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Profile of Patients Responding to Positive End-Expiratory Pressure and Prone Position during ARDS Related to COVID-19: A Case of the Sens Hospital

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Abstract

Background: There is a paucity of data on the efficacy of ventilatory strategies in COVID-19-related ARDS. The aim of this study was to describe the effect of positive end-expiratory pressure (PEEP) and prone position (PP) on oxygenation and determine the profile of responders. **Methods:** This was a cross-sectional study of patients admitted to the intensive care unit of the Sens Hospital with COVID-19-related ARDS who were invasively ventilated for more than 24 hours between 1 March 2020 and 2 March 2021. A good oxygenation response to PEEP and/or PP was defined as an increase in the PaO_2/FiO_2 ratio (pre-post) of more than 20% within 4 hours after the application of these measures. **Results:** Forty patients were recruited, 28 of whom were men. Standard ventilation allowed us to observe 3 subgroups of patients: 5 (12.5%) requiring protective ventilation with a PEP ≤ 8 cmH_2O, 5 (12.5%) requiring protective ventilation with a PEEP > 8 cmH_2O, and finally 30 (75%) requiring protective ventilation with a PEEP > 8 cmH_2O combined with PP sessions. Almost all (80%) of the patients (the majority of whom were obese) placed on PP with PEP > 8 cmH_2O had a good response to oxygenation. No characteristic was associated with non-response. **Conclusion:** The use of PEEP and the use of prone position increased the PaO_2/FiO_2 ratio in the vast majority of patients, particularly those who were obese. No characteristic was associated with non-response, so prone position can be offered to those with the indication. A high-powered study is needed to confirm this profile and assess the benefit of PP on mortality.

Keywords

ARDS, COVID-19, Positive End-Expiratory Pressure, Oxygenation, Prone Position

1. Introduction

Acute respiratory distress syndrome (ARDS), defined by diffuse radiological lesions, PaO_2/FiO_2 less than 300 mmHg within seven days of pulmonary or extra-pulmonary injury [1], is a common and serious complication of coronavirus disease (COVID-19). In fact, of the 5% of patients with COVID-19 who require intensive care, approximately 88% present with severe hypoxaemia fulfilling the criteria for ARDS, requiring mechanical ventilation in the study of Grasselli *et al.* [2]; 81% in the study done by Yang *et al.* [3] and all the patients were admitted for hypoxemic respiratory failure; 75% needed mechanical ventilation in the study of Bhatraju *et al.* [4]. Finally, follow-up of large series has shown that the characteristics of ARDS associated with COVID-19 are identical to those of ARDS associated with other causes [5].

Therefore, based on the current state of knowledge, there is no good reason to propose specific ventilatory management in ARDS in the context of COVID-19. The COVID-19 subcommittee of the surviving sepsis campaign (SSC) [6] recommends that the same principles of protective mechanical ventilation combined with the prescription of prone sessions should be applied to these patients as to patients with "classic" ARDS.

As a reminder, the so-called "protective" ventilation technique consists of combining low tidal volumes of around 6 to 8 ml/kg of weight predicted by height (WPH) with a limitation of airway pressures (maximum alveolar pressure at 30 cmH_2O).

If the patient's oxygenation remains inadequate, ventilation should be optimised by adjusting end-expiratory pressure (EEP), curarisation and possibly positioning the patient in the prone position (PP) [7].

In 2013, a multi-centre randomised trial (PROSEVA trial) [8] demonstrated a reduction in mortality from 32.8% to 16% ($p < 0.001$) in patients with ARDS who received 16 hours of protective mechanical ventilation per day in the prone position compared to patients who remained in the supine position.

With particular reference to patients with COVID-19, studies have shown that patients receiving a mechanical ventilation protocol identical to that used in PROSEVA, combining protective ventilation and prone positioning, improved their oxygenation with a success rate of over 80% [5] [9]. Prone positioning has even been suggested for non-intubated patients, with a possible benefit on intubation rates and in-hospital mortality [10].

It has therefore been established that the use of PEEP and the use of PP in patients with COVID-19 improves their oxygenation. However, the physiological aspects of this efficacy are not fully elucidated. The data currently available have shown that the response of COVID-19 patients is highly variable from one patient to another, without it being known which type of patients are good responders [11]. We therefore thought it would be useful to characterise COVID-19 patients who respond to the ventilatory strategy recommended for "classic" ARDS. For this reason, we conducted the present study on patients under our care in the intensive care unit of the Gaston Ramon Hospital in Sens, France, during the public health crisis of the COVID-19 pandemic.

2. Methods

2.1. Type, Period and Setting of the Study

This was a cross-sectional study carried out prospectively from 1 March 2020 to 2 March 2021 at the Multi-Purpose Intensive Care Unit of the Gaston Ramon Hospital in Sens.

2.2. Study Population, Recruitment and Selection of Patients

Our study included all patients admitted to the intensive care unit of Sens Hospital with COVID-19-related ARDS (positive COVID PCR and chest CT scan) who were placed on mechanical ventilation. Recruitment was prospective and consecutive.

Patients aged 18 years or older with biologically confirmed SARS-CoV2 pneumonia by PCR-RT test, who required intubation and mechanical ventilation for ARDS according to the Berlin definition and who were ventilated for more than 24 hours were included. Because it is difficult, if not impossible, to place a pregnant woman in the prone position, pregnant women and patients with missing important data were excluded.

2.3. Mechanical Ventilation Protocol

Figure 1 shows the mechanical ventilation protocol.

After orotracheal intubation, we used protective ventilation from the outset in all patients. This involved a tidal volume (Vt) set at 6 ml per kilogram of body weight predicted by height (WPH), and a low positive end-expiratory pressure (PEEP) of between 5 and 8 cmH_2O.

Subsequently, PEEP was adjusted to maintain a plate pressure below 30 cmH_2O and a driving pressure below 15 cmH_2O. If the PaO_2/FiO_2 (P/F) ratio fell below 150 mmHg despite high PEEP, the prone position (PP) was then used for at least 16 hours per day, unless cardiopulmonary resuscitation was required. All members of the medical and paramedical team received video training in prone positioning. Finally, if the patient still had a P/F ratio of less than 80 mmHg in prone position after optimizing protective ventilation and there were no contraindications, the patient was transferred to another hospital for extracorporeal membrane oxygenation (ECMO). As some studies had suggested that the risk of barotrauma seemed to be increased in patients with ARDS-COVID compared with ARDS of other origins, we decided to use the 8 cmH_2O threshold to quickly place the patient in the prone position [12].

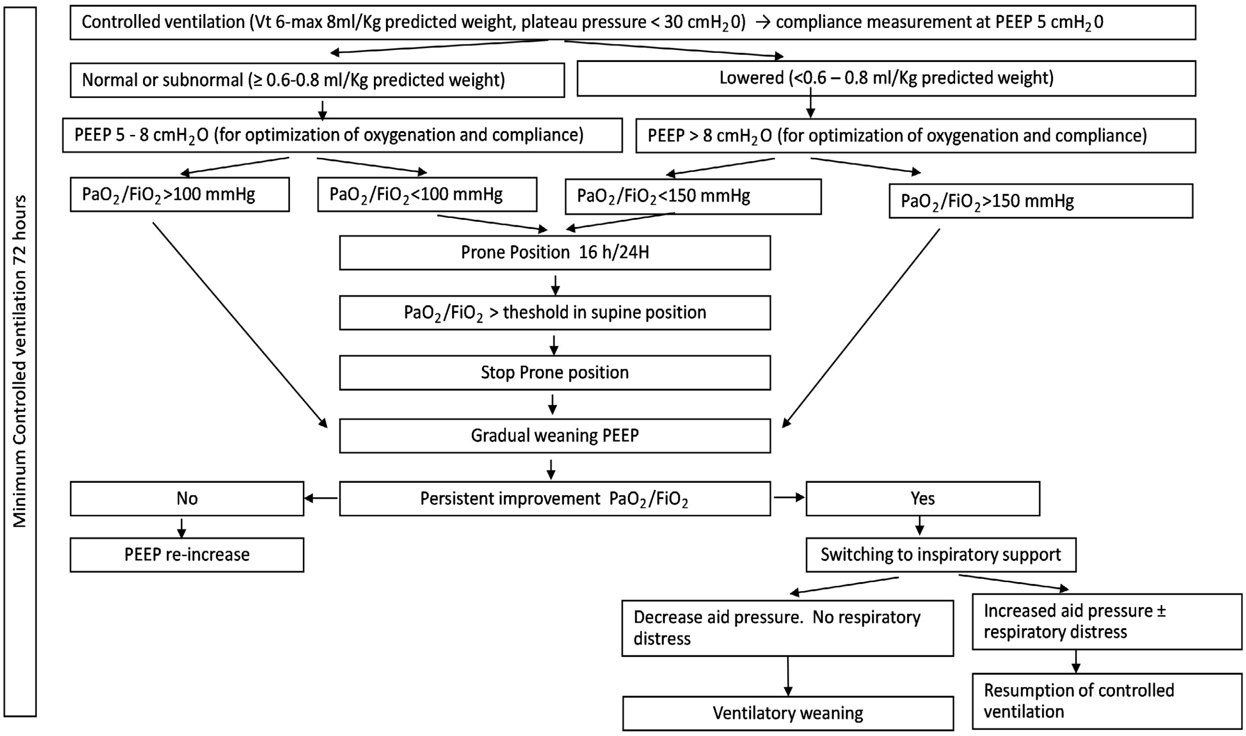

Figure 1. Mechanical ventilation protocol.

2.4. Data Collection

Data were prospectively collected by the investigator of this study from medical records containing information on demographics (age, sex), comorbidities (obesity, diabetes, high blood pressure, chronic lung disease, ischaemic heart disease, history of cancer, immunodeficiency), laboratory data (number of lymphocyte, CRP, lactates) including pre- and post-intubation blood gases (pH, PaO_2, $PaCO_2$, HCO_3, ratio PaO_2/FiO_2 (calculated)) mechanical ventilation parameters (FiO_2, Vt, PEEP, plate pressure, compliance (calculated), driving pressure (calculated)) concomitant treatments, intercurrent events during intensive care unit (ICU) stay, and patient outcomes.

A computerised database was set up for this purpose at the beginning of the pandemic. Each patient was followed until discharged from intensive care.

2.5. Evaluation Criteria

The primary endpoint was oxygenation, assessed by the PaO_2/FiO_2 (P/F) ratio, before and after the initial application of PEEP and/or prone positioning. A positive response was defined a priori as an increase in the PaO_2/FiO_2 ratio > 20%.

Secondary endpoints were ICU mortality and the rate of occurrence of complications related to mechanical ventilation or disease progression (accidental extubation, tracheostomy, thromboembolic disease, pneumothorax or pressure sores).

2.6. Operational Definitions

The following definitions were used in this paper:

- Good responder: A patient who shows an increase in P/F ratio of at least 20% in the 4 hours following an increase in PEEP above 8 cmH_2O and/or the first prone position session.
- Poor responder: A patient whose P/F increase does not exceed 20%.
- Low PEEP patient: A patient whose spontaneous gas evolution was favourable, but only with PEEP < 8 cmH_2O.
- High PEEP: In the context of this study, PEEP is greater than 8 cmH_2O.
- Ideal theoretical weight (ITW) or weight predicted by height (WPH): X + 0.91 (height in cm − 152.4), where X = 45.5 for females and 50 for males.
- Low tidal volume (Vt) = Vt < 8 ml/kg ITW or WPH.
- *Compliance*: $C = \frac{\text{Tidal volume}}{[\text{P.Plat} - \text{PEEP total}]}$ (Pplat: plate pressure).
- Drive pressure: Pplat − PEEP.
- Documented ventilator-associated pneumonia (VAP): Mechanically ventilated pneumonia, defined in this study as the identification of a pathogen in bronchoalveolar lavage fluid associated with clinical deterioration in a mechanically ventilated patient.

3. Results

3.1. Patient Flow Diagram

The patient flow diagram is shown in Figure 2.

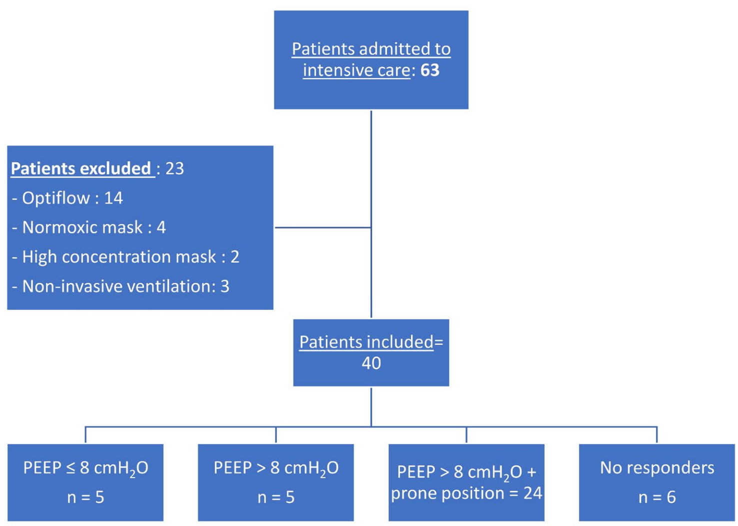

Figure 2. Patient flow diagram.

Between 1 March 2020 and 2 March 2021, 63 patients were admitted to our intensive care unit with a confirmed diagnosis of COVID-19-related pneumonia. Mask oxygen therapy was required and sufficient in 6 patients, high flow nasal oxygen therapy (HFNO) was sufficient in 14 patients and non-invasive ventilation (NIV) was sufficient in 3 patients. These patients were not intubated and were excluded from the study. On the other hand, 40 patients in the sample required intubation and mechanical ventilation. These patients were included in the study and received standard ventilation. Five (12.5%) patients required protective ventilation with PEEP ≤ 8 cmH_2O, 5 (12.5%) other patients required protective ventilation with PEEP > 8 cmH_2O and finally 30 (75%) patients required protective ventilation with PEEP > 8 cmH_2O combined with prone position.

3.2. Baseline Patient Characteristics

Table 1 shows the clinical and biological characteristics of the patients on admission.

Table 1. Clinical and laboratory characteristics on admission to the intensive care unit.

Variables	n = 40	%
Age, year, X ± SD	**69.05** (65.91 - 73.01) ± 10.81	
Sex, Male	28	70.0
Comorbidities, X ± SD	**2.47** (1.98 - 2.92) ± 1.66	
BMI, kg/m^2, X ± SD	**30.37** (28.09 - 33.00) ± 6.89	
Obesity	22	55.0
Overweight	9	22.5
Chronic lung disease*	8	20.0
High blood pressure	29	72.5
Ischaemic heart disease	7	17.5
Diabetes	13	32.5
History of cancer	10	25.5
Immunodeficiency	1	2.5
Without comorbidities	1	2.5
Time from symptom onset to intensive care admission, day, X ± SD	**8.32** (7.13 - 9.91) ± 5.07	
Biological		
Number of lymphocytes per µl	**682.50** (514.09 - 849.16) ± 391.50	
CRP, mg/l	**171.95** (137.83 - 201.27) ± 94.76	
D-Dimers ng/ml	**4505.33** (2034.80 - 7375.97) ± 5879.39	
SSI, X ± SD	**42.87** (38.87 - 47.19) ± 11.77	

Legend: BMI = body mass index; *chronic lung disease (COPD) = chronic obstructive bronchopneumopathy, asthma, emphysema, etc.; X = mean (average); SD = standard deviation; SSI = simplified severity index.

The average age of the patients was 69 years, with extremes ranging from 65 to 73 years. Of the total number of patients, 28 (70%) were male and the mean duration of symptoms before admission to the intensive care unit was 8 days. The most common comorbidities were hypertension (72%), obesity (55%), diabetes (32.5%) and a history of cancer (25.5%). Biological tests showed lymphocytopenia at 682.50 µL, with an elevated CRP of 171.95 mg/l. Elevated D-dimer levels were observed. The mean simplified severity index (SSI) was 42.87.

3.3. Ventilatory Parameters and Associated Treatment

Table 2 shows the ventilatory parameters and associated treatment.

Table 2. Ventilatory parameters and associated treatment after initiation of ventilation.

Variables	n = 40
Vt, ml/kg de WPH, X ± SD	**7.06** (6.82 - 7.46) ± 0.82
FiO_2, %, X ± SD	**89.36** (83.77 - 93.19) ± 14.96
pH, X ± SD	**7.29** (7.26 - 7.34) ± 0.10
$PaCO_2$, mmHg, X ± SD	**51.38** (44.97 - 58.45) ± 18.51
PaO_2, mmHg, X ± SD	**112.67** (94.62 - 138.02) ± 64.67
HCO_3, mmol/l X ± SD	**24.32** (23.36 - 25.5) ± 2.96
Ratio PaO_2/FiO_2, mmHg, X ± SD	**131.79** (106.84 - 160.93) ± 80.55
Lactates, mmol/l**,** X ± SD	**1.59** (1.30 - 1.75) ± 0.65
PEEP, cmH_2O, X ± SD	**8.79** (8.00 - 9.38) ± 1.79
Plate pressure, cmH_2O X ± SD	**24.675** (23.53 - 26.19) ± 4.01
Compliance, ml/cmH_2O, X ± SD	**28.43** (26.10 - 31.41) ± 6.76
Driving pressure, cmH_2O X ± SD	**16.05** (14.82 - 17.72) ± 3.64
ARDS stage	
Severe ARDS	**19** (47.5)
Moderate ARDS	**16** (40.0)
Light ARDS	**5** (12.5)
PEEP max, cmH_2O, X ± SD	**10.03** (9.55 - 10.65) ± 1.54
Associated treatment	
Hydroxychloroquine in 24 hours, n (%)	17 (42.5)
Noradrenaline, n (%)	32 (80)
Corticoids in 48 hours	26 (65)

Legend: FiO_2: fraction of inspired oxygen; VT = tidal volume; PEEP = positive end-expiratory pressure; WPH: weight predicted by height; ARDS = acute respiratory distress syndrome; X = mean; SD = standard deviation; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; pH = hydrogen potential.

After intubation, patients were ventilated with a mean tidal volume of 7.06 ml per kg of weight predicted by height (WPH), a mean PEEP of 8.79 cmH_2O. The mean PaO_2/FiO_2 ratio was 131.79 mmHg. Mean lung compliance was low at 28.43 ml/cmH_2O. Almost half of our patients (47.5%) had severe ARDS according to the Berlin definition.

Apart from ventilation, all patients were curarised on the first day. Enoxaparin at an anticoagulant dose (100 IU/kg) was used in all patients. Vasoactive support with noradrenaline was introduced in 80% of patients. Hydroxychloroquine was administered in 42% of patients. More than half the patients (65%) received corticosteroid therapy (dexamethasone). No patient received antiviral treatment.

3.4. Response to PEEP and Prone Positioning

Figure 3 shows the response to the application of PEEP and to positioning in prone position.

According to the response to the mechanical ventilation applied, 3 subgroups of patients were identified:

- 1st Type: PEEP ≤ 8 cmH_2O: Including 5 patients (12.5%) who had a favourable outcome with a PEEP of less than or equal to 8 cmH_2O.
- 2nd Type: PEEP > 8 cmH_2O: Consisting of 5 patients (14.3%) who improved their oxygenation when the remaining 35 patients were subjected to high PEEP after failing to respond to low PEEP.
- 3rd Type: PP + PEEP > 8 cmH_2O: Comprising 24 patients (80%) who improved their oxygenation when the 30 patients received both high PEEP (defined as >8 cmH_2O) and prone positioning (PP) after not-response to low and then high PEEP.

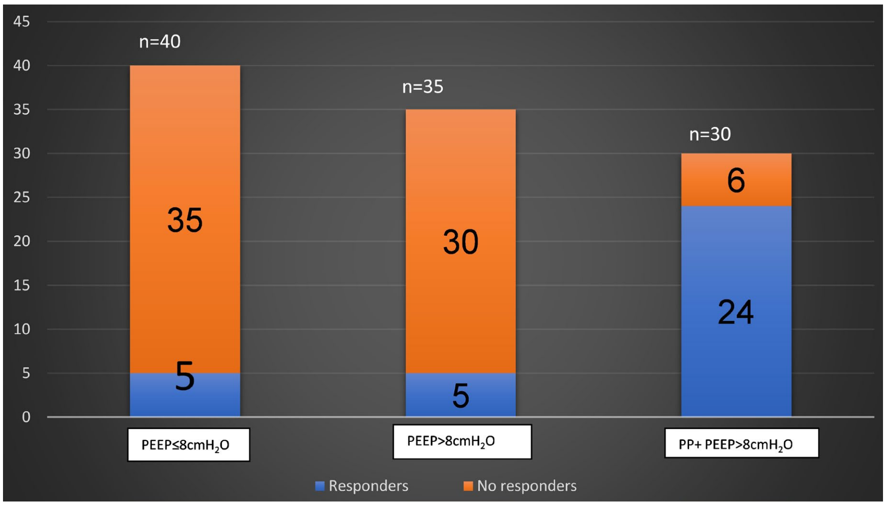

Figure 3. Distribution of patients according to their response to low PEEP, high PEEP or high PEEP combined with prone position (PP). Legend: PP = prone position; PEEP = positive end-expiratory pressure.

3.5. Response Profile to PP + PEEP > 8 cmH_2O

Figure 4 below shows the 30 patients who received prone positioning combined with PEEP > 8 cmH_2O. The P/F ratio increased from 93.63 ± 32.7 mmHg in the supine position to 154.20 ± 61.0 mmHg in the prone position (PP). It also shows the heterogeneous nature of the response.

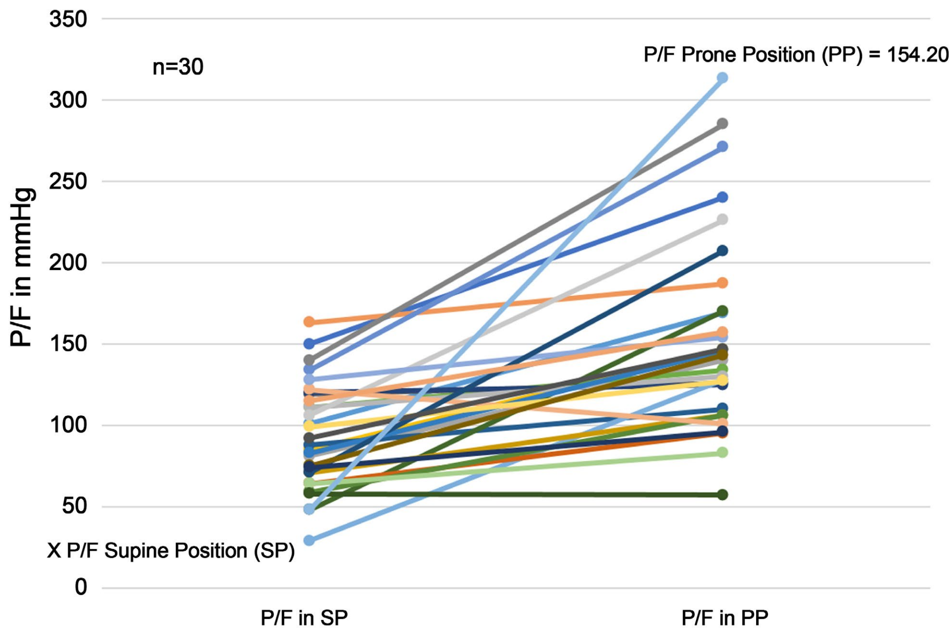

Figure 4. Evolution of the P/F ratio in the 4 hours following the 1st prone session with increased PEEP. Legend: SP = supine position; PP = prone position; P/F = ratio between the partial pressure of oxygen in arterial blood and the fraction of inspired oxygen.

3.6. Patient Characteristics According to Response

Table 3 shows the characteristics of patients according to their response.

Of the 30 patients who benefited from prone positioning combined with high PEEP, there was no significant difference between good responders and poor responders to this strategy, although good responders tended to be obese.

Table 3. Characteristics of good and poor responders to prone position + PEEP > 8 cmH_2O

Variables	Responders PP + PEEP (n = 24)	No responders PP + PEEP (n = 6)	p
Age, year, X ± SD	**67.79** ± 12.58	**70.16** ± 9.62	0.671
Sex			
Male	13 (54.17)	5 (83.33)	0.192
Female	11 (45.83)	1 (16.67)	
BMI, kg/m^2, X ± SD	**32.38** ± 6.40	**28.70** ± 3.15	0.186
Compliance, ml/cmH_2O, X ± SD	29.00 ± 7.17	28.33 ± 6.12	0.836
Drive pressure, cmH_2O, X ± SD	15.75 ± 3.79	15.67 ± 3.61	0.962
SSI, X ± SD	43.37 ± 10.39	41.0 ± 10.19	0.620
FiO_2, %, X ± SD	93.95 ± 10.52	86.66 ± 12.11	0.151
pH, X ± SD	7.29 ± 0.12	7.25 ± 0.03	0.139

Continued

PaO_2, X ± SD	110.04 ± 76.50	94.5 ± 22.71	0.630
$PaCO_2$, X ± SD	51.91 ± 22.81	56.16 ± 6.91	0.659
HCO_3, X ± SD	24.12 ± 3.02	25.11 ± 2.52	0.466
P/F ratio, X ± SD	118.04 ± 75.78	112.33 ± 37.93	0.861
Plate pressure	24.0 ± 4.34	25.0 ± 2.68	0.597
ARDS stage			
Severe	14 (58.33)	3 (50)	
Moderate	7 (29.16)	3 (50)	
Light	3 (12.5)	0 (0)	
Hydroxychloroquine	10 (41.67)	4 (66.67)	0.272
Noradrenaline	22 (91.67)	4 (66.67)	0.107
Corticoids	17 (70.83)	3 (50.0)	0.333
Death	10 (41.67)	2 (33.33)	0.659

Legend: PP = prone position; SSI = simplified severity index; BMI = body mass index; FiO_2: fraction of inspired oxygen; PEEP = positive end-expiratory pressure; ARDS = acute respiratory distress syndrome; X = mean; SD = standard deviation; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; P/F: ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen; pH = potential hydrogen.

3.7. Patient Outcome

Patient outcomes are shown in Table 4.

For patients who required prone positioning, the average number of sessions was 1.94, with extremes ranging from 1 to 6, and an average duration of 18 hours.

For all patients, the duration of mechanical ventilation was 20 days and the length of stay in intensive care was 26.63 days. Overall mortality in our series was 40%.

Table 4. Patient outcome.

Variables	N	%
Evacuation	9	22.5
ECMO	4	10
Death	**16**	**40.0**
LCAT	5	12.5
Tracheostomie	2	5.0
Number of PP, X ± SD	1.94 (1.49 - 2.39) ± 1.37	
Duration ventilation, day, X ± SD	20.12 (14.52 - 25.17) ± 18.33	
Length of stay in ICU, day, X ± SD	26.63 (21.71 - 37.19) ± 21.88	

Legend: ECMO = extracorporal membrane oxygenation; LCAT = limitation or cessation of active therapy; PP = prone position; X = mean; SD = standard deviation.

4. Discussion

In our study, all patients received standard ventilation and the use of positive end-expiratory pressure (PEEP) alone improved oxygenation in 12.5% of patients. The combination of high PEEP and prone position (PP) was necessary to improve oxygenation in 60% of patients. Patients who responded well to this strategy tended to be obese, although this was not statistically significant.

The characteristics of the patients in our study were similar to previously published studies in terms of age, sex ratio, comorbidities and symptoms on admission. The mean age in our study was 69.05 (65 - 73) ± 10.81 years. In a study conducted in Amiens, France, Brault *et al.* [13] found a mean age of 67 years. In an Italian series, Scaramuzzo *et al.* [14] found an average age of 66.

It is now known that people of any age can contract this infection. However, patients aged ≥ 60 years and those with underlying medical comorbidities have an increased risk of developing a severe form of COVID-19. The immune system deteriorates with age, making patients more vulnerable to attacks, particularly viral attacks. In addition, the onset of comorbidities is correlated with increasing age, which increases the risk of developing severe forms of COVID-19.

In addition, as in our study, several authors have reported a predominance of males among patients admitted to the intensive care unit (ICU). In our study, 70% were men. In a study of 149 ICU in France, Belgium and Switzerland, the proportion of men was 74% [15].

Several studies in different countries have shown that the angiotensin converting enzyme 2 (ACE2) plays a crucial role in the greater susceptibility of men, due to higher blood concentrations of ACE2.

Certain organs are thought to act as "reservoirs" for the virus: the lungs, the digestive system, the kidneys and the testicles. In addition, some authors suggested that women develop a stronger immune response, mainly due to the presence of two X chromosomes. As their innate and adaptive immune responses are higher than those of men, this would favour more rapid elimination of the virus [16].

We found a predominance of obesity and hypertension among the comorbidities of patients in our cohort. This finding agrees with the literature. In fact, the presence of comorbidities such as diabetes, hypertension, heart disease, chronic lung disease and cancer have been described as risk factors for severe forms of COVID-19 that may lead to intensive care hospitalisation [17].

A high number of comorbidities were associated with the severity and mortality in patients with COVID-19 ARDS [18]-[20]. The need for hospitalisation was six times higher in patients with pre-existing health problems (45.4% versus 7.6%) [19]. Similarly, mortality was 12 times higher in this category of the population (19.5% versus 1.6%) [19].

The ventilatory mechanics of the patients in our series were similar to those reported in series of critically ill patients requiring resuscitation [5]. The mean compliance of our patients was 28.43 ml/cmH_2O (26.10 - 31.41) ± 6.76.

In the series by Zierh *et al.* [5] of 66 intubated critical care patients, compliance was 35ml/cmH_2O IQR (30 - 43).

The majority of patients in this series presented with bilateral hypoxaemic radiological lesions without cardiogenic cause, meeting the definition of ARDS.

The only criterion not included in the definition of ARDS for the patients in our series was the time from symptom onset to ICU admission, which was 8.3 days, longer than the 7 days set by the Berlin definition [1]. Several authors have reported a delay of between 8 and 12 days [3], which is beginning to raise the interest in revising or updating the Berlin definition.

After orotracheal intubation, our patients received "protective" ventilation as described by learned societies [7]. According to the current state of knowledge, there is no indication that a specific ventilator adjustment strategy different from that recommended for conventional ARDS should be used for COVID-related ARDS [6].

We systematically started ventilation with low PEEP, less than or equal to 8 cmH_2O, but ≥5 cmH_2O as recommended [7]. This was then increased above 8 cmH_2O only if there was no response to low PEEP. A total of 10 patients (25%) improved their oxygenation with "titrated" PEEP.

In a series of 25 patients with COVID-19 ARDS, Beloncle F found that 64% of patients had a high relapse rate with a good response to PEEP. At the same time, he noted the heterogeneity of the response and advocated titration of PEEP to limit its adverse effects [21].

After initiation of prone position, we observed a response rate of 80%. This rate is similar to those reported in the literature for patients with COVID-19 ARDS [9] [12] and those with non-COVID ARDS [8] [22]. In fact, as in our series, Gleissman *et al.* in Sweden [9] and Brault *et al.* [13] in France both found an 82% response rate to prone position in patients with severe COVID-19 ARDS. In ARDS of other causes, similar rates have been reported [8] [22]. The response to prone position seems to be common to all ARDS without aetiological distinction.

In our series, obese patients required prone positioning and high PEEP. Advanced age seemed to be a factor in good response to high PEEP. In Gleissman *et al.*'s series in Sweden [9], age, sex, BMI or SAPS 3 did not predict the success of increasing the P/F ratio in his 44 patients. In obese patients, the negative effects of chest wall weight and abdominal fat mass on lung compliance lead to a reduction in functional residual capacity (FRC) and arterial oxygenation. These phenomena are exacerbated in the supine position and worsen after sedation and mechanical ventilation, leading to atelectasis. These are recruited in prone position, hence the good response to oxygenation. Older age, which appears to be a factor in non-response to prone position in our series, may be a confounding factor because obesity, although increasing with age, is less prevalent after the 7th decade of life [23]. Older patients would therefore be less obese and therefore less likely to respond to prone position placement due to a lack of areas to re-aerate. Although, we seem to find certain characteristics of responders unlike other authors, we cannot formally confirm this.

The mortality rate was 40%. In the literature, the mortality rate varies between 26% and 61.5% in patients with severe forms of COVID [2]-[4]. Our mortality rate is very close to those found by Scaramuzzo *et al.* in Italy [14] and Brault *et al.* in Amiens [13], which were 42% and 43% respectively. This closeness can be justified by the overall similarity of the population. The clinical characteristics of our patients were similar in terms of age, sex, comorbidities, ethnic origin and ventilatory mechanics.

Our limitations include the small sample size and the lack of a supine control group. However, our study serves to guide the design of randomised trials to determine the clinico-biological characteristics that predict response to prone position with a view to prioritising management decisions.

5. Conclusions

At the end of this study, patients with COVID-19 ARDS had ventilatory mechanics similar to those described in patients with non-COVID-19 ARDS. The use of PEEP and the use of prone position increased the P/F ratio in the vast majority of patients, particularly those who were obese. No characteristic was associated with non-response.

Our study shows the value of systematically including all patients with an indication for prone position, regardless of their characteristics.

Analytical studies with much larger sample sizes should be carried out to identify the real factors associated with good or poor response to prone positions.

Authors' Contributions

Chris Nsitwavibidila: Study design, data collection and drafting of the manuscript. Wilfrid Mbombo: Drafting of the manuscript. John Nsiala: Study design, bibliographic research and corrections of the manuscript. Daniel Tonduangu: Bibliographic research and correction of the manuscript. Dominique Gizolme: Database creation and data collection. Junior Poba: Statistical analysis. Youssef Lutangu: Generation of tables and figures. All other authors: Correction of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ranieri, V.M., Rubenfeld, G.D., Thompson, B.T., Ferguson, N.D. and Caldwell, E. (2012) Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*, **307**, 2526-2533. https://doi.org/10.1001/jama.2012.5669

[2] Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., *et al.* (2020) Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*, **323**, 1574-1581. https://doi.org/10.1001/jama.2020.5394

[3] Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., *et al.* (2020) Clinical Course and Outcomes of Critically Ill Patients with SARS-CoV-2 Pneumonia in Wuhan, China: A Single-Centered, Retrospective, Observational Study. *The Lancet Respiratory Medicine*, **8**, 475-481. https://doi.org/10.1016/S2213-2600(20)30079-5

[4] Bhatraju, P.K., Ghassemieh, B.J., Nichols, M., Kim, R., Jerome, K.R., Nalla, A.K., *et al.* (2020) Covid-19 in Critically Ill Patients in the Seattle Region-Case Series. *The New England Journal of Medicine*, **382**, 2012-2022. https://doi.org/10.1056/NEJMoa2004500

[5] Ziehr, D.R., Alladina, J., Petri, C.R., Maley, J.H., Moskowitz, A., Medoff, B.D., Hibbert, K.A., Thompson, B.T. and Hardin, C.C. (2020) Respiratory Pathophysiology of Machanically Ventilated Patients with COVID-19: A Cohort Study. *American Journal of Respiratory and Critical Care Medicine*, **201**, 1560-1564. https://doi.org/10.1164/rccm.202004-1163LE

[6] Alhazzani, W., Møller, M.H., Arabi, Y.M., *et al.* (2020) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Medicine*, **46**, 854-887. https://doi.org/10.1007/s00134-020-06022-5

[7] Papazian, L., Aubron, C., Brochard, L., Chiche, J.D., Combes, A., Dreyfuss, D., *et al.* (2019) Formal Guidelines: Management of Acute Respiratory Distress Syndrome. *Annals of Intensive Care*, **9**, Article No. 69. https://doi.org/10.1186/s13613-019-0540-9

[8] Guerin, C., Reignier, J., Richard, J.-C., Beuret, P., Gacouin, A., Boulain, T., Mercier, E., Badet, M., Mercat, A., Baudin, O., *et al.* (2013) Prone Positioning in Severe Acute Respiratory Distress Syndrome. *The New England Journal of Medicine*, **368**, 2159-2168. https://doi.org/10.1056/NEJMoa1214103

[9] Gleissman, H., Forsgren, A., Andersson, E., Lindqvist, E., Lipka Falck, A., Cronhjort, M., Dahlberg, M. and Günther, M. (2021) Prone Positioning in Mechanically Ventilated Patients with Severe Acute Respiratory Distress Syndrome and Coronavirus Disease 2019. *Acta Anaesthesiologica Scandinavica*, **65**, 360-363. https://doi.org/10.1111/aas.13741

[10] Behesht Aeen, F., Pakzad, R., Goudarzi Rad, M., Abdi, F., Zaheri, F. and Mirzadeh, N. (2021) Effect of Prone Position on Respiratory Parameters, Intubation and Death Rate in COVID-19 Patients: Systematic Review and Meta-Analysis. *Scientific Reports*, **11**, Article No. 14407. https://doi.org/10.1038/s41598-021-93739-y

[11] Pan, C., Chen, L., Lu, C., Zhang, W., Xia, J.-A., Sklar, M.C., Du, B., Brochard, L. and Qiu, H.B. (2020) Lung Recruitability in COVID-19—Associated Acute Respiratory Distress Syndrome: A Single-Center Observational Study. *American Journal of Respiratory and Critical Care Medicine*, **201**, 1294-1297. https://doi.org/10.1164/rccm.202003-0527LE

[12] McGuinness, G., Zhan, C., Rosenberg, N., *et al.* (2020) High Incidence of Barotrauma in Patients with COVID-19 Infection on Invasive Mechanical Ventilation. *Radiology*, **297**, 247-494. https://doi.org/10.1148/radiol.2020202352

[13] Brault, C., Zerbib, Y., Kontar, L., Fouquet, U., Mathieu Carpentier, M., *et al.* (2020) Syndrome de détresse respiratoire aiguë COVID-19- versus Non-COVID-19: Différences et similitudes. *American Journal of Respiratory and Critical Care Medicine*, **201**, 1301-1304. https://doi.org/10.1164/rccm.202005-2025LE

[14] Scaramuzzo, G., Gamberini, L., Tonetti, T., *et al.* (2021) Sustained Oxygenation Improvement after First Prone Positioning Is Associated with Liberation from Mechanical Ventilation and Mortality in Critically Ill COVID-19 Patients: A Cohort Study. *Annals of Intensive Care*, **11**, Article No. 63. https://doi.org/10.1186/s13613-021-00853-1

[15] COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators (2021) Clinical Characteristics and Day-90 Outcomes of 4244 Critically Ill Adults with COVID-19: A Prospective Cohort Study. *Intensive Care Medicine*, **47**, 60-73. https://doi.org/10.1007/s00134-020-06294-x

[16] Wang, J., Syrett, C.M., Kramer, M.C., Basu, A., Atchison, M.L. and Anguera, M.C. (2016) Unusual Maintenance of X Chromosome Inactivation Predisposes Female Lymphocytes for Increased Expression from the Inactive X. *Proceedings of the National Academy of Sciences of the United States of America*, **113**, 2029-2038. https://doi.org/10.1073/pnas.1520113113

[17] Piva, S., Filippini, M. and Turla, F. (2020) Clinical Presentation and Initial Management Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Brescia, Italy. *Journal of Critical Care*, **58**, 29-33. https://doi.org/10.1016/j.jcrc.2020.04.004

[18] Cascella, M., Rajnik, M., Aleem, A., *et al.* (2022) Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls Publishing.

[19] Jin, J.M., Bai, P., He, W., Wu, F., Liu, X.F., Han, D.M., Liu, S. and Yang, J.K. (2020) Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Frontiers in Public Health*, **8**, Article 152. https://doi.org/10.3389/fpubh.2020.00152

[20] Finelli, L., Gupta, V., Petigara, T., Yu, K., Bauer, K.A. and Puzniak, L.A. (2021) Mortality among US Patients Hospitalized with SARS-CoV-2 Infection in 2020. *JAMA Network Open*, **4**, e216556. https://doi.org/10.1001/jamanetworkopen.2021.6556

[21] Beloncle, F.M., Pavlovsky, B., Desprez, C., Fage, N., Olivier, P.Y., Asfar, P., Richard, J.C. and Mercat, A. (2020) Recruitability and Effect of PEEP in SARS-Cov-2-Associated Acute Respiratory Distress Syndrome. *Annals of Intensive Care*, **10**, Article No. 55. https://doi.org/10.1186/s13613-020-00675-7

[22] Richard, K. and Albert, M.D. (2000) Prone Ventilation. *Clinics in Chest Medicine*, **21**, 511-517. https://doi.org/10.1016/S0272-5231(05)70162-3

[23] Verdot, C., Torres, M., Salanave, B. and Deschamps, V. (2017) Corpulence des enfants et des adultes en France métropolitaine en 2015. Résultats de l'étude ESTEBAN et évolution depuis 2006. *Bulletin Épidémiologique Hebdomadaire*, **13**, 234-241.