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Impact of Positive End Expiratory Pressure (PEEP) in Influencing Discharge Outcomes in COVID-19 Patients: An Observational Study

Anees A. Sindi[1,2]
[1]Department of Anesthesia and Critical Care, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [2]International Medical Center, Jeddah, Saudi Arabia

Abstract— Background: Studies suggest Positive End Expiratory Pressure (PEEP) could affect clinical outcomes and pulmonary vascular resistance. **Objective**: To explore the influence of high PEEP versus low PEEP on pulmonary function and clinical outcomes in critically ill COVID-19 patients. **Methods**: This single-centred retrospective observational study included 107 patients admitted to a tertiary care centre in Saudi Arabia. Demographic data included age, gender, comorbidities, oxygen saturation, length of intensive care unit (ICU) stay, mechanical ventilation requirement, supplemental oxygen requirement, PEEP, peak pressure, driving pressure, and tidal volume (TV). PEEP $\geq$10cm H_2O was considered high and $<$10cm H_2O was considered low. **Results**: High PEEP was associated with higher mortality than low PEEP (82% versus 50%, $p<0.05$). The regression model also showed that high PEEP increases the risk of mortality (B= 0.51, R^2=57%, $p<0.04$). PEEP was higher in patients with severe consolidation/progressive lung lesions (r=0.48). Lower PEEP related to improved outcomes (r=-0.21). Hypercapnia (r=-0.28) or higher respiratory rate (r=-0.61) and FiO_2 (r- -0.24), were associated with poorer outcomes. The intercept was highly significant ($p<0.05$), indicating there could be other independent variables influencing discharge outcomes. **Conclusion**: Higher PEEP was associated with higher mortality. Driving pressure, peak pressure, and TV should be considered alongside PEEP to evaluate mortality risk in COVID-19 patients.

Keywords - ICU, COVID-19, ventilatory support, mortality, PEEP, peak pressure

1. Introduction

The novel coronavirus disease of 2019 (COVID-19) remains a pandemic despite the availability of vaccines and antiviral medications [1]. COVID-19 is featured by bilateral pneumonia and severe acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 (severe acute respiratory distress syndrome coronavirus II), and ventilatory support is crucial to prognosis [2-4]. Supplemental oxygen, either through invasive or non-invasive modalities, remains the first essential step for treating resultant hypoxemia when managing COVID-19 patients, especially in resource-limited settings [3]. On the other hand, the impact of the timing of intubation and parameters such as Positive End Expiratory Pressure (PEEP), Tidal Volume (TV), Plateau pressure, and Driving pressure, that are associated with mechanical ventilation in influencing the prognosis of COVID-19 patients, remains inconclusive. The evidence suggests that the mode and capacity of mechanical ventilation could influence outcomes in COVID-19 patients.

Since hypoxemia is well tolerated in COVID-19 patients, it is necessary to identify the pulmonary functions that might deteriorate patient outcomes if the choice of respiratory support is inappropriate [3]. Thus, selecting the most appropriate respiratory support for managing SARS-CoV-2 patients has remained a dilemma among healthcare professionals [6]. Even though co-morbidities such as hypertension, diabetes mellitus (DM), and dyslipidemia account for substantial mortality in moderate to severe COVID-19 patients admitted to the intensive care unit (ICU), the involvement of pulmonary functions in influencing patient outcomes remains unquestionable [7]. This is not surprising because the lungs are the major end organs that

are affected by the virus resulting in ARDS. However, the ARDS associated with COVID-19 is different from that associated with pneumonia and restrictive lung diseases. In the latter, respiratory distress (dyspnea) is often linearly related to oxygen saturation (SpO_2) levels, and a SpO_2 of less than 88% would cause significant respiratory distress in patients [8]. However, COVID-19 patients could well tolerate SpO_2 levels below 88% without experiencing dyspnea or fatigue [3,4].

Although supplementary oxygen through non-invasive ventilation (NIV) is useful in resource-limited settings and when intubation is contraindicated, ventilatory parameters, such as PEEP, remain a vital determinant for managing hypoxia, hypercapnia, or type II respiratory failure. Further, the issues related to leakage, purity, pressure, electric supply, and filter attributes of supplemental oxygen therapy impact oxygenation, which could be detrimental to patients suffering from severe hypoxia. The physical and physiological challenges of high work of breathing, influenced by PEEP and driving pressure, also impact oxygen saturation and FiO_2. Hence, PaO_2, $PaCO_2$, and pH are dependent on ventilatory parameters such as PEEP, peak pressure, driving pressure, TV, and plateau pressure [5].

PEEP could be applied through continuous positive airway pressure (CPAP) or NIV or invasive mechanical ventilation (MV) [3.9]. Although NIV can generate PEEP and deliver additional inspiratory pressure for assisting inspiration [10], their use in treating Middle East Respiratory Syndrome (MERS) caused high failure as it did not prevent intubation. On the contrary, invasive ventilation could reduce mortality in patients with severe respiratory distress by ensuring high PEEP levels. However, such decisions could also cause damage to the pulmonary tissues that increases the risk of acute lung injury further [11]. This damage includes barotrauma, volutrauma (pulmonary edema due to high TV), atelectrauma (repetitive opening and closing of vulnerable airways), biotrauma (local inflammation due to the spillage of local inflammatory mediators), and oxytrauma (free radical generation) [3]. Therefore, in recent years, there has been less emphasis on using higher PEEP to prevent atelectrauma.

Although ARDS is a feature of moderate to severe COVID-19, the impact of ventilation in COVID-19 patients is quite different from that required for conventional ARDS patients [12]. This is because of the nature of the affected lung tissues in the former [5]. The major difference in COVID-19 patients is the coexistence of severely affected lung tissues adjacent to healthy lung tissues and unaffected areas [13,14]. Although the areas at risk of atelectasis are not very difficult to open with recruitment procedures or high PEEP, the unaffected areas are at risk of over-distension by high PEEP levels[3]. Thus, preventing atelectrauma in such patients could lead to respiratory failure if the PEEP levels are increased. This attribute is analogous to the proposed tailored MV as per ARDS phenotypes. Based on those phenotypes, COVID-19 patients should be categorized into non-recruitable ARDS where the use of higher PEEPs could cause ventilator-induced injury and higher mortality rates. Thus, the initial regulations of achieving early normoxia and normocapnia in all types of COVID-19 patients could be challenged [3,13,14]. The aim of ventilation should be to prevent damage caused by the ventilator by protecting the undamaged and otherwise fragile lung tissues [3]. The present study aimed to evaluate the effect of PEEP, peak pressure, and driving pressure on mortality outcomes in COVID-19 patients.

2. Material and methods

This study was a single-centered retrospective observational study conducted at a tertiary care center in Saudi Arabia. All patients, aged over 18 years, admitted to the ICU from March 1 to December 31 in 2020 were included in the study. Patients who did not require ICU admission and those with incomplete health records were excluded from the study. Power analysis was conducted retrospectively with Clincalc software https://clincalc.com/stats/samplesize.aspx. The power analysis was conducted based on the incidences of

COVID-19 in the Saudi Arabia population. As the incidence of COVID-19 was less than the global episode, we got an 80% power at a 0.95 level of significance with the sample size that was incorporated.

The demographic profile that was obtained included age, gender, major comorbidities, body mass index (BMI), mean SpO_2, duration of ICU stay, percentage of patients on MV, and patients requiring different modes of supplemental oxygen such as a nasal cannula, breather or non-breather mask, face mask, NIV, and MV. The pulmonary function was compared in terms of arterial blood gas (ABG) parameters (pH, PaO_2, $PaCO_2$) and pulmonary pressures (PEEP, Plateau pressure, and peak pressure) before and after intubation (a subcategory of patients who eventually required intubation despite all approaches to NIV).

The results were reported as descriptive statistics including frequency and percentages, while the inferential statistics include OR (odds ratio), correlation coefficients, regressions, and analysis of variance (ANOVA). The correlation matrix was constructed with numerical and categorical variables. The correlation coefficient was considered high if it was more than 0.60, moderate (0.4 to 0.6), low (0.1 to 0.3), and <0.1 (weak/non-significant). The categorical variables including discharge outcome (death or healthy discharge and consolidation) were assigned alphanumeric values. For example, hospital discharge was coded as death=1 and discharge home=2, while consolidation was coded as yes=1 and no=2. All statistical tests of inference were evaluated at the 0.05 level of significance. The study was conducted after obtaining appropriate permission from the Institutional Review Board (IRB). The identity of each patient was kept confidential throughout and after the study. Data analysis was done using Clincalc and SPSS software version 22.

3. Results

The demographic details of the patients are presented in **Table 1**. A total of 107 patients (male 85 and female 23) were included in this study with a mean age of 57.52±12.92years. The major comorbidities include DM and hypertension, observed in almost 50% of the patients. The mean SpO_2 at admission was 79.6±5.6%. The mean duration of ICU admission was 11.78 days and 51% of the patients required MV.

Table 1. Descriptive statistics on patients' profiles (n=107).

Parameters	Values
Age in years (mean/SD)	57.52±12.92
Gender (n/%)	
Male	85 (78.7%)
Female	23 (22.3%)
Major comorbidities (n/%)	
Diabetes mellitus	60(46.0)
Hypertension	61(50.0)
Heart failure	13(19.6)
Chronic kidney disease	17 (15.7)
Chronic obstructive pulmonary disease	1(0.9)
Mean oxygen saturation on room air at admission (%, mean/SD)	79.6 (5.6)
Days of ICU admission (Mean/SD)	11.78 (11)
Mechanical ventilation (n/%)	
Yes	51 (47.2)
No	56 (53.8)
PEEP[1] on mechanical ventilation	22 (43.1)

High (≥10cm H_2O) Low (<10cm H_2O)	29 (56.9)

[1]Positive End Expiratory Pressure

Table 2 presents the clinical parameters of the recruited patients at the time of admission to the ICU. Most of the patients were initiated on non-breathing masks (66.3%) while 28% were supplemented through a nasal cannula or face mask. Around 78% of the patients were initiated with NIV and supplemental oxygen therapy; however, 47.2% eventually went on to receive MV. Approximately, 20% of the patients required invasive ventilation at the time of admission to the ICUs.

Table 2. Pulmonary parameters based on ICU admission status.

Variables	n (%)
Maximum oxygen therapy types	
Nil	25 (23)
1-3L/min nasal cannula	8 (7.4)
>4 L/min nasal cannula	5 (4.6)
Face mask	14 (13)
Non-rebreather mask	24 (22.8)
High-flow nasal oxygen (HFNO)	1 (0.8)
Intubation & mechanical ventilation within 24h of admission to	20 (18.6)
ICU (P/F ratio <100)	8 (7.4)
Non-invasive Ventilation/ BiPAP	
Total patients on mechanical ventilation (during hospital stay)	51 (47.6)
Hypotension requiring inotropes	15(14)
Shortness of breath (SOB)	87(81)
Consolidation on chest x-ray	52(48.5)
Bilateral lung infiltrate	46.0(42.9)
Unilateral lung infiltrate	5(4.6)
Reason for ICU admission	
1. Respiratory failure	76(71)
2. Altered consciousness	18(17)
Extubated successfully	25(23.3)

Approximately 50% of the patients exhibited consolidation in the lung fields with bilateral infiltrate noted in 42.9% of the patients, and 14% of the patients required inotropes for managing hypotensive crises. Of the 51 patients requiring MV, 25 patients were extubated successfully while the rest either died or were moved to other facilities at follow-up. These patients include those discharged to home or step-down care. **Table 3** showed that age, gender, and comorbidities individually did not affect mortality as the p-values were non-significant (p>0.05).

Table 3. Relationship of demographic variables with mortality.

Variables	Mortality (%)	P-value
Age		
< 50 years	50	0.13

>50 years	66	
Gender Male Female	 68 55	 0.27
Comorbidity No Yes	 55 70	 0.21

The comparison of pulmonary function (Table 4) reflected that MV/intubation significantly improved PaO_2, $PaCO_2$, and SpO_2 in comparison to NIV or supplemental oxygen therapies. The average PEEP and Peak pressures were significantly increased with intubation; however, plateau pressure was not significantly raised.

Table 4. Comparison between pulmonary parameters before and after intubation (NIV versus intubation).

	NIV[1] (Mean/SD)	**MV[2]-intubation (Mean/SD)**	**P-value**
ABG[3] parameters			
pH	7.3 (0.17)	7.25 (0.12)	>0.05
$PaCO_2$ (mm)	48.32 (25.56)	44.42 (16)	<0.05
PaO_2 (mm)	57.88 (20.95)	78.6 (121)	<0.001
SPO_2 (%)	73.3 (20.32)	89.2 (7.8)	<0.001
Pulmonary pressures (cm H_2O)			
PEEP[4]	8.4 (3.18)	9.6 (3.1)	0.005
Plateau pressure	29.1 (9.5)	29.4 (6.4)	0.78
Peak pressure	27.4 (4.4)	29.07 (8.5)	0.02

[1]non-invasive ventilation [2]mechanical ventilation [3]arterial blood gas [4]Positive End Expiratory Pressure

The correlation matrix (Table 5) indicated that PEEP was positively correlated with peak pressure, mode of oxygen delivery, consolidation, PCO_2, and FiO_2. PEEP values positively correlated with the mode of supplemental oxygen (being highest for intubation and lowest with nasal cannula). TV was positively correlated with a positive outcome. PO_2 and the mode of supplemental oxygen delivered were unrelated and weakly related to outcomes.

Table 5. Correlation Matrix for Pulmonary Pressures, Discharge Outcomes, Lung volume, and mode of supplemental oxygen (n = 107).

	Outcome+	**Mode O_2 delivery**	**Consoli-dation**	**PO_2 value on ABG (mmHg)**	**PCO_2 value on ABG (mmHg)**	**Peak pressure (cmH_2O)**	**PEEP (cmH_2O)**
Outcome+	1						
O_2 Mode ++	-0.13*	1					
Consolidation	0.33*	0.21*	1				
PO_2 (mmHg)	-0.05	-0.27*	-0.1	1			
PCO_2 (mmHg)	-0.28*	-0.12*	-0.1	0.2*	1		

Peak pressure (cmH_2O)	-0.06	0.41*	0.56*	-0.2*	0.16*	1	
PEEP[1] (cmH_2O)	-0.21*	0.22*	0.48*	0.06	0.3*	0.67*	1
FiO_2 (%)	-0.24*	0.12*	-0	-0.4*	0.32*	0.67*	0.5*
Tidal volume	0.41*	-0.12*	0.2*	-0.4*	-0.2*	0.24*	-0
Respiratory rate	-0.61*	-0.01	0.02	-0	0.32*	0.42*	0.5*

[1]Positive End Expiratory Pressure, +: Death :0 and Discharge Home: 1, ++: nasal cannula=1 and MV=6

The relation between PEEP level and mortality is depicted by the regression model (Table 6). The regression model depicted that discharge outcomes were significantly influenced by PEEP (B= -0.5, p=0.04) and intercept of the regression model (0.000).

Table 6. Regression Model of Mortality on PEEP.

	B	t (p)	95% CI	ANOVA[1] (p-value)
Intercept PEEP[2]	1.5 0.5	9.48(0.00) -2.23 (0.04)	1.14 to1.85 -0.99to - 0.0017	0.04

[1]Analysis of Variance, [2]Positive End Expiratory Pressure, Dependent variable=Mortality

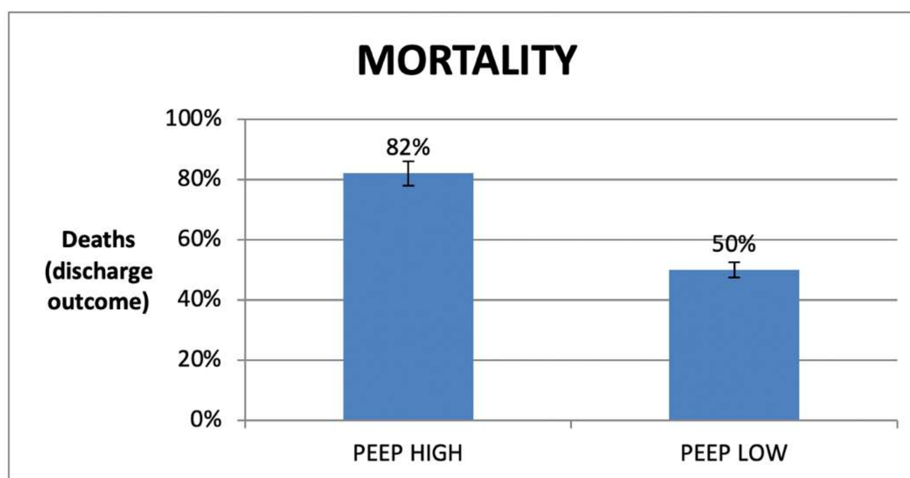

Figure 1. Mortality rate in High PEEP (n=22) and Low PEEP (n=29) patients. The regression model also showed that high PEEP increases the risk of mortality (B= 0.51, R^2=57%, p<0.04).

4. Discussion

The present study evaluated the relationship between PEEP and mortality from the perspective of various parameters underpinning ventilatory efforts in COVID-19 patients. The study was based on the evidence that COVID-19 patients experience significant mortality even with improved oxygen saturation [15]. The study showed that lower PEEP values were related to improved outcomes while hypercapnia and higher respiratory rate, FiO_2, and PEEP were associated with poorer outcomes and higher mortality. Initially, 20 patients required intubation at admission, while 51 patients eventually required intubation post-admission. The regression model depicted that high PEEP significantly impacted the discharge outcomes (p=0.049)

toward a higher risk of mortality. On the contrary, such an assumption might be an overstatement because high values of PEEP are also associated with positive outcomes. Hence, mortality was evaluated from the perspective of high and low PEEP values (Figure 1). Patients were from all the age groups (below 70 years) with a mean age of 57.52 years. Being retrospective data, we could not control for gender at baseline. Nevertheless, we found no correlation between gender and outcome.

The regression model depicted that the intercept was also highly significant ($p<0.05$), which indicated that there could be more independent variables apart from PEEP that influence discharge outcomes such as underlying diseases and mode of oxygen delivery. This finding supported the assumption that PEEP optimization is necessary based on other ventilation parameters such as peak pressure, driving pressure, TV, and plateau pressure. All these parameters influence lung compliance and impact the ventilation-perfusion ratio. SARS-CoV-2 patients develop effective intrapulmonary shunt that bypasses the portions of the lungs affected by the virus [16]. As a result, COVID-19 patients often exhibit preserved lung compliance in portions of the lungs that are not affected by the consolidation [3]. Therefore, it is necessary to identify the ventilatory parameters that deteriorate prognosis in COVID-19 patients [17,18]. Among different ventilatory variables, PEEP, PaO_2/FiO_2, and driving pressure have received significant importance in affecting the outcomes in COVID-19 patients. High FiO_2 levels decrease the PaO_2/FiO_2 ratio which marks the severity of ARDS in SARS-CoV-2-affected patients. As a result, increasing the PEEP level might be necessary to reduce FiO_2, without compromising the ventilation-perfusion ratio.

We found that TV and respiratory rate were positively and negatively related to improved outcomes, respectively. However, we found that PEEP was not correlated with TV, which indicates that TV is an independent ventilation parameter that improves outcomes in COVID-19 patients. Our study showed that nasal cannula use was associated with lower mortality, while intubation was associated with higher mortality, but the relationship was weak. The high mortality with MV could be due to the severity of the disease rather than the method of administering supplemental oxygen. This finding was complemented by the observation that invasive ventilation improved PaO_2 and reduced PCO_2 compared to NIV. We also found that baseline hypoxemia did not affect discharge outcomes. This finding endorsed the previous findings that COVID-19 patients could tolerate hypoxemia because of the unaffected lung tissues lying adjacent to the affected parts, due to shunt functions. Therefore, the decision for MV in preference to NIV in COVID-19 patients' needs to be advocated beyond hypoxemia. This suggested that the driving pressure was not lowered with higher PEEP because of the plateau pressure or peak pressure, and a rise in the latter perhaps increased the driving pressure in certain patients.

It is imperative that most of the moderate to severe COVID-19 patients would require MV due to severe hypercapnia and hypoxemia [19]. However, the rise in PEEP and peak pressure indicated that increases in driving pressure would cause over-distension of the lungs; thereby, reducing lung compliance in the long run [20,21]. Similarly, the rise in PEEP could have affected the unaffected parts of the lungs (barotrauma). This assumption is grounded on the evidence that PEEP levels should be 4 to 7 cm H_20, beyond which the chances of pulmonary damage increase [3]. PEEP should be considered in association with peak pressure, and TV, FiO_2%, paO_2, and $paCO_2$ for prognosis of respiratory distress [22]. The evidence suggests that both higher PEEP ($\geq$10 cm) and lower PEEP could increase pulmonary vascular resistance and aggravate respiratory failure [3].

In our study, there was no participant with PEEP less than 1cm H_2O, so lower PEEP values were between 4 to 9cm H_2O. Although the mean PEEP in this study with MV was 9.6 cm H_2O, it was >10cm H_2O in 21.7% (n=22) of the patients. Our study showed that the mortality rate in patients receiving high PEEP (>10 cm

H_2O) was significantly higher than those receiving PEEP <10cm H_2O (82% versus 50%, $p<0.05$).
High PEEP compromises circulation due to overdistension of the lungs. Therefore, in COVID-19 patients requiring high doses of vasopressors, the risk of high PEEP should be considered [24]. In our study, 14% of the patients required ionotropic support. Nonetheless, some COVID-19 patients would benefit from lung recruitment maneuvers and high PEEP (between 10cm to 20cm H_20). In this regard, the role of lung ultrasound in monitoring recruitable lung lesions versus hyperinflation at higher PEEP levels is under active consideration [25]. High driving pressure (the difference between peak or plateau pressure and PEEP) is associated with poor outcomes.

Driving pressure could be lowered by limiting the TV and adequate titration of PEEP. Too much lowering of PEEP could increase the driving pressure that increases the risk of atelectasis. The evidence suggests that COVID-19 patients should be maintained with low driving pressure of less than 15 cm H_2O, preferably at 5 to 7cm H_2O. Thus, it could be inferred that higher PEEP values could lower driving pressure below 15cm considering the peak or plateau pressure to be constant. In this regard, the evidence suggests that PEEP values should be kept moderate in COVID-19 patients as it would provide the possibility for diverting pulmonary blood flow from the damaged part of the lungs to the non-damaged part. On the contrary, if the PEEP values are increased, the recruitment effect would be minimal without the action of vasopressors or fluids [26].
As deterioration in lung volumes including TV is a marker of mortality, the optimization of PEEP as a function of TV is important. Optimizing PEEP is also important from the perspective of the paO_2/ FiO_2 ratio because low ratios indicate the severity of ARDS. Hence, PEEP levels should ensure that paO_2/FiO_2 either remains constant or increases with time. The heterogeneous effect of high and low PEEP on pulmonary function was reported. PEEP values of 15cm H_2O increase lung elastance, lung stress, mechanical power, PaO_2/FiO_2, $PaCO_2$, and pulmonary function parameters when compared to PEEP values of 5cm H_2O [27]. High PEEP values were also associated with a lower number of ventilator-free days, higher acute kidney injury, and higher requirements for renal replacement therapy [28]. Therefore, the evidence suggests ventilation management should consider lung compliance, prone positioning, and TV for setting PEEP [29]. PEEP adjustments should also be in line with permissive hypoxia because the presence of oxygen within the lungs would compromise the removal of CO2 and aggravate hypercapnia [30].

This study has certain limitations despite the fact that power of the study as per sample size was more than 80%. Firstly, the study was biased toward gender because the number of male patients was higher than female patients. Secondly, the study did not address pulmonary function and associated outcomes in COVID-19 patients under very low PEEP values (<1cm). Therefore, the study is more sensitive to outcomes related to PEEP values around 10 cm H_20. As the study was retrospective in nature, certain confounding variables such as ethnicity, pulmonary function, and immune status could not be controlled at the baseline.

5. Conclusion

The study showed that higher PEEP values could increase the risk of mortality by causing over-distension of the lungs. Comorbidity, mode of O2 delivery, and age could impact outcomes in COVID patients. PEEP should be optimized in ensuring effective ventilatory support and improved prognosis in COVID-19 patients.

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