectively. HACOR score of >5 and ROX index <4.88 at 12 hours have been shown to predict failure of NIV and HFNC, respectively, in AHRF. All our patients had an initial NIV and/or HFNC trial for 24–48 hours, but failed to improve some were worsening too. Prone position was the additional intervention that improved oxygenation and aided in weaning of ventilatory support.

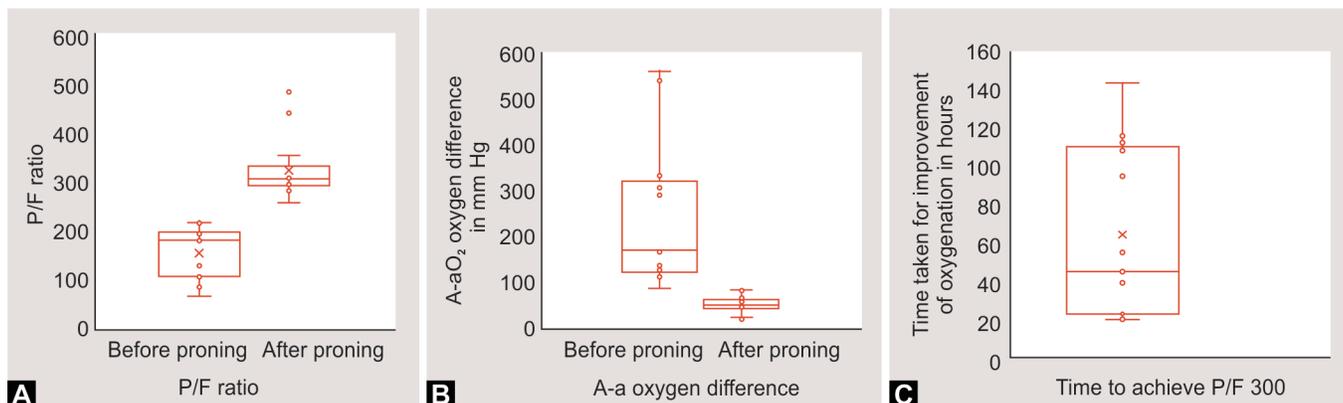
In terms of specific conditions associated with AHRF, use of NIV and more specifically HFNC in immunocompromised patients have had lower intubation rates, lower mortality, and reduced length of ICU stay.<sup>15–18</sup> Eight of our patients (61.5%) were immunocompromised of which, seven were hematology patients, and one with rheumatoid arthritis on methotrexate and corticosteroid. Six patients had pneumonia. Effective airway toileting was feasible in all our patients as they were not intubated and/or heavily sedated. Noninvasive ventilation and HFNC have been used in postextubation AHRF<sup>19–21</sup> and shown to have reduced the need for endotracheal intubation. High-flow nasal cannula also has been shown to be non-inferior to NIV.<sup>19</sup> Two of our patients had postextubation respiratory failure and improved on assuming PP of which one was originally ventilated for pneumonia.

Sepsis and septic shock increases the risk of failure of NIV by 1.5 to 2.5 times, respectively, with no difference between pulmonary and non-pulmonary source.<sup>22</sup> Sepsis was present in seven cases in our series. Six cases had pneumonia and one had cellulitis leg, but none of them were in shock. The patient with cellulitis leg had a poor mask fit because of the beard, which he refused to remove. Prone position improved oxygenation in this patient without and positive pressure support.

In terms of degree of hypoxia, two had mild, nine moderate, and two severe hypoxia. In the LUNG SAFE<sup>23</sup> study, continuing NIV in patients with P/F ratio of <150 was associated with poor outcome. In an *ad hoc* analysis of the FLORALI<sup>24</sup> trial, a P/F ratio of <200 was an indicator of need for intubation. In the PROSEVA<sup>1</sup> trial patients, with severe hypoxia classified as P/F <150 had a better outcome in PP. Eleven of our patients had P/F ratio <200, out of which, 6 had P/F ratio <150. It took an average period of 65.4 ± 43.7 hours for the improvement of oxygenation close to a P/F of 300 with patients with moderate to severe hypoxemia taking longer time. Thus, patients with moderate to severe hypoxemia

**Table 3:** P/F ratio and A-a oxygen gradient pre- and end of prone intervention

	P/F ratio (mean ± SD)	A-a O <sub>2</sub> diff [median (interquartile range)]
Before proning	154.3 ± 52.3	170.5 (127.8, 309.7)
End of prone intervention	327.8 ± 65.4	49.1 (45.0, 56.6)
p value	<0.0001	0.0015



**Figs 3A to C:** Box and Whisker plots for P/F ratio, A-a oxygen difference and time to achieve stable P/F around 300



also benefited from the voluntary prone maneuver. An argument that the HFNC/NIV applied in PP may also have had a role in the improvement of oxygenation may be valid, but oxygenation as assessed by pulse oximetry was always better in prone compared to supine position with the same settings of ventilatory assistance. This enabled in weaning inspired oxygen and progress to less intense ventilatory support (e.g., NIV to venturi mask) in all the cases when they were in PP.

Valter et al.<sup>25</sup> reported voluntary proning in AHRF as early as 2003. Noninvasive ventilation or any other positive pressure was not used in their set of four patients. The literature in the last couple of months has at least three publications<sup>26–28</sup> on voluntary PP in hypoxemic respiratory failure with varying success in improving oxygenation. There is also one pilot study<sup>29</sup> underway on voluntary proning in AHRF (ClinicalTrials.gov Identifier: NCT03095300).

Our study demonstrates that prone ventilation for an awake and cooperative patient is feasible and has favorable results. The maneuver was useful in varying degrees of hypoxemia, even severe ones as long as the patient was cooperative. The duration of PP was dependent on the severity of hypoxemia. Although this method may not apply to all patients, our results indicate that it is a reasonable treatment strategy if the patient's condition permits and if the treating team is vigilant and ensures encouragement. Treatment of AHRF is a combination of an art and science and the success in AHRF may depend on the selection of patients, interface used, and close monitoring for early evidence of failure.<sup>30</sup>

## CONCLUSION

Voluntary PP improved oxygenation and prevented endotracheal intubation in a selected group of patients with AHRF. Our case series demonstrates that this technique can be applied safely in various etiologies of AHRF. The method of respiratory support during PP should be tailored to the need and comfort of the patient and experience of the team.

## CLINICAL SIGNIFICANCE

Avoiding endotracheal intubation removes the risk of complications of intubation. Voluntary PP has an important role as it reduces all the well-known clinical and economic impacts of mechanical ventilation and allows for better utilization of critical care resources. All these are very relevant not only during this ongoing COVID pandemic but also during other times.

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